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Long-Term Outcomes After Stereotactic Radiosurgery for Spine Metastases: Radiation Dose–Response for Late Toxicity

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Abstract

Purpose: To document the 5- and 10-year rates of late toxicity and vertebral compression fracture (VCF) in long-term survivors after stereotactic radiosurgery for spine metastases.

Methods and Materials: A retrospective review was performed on 562 patients treated with SRS for spine metastases between April 2001 and July 2011. Selecting those with at least 5-year survival after SRS, included were 43 patients who collectively underwent 84 treatments at 54 spine sites. Most were treated with single-fraction stereotactic radiosurgery to a median dose of 16 Gy (range, 12–24 Gy), and 56% of sites had received prior external beam radiation therapy. Late toxicities and VCFs occurring in the absence of tumor progression were recorded. Binary logistic regression was used to identify predictors of late complications.

Results: Nine patients (17% of treatment sites) developed grade 2 late toxicities at a median time of 12.8 months (range, 4.2–59.0 months). Actuarial 5- and 10-year rates of grade 2 late toxicity were 17% and 17%, respectively. On multivariate analysis, only cumulative biologically effective dose (BED₃) > 200 Gy (or EQD₂_{2Gy} [2-Gy equivalent dose calculated using an α/β ratio of 2] > 130 Gy) was associated with grade 2 late toxicity ($P = .036$). Maximum point BED₃ > 110 Gy (or EQD₂_{2Gy} > 70 Gy) to spinal cord or cauda equina was associated with grade 2 late neuropathy ($P = .017$). Nine VCFs (18%) occurred at a median time of 10.2 months (range, 3.2–57.2 months), with 5- and 10-year VCF rates of 17% and 17%, respectively.

Conclusion: Stereotactic radiosurgery for primary treatment and reirradiation of spinal metastases is associated with a moderate risk of late toxicity with 10-year follow-up. Risk of late toxicity significantly increases with cumulative BED₃ > 200 Gy and spinal cord or cauda equina

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point $BED_3 > 110$ Gy. Patients remain at moderate risk of VCF up to 5 years after treatment, with a plateau in incidence thereafter up to 10 years.

Summary

Assuaging concerns of late effects being underestimated by short follow-up in previous studies, in a retrospective cohort study with a minimum of 5-year follow-up, stereotactic radiosurgery for reirradiation of spine metastases is associated with moderate 5- and 10-year grade 2 toxicity rates of 17%/17%, with a plateauing of toxicity and vertebral compression fractures after 5 years. Risk of late toxicity is significantly higher with cumulative $BED_3 \geq 200$ Gy and spinal cord or cauda equina $BED_3 \geq 110$ Gy.

Introduction

Made possible with the use of modern intensity modulated radiation and image guided radiation therapy techniques, stereotactic radiosurgery (SRS) is a novel treatment option for spinal metastases that allows precise delivery of high biologically equivalent doses with enhanced dose conformality. It is particularly useful in the treatment of previously irradiated tumors, where dose to the spinal cord is a limiting factor often precluding the use of conventional radiation therapy. In addition, because SRS delivers higher total doses to tumor compared with conventionally fractionated radiation therapy, SRS may result in improved local control and pain relief. A large body of data supports the safety and efficacy of SRS for the primary treatment and reirradiation of spine metastases (1), with local control rates ranging from 80% to 85% at 1 year and effective pain control lasting up to 12 months after treatment (2-6). However, concerns regarding late toxicity inherent to hypofractionation remain. Late effects, such as spinal cord myelopathy and vertebral compression fracture (VCF), may be underestimated and tumor control overestimated, because there are limited data beyond the expected 1- to 2-year survival of even the best selected cohorts (1). In the subset of long-term survivors after spine SRS, late toxicities are of paramount significance because they may detract from quality of life and ultimately negate the benefits of palliative SRS treatment. Thus, we aimed to document the 5- and 10-year rates of late toxicity and VCF in long-term survivors after SRS for spine metastases.

