

## Palliative Radiation Therapy for Intramedullary Spinal Cord Metastasis

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**Abstract.** *Background/Aim:* The purpose of this study was to retrospectively review the outcomes of intramedullary spinal cord metastasis (ISCM) and identify predictors for ambulation after radiotherapy (RT). *Patients and Methods:* We analyzed 16 lesions in 15 patients treated with RT for ISCM at our clinic from October 2009 to April 2020 to evaluate predictors for improved ambulation following RT. *Results:* The primary diseases included nine cases of lung cancer, two cases of breast cancer, and several others. The RT schedule was primarily 30 Gy/10 fractions in seven cases, while others were applied to nine cases. The median overall survival time was 99 days. After RT, all seven patients who could walk prior to RT were still able to walk (100%), whereas only two of nine patients who could not walk prior to RT were able to walk (22%,  $p=0.004$ ). *Conclusion:* Ambulation prior to RT was a significant predictor of ambulation ability after RT.

Intramedullary spinal cord metastasis (ISCM) is rare, accounting for 0.9%-2.1% of autopsies and 8.5% of central nervous system metastasis (1). The incidence of ISCM continues to rise as cancer diagnosis and treatment improve and more cancer patients survive (2-4). Patients with ISCM

still have a poor prognosis, and many have neurological deficits and pain. Early detection and appropriate intervention are critical for preventing neurological deficits and prolonging patients' survival (5). Although there have been no prospective clinical trials on the treatment of ISCM, radiation therapy (RT) is the first therapeutic option for ISCM due to its definite efficacy and acceptable toxicity (4, 6, 7). One of the main goals of ISCM treatment is to maintain or improve ambulation. However, few reports have evaluated improving or maintaining gait after RT for ISCM (6, 8), and no reports have assessed their predictors. The purpose of this study was to retrospectively assess the feasibility, toxicities, and treatment outcomes and identify predictors for improved ambulation following RT for ISCM. To the best of our knowledge, this is the first study to analyze predictors of ambulation improvement following RT in patients with ISCM.

### Patients and Methods

**Patients.** This study was conducted in accordance with the Helsinki Declaration and was approved by the Institutional Review Board of Kyoto Prefectural University of Medicine (ERB-C-1802). The study included consecutive patients with ISCM who received palliative RT at our institution between October 2009 and April 2020. All clinical data were obtained retrospectively from electronic medical records.

**Radiotherapy.** Irradiation was primarily delivered via a single posterior field or parallel opposition field with 6 or 10 MV photons from a linear accelerator, either the Synergy® LINAC (Elekta Instrument, Stockholm, Sweden) or the Primus (Siemens, München, Germany). Treatments were planned using either Monaco® Xio® (Elekta Instrument, Stockholm, Sweden) or Pinnacle (Philips Radiation Oncology Systems, Fitchburg, WI, USA) systems.

The gross tumor volume was defined as ISCM as detected by magnetic resonance imaging, while clinical target volume was defined as gross tumor volume with clinically suspected tumor invasion. For planning target volume, the clinical target volume was expanded by a margin of 0.5-1.0 cm. The radiation schedule

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**Key Words:** Intramedullary spinal cord metastasis, radiotherapy, prognosis, central nervous system, ambulation.

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Table I. Frankel grade classification.

Frankel grade	Description
A	Complete motor and sensory loss (paraplegia).
B	Complete motor loss, incomplete sensory loss (paraplegia).
C	Incomplete motor loss, of no practical use (paraparesis).
D	Incomplete motor loss, able to ambulate with or without walking aids.
E	No neurological symptoms or signs.

was primarily determined by consensus among primary care physicians and radiation oncologists based on prognosis or histology. The patient's gait before and after RT was assessed using the Frankel classification (Table I) (9). Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4.0. Written informed consent was obtained from the patients for the procedures described in the study.

**Statistical analysis.** All statistical analyses were performed using the EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria), and a modified version of the R commander designed to add statistical functions commonly used in biostatistics (10). Overall survival (OS) was assessed from the date of treatment initiation to the date of the last follow-up or death from any cause. OS was calculated using the Kaplan–Meier method. Differences between the groups were estimated using the log-rank test. The change in Frankel grade before and after RT was assessed using the Wilcoxon signed-rank test. The predictors of ambulation were analyzed using Fisher's exact test. A *p*-value of less than 0.05 was considered significant.

