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Scientific Article

Clinical Outcomes of Dose-Escalated Hypofractionated External Beam Radiation Therapy (5 Gy × 5 Fractions) for Spine Metastasis

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Abstract

Purpose: The objective of this study was to determine the toxicities and outcomes of patients with spinal metastasis treated with external beam radiation therapy (EBRT) to 25 Gy in 5 fractions.

Methods and Materials: Data were extracted from an institutional tumor registry for patients with spinal metastasis who were treated with EBRT to 25 Gy in 5 fractions to their spinal lesion(s). Cox regression and Kaplan-Meier analyses to determine local control and overall survival (OS) were employed.

Results: Seventy-five patients with 86 total treated spinal metastatic tumors were identified. The median follow-up was 7 months. The median age was 66 years. Fifty-six patients (75.7%) experienced partial or complete pain relief for a median duration of 6 months (range, 1-33). Fifty-one (59.3%) cases were planned using intensity modulated radiation therapy while 19 (22.1%) employed 3-dimensional conformal radiation therapy and 16 (18.6%) cases used nonconformal radiation technique. Greater than 90% of cases had a point dose maximum to the spinal cord/cauda equina <27.5 Gy. No patient experienced treatment-related myelopathy. The most common toxicities were fatigue (23.3%), pain flare (14.0%), and nausea (8.1%). There were no grade 3 toxicities. One-year local control was 80.6%, and 1-year OS was 38.4%. Higher Karnofsky performance status ($P = .001$) and radiosensitive tumor histology ($P = .014$) were significant predictors for better OS.

Conclusions: Our single-institutional retrospective analysis of patients with spinal metastasis suggested that palliative EBRT to 25 Gy in 5 fractions is safe, with a low toxicity profile and minimal risk for myelopathy with an achievable dose maximum to the spinal cord and cauda equina ≤27 Gy (equivalent total dose in 2-Gy fractions ≤50 Gy), and it may provide durable palliation and local control in cases where stereotactic body radiation therapy may not be indicated.

Introduction

Cancer spread to the spine continues to be a devastating complication for many patients with cancer, with approximately 70% of patients experiencing spine metastasis during their disease course.[1] Symptoms resulting from spine metastasis may include pain, ambulatory difficulty, and/or neurologic deficits. A significant number of patients receive palliative radiation therapy (RT), which

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typically employs various regimens, including 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions.[2]

Previous studies have compared 25 Gy in 5 fractions using intensity modulated radiation therapy (IMRT) to other standard fractionations. This includes to 20 Gy in 5 fractions in which a multicenter phase III trial showed that 25 Gy in 5 fractions was associated with better 6-month local progression-free survival on propensity-score analysis ($P = .03$).[3] Another study investigating data from 3 prospective trials compared 25 Gy in 5 fractions using IMRT to 30 Gy in 10 fractions and showed either regimen to be similarly effective in terms of 6-month local progression-free survival ($P = .36$).[4]

Historically, patients with stage IV cancer have been treated with chemotherapy alone. However, the relatively recent developments and additions of immunotherapy and targeted molecular agents have ushered in a new era of cancer treatment, leading to overall survival (OS) benefits for different cancer primary types.[5-7] Subsequently, patients with metastatic cancer are living longer and a substantial proportion are still very functional without significant issue regarding their activities of daily living. As a result, there is a need to continue to find ways to improve the convenience of palliative RT and durability of local control.

Higher biologic effective dose has been shown in various cancer primary types to be associated with improved palliation, local control, and patient outcomes.[8-11] Ablative RT using stereotactic body radiation therapy (SBRT) to treat spine metastasis is being actively investigated with encouraging results on efficacy and safety.[12] However, not all cancer treatment facilities possess the capabilities and resources required for the complexities associated with spine SBRT. Furthermore, insurers may deny SBRT if treatment indications do not meet specific criteria.

