Dynamic contrast-enhanced MR imaging findings of bone metastasis in patients with prostate cancer

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Abstract

AIM: To evaluate the dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) findings of bone metastasis in prostate cancer patients.

METHODS: Sixteen men with a diagnosis of metastatic prostate cancer to bones were examined with DCE-MRI at 1.5 Tesla. The mean contrast agent concentration vs time curves for bone metastasis and normal bone were calculated and Ktrans and ve values were estimated and compared.

RESULTS: An early significant enhancement (wash-out: \( n = 6 \), plateau: \( n = 8 \) and persistent: \( n = 2 \)) was detected in all bone metastases \( (n = 16) \). Bone metastasis from prostate cancer showed significant enhancement and high Ktrans and ve values compared to normal bone which does not enhance in the elderly population. The mean Ktrans was 0.101/min and 0.0051/min \( (P < 0.001) \), the mean ve was 0.141 and 0.0038 \( (P < 0.001) \), for bone metastases and normal bone respectively.

CONCLUSION: DCE-MRI and its quantitative perfusion parameters may have a role in improving the detection of skeletal metastasis in prostate cancer patients.

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Key words: Prostate; Cancer; Bone; Metastasis; Dynamic contrast-enhanced MR imaging

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INTRODUCTION

Prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States. As per the latest estimates by American Cancer Society in 2009 about 192,280 new cases of prostate cancer will be diagnosed and 27,360 men will die of the disease[1]. It is known that most patients with locally advanced prostate cancer will also have probable occult metastases at diagnosis. The...
most important determinant of potentially curative therapies and of appropriate palliative management for prostate cancer during early staging is accurate assessment of the extent of the metastatic process\[8\].

The most frequent sites of distant metastases of prostate cancer are bones and typically vertebrae\[15\]. The diagnosis, location, burden and monitoring of metastatic bone involvement plays a crucial role in patient management and prognosis. Imaging bone disease in prostate carcinoma generally involves a cascade of studies starting with bone scintigraphy followed by magnetic resonance imaging (MRI), computed tomography (CT) or positron emission tomography/CT. Conventional MRI is sensitive to early changes in bone marrow that precede the osteoblastic response in the bone matrix. However, detection rates for bone metastases using MR range between 7% and 38% and its use is still limited\[4,5\]. Recently, newer MRI methods such as diffusion-weighted imaging and dynamic contrast-enhanced MRI (DCE-MRI) are also addressing the lack of quantitative assessment of skeletal metastases.

DCE-MRI has been increasingly used as an additional technique to characterize various bone lesions, grading disease, planning and guiding biopsy and monitoring response to radio- and/or chemotherapy and detecting early local recurrence\[6,7\]. It provides a powerful tool for assessing angiogenesis and measuring properties of tissue vasculature, including blood volume and vascular permeability in tumor tissues. In this study, we aimed to evaluate DCE-MRI findings of bone metastasis in patients with prostate cancer.

**MATERIALS AND METHODS**

**Subjects**

The study group consisted of 16 men (age range: 49-79 years; median age: 65 years) with histologically proven adenocarcinoma of the prostate with skeletal metastasis. The study was approved by the institutional review board and informed consent was obtained. Each patient underwent clinical CT scan and bone scan prior to this study and the sites of bone metastasis was determined based on CT and bone scan findings. As part of the research protocol, bone metastases in regions with minimal motion artifact were scanned by research DCE-MRI protocol. In one patient, the scanned bone metastasis was in the shoulder and in 15 patients it was in the pelvic region. None of the metastatic lesions were treated before MRI.

