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Local failure and vertebral body fracture risk using multifraction stereotactic body radiation therapy for spine metastases

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Abstract

Purpose: Single-fraction radiation surgery for spine metastases is highly effective. However, a high rate (20-39%) of vertebral body fracture (VBF) has been associated with large, single-fraction doses. We report our experience using multifraction stereotactic body radiation therapy (SBRT).

Methods and materials: All patients who were treated with multifraction SBRT for spine metastases at our institution between 2009 and 2017 were retrospectively analyzed. SBRT was delivered in 2 to 5 fractions using the Cyberknife System (Accuray, Sunnyvale, CA). Patients were followed clinically and with magnetic resonance imaging every 3 to 6 months. Local control, complications (including VBF), and overall survival were evaluated. Patient, disease, and treatment variables were analyzed for a statistical association with outcomes.

Results: A total of 83 patients were treated to 98 spine lesions with a median follow-up of 7.6 months. Histologies included non-small cell lung cancer (NSCLC; 24%), renal cell carcinoma (RCC; 18%), and breast cancer (12%). Surgery or vertebroplasty were performed before SBRT in 21% of cases. Patients received a median SBRT dose of 24 Gy in a median of 3 fractions. Local control was 93% at 6 months and 84% at 1 year. Higher prescribed dose, higher biologic effective dose, higher minimum dose to 90% of the planning target volume, tumor histology, and smaller tumor volume predicted improved local control. The cumulative dose was 23 Gy versus 26 Gy for patients with and without failure ($P = .02$), higher biologic effective dose 39 Gy versus 46 Gy, ($P = .01$), and higher minimum dose to 90% of the planning target volume 23 Gy versus 26 Gy ($P = .03$). VBF occurred in 4.2% of all cases and 5.3% of those without surgery or vertebroplasty prior to SBRT. Only preexisting VBF predicted risk of post-SBRT VBF ($P < .01$).

Conclusions: Multifraction SBRT results in a high local control rate for metastatic spinal disease with a low VBF rate, which suggests a favorable therapeutic ratio compared with single-fraction SBRT.

Introduction

Spinal metastases are a common complication of cancer and can result in significant morbidity for patients.[1] Stereotactic body radiation therapy (SBRT) is a technique whereby high doses of radiation can be delivered to the vertebra while limiting doses to the spinal cord and/or cauda equina. This technique allows for dose escalation, which results in improved local disease control for patients with a favorable prognosis or those with relatively radiation resistant histologies.[2] SBRT also allows for the effective and safe reirradiation of previously treated spinal metastases.[3]

However, vertebral body fractures (VBF) have been reported as a common complication of SBRT and rates of VBF as high as 39% have been shown.[4] Analysis has demonstrated that high-dose, single-fraction regimens are associated with this complication.[5] Therefore, the delivery of SBRT in 2 to 5 fractions has been postulated to result in equivalent rates of local control (LC) but a lower rate of VBF. Thus, we report our institutional experience with multifraction SBRT for spine metastases in a cohort of patients who were treated with the Cyberknife System (Accuray, Sunnyvale, CA).

Methods and materials

After approval by the institutional review board (IRB#867840), a retrospective analysis was performed of patients who were treated with multifraction SBRT for spine metastases. All consecutive patients who were treated at our institution between 2009 and 2017 were reviewed. Patient demographics, disease characteristic, treatment parameters, and outcomes were analyzed. The Bilsky Epidural Spinal Cord Compression Scale was used to evaluate the extent of epidural disease before treatment and the Spinal Instability Neoplastic Score to determine mechanical instability prior to treatment.[6,7] The presence of lytic disease and the extent of vertebral body involvement were based on a review of pretreatment computed tomography (CT) and magnetic resonance imaging (MRI) scans.