As such, continuing to improve outcomes using external beam RT (EBRT) to treat cancer metastasis remains essential. The development of 3-dimensional conformal RT (3D-CRT), IMRT, and image-guided RT has allowed for more precise RT delivery, allowing for dose escalation. Additionally, hypofractionated regimens have increased patient convenience by decreasing the total number of treatment days. In this single-institutional analysis, we investigate the outcomes of patients with spine metastasis who were treated with hypofractionated EBRT to 25 Gy in 5 fractions including those receiving nonconformal 2D or 3D-CRT, radiation delivery techniques not previously studied using this regimen, in addition to IMRT.

Methods and Materials

Patients

This retrospective study was approved by the institutional review board. The records of 173 patients with 571 osseous metastasis cases treated to 25 Gy in 5 fractions between November 2006 and August 2020 were reviewed. Of those, 75 patients received EBRT to 86 spine metastases (Table 1). All patients had pathologic diagnosis of malignancy and radiographically confirmed disease on pretreatment computed tomography (CT), magnetic resonance imaging (MRI), and/or positron emission tomography scan. Tumor histologies classified as radiosensitive included prostate, breast (nontriple negative), and human papillomavirus positive head and neck cancers.

Table 1 Patient and clinicopathologic characteristics

	n	Percent
Age (years)		
Median (range)	66 (32-90)	
Sex		
Female	30	40.0%
Male	45	60.0%
Race		
White	60	80.0%
Black	9	12.0%
Asian	6	8.0%
KPS		
50	1	1.3%
60	4	5.3%
70	24	32.0%
80	30	40.0%
90	15	20.0%
100	1	1.3%
Expired		
Yes	62	82.7%
No	13	17.3%
Primary site of disease		
Lung	27	31.4%
Prostate	18	20.1%
Breast	12	13.9%
Head and neck	8	9.3%
Bladder	4	4.6%
Pancreas	3	3.5%
Esophagus	2	2.3%
Colon	2	2.3%
Cervix	1	1.1%
Kidney	1	1.1%
Germ cell (mediastinum)	1	1.1%

(*continued on next page*)

Table 1 (*Continued*)

	n	Percent
Penile	1	1.1%
Rectum	1	1.1%
Merkel cell (upper extremity)	1	1.1%
Skin	1	1.1%
Unknown	3	3.5%
Radiosensitive histology		
Yes*	31	36.0%
No	52	60.4%
Unknown	3	3.5%
Radiation technique		
IMRT	51	59.3%
3D-CRT	19	22.1%
Nonconformal	16	18.6%
Concurrent chemo		
Yes	4	4.6%
No	82	95.3%
Local progression		
Yes	16	18.6%
No	86	81.4%

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy; IMRT = intensity modulated radiation therapy; KPS = Karnofsky performance status.

* Prostate, breast (nontriple negative), human papillomavirus positive head and neck cancers

RT

CT-guided simulation was performed on all patients. Patients were treated to a prescription dose of 25 Gy in 5 fractions using either nonconformal 2D technique, 3D-CRT, or IMRT. All treatment plans were generated using Eclipse (Varian Medical Systems, Palo Alto, CA).

Follow-up and outcomes

Final follow-up was performed on December 13, 2021. The Karnofsky performance status (KPS) index was used as the assessment tool for functional impairment. The endpoints analyzed were treatment-related toxicity, pain control, local control (LC), and OS. Treatment-related toxicities associated with the irradiated lesion were assessed according to electronic medical record documentation and the Common Toxicity Criteria for Adverse Events version 4.0. Pain control for the irradiated lesion was assessed according to electronic medical record documentation. Local failure was defined as progression of infield disease, and disease was noted on diagnostic CT, MRI, and/or positron emission tomography scan as reviewed on imaging and documented on the radiologist report, with or without biopsy. Fifty-eight (77.3%) of 75 patients had restaging CT and/or MRI spine surveillance imaging after EBRT completion, and 29 (38.7%) patients had MRI spine surveillance imaging. LC was defined as the interval between date of EBRT completion for the irradiated lesion and date of local recurrence, censored at the time of last follow-up or time of death for those without recurrence. OS by patient was defined as the interval between the date of EBRT completion and date of death, censored at the time of last follow-up.

