



BRIEF REPORT

MRI Grading Scale Predicts Ambulatory Function After Radiotherapy for Metastatic Spinal Cord Compression: A Prospective Single-Institution Observational Study

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ABSTRACT

Introduction: Although magnetic resonance imaging (MRI) is an important modality for the diagnosis of metastatic spinal cord compression (MSCC), there are only a few reports on MSCC findings and symptoms after radiotherapy. We aimed to reveal the factors related to ambulatory function after treatment, including the MRI findings, in a prospective observational study.

Methods: Patients with suspected MSCC who were treated with radiotherapy were included in this study. Orthopedic surgeons evaluated the neurological function according to the Frankel grade. All patients underwent spinal MRI, and the degree of spinal cord compression was assessed by a radiologist and a radiation oncologist using an MRI grading scale. One month

after treatment, orthopedic surgeons reassessed the Frankel grade. Twenty-three patients who were evaluated 1 month after radiotherapy were included in the analysis.

Results: Before radiotherapy, 17 patients were ambulatory and six were unable to walk. Furthermore, 13 patients were diagnosed with grade 3 compression on MRI (spinal cord compression with no cerebrospinal fluid seen on axial T2-weighted imaging). Patients with grade 3 MSCC were significantly more likely to be non-ambulatory at 1 month.

Conclusions: The MRI grading scale for MSCC may be a prognostic factor for ambulatory function after radiotherapy. MRI findings could aid in determining the indication for radiotherapy.

Keywords: Ambulatory function; Magnetic resonance imaging; Metastatic spinal cord compression; Radiotherapy

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Key Summary Points

We evaluated the relationship between MRI findings and ambulatory function after radiotherapy (RT) for metastatic spinal cord compression (MSCC).

Grade 3 MRI findings were significantly associated with poor ambulatory function post-RT.

MRI grading scale for MSCC could aid in determining the indication for radiotherapy.

INTRODUCTION

Metastatic spinal cord compression (MSCC) is a common complication among patients with malignant tumors. MSCC is estimated to occur in over 2–5% of all cancer patients [1]. In addition to pain, it causes limb paralysis, bladder bowel dysfunction, and severely reduces patient quality of life. As many as 50–68% of patients are unable to walk when they are first diagnosed with MSCC [1].

To improve neurological outcomes, spinal surgery should be performed within 48 h [2]. However, in practice, surgery is often not indicated because of the poor condition or poor prognoses of these patients. Patients with multiple spinal involvement of MSCC or widespread disease are not suitable for surgery. Radiotherapy (RT) is relatively less invasive and is used for many patients if they are not indicated for surgery [3, 4]. In accordance with surgery, radiotherapy is also considered preferable to be commenced within 48 h.

Several studies have been conducted to elucidate the prognostic factors of ambulatory function after RT. It has been shown that pre-RT motor function predicts ambulatory status after treatment [5, 6]. Other studies have reported that the RT schedule is not associated with post-RT ambulatory function or patient-reported symptoms [7–10].

The MRI grading system developed by Bilsky et al. [11], supported by the Spine Oncology Study Group, is a simple way of describing the degree of spinal cord compression on magnetic resonance imaging (MRI). Although imaging tests, such as MRI, are often required for the diagnosis of MSCC, there are only a few reports that have focused on MRI findings in relation to post-RT symptoms.

In the present study, we conducted a prospective single-institution observational study to identify factors, including the MRI findings, which are associated with ambulatory function after RT.

METHODS

Ethics

This prospective study was approved by the Ethical Review Committee of the Yamagata University, Faculty of Medicine (No. 2019-360) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants.

Patients

Although all the patients who were referred to the RT department and underwent computed tomography (CT) scans were considered for this study, only patients with suspected MSCC based on their CT findings and symptoms were deemed eligible for this observational study. Patients who could not undergo MRI scans, had indications for surgery, had histories of spinal surgery, or had histories of RT on the same sites as the upcoming RT were excluded. Patients indicated for surgery in our institution were: (1) patients with confirmed primary tumor and only one site of spinal metastasis, and (2) patients with progressive paralysis and required tissue collection for diagnosis. In both cases, physical condition must be satisfactory for surgery. When primary tumor was confirmed, patients with good prognosis were eligible for surgery.

At the first visit to the radiation oncologist, clinical information, including age, sex, type of primary tumor, Eastern Cooperative Oncology Group performance status (PS), MRI findings, ambulatory status, presence of visceral metastases, and administration of bone-modifying agents (BMA) and steroids, was collected. The BMAs included bisphosphonates and denosumab. It was left to the discretion of the attending doctor to decide whether to use steroids and BMAs.