Patients were evaluated by the multidisciplinary spine tumor team to determine optimal treatment. SBRT was generally selected for patients with spine metastases in or abutting a prior irradiated field, oligometastatic disease, expected long-term survival, or relatively radiation-resistant tumor histology. Oligometastatic disease was defined as disease that was limited to 1 to 3 metastatic sites. Surgery was generally considered for patients with symptomatic cord compression, high-grade radiographic cord impingement (Bilsky grade 2 and 3), or mechanical instability. Biological effective dose (BED) was used to compare various dose-fractionation schedules. BED was calculated using the linear-quadratic formula utilizing an α/β ratio of 10 for tumor and 3 for normal tissues.[8]

SBRT was performed using the Cyberknife System. Patients underwent a CT simulation in the supine position. High-resolution MRI using T1- and T2-weighted sequences with gadolinium contrast were fused to delineate target volumes and organs at risk. If the spinal cord could not be visualized on MRI due to artifacts from hardware, a CT myelogram was performed to accurately delineate the spinal cord. The gross tumor volume, clinical tumor volume, and primary tumor volume (PTV) were defined in accordance with published consensus guidelines.[9,10] Treatment planning was performed using Multiplan (Accuray, Sunnyvale, CA) to optimize PTV coverage and conformality while respecting spinal cord tolerance. The Ray-Tracing algorithm was used for planning. Select lesions in the thoracic spine underwent Monte Carlo algorithm verification and/or reoptimization because the Ray-Tracing algorithm for beams that traverse pulmonary tissue may be less accurate.[11,12]

The maximum dose to the spinal cord was restricted to 22 Gy in 3 fractions and 30 Gy in 5 fractions for de novo treatments. Spinal cord dose constraints were individualized in the retreatment setting and take into account prior radiation cord dose and time interval since the prior treatment. Plans were also optimized to keep the prescription isodose line ≥80% when achievable to minimize hot spots within the treated vertebral body. Treatment dose and fractionation was selected for each case on the basis of tumor volume, prior radiation dose, and spinal cord tolerance. Treatment was delivered utilizing Xsight spine image tracking.

Patients underwent a clinical evaluation and MRI every 3 months for 1 year and then every 6 months thereafter. Actuarial LC and overall survival (OS) were analyzed using the Kaplan-Meier method.[13] Local failure was defined as a progressively enhancing lesion or soft tissue mass at the treated vertebral level(s) or pathology that demonstrated malignancy. SBRT-related complications were evaluated including esophageal toxicity, radiculopathy, myelopathy, and VBF. VBF was defined as a new or worsened compression fracture within the treatment volume.

The statistical analysis was performed using STATA/SE 14.2. Actuarial local failure and survival were calculated using the Kaplan-Meier method. Local failure and VBF analysis were performed using Student's t test for all numerical variables and analysis of variance for categorical variables (eg, tumor histology and Bilsky grade). The Kaplan-Meier and Log-rank methods were used for survival analyses with relative risks calculated using the Mantel-Haenszel method. A two-tailed P-value of $< .05$ was considered statistically significant.

Results

A total of 83 patients were treated to 98 spine lesions. Patient demographics are shown in Table 1. The median patient age was 64 years. The most common primary tumor histologies were NSCLC (24%), RCC (18%), and breast cancer (12%). Tumor location was thoracic in 52%, lumbar in 30%, cervical in 15%, and sacral in 4% of cases. Systemic disease was controlled in 35%, progressive in 60%, and new presentation/not yet treated in 6% of cases. Oligometastatic disease accounted for 35% of patients and 59% had prior radiation therapy.

Of the 98 treated lesions, 61% had epidural extension. The Bilsky grade was 1c in 10%, 2 in 6%, and 3 in 5%. Lytic tumors composed 44% of cases. The vertebral body that was involved was extensive (>40%) in 67% of lesions and any degree of preexisting VBF was present in 30%. Mechanical instability was present in 5%. Disease that was limited to only the posterior elements was present in 5% of lesions.

SBRT was delivered in a median prescription dose of 24 Gy (Range, 14-44 Gy) in 3 fractions (Range, 2-5 fractions). The most common schedules used were 24 Gy in 3 fractions (25%), 27 Gy in 3 fractions (21%), and 30 Gy in 5 fractions (11%). This corresponds to a median higher biologic effective dose (BED_{10}) of 43 Gy (Range, 23-72 Gy). The mean PTV was 46 cc (Range, 0.8-271 cc). Surgical resection and/or stabilization prior to SBRT was performed in 18% of patients and vertebroplasty prior to SBRT in 5% of patients. The median time between surgery and SBRT was 1.7 months (Range, 0.8-4.4 months).

