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CLINICAL INVESTIGATION **Spine**

STEREOTACTIC BODY RADIOTHERAPY IS EFFECTIVE SALVAGE THERAPY FOR PATIENTS WITH PRIOR RADIATION OF SPINAL METASTASES

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Purpose: To provide actuarial outcomes and dosimetric data for spinal/paraspinal metastases, with and without prior radiation, treated with stereotactic body radiotherapy (SBRT).

Methods and Materials: A total of 39 consecutive patients (60 metastases) were treated with SBRT between April 2003 and August 2006 and retrospectively reviewed. In all, 23 of 60 tumors had no previous radiation (unirradiated) and 37/60 tumors had previous irradiation (reirradiated). Of 37 reirradiated tumors, 31 were treated for "salvage" given image-based tumor progression. Local failure was defined as progression by imaging and/or clinically.

Results: At last follow-up, 19 patients were deceased. Median patient survival time measured was 21 months (95% CI = 8–27 months), and the 2-year survival probability was 45%. The median total dose prescribed was 24 Gy in three fractions prescribed to the 67% and 60% isodose for the unirradiated and reirradiated cohorts, respectively. The median tumor follow-up for the unirradiated and reirradiated group was 9 months (range, 1–26) and 7 months (range, 1-48) respectively. Eight of 60 tumors have progressed, and the 1- and 2-year progression-free probability (PFP) was 85% and 69%, respectively. For the salvage group the 1 year PFP was 96%. There was no significant difference in overall survival or PFP between the salvage reirradiated vs. all other tumors treated ($p = 0.08$ and $p = 0.31$, respectively). In six of eight failures the minimum distance from the tumor to the thecal sac was $\leq$1 mm. Of 60 tumors treated, 39 have $\geq$6 months follow-up and no radiation-induced myelopathy or radiculopathy has occurred.

Conclusion: Spine SBRT has shown preliminary efficacy and safety in patients with image-based progression of previously irradiated metastases. © 2009 Elsevier Inc.

Stereotactic body radiotherapy, Spine metastases, Radiosurgery, Reirradiation, Local control.

INTRODUCTION

Stereotactic body radiotherapy (SBRT) has emerged with the advent of sophisticated radiation technologies including image-guided radiotherapy (IGRT) (1). This technique has been developed in the treatment of lung cancers (2), liver tumors (2), and more recently, spinal, and paraspinal tumors (1, 3–8).

One system capable of SBRT is the Cyberknife (Accuray, Inc., Sunnyvale, CA). This system has been extensively described elsewhere (1, 4, 7, 9, 10). However, in brief, the Cyberknife is a frameless image-guided SBRT consisting of an X-Band 6 MV linear accelerator, a high precision six-axis manipulator (robotic arm), and a near real-time intrafractional image correlating system. The near real-time intrafractional stereoscopic kilovoltage image-guidance system is particularly useful for spine tumors where even slight inaccuracies can lead to overdosing of the spinal cord or the adjacent organs (11). Even though the mechanical accuracy has been reported to be within 1 mm (12), the residual target motion (target movement between successive image-guided corrections) has been reported to be patient specific and up to 2 mm (13).

The aim of this study is to compare clinical outcomes for SBRT in patients with previously irradiated spinal and

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Table 1. Patient/tumor characteristics

Characteristic	No prior XRT Patients: $n = 14$ Tumors: $n = 23$	Prior XRT Patients: $n = 25$ Tumors: $n = 37$	p Value
Median age (range)	57 (14–86)	59 (13–83)	0.68
Radiosensitive	8/23	34/37	<0.0001
Radioresistant	15/23	3/37	
Cervical	2/23	5/37	
Thoracic	11/23	17/37	0.16
Lumbar/sacrum	10/23	15/37	
Median tumor volume (cc)	8.3 (2.1–106)	21 (0.4–177)	0.96
Median/mean minimum distance of GTV to CNS (mm)	0.7/1.6 (0.2–9)	1/2.8 (0.1–30)	0.32
Extraspinous Metastases	4/14	8/25	0.82
Pain at presentation	13/23	33/37	0.004
Time to first metastases:			
<6 months	4/14	12/25	0.50
6–12 months	4/14	5/25	
>12 months	6/14	8/25	
Primary therapy vs.	18/23	37/37	NA
Postoperative SBRT	5/23	0/37	
Median tumor follow-up (mo)	9 (1–26)	7 (1–48)	0.02

Abbreviations: CNS = critical neural structure; GTV = gross tumor volume; NA = not applicable; SBRS = stereotactic body radiosurgery; XRT = radiation therapy.

paraspinal metastases (''reirradiated'' patients) to those with no prior irradiation (''unirradiated'' patients).

