Jour. of Radiosurgery and SBRT, Vol. 5, pp. 99-105
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Clinical Investigation

Pain flare after stereotactic radiosurgery for spine metastases

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(Received: July 24, 2017; Accepted: October 19, 2017)

ABSTRACT

Purpose: Understanding of pain flare (PF) following spine stereotactic radiosurgery (sSRS) is lacking. This study sought to determine the incidence and risk factors associated with PF following single fraction sSRS.

Materials/methods: An IRB-approved database was compiled to include patients who underwent sSRS. Patient and disease characteristics as well as treatment and dosimetric details were collected retrospectively. Pain relief post-sSRS was prospectively collected using the Brief Pain Inventory (BPI). These factors were correlated to the development of PF (defined as an increase in pain within 7 days of treatment which resolved with steroids). Survival was calculated using Kaplan-Meier analysis and logistic regression was utilized to evaluate the association between the clinical and treatment factors and occurrence of PF.

Results: A total of 348 patients with 507 treatments were included. Median age and prescription dose were 59 years and 15 Gy (range: 7-18), respectively, and 62% of patients were male. Renal cell carcinoma (24%), lung cancer (14%), and breast cancer (11%) were the most common histologies, and 74% had epidural disease and 43% had thecal sac compression. The most common location of metastases was in the cervical/thoracic spine (59%), followed by lumbar spine (32%), and sacral spine (9%). Most common reason for treatment was pain (73%), followed by pain and neurological deficit (13%), asymptomatic disease (10%), and neurologic deficit only (3%). Median time to pain relief was 1.8 months. Median overall survival, time to radiographic failure, and time to pain progression were 13.6 months, 26.5 months, and 56.6 months, respectively. Only 14.4% of treatments resulted in the development of PF. Univariate analysis showed that higher Karnofsky performance score (KPS) (OR=1.03, p=0.03), female gender (OR=1.80, p=0.02), higher prescription dose (OR=1.30, p=0.008), and tumor location of

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cervical/thoracic spine vs lumbar spine (OR=1.81, p=0.047) were predictors for the development of PF. On multivariate analysis, higher consult KPS (OR=1.03, p=0.04), female gender (OR=1.93, p=0.01), higher prescription dose (OR=1.27, p=0.02), and tumor location of cervical/thoracic spine vs lumbar spine (OR=1.81, p=0.05) remained predictors of PF. No other dosimetric parameters were associated with the development of PF.

Conclusion: PF is an infrequent complication of sSRS. Predictors for the development of PF include higher consult KPS, female gender, higher prescription dose, and cervical/thoracic tumor location. Dose to the spinal cord was not a predictor of PF. Since a minority (14.4%) of treatments result in PF, we do not routinely utilize prophylactic steroid treatment; however, prophylactic steroids may be considered in female patients with cervical/thoracic metastases receiving higher dose sSRS.

Keywords: pain flare, spine radiosurgery, spine metastasis

INTRODUCTION

The spinal column is the most common location for bony metastasis in cancer patients, and up to 40% of all cancer patients will develop spine metastasis[3,10]. In the last few years, spine stereotactic radiosurgery (sSRS) has increasingly been used for the treatment of spinal metastasis[2,12]. sSRS allows high doses of radiation to be delivered to a target volume, providing a higher biologically equivalent dose (BED) while minimizing the volume of normal tissue that is in the irradiated field to minimize both acute and late toxicity[16].

Both conventionally fractionated radiotherapy and sSRS have been associated with the development of pain flare, i.e. transient increase in pain that can occur both during and shortly after the completion of radiotherapy. Conventionally fractionated radiotherapy has been associated with 2-40% incidence of pain flare[5,7,11]. Given the higher dose per fraction delivered with sSRS, there has been concern that the risk of development of acute pain flare is higher than that from conventionally fractionated radiotherapy. However, there have been few studies evaluating the incidence and risk factors of pain flare after sSRS. While one prospective trial reported the incidence to be up to 68%, a review of phase I/II sSRS trials showed the incidence much lower at only 23% with a reduced risk if multiple fractions were used for treatment[4,13]. The goal of our study was to report our institutional experience for the development of pain flare following single fraction sSRS and to determine the associated risk factors.