Methods and Materials

With institutional review board approval, a single-institution retrospective review was performed on 562 patients treated with spinal SRS between April 2001 and July 2011 at the University of Pittsburgh. Given the focus of this article on late effects and tumor control at 5 to 10 years, patients were selected for those with a minimum of 5-year survival after SRS. Stereotactic radiosurgery was delivered using either the Cyberknife (Accuray, Sunnyvale, CA), Synergy S (Elekta, Stockholm, Sweden), or TrueBeam/Trilogy (Varian Medical Systems, Palo Alto, CA) radiosurgical delivery platforms. Treatment localization was performed using either 6-D tracking, daily cone beam computed tomography, and/or ExacTrac (Brainlab, Novalis, Munich, Germany). For patients treated using linear accelerator platforms, Bodyfix (Elekta) immobilization was used whenever feasible. Single-fraction SRS to between 12 and 24 Gy was prescribed, most commonly to the 80% isodose line. Because the majority of patients included were treated before published guidelines for

target definition, target volume was variable early in our experience (7, 8). For some patients, treatment was based on gross tumor volume only, whereas for more recently treated patients, a clinical target volume was delineated to include the involved vertebral segment. Planning target volume margin ranged from 0 to 2 mm, with editing to exclude the spinal cord or cauda equina when there was overlap. Delineation of the spinal cord and equina varied according to physician preference; spinal volumes consisted of either the entire spinal canal or the cord plus a 1-mm margin to create a planning risk volume. For the 58 treatments for which these data were available, the entire spinal canal was contoured in 22 (62.1%), and the spinal cord alone was contoured in 22 (37.9%). Nerve roots and plexuses were not separately contoured. Consistent with published international consensus recommendations, patients were generally recommended to have imaging follow-up, preferably with spine magnetic resonance imaging (MRI), 3 months after SRS, with further imaging protocols varying across the time periods examined, according to physician preference (9).

A single spine treatment site was defined as spanning 1 to 2 vertebral bodies. For the purposes of analysis, when patients were re-treated with SRS for local failure at the same vertebral level or within 1 adjacent vertebral level, this would be considered as having received multiple courses of SRS to the same treatment site. Single-fraction SRS was used for all repeat treatments to the same site.

Late toxicities occurring >3 months after treatment were graded using Common Terminology Criteria for Adverse Events version 4, based on retrospective review of follow-up records. Late toxicity was analyzed on a per-treatment-site basis, to better account for cumulative dose effects, given prior external beam irradiation and multiple re-treatments with SRS in a significant subset of patients. Univariate and multivariate binary logistic regression was used to identify potential predictors of late toxicity, such as age, sex, primary disease site, level treated (cervical, thoracic, lumbar, or sacral), cumulative biologically effective dose (BED₃), and cumulative 2-Gy equivalent dose. The BED₃ for each course of external beam radiation and SRS was calculated from the prescription dose, using the linear-quadratic model, with a normal tissue α/β ratio of 3. Owing to the wide range of published estimates of spinal cord α/β ratio with values varying between 0.9 and 4.0 (10, 11), we chose to use a uniform value of 3 for all levels of spine and cauda equina in our BED calculations. Cumulative BED₃ was defined as the sum of the BED₃ of all prior external beam treatments and SRS courses to a given treatment site, censored at the date of late toxicity. Because most late toxicities consisted of neuropathy, we performed a similar analysis to identify potential predictors of neuropathy, including cumulative point BED₃ delivered to the spinal cord or cauda equina. Spinal cord and cauda equina point BED₃ were calculated according to the prior external beam prescription dose and the maximum point dose delivered to the spinal cord (for lesions above L2) or cauda equina (for lesions below L2), for each SRS course delivered to a given treatment site. Finally, to make our results more comparable to other studies in which the 2-Gy equivalent dose was calculated using an α/β ratio of 2 (EQD₂_{2Gy}) for the spinal cord (11, 12), we performed a similar analysis with the cumulative EQD₂_{2Gy} delivered to each treatment site.