METHODS AND MATERIALS

The components of the image-guided Cyberknife radiosurgery system have been described above. However, we will describe briefly our radiosurgery process. Initially, patients had implanted fiducials (three to five stainless steel, screw-shaped fiducials) into the vertebral bony elements adjacent to the tumor to be treated. However, patients were eventually spared this invasive procedure after the acquisition in early 2006 of the XSight skeletal tracking system (Accuray, Sunnyvale, CA), which co-relates imaging using bony anatomy, rather than fiducials, to provide intra-fractional kilovoltage X-ray image guidance. All patients were treated in the supine position, and for treated patients with cervical spine tumors, a thermoplastic patient-specific mask was used to provide additional stability given the greater potential for patient neck and head movement as opposed to torso.

Patient treatment planning began with a planning computed tomography (CT) scan and acquisition of axial images with a slice thickness of 1.25 mm. Magnetic resonance images were obtained before treatment planning to confirm the location of the metastases, and ensure no radiographic evidence of malignant epidural spinal cord compression. We did not typically fuse the MRI and CT images to avoid introducing small fusion-related errors; however, MRI information was used to guide contouring of the target on the planning CT scan. The gross tumor volume (GTV) was contoured without any intended margin (*i.e.,* GTV = PTV). For postoperative cases, gross residual disease was delineated as GTV and a margin was applied to encompass the surgical bed as potential areas at risk of microscopic disease (GTV + surgical bed = CTV).

Critical neural structures (CNS), which consisted of the spinal cord and the cauda equina, were delineated. The spinal cord contour consisted of the entire thecal sac contoured at the level of the tumor and typically 2 cm beyond both superiorly and inferiorly. Similarly, for the cauda equina the entire thecal sac was contoured. CT imaging was sufficient for contouring the thecal sac. Furthermore, delineating the thecal sac rather than the spinal cord itself allowed for a safety margin of approximately 0.5-1 mm beyond the spinal cord. All other organs at risk (*e.g.,* esophagus, small bowel, and larynx, etc.) were contoured without any margin. A proprietary inverse planning computer algorithm (Multiplan, Accuray, Sunnyvale, CA) determined the number, direction, diameter, and duration of treatment beams.

The University of California, San Francisco (UCSF) Cyberknife was acquired in April, 2003 and we retrospectively included all cases treated up to August, 2006. All treatment plans were reviewed and dose-volume histogram (DVH) data were collected. The minimum distance from the tumor edge (PTV) to the CNS (thecal sac) was retrospectively documented for each case. A total of 39 patients (60 spinal/paraspinal metastatic tumors) were treated, and patients were identified based on a prospective database search with institutional research board approval. In 37 of the 60 tumors had been previously irradiated, and patient characteristics and tumor type are presented in Table 1. Sarcoma, renal cell cancer, melanoma, and drop metastases from glioma were deemed radioresistant, and all other histologies were deemed radiosensitive.

We defined local failure as progression based on imaging (any tumor growth) and/or symptoms (worsening of pain >2 weeks post-SBRT or any neurologic deterioration). Because this patient population was terminally ill, follow-up imaging was often not available (only 28 of 60 tumors treated had follow-up imaging). Therefore, we defined a clinically relevant measure of local control to be absence of either symptomatic or radiographic progression. All failure cases were reviewed with a neuroradiologist at UCSF. Toxicity was graded retrospectively according to the NCI-Common Toxicity Criteria v. 3.0. Pain and neurologic status were determined by retrospective review. Because UCSF is a large tertiary care center with patients referred from a distance, follow-up on patient status was done by in person or, in some cases, by phone. Pain and neurologic status results are reliable, but the degree of SBRT benefit cannot be graded beyond better/stable or worse. As more than one tumor per patient had been treated, and at different times, survival was determined based on the time from completion of SBRT for each patient to last known follow-up or death. Progression-free-probability for each tumor treated (PFP) was defined from the date of completion of SBRT to last known documented tumor status.

Descriptive statistics were reported as median and range for continuous variables, and frequencies and proportions for categorical variables. Fisher's exact test, Pearson's χ^2 test, and the Mann-Whitney nonparametric test were used for statistical evaluation. The time-to-progression for the reirradiated and unirradiated cohorts were compared with the log-rank test. Univariate and multivariate analyses were performed to identify factors associated with local control by using the Cox proportional hazard model. Both PFP and overall survival (OS) were calculated according to the Kaplan-Meier method. Differences between survival curves were analyzed by the log-rank test. Results were considered significant at

Table 2. Tumor dosimetric characteristics

Parameter	No Prior XRT $n = 23$	Prior XRT $n = 37$
Median total dose (Gy)/Frx	24 (7–40)/3 (1–5)	24 (8–30)/3 (1–5)
Median prescription isodose (%)	67 (44–84)	60 (38–78)
Median D100 (Gy)	14.8 (5.1–22.0)	10.6 (3.0–24.5)
Median D90 (Gy)	24.3 (10–46)	19.9 (6.7–32)
Median BED-D90 (Gy_{10})	42 (20–115)	31 (12–60)
Median BED-D100 (Gy_{10})	20 (7–31)	14 (2–37)
Median V100 (%)	89 (71–100)	83 (26–99)
Median V115 (%)	43 (4–72)	50 (2–95)
Median V95 (%)	91 (74–100)	86 (41–99)
Median max tumor point dose	35.8 (20.2–80)	36.9 (14.3–57.7)
Median total dose/frx of Previous XRT (Gy/frx)	N/A	36 Gy/14 frx
Median BED Previous XRT (Gy_{10})	N/A	47