Neurological function was evaluated by an orthopedic surgeon according to the Frankel grade (A: complete motor and sensory paralysis, B: partial sensory paralysis but complete motor paralysis, C: some motor power present but no practical use, D: practical motor power present and patients could walk with or without aid, and E: free of neurological symptoms) [12]. The Frankel grade was used to classify ambulatory function, wherein patients with grades D and E were considered ambulatory, and it was assessed before the start of RT or by the day after the RT start date.

MRI was required for all patients to evaluate the MSCC severity. If an MRI was not possible before the first referral to a radiation oncologist, it was allowed to be performed up to 5 days after the day of referral. The degree of spinal cord compression was evaluated based on the MRI grading scale developed by Bilsky et al. [11]. According to this scale, the MSCC was evaluated based on the axial T2-weighted MRI images (grade 1, epidural impingement without spinal cord compression; grade 2, with spinal cord compression but cerebrospinal fluid is visible around the spinal cord; and grade 3, with spinal cord compression and no visible cerebrospinal fluid). A diagnostic radiologist and a radiation oncologist evaluated the MRI images separately. When their interpretations were different, the decision was made by consensus between them.

Treatment

RT was performed using a linear accelerator and 10-MV photons. Either three-dimensional conformal radiation therapy (3D-CRT) or intensity-modulated radiation therapy (IMRT) was

performed. It has been reported that short fractionation RT (\leq five fractions) is not inferior to longer fractionation RT in terms of the prognosis of walking function [7–10]. Furthermore, precision RT does not improve motor function [13]. Thus, in this observational study, dose fractionation, treatment volumes, and treatment timing were left to the discretion of the radiation oncologist in charge.

Evaluation

The primary endpoint was the ambulatory status 1 month after RT. The Frankel grade at 1 month after RT was determined by an orthopedic surgeon. For those who could not visit the doctor (three patients), a questionnaire was mailed to them for evaluation. The toxicity was evaluated by radiation oncologists using the Common Terminology Criteria for Adverse Events version 4.0 [14].

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics software (version 23, SPSS Inc., Chicago, IL, USA). The association between each factor and the post-RT ambulatory function was examined using Fisher's exact test. All the *P* values were two-sided, and *P* values < 0.05 were considered to be statistically significant. A multivariate analysis was not performed because of the small number of cases.

RESULTS

Patients

From January 2020 to March 2021, 30 patients were deemed eligible for RT for MSCC. Those who were evaluable 1 month after RT were included in the analysis. Of the 30 patients, seven could not be followed up after a month because they had died, or their condition had worsened. Finally, 23 patients, including 16 men and seven women, were enrolled in the study.

Table 1 Patient characteristics ($n = 23$)

	Patients	
Sex		
Male	16	(70%)
Female	7	(30%)
Median age (range)	68	(55–85)
Frankel grade [12]		
A	0	(0%)
B	1	(4%)
C	5	(22%)
D	6	(26%)
E	11	(48%)
MRI grading scale [11]		
Grade 1	2	(9%)
Grade 2	8	(35%)
Grade 3	13	(56%)
Performance status		
0–2	20	(87%)
3–4	3	(13%)
Dose fractionation		
30 Gy in 10 fractions	14	(61%)
20 Gy in 5 fractions	7	(31%)
20 Gy in 10 fractions	1	(4%)
24 Gy in 3 fractions	1	(4%)
Primary tumor		
Prostate cancer	4	(17%)
Lung cancer	4	(17%)
Breast cancer	3	(13%)
Renal cell carcinoma	3	(13%)
Thyroid cancer	2	(9%)
Others	7	(31%)

MRI magnetic resonance imaging

Patient characteristics are shown in Table 1. The median age was 68 years (range, 55–85). Seventeen patients with Frankel grades D and E

