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Does T1- and diffusion-weighted magnetic resonance imaging give value-added than bone scintigraphy in the follow-up of vertebral metastasis of prostate cancer?

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Purpose: To evaluate the effectiveness of limited Magnetic Resonance (MR) images including T1- and diffusion-weighted image (DWI) for monitoring vertebral metastasis in patients with prostate cancer.

Materials and Methods: From July 2014 to November 2016, patients diagnosed with spinal metastasis from prostate cancer using 99mTc bone scintigraphy were enrolled. Regardless of the primary local therapy, the changes in spinal metastasis were followed up using bone scan and biparametric MR (T1+DWI). All tests were followed up for more than 3 months.

Results: Among the 14 follow-ups of 10 patients, 6 and 10 (including all progressed cases on bone scan) follow-ups were determined to show progressive disease using bone scan and biparametric MR, respectively. Otherwise, we could have predicted neurologic sequela earlier using biparametric MR. Examination time for biparametric MR was 15 minutes, and it was 4 hours for bone scan, respectively.

Conclusions: Although bone scan has been considered the standard test for bony metastasis in men with prostate cancer, limited MR including T1 and DWI has an additional benefit in monitoring spinal metastasis in patients who are already diagnosed as having spinal metastasis. The limited MR is more sensitive in detecting progressive disease. In addition, it can reduce neurologic complications caused by spinal metastasis.

Keywords: Magnetic resonance imaging; Neoplasm metastasis; Prostatic neoplasms; Spine

INTRODUCTION

Prostate cancer is a common malignancy with a relatively good prognosis [1]. Active surveillance has recently been recognized as one of the standard treatments for low-risk prostate cancer [2]. However, not a few prostate cancers still have a poor prognosis, leading to death after multiple metastases including bone metastases. Approximately 10%–20% of prostate cancer patients develop metastatic castration resistant prostate cancer in the first 5 years after diagnosis

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[3]. In addition, more than 10% of newly diagnosed prostate cancer patients have bone metastasis at the time of diagnosis [4]. Although the incidence of metastatic castration resistant prostate cancer is increasing, the survival rate is improved due to development of new drug, such as enzalutamide and abiraterone [5-7]. Therefore, it is becoming more important to prevent skeletal-related events in these patients.

In the case of bone metastasis, disease progression and secondary sequela including spinal cord compression require an aggressive follow-up [8]. In the literatures, symptomatic spinal cord compression among prostate cancer patients occurs in about 7% of patients [9]. Approximately, one third of patients with spinal metastases have clinically occult spinal cord compression on magnetic resonance (MR) [10,11].

Unfortunately, the prostate-specific antigen (PSA) test alone is not enough to determine the treatment of metastatic prostate cancer, and it should be accompanied by imaging [8]. Computed tomography (CT) and bone scan are not sufficient for the follow-up of metastasis, especially spinal metastasis [12]. Sensitivity of bone scan combined with CT and of whole-body MR for detecting metastases was 85% and 100%, respectively, and specificity was 88% and 100%, respectively [13]. In another study, the sensitivity of bone scan and whole-body MR for detecting bone metastasis was 86% and 98%–100%, respectively [14]. Because of these results, the importance of MR as a replacement for CT and bone scan, which is the standard diagnostic method, is emerging.

Efforts have been made to evaluate the efficacy of MR image to determine whether it can replace bone scan [14-17]. Multiparametric MR has a high accuracy and sensitivity, but it is limited by the complexity of the test and the use of contrast agents. And, whole-body MR requires special equipment and a long time for examination. Therefore, we prospectively compared the usefulness of biparametric MR (only T1- and diffusion-weighted images, DWI) and bone scans in the follow-up of patients with spinal metastasis.

MATERIALS AND METHODS

After Institutional Review Board review, this prospective study was approved (approval number: 05-2013-024). The study period ranged from July 2014 to November 2016. Patients who were diagnosed with vertebral metastasis using bone scan and rising PSA were enrolled. Men who had any malignancy other than prostate cancer were excluded. Patients who underwent surgery or radiation for other spinal diseases were excluded. In addition, men with extensive lymph node or visceral metastasis were excluded. All patients underwent both biparametric MR and bone scan at the beginning and end of the follow-up period in a prospective manner. Bone scan and biparametric MR during the same evaluation period were performed within 2 weeks, and each evaluation period was more than 3 months apart. Clinical data, including serum PSA level and related symptoms and signs, were collected prospectively.