Abbreviations: BED = biologic effective dose; frx = fractions; max = maximum; NA = not applicable; SBRS = stereotactic body radiosurgery; XRT = radiation therapy.

p values ≤ 0.05. All analyses were performed with SAS 9.1 (SAS Institute, Cary, NC).

RESULTS

Patients

Patient characteristics are presented in Table 1. In the unirradiated cohort there were significantly more radioresistent tumors treated than in the reirradiated cohort. There was no significant difference in the time to first metastases, presence of extraspinal metastases at the time of SBRT, or age, which are prognostic factors which can affect survival analysis (14–17). A total of 37 tumors in 25 patients had been previously irradiated, with imaging-confirmed tumor progression in the previously irradiated volume. In six of these tumors (5 patients), prior radiation had not been directed at local spinal or paraspinal targets, but the relevant CNS was within the field during radiation for the initial primary lesion. The SBRT was subsequently delivered as a result of metastases presenting within the previously irradiated CNS volume. An example of this would be a case in which lung radiation had exposed the spinal cord to a certain dose, and subsequent de novo spinal metastases appeared within that field, with SBRT being used to treat the tumor and spare the spinal cord. We analyzed all 37 reirradiation tumors as a group, with selected subgroup data analyzed for the 31 of the 37 treated specifically for salvage of previously radiated metastases. For all patients the median time to SBRT from prior radiation was 11 months. Five patients were treated with postoperative spinal SBRT because of the presence of gross residual tumor. The median patient follow-up for the entire cohort was 8.5 months (1–48). All patients had an ECOG performance status ≤ 2, and a KPS ≥ 70.

Tumors

Dosimetric data for the tumors in the reirradiated and unirradiated cohorts are provided in Table 2. The median total dose was 24 Gy delivered in three fractions prescribed to the 67% and 60% isodose for the unirradiated and reirradiated cohorts, respectively. The coverage of the tumor was frequently sacrificed at the CNS interface, and dosimetric data are therefore provided. Biologic effective dose (BED) is provided based on the linear quadratic model, and based on the total dose to 90% of the tumor volume (D90) and 100% of the tumor volume (D100, represents the minimum tumor dose). The percent volume obtaining 100%, 115%, and 95% of the prescribed dose is also provided (V100, V115, V95). The median BED exposed to the spinal cord and cauda equina (with $\alpha/\beta = 2$ for late toxicity) was 47 Gy_2 and 84 Gy_2, respectively.

Critical neural structures

An extensive dosimetric analysis is provided in Table 3. Absolute and relative dosimetric data based on the thecal sac contour are provided and stratified according to spinal cord or cauda equina targets and reirradiated vs. unirradiated cohorts. The BEDs are provided because the fractionation varied.

Survival and failure analysis

At the time of follow-up analysis, 19 patients were deceased. Median patient survival time measured was 21 months (95% CI = 8–27 months), and the 2-year survival probability was 45%. There was no significant difference in overall survival between the reirradiated and unirradiated cohort ($p = 0.41$, Fig. 1). The subgroup of those patients specifically treated with salvage SBRT for progression of previously irradiated spinal metastases was compared with all other patients, and no significant difference in survival was found ($p = 0.08$, Fig. 2). Likewise, no significant difference in survival was found when comparing radioresistant to radiosensitive lesions ($p = 0.82$) or that was caused by age ($p = 0.35$), time to first metastases ($p = 0.82$), or presence of extraosseus metastases ($p = 0.72$).

Follow-up for local control was shorter than for survival. Some patients had more than one spine radiosurgery procedure, with subsequent procedures obviously having less time to assess local control. In addition, several patients were moved to long-term hospice facilities, where reliable local control data were impossible to obtain, although survival data were not. This highlights the importance of reporting actuarial rates of local control. Eight tumors of the 60 treated recurred. Of note, a second course of spinal SBRT was given for two tumors after failure (Tumors 3 and 4 in Table 4), and they are controlled now 9 months after the second course of treatment with SBRT. The median