METHODS AND MATERIALS

We reviewed our institutional IRB-approved database of patients who underwent a single fraction sSRS who had a histologic diagnosis of cancer and radiographic evidence of spine metastasis. Our indications for sSRS included symptoms, such as pain or neurological deficits, or epidural extension of tumor. Patients presenting with rapidly progressive neurological compromise were not treated with sSRS, however, patients with spinal cord compression who were not surgical candidates were included. The presence of paraspinal disease, defined as any disease in the soft tissues outside of the vertebral body or bony posterior elements, was not a contraindication to treatment. sSRS was used as both primary treatment and as salvage treatment after conventional radiotherapy.

Our treatment technique and setup has been previously described[1,2]. Briefly, all patients underwent a CT simulation in the supine position for planning purposes. Patients who have a metastatic lesion at T4 or above are immobilized using a 5-point thermoplastic head mask, and those individuals with lesions below T4 were immobilized in a BodyFix mold (Medical Intelligence; Elekta, Stockholm, Sweden) with a vacuum bag. The simulation CT and high-definition magnetic resonance images (MRI) were fused to aid with target and spinal cord delineation. The target volume was contoured to include the entire vertebral body, for lesions involving the vertebral body, or all of the posterior elements, for lesions involving the lamina, pedicles, or spinous process[15]. No additional margins were added to the target volume. The spinal cord was contoured 4.5 mm above and below the target volume. Treatment planning was initially performed using BrainScan (Brainlab, Munich, Germany) and, more recently, using iPlan (Brainlab) or Pinnacle (Phillips, Mayfield Heights, OH). Image guidance was accomplished using the Exactrac system and/or cone beam CT (CBCT) before treatment delivery depending on the treatment machine[14]. The following dose constraints are used at our institution: 14 Gy maximum dose to the spinal cord with less than 10% of the volume of the spinal cord receiving ≥10 Gy, and 16 Gy maximum dose to the cauda equina with less than 10% of the vol-

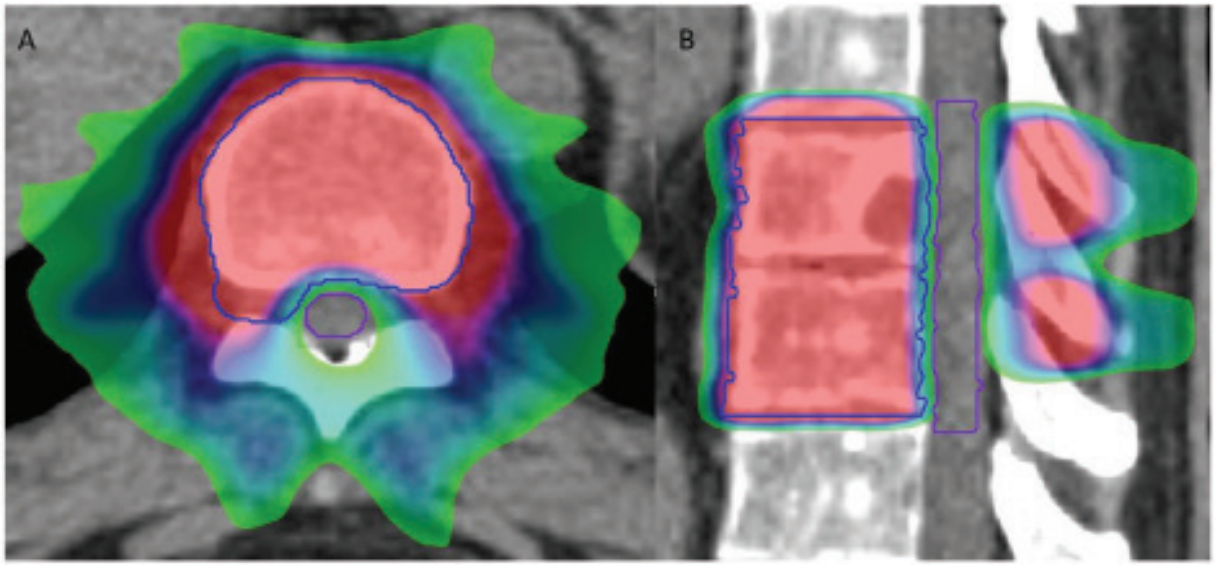

Figure 1. Spine radiosurgery treatment plan (axial [a] and sagittal [b]) for treatment at T9-10 (16 Gy in 1 fraction). Blue line represents the target volume contour, purple line represents the spinal cord contour. The red shaded region represents the 16 Gy dose distribution and the green shaded region represents the 10 Gy dose distribution.