The median follow-up time after SBRT was 7.6 months (Range, 0.2-82 months). Fifteen patients developed local failure that resulted in an actuarial LC rate of 93% at 6 months and 84% at 1 year (Fig 1). On univariate analysis, smaller tumor volume, tumor histology, higher cumulative prescribed dose, higher cumulative BED_{10} of the prescription dose, and higher minimum dose covering 90% of the PTV (D90%) were statistically associated with improved overall LC (Table 2).

The average volume for tumors with local failure and those without failure was 87 cc and 58 cc, respectively ($P = .04$). At the last follow-up, breast cancer and prostate cancer cases had no local failure, NSCLC had an overall

Table 1	Patient and disease characteristics
Characteristic	
Age (median, range)	64 years (8-83 years)
Sex	57% male
	43% female
Pretreatment ECOG PS (mean, range)	1.0 (0-4)
Pretreatment pain CTCAE v4.0 (mean, range)	1.8 (0-3)
Tumor locations	
Thoracic	54%
Lumbar	31%
Cervical	16%
Sacral	4%
Primary tumor histology	
Non-small cell lung cancer	24%
Renal cell carcinoma	18%
Breast cancer	12%
Thyroid	7%
Prostate cancer	6%
Colorectal cancer	6%
Sarcoma	4%
Hepatocellular carcinoma	3%
Other	18%
Planning target volume (median, range)	46.7 cc (0.8-270.9 cc)
Prescribed isodose lines (median, range)	80% (58%-89%)
Lytic tumors	44%
>40% vertebral body involvement	66%
Preexisting VBF	30%
Mechanical instability	5%
Pre-SBRT surgery	22%
Pre-SBRT vertebroplasty	5%
Bilsky grade	
0	39%
1a	9%
1b	21%
1c	10%
2	6%
3	5%

CTCAE v4.0, Common Terminology Criteria for Adverse Events version 4.0; ECOG PS, Eastern Cooperative Oncology Group performance status; SBRT, stereotactic body radiation therapy; VBF, vertebral body fracture.

failure rate of 9%, and RCC had a failure rate of 22% ($P = .02$). The cumulative prescribed dose was 23 Gy versus 26 Gy for tumors with and without failure ($P = .02$) and the BED_{10} was 39 Gy and 46 Gy, respectively ($P = .01$). D90% of the PTV was 23 Gy for tumors with failure versus 26 Gy for tumors without failure ($P = .03$). Higher Bilsky grade also trended but did not reach significance for increased local failure ($P = .09$). The rate of local disease control was not associated with previous radiation therapy or surgical resection before SBRT.

In general, treatment was well tolerated with few complications. One patient had transient radiculopathy and no patient developed myelopathy. There was no late esophageal toxicity. After SBRT, VBF was uncommon and occurred
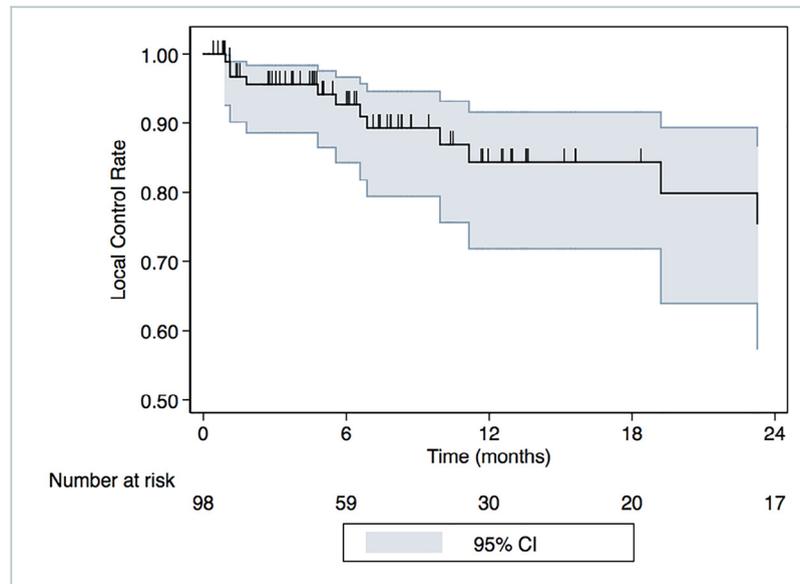
Figure 1   Actuarial local control. Kaplan-Meier estimate of the percentage of tumors with local control over time.

