Original Article

Adjacent level fracture incidence in single fraction high dose spinal radiosurgery

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Background: Vertebral body compression fracture (VCF) is a complication following spinal stereotactic radiosurgery (SRS). However, the incidence of VCF in vertebrae adjacent to the level of SRS is unknown. This study aimed to determine the incidence of adjacent level VCF (adjVCF) following spinal SRS.

Methods: A retrospective review of 239 lesions treated with single-fraction SRS from 2011–2014 was performed. Clinical and pathologic factors were collected including evaluation of VCFs in adjacent levels to SRS site. In patients with adjVCFs, dose-volume histograms for adjacent-level endplates were calculated. Cox regression analysis was performed to determine any association among clinical factors and adjVCF occurrence.

Results: Median follow-up was 14.7 months. Twenty-six adjVCFs occurred (10.8%). Of the adjVCFs, 19 had metastases following SRS, and seven did not (2.9% of total treatments). Median time to fracture post-SRS was 13.5 months. In adjVCFs, median of the mean dose to adjacent level fractured endplate was 23.3 Gy, and median of the mean dose of sixteen non-fractured endplates immediately adjacent to the SRS site was 19.1 Gy. Age, gender, and histology were not associated with adjVCF.

Conclusions: AdjVCF after spinal SRS occurs at a rate of 2.9%, when excluding metastatic sites of disease. Adjacent level endplates should be investigated as an organ at risk during SRS planning.

Keywords: Stereotactic radiosurgery; spine complications; compression fracture; spine metastases; oncology

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Introduction

Spinal metastases occur in approximately 20,000 American patients each year (1,2). With advances in chemotherapy, biologic therapy, immunotherapy, surgical techniques and radiation treatment, patients are living longer with better quality of life, and the number of patients experiencing spinal metastatic disease is anticipated to grow further. Spine stereotactic radiosurgery (SRS) has emerged as a method to provide local control with minimal toxicity or interruption in systemic therapy. SRS provides highly conformal radiation to tumor volumes with steep radiation gradients to avoid injury to local structures such as the spinal cord and esophagus. Treatment of spinal metastases is palliative, but safe and excellent durable local disease

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control has been achieved with local control rates of 70–90% or higher at 1 year or longer with the use of new treatment paradigms (3-7). Despite impressive local control, SRS has complications, the most studied of which is vertebral compression fractures (VCFs).

VCFs following radiosurgery at the irradiated level have been reported at incidences ranging from 6–39% (8-14). The vertebral body level, amount of vertebral body replaced with tumor (10), patient age, pre-existing fracture (8) and radiation dose (9,11,14) have all been reported as risk factors for VCF. Thus far, studies have evaluated the incidence and risk factors for VCF at the level of vertebral tumor invasion and not for VCF occurring in vertebral bodies adjacent to the target treatment level. However, VCFs above and below the irradiated level have occurred. This paper represents the first study to our knowledge evaluating adjacent level VCFs in patients undergoing spinal SRS.

Methods

IRB approval was obtained. We identified 206 patients who underwent single fraction radiosurgery in a single dose of 24 Gy to the mobile spine from 2011 to 2014 from a prospective database. Patients with sacral SRS were excluded. Patients undergoing multiple single-fraction SRS treatments were included so long as therapy was directed at non-adjacent vertebral levels. A total of 239 treatments met inclusion criteria. All patients had a histologically confirmed diagnosis of malignancy. Patients underwent simulation for radiation planning with CT images with 2-mm slice thickness. A myelogram or magnetic resonance image fusion was utilized to delineate spinal cord anatomy and tumor volumes. Patients were immobilized using a patient-customized cradle for both SRS simulation and therapy (6). Treatment planning was performed with either in-house software or Eclipse (Varian Medical Systems) with inverse treatment planning. The gross tumor volume (GTV) was outlined according to CT and MRI images after review by the treating radiation oncologist and neurosurgeon. The clinical target volume (CTV) encompassed GTV as well as adjacent bone according to Cox *et al.* (15). The planning target volume (PTV) was a 2 mm expansion from CTV, excluding thecal sac and also esophagus if not abutting GTV. The prescribed dose was 24 Gy to the PTV in a single fraction, and dose was prescribed to the 100% isodose line as allowed by spinal cord dose constraints. Dose constraints were defined per the standard at our institution. The spinal cord, defined on a simulation CT myelogram, was constrained to a maximum dose of 14 Gy to a single voxel, or 12 Gy if circumferential PTV or prior radiation treatment. The cauda equina and brainstem were limited to maximum dose of 18 Gy. The esophagus was constrained to 14 Gy to 2.5 mL of esophagus. Bowel was constrained to allow no more than 5 mL to receive more than 16 Gy.