Ten patients were enrolled and 1 patient underwent a total of 6 tests, 5 follow-ups. We analyzed data from 14 follow-ups. Bone scan was interpreted by an expert in the radionuclide image and biparametric MR was interpreted by an expert in the MR image of the musculoskeletal system. Clinical information was not provided to them.

Biparametric MR image consists of only DWI and T1 weighted images. This limited MR was carried out with a 3.0-Tesla MR unit (Siemens Medical Solutions, Erlangen, Germany). Spinal MR images were acquired in the transverse plane with sagittal images of the spine. Slice thickness was 3 mm.

Response Evaluation Criteria in Solid Tumors (RECIST) criteria were used for determining the MR findings as progressive disease or stable disease. Progressive disease was defined when there was at least a 20% increase in the sum of diameters of target lesions, or an absolute increase of at least 5 mm, or appearance of one or more new lesions [18]. However, RECIST criteria is not appropriate for determining bone scan finding. So, our specialist of nuclear medicine determined as progressive disease when new lesion, increased extent or intensity of lesion in bone scan findings.

RESULTS

A total of 10 patients were enrolled and they completed at least a single follow-up. One patient received 5 follow-ups. Therefore, we analyzed data from 14 follow-ups. Median age was 63 years (range, 48–76 years), and the median PSA level was 12 ng/mL (range, 0–303 ng/mL). The number of patients with Gleason scores 7, 8, and 9 was 2, 4, and 4, respectively. Among the 10 patients, 7 men had castration-resistant prostate cancer and 3 men had hormone-sensitive prostate cancer. Median interval of each follow-up was 3 months (range, 3–8 months).

Among the 14 follow-ups, 6 follow-ups (42.9%) were determined to show progressive disease using bone scan, while 10 follow-ups (71.4%, including all progressed cases on bone scan), were determined to show progressive disease using biparametric MR (Table 1).

Fig. 1 shows the images of bone scan and biparametric MR for vertebral metastasis during the 1st–2nd follow-up in the Table 1. While the patient had no back pain with slightly

Table 1. Summary of bone scan and T1- and diffusion-weighted magnetic resonance imaging in study cohort (n=14)

Patient	Age (y)	GS	Primary diagnosis (mo/y)	Previous therapy	ADT duration (mo)	Follow-up duration (mo)	PSA at exam	Clinical finding	Bone scan finding	MR finding	RECIST response bone scan/MR
1-1	61	4+4	Dec/2009	RP, RT, CH, ENZ	79	3	3.4	NSIC	NSIC	NSIC	SD/SD
1-2	61	4+4	Dec/2009	RP, RT, CH, ENZ	82	3	9.0	Mild back pain onset	NSIC	Epidural and paravertebral extension, TL (10 mm → 12 mm)	SD/PD
1-3	62	4+4	Dec/2009	RP, RT, CH, ENZ	85	3	12.1	NSIC	NSIC	NL	SD/PD
1-4	62	4+4	Dec/2009	RP, RT, CH, ENZ	88	3	12.4	Severe back pain, L-spine operation	Postoperative change in L-spines	Postoperative change and remnant tumor at L-spine, multiple NL at T-spine	SD/PD
1-5	62	4+4	Dec/2009	RP, RT, CH, ENZ	91	3	121.5	Back pain aggravation, decreased motor tone of lower limb	Interval increased intensity and extent of uptake	Multiple NL at C,T, L, S- spine, both pelvic bone	PD/PD
2	60	4+5	Sept /2015	ADT only	12	6	4.3	NSIC	NSIC	NSIC	SD/SD
3	76	5+4	Dec/2014	RT, CH	20	3	14.1	Severe back pain onset	NSIC	Epidural and paravertebral extension, TL (3 mm → 6 mm)	SD/PD
4	48	4+5	Apr/2013	CH	36	6	302.9	Mild back pain onset, weakness of lower limb	NL	NL, extradural extension with spinal cord compression	PD/PD
5	72	4+3	Sept /2014	RT	22	3	33.4	NSIC	NSIC	NSIC	SD/SD
6	66	4+4	Nov/2011	RT, CH, ENZ	57	3	239.2	Aggravation of back pain	NL, increased intensity	TL (6 mm → 8 mm)	PD/PD
7	75	4+4	Jun/2015	ADT only	12	8	0.1	NSIC	NL	TL (8 mm → 10 mm)	PD/PD
8	64	3+4	Apr/2015	ADT only	12	5	0.1	NSIC	NSIC	TL (4.5 mm → 5 mm)	SD/SD
9	73	4+5	Mar/2015	ADT, CH	12	3	0.5	NSIC	Interval increased extent of uptake	TL (4 mm → 5 mm)	PD/PD
10	65	4+4	Apr/2012	ADT, CH, ENZ	36	3	72.2	NSIC	Interval increased intensity and extent of uptake	TL (18 mm → 30 mm), NL	PD/PD

