Neurologic Outcomes After Radiation Therapy for Severe Spinal Cord Compression in Multiple Myeloma

A Study of 162 Patients

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Background: Bone destruction is the most frequent disease-defining clinical feature of multiple myeloma (MM), resulting in skeletal-related events such as back pain, pathological fractures, or neurologic compromise including epidural spinal cord compression (ESCC). Up to 24% of patients with MM will be affected by ESCC. Radiation therapy has been proven to be highly effective in pain relief in patients with MM. However, a critical knowledge gap remains with regard to neurologic outcomes in patients with high-grade ESCC treated with radiation.

Methods: We retrospectively included 162 patients with MM and high-grade ESCC (grade 2 or 3) who underwent radiation therapy of the spine between January 2010 and July 2021. The primary outcome was the American Spinal Injury Association (ASIA) score after 12 to 24 months, or the last known ASIA score if the patient had had a repeat treatment or died. Multivariable logistic regression was used to assess factors associated with poor neurologic outcomes after radiation, defined as neurologic deterioration or lack of improvement.

Results: After radiation therapy, 34 patients (21%) had no improvement in their impaired neurologic function and 27 (17%) deteriorated neurologically. Thirty-six patients (22%) underwent either surgery or repeat irradiation after the initial radiation therapy. There were 100 patients who were neurologically intact at baseline (ASIA score of E), of whom 16 (16%) had neurologic deterioration. Four variables were independently associated with poor neurologic outcomes: baseline ASIA (odds ratio [OR] = 6.50; 95% confidence interval [CI] = 2.70 to 17.38; $p < 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status (OR = 6.19; 95% CI = 1.49 to 29.49; $p = 0.015$), number of levels affected by ESCC (OR = 4.02; 95% CI = 1.19 to 14.18; $p = 0.026$), and receiving steroids prior to radiation (OR = 4.42; 95% CI = 1.41 to 16.10; $p = 0.015$).

Conclusions: Our study showed that 38% of patients deteriorated or did not improve neurologically after radiation therapy for high-grade ESCC. The results highlight the need for multidisciplinary input and efforts in the treatment of high-grade ESCC in patients with MM. Future studies will help to improve patient selection for specific and standardized treatments and to clearly delineate which patients are likely to benefit from radiation therapy.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

Multiple myeloma (MM) is a malignant plasma cell dyscrasia[1]. It is the second most frequently diagnosed hematological malignancy in developed countries, and it is rising in incidence[2]. Bone destruction, caused by diffuse monoclonal proliferations of plasma cells in the bone marrow, is the most frequent disease-defining clinical feature of MM[3,4]. Approximately 80% of patients with MM have lytic bone lesions[4,5]. These lesions lead to an increased risk of skeletal-related events including pathological fractures, back pain, and neurologic compromise

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through epidural spinal cord compression or cauda equina compression (ESCC/CEC)[4,6,7].

ESCC/CEC is reported to develop in up to 24% of patients with MM[8,9]. ESCC/CEC occurs when a myelomatous soft-tissue mass extends into the spinal canal, or via fragments of a pathologically fractured vertebral body[10,11]. If symptomatic, it presents mostly as pain, weakness, numbness, paresthesias, loss of bowel or bladder function, or gait dysfunction[10]. ESCC/CEC often requires rapid diagnosis and prompt treatment to prevent permanent neurologic dysfunction[12]. When systemic therapy is not sufficient to treat the symptoms and complications from ESCC/CEC, radiation therapy can be considered[13]. Radiation therapy has been proven to be highly effective for pain relief in patients with MM and it can improve symptoms caused by (impending) ESCC/CEC through reduction in tumor size[4]. The goal of radiation therapy in patients with MM is to achieve local tumor control, restore or preserve neurologic function, prevent loss of mechanical stability of the spine, manage pain, and improve health-related quality of life[12].

However, the optimal treatment for MM-related high-grade ESCC/CEC remains unclear. A better understanding of which patients are likely to benefit from radiation therapy facilitates patient selection for specific treatments and allows more informed care decisions. Therefore, the objective of this study was to evaluate the neurologic outcomes of patients with MM-related high-grade ESCC/CEC treated with radiation therapy. The secondary objectives were to determine the rate of repeat treatment (either surgery or repeat irradiation) after initial radiation therapy and to identify factors associated with poor neurologic outcomes.