Statistical analysis

All data analyses were performed using SPSS 26.0 (IBM Corp, Armonk, NY). LC was assessed at the level of the individual lesion, while OS was assessed at the patient level. Kaplan-Meier plots were generated to estimate LC and OS. Cox regression analysis was used to identify associated prognostic factors and determine their hazard ratios. *P* values of less than .05 were considered statistically significant.

Results

Patient and treatment characteristics

The median age of the cohort was 66 years (range, 32-90). The median follow-up time was 7 months (range, 1-126). Seventy (93.3%) patients had a KPS $\geq$ 70. Most patients had either lung (n = 27; 31.4%), prostate (n = 18; 20.1%), or breast (n = 12; 13.9%) cancer as their primary site of disease. Six (6.9%) of the 86 cases presented with documented radiographic cord compression. Most cases were treated using IMRT (n = 51; 59.3%), while the remainder were treated using 3D-CRT (n = 19; 22.1%) or nonconformal technique (n = 16; 18.6%). The majority of cases (n = 38; 95.0%) with known spinal cord dose had a point maximum dose (D_{max}) of <110% of the prescription dose (Fig E1), with the 1 exception a case that had a spinal cord D_{max} of 28.5 Gy (114.2%) and another with a D_{max} of 27.52 Gy (110.1%). All cases with known cauda equina dose had a D_{max} of <110% (Fig E2). The majority of cases (n = 51; 87.9%) had a $D_{max} \leq 27$ Gy (D_{max} of <108%).

Patient relief and toxicities

Seventy-four (86.0%) of the 86 cases initially presented with pain (Table 2). Of those, 56 (75.7%) experienced partial or complete pain relief, with a median pain relief

Table 2 Palliation and toxicity outcomes

	n	%
Pain relief (of those tumors initially presenting with pain; n = 74)		
Yes	56	75.7%
Partial	38	51.3%
Complete	18	24.3%
No	18	24.3%
Pain relief duration (months)		
All patients		
Median (range)	6 (1-33)	
Patients living ≥6 months		
Median (range)	9 (6-33)	
Patients living ≥12 months		
Median (range)	18 (12-33)	
Myelopathy		
Yes	0	0.0%
No	86	100.0%
Fatigue		
Yes	20	23.3%
No	66	76.7%
Pain flare		
Yes	12	14.0%
No	74	86.0%
GI toxicity		
None	71	82.5%
Diarrhea	1	1.2%
Nausea	7	8.1%
Vomiting	2	2.3%
Dysphagia	3	3.5%
Esophagitis	5	5.8%
Skin toxicity		
Yes	2	2.3%
No	84	97.7%

Abbreviation: GI = gastrointestinal.

duration of 6 months (range, 1-33). Of patients who lived ≥6 months (n = 50) after RT completion, the median pain relief duration for the irradiated lesion was 9 months (range, 2-33). Of patients who lived ≥12 months (n = 26), the median pain relief duration was 20 months (range, 12-33). No case was associated with treatment-related myelopathy. The most common side effect was fatigue in 20 (23.3%) cases. Twelve (14.0%) cases were associated with treatment-related pain flare. Only 2 (2.3%) cases were associated with skin toxicity. There were no grade 3 toxicities.

