Quantitative Assessment of Bone Metastasis in Prostate Cancer Using Synthetic Magnetic Resonance Imaging

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Objective: The aims of this study were to evaluate the feasibility of quantitative synthetic magnetic resonance imaging (SyMRI) for characterizing bone lesions in prostate cancer and to discriminate viable progressive osteoblastic bone metastases from nonviable bone metastases with treatment-induced sclerosis during the treatment course.

Materials and Methods: This institutional review board–approved prospective study included 96 consecutive prostate cancer patients who underwent whole-body MRI including diffusion-weighted imaging at the time of staging at diagnosis or starting a new line of anticancer treatment. Additional synthetic MRI of the lumbosacral spine, pelvis, and proximal femurs was performed. A region of interest of 1.0 cm in diameter was set in each bone lesion by 2 independent readers who were blinded to bone lesions’ diagnosis. Differences in SyMRI variables between the different bone lesions were compared with the Wilcoxon rank sum test, and associations of SyMRI variables with active disease were analyzed with logistic regression analysis. Performance of T1, T2, and proton density (PD) for diagnosing active disease was assessed using the area under the receiver operating characteristic curve.

Results: Ninety-three bone lesions were eligible for analysis. The PD values of active (viable) bone metastatic lesions were significantly higher than those of inactive (nonviable) bone metastatic lesions without sclerosis and those of red bone marrow (P < 0.001 for both readers). The PD values of inactive bone metastatic lesions with sclerosis were significantly lower than those of inactive bone metastatic lesions without sclerosis and red bone marrow (P < 0.001 for both readers). The PD value proved to be an independent significant indicator of red bone marrow. The areas under the curve of T1/T2/PD for identifying active disease were 0.81/0.69/0.93 for reader 1 and 0.78/0.70/0.92 for reader 2, respectively.

Conclusions: Signal quantification on SyMRI provides objective assessment of bone lesions in the lower trunk. The PD value can be useful to determine the viability of bone metastasis in prostate cancer.

Key Words: magnetic resonance imaging, bone marrow, sclerosis, protons, biomarkers

Prostate cancer is the second most common cancer and the fifth leading cause of cancer death among men worldwide. Prostate cancer frequently metastasizes to bone, representing 91.1% of metastatic sites of stage IV prostate cancer. Bone metastases may cause pain, neuropathy, pathologic fractures, and hypercalcemia, which negatively affect patients’ quality of life.

There are some problems in terms of evaluating bone lesions’ characteristics in prostate cancer patients by using conventional serum and imaging evaluation techniques. For example, although prostate-specific antigen (PSA) is the most widely used clinical biomarker of prostate cancer, a dissociation between PSA levels and state of disease may occur in castration-resistant prostate cancer patients. Bone scintigraphy has been the most popular imaging method for the evaluation of bone metastases. However, because bone scintigraphy relies on the detection of osteoblastic activity, it suffers from false-negative findings when osteolyis predominates and false-positive findings after treatment known as the flare phenomenon. The Response Evaluation Criteria in Solid Tumors regards bone scintigraphy as insufficiently appropriate for an evaluation of tumor activity of bone metastases, particularly in osteoblastic bone metastases. The same applies to plain radiography and 18F-fluoro-2-deoxy-d-glucose positron emission tomography. Prostate cancer patients may harbor both viable osteoblastic bone metastases and treatment-induced sclerosis during the treatment course. Although computed tomography (CT) and bone scintigraphy are widely used to survey these calcified lesions, they are unable to discriminate between these 2 entities.

Diffusion-weighted imaging (DWI) is a functional magnetic resonance imaging (MRI) technique, which captures the random Brownian motion of water molecules. Diffusion-weighted imaging offers a qualitative assessment of tumor activity for both sclerotic and lytic bone metastases, and does not suffer from a flare response as seen in bone scintigraphy. The European Organisation for Research and Treatment of Cancer imaging group has positioned whole-body DWI as a potential first choice for monitoring the response of bone metastases to treatment, along with [11C]-choline and [18F]-fluorocholine positron emission tomography. The Metastasis Reporting and Data System for Prostate Cancer has emerged as a standard for data acquisition, assessment, and reporting for whole-body MRI (WB-MRI) including DWI. Nevertheless, an additional in-phase/out-of-phase gradient echo acquisition is still required to detect out-of-phase signal loss as seen in red bone marrow (RBM), the latter which may mimic an active metastatic lesion with low signal intensity (SI) on T1-weighted images (T1WIs) and high SI on DWI.