Materials and Methods

Study Design

This retrospective cohort study was performed at 2 tertiary care centers in the United States after approval by our institutional review board. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines were followed for clear reporting[14].

Patient Selection

We identified 1,694 patients who had an International Classification of Diseases, Ninth Revision (ICD-9) and/or ICD-10 code corresponding to MM (203.0 and C90) and an encounter with the Radiation Oncology Department at 1 of the 2 study centers. The following inclusion criteria were applied: (1) diagnosis of MM, (2) diagnosis of spinal myeloma lesions, (3) receipt of radiation therapy for ESCC/CEC (referred to as "ESCC" for the remainder of the paper to improve readability) between January 1, 2010, and July 31, 2021, and (4) an ESCC that was determined to be grade 2 or 3 (see Appendix Table A1) on a cross-sectional T2-weighted magnetic resonance imaging (MRI) scan made within 6 weeks before radiation. Patients were excluded if they had (1) another major neurologic disease that might be associated with motor deficits; (2) concurrent ESCC at another, distant spinal level; (3) prior surgery or radiation therapy in the same area; or (4) a missing baseline or follow-up American Spinal Injury Association (ASIA) score[15]. Manual screening of the medical records determined that 162 patients met the selection criteria (Fig. 1).

Epidural Spinal Cord Compression

High-grade ESCC is compression of the spinal cord with or without some surrounding cerebrospinal fluid. The pre-radiation ESCC of the area that was subsequently irradiated was graded by 3 independent orthopaedic residents, blinded to neurologic outcomes, using criteria defined by Bilsky et al.[16] and Lee et al.[17] (see Appendix Table A1). When a minimum of 2 raters agreed on the grade, that grade was chosen as the definitive grade. When all 3 raters disagreed on the grade (n = 3 of 287), a senior surgeon (J.H.S.) joined a discussion in which the definitive call was made.

Variables

The primary outcome was the ASIA score[15] at the last follow-up (at 12 to 24 months). ASIA scores were extracted from the physicians' notes at 4 different intervals: baseline, 3 to 6 months, 6 to 12 months, and 12 to 24 months. When a patient underwent surgery (n = 31), had repeat irradiation (n = 5), or died (n = 97) before the last follow-up interval, the last known ASIA score was used. For logistic regression analysis, the final ASIA outcomes were dichotomized as "good" (a score of E or an improvement to a minimum of D), coded as "0," or "poor" (a neurologic deficit that did not improve or deterioration of the neurologic status [directly related to the treated area]), coded as "1." The secondary outcome was defined as repeat treatment of the irradiated area by either surgery or repeat irradiation after the initial radiation therapy. Twenty-two explanatory variables were manually collected from the patients' electronic medical records (see Appendix Table A2).

Statistical Analyses

Categorical variables were presented as the count (%) and continuous data, as the median (interquartile range ([IQR]) as they were found to be nonparametric after inspection of histograms. Baseline differences were compared between those with good and poor neurologic outcomes using chi-square tests and Fisher exact tests for categorical variables or Mann-Whitney U tests for continuous variables. Independent risk factors were identified by the purposeful selection approach described by Hosmer and Lemeshow, where covariates are removed from the model if they are non-significant and not a confounder (this iterative process is described in detail in Appendix Table A3)[18]. Sixteen patients who had missing values were excluded from the analyses of independent risk factors (but were included for the analysis of the primary outcomes): 5 each were missing the Eastern Cooperative Oncology Group [ECOG] performance status, Spinal Instability Neoplastic Score [SINS] category, and duration of neurologic symptoms, and 1 was missing the International Staging System [ISS] disease stage. All statistical analyses were performed with the Python programming language, version 3.9.7 (Python Software Foundation). A 2-tailed p value of <0.05 was considered significant.