ume of the cauda equina receiving ≥12 Gy. We attempt to achieve a minimum of 90% coverage of the CTV by the prescription dose as long as the spinal cord and cauda equina tolerance is met. Figure 1 illustrates a representative treatment plan for a patient treated with sSRS.

Clinical records, including all consultation, completion and follow-up notes were reviewed for each patient. For each patient, information was collected on age, sex, Karnofsky performance status (KPS), histology, reason for treatment (asymptomatic, pain alone, neurologic deficit alone or both), presence or absence of epidural disease, thecal sac compression as well as dosimetric factors such as prescription dose, maximum target dose, maximum cord dose. At consultation, and at each follow-up visit, each patient underwent a comprehensive neurological examination performed either by a neurosurgeon or a radiation oncologist. Each patient's neurological and pain symptoms were characterized in detail. Pain was characterized prospectively using the Brief Pain Inventory (BPI)[6]. The BPI was conducted at initial consultation and at 1, 2, and 4 weeks after treatment, and then at each subsequent follow-up. Pain scores were adjusted for narcotic usage according to the RTOG protocol 0631 criteria[15]. Complete pain relief was recorded if the patient did not have any pain and had successfully discontinued pain medications. Patients with a decrease of at least 3 points on the BPI and/or with stable to decreased use of pain medications were recorded as having achieved partial pain relief. Pain flare was defined as an increase in pain within 7 days of treatment and required initiation of steroids. The typical dexamethasone regimen was 24 mg on day 1, 20 mg on day 2, 16 mg on day 3, 12 mg on day 4, 8 mg on day 5, 4 mg on day 6.

Univariate analysis (UVA) and multivariable analysis (MVA) were performed using logistic regression to identify patient and treatment characteristics associated with pain flare. Variables with a p-value <0.5 on univariate were included in the multivariable model. Kaplan-Meier analysis was done to estimate times for pain relief, radiographic progression, pain progression, and overall survival. Analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). A p-value of <0.05 was considered to be statistically significant.

RESULTS

A total of 507 lesions treated in 348 patients were included in our analysis. Baseline patient tumor and treatment characteristics are described in Table 1. The median age, KPS, and follow-up were 59 years old, 80 and 8 months, respectively. Fifty-nine percent of patients had a lesion in the cervical or thoracic spine, and 73.4% of patients were offered sSRS for pain alone. The median sSRS dose was 15 Gy (range, 14-18 Gy). The median time to pain relief for patients who presented with pain was 1.8 months. The rates of pain relief for patients who presented with pain are shown in Figure 2. Actuarial median overall survival, median

Table 1. Patient, Tumor and Treatment Characteristics.

Variable	Statistic
Age	59 years
Follow-up	8 months (1 – 72 months)
Gender	
Male	61.5%
Female	38.5%
Epidural Disease	74%
Thecal Sac Compression	43.2%
Histology	
Renal Cell Carcinoma	23.7%
Lung Cancer	14.2%
Breast Cancer	11.4%
Tumor Location	
Cervical/Thoracic	59%
Lumbar	32%
Sacral	8.9%
Reason for Treatment	
Pain Alone	73.4%
Neurologic Deficit Alone	2.8%
Pain and Neurologic Deficit	13.2%
Asymptomatic	10.1%
Prescription Dose (Gy) median (Range)	15 (14-18)

time to radiographic failure after sSRS and the median time to pain progression after sSRS was 13.6, 26.5 and 56.6 months, respectively.

In our series, 73 treatments (14.4%) resulted in the development of a pain flare. All patients were successfully treated with a short steroid taper. The occurrence of pain flare was not associated with either pain progression or radiographic progression ($p>0.05$ for both comparisons).