ADT, antiandrogen therapy; PSA, prostate-specific antigen; MR, magnetic resonance; RECIST, response evaluation criteria in solid tumors; GS, Gleason score; RP, radical prostatectomy; RT, radiation therapy; CH, chemotherapy; ENZ, enzalutamide; NSIC, no significant interval change; SD, stable disease; TL, target lesion; PD, progressive disease; NL, new lesion.

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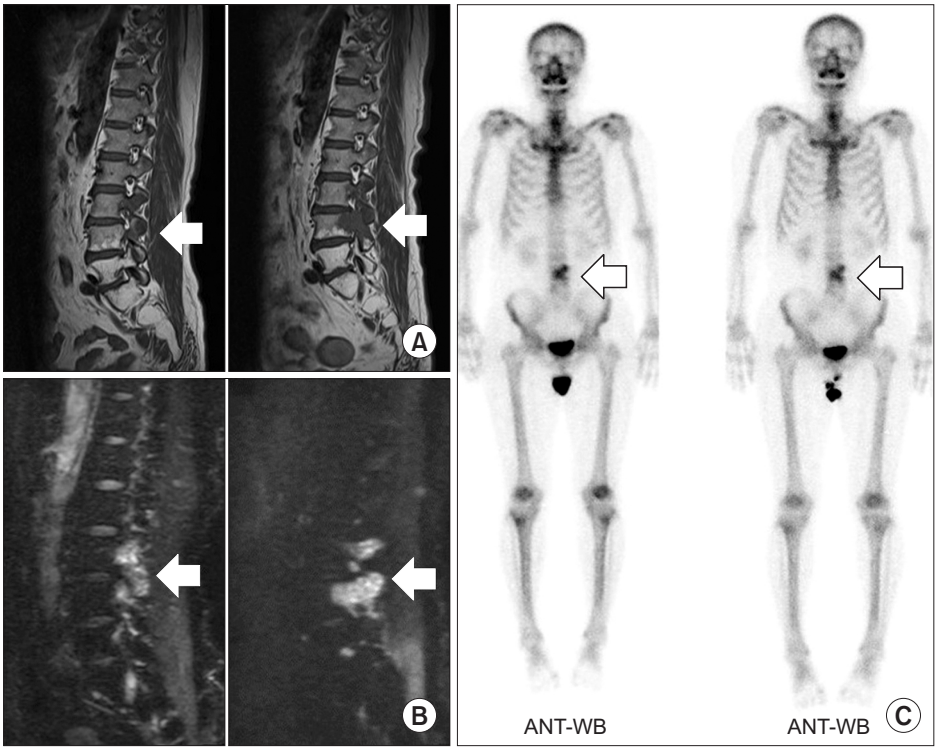

Fig. 1. The images of the 1st–2nd follow-up in the Table 1. Each right figure shows the 3-month follow-up images. T1-weighted image (A), diffusion-weighted image (B), and bone scan (C). ANT-WB, anterior view-whole-body.

increased uptake in the lumbar vertebra on bone scan at baseline evaluation, he complained of a mild back pain without any significant interval change on bone scan after 3 months. However, there was epidural and paravertebral extension of the tumor on subsequent biparametric MR. It was able to detect neurologic deterioration early. In addition, the 3rd follow-up in the Table 1. also showed neurological complications early using biparametric MR before an abnormality was found on bone scan.