## Results

**Patient characteristics.** During the study period, 16 patients were consecutively enrolled. The clinical characteristics of the studied patients are presented in Table II. There were 6 men and 10 women, with a median age of 68 years (range=51-79 years). One woman with small cell lung carcinoma was irradiated twice at different sites. The most common primary tumor was lung cancer (n=10), including adenocarcinoma (n=5) and small cell carcinoma (n=5). The other six cases involved two breast cancers, uterine endometrial cancer, peritoneal cancer, ovarian cancer, and esophageal cancer. The RT schedule was 30 Gy/10 fractions (frs) in seven cases (44%), 8 Gy/1 fr in four cases (25%), and 15 Gy/3 frs in two cases (12.5%), as well as 20 Gy/4 frs, 20 Gy/5 frs, and 16 Gy/2 frs in one case (6%). Prior to RT, the Frankel Classification D or E was detected in 44% (7/16) of patients.

Table II. Patient characteristics.

Characteristics	Number of patients (%)
Median age (range), years	68 (51-79)
Sex, n (%)	
Male	6 (38)
Female*	10 (62)
ECOG PS, n (%)	
≤2	10 (62)
≥3	6 (38)
Primary tumor, n (%)	
Lung cancer	10 (62)
Others	6 (38)
Lesion location, n (%)	
Above lumbar	11 (69)
Lumbar	5 (31)
Chemotherapy, n (%)	
Yes	8 (50)
No	8 (50)
Total RT dose, n (%)	
30 Gy/10 fractions	7 (44)
Others	9 (56)
Segment, n (%)	
Single	9 (56)
Multiple	7 (44)
Onset to RT, n (%)	
≤1 week	6 (38)
>1 week	10 (62)
Steroid use with RT, n (%)	
Yes	11 (69)
No	5 (31)
Ambulation ability before RT, n (%)	
Yes (Frankel grade D/E)	7 (44)
No (Frankel grade A-C)	9 (56)
Brain metastases, n (%)	
Yes	14 (87)
No	2 (13)

\*One woman was treated twice with radiation therapy (RT). ECOG PS: Eastern Cooperative Oncology Group Performance Status; ISCM: intramedullary spinal cord metastasis; OS: overall survival.

**Treatment outcomes.** Radiotherapy was completed in all patients. During the follow-up period, 14 patients died from intercurrent disease, and only one patient with anaplastic lymphoma kinase-positive lung cancer survived. At 3 and 6 months after RT, the OS rates were 50% and 31%, respectively, and the median survival time (MST) was 99 days (95% confidence interval=18-472 days, Figure 1). The predictors for ambulation after RT and OS are shown in Table III. Patients who could walk after RT had a significantly better OS than those who could not (MST: 344 days vs. 97 days, *p*=0.025). After being diagnosed with ISCM, seven out of 15 patients received chemotherapy. Patients who received chemotherapy had a significantly better OS than those who did not (MST: 273 vs. 47 days, *p*=0.013, Figure 2). The number of ambulatory patients before and after RT was 7 and 9, respectively. All

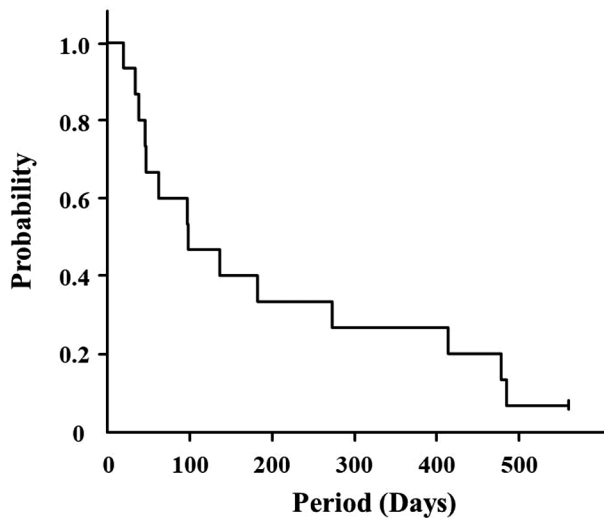


Figure 1. Overall survival (OS). The Kaplan–Meier estimate of overall survival for patients with intramedullary spinal cord metastasis showed OS rates of 50% and 31% at 3 and 6 months after radiation therapy, respectively.