Univariate analysis demonstrated that higher KPS at time of consultation (OR=1.03, p=0.03), female gender (OR=1.80, p=0.02), higher prescription dose (OR=1.30, p=0.008), and cervical or thoracic spine location vs. lumbar spine (OR=1.81, p=0.047) were predictors for the development of pain flare (Table 2). Patients with pre-existing pain were not found to be at higher risk for the development of pain flare. Multivariate analysis confirmed that higher KPS (OR=1.03, p=0.04), female gender (OR=1.93, p=0.01), higher prescription dose (OR=1.27, p=0.02), and cervical or thoracic location (OR=1.81, p=0.05) were associated with an increased risk of pain flare (Table 2).

DISCUSSION

Our series represents the largest single institutional series evaluating pain flare in patients treated with single fraction sSRS. Our results showed that the overall incidence of pain flare was 14.4% which is less than in previously published series[4,13]. We also found that higher KPS, female gender, higher prescription dose and cervical/thoracic spine location were associated with higher risk for occurrence of pain flare.

Pain flare is a well-established toxicity of radiation treatment to the bone and recent attempts have been made to help quantify the incidence of pain flare in both conventional external beam radiotherapy (EBRT) as well as sSRS. One of the earliest studies that investigated the incidence of pain flare after EBRT showed an overall incidence of pain flare to be 14% on day 1 in patients who received single fraction of 8-10 Gy and 15% on patients who received 20 Gy in 5 fractions[5]. Hird et al. examined the incidence of pain flare from three Canadian centers, showing a higher incidence of pain flare in patients treated with single (44%) vs. multi-fraction (24%) conventional EBRT, although the difference was not statistically significant[7]. Other series have shown an incidence of pain flare to be up to 40% with no difference in occurrence based upon number of fractions[4,7].

There is a relative paucity of data evaluating the incidence of pain flare after SRS in the treatment of bone metastasis, and even fewer studies evaluating pain flare after sSRS. A summary of published studies evaluating the incidence of pain flare following sSRS is shown in Table 3. Chiang et al. examined the incidence of pain flare in sSRS patients in a prospective clinical trial of 41 patients with pain assessment at baseline, during and 10 days post-treatment using the BPI. They defined pain flare as a 2 point increase in the worst pain score, a 25% increase in analgesic intake, or if corticosteroids were initiated after sSRS because of pain. They demonstrated a 68% incidence of pain flare that occurred most commonly within the first 3 days of treatment[4]. Their incidence of pain flare was much higher than the report by Pan et al., who performed a secondary analysis of prospective phase I and phase II sSRS trials and demonstrated a 23% incidence of pain flare which they defined as an increase in pain score of 3. They also noticed that the risk of pain flare was higher in 1-fraction vs. 3-fraction vs. 5-fraction sSRS[13]. In our study, the rate of pain flare appears to be lower than most published series. In fact, our incidence of pain flare was in a patient population without any premedication with steroids and com-