LC and OS

The Kaplan-Meier 1-year LC rate was 80.6% (Fig 1) while the 1-year OS rate was 38.4% (Fig 2). The median OS was 7.4 months. On Cox regression analysis for local failure, neither age, gender, race, KPS, RT technique, nor tumor radiosensitivity were predictive factors (Table 3). Ninety-five percent of the target volume was covered by greater than 95% of the prescription dose in 76 (91.6%) of 83 evaluable cases. On Cox regression multivariable

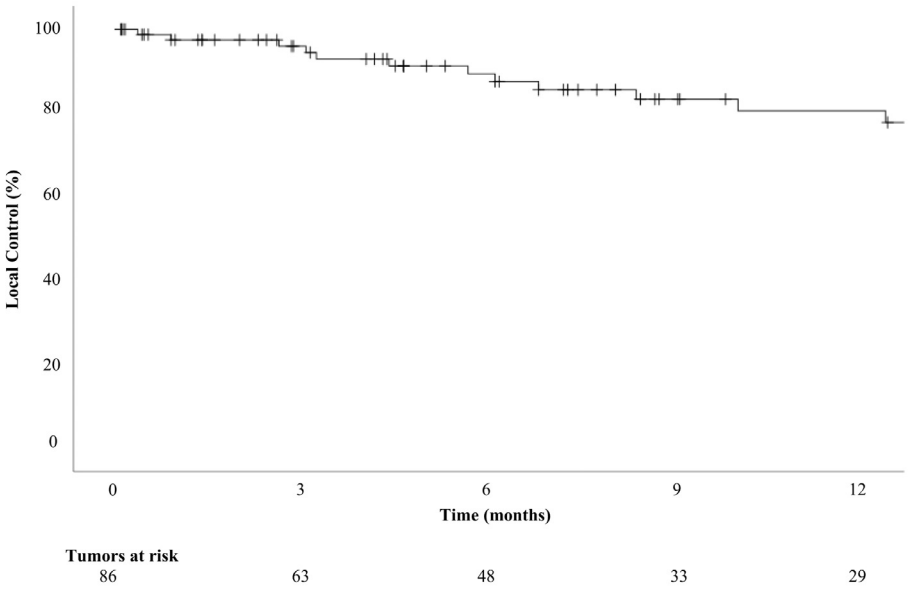

Fig. 1 Kaplan-Meier local control (n = 86)

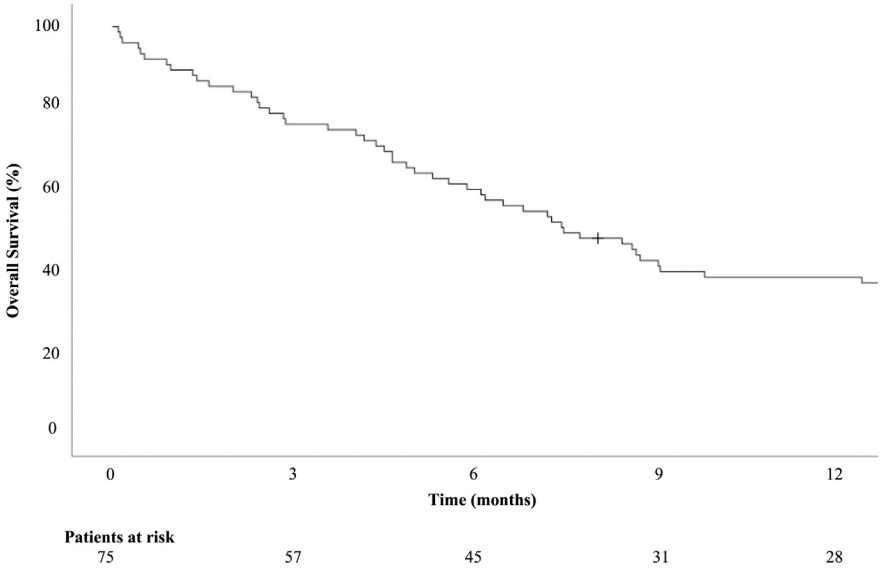

Fig. 2 Kaplan-Meier overall survival (n = 75)

analysis, higher KPS (P = .002) and radiosensitive tumor histology (P = .008) were significant prognostic factors for greater OS (Table 4).