The incidence of de novo VCF or progression of pre-existing VCFs occurring in the absence of tumor progression was recorded, based on review of follow-up computed tomography or

MRI spine imaging where available, in conjunction with review of clinic follow-up notes. In cases in which imaging was not available for review, such as with outside hospital films, the follow-up notes or radiology read describing the findings were used. Potential predictors of VCF, such as age, sex, primary tumor type, sclerotic versus lytic lesion type, presence of pre-existing compression fracture, SRS dose, cumulative BED₃ of all prior treatments, and gross tumor volume, were analyzed using binary logistic regression. Local failure was defined as tumor progression at the treated level or within 1 vertebral body of the treated level, to conservatively account for marginal failures. The Kaplan-Meier method was used to estimate actuarial rates of local control, late toxicity, and VCF at 5 and 10 years. All endpoints were calculated from the date of first SRS treatment.

Results

Baseline patient characteristics

Of 84 treated lesions in 43 patients, 70 had a follow-up time of at least 5 years and were included in the analysis. There were 54 treatment sites. Table 1 summarizes baseline characteristics for included patients.

Efficacy: local control and pain relief

The median follow-up was 81.6 months (range, 60.3-133.5 months). Pain relief was achieved after 89% of treatments. The crude local failure rate was 44.4% (n = 24). Actuarial 1-year, 5-year, and 10-year rates of local control were 82.7%, 57.7%, and 54.3%, respectively (Fig. 1). The median time to local recurrence was 21.0 months (range, 2.0-137.4 months). Ten local recurrences occurred outside the radiation field, 13 occurred in-field, and 1 occurred both within and outside the field. Age, prior surgery, primary tumor type, level treated, SRS dose, and treatment volume were not associated with local control. Salvage therapy consisted of repeat SRS in 16 cases, surgery in 4, surgery followed by repeat SRS in 2, systemic therapy in 1, and none in 1 case.

Late toxicities

Nine patients (20.9% of patients, 16.7% of treated sites) developed grade 2 late toxicities at a median time of 12.8 months after SRS (range, 4.2-59.0 months) (Table 2). This included 5 patients who developed grade 3 late toxicity consisting of painful sensory neuropathy (n = 3), esophageal stricture (n = 1), and radiation-induced ureteral stricture requiring chronic stent placement (n = 1) (Fig. 2). The patient with the ureteral stricture also developed a grade 4 nonhealing wound secondary to radiation-related ischemia, requiring hyperbaric oxygen therapy.

All 3 patients who developed grade 3 sensory neuropathy had been treated with external beam radiation therapy to the sacrum, followed by 3 to 5 courses of SRS to the L5–sacrum region. Management of grade 3 neuropathy cases is described in Table E1 (available online at www.redjournal.org). Management of patients with grade 2 painful neuropathy consisted of medications for neuropathic pain, physical therapy, or narcotics, as needed. Table E2 (available online at www.redjournal.org) shows the number and intervals of re-treatments by presence or absence of grade 2 late neuropathy.

Actuarial 5- and 10-year rates of grade 2 and grade 3 toxicity were 17%/17% and 9%/9%, respectively. On univariate analysis, cumulative BED₃ of all prior treatments > 200 Gy was associated with any grade 2 late toxicity ($P = .012$), and there was a trend to higher rates of grade 2 late toxicity with treatment of sacral lesions ($P = .055$) (Figs. 3A and 3B). On multivariate analysis, only cumulative BED₃ > 200 Gy remained significant ($P = .036$, hazard ratio 12.05, 95% confidence interval [CI] 1.2-123.0). Age, sex, and primary tumor site were not associated with late toxicity. Although there was no significant interaction between BED₃ > 200 Gy and treated spine level according to χ^2 testing ($P = .21$), a larger proportion of sacral lesions (75.0%) received BED₃ > 200 Gy, compared with 33.3% of cervical lesions, 41.7% of thoracic lesions, and 30.8% of lumbar lesions. When we repeated the analysis using EQD₂_{2Gy}, we found that EQD₂_{2Gy} > 130 Gy is an equivalent predictor to the cut point of BED₃ > 200 Gy.