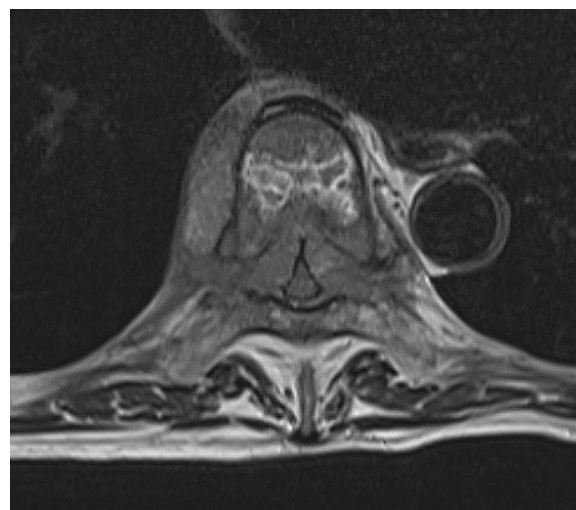


Fig. 1 T2-weighted magnetic resonance image of grade 3 thoracic cord compression seen in a 77-year-old woman with follicular carcinoma of the thyroid. Frankel grade was C before treatment. Radiotherapy was delivered at 20 Gy in 5 fractions, and Frankel grade remained at C after 1 month

were ambulatory, and six with grades B and C were not ambulatory. No patient was diagnosed with grade A.

Thirteen patients were diagnosed with grade 3 on MRI using the MSCC grading scale. Additionally, the thoracic spine was the most frequently compressed site. Figure 1 shows a typical case of grade 3 compression. Seventeen patients underwent an MRI the day before their RT started, while six patients underwent an MRI up to 4 days after the initiation of RT.

Table 2 Relation between the Frankel grade and MRI grading scale ($n = 23$)

Frankel grade [12]	MRI grading scale [11]	
	1–2	3
A	0	0
B	0	1
C	1	4
D	2	4
E	7	4

MRI magnetic resonance imaging

Table 2 shows the relation between the Frankel grade and the MRI grading scale. Patients with lower MRI grades were more likely to be ambulatory.

There was a wide variety of primary tumors, with prostate cancer and lung cancer being the most common, followed by breast cancer, renal cell carcinoma, and thyroid cancer. Other cancers included stomach cancer, esophageal cancer, hepatocellular carcinoma, ureteral cancer, multiple myeloma, malignant lymphoma, and soft tissue liposarcoma. Fourteen patients were treated with 3D-CRT at 30 Gy in ten fractions over 2 weeks, while only one patient underwent IMRT with a dose of 24 Gy in three daily fractions.

Ambulatory Status

Table 3 shows the relationship between each factor and the ambulatory status at 1 month after RT. Patients with MRI grade 3 were significantly more likely to be unable to walk after 1 month than patients with grade 1 or 2 ($P = 0.046$). Patients who were ambulatory at their RT also exhibited good walking condition after 1 month ($P < 0.001$). PS, visceral metastasis, BMA administration, steroid administration, and radiosensitivity of the primary tumor were not associated with any significant differences in ambulatory status after RT. Lymphoma, myeloma, breast cancer, and prostate cancer were considered to be radiosensitive in the present study [15].

The change in ambulatory function between pre- and post-treatment based on MRI grading scale is described in Table 4. All the patients who were not ambulatory before treatment with MRI grade 3 remained non-ambulatory even after treatment. In contrast, one patient with MRI grade 1–2 had regained the ambulatory function.

Toxicities

Grade 2 esophagitis was observed in one patient who received 20 Gy in five fractions to the thoracic spine. No adverse events of grade 3 or higher were observed.

Table 3 Bivariate analysis of motor function 1 month after radiotherapy

	After 1 month		P value
	Ambulatory	Not ambulatory	
MRI grading scale [11]			
1–2	10	0	0.046*
3	8	5	
Pre-RT motor function			
Ambulatory	17	0	< 0.001*
Not ambulatory	1	5	
Performance status			
0–2	17	3	0.1
3–4	1	2	
Visceral metastasis			
Yes	8	4	0.32
No	10	1	
BMA			
Yes	7	3	0.367
No	11	2	
Steroids			
Yes	5	0	0.55
No	13	5	
Radiosensitivity			
High	6	3	0.34
Low	12	2	

MRI magnetic resonance imaging, RT radiotherapy, BMA bone-modifying agent

* $P < 0.05$, P value result is from Fisher’s exact test

Table 4 Pre- and post-treatment ambulatory function based on MRI grading scale

	Ratio of non-ambulatory patients	
	Pre-treatment (%)	Post-treatment (%)
MRI grading scale [11]		
1–2 ($n = 10$)	10	0
3 ($n = 13$)	38	38