The recently developed technique of synthetic MRI (SyMRI) allows generating various image contrasts (including fluid-attenuated inversion recovery images, T1WIs, T2-weighted images, double inversion recovery sequences) and adjusting subtle parameter values to improve lesion visualization using the information from one single scan, and it also allows for quantitative analysis of T1, T2, and proton density (PD). The clinical utility of SyMRI in neurological disorders and internal derangement of the knee has been shown. Synthetic MRI of the knee was demonstrated to be accurate for T1, T2, and PD quantification by a recent phantom validation study. However, so far the application of the
SyMRI technique has been limited to intracranial and knee structures, because SyMRI data acquisition requires relatively still-standing objects. According to a previous study in which normal lumbar vertebral bone marrow T1 and T2 relaxation times were evaluated by the conventional inversion recovery method with different inversion times and the multiple spin-echo technique with different echo times, respectively, SyMRI has a potential to quantitatively define bone marrow lesion characteristics faster and in a more clinical-practical way than before. We apply this technique in assessing the bones in the lower trunk of the body. The aims of this study were to evaluate the feasibility of quantitative SyMRI for characterizing bone lesions in prostate cancer and to discriminate viable progressive osteoblastic bone metastasis from non-viable bone metastases with treatment-induced sclerosis during the treatment course.

**MATERIALS AND METHODS**

**Patients**

This institutional review board–approved study (study number: M2016–170) enrolled patients with histologically proven prostate cancer. Patients who underwent diffusion-weighted whole-body imaging with background body signal suppression (DWIBS), SyMRI, and CT for evaluating whether sclerosis existed or not, at the time of staging at diagnosis or initiation of a new line of anticancer treatment from November 2016 to November 2017, were included in this prospective study. Patients underwent SyMRI at the time of WB-MRI. All patients gave written informed consent for enrollment into the study. Patients who underwent therapeutic or palliative radiotherapy for bone lesions were excluded.

**Magnetic Resonance Imaging Protocol**

Synthetic MRI was performed at the time of WB-MRI including DWIBS with a 3.0-T MR scanner (Philips Ingenia 3.0 T Release 5.1.9; Philips Healthcare, Best, the Netherlands), using a multiple coil system consisting of the head-neck top coil, the base coil, the anterior coil, and the posterior coil (dS Torso; Philips Healthcare, Best, the Netherlands). A single-shot echo-planar imaging sequence with a short inversion time inversion recovery (STIR) prepulse for fat suppression was used for the DWIBS sequence. Applied sequence parameters for DWIBS were as follows: repetition time (TR)/echo time (TE)/inversion time (TI) of 5300/69/250 milliseconds, voxel size of 3.45 × 3.59 × 4.50 mm³, b-value of 999 s/mm², acquisition time of 2:39 minutes per station, and total 3 stations. For SyMRI, quantification of T1 and T2 relaxation rates as well as PD was performed using the QRAPMASTER pulse method sequence, which is a multislice, multiecho, and multisaturation delay acquisition sequence. Two sets of TE and 4 sets of delay times were used to generate 8 complex images in each section in order to quantify T1, T2, and PD. The TEs were 12.5 and 100 milliseconds, the delay times were 151, 604, 2115, and 4382 milliseconds, and the TR was 4533 milliseconds. Thirty-two slices were acquired, voxel size was 1.48 × 2.13 × 5.00 mm³, and total acquisition time was 3:47 minutes. Synthetic MRI was performed to include the pelvis from at least the
level of L1 to the proximal femurs (craniocaudal distance of 38 cm). Synthetic images including T1, T2, and PD maps were created using SyMRI StandAlone software (SyntheticMR AB, Linköping, Sweden). The TR/TE values of 500/10 milliseconds were used for (synthetic) T1WI. The MRI examination also included a modified DIXON (mDIXON) sequence.