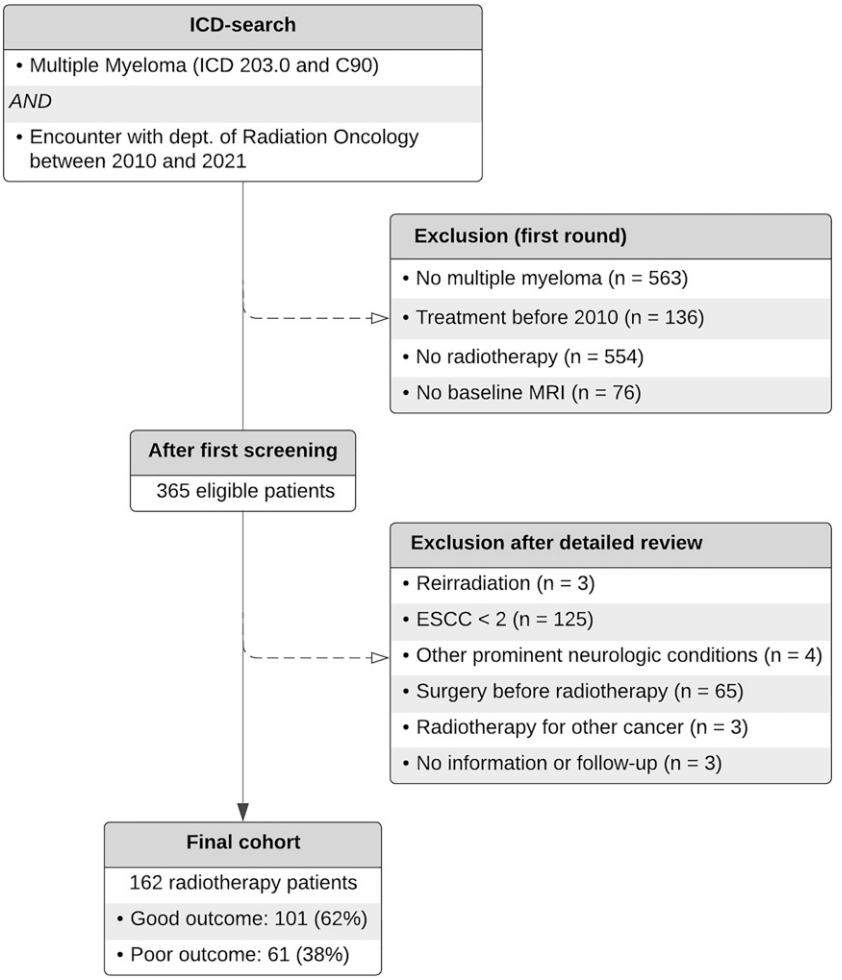

Fig. 1

Flowchart of inclusion and exclusion. ESCC <2 indicates an epidural spinal cord compression grade of <2.

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This research received no support from any funding agency in the public, commercial, or not-for-profit sectors.

Results

Patient Characteristics

The median age at radiation therapy was 67 years (IQR = 58 to 72), and 66 (41%) of the patients were female. ISS 2 was the most common disease stage (35%); most patients were capable of all self-care (ECOG 0 to 2; 81%) and had an age-adjusted Charlson Comorbidity Index of 0 to 4 (59%) (Table I). The most common radiation protocol was 10 fractions of 3 Gy (37%). Nine patients (5.6%) had a single fraction of 8 Gy (Table II). The median time from the initial MM diagnosis to the initiation of radiation therapy was 12 months (IQR = 0.3 to 49). Prior to radiation therapy, 102 patients (63%) experienced either subjective or objective neurologic symptoms (or a combination), and for 56 (55%) of them these symptoms had been present for <2 weeks. Sixty-two patients (38%) presented with impaired neurologic function. The thoracic spine was the most common location for radiation therapy (51%). Using the SINS criteria, 15% of the vertebrae were classified as unstable. Vertebral fractures were present in 52% of the patients, and most of those patients (57%) had at least 1 severe fracture (Genant grade[19] 3).

Neurologic Outcomes

Of the 162 patients, 27 (17%) deteriorated neurologically and 34 (21%) had no improvement of their impaired pre-radiation neurologic function. The status deteriorated 3 scale points (from ASIA E to ASIA B) in 1 patient, 2 points (from ASIA E to C) in 2, and 1 point (multiple combinations) in 24 (Fig. 2). One hundred patients were neurologically intact at baseline (ASIA E), of whom 16 (16%) deteriorated neurologically. Twenty-three patients had an unstable vertebra according to the SINS score. Of those, 7 (30%) had a poor neurologic outcome.