A receiver operating characteristic (ROC) curve was generated to better assess the most reliable BED₃ threshold and its accuracy in predicting for grade 2 late toxicity (Fig. E1, available online at www.redjournal.org). The area under the curve value was 0.86 (95% CI 0.7-1.0), suggesting that the BED₃ is a good predictor for toxicity. In reviewing the coordinates of the curve, which are displayed in Table E3 (available online at www.redjournal.org), the optimal cut-off point seems to be at a BED₃ threshold of 259 Gy, where the sensitivity is 89% and the specificity is 89%. This threshold is higher than the threshold of 200 Gy identified on multivariate analysis. Eight of 9 patients who experienced grade 2 late toxicities all received a BED₃ of >260 Gy to a single treatment site. No late toxicity was seen below a cumulative BED₃ of 260 Gy (Fig. 3C), with the exception of 1 patient who received a single SRS treatment to the C2 level to a BED₃ of 60 Gy, with no prior external beam radiation therapy, and subsequently developed bilateral hand and finger numbness 3 months after SRS, with repeat spine MRI negative for tumor progression. Multiple cut-off points were tested during logistic regression, and in fact both >260 Gy and >200 Gy were identified as significant predictors on univariate analysis; however, >200 Gy was ultimately chosen for inclusion in multivariate analysis because it was the more conservative value.

Maximum point BED₃ > 110 Gy delivered to the spinal cord or cauda equina was associated with grade 2 late neuropathy ($P = .017$). Although multiple cut-off points were tested, 110 Gy was the most conservative. A ROC analysis showed an area under the curve value of 0.82 (95% CI 0.7-1.0) (Fig. E2 and Table E4, available online at www.redjournal.org). The ROC analysis suggests an optimal cut-off at a BED₃ threshold of 121 Gy, where the sensitivity is 86% and the specificity is 76%. When we repeated the analysis using EQD₂_{2Gy}, we found that a maximum point EQD₂_{2Gy} > 70 Gy is an equivalent predictor to maximum point BED₃ > 110 Gy.

Vertebral compression fractures

Sixteen lesions (22.9%) were managed with spinal surgery before SRS, including 9 kyphoplasties for pre-existing pathologic fracture and 5 decompressive surgeries. The decision for surgical stabilization, either using percutaneous cement augmentation or

instrumented fixation, was based on the degree of mechanical instability as determined by the Spinal Instability Neoplastic Score (13).

Of 54 sites, 9 VCFs (16.7% of treated sites) occurred at a median time of 10.2 months (range, 3.2-57.2 months). The 5- and 10-year rates of VCF according to whether surgery was performed before first course of SRS are described in Table E5 (available online at www.redjournal.org) and Figure 4. Seven vertebral compression fractures (77.8%) occurred de novo, and 2 (22.2%) were progression of a pre-existing fracture. Eight fractures (88.9%) were symptomatic with pain, and 5 (55.6%) required surgical stabilization with kyphoplasty (n = 4) or posterior spinal fusion (n = 1). Among the patients who were symptomatic but did not undergo surgical treatment of their fracture, 1 patient was offered a kyphoplasty but refused; 1 patient was managed nonsurgically because she also developed grade 3 neuropathic pain, eventually managed with a morphine pump, and it was not thought that a kyphoplasty would alleviate her symptoms; and 1 patient had had prior kyphoplasty, although subsequent imaging showed loss of 50% of anterior vertebral height, and was offered conservative management. Age, sex, primary tumor type, sclerotic versus lytic lesion type, presence of pre-existing compression fracture, SRS dose, cumulative BED₃ of all prior treatments, and gross tumor volume did not predict for vertebral compression fracture.

Discussion

Re-irradiation of spinal metastases with traditional external beam radiation therapy techniques is limited by dose tolerance limits of normal organs, especially the spinal cord. Although numerous series have demonstrated the safety and efficacy of SRS, follow-up in most series is limited to 1 to 2 years (1-6). In the era of improving systemic therapy, the effect of late toxicities on long-term survivors becomes increasingly important. Our series is the first to report long-term follow-up up to 10 years in this population, with a median follow-up of 81 months per lesion. We found that SRS for the primary treatment or reirradiation of spine metastases is associated with 5-year rates of grade 2 and grade 3 late toxicity of 17% and 9%, respectively, with no further increase in toxicity up to 10 years. Similarly, we found the 5-year and 10-year rates of vertebral compression fracture were both 17%, indicating a plateau in incidence after 5 years.