Discussion

The spine is the most common site of osseous metastases and most patients with cancer harbor metastatic spine disease.[13,14] The 1-year OS rates of patients with spine metastasis varies depending on primary tumor site, but they range from 0% to 83%.[15] More recently, however, newly developed systemic therapeutic agents have improved the OS for those with metastatic cancer, including the most common cancer sites, such as prostate,[5] lung,[7] and breast,[16] and the median OS for certain favorable tumor sites and histologies can be on the order of years.[6,17] Furthermore, certain patients with oligometastatic disease may benefit from metastasis-directed therapy and achieve durable remission.[18] Given these developments, there is a growing need for convenient cancer treatment that can lead to durable palliation and LC in patients with metastatic cancer. Although only limited conclusions can be made from our retrospective analysis, it demonstrates that EBRT to 25 Gy in 5 fractions can be delivered conveniently without significant toxicity and with minimal risk for myelopathy. It has the potential for durable palliation and LC in the treatment of spine

Table 3 Cox regression analysis for local failure

	Univariate (local failure)			Multivariable (local failure)		
Variable	**Hazard ratio**	**95% CI**	***P* value**	**Hazard ratio**	**95% CI**	***P* value**
Age at diagnosis*	1.011	0.969-1.053	*P* = .619	1.005	0.958-1.055	*P* = .835
Sex						
Female	Reference					
Male	2.585	0.726-9.204	*P* = .143	2.415	0.654-8.914	*P* = .186
Race						
Non-black	Reference					
Black	0.624	0.081-4.790	*P* = .650	0.609	0.068-5.441	*P* = .657
KPS*	1.005	0.945-1.069	*P* = .877	1.000	0.941-1.063	*P* = .997
Radiosensitive tumor†						
No	Reference					
Yes	0.571	0.199-1.637	*P* = .297	0.533	0.183-1.549	*P* = .248
Radiation technique						
Nonconformal	Reference					
3D/IMRT	0.286	0.086-0.957	*P* = .042	0.316	0.085-1.176	*P* = .086

Abbreviations: 3D = 3-dimensional; CI = confidence interval; IMRT = intensity modulated radiation therapy; KPS = Karnofsky performance status.
* Analyzed as a continuous variable
† Prostate, breast (nontriple-negative), human papillomavirus positive head and neck cancers

metastases, which is particularly important when SBRT may not be indicated or authorized by insurers. Our data suggest that keeping the D_{max} to the spinal cord and cauda equina ≤27 Gy (≤108% of the prescription dose) is achievable using nonconformal, 3D-CRT, or IMRT technique to minimize risk for myelopathy.

Palliative EBRT remains an important modality in the treatment of metastatic spine disease, and regimens including 8 Gy in 1 fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions have been recommended by the American Society for Radiation Oncology.[2] An international survey found that the majority of practicing radiation oncologists in the United States and Europe prescribe 20 Gy in 5 fractions or 30 Gy in 10 fractions.[19] The 5-fraction hypofractionated regimen is particularly convenient for the patient in that it can be easily

Table 4 Cox regression analysis for overall survival

	Univariate (overall survival)			Multivariable (overall survival)		
Variable	**Hazard ratio**	**95% CI**	***P* value**	**Hazard ratio**	**95% CI**	***P* value**
Age at diagnosis*	0.995	0.974-1.017	*P* = .675	0.989	0.967-1.011	*P* = .327
Sex						
Female	Reference					
Male	0.823	0.490-1.383	*P* = .462	0.819	0.482-1.392	*P* = .461
Race						
Non-black	Reference					
Black	1.037	0.471-2.286	*P* = .927	0.959	0.416-2.211	*P* = .921
KPS*	0.955	0.930-0.982	*P* < .001	0.956	0.929-0.984	*P* = .002
Radiosensitive tumor†						
No	Reference					
Yes	0.442	0.255-0.768	*P* = .004	0.469	0.269-0.819	*P* = .008

Abbreviations: CI = confidence interval; KPS = Karnofsky performance status.
* Analyzed as a continuous variable
† Prostate, breast (nontriple negative), human papillomavirus positive head and neck cancers

scheduled in between cycles of systemic therapy without need for interruption or delay. As such, it is a commonly used fractionation scheme for the palliative treatment of osseous metastasis.