Otherwise, neurologic symptoms and pain could be monitored using biparametric MR. Four patients experienced increasingly severe back pain during the observation period and disease progression on MR was observed in all of them. Among those, 2 suffered radiating pain due to paravertebral extension. In particular, 2 patients with weakness of lower leg were diagnosed with spinal cord compression. One patient underwent decompressive laminectomy and bone fusion without sequela. After early release of cord compression, he could restore motor function of lower limb. He continued to undergo palliative management in castration resistant prostate cancer and died of secondary cerebral hemorrhage due to brain metastasis. Another patient with spinal cord compression was recommended decompressive surgery in our hospital. However, he chooses the other treatment modality, gamma-knife, in other hospital.

The acquisition time for T1-weighted image and DWI of the whole spine was 7 and 8 minutes, respectively. Therefore, biparametric MR took about 15 minutes in total. The acquisition time for radionuclide planar bone scan was 45 minutes. Whole-body images were obtained 3 hours after injection (99^{m} technetium-methylene diphosphonate). Bone scan took about 4 hours for the combination.

DISCUSSION

Bone is a common site of metastasis after lymph nodes in men with prostate cancer. The incidence of bony metastasis is over 70% in men with metastatic castration-resistant prostate cancer [19]. In patients with high risk prostate cancer who have PSA levels greater than 20 ng/mL, Gleason score of at least 8 or clinical stage T3, bone metastasis was more frequently found during radiologic evaluation. Accordingly, most guidelines universally recommend bone scan and CT or magnetic resonance imaging (MRI) to assess the precise stage of metastasis at diagnosis [20-23]. At diagnosis, precise evaluation of metastasis is important in order to make a decision in patients with prostate cancer. The initial treatment modality including prostatectomy and androgen deprivation therapy could be based on the presence of metastasis on radiologic evaluation.

This radiologic evaluation is important in men with metastatic prostate cancer for not only the initial diagnosis, but also the follow-up. The European Association of Urology - European Society for Radiotherapy & Oncology

- International Society of Geriatric Oncology developed a consensus guideline in 2016 recommending the use of bone scan to monitor the extent and the response of bone metastasis as it is a widely available and relatively inexpensive imaging modality [24]. The most important reason for this recommendation is that detection of early progression could be a milestone in increasing the overall survival and cancer-specific survival because it could quickly change the treatment to the next step.

So far, bone scan is the most popular imaging tool to detect progression of bony metastasis. MRI and positron emission tomography could be used, but the latest guideline stated that these tools are under active investigation for their use as a standard modality for follow-up [25]. However, several studies have suggested that the use of bone scan should be restricted to the evaluation of prostate cancer in the pretreatment stage since both the sensitivity and specificity of bone scan are relatively low [12,14]. Bone scan could detect bone metastasis after progression to an advanced stage of tumor infiltration when osteoblastic reaction to metastatic cell deposits has occurred [17]. Therefore, it is suitable for the initial diagnosis of bone metastasis, but it is not sufficient to address the small and new progressive lesions. However, MRI could overcome the limitations of bone scan according to recent literatures [14,15,26-28].

MRI is highly sensitive in detection of bone metastasis and appears to be a promising modality for measuring the response to therapy in patients with metastatic prostate cancer. Its superiority over bone scan has been repeatedly demonstrated [14,15,26,27]. One advantage of MRI is that it enables detection of bone marrow invasion regardless of whether there is osteoclastic or osteoblastic activity [28]. The superiority of MRI lies in its ability to detect early tumor cell seeding into the fat-containing hematopoietic compartment, thus identifying bone metastasis at an earlier stage, before bone cells induce reactive changes in the trabeculae that are visible on bone scan [16].