Rate of Repeat Treatment

Within 90 days, 20 patients (12%) underwent repeat treatment, consisting of repeat irradiation in 2 and surgery in 18 (Table III). Two patients required a second surgery within 90 days after the first unplanned surgery, 1 because of persisting pain and 1 because of wound/implant-related complications. Within 3 to

TABLE I Baseline Characteristics, Grouped by Outcome*

Baseline Characteristic	Total (N = 162)†	Good Outcome (N = 101)	Poor Outcome (N = 61)	P Value‡
Age *(yr)*	67 [58-72]	67 [59-72]	67 [56-73]	0.760
Time from MM diagnosis to RT *(days)*	363 [10-1,499]	197 [7-1,499]	530 [73-1,498]	0.230
Female	66 (40.7%)	40 (39.6%)	26 (42.6%)	0.831
BMI *(kg/m^2)*	27.1 [24.2-30.1]	26.8 [24.2-30.0]	27.7 [23.3-30.1]	0.975
ISS disease stage				0.145
1	52 (32.3%)	37 (36.6%)	15 (25.0%)	
2	57 (35.4%)	32 (31.7%)	25 (41.7%)	
3	44 (27.3%)	25 (24.8%)	19 (31.7%)	
Plasmacytoma	8 (5.0%)	7 (6.9%)	1 (1.7%)	
Back pain	153 (93.8%)	95 (94.1%)	58 (95.0%)	0.567
ECOG score				**<0.001**
0-2	127 (80.9%)	89 (90.8%)§	38 (64.4%)	
3-5	30 (19.1%)	9 (9.2%)	21 (35.6%)#	
Age-adjusted CCI				0.568
0-4	96 (59.3%)	60 (59.4%)	36 (59.0%)	
5-9	61 (37.7%)	39 (38.6%)	22 (36.1%)	
10-14	5 (3.1%)	2 (2.0%)	3 (4.9%)	
ASIA impairment score				**<0.001**
E	100 (61.7%)	84 (83.2%)§	16 (26.2%)	
D	50 (30.9%)	15 (14.9%)	35 (57.4%)	
C	12 (7.4%)	2 (2.0%)	10 (16.4%)#	
Motor symptoms	83 (51.2%)	37 (36.6%)	46 (75.4%)#	**<0.001**
Sensory symptoms	21 (13.0%)	13 (12.9%)	8 (13.1%)	1.00
Duration of neurologic symptoms prior to RT				**<0.001**
<24 hours	2 (2.0%)	0 (0%)	2 (3.8%)§	
24-48 hours	4 (4.1%)	1 (2.2%)	3 (5.7%)	
3-7 days	32 (32.7%)	16 (35.6%)	16 (30.2%)	
8-14 days	18 (18.4%)	5 (11.1%)	13 (24.5%)	
>14 days	42 (42.9%)	23 (51.1%)#	19 (35.9%)	
Chemotherapy regimen				0.977
RVD	81 (50.0%)	51 (50.5%)	30 (49.2%)	
Other	70 (43.2%)	43 (42.6%)	27 (44.3%)	
No chemotherapy	11 (6.8%)	7 (6.9%)	4 (6.6%)	
Chemotherapy timing				**0.003**
Before RT	109 (72.2%)	60 (63.8%)	49 (86.0%)§	
After RT	42 (27.8%)	34 (36.2%)#	8 (14.0%)	
Received bisphosphonates	107 (66.0%)	67 (66.3%)	40 (65.6%)	1.00
Received high-dose steroids	104 (64.6%)	56 (55.4%)	48 (80.0%)#	**0.003**
Steroid responsiveness	61 (41.8%)	37 (38.5%)	24 (48.0%)	0.356
Treated region				0.534
Cervical	9 (5.6%)	7 (6.9%)	2 (3.3%)	
Thoracic	82 (50.6%)	51 (50.5%)	31 (50.8%)	
Lumbar	16 (9.9%)	9 (8.9%)	7 (11.5%)	
Sacral	3 (1.9%)	3 (3.0%)	0 (0%)	
Transitional	52 (32.1%)	31 (30.7%)	21 (34.4%)	

continued

TABLE I (*continued*)