Table 3. Spinal cord and cauda equina dosimetric parameters

Dosimetric parameter	Spinal cord/thecal sac		Cauda equina/thecal sac	
	No Prior XRT n = 13	Prior XRT n = 22	No Prior XRT n = 10	Prior XRT n = 15
Median max dose (Gy)	16.8 (10.7–26)	12.8 (5.4–27)	28.1 (3–32)	13 (8–21)
Median max BED (Gy_2)	56 (30–114)	36 (20–98)	132 (4–160)	45 (22–145)
Median dose 0.1 cc (Gy)	14.7 (9–21.3)	9.4 (2–27.3)	21.9 (1–27.1)	8.2 (5–25)
Median 0.1 cc BED (Gy_2)	50 (18–106)	22 (4–102)	101 (1–125)	30 (14–129)
Median dose 1 cc (Gy)	8.1 (5–18)	6.6 (3.6–20.4)	16.4 (2–21.1)	7 (3–26)
Median 1 cc BED (Gy_2)	19 (3–98)	14 (3–54)	61 (3–96)	25 (6–106)
Median dose 2 cc (Gy)	6.6 (2–17.4)	5.4 (0–19)	13 (2–17.4)	6.1 (1.6–25.1)
Median 2 cc BED (Gy_2)	14 (2–93)	9 (0–54)	41 (3–76)	16 (3–96)
Median dose 5 cc (Gy)	4.4 (0.1–16.2)	2.8 (0–16.8)	6.2 (1–11)	4 (0.5–18.3)
Median 5 cc BED (Gy_2)	7 (2–81)	4 (0–44)	16 (1.2–36)	7.1 (0.5–74)
Median V≥8 Gy (cc)	1.2 (0–11.5)	0.3 (0–28)	4.1 (0–8.5)	0.3 (0–17)
Median V≥10 Gy (cc)	0.6 (01–11)	0.0 (0–25)	2.8 (0–5.5)	0 (0–13.7)
Median V≥15 Gy (cc)	0 (0–11)	0.0 (0–9.3)	1.4 (0–3.4)	0 (0–9.2)
Median BED Previous XRT (Gy_2)	N/A	47 (10–64)	N/A	84 (31–103)
Median time from previous XRT (mo)	N/A	11 (3–85)	N/A	15 (5–68)
Median follow-up (mo)	8 (1–26)	10 (1–48)	9 (6–22)	7 (1–42)

Abbreviations: BED = biologic effective dose; NA = not applicable; SBRS = stereotactic body radiosurgery; XRT = radiation therapy.

PFP has not been reached, and the 1- and 2-year PFP was 85% and 69%, respectively. There was no significant difference in PFP comparing reirradiated with unirradiated cohorts (p = 0.09, Fig. 3), or when the salvage subgroup was compared with all other spinal metastases treated (p = 0.31, Fig. 4).

Table 4 provides data specifically for failures. These factors were subjected to univariate analysis to identify predictors of local failure for the entire cohort. On univariate analysis the minimum distance from the GTV to the CNS of ≤1 mm vs. >1 mm was not significantly different (p = 0.8). On multivariate analysis, the minimum distance from the GTV to the CNS approached a trend for significance (p = 0.1). An exploratory univariate analysis was performed for different thresholds for the risk of local failure and the distance of the GTV to the CNS where cut-off values of 1 mm, 0.4 mm, 0.2 mm, and 0.1 mm resulted in p values of 0.8, 0.6, 0.3, and 0.02, respectively. This analysis supports a possible trend of increased risk of local failure as the tumor approaches the CNS.

All patients who failed to respond also suffered worsening of pain (beyond 2 weeks post-SBRT). All other patients with pain at presentation were at best stable, and we could not determine true benefit because of the retrospective nature of the data collection and lack of standardized pain outcome tool use. Six of the eight local treatment failures had imaging-verified tumor progression (the remaining 2 patients were too ill for follow-up MRI). Progression occurred diffusely within the treated volume and no apparent pattern of failure other than in-field failure could be determined. A case of tumor progression from this series has been published elsewhere (1).

No Grade 3 or greater toxicity occurred in any patient treated in either the acute (up to 2 weeks post-treatment) or late period. Grade 1/2 toxicity consisted of nausea

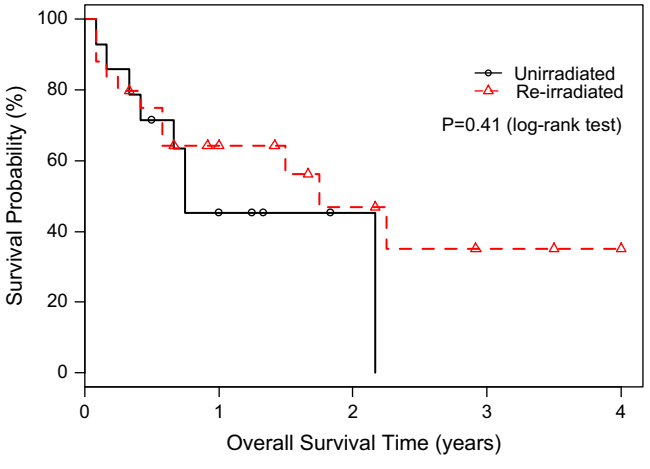

Fig. 1. Overall survival for reirradiated vs. unirradiated cohorts.