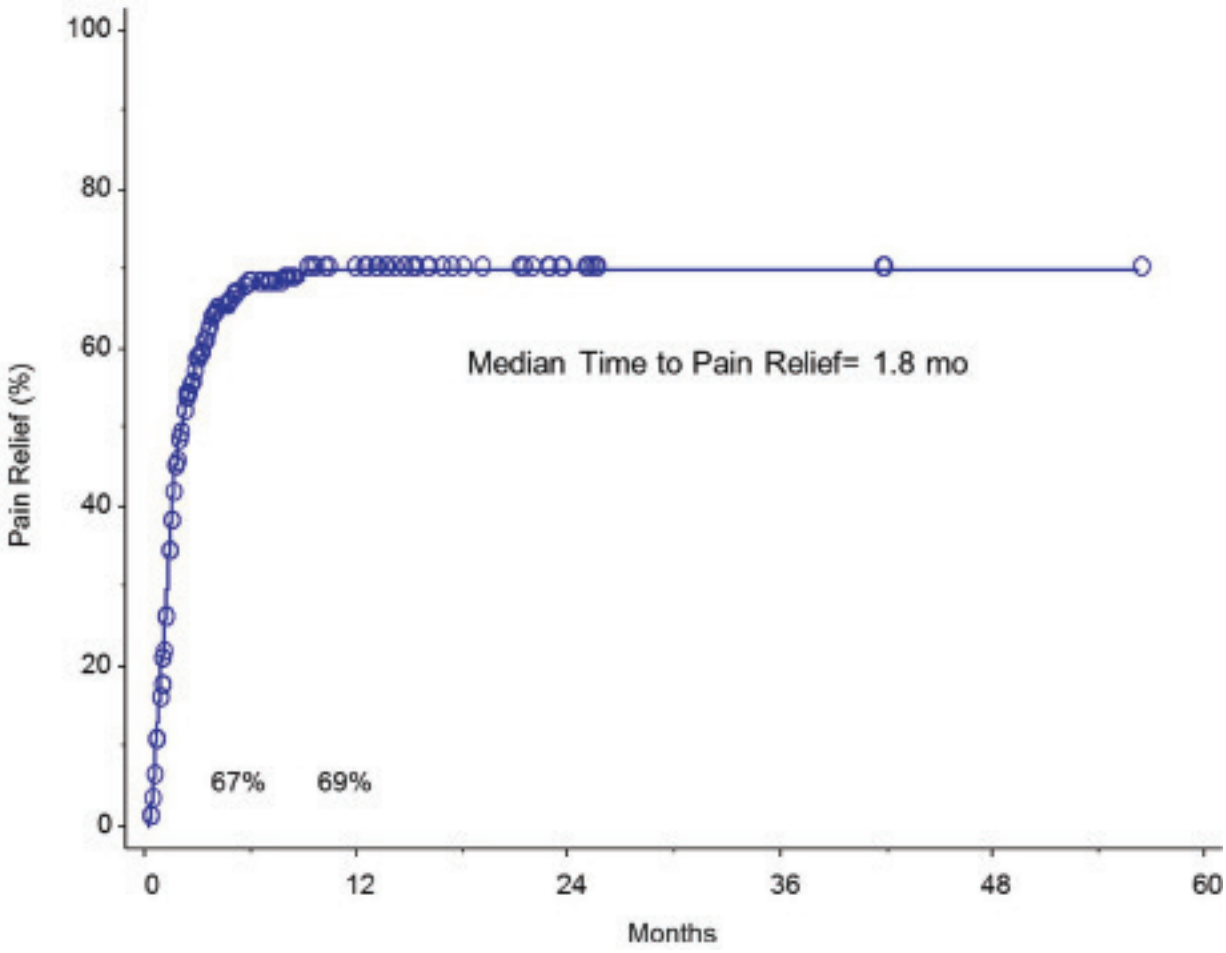

Figure 2. Pain relief after spine SRS for patients with symptomatic spine metastases at the time of treatment (n = 439).

Table 2. Statistical analyses evaluating risk factors for the occurrence of pain flare. Cervical/Thoracic (C/T), External Beam Radiotherapy (EBRT), Karnofsky performance score (KPS), Lumbar (L), Sacrum (S).

	UVA			MVA		
Variable	OR	CI	p-value	OR	CI	p-value
KPS	1.025	1.003 – 1.049	**0.03**	1.025	1.001 – 1.049	**0.04**
Female gender	1.795	1.091 – 2.959	**0.02**	1.927	1.153 – 3.215	**0.01**
Prescription Dose	1.301	1.071 – 1.580	**<0.01**	1.274	1.043 – 1.556	**0.02**
Tumor location						
C/T vs L	1.808	1.008 – 3.244	**0.05**	1.810	1.000 – 3.279	**0.05**
C/T vs S	2.160	0.741 – 6.289	0.16	2.079	0.688 – 2.079	0.19
L vs S	1.193	0.381 – 3.745	0.76	1.149	0.353 – 3.731	0.82
Prior EBRT	0.521	0.271 – 1.001	**0.05**	-	-	-

pares favorably to a report published by Khan et al. that showed giving prophylactic dexamethasone of either 4mg or 8 mg reduced the incidence of pain flare from 68% to 19%[8,9]. It is important to note that patients in Khan's study were asked to keep a daily diary after SRS, which likely provided more detailed information regard-

Table 3. Review of literature reporting incidence of pain flare following spine SRS. Number (#); Gray (Gy); stereotactic radiosurgery (SRS); fractions (fx); odds ratio (OR); Karnofsky performance status (KPS).