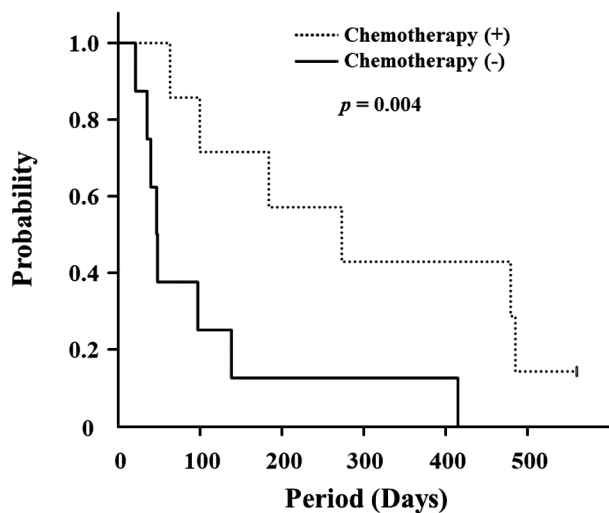


Figure 2. Overall survival (OS) curves with and without chemotherapy. Patients who received chemotherapy had a significantly better OS than those who did not (median survival time: 273 vs. 47 days,  $p=0.013$ ).

Table III. Predictors of ambulation ability and overall survival (OS) after radiation therapy (RT).

Characteristics	Ambulation ability (%) n=16	p-Value	Median OS (days)	p-Value
Age				
≤67	62%	1	231	0.278
≥68	50%		99	
Sex				
Male	50%	1	54	0.381
Female*	60%		137	
ECOG PS				
≤2	80%	0.035	137	0.342
≥3	16%		68	
Primary tumor				
Lung cancer	50%	0.633	99	0.959
Others	67%		185	
Lesion location				
Above lumbar	45%	0.633	160	0.127
Lumbar	80%		62	
Chemotherapy				
Yes	75%	0.06	273	0.013
No	38%		47	
Total RT dose				
30 Gy/10 fractions	71%	0.358	183	0.789
Others	44%		55	
Segment				
Single	78%	0.315	167	0.961
Multiple	28%		99	
Onset to RT				
≤1 week	67%	0.633	80	0.748
>1 week	50%		137	
Steroid use with RT				
Yes	45%	0.212	117	0.397
No	80%		99	
Ambulation before RT				
Yes (Frankel grade D/E)	100%	0.004	117	0.612
No (Frankel grade A-C)	22%		99	
Ambulation after RT				
Yes (Frankel grade D/E)	-		344	0.025
No (Frankel grade A-C)	-		97	
Brain metastases				
Yes	50%	0.475	97	0.326
No	0%		379	

\*One woman was treated twice with RT. ECOG PS: Eastern Cooperative Oncology Group Performance Status; ISCM: intramedullary spinal cord metastasis.

seven patients who could walk before RT were able to walk again after treatment, while only two of the nine (22%) who could not walk before RT were able to walk again ( $p=0.004$ ). There was no statistically significant difference in ambulation after RT based on age, sex, primary tumor, lesion location, total RT dose, segment, onset to RT, or steroid use with RT. Three of 16 patients (18.7%) responded well to RT, and their Frankel

grades improved, with two moving from C to D and one moving from D to E. One case improved during RT, one to two weeks after RT, and one seven weeks after RT. For all patients, the Wilcoxon signed-rank test did not confirm a statistically significant improvement in Frankel grade before and after RT ( $p=0.15$ , Figure 3). There were no adverse events of Grade 2 or higher associated with RT.

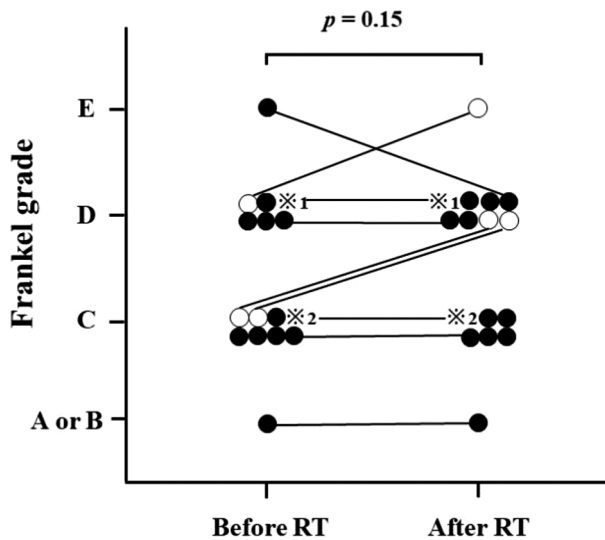


Figure 3. Frankel grade changes before and after radiotherapy (RT). White circles represent improved cases, black circles represent non-improved cases, \*1 represents the first RT, and \*2 represents the second RT.