Baseline Characteristic	Total (N = 162)†	Good Outcome (N = 101)	Poor Outcome (N = 61)	P Value‡
Disease spread				0.232
Single vertebra	41 (25.3%)	31 (30.7%)	10 (16.4%)	
2-4 vertebrae	25 (15.4%)	15 (14.9%)	10 (16.4%)	
Scattered	96 (59.3%)	55 (54.5%)	41 (67.2%)	
ESCC grade				0.963
2	92 (56.8%)	58 (57.4%)	34 (55.7%)	
3	70 (43.2%)	43 (42.6%)	27 (44.3%)	
Levels involved in ESCC				**<0.001**
1-2	121 (74.7%)	87 (86.1%)§	34 (55.7%)	
≥3	41 (25.3%)	14 (13.9%)	27 (44.3%)#	
SINS category				0.491
Stable	21 (13.5%)	11 (11.3%)	10 (17.2%)	
Potentially unstable	111 (71.6%)	70 (72.2%)	41 (70.7%)	
Unstable	23 (14.8%)	16 (16.5%)	7 (12.1%)	
Number of VCFs				0.152
0	78 (48.1%)	44 (43.6%)	34 (55.7%)	
1	68 (42.0%)	44 (43.6%)	24 (39.3%)	
≥2	16 (9.9%)	13 (12.9%)	3 (4.9%)	
Highest Genant grade				0.426
1	15 (17.9%)	11 (19.3%)	4 (14.8%)	
2	21 (25%)	13 (22.8%)	8 (29.6%)	
3	48 (57.1%)	33 (57.9%)	15 (55.6%)	
Deceased	109 (67.3%)	57 (56.4%)	52 (85.2%)#	**<0.001**

*Values are presented as the number (%) or median [interquartile range]. Good outcome = ASIA E or improvement to ASIA D, poor outcome = final ASIA score of A, B, or C or worsening of neurologic status. MM = multiple myeloma, RT = radiation therapy, BMI = body mass index, ISS = International Staging System, ECOG = Eastern Cooperative Oncology Group, CCI = Charlson Comorbidity Index, ASIA = American Spinal Cord Injury Association, RVD = Revlimid (lenalidomide)-Velcade (bortezomib)-dexamethasone, ESCC = epidural spinal cord compression, SINS = Spinal Instability Neoplastic Score, VCFs = vertebral compression fractures. †The total number of patients included in this study is larger than our previous cohort (study not published at the time of writing) due to longer follow-up. ‡P values are shown for differences between groups using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. Significant p values ($p < 0.05$) are in bold. §Indicates the group with the highest proportion in the lowest category (identified only for the significant differences in categorical variables). #Indicates the group with the highest proportion in the highest category (only for the significant differences).

30 months, 16 patients (9.9%) underwent repeat treatment, including repeat irradiation in 3 and surgery in 13. All repeat treatments were in the initially treated area, except in 2 patients in whom the ESCC expanded to adjacent levels. Of the patients who had an unstable spine at baseline, 8 (35%) had repeat treatment.

One patient with ASIA E, ESCC 2, and 1 affected level received 3 repeat treatments: a kyphoplasty because of worsening pain at the treated level, followed by a laminectomy because of expansion of the ESCC to adjacent levels, and lastly another course of radiation to those levels because of worsening to ASIA C.

Factors Associated with Poor Neurologic Outcomes

Basic comparative analyses of the baseline characteristics showed that patients with a good outcome had, compared with patients with a poor outcome, better ECOG scores, better ASIA scores, less subjective weakness, a longer duration of neurologic symptoms, fewer levels affected by the ESCC, and a lower rate of steroid treatment prior to radiation (all $p < 0.05$; Table I). In multivariable analyses, 4 variables remained independently associated with a poor neurologic outcome after full adjustment for potential confounders: baseline ASIA score (odds ratio [OR] = 6.50; 95% confidence interval [CI] = 2.70 to 17.38; $p < 0.001$), ECOG score (OR = 6.19 for ECOG of 3 to 5; 95% CI = 1.49 to 29.49; $p = 0.015$), number of levels affected by the ESCC (OR = 4.02 for >2 levels; 95% CI = 1.19 to 14.18; $p = 0.026$), and receiving intravenous or intramuscular steroids prior to radiation (OR = 4.42; 95% CI = 1.41 to 16.10; $p = 0.015$) (Table IV). The number of vertebral compression fractures and the highest Genant grade[19] in the irradiated area were included as covariates because of significance in step 2 of the purposeful regression method, but they lost their significance when adjusted for other covariates. Time from MM diagnosis to radiation was retained in the analysis because of clinical relevance. Variables that were identified as confounders were the number