**MR imaging**

MR images were acquired on a 1.5 T GE MRI scanner (SIGNA™, GE Medical Systems, Waukesha, WI, USA). Following a scout scan to localize the lesions, T1-weighted (T1W) images were acquired at 2 s temporal resolution for 1 min before and 6 min after the injection of 0.1 mmol/kg gadodiamide (Omniscan, GE Healthcare, Chalfont St. Giles, UK). The contrast agent and 20 mL saline flush was injected with an automated injector (Medrad, Indianola, PA, USA) at the rate of 2 mL/s in an ante-cubital vein. A 2D fast spoiled gradient-echo pulse sequence was used with TR/TE = 7.8/1.7 ms, flip angle 60°, matrix size 256 × 128, field of view 30-35 cm, 2 slices, slice thickness 8 mm, slice spacing 1 mm. The axial slices in which the lesion was in its largest dimension were selected.

**Data analysis**

For each subject, an experienced radiologist placed the region of interest (ROI) on the bone metastasis and normal bone in the DCE-MRI after reviewing the clinical CT and bone scan images. Any vessels at the lesion margin were carefully excluded from the bone metastasis ROI. For normal bone, muscle and bone metastasis the mean ROI size was 3.1 cm² (median 3.2 cm², range 1.1-5.7 cm²), 16.4 cm² (median 13.9 cm², range 6.6-33.8 cm²) and 14.3 cm² (median 10.0 cm², range 5.0-33.7 cm²), respectively.

The enhancement patterns of bone metastasis and normal bone were analyzed regarding presence of early enhancement, washout, plateau and persistence of enhancement. The contrast agent concentration was calculated as previously described8. Contrast agent arterial input function (AIF), which is the contrast agent concentration in the blood plasma, was estimated with a multiple reference tissue method using tumor voxels and muscle as described by Yang et al.89. The mean contrast agent concentration vs time curve [C(t)] was calculated for each bone metastasis ROI and normal bone ROI. Using the estimated individual AIF, contrast agent transfer rate between blood and tissue (Ktrans) and the extra-vascular extra-cellular fractional volume (v), were then estimated under the Tofts model10.

**Statistical analysis**

Two-tailed paired Student’s t-test was used to test the difference in Ktrans and v between bone metastasis and normal bone. Statistical analysis was performed using SPSS Software System version 15.0 (SPSS Inc., USA).

**RESULTS**

All of the bone metastases showed early significant enhancement (wash-out: 6, plateau: 8 and persistent: 2) (Figures 1 and 2). On the other hand, normal bone demonstrated negligible enhancement in 15 patients. There was minimal enhancement of normal bone in only one patient. For the 16 bone metastases, the mean $K_{trans}$ was 0.101/min (range 0.034-0.290/min, median 0.071/min) and mean $v$ was 0.141/min (range 0.080-0.234/min, median 0.141/min). For the 16 normal bones, the mean $K_{trans}$ was 0.0051/min (range 0.0-0.080/min, median 0.0/min), (P < 0.001). The mean $v$ of normal bone was 0.0038 (range from 0.0-0.048, median 0.0) also significantly lower than that in bone metastases (P < 0.001). Based on quantitative analysis, normal bones showed slightly negative enhancement or very weak enhancement. In one 69-year-old patient, the normal bone showed a moderate enhancement with a $K_{trans}$ value of 0.080/min and a small $v$ value of 0.048. Figure 2 shows the C(t) curve of bone metastasis and normal bone, as well as the pre-contrast image, the average early subtrac-
They showed that the steepest slopes of metastatic lesions were significantly higher than those of benign lesions and no characteristic distribution of the TIC pattern was found to help in differentiation of benign and metastatic lesions. Chen et al investigated the peak contrast enhancement percentage, enhancement slope and the TIC patterns of the first pass of contrast into vertebral lesions. They found that metastatic vertebral lesions had a higher peak enhancement percentage and steeper enhancement slope than lesions of benign etiology. They also concluded that type D (rapid wash in and wash out) and E (rapid wash in followed by a second slow-rising phase) curves are valuable in differentiating benign and malignant vertebral lesions. Both of these studies evaluated angiogenesis and perfusion of bone metastasis using semi-quantitative parameters. Recently, a few studies have looked into more advanced quantitative analysis methods to potentially increase accuracy and reproducibility of DCE-MRI. Baurle et al evaluated the amplitude and exchange rate constant (Kep) of the enhancement of bone metastasis in an animal model of breast cancer. They found that amplitude decreased significantly prior to changes in osteolytic lesion size following treatment of bone metastasis. On the other hand, there was no significant change in Kep between the treated group and control group.