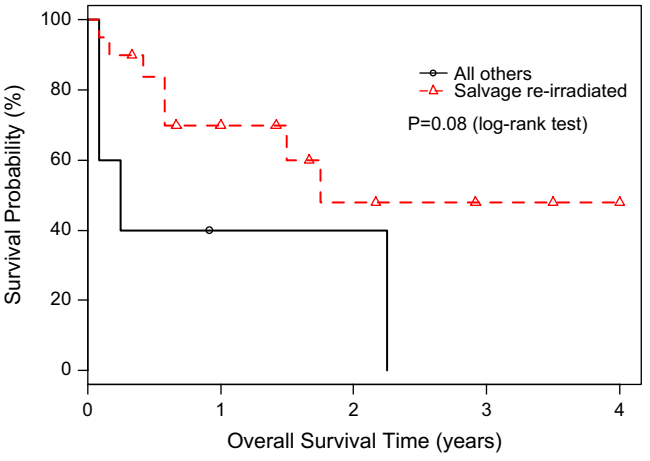

Fig. 2. Overall survival for salvage reirradiated patients vs. all others.

Table 4. Local failures

Tumor	Primary Site	Prev XRT	Tumor volume (cc)	Min distance to CNS (mm)	D90 (Gy)	D100 (Gy)	BED-D90 (Gy_{10})	BED-D100 (Gy_{10})
1	Melanoma	No	3.9	3	25.7	20.1	50	34
2	Sarcoma	No	82.2	2	20.6	27.3	42	29
3	Pancreas	No	36.2	0.8	18.4	14.5	29	21
4	Pancreas	No	53	0.4	10.3	8.1	20	15
5	Melanoma	No	8.7	0.6	30.7	24.6	50	37
6	Bladder	37.5 Gy/15 frx	109.4	1	15.5	5.2	24	6
7	Myeloma	45 Gy/25 frx	29	0.1	31.4	21.9	51	32
8	Glioma	36 Gy/18 frx	0.4	0.1	19.6	18.9	27	26

Abbreviations: BED = biologic effective dose; frx = fractions; Min = minimum; XRT = radiation therapy.

during treatment for 3 patients treated, and 1 patient had constipation requiring a treatment delay (unrelated to but did occur during therapy). Immediately after treatment, 3 patients had a transient increase in tumor-related pain. Of 60 tumors treated, 39 have received ≥6 months follow-up, and no radiation-induced myelopathy or radiculopathy has occurred.

Figure 5 illustrates a case in which a nasopharyngeal cancer patient with a spinal metastases and prior radiation to part of the affected area was treated with spinal SBRT. The initial CT–positron emission tomography (PET) scan had uptake in the region, with a standardized uptake value (SUV) of 8. After spinal SBRT, the CT-PET showed a complete biologic response, with a SUV of 0.

DISCUSSION

This report highlights that, in selected patients with spinal or paraspinal metastases, relatively long-term tumor control and survival is observed. In our cohort, the 2-year survival probability was 45%, and the median survival was 21 months. Ryu *et al.* reported median overall survival rates in patients treated with spinal SBRT of 11.4, 12, and 16 months for patients with metastatic multiple myeloma, prostate cancer, and breast cancer patients, respectively; however, median overall survival was only 1.8 and 3.2 months for patients with lung and kidney cancer, respectively (18). Therefore patients with metastatic disease can have long-term survival and, in those who are expected to live longer, aggressive irradiation of spinal metastases (greater BED than possible with conventional radiation) may be warranted to maximize the possibility of durable pain relief and tumor control.

Specifically for spinal metastases, Chow *et al.* reported outcomes within the meta-analysis of randomized trials investigating conventional radiotherapy regimens for bone metastases (19). These investigators reported no significant difference both in pain outcomes with fractionated (*e.g.,* 20 Gy in five fractions) vs. single fraction (*e.g.,* 8 Gy in one fraction) radiotherapy, nor in progression to malignant epidural spinal cord compression (MESCC) (19). However, there was a greater re-treatment rate because of pain with the single-fraction treatments. These data are based on low BED treatments, whereas the aim of spinal SBRT is to deliver high BED. Excellent long-term outcomes have been reported based on analysis of 500 cases of spinal metastases treated with SBRT by Gerszten *et al.* (4), who reported 90% long-term tumor control and 86% long-term pain improvement (median follow-up, 21 months; range, 3–53 months). As a consequence of emerging data for unirradiated tumors, spinal SBRT is gaining acceptance as a potentially better