Detection and Classification of Bone Lesions

Bone lesions 1.0 cm or larger in diameter in the lumbosacral spine, pelvis, and proximal femurs were prospectively identified and categorized by 2 radiologists (who were both different from the reader 1 and reader 2, which we will describe later on) working in consensus into the following 5 groups: (1) “RBM” group, (2) “active disease (S+)” group, (3) “active disease (S−)” group, (4) “inactive disease (S+)” group, and (5) “inactive disease (S−)” group. Image analysis was performed at a multimodality workstation (SDS viewer; TechMatrix Corporation, Tokyo, Japan), and all available clinical and imaging information including treatment history and previous DWIBS examinations were reviewed.8,20 First, an “RBM” focus was defined as low SI similar to muscle or slightly hyperintense to muscle on T1WI that was hyperintense on DWIBS images and showed signal loss on out-of-phase images compared with in-phase images with no evidence of metastatic bone disease by referring to all available clinical and previous imaging information. Second, an “active disease (S+)” lesion was defined as low SI similar to muscle on T1WI that was hyperintense to normal background bone marrow on DWIBS images and was compatible with a viable lesion by referring to all available clinical and previous imaging information and showed massive sclerosis on CT. Third, an “active disease (S−)” lesion was defined as low SI similar to muscle on T1WI that was hyperintense to normal background bone marrow on DWIBS images and was compatible with a viable lesion by referring to all available clinical and previous imaging information and did not show significant sclerosis on CT. Fourth, an “inactive disease (S+)” lesion was defined as low SI similar to muscle on T1WI that was equally hypointense to normal background bone marrow on DWIBS images and was compatible with a nonviable lesion by referring to all available clinical and previous imaging information and showed massive sclerosis on CT. Five, an “inactive disease (S−)” lesion was defined as low SI similar to muscle on T1WI that was equally hypointense to normal background bone marrow on DWIBS images and was compatible with a nonviable lesion by referring to all available clinical and previous imaging information and did not show significant sclerosis on CT. Each lesion was evaluated and categorized as active (viable) or inactive disease (nonviable) based on its signal on DWIBS, and all available clinical and previous imaging information according to the guidelines by the European Organisation for Research and Treatment of Cancer imaging group.8,20 Bone lesions that did not fit in any of the 5 aforementioned groups, including bone cysts, and that were all smaller than 1.0 cm in diameter were excluded from the analysis.

### TABLE 1. Patient and Bone Lesion Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Median (range) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>75 (66–90)*</td>
</tr>
<tr>
<td>Cancer status</td>
<td>Castration-naive/ sensitive/ resistant</td>
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<tr>
<td>PSA level, ng/mL</td>
<td>21.1 (0.03–892)*</td>
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<tr>
<td>Alkaline phosphatase level, IU/L</td>
<td>344 (98–1203)*</td>
</tr>
<tr>
<td><strong>Bone lesion characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Size, mm</td>
<td>21 (14–51)*</td>
</tr>
<tr>
<td>Site</td>
<td>Lumbar/sacral/pelvis/femur 22 (30.1)/10 (13.7)/33 (45.2)/8 (11.0)*</td>
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*Median (range). †n (%). PSA indicates prostate-specific antigen.