The majority of late toxicities observed in this study consisted of nervous system injury. Preclinical studies on spinal cord tolerance in animals suggest that the pathogenesis of radiation-induced spinal cord injury includes vascular endothelial damage as the primary event leading to white matter necrosis and resultant radiation myelopathy (14). Animal studies on the repair kinetics of radiation injury to the spinal cord support a time-dependent model of spinal cord recovery (15-18). Using a rat model, the half-time of repair for the spinal cord has been estimated at 1.5 hours (18), whereas others have used primate models to develop a long-term reirradiation tolerance model wherein the estimated long-term recovery at 1, 2, and 3 years was 34 Gy, 28 Gy, and 45 Gy, respectively (16).

In the setting of reirradiation with conventional external beam radiation therapy, the risk of radiation myelopathy has been minimized with maintaining a cumulative BED₂ < 120 Gy, although other factors affecting the safety of reirradiation include the reirradiation interval

and volume of spinal cord irradiated (12, 19). A BED_2 of 120 Gy is equivalent to 60 Gy in 2-Gy fractions, which is roughly half the cumulative EQD_{2Gy} limit of 130 Gy that we identified in our study. Our results demonstrate the utility of SRS in allowing safe dose escalation in the setting of reirradiation, where not possible with external beam radiation therapy.

We identified spine or cauda equina maximum point $EQD_{2Gy} > 70$ Gy as a predictor for grade 2 late neuropathy. Despite variations in the methods for delineation of the spinal cord, this finding corroborates a small, earlier study by Sahgal et al (12), who similarly recommended limiting the maximum dose to the thecal sac for reirradiation SRS to an EQD_{2Gy} of 25 Gy, for a cumulative EQD_{2Gy} of 70 Gy. Others have not identified a dose–response relationship for radiation-induced toxicity. Thibault et al (20) reported on 56 spinal levels in 40 patients irradiated with a second course of SRS to the same level, to a median dose of 30 Gy in 4 fractions (20). With a median follow-up of 6.8 months, no radiation-induced VCF or myelopathy was observed, likely a result of the limited follow-up time. The dose–response relationship identified herein, with cumulative $EQD_{2Gy} > 130$ Gy or $BED_3 > 200$ Gy predicting for grade 2 toxicity, may help guide the application of reirradiation with SRS, because these patients often have limited additional treatment options and are otherwise left to endure the sequelae of uncontrolled spine metastases.

We identified a trend to higher rates of grade 2 late toxicity with treatment of sacral lesions ($P = .055$) on univariate analysis, although this factor was nonsignificant on multivariate analysis. We hypothesize an interplay between dose and level treated, whereby higher doses are delivered to sacral lesions owing to the perceived higher dose tolerance of the cauda equina compared with the spinal cord. However, our data suggest that the cauda equina may not have as high a tolerance as previously thought. Others have noted that single-fraction spine SRS for spine metastases is associated with a <3% risk of peripheral nervous system injury at 3 years, with the most common sites of injury being lumbosacral and brachial plexus (21).

The Memorial Sloan-Kettering Cancer Center recently published a series on 31 patients with 36 treated spinal lesions who survived 5 years after treatment with single-fraction SRS to 24 Gy (22). In contrast to our results, no dose–response relationship was identified, and there were no high-grade late toxicities. Late toxicities were reported in 8 patients (22%) who developed grade 2 neurologic morbidity consisting of paresthesia or neuropathic pain, 8 (22%) with skin toxicity, 3 (8%) with myalgia or myositis, and 2 patients (6%) with gastrointestinal discomfort. The lack of late high-grade toxicity may be explained by the fact that 35 of the lesions (97%) were treated with spinal SRS as the first course of irradiation, whereas 56% of treatment sites in our study had received prior external beam radiation therapy, with some patients later receiving repeat spinal SRS at the same site for local failure.