In the present study, 6 follow-ups (42.9%) were determined to show progressive disease using bone scan, while 10 follow-ups (71.4%, including all progressed cases on bone scan) were determined to show progressive disease using biparametric MRI. An additional 4 follow-ups showing bone metastasis were detected earlier when we used biparametric MRI as a follow-up imaging tool than those when we used bone scan. These 4 progressive lesions were detected in another spine, which were diagnosed as a normal lesion on bone scan. If we had used bone scan only for these patients, we would be able to detect the new metastatic lesion after it had a larger tumor activity.

Another advantage of MRI is that it enables evaluation of epidural and paravertebral extension of the metastatic tumor. When we used bone scan as a follow-up imaging tool, we could gain information on how many new sites of metastasis were increased and how much the existing metastatic lesions were bigger in the extent of bone uptake and thicker in the intensity of bone uptake. For these reasons, it was difficult to predict the complications of bone metastasis including bone fracture and spinal cord compression. In case of spinal cord compression, irreversible neurological damage could occur if the emergent treatment is not performed. However, even though spinal cord compression progresses slowly, most of the patients showed normal neurologic examination. If the patients complained of back pain, although a nonspecific symptom, only then we could predict that spinal cord compression could occur. Early diagnosis and treatment of patients with spinal cord compression is essential for preservation of neurological function and also before the appearance of clinical manifestations such as neurological deficit or intractable pain due to severe spinal cord compression [10,29,30].

In the present study, we found 4 follow-ups of patients who had epidural and paravertebral extension without interval change in the bone scan finding. If the increased intensity or the extent of bone uptake were found on bone scan, we could predict the progression of bone metastasis. However, in the 4 follow-ups of patients mentioned above, there was no interval change between bone scan series. Also, we could observe how much the epidural and paravertebral extension had progressed using MRI imaging. Using this information, we could predict neurologic deterioration caused by spinal cord syndrome and 1 patient could undergo spinal surgery for decompression to prevent neurologic deterioration preemptively.

In Korea, the cost of multiparametric MRI is US $650 and that of bone scan is US $150. Therefore, to reduce the additional cost of MRI, we perform biparametric MR (T1+DWI) only. In our institute, the cost of biparametric MR (T1+DWI) is US $350. However, considering the Korean national medical reimbursement system for the patients who had been diagnosed with prostate cancer, the actual cost of biparametric MR and bone scan is US $15.9 and US $5.6, respectively. Therefore, the difference of cost in each test could be affordable. Another advantage of biparametric MRI was the shorter acquisition time to achieve images. The acquisition time for biparametric MR (T1+DWI) was only 15 minutes, while it was 4 hours for bone scan as well as there was no need of contrast agents.

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After considering these advantages, it would be desirable to perform biparametric MRI as the follow-up imaging tool to monitor metastatic lesions instead of bone scan as the conventional imaging tool for early diagnosis of disease progression in patients who had been diagnosed with bone metastasis. There were several limitations in the current study. First, the number of patients was limited to 10 patients and a total of 14 follow-ups because we performed this study as a pilot study. Larger studies are needed for deriving a definite conclusion. Second, we did not confirm the histopathological diagnosis at the sites of metastasis. Generally, the sites of metastasis on bone were not resected. Third, accompanying abdominal or chest radiographs were not constant. We did not specify these accompanying radiographs in the initial protocol.

CONCLUSIONS

Until now, bone scan has been considered the most useful test for detecting and monitoring bone metastasis in patients with prostate cancer. However, limited MR including T1 and DWI has an additional benefit for monitoring spinal metastasis in patients who have already been diagnosed with spinal metastasis. This biparametric MR (T1+DWI) for the spine is more sensitive in detecting progressive disease. In addition, early detection of neurological complications, such as spinal cord compression, can reduce the occurrence of irreversible deterioration.

The acquisition time for biparametric MR (T1+DWI) was only 15 minutes, while it was 4 hours for bone scan as well as there was no need of contrast agents. In the Korean medical reimbursement system, cost difference in each test can be affordable. Additional data need to be collected with this pilot study.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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