in only 4.2% of all cases and 5.3% of those without surgery or vertebroplasty prior to SBRT. The median time to VBF after SBRT was 5.8 months. VBF was only associated with preexisting VBF (Table 3). The rate of VBF was 10.7% for

lesions with and 0% for lesions without preexisting VBF ($P < .01$).

Actuarial survival at 1 year was 46% (Fig 2). Prolonged survival was associated with better baseline performance status (relative risk [RR]: 2.06; $P < .01$), controlled systemic disease (RR: 1.68; $P = .02$), and oligometastatic disease (RR: 1.95; $P = .01$; Table 4). Survival also varied by tumor histologies and NSCLC had the least favorable survival rate ($P = .04$). Local failure did not predict for worsened OS.

Discussion

SBRT delivered in a single fraction has been shown to be highly effective to treat spine metastases. However, high rates of VBF have been associated with high, single-dose treatments. Most patients with spinal metastases will succumb to their cancer; therefore, quality of life and minimizing treatment toxicity are key priorities of therapy. Multifraction SBRT may potentially have an improved therapeutic ratio with a high rate of local disease control but a lower rate of VBF.

Table 2   Univariate analysis of local failure

	P-value
Tumor histology	**.02**
Tumor volume	**.04**
Cumulative dose	**.02**
Cumulative BED$_{10}$	**.02**
Minimum dose to 100% PTV	.45
Minimum dose to 95% PTV	.08
Minimum dose to 90% PTV	**.03**
Number of fractions	.27
Bilsky grade	.09
Pre-SBRT surgery	.82
Prior radiation therapy	.70

BED$_{10}$, biologically effective dose, $\alpha/\beta = 10$; PTV, primary tumor volume; SBRT, stereotactic body radiation therapy.

Table 3   Univariate analysis of vertebral body fracture

	P-value
Lytic lesion	.42
>40% vertebral body involvement	.11
Preexisting VBF	**< .01**
Tumor volume	.08
Cumulative dose	.34
Cumulative BED$_3$	.30
Number of fractions	.42
Prior radiation	.63

BED$_3$, biologically effective dose, $\alpha/\beta = 3$; VBF, vertebral body fracture.

Table 4   Univariate analysis of survival

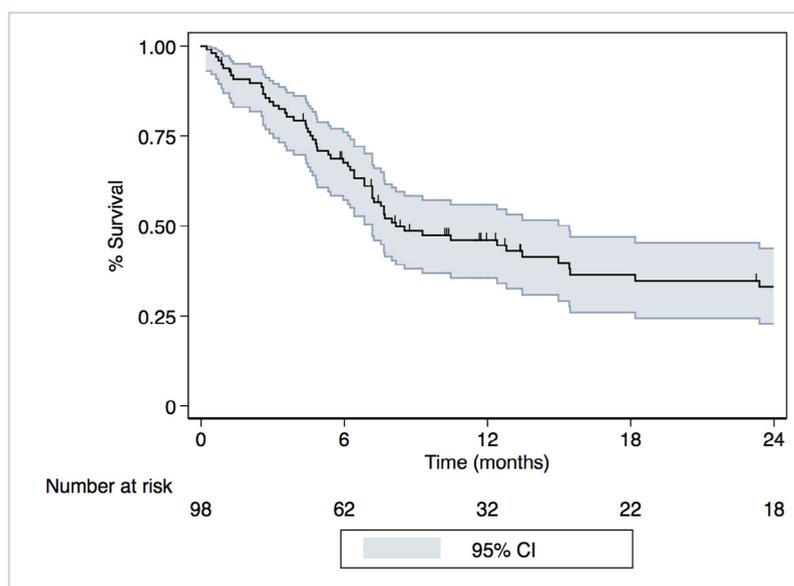|	P-value
Performance status	**< .01**
Extent of systemic disease (Oligometastatic vs. Extensive)	**.01**
Uncontrolled systemic disease	**.02**
Tumor histology	**.04**
Local failure	.74

Figure 2   Survival. Kaplan-Meier estimate for survival over time.