In the Memorial Sloan-Kettering study, VCF occurred at 13 treated levels (36%), of which 5 (14%) were symptomatic and required percutaneous cement augmentation or surgical management (22). Our VCF rate was lower at 17% overall, which may be due to our institutional preference for aggressive pre-SRS surgical stabilization in patients with a

potentially unstable pre-existing pathologic fracture. In our series, 23% of lesions were stabilized with spinal surgery before SRS, an approach that has been shown to be an effective management strategy for patients presenting with pathologic fractures secondary to spine metastasis (23). Our VCF rate was within the range of 6% to 20% reported in most other series (24-28). Although others have reported various predictive factors for VCF, such as percentage of vertebral body tumor replacement, presence of lytic disease, and pre-existing VCF (27-29), our study did not identify any predictive factors, likely owing to our smaller sample size consisting of only those with long-term follow-up. The plateau of VCF beyond 5 years supports the idea that VCF remains predominantly an acute or subacute phenomena.

A recent multi-institutional analysis was published on 215 patients with 247 spinal target volumes treated with salvage reirradiation SRS to the spine, at a median interval of 13.5 months after prior conventional external beam radiation therapy (30). The median dose of initial external beam radiation therapy was 30 Gy in 10 fractions, and the median SRS dose used was 18 Gy in 1 fraction. With a limited median follow-up of 8.1 months, no cases of radiation myelopathy or radiculopathy were identified, and the VCF rate was 4.5%. Of the 11 VCFs identified, 5 were de novo, and 6 were fracture progression.

Our study is limited by the inherent biases of its retrospective design, including a lack of standardization of volume definition over time, treatment delivery, follow-up, and imaging. In addition, radiobiological data suggest that direct tumor cell death cannot account entirely for the efficacy of SRS. Preclinical evidence suggests that irradiation of tumors with high dose (>10 Gy) per fraction damages tumor vasculature and thus destroys the tumor microenvironment, leading to indirect, ischemic tumor cell death (31). Therefore, our calculation of BED and EQD2 based on the linear-quadratic model, which only accounts for direct cell death caused by DNA strand breaks, may not be an accurate representation of the true dose delivered (32). Nevertheless, our data still indicate an association between cumulative dose delivered and risk of late effects.

Another limitation of this study stems from the inability to differentiate radiation-induced neuropathy from other, confounding causes of neuropathy. The majority of patients experiencing late toxicity in this series had painful neuropathy as a component of their symptoms. However, some patients' symptoms may have been multifactorial owing to the complex interplay between potentially radiation-induced neuropathy or myelopathy, neurotoxic chemotherapy, and subsequent salvage surgeries leading to increased risk of nerve injury. Nevertheless, to avoid underreporting of toxicity, such patients were conservatively graded to have radiation-related toxicity for the purposes of this analysis. Thus, late toxicity may have been overestimated in our study.

Conclusion

Extreme hypofractionation with SRS for the primary treatment and reirradiation of spinal metastases achieves excellent pain relief and durable local control and is associated with a moderate risk of late toxicity with 10-year follow-up. Risk of late toxicity is a function of total dose and is significantly higher with cumulative $BED_3 > 200$ Gy (or $EQD2_{2Gy} > 130$

Gy) and spinal cord or cauda equina point $BED_3 > 110$ Gy (or $EQD_{2Gy} > 70$ Gy). Patients remain at moderate risk of VCF up to 5 years after treatment, with a plateau in incidence thereafter up to 10 years.