Bone lesions 1.0 cm or larger in diameter in the lumbosacral spine, pelvis, and proximal femurs were prospectively identified and categorized by 2 radiologists (who were both different from the reader 1 and reader 2, which we will describe later on) working in consensus into the following 5 groups: (1) “RBM” group, (2) “active disease (S+)” group, (3) “active disease (S−)” group, (4) “inactive disease (S+)” group, and (5) “inactive disease (S−)” group. Image analysis was performed at a multimodality workstation (SDS viewer; TechMatrix Corporation, Tokyo, Japan), and all available clinical and imaging information including treatment history and previous DWIBS examinations were reviewed.8,20 First, an “RBM” focus was defined as low SI similar to muscle or slightly hyperintense to muscle on T1WI that was hyperintense on DWIBS images and showed signal loss on out-of-phase images compared with in-phase images with no evidence of metastatic bone disease by referring to all available clinical and previous imaging information. Second, an “active disease (S+)” lesion was defined as low SI similar to muscle on T1WI that was hyperintense to normal background bone marrow on DWIBS images and was compatible with a viable lesion by referring to all available clinical and previous imaging information and showed massive sclerosis on CT. Third, an “active disease (S−)” lesion was defined as low SI similar to muscle on T1WI that was hyperintense to normal background bone marrow on DWIBS images and was compatible with a viable lesion by referring to all available clinical and previous imaging information and did not show significant sclerosis on CT. Fourth, an “inactive disease (S+)” lesion was defined as low SI similar to muscle on T1WI that was equally hypointense to normal background bone marrow on DWIBS images and was compatible with a nonviable lesion by referring to all available clinical and previous imaging information and showed massive sclerosis on CT. Five, an “inactive disease (S−)” lesion was defined as low SI similar to muscle on T1WI that was equally hypointense to normal background bone marrow on DWIBS images and was compatible with a nonviable lesion by referring to all available clinical and previous imaging information and did not show significant sclerosis on CT. Each lesion was evaluated and categorized as active (viable) or inactive disease (nonviable) based on its signal on DWIBS, and all available clinical and previous imaging information according to the guidelines by the European Organisation for Research and Treatment of Cancer imaging group.8,20 Bone lesions that did not fit in any of the 5 aforementioned groups, including bone cysts, and that were all smaller than 1.0 cm in diameter were excluded from the analysis.

### FIGURE 2. Flow diagram of patient and bone lesion selection.

SyMRI indicates synthetic magnetic resonance imaging; DWIBS, diffusion-weighted whole-body imaging with background body signal suppression; ROI, region of interest; RBM, red bone marrow.
Region of Interest Setting

The synthetic images were generated using a standardized setting in the SyMRI software. Figure 1 shows an example of SyMRI and T1, T2, and PD maps.

A region of interest (ROI) of 1.0 cm in diameter was set in each bone lesion on synthetic T1WI with coronal orientation by 2 independent readers 1 and 2. Readers 1 and 2 only reviewed coronal synthetic T1WIs and were blinded to the lesion's classification diagnosis and all clinical and other imaging information. Dedicated analysis software for SyMRI automatically calculated a value of T1, T2, and PD for all pixels in the ROI. The PD level of pure water was set at 100%.

Statistics

Mean values of T1, T2, and PD of the pixels within the ROI were used as SyMRI variables in the following analyses. The intraclass correlation coefficient and Bland-Altman analyses were performed to determine the observer variability of the SyMRI variables. Differences in SyMRI variables between the bone lesions’ characteristics were compared with Wilcoxon rank sum test, and associations of SyMRI variables with active disease were analyzed with logistic regression analysis. Performance of T1, T2, and PD for diagnosing active disease was assessed using the area under the receiver operating characteristic curve. All statistical analyses were executed using JMP 14.0 statistical software (SAS Institute, Cary, NC), and P < 0.05 was considered significant.

RESULTS

Patients and Bone Lesions’ Characteristics

A total of 96 patients with prostate cancer were prospectively enrolled in this study. Bone lesions in the lumbar sacral spine, pelvis, and proximal femurs were pointed out in 38 patients. Among these patients, 8 patients whose bone lesions were all smaller than 1.0 cm in diameter were excluded from the analysis. In the remaining 30 patients (median age, 75 years [range, 66–90 years]), a total of 93 lesions were eligible for analysis. All SyMRI scans were successfully performed and reconstructed with no significant artifacts. Patient characteristics are shown in Table 1, and patient selection and lesion count are shown Figure 2. Whole-body MRI was performed at the time of staging at diagnosis (n = 2) or initiation of a new line of anticancer treatment (n = 28).