Deliverable spine RT dose is mainly limited due to concern for radiation myelopathy of the spinal cord. The suggested point maximum dose (D_{max}) varies. In a multicenter phase II study on 40 patients with metastatic spinal cord compression treated to 25 Gy in 5 fractions using IMRT, Rades et al[3] kept the maximum spinal cord dose <101.5% of the prescription (equivalent total dose in 2-Gy fractions [EQD2] of 44.9 Gy using α:β ratio 2 Gy) and no cases of myelopathy were observed. A literature search limited to peer-reviewed spine SBRT papers published between 2005 and 2018 found that a spinal cord D_{max} of 25.3 Gy (EQD2 = 44.6 Gy) was estimated to be associated with a 1% to 5% risk of radiation myelopathy when SBRT is delivered in 5 fractions.[20] In contrast, the report of the American Association of Physicists in Medicine Task Group 101 suggests that a D_{max} of 30 Gy (EQD2 = 60.0 Gy) is associated with ≤5% risk for spinal cord myelopathy.[21] This D_{max} has been employed in Radiation Therapy Oncology Group 0813, which treated lung tumors with SBRT to 50 Gy in 5 fractions, without report of radiation myelopathy.[22] In our current series, there were no cases resulting in myelopathy. All but 2 patients had a spinal cord D_{max} ≤ 27.5 Gy, and the majority of patients with known cord dose (n = 37; 92.5%) had a D_{max} ≤ 27 Gy (≤108% of prescription dose; EQD2 of ≤50 Gy using α:β ratio 2 Gy).

Emerging data suggest that higher delivered biologically effective dose may be associated with more durable palliation from painful spine metastasis. In the Rades et al[3] phase II study on patients with metastatic spinal cord compression using IMRT, 25 Gy in 5 fractions was found to be superior compared with a historical control group treated to 20 Gy in 5 fractions using propensity score analysis with regards to local progression-free survival up to 6 months after IMRT (P = .03). In those receiving SBRT, preliminary phase III data from the Canadian Cancer Trials Group and Trans Tasman Radiation Oncology showed that more than twice as many patients treated with 24 Gy in 2 fractions had more durable and complete reduction in pain compared with those treated with nonconformal radiation to 20 Gy in 5 fractions.[12] After 3 months, 35% of patients receiving SBRT had a complete response or no remaining pain from their lesions compared with 14% of those receiving 20 Gy in 5 fractions (P < .001). SBRT spine metastasis treatment decision-making and planning are complex processes, and not all facilities are adequately equipped to treat patients with spine metastases with SBRT.[23,24] Additionally, insurance coverage policies vary between insurers, and insurance authorization of SBRT may be delayed or denied.[25] In our analysis of hypofractionated EBRT-treated patients using nonconformal technique, 3D-CRT, or IMRT to 25 Gy in 5 fractions, we observed durable and clinically meaningful pain relief in patients (median, 6 months; range, 1-33) and LC > 6 months (median, 7 months; range, 1-46).

To the authors' knowledge, this single-institutional retrospective analysis is the largest study to date investigating a prescription EBRT dose of 25 Gy in 5 fractions for the treatment of spine metastasis and the first to analyze those undergoing nonconformal or 3D-CRT technique, in addition to IMRT. The main limitations of our investigation are inherent to a single-institutional retrospective analysis, and our results need to be interpreted with caution due to the potential for selection bias. Additionally, this regimen is strictly palliative and, given the relatively low 1-year OS, may not apply to long-term survivors. However, our data suggest that treating spine metastases using dose-escalated hypofractionated EBRT to 25 Gy in 5 fractions is safe and effective as an alternative method of maximizing palliation, LC, and patient convenience in settings where SBRT may not be indicated or authorized or where SBRT resources are limited.

Supplementary materials

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.adro.2022.100906.

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