Extended Data

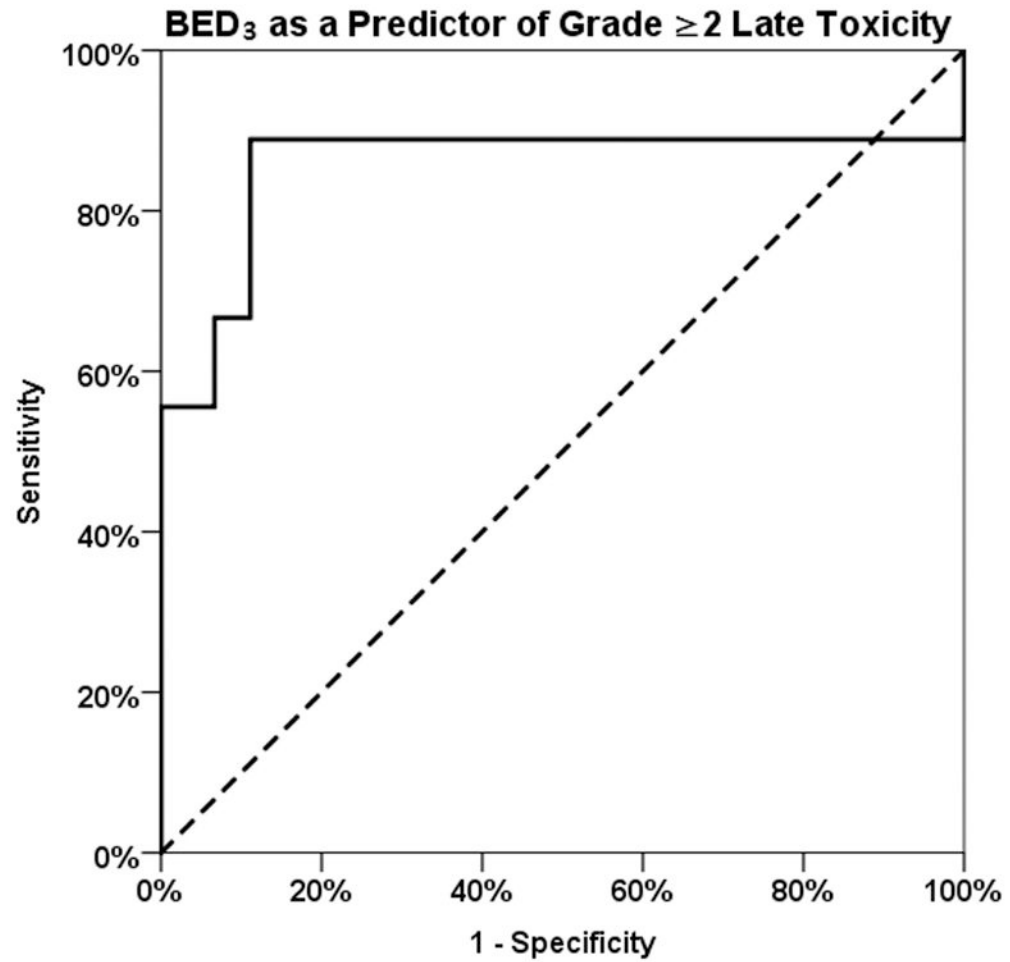


Fig. E1.