The characteristics and classification of the metastatic bone lesions and RBM are shown in Table 1. The bone lesions were categorized into active disease (S+; n = 15), active disease (S−) group (n = 13), inactive disease (S+; n = 14), inactive disease (S−) group (n = 31), and RBM group (n = 20; Fig. 2). The number of ROIs set in each patient was 1/2/3/4/>5 in 14/4/4/1/7 patients, respectively.

Twenty of 30 patients had previous DWIBS examinations to compare the SI of the lesions between the current and the past scans. Nine other patients had follow-up DWIBS examinations to compare the SI of the lesions between the current and follow-up scans. The remaining patient has no previous or follow-up DWIBS examinations. Results among these 3 groups were not significantly different.

Relationships of Quantitative Values Among 5 Groups

Synthetic MRI variables of bone lesions are shown in Figure 3. Interobserver analysis between reader 1 and 2 revealed an excellent intraclass correlation. The coefficients for T1, T2, and PD were 0.80, 0.86, and 0.96, respectively. Any systematic difference between readers was not identified by Bland-Altman plots.

Regarding the PD value, active disease (S+) showed significantly higher PD than inactive disease (S−) (P < 0.001 for both readers; Fig. 3C). Active disease (S+) and active disease (S−) both showed significantly higher PD than inactive disease (S−), RBM, and inactive disease (S+) (P < 0.001 for both readers). Furthermore, inactive disease (S−) showed significantly lower PD than inactive disease (S−) and RBM (P < 0.001 for each for both readers). There was neither a significant difference between active disease (S+) and active disease (S−) (P = 0.98 for reader 1, P = 0.46 for reader 2), nor between inactive disease (S−) and RBM (P = 0.13 for reader 1, P = 0.13 for reader 2).
FIGURE 4. Representative images of an RBM focus in a 77-year-old man with prostate cancer (cT3bN0M1b, PSA 6.4 ng/mL, Gleason score 4 + 4). A, The coronal fusion image of STIR and DWIBS showed high SI on DWIBS of the lesion in the sacrum (white arrow). B, The coronal out-of-phase gradient echo image showed signal loss compared with the in-phase image. C, The coronal synthetic T1-weighted image with a region of interest of 1.0 cm in diameter by reader 1 (red circle).

FIGURE 5. Representative images of an active disease (S+) lesion in a 77-year-old man with prostate cancer (cT3bN0M1b, PSA 374.6 ng/mL, Gleason score 4 + 4). A, The coronal fusion image of STIR and DWIBS. The lesion showed hyperintense to background normal bone marrow on DWIBS. B, The coronal CT image (bone settings) showed sclerosis of the lesion in the third lumbar vertebra (white arrow). C, The coronal synthetic T1-weighted image with a region of interest of 1.0 cm in diameter by reader 1 (red circle). The lesion showed low SI similar to muscle on T1WI.
The T2 values of active disease (S+) and active disease (S−) were both significantly higher than that of inactive disease (S−), respectively (P < 0.05 for each for both readers), whereas there was no significant difference between the other pairs of 5 groups (P > 0.05 for each for both readers; Fig. 3B).

Differentiation of Active Disease From Any Other Groups

The PD values of active disease were significantly higher than the other groups (inactive disease [S+], inactive disease [S−], and RBM group; P < 0.001, for both readers, Figs. 3C, 4–6). We investigated the role of SyMRI variables in differentiating active disease from others. On multivariate analysis, only PD was a significant factor for the differentiation of active disease (combined [S+] and [S−]; n = 28) from any other group (n = 65; P < 0.001, for both readers, Table 2). The areas under the receiver operating characteristic curve of T1/T2/PD for active disease were 0.81/0.69/0.93 for reader 1 and 0.78/0.70/0.92 for reader 2, respectively.