Study	# Patients # Treatments	Steroid Prophylaxis	Median Prescription Dose (Gy) and Fractions	Pain Flare Incidence	Other Findings
Chiang et al. (2013)[4]	41 / 41	Not routinely.	24 Gy [20-35] / 3 Fx [1-5]	68%	Higher KPS (OR 1.16) and cervical (OR 11.30) or lumbar (OR 28.79) lesions associated with pain flare.
Pan et al. (2014)[14]	195 / 195	Not routinely. 17% received steroids before or after SRS.	27 Gy [18-30] / 3 Fx [1-5]	23%	More fractions protective against pain flare (OR 0.66)
Khan et al. (2015)[9]	47 / 47	Yes, randomized to 4mg or 8mg dexamethasone. Steroids taken before and after SRS.	24 Gy [20-30] / 3 Fx [1-5]	19% total. 25% (4mg) vs. 13% (8mg), p=0.46	Functional outcomes slightly better in 4mg cohort. Prophylactic steroids reduces worst pain and improves general activity interference.
Naik et. al (Present Study)	348 / 507	No	15 Gy [14-18] / 1 Fx	14%	Higher KPS (OR 1.03), female gender (OR 1.80), higher dose (OR 1.30), and cervical/thoracic (OR 1.81) associated with pain flare.

ing pain flare than the BPI used in our study which was done at discreet time points. The discrepancy in incidence of pain flare may be due to patient-reported outcomes as in our series patients were coded to have a pain flare if they developed worsening of pain after sSRS as well as required initiation of steroids.

We were also interested in identifying patient and treatment characteristics to identify a patient population that would benefit from steroid premedication. We evaluated a range of variables and found that on multivariable analysis KPS, female gender, higher prescription dose, as well as a cervical or thoracic spine location were associated with a higher incidence of pain flare. Our results were in congruence with Chiang et al. who also showed patients with a higher performance status were more likely to have a pain flare[4]. It is important to note that while all patients treated at our institution were treated with single fraction sSRS, it is still unclear whether fractionated sSRS leads to decreased risk for pain flare. Results from Pan et al. suggest that fractionated sSRS may allow further reduction in the incidence of pain flare, however, an observational cohort study from University of Toronto did not report a difference in incidence amongst patients who receive single fraction vs 2-fraction sSRS[8]. It is also unclear why female patients as well as SRS in the cervical/thoracic spine leads to increase in risk for pain flare, however, one can postulate that a narrower spinal canal may predispose for the development of pain flare.

Steroids are widely used in the management of patients with pain flare, and have been shown to decrease the incidence of pain flare in both EBRT and SRS[17]. Since the results of this study demonstrated a low overall incidence of pain flare with single fraction sSRS, we do not routinely offer prophylactic steroid treatment to our patients.

Our study has several limitations, most importantly its retrospective design. Furthermore, the lower incidence of pain flare may have been the result of physician reported outcomes compared to patient reported outcomes due to the retrospective nature of this study; only those patients that developed pain flare significant enough to start steroids were coded as having developed this toxicity. Furthermore, despite having physician reported outcomes, one of the important strengths of our study is that our patients are followed closely, and BPI was obtained pro-

spectively which allowed for a robust analysis. Importantly, since all patients in this study received single fraction sSRS, our study did not address whether multiple fraction sSRS has the potential to reduce the incidence of pain flare and further study is warranted.

ACKNOWLEDGMENTS

Authors' disclosure of potential conflicts of interest

Dr. Chao reports "honorarium" from Varian Medical Systems, outside the submitted work. Dr. Suh reports grants from Varian Medical Systems and "travel and lodging" from Elekta, outside the submitted work. Drs. Angelov, Balagamwala, Djemil, Magnelli, Naik, and Reddy have nothing to disclose.

Author contributions

Conception and design: Ehsan Balagamwala, Samuel Chao
Data collection: Ehsan Balagamwala
Data analysis and interpretation: Chandana Reddy, Ehsan Balagamwala, Samuel Chao
Manuscript writing: Mihir Naik, Ehsan Balagamwala
Final approval of manuscript: Ehsan Balagamwala, Mihir Naik, Chandana Reddy, Lilyana Angelov, John Suh, Toufik Djemil, Anthony Magnelli, Samuel Chao

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