In our study, by using quantitative parameters obtained from high temporal resolution DCE-MRI data, we demonstrated that in elderly prostate cancer patients, bone metastasis showed much faster and higher enhancement than normal appearing bones. The difference in their contrast concentration levels lasted for the entire 5.5 min of contrast enhancement duration. These results suggest that it may be possible to detect bone metastasis at a delayed contrast enhanced phase after 3 min of contrast administration instead of imaging the patients continuously at high temporal resolution for several minutes. However, quantitative analysis of DCE-MRI data can provide quantitative information about the bone metastasis which cannot be obtained by bone scan and CT. Further studies are needed to investigate whether DCE-MRI derived perfusion parameters may be used as biomarkers in evaluation of treatment response of bone metastasis in patients with prostate cancer.

The limitation of our study is that the quantitative parameters obtained from metastatic lesions were compared with the findings of normal bone in the same patient rather than benign bone lesions. The parameters of metastatic bone lesions other than prostate were also not compared. Moulopoulos et al evaluated cancer patients with metastasis to bone marrow including lymphoma, chronic lymphocytic leukemia, carcinoma of the cervix, breast, lung and bladder. They compared the wash-in and wash-out rates, time to peak, and time to maximum slope values of control group with no history of malignancy and reported a significant difference for all values.

In conclusion, bone metastasis from prostate cancer demonstrates significant enhancement leading to high Ktrans and ν in contradiction to normal bone which does not enhance in the elderly population. DCE-MRI and its
quantitative analysis may have a role in improving the detection of bone metastasis from prostate cancer.

Figure 2 Pelvic bone metastasis on the left side in a patient with prostate cancer compared with normal pelvic bones on the right side. A: Contrast agent concentration vs time curve of bone metastasis region of interest (ROI) and normal bone ROI; B: Pre-contrast image (arrow: bone metastasis, arrowhead: normal bone); C: The average subtraction image for the first minute after bolus arrival; D: The average subtraction image for the last 1 min in two representative patients (arrow: bone metastasis, arrowhead: normal bone).
COMMENTS

Background
Prostate cancer is a major health problem and a major cause of death in men. It is crucial to determine the assessment of the metastatic process of prostate cancer for designing a proper treatment. The most frequent sites of distant metastases of prostate cancer are bones. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and its quantitative analysis may contribute to improve the detection of bone metastasis from prostate cancer.

Research frontiers
DCE-MRI has been increasingly used as an additional technique to characterize various bone lesions. It provides a powerful tool for assessing the tissue vascularization in tumor tissues. In this study, the authors demonstrate the contribution of DCE-MRI for detection of bone metastasis in patients with prostate cancer.

Innovations and breakthroughs
In recent studies the utilization of open MRI is increasing in patients with prostate cancer. However, the potential of this technique for the detection of bone metastasis is not fully evaluated. The authors present an innovative method for detection of bone metastasis.

Applications
Quantitative measurements of DCE-MRI data may improve the diagnosis of bone metastasis by providing quantitative analysis which cannot be obtained by bone scan and CT. Therefore, this study may represent a future perspective for DCE-MRI derived perfusion parameters which may be used as biomarkers in evaluation of treatment response of bone metastasis in patients with prostate cancer.

Terminology
DCE-MRI provides a powerful tool for measuring alterations in the microvascular environments of the tissue. Ktrans and Ku are quantitative parameters of DCE-MRI and they are expected to be increased in bone metastasis from prostate cancer, in contrast to normal bone in the elderly population.

Peer review
Although this study did not perform the reproducibility of quantitative perfusion parameters in bone metastasis from prostate cancer, the topic of this article may draw the readers’ attention. This study may be an initial step to assess the roles of quantitative perfusion parameters in monitoring or predicting therapeutic responses for advanced prostate cancer patients in the future studies. Generally this article is well-written.

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