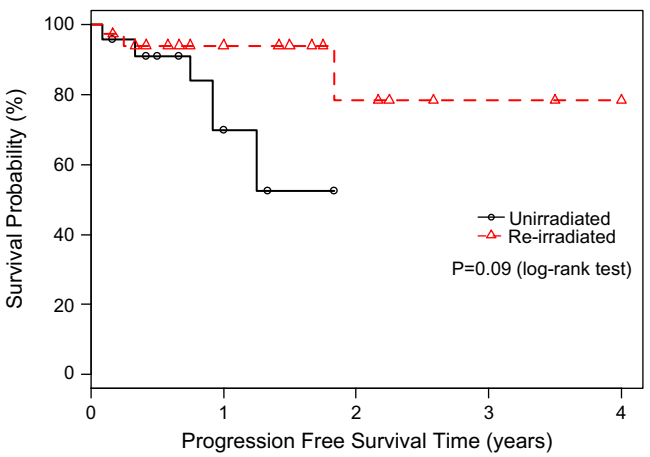

Fig. 3. Progression-free probability for reirradiated vs. unirradiated tumors.

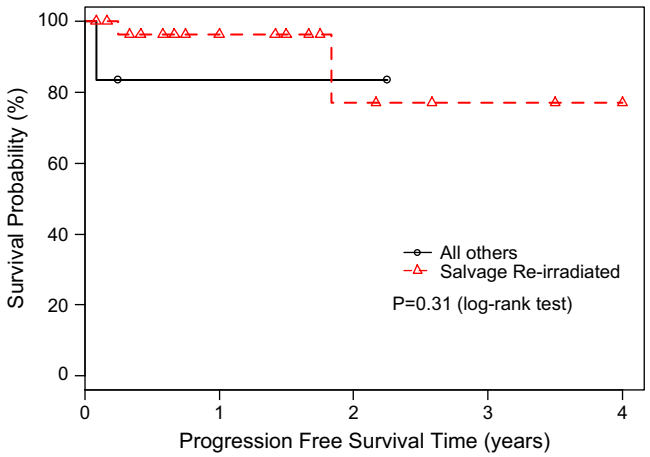

Fig. 4. Progression-free probability for salvage reirradiated patients vs. all others.