The present series supports this accretion. The LC rate was 84% at 1 year, which is comparable to other series that cumulatively showed LC rates of 85% to 90% including those using single fraction regimens.[2] Rose et al. reported a LC rate of 89% in 71 spine lesions that were treated to a dose of 18 Gy to 24 Gy in a single fraction.[4] Yamada et al. reported 103 spine lesions that were treated with a median dose of 24 Gy in a single fraction.[14] At a median follow-up of 15 months, the actuarial rate of LC was 90%. Sellin et al. reported on 40 spine renal cell metastases that were treated with a median dose of 24 Gy in a single fraction.[15] The crude rate of LC was 57% at a median follow-up of 16 months. Garg et al. reported results of a prospective phase 1/2 study of single fraction SBRT using 16 Gy to 24 Gy in 63 lesions.[16] The actuarial rate of LC at 18 months was 88%. Chang et al. showed a 1-year LC rate of 89% in 131 de novo spine lesions and 81% in 54 previously treated lesions.[17] The median dose was 20 Gy in 1 fraction. Lastly, Staehler et al. reported on 105 renal cell carcinoma lesions that were treated to a median dose of 20 Gy in 1 fraction.[18] The 1-year actuarial LC was 94%. Systematic reviews have been performed by Huo et al. and Redmond et al., which concluded that there is currently no evidence to suggest that LC is superior with either single fraction or multifraction SBRT.[19,20]

In the present analysis, local failures were associated lower cumulative dose, lower prescription dose (BED$_{10}$), and lower tumor D90%. Therefore, not only is the prescription dose important to achieve LC but minimizing underdosing at the tumor-spinal cord interface is critical. This is consistent with patterns of failure analysis that have shown that recurrence in the epidural space at the interface of the spinal cord is one of the primary mechanisms of failure after spine SBRT.[21] Tumors that abut the spinal cord are often underdosed to meet dose constraints. The surgical removal of epidural tumors has been proposed as a means to increase the spacing between the tumor and spinal cord.[22] This approach can improve the minimum radiation dose to the tumor and thus decrease the rate of local failure.

RCC and other relatively radiation-resistant histologies have higher rates of local failure that employ conventionally fractionated radiation. However, these tumors respond well to large dose-per-fraction treatments.[23,24] Actuarial LC for RCC in this series (81% at 1 year) was higher compared with conventional fractionation but significantly worse compared with NSCLC, breast, and prostate primaries: 94%, 100%, and 100%, respectively, at 1 year. Dose escalation to single fraction doses of 20 Gy to 24 Gy has been proposed to improve LC for RCC. Data that support this approach have shown 1-year LC rates in excess of 90%.[18,25] This approach achieves a BED$_{10}$ of 60 Gy to 82 Gy, which is substantially higher than the median BED$_{10}$ of 43 Gy that is employed in this study. Higher doses that use a fractionated approach such as 30 Gy to 36 Gy in 3 fractions would result in a similar BED$_{10}$ and may result in a higher LC rate for RCC.

Across studies, VBF after SBRT has been reported with an incidence of 11% to 39% (Table 5).[4,6,26,27] This is substantially higher than the reported rate of <5% after conventional external beam irradiation.[28] Rose et al. reported on a series of 62 patients who were treated to 71 spinal sites using a single-fraction SBRT regimen of 18 Gy to 24 Gy[4] as well as a VBF rate of 39%. The analysis showed that VBF was associated with lytic disease, spinal location at T10 or lower, and percent of the vertebral body involved with the disease. The radiation dose that was used over the narrow range was not associated with VBF.