Treatment was delivered with linear accelerators using 6-mv and/or 15-mv photons. Cone-beam CTs were utilized to verify patient positioning prior to treatment. A representative treatment plan is shown in *Figure 1*.

A retrospective chart review was carried out collecting patient and tumor characteristics and follow-up information. The primary outcome was development of an adjacent level VCF (which included endplate fractures and collapse deformities). Each patient had at least one documented imaging methodology for review. For each patient included, all pre-SRS treatment and post-SRS imaging (CT, MRI, plain films) radiology reports were initially screened for mention of adjacent level fractures or similar indication. Vertebral body fractures were defined as loss of vertebral body height or endplate infarctions, adjacent to the level of prior radiation. Positive findings were documented, and all associated images underwent subsequent viewing to confirm fracture state. After further viewing, images that remained under question underwent further review by a single neuroradiologist for final diagnosis. Cox regression univariate analysis modeling was performed with IBM SPSS software to determine any associations between clinical factors and adjacent level VCFs.

The fractured endplates of all pure adjacent segment VCFs were contoured as well as sixteen non-fractured endplates, and dose volume histograms were calculated. Mean and maximum doses in Gy were collected.

Results

Patient and tumor characteristics are summarized in *Table 1*. There were 206 patients treated to a total of 239 treatment sites with SRS to the mobile spine, and all patients were treated to dose 24 Gy in 1 fraction. The median patient age was 60 years (range, 20–84 years), and 18.6% patients were greater than age 70. The majority of patients were male (66.5%). A total of 198 patients (96.1%) underwent SRS for metastatic disease to the spine, while 8 patients (3.9%) were treated for primary spinal tumors. The most common tumor histology was carcinoma (78%), as compared to sarcoma or other. The majority of tumors treated were located in the thoracic spine (49.0%) or lumbar spine

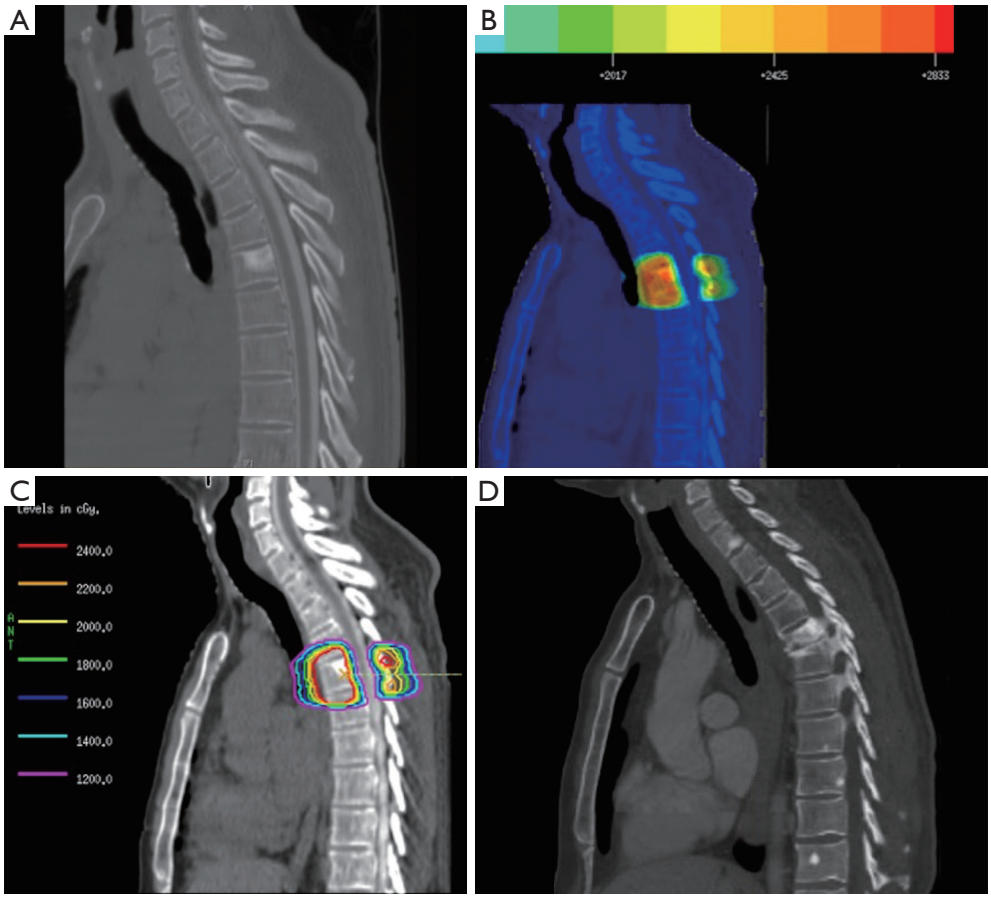

Figure 1 (A) Pre-SRS sagittal CT of the spine demonstrating metastasis at T5; (B) SRS plan demonstrating dose to each area in dose color wash and (C) isodose lines; (D) post SRS adjacent level fracture at the adjacent endplate (superior endplate) of T6. SRS, stereotactic radiosurgery.