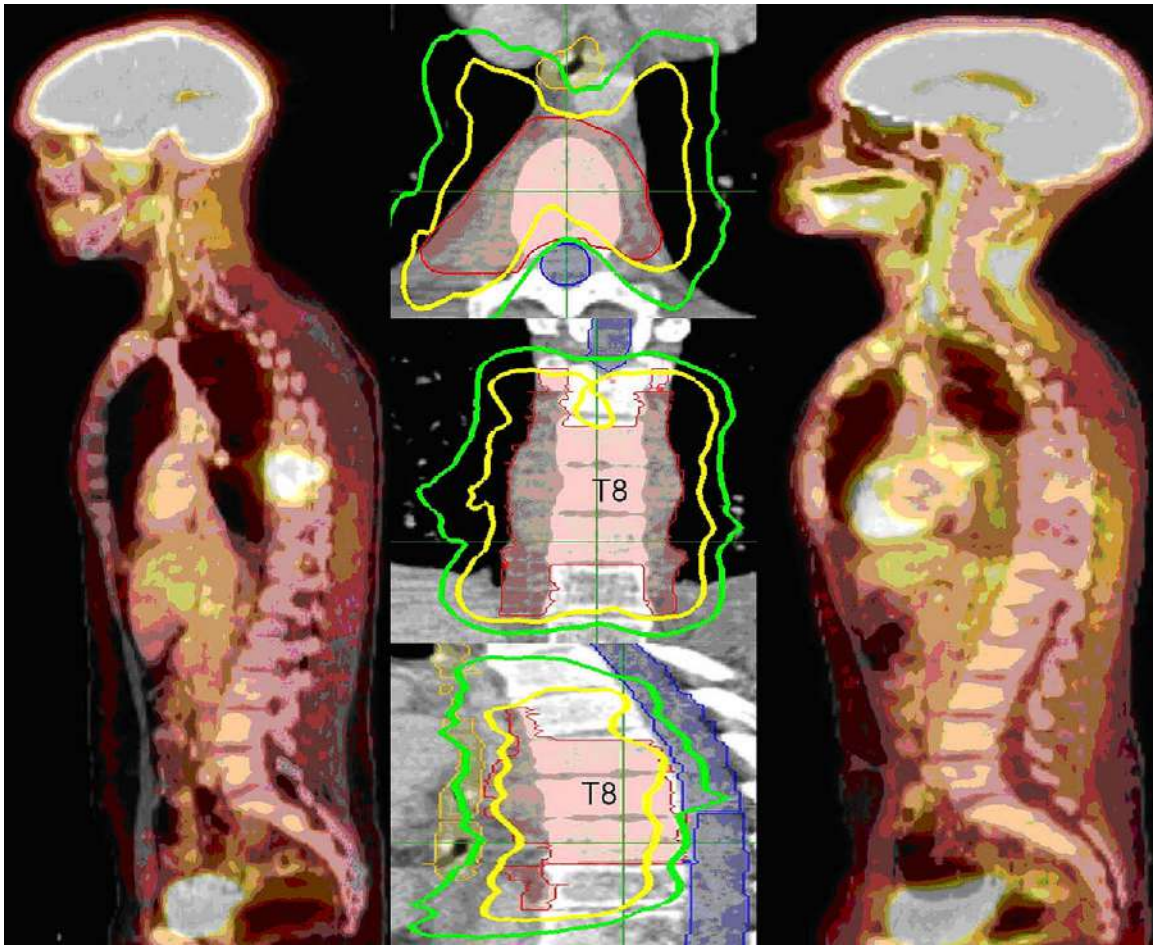

Fig. 5. Patient with symptomatic isolated complex spinal/paraspinal metastases centered within the T8 vertebral body secondary to nasopharyngeal cancer. Disease extended into adjacent vertebral bodies with extension bilaterally into paraspinal tissues. The patient had prior conventional radiation from T9 to L1 consisting of 30 Gy in 10 fractions. On the left is the pre–stereotactic body radiotherapy (SBRT) computed tomography–positron emission tomography (CT-PET), indicating uptake primary at T8 region with a standardized uptake value (SUV) of 8. The center panel displays axial, coronal, and saggital views of the isodose distribution where the patient was treated with 30 Gy in five fractions prescribed to the 52% isodose. The axial distribution corresponds to a region in the previously irradiated field. The 30-Gy isodose line is in yellow, the 20-Gy isodose line in green, the thecal sac in blue, the esophagus in orange, and the planning target volume (PTV) in red. On the saggital view, inferiorly to T8, isodose lines draw inward to restrict dose to the thecal sac because of previous radiation in that region. Right panel depicts follow-up CT-PET 11 months post-SBRT, with no SUV uptake in the T8 treated region.

therapeutic option (1). However, for patients with pain and imaging evidence of tumor recurrence presenting without paralytic neurologic deficit, or dangerously unstable vertebral destruction, SBRT clearly provides a therapeutic option that was previously unavailable, and the technique was initially developed for this indication (20). A complex case treated with SBRT to a partially previously irradiated spinal/paraspinal metastases is illustrated in Fig. 5.

This series reports data specifically for patients with prior radiation requiring spinal SBRT, and compares outcomes with those of patients without prior radiation treated with SBRT as primary therapy. The tumor treatment cohorts were unbalanced in that there were greater radioresistant histologies in the unirradiated cohort, and a greater proportion of patients with pain at presentation in the reirradiation group. These imbalances could translate into greater failure rates in the unirradiated cohort because of the greater proportion of radioresistant histology cases; however, there was a greater potential for failure because of pain relapse or worsening in the reirradiation group.

Both clinical and imaging criteria were incorporated into our definition of failure for local control analysis. It was decided to incorporate both these factors in the failure definition to make it clinically relevant to the metastases population. Image-based tumor control is an important endpoint; but as these patients are palliative with pain, if we do not palliate their pain then we have not benefitted these patients despite gross tumor control. The optimal definition of local control is controversial (1, 21). In this study, shortcomings include lack of sufficient follow-up with imaging (only 28 of 60 metastases treated had imaging follow-up) and the subjectiveness of pain worsening without a standardized tool to monitor patients that would incorporate modifications in analgesic use (21).

Table 5. Current studies on spine (SBRT) with reported local control for patients with the indication for salvage SBRT for image-based tumor progression and prior radiation

Author/year (Ref.)	Total No. tumors/patients	No. Retx tumors/patients	Retx tumors for salvage (*n*)	Follow-up, Mo (range)	Target volume	Local control
Milker-Zabel *et al.*/2003 (19)	19/18	19/18	18	Median 12 (4–33)	PTV=GTV plus entire VB	95% (18/19)
Hamilton *et al.*/1995(20)	5/5	5/5	5	Median 6 (1–12)	GTV + areas suspicious of extension	100%
Mahan *et al.*/2005 (21)	8/8	8/8	8	Mean 15.2	PTV: GTV + 3 mm excluding the cord volume	100%
Gerszten *et al.*/2007 (22)	500/393	344/N.R.	51	Median *21 (3–53)	PTV=GTV	88%
Present series	60/38	37/26	31	Median 7 (1–48)	GTV=PTV	90% (28/31)1 year PFP: 96%

Abbreviations: GTV = gross tumor volume; PFP = progression free probability; PTV = planning target volume; Retx = reirradiation.
* Follow-up is for the entire cohort and not specifically for salvaged cases.