Table 5   VBF series

Study	Number of cases	Fractionation	Median dose (Range)	VBF rate
Rose et al.[4]	71	Single-fraction	24 Gy (18-24 Gy)	39%
Boehling et al.[25]	123	Mixed	18 Gy	20%
Cunha et al.[26]	167	Mixed	Not reported (8-35 Gy)	11%
Sahgal et al.[5]	410	Mixed	≥24 Gy	39%
			20-23 Gy	19%
			≤19 Gy	10%
Current series	98	Multifraction	24 Gy (14-44 Gy)	4%

VBF, vertebral body fracture.

Boehling et al. reported on 93 patients who were treated to 123 spinal lesions using both single- and multifraction regimens.[26] One-third of patients were treated using a single-fraction regimen of 18 Gy. An overall VBF rate of 20% was reported and VBF was associated with preexisting VBF, lytic disease, and patient age >55 years.

Cunha et al. reported on 167 lesions that were treated with SBRT and demonstrated a VBF rate of 11%.[27] Both single- and multifraction SBRT was used. VBF was associated with lytic tumors, kyphosis, hepatocellular carcinoma, and lung histologies and a dose-per-fraction of more than 20 Gy. Sahgal et al. performed a multi-institutional analysis of data from the University of Toronto, MD Anderson Cancer Center, and Cleveland Clinic and reported on a total of 252 patients who were treated to 410 spinal lesions using either single- or multifraction regimens.[5] Single-fraction SBRT was used in 51% of cases. An overall VBF rate of 14% was reported and dose-per-fraction, lytic disease, preexisting VBF, and spinal deformity were associated with VBF. The rate of VBF was 39% for ≥24 Gy per fraction, 19% for 20 Gy to 23 Gy per fraction, and 10% for ≤19 Gy per fraction. Our analysis shows a favorable rate of VBF of only 4.2% using solely a multifraction SBRT approach.

Although the mechanism of VBF is not fully understood and likely multifactorial in nature, pathologic analyses have demonstrated that osteoradionecrosis plays an important role.[29] Osteoradionecrosis of the bone is not only dependent on the total radiation dose but the dose-per-fraction.[30-32] Thus, even a small degree of fractionation (2-5 fractions) can result in a decrease in risk of osteoradionecrosis and thus a decrease in the rate of VBF. The data presented by Sahgal et al. and the current analysis support this hypothesis.[5] An additional factor that contributes to VBF may be the inhomogeneity of the delivered dose (ie, hot spots within the vertebral body). Although treatment using the Cyberknife platform often results in an inhomogeneous dose distribution within the target volume, our planning optimization protocol limited the overall hot spot by generally prescribing to ≥ 80% of the maximum dose.

OS in this analysis was dictated by systemic disease status and not local treatment. Patients with an extensive systemic disease burden or those with progressive systemic disease had a worse OS but patients who developed local failure did not experience a detriment in survival. Therefore, systemic disease status is important to assess to most appropriately select patients who are likely to benefit from aggressive local therapy such as SBRT.

Our analysis demonstrates the feasibility of using multifraction SBRT to effectively and safely treat spinal metastases in a fairly large and diverse cohort of patients. Moreover, our results on VBF are clinically relevant given the frequency with which this complication can occur. However, this study does have several limitations. This was a retrospective cohort analysis and thus subject to the well-known limitations and potential biases of such analyses. This study had a relatively small number of cases with radiation resistant histologies including RCC (18 cases) and melanoma (2 cases), which limited the generalizability of our results around these histologies.

The Ray-Tracing algorithm used for treatment planning can be less accurate in determining PTV coverage and spinal cord dose. In this series, all patients did not undergo Monte Carlo algorithm verification. Although this is unlikely to affect VBF rate, LC and risk of myelopathy could be impacted. Lastly, the high mortality rate of patients with metastatic disease is a competing risk and limits available follow-up. Thus, the true rates of local failure and VBF may be underestimated.

Conclusions

Multifraction SBRT for spine metastases results in a high rate of local disease control. However, the rate of VBF is low compared with the use of single-fraction treatment regimens, which suggests a more favorable therapeutic ratio. Further studies are needed to determine the optimal dose and fractionation schedule.

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