TABLE II Radiation Therapy Details, Grouped by Outcome*

RT Parameter	Total (N = 162)	Good Outcome (N = 101)	Poor Outcome (N = 61)	P Value†
RT technique				0.237
AP/PA/3D	89 (56.0%)	50 (50.0%)	39 (66.1%)	
VMAT/IMRT	65 (40.9%)	47 (47.0%)	18 (30.5%)	
SRS	5 (3.1%)	3 (3.0%)	2 (3.4%)	
Total dose *(Gy)*				**0.012**
<10	13 (8.1%)	4 (4.0%)	9 (15.0%)	
10-19	8 (5.0%)	3 (3.0%)	5 (8.3%)	
20-29	61 (37.9%)	37 (36.6%)	24 (40.0%)	
≥30	79 (49.1%)	57 (56.4%)	22 (36.7%)	
Fractions				**0.013**
1	9 (5.6%)	4 (4.0%)	5 (8.2%)	
2-5	5 (3.1%)	0	5 (8.2%)	
6-9	60 (37.0%)	35 (34.7%)	25 (41.0%)	
10-14	75 (46.3%)	52 (51.5%)	23 (37.7%)	
15-19	8 (4.9%)	5 (5.0%)	3 (4.9%)	
≥20	5 (3.1%)	5 (5.0%)	0	

*Values are presented as the number (%). Good outcome = ASIA E or improvement to ASIA D, and poor outcome = final ASIA score of A, B, or C or worsening of neurologic status. RT = radiation therapy, AP/PA = anterior-posterior/posterior-anterior, VMAT/IMRT = volumetric modulated arc therapy/intensity-modulated radiation therapy, SRS = stereotactic radiosurgery. †Significant p values ($p < 0.05$) are in bold.

ASIA Score		No. (%)		
Baseline	**Final***	**Total**	**Repeat treatment**	**Deceased‡**
E (n = 100)	**E (stable)**	84 (84%)	13 (13%)	36 (36%)
	D (worse)	13 (13%)	6 (6%)	7 (7%)
	C (worse)	2 (2%)	2 (2%)	0
	B (worse)	1 (1%)	1 (1%)	0
D (n = 50)	**E (improved)**	15 (30%)	0	4 (8%)
	D (stable)	29 (58%)	5 (10%)	40 (80%)
	C (worse)	6 (12%)	4 (8%)	6 (12%)
	B (worse)	0	0	0
C (n = 12)	**E (improved)**	0	0	0
	D (improved)	2 (17%)	1 (8%)	0
	C (stable)	5 (42%)	0	7 (58%)
	B (worse)	5 (42%)	4 (33%)	4 (33%)

Fig. 2

Changes in ASIA scores and rates of repeat treatment. *The final ASIA score was defined as the score at the last follow-up interval (between 12 and 24 months) or the last known score before a repeat treatment or death. Improved, stable, and worse indicate the change (or lack of change) in the ASIA score from baseline to final follow-up. For example, 6 patients with an ASIA score of D at baseline had deterioration to ASIA C. Repeat treatments consisted of revision surgery or unplanned repeat irradiation before the last follow-up interval (of 12 to 24 months). For example, 6 patients who had an ASIA score of E at baseline and deterioration to ASIA D at final follow-up had repeat treatment. ‡Deceased patients are those who died before the last follow-up interval (of 12 to 24 months). For example, 36 patients who had an ASIA score of E at baseline and no deterioration died within 1 year.

TABLE III Repeat Treatments, Grouped by Indication*

Indication for Repeat Treatment	Repeat Treatment (N = 36)	
	In Short-Term Follow-up Interval	In Long-Term Follow-up Interval
First repeat treatment	20	16
Local recurrence of ESCC†	2 (10%)	5 (31%)
New neurologic deficits	13 (65%)	5 (31%)
Pain	5 (25%)	5 (31%)
Pathologic fracture	—	1 (6%)
Second repeat treatment	2	1
Pain	1 (50%)	—
Wound/implant-related	1 (50%)	—
Adjacent-segment disease	—	1 (100%)
Third repeat treatment	0	1
Adjacent-segment disease	—	1 (100%)

*Values are presented as the number (%). Short-term is 0 to 90 days post-treatment and long-term is 3 to 30 months post-treatment. For second and third repeat-treatment data, days are counted from the last intervention, so short-term means within 90 days from the last intervention. †ESCC = epidural spinal cord compression.

of levels affected by the ESCC, irradiated portion of the spine, SINS category, and total radiation dose.