Our results indicate that the PFPs were not significantly different between the two cohorts, and that the patterns of failure were not significantly different (five failures in the unirradiated group and three in the reirradiated group). Because OS was not significantly different between the two cohorts, our reirradiation cohort was clearly a well-selected group of good functioning patients with expected longer survival than typical metastatic patients with relapsed disease. These results indicate that spinal SBRT is an effective treatment for well-selected patients with prior radiation allowing long-term tumor control. Similar results were reported by Gagnon *et al.*, who performed a matched pair analysis of patients with breast cancer treated with SBRT as salvage for progressing spinal metastases despite prior radiation to unirradiated patients treated with conventional radiotherapy. They report no significant difference in terms of ambulatory status, performance status, pain relief, or survival over time (but did not report specifically local control), and conclude SBRT is as efficacious in the salvage setting as conventional radiotherapy in the unirradiated upfront setting (22).

In our series, for tumor progression after prior radiation (31 of 37 reirradiated tumors), spinal SBRT was effective at controlling the tumors. Two of the eight failures occurred in re-treated salvage patients. Figures 2 and 4 indicate no significant difference in overall survival or PFP when compared with all other tumors/patients. Table 5 provides an overview of the published literature where outcomes are reported specifically for image-based tumor progression despite prior radiation. Based on these data, spinal SBRT seems to be effective in providing local tumor control for this indication. The most number of tumors treated specifically for salvage has been reported by Gerszten *et al.*, who report 88% local tumor control for 51 salvage cases (4). Our report is unique in that extensive dosimetric details for the reirradiation cohort (both for the tumor and CNS) and actuarial outcomes are provided (Table 2 and 3). Because the fractionation varied relevant BED are also provided. One limitation in the BED dose provided is the potential lack of applicability to hypofractionated radiotherapy (*i.e.,* it may not be applicable at such extreme fractionation schedules), as it was intended for protracted schemes (1.8–2.0 Gy/day) and homogeneous dose distributions. Radiobiologic modeling in this area is an active area of investigation (23).

Based on these dosimetric data, one can appreciate that coverage of the planning target volume (PTV) according to the median V100 and V95 is sacrificed to prevent high dose to the thecal sac. Dosimetric data to the spinal cord and cauda equina (using the thecal sac contour, Table 3) clearly indicate that both the absolute dose and volume receiving ≥8, 10, and 15 Gy were less for reirradiated cases compared with the unirradiated tumors treated.

An analysis was performed to determine potential factors associated with local failure. Dosimetric data and the minimum distance from the PTV to the CNS were tabulated (Table 4). In six of the eight failures, the minimum distance from the PTV to the CNS was ≤1 mm, however, only in the multivariate analysis did a distance ≤1 mm suggest a trend to predict local failure ($p = 0.1$). We then performed an analysis of different cut-off distances. As the distance from the PTV to the CNS grew closer, the p value approached significance. The exploratory analysis suggested significance when the distance from the PTV to the CNS is <0.1 mm ($p = 0.02$); however, only three tumors comprised this category. These data are only suggestive because of the small number of patients who failed, and although the bulk of the tumor failure in each of the cases occurred at the PTV–CNS interface, the tumor progressed diffusely within the treatment volume. A case example of this pattern of failure from our series has been published elsewhere (1). In

observing the BED-D100 (minimum BED dose within the tumor volume) in either the no prior radiation and prior radiation cohort, the median was only 20 and 14 Gy_{10}, respectively. The BED D100 was not a factor found in the univariate or multivariate analysis to predict for failure, and this may be due to our overall good coverage of the tumor volume with a median V95 of 91% and 86%, respectively. Furthermore, at this point the significance of low point doses within a tumor volume is unknown and has yet to predict for local failure. These data highlight that the optimal dosimetric criteria and tumor dose to control spinal metastases are as yet unknown and are subject to further investigation.

Chang *et al*. reported a detailed analysis of the pattern of failure in a Phase 1/2 trial of spinal SBRT for metastases (3). In only seven of their 17 failures did patients have prior radiation to the treated area. This supports our data that prior radiation does not necessarily result in a lack of efficacy of SBRT. In six of the 17 local failures, underdosing in order to respect spinal cord constraints was the reason for failure, and in four of these six cases (four of 17 failures overall) was the primary area of failure at the epidural space. These data also support the hypothesis that underdosing may result in an increased risk of failure as the tumor approaches the epidural space.

No case of radiation-induced myelopathy was observed in this series. There have been reported cases of radiation induced myelopathy with spinal SBRT (5, 18, 24–26). For previously unirradiated tumors, conventional radiotherapy poses little risk of this complication. However, sufficient dose cannot be delivered in the reirradiation scenario with conventional techniques, and spinal SBRT is an important treatment option for these patients. The risk:benefit ratio has to be individualized for each patient and their overall situation. Insufficient data are available to recommend a threshold for safety, and the data provided here only serve as a guide when taken in their entirety. A pooled dosimetric analysis of known SBRT-induced myelopathy is ongoing for patients with no prior radiation, and this hopefully will provide some guidance (27).

CONCLUSION

In conclusion, spinal SBRT is an effective treatment modality for spinal metastases. Patients previously receiving radiation for spinal metastases with tumor progression can be treated as effectively and safely with spinal SBRT as patients with previously unirradiated spinal metastases.

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