Cord or Equina BED₃ as a Predictor of Grade ≥ 2 Late Neuropathy

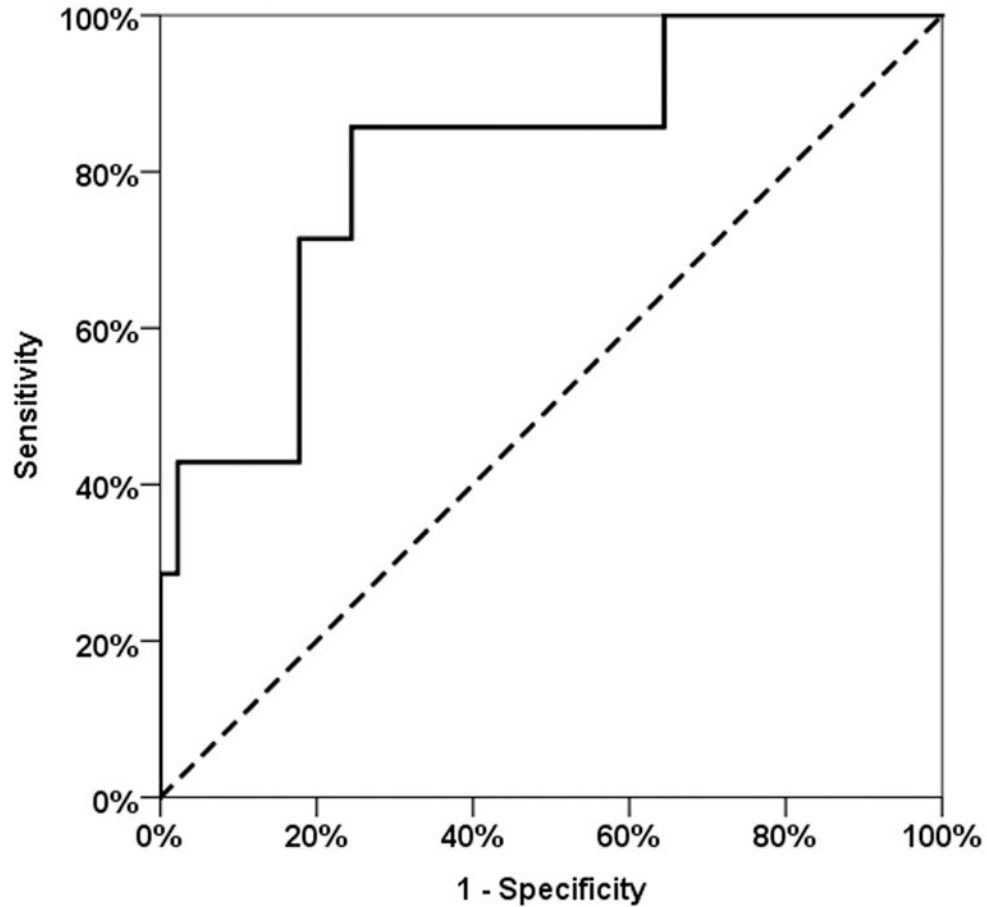


Fig. E2.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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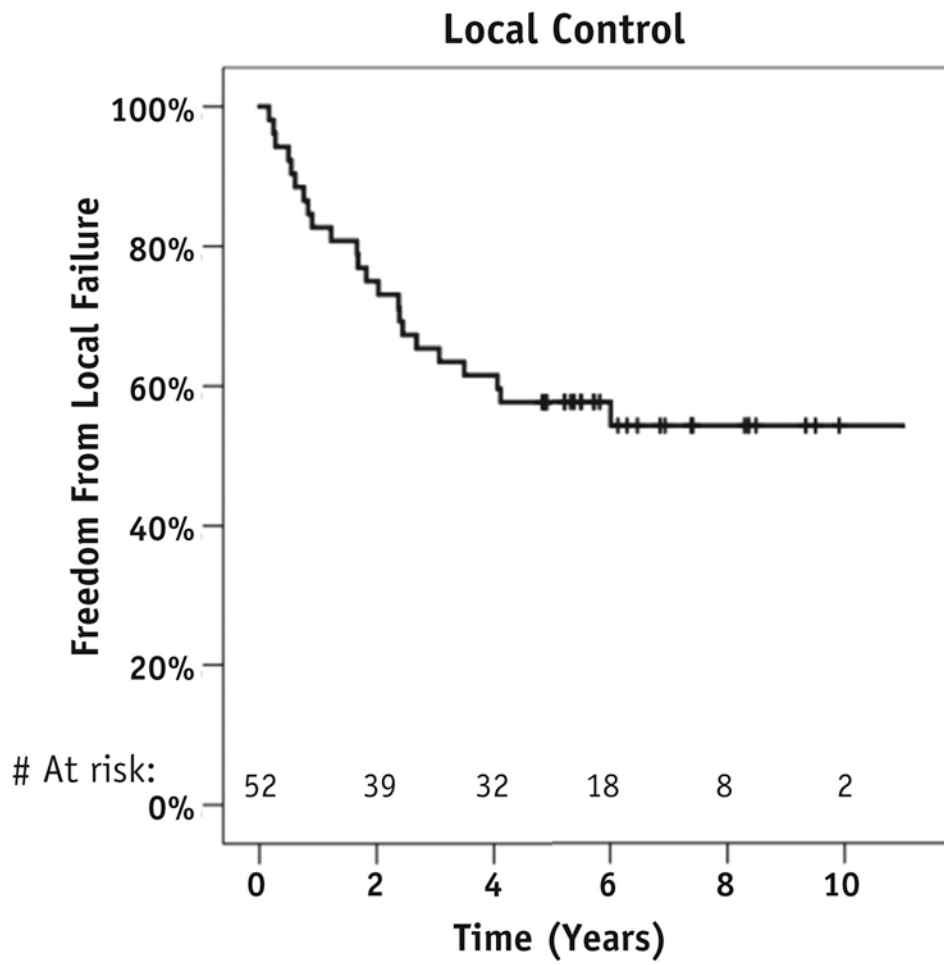


Fig. 1.