## Discussion

The current study found that the MST for ISCM was only 3 months, which indicates a dismal prognosis and is consistent with previous studies (3, 4, 8, 11). OS rates were significantly higher in our patients who were able to receive chemotherapy than in those who were not (MST: 273 vs. 47 days,  $p=0.013$ ) or who were ambulatory after RT than in those who were not (MST: 344 vs. 97 days,  $p=0.025$ ). The analysis of RT effectiveness for ISCM revealed that ambulation prior to RT was a predictor of ability maintenance and improvement after RT (100% vs. 22%,  $p=0.004$ ). To the best of our knowledge, this is the first study to identify predictors for improved ambulation after RT in patients with ISCM.

In terms of RT efficacy, Hashii *et al.* reported that RT improved ambulation in one (Frankel grade B to D) out of 18 patients with ISCM, and the number of patients who were able to walk increased from nine (50%) to ten (56%) after RT (8). David *et al.* studied ambulation in 40 different treatment groups (35 RT, 5 surgery/others) (6). The ambulatory rate was 23 (57.5%) prior to RT and 24 (60%) after RT, with 21 patients (52.5%) still ambulatory on the last follow-up day. In our study, seven of 16 patients (44%) were able to walk prior to RT, and nine patients (56%) were able to walk after RT. Three out of 16 patients (18.7%) improved their ambulation (two from C to D and one from D to E), which is consistent with previous studies.

In terms of metastatic spinal cord compression (MSCC), Birgitt *et al.* reported that patients with MSCC who were ambulatory at the start of RT (Frankel grade D or E) have an 80% chance of retaining the ability to walk. However, in

paraparesis (Frankel C) and paraplegia (Frankel Grade A or B), the probability of regaining walking ability decreased to 40% and 7%, respectively (12). In patients with MSCC, one of the most important predictors for the ambulatory outcome is the pretherapy ambulatory function (13). In our study, seven patients who could walk prior to RT (Frankel Grade D or E) remained able to walk after RT (100%). However, only two of eight patients (25%) with Frankel Grade C prior to RT were able to regain ambulation after RT, while one patient with Frankel grade A or B was unable. The effects of RT on improving or maintaining gait in patients with ISCM may be similar to those observed in patients with MSCC.

The optimal irradiation schedule for patients with ISCM to improve gait function remains unknown. Our study showed no correlation between RT schedule and ambulation improvement, which is consistent with previous reports on RT schedules for patients with MSCC and motor dysfunction (14). Patients with ISCM who have difficulty walking prior to treatment are unlikely to improve their gait after treatment. Therefore, regardless of the RT schedule, it is important to apply RT promptly while the patients are ambulatory.

Several spread patterns have been proposed for ISCM, including lymphatic or hematological spread, meningeal spread, or direct invasion, but the exact mechanisms have not been identified (11, 15). In a recent review, extraspinal metastasis was found in 76.6% of patients, concomitant brain metastasis in 55.8%, leptomeningeal involvement in 20%, and vertebral metastasis in 19.5% (16). It suggests that ISCM often develops as part of severe systemic disease, and that systemic therapy may play a significant role in the pathogenesis. In our study, patients who could receive chemotherapy had better ambulation than those who could not (75% vs. 38%,  $p=0.06$ ). Although the indication for chemotherapy relies on the physician's clinical judgment, including the patient's general condition and age, adjuvant systemic therapy may maintain the patient's walking ability while also improving survival. In recent years, immunotherapy has attracted attention as a less invasive systemic therapy than chemotherapy. Immunotherapy, which has the potential to change the cancer treatment paradigm, may hold promise for more patients with ISCM in the future as a new era of systemic therapy with fewer side effects (17).

Our study had several limitations, including a retrospective design, a small sample size, and a short follow-up period, all of which have reduced statistical power. Furthermore, the possibility of comorbid brain metastases being the cause of gait disturbance cannot be completely ruled out. Therefore, a prospective, randomized, controlled study with a large number of patients and a long follow-up period is required to select the most appropriate treatment option for ISCM.

In conclusion, the OS rate in patients with ISCM remains low. Ambulation prior to RT was a significant predictor of ambulation ability after RT. Chemotherapy may improve survival as well as neurologic outcomes in certain patients.

## Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

## Authors' Contributions

T.N. designed the study, contributed to data acquisition, performed the statistical analysis, and prepared the manuscript. H.Y., G.S., and K.Y. designed the study and prepared the manuscript. S.W., S.N., K.K., T.K., N.A., and K.M. contributed to data acquisition. All Authors have read and approved the final manuscript.

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Received August 30, 2022  
Revised September 21, 2022  
Accepted September 22, 2022