MRI magnetic resonance imaging

DISCUSSION

To the best of our knowledge, this was the first prospective report on the relationship between MRI findings and post-RT ambulatory function. MRI is useful for the diagnosis of MSCC, and its findings are often used to discuss treatment strategies. MRI also provides detailed information on the bone marrow and helps detect the extension of the tumor into the spinal canal. Well-known MRI features that distinguish between vertebral fractures caused by metastases and osteoporosis are the backward convexity of the posterior walls of the vertebral body, epidural masses, and heterogeneous high signals of the vertebral body on T2-weighted images. Previous reports examining the accuracy of MRI for MSCC have shown that the sensitivity, specificity, and accuracy were 93, 97, and 95%, respectively [16]. With regard to CT, typical findings, such as posterior vertebral body cortical destruction and spongiform bone destruction, have shown a high sensitivity and specificity of 69% and 100%, respectively. However, when it comes to the detection of soft tissue masses compressing the spinal cord, CT is less sensitive (56–59%) than MRI (80%) [17]. In the present study, some patients were diagnosed with grade 1 spinal cord compression by MRI, although MSCC was suspected based on the CT findings and symptoms. Therefore, an MRI assessment of MSCC is considered reasonable and objective.

Bilsky et al. [11] developed a scale to assess the degree of spinal cord compression using MRI, wherein grade 3 was defined as the most severe spinal cord compression with no visible cerebrospinal fluid. Oshima et al. [18] reported that neurological dysfunction was determined by the magnitude of the circumferential cord compression. In their study, when more than half of the entire circumference was compressed, the ambulatory rate was significantly reduced after treatment. Although their study was a retrospective study that included patients who underwent surgeries, the results are in accordance with those of our study. In a prospective study by Young et al. [19], it was noted that patients with complete blocks on myelography may have better ambulatory outcomes with RT plus surgery compared to RT alone. It is assumed that the greater the degree of compression, the stronger the mass effect is on the spinal cord. RT takes a longer time to shrink the mass, and nerve damage may occur, whereas surgery can reduce the mass effect faster and improve symptoms. This may be the reason why patients with grade 3 MSCC in the present study tended to have poor walking function after treatment.

Several reports have shown that steroids may improve the neurological symptoms caused by MSCC. In a randomized control study performed by Sørensen et al. [20], it was shown that high-dose glucocorticoids may lead to better neurological outcomes. According to a review by Loblaw et al. [21], steroids are recommended for any patient with suspected or confirmed neurologic deficits. In contrast, it has also been reported that there is no difference in symptom improvement regardless of steroid use in patients at high risk for adverse events [22]. In addition, the optimal dose of steroids is still under debate. It was reported that there was no difference in the improvement of symptoms between patients given 16 mg of dexamethasone and those given 96 mg, while more side effects were observed in patients given the higher dose [23, 24]. Even at doses of < 16 mg, the toxic effects of dexamethasone are still dose-dependent [25]. Considering these results, the Cochrane Review states that the grade of evidence for the positive effects of steroids is low

[26]. Therefore, steroids are not used often in Japan, and if they are used, small doses of dexamethasone (≤ 16 mg) are preferred. In the present study, the decision to use steroids was left to the discretion of the patients' physicians, and only five patients were administered steroids. No association was observed between steroid administration and the ambulatory function after RT. The variation in steroid use is a potential confounder; however, the use of steroids remains controversial and had only a minor impact on this study.

There have been various reports on ambulatory function after RT. A previous large prospective study has shown that pre-RT ambulatory function is the main prognostic factor for post-RT ambulatory function [5]. It has also been reported that patients with a slow progression of symptoms before RT have a better functional prognosis [27], and this may be because patients with a slow progression tend to preserve their ambulatory function. In the present study, we confirmed that there was a significant relationship between the ambulatory status before and after RT.

There were several limitations to this study. First, it was performed at a single institution, and the number of eligible patients was small. A multivariate analysis was not performed because of the small number of cases. Second, treatment methods, such as dose fractionation, steroid administration, and the time from enrollment to the start of RT, were not standardized. However, as mentioned above, it has been reported that differences in dose fractionation do not result in significant differences in symptom improvement [7–10, 13].

CONCLUSIONS

This was the first prospective study to evaluate the relationship between MRI findings and ambulatory function after RT. In conclusion, the present study revealed that the MRI findings of grade 3 MSCI were significantly associated with poor ambulatory function post-RT. This may be one of the factors that determine the indication for radiotherapy based on MRI findings, and physicians need to pay attention to

patients with MSCI and perform radiotherapy before they progress to grade 3 MRI findings.

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Compliance with Ethics Guidelines. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethical Review Committee of Yamagata University Faculty of Medicine (No. 2019-360).

Data Availability. The datasets generated and analyzed during the current study are not publicly available due to the privacy of individuals that participated in the study.

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