Discussion

There is little evidence supporting clinical decision-making for patients with MM who present with high-grade ESCC. As MM is considered a radiosensitive tumor, radiation therapy is expected to be effective in the majority of patients without spinal instability, regardless of ESCC grade[20-22]. However, literature on the effect of radiation therapy on neurologic outcomes in patients with MM is scarce. In our study, more than a third of the patients had a poor neurologic outcome after radiation therapy, defined as a lack of improvement or neurologic deterioration. A fifth of the patients needed a secondary treatment. Patients with worse baseline ASIA scores and more vertebral levels affected by the ESCC had a higher risk of worse neurologic outcomes.

In a literature review published in 2012, Kim et al. analyzed 34 studies comparing radiation to surgery (with or without radiation) in a total of 2,495 patients with spinal metastatic disease and ESCC[23]. In total, clinical deterioration occurred in 9% of ambulatory patients treated with radiation therapy alone. In our cohort, this proportion was substantially larger, with 16% of patients with ASIA E deteriorating neurologically. Kim et al. also found that, among patients who were nonambulatory (ASIA A, B, or C) before treatment, 29% regained their ability to walk after receiving isolated radiation therapy[23]. In our study, there were 12 nonambulatory patients (ASIA C), but only 2 regained ambulatory function (ASIA D, 17%) and none improved to ASIA E without secondary treatment. It must be noted that the review by Kim et al. investigated a patient cohort of which only 54% had radiosensitive tumors[20,23]. Since MM is generally considered to be radiosensitive, the results of our study cannot be directly compared with theirs. Nevertheless, since we found worse results rather than better, these differences suggest that radiation therapy outcomes for patients with MM differ from those of patients with other spinal metastatic diseases and that radiation therapy in nonambulatory patients with MM-related ESCC might not be sufficient if ambulation is a goal.

A worse baseline ASIA score had the highest association with poor neurologic outcomes. This finding is consistent with literature regarding neurologic outcomes after radiation therapy for ESCC due to spinal metastatic diseases other than MM. In a randomized controlled trial of patients with ESCC due to

TABLE IV Multivariable Logistic Regression Assessing Risk Factors for Poor Neurologic Outcomes After Radiation Therapy*

Parameter	OR	95% CI	P Value†
Baseline ASIA score, per increase of 1	6.50	(2.70-17.38	**<0.001**
Time from MM to RT†			
0-3 months	Reference		
3-6 months	4.47	0.66-30.39	0.121
6-12 months	1.15	0.14-8.87	0.895
>12 months	1.35	0.42-4.41	0.612
ECOG score			
0-2	Reference		
3-5	6.19	1.49-29.49	**0.015**
Number of VCFs	1.74	0.82-3.98	0.163
Highest Genant grade, per increase of 1	0.38	0.06-1.70	0.231
SINS category§			
Stable	Reference		
Potentially unstable	1.74	0.39-8.40	0.476
Unstable	0.92	0.08-9.77	0.944
>2 levels affected by ESCC§	4.02	1.19-14.18	**0.026**
Steroids prior to radiation	4.42	1.41-16.10	**0.015**
Treated region§			
Cervical	Reference		
Thoracic	2.40	0.34-26.24	0.415
Lumbar	5.51	0.56-78.01	0.165
Transitional	1.30	0.16-14.38	0.813
Total radiation dose, per Gy§	0.98	0.92-1.05	0.646

*OR = odds ratio, CI = confidence interval, ASIA = American Spinal Cord Injury Association, MM = multiple myeloma, RT = radiation therapy, ECOG = Eastern Cooperative Oncology Group, VCFs = vertebral compression fractures, SINS = Spinal Instability Neoplastic Score, ESCC = epidural spinal cord compression. †Significant p values ($p < 0.05$) are in bold. ‡Retained because of clinical relevance. §Included because of confounding effect.