(42.3%), followed by cervical spine (8.8%). The median follow-up was 14.4 months (range, 0–64 months) from date of SRS. Eighteen patients, comprising 20 treated lesions, had no post-SRS imaging for review.

There were 26 incidents (10.8% of treatments) of adjacent level VCFs observed in 26 patients. Five cases had both instrumentation and metastatic disease present at the level of VCF. Fourteen cases occurred at sites harboring metastatic disease without hardware present. There were seven (2.9% of all treatments) adjacent level VCFs without hardware or metastases present at the level of VCF. Five of these seven cases had compression fracture of the irradiated index level as well. The median time to fracture post-SRS was 13.5 months (range, 2.1–35.1 months) for all adjacent level VCFs. Asymptomatic fractures were monitored with follow-up imaging. Symptomatic patients were treated using pain medications and, if the pain did not resolve, underwent cement stabilization of the fracture.

In a subset analysis of the seven adjacent level VCFs without metastases or hardware, the median time to adjacent level VCF was the same at 13.5 months post-SRS (range, 5–25 months). There were two lumbar, three thoracic and two cervical pure adjacent VCFs. There were three mobile spine, two junctional, and two semi-rigid locations according to spinal instability neoplastic score (SINS) criteria (16). Five of the seven (71%) pure adjacent level VCFs were associated with collapse of the irradiated vertebral body, three occurring simultaneously and two afterward. All pure adjacent level VCFs occurred after SRS. Four of the adjacent level fractures occurred at the endplate adjacent to the irradiated vertebral body, and three adjacent level fractures occurred at the opposite endplate. The mean of the mean dose to adjacent level fractured endplate immediately adjacent to the irradiated vertebral body was

Table 1 Patient and tumor characteristics

Characteristics	N (%)
Patient	206
Patient age, median (range), years	60 [20–84]
Patient age, years	
>70	38 (18.4)
≤70	168 (81.6)
Patient sex	
Male	137 (66.5)
Female	69 (33.5)
Tumor	239
Tumor location	
Cervical spine	21 (8.8)
Thoracic spine	117 (49.0)
Lumbar spine	101 (42.3)
Primary tumor site	
Renal	57 (23.8)
Lung	42 (17.6)
Sarcoma	31 (12.9)
Prostate	22 (9.2)
Colorectal	21 (8.8)
Thyroid	14 (5.9)
Melanoma	12 (5.0)
Breast	9 (3.8)
Gynecological	7 (2.9)
Chordoma	4 (1.7)
Hepatobiliary	4 (1.7)
Unknown	5 (2.1)
Other[†]	11 (4.6)

[†], other (bladder, head and neck, salivary gland, pancreas, adrenal).

22.5 Gy, and the median mean dose was 23.3 Gy. The mean of the mean dose of sixteen non-fractured endplates immediately adjacent to the SRS site was 18.8 Gy with a median mean dose of 19.1 Gy.

Cox regression analysis was performed for the seven adjacent level fractures without hardware or metastatic disease with a univariate model for sex, age, and tumor histology for VCF. No statistically significant differences were noted, as shown in *Table 2*.

This was again performed for the subset of four patients who had fractures at endplates adjacent to the irradiated vertebral body and is shown in *Table 3*.

A cumulative incidence curve for the development of adjacent level VCF is shown in *Figure 2*.

Conclusions

To our knowledge, these data represent the first study evaluating adjacent level VCFs in spine SRS. Given that spine SRS is palliative in nature, avoiding complications is desirable. The number of patients receiving spinal SRS will continue to increase and therefore knowledge of its complications are important for both patients and physicians. Previous studies have demonstrated a radiation dose dependent risk of fracture in the axial skeleton in both traditionally fractionated and hypofractionated treatment schedules (17,18). While the intent of radiosurgery is to treat the tumor volume along with tissues at risk of microscopic tumor invasion, adjacent organs at risk (OAR) receive subtherapeutic radiation doses. While VCF at target site has been studied, presence of fracture at adjacent-level endplates has not been reported. As demonstrated in *Figure 1*, adjacent level endplates can receive doses at or near 20 Gy. Interestingly, in this study, the average radiation to the fractured adjacent level endplate was 23.3 Gy. It should be noted that conformality of SRS dose is more precise in the axial plane than the sagittal plane, and that some excess dose may be delivered to the adjacent

Table 2 Univariate analysis of clinical factors and association with adjacent level VCFs using Cox linear regression model (7 patients)

Clinical variable	Hazard ratio	95% confidence interval	P value
Age (continuous)	0.992	0.993–1.054	0.789
Sex (female *vs.* male)	0.302	0.036–2.509	0.268
Histology (carcinoma *vs.* other)	0.484	0.058–4.020	0.501

VCF, vertebral body compression fracture.