DISCUSSION

Synthetic MRI is a novel technique that quantifies T1, T2, and PD values within a single scan. From this single SyMRI scan, T1-weighted, T2-weighted, PD-weighted, and inversion recovery images can be generated with a postprocessing step. The SyMRI technique was first introduced for brain imaging. The clinical application has

<table>
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<tr>
<th>TABLE 2. Univariate and Multivariate Analyses of SyMRI Variables for Differentiating Active Bone Metastasis From Other Groups (Inactive Disease [S+], Inactive disease [S−], and RBM Group)</th>
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<tbody>
<tr>
<td>Reader 1</td>
</tr>
<tr>
<td>Variables</td>
</tr>
<tr>
<td>T1 value</td>
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<tr>
<td>T2 value</td>
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<tr>
<td>PD value</td>
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</table>

Full model: all explanation variables were used for multivariate analysis.
Reduced model: explanation variables, which were not significant, were reduced.
SyMRI indicates synthetic magnetic resonance imaging; RBM, red bone marrow; OR, odds ratio; CI, confidence interval; PD, proton density.
just begun to expand to other organs with little respiratory movement, and the clinical usefulness of SyMRI in the diagnosis of knee disease has recently been reported.\(^\text{15,16}\)

In the current study, we evaluated the utility of SyMRI in characterizing bone lesions in the lower trunk of prostate cancer patients. The PD value quantified by SyMRI allowed to identify active bone metastasis regardless of whether sclerosis is present or not, and with a relatively high concordance between readers. Moreover, the PD values allowed differentiating active disease (S+) from inactive disease (S−), which both demonstrate similar sclerosis and may not be accurately discriminated with CT. These findings indicate that PD has a potential to be a useful biomarker of bone metastasis in patients with prostate cancer.

The formation of prostate cancer metastasis occurs through de novo monoclonal seeding from metastatic sites and multiple tumor clone transfer between metastatic sites.\(^\text{21}\) In the context of the complex pattern of metastatic spread and the resistance development of prostate cancer, each castration-resistant prostate cancer metastatic site may have heterogeneity in terms of treatment susceptibility. Therefore, urologists and oncologists require imaging biomarkers to be established, which can evaluate treatment response in individual lesions accurately and independently from differences in imaging conditions such as vendors or pulse sequences used. The SyMRI-derived PD value showed high diagnostic ability to discern tumor activity in individual lesions. Furthermore, with the QRAMASTER method of SyMRI, a monoexponential decay is assumed for relaxation rates, and this quantification method is consistent for every acquisition,\(^\text{2,11}\) which may enable SyMRI to detect bone lesions with relatively high reproducibility.

Although SyMRI has a potential to be an imaging biomarker, which enables quantitatively characterizing bone lesions, in-phase/out-of-phase gradient echo images are still needed to differentiate RBM from inactive disease (S−). The current study showed the usefulness of the PD value in discriminating active bone metastatic lesions from inactive lesions or RBM, regardless of whether sclerosis was present or not.

In this study, the PD values of inactive disease (S+/−) were significantly lower than those of inactive disease (S−). Based on this result, it seems that the existence of sclerosis may reduce PD values. Nevertheless, there was no significant difference in PD values between active disease (S+/−) and active disease (S−). Further investigation is needed to explain this contradictory phenomenon.

We acknowledge the potential limitations of this study. First, histopathology techniques to confirm the exact classification of each bone lesion were not obtained in this study because biopsies of bone metastases in prostate cancer are not common practice. Therefore, we have used all available clinical and imaging information including the comparison of DWIBS signals between the current and previous and follow-up examinations for diagnostic classification.\(^\text{1,2}\) Second, the scanned area was limited due to the long acquisition time of SyMRI. We applied SyMRI to the lower trunk area, because the bone metastases of prostate cancer are known to be most frequent in the pelvis.\(^\text{21}\) Future technical developments are needed to shorten the scan time of SyMRI to allow for whole-body assessment. Finally, because of the limited sample size of our pilot study, a larger population would be needed for future validation of these data.

CONCLUSIONS

Synthetic MRI variables lead to quantitative assessment of bone lesions in the lower trunk. The PD value can be useful to determine the viability of bone metastases in prostate cancer, regardless of whether sclerosis is present or not.

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