spinal metastatic disease, Patchell et al. reported that surgery followed by radiation therapy was superior to radiation therapy alone in restoring the ability to walk, with an increase in the duration for which the patients could walk and in the survival of these patients[24]. The pre-treatment neurologic score had the highest association with post-treatment neurologic outcomes. Our study results support this finding. However, while surgical intervention has been shown to improve neurologic outcomes in patients with spinal metastatic disease, including restoration of ambulatory status and improved survival, the role of surgery in MM-related ESCC remains unclear. Due to the diffuse bone loss and hematologic deficiencies associated with MM, postoperative complications and the risk of infection are increased[25,26], and the benefits of surgery must be carefully weighed against potential risks on an individual basis. Our study suggests that radiation may be less effective in patients with substantial neurologic deficits, underscoring the need for further research to determine the most effective approach to managing neurologic outcomes in this patient population.

The number of levels affected by the ESCC—i.e., extension of the ESCC over >2 levels—was independently associated with worse post-treatment neurologic outcomes. In 41 patients (25%) in our cohort, ≥3 vertebral levels were involved in the ESCC and 27 (66%) of those patients had a poor neurologic outcome. To our knowledge, this factor has not been studied before in risk-assessment studies. A possible explanation for this finding is that ESCC can lead to vascular compromise, vasogenic edema, and demyelination[12]. If this happens over a larger region, it is likely that this damage is less reversible. Additional work remains to be done before a full understanding of the efficacy of radiation in patients with widespread ESCC is established.

From the results, it is clear that most of the factors that influence neurologic outcomes are non-modifiable. It is almost impossible to lower a patient's ECOG score, improve their ASIA score, or shrink the tumor so that it only affects ≤2 vertebral levels in a short period of time before radiation. The most important factor seems to be early recognition of ESCC, before neurologic deficits are present and before the compression has spread to >2 levels. Patients should be educated on the possibility of this complication so that they can present themselves to the hospital at the earliest signs of spinal tumor growth, and MRI should be performed with a low threshold in this population.

Limitations and Recommendations

Several limitations of this study need to be considered. The main one is the retrospective nature of the study, which made it difficult to score pre- and post-treatment neurologic status in a standardized manner. We had to rely on a physician's assessment and documentation of the patient's neurologic status, which imposes the risk of measurement bias. Second, the sample size was relatively small for risk-assessment studies, although most other studies investigating MM are substantially smaller because of the low incidence of MM. Furthermore, the OR for the effect of receiving steroids prior to radiation (4.42) implies a negative effect of steroids on post-radiation neurologic outcomes. It is well recognized that the use of steroids in the treatment of ESCC is effective in improving neurologic function and reducing complications after a spinal intervention[11,13,27-29]. We assume that this contradictory effect arose from a selection bias in which steroids were not given to patients without neurologic symptoms or when the situation appeared favorable in general, which caused the seemingly beneficial effect of not receiving steroids prior to radiation. Therefore, we do not recommend that physicians refrain from using steroids in the treatment of MM-related ESCC based on these results. Next, there was a selection bias in terms of which patients were given radiation therapy. Patients with worse ECOG scores, more aggressive MM, and a lower life expectancy might be selected for (palliative) radiation, and this bias might have caused a higher prevalence of neurologic deterioration. Lastly, there was substantial heterogeneity in radiation modalities, which limits the applicability of the results to specific radiation protocols. In terms of future research, it would be useful to extend the current findings by examining ECOG scores, ASIA scores, and the number of levels affected by the ESCC together with other potential risk factors in larger, multicenter studies to improve patient selection for specific and standardized treatments and to clearly delineate which patients are likely to benefit from radiation therapy.

Conclusions

This retrospective study demonstrates that more than a third of patients with MM and high-grade ESCC deteriorated or did not improve neurologically after radiation therapy. A fifth of the patients needed secondary treatment. Patients with worse baseline ASIA scores and multiple levels affected by the ESCC had a higher risk of worse neurologic outcomes. These results highlight the need for multidisciplinary efforts in the treatment of high-grade ESCC in patients with MM. Future, prospective studies will help to improve patient selection for specific and standardized treatments and to clearly delineate which patients are likely to benefit from radiation therapy.

Appendix

eA Supporting material provided by the authors is posted with the online version of this article as a data supplement at jbjs.org (http://links.lww.com/JBJS/H569). ■

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