Table 3 Univariate analysis of clinical factors and association with adjacent level VCFs which fractured at the endplate adjacent to the irradiated vertebral body using Cox linear regression model (4 patients)

Clinical variable	Hazard ratio	95% confidence interval	P value
Age (continuous)	1.015	0.933–1.105	0.726
Sex (female *vs.* male)	0.627	0.065–6.036	0.686
Histology (carcinoma *vs.* other)	1.010	0.105–9.717	0.993

VCF, vertebral body compression fracture.

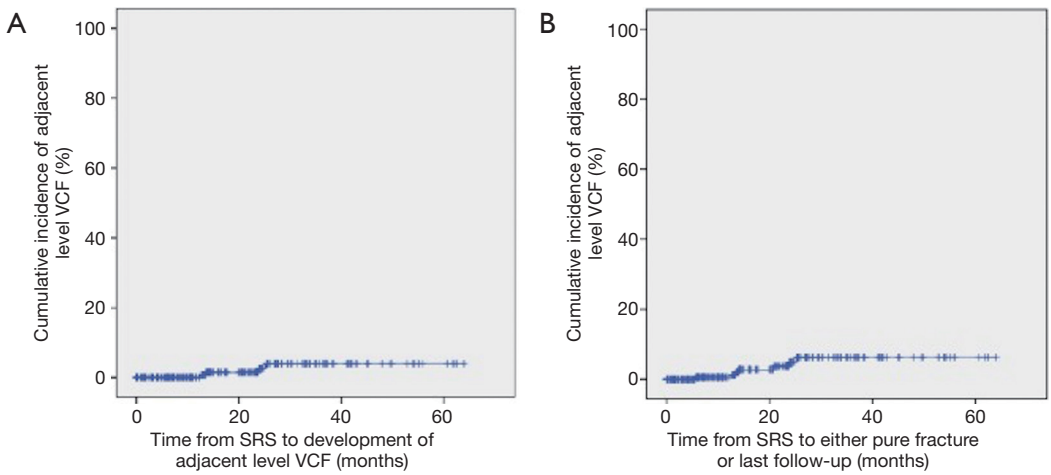

Figure 2 Cumulative incidence curve for the development of adjacent level VCF following single fraction SRS to the mobile spine. (A) VCFs occurring at endplate adjacent to irradiated vertebral body (four patients) and (B) includes all adjacent level fractures without hardware or metastatic involvement (seven patients). VCF, vertebral body fracture; SRS, stereotactic radiosurgery.

endplates as part of this error arising from uncertainty in patient positioning, machine calibration, imaging, etc. (19). Endplates of adjacent levels may experience higher doses than planned, contributing to adjacent level collapse. In our study, multilevel vertebral body compression fractures were present in 71.4% of the adjacent level fractures indicating some poorly understood disruption of local biomechanics may be implicated in adjacent level fractures as well.

This paper serves to define the incidence of adjacent level fractures in those undergoing spinal SRS and raises the question of whether adjacent level endplates should be considered an OAR during SRS planning, similar to the spinal cord, esophagus, or kidneys.

In conclusion, we report that adjacent level VCFs are infrequent in the setting of single fraction SRS to the mobile spine, occurring in 2.9% of treatments. Understanding the incidence is important for care in patients undergoing spinal SRS, as use of SRS to treat spinal pathologies will continue to increase in number. Further studies are needed to validate these results and determine risk factors to adjacent level VCF in an effort to avoid or minimize this complication. Given our findings, further investigation is warranted as to whether adjacent level endplates should be considered an organ at risk during SRS planning.

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Footnote

Conflicts of Interest: Dr. Yamada is a consultant for Varian Medical Systems and on the Speakers' Bureau of the Institute for Medical Education. Dr. Laufer receives consulting fees from DePuy/Synthes, SpineWave and Globus. Dr. Bilsky receives consulting fees from DePuy/Synthes, Globus and BrainLab. The other authors have no

conflicts of interest to declare.

Ethical Statement: The study was approved by IRB ethics committee (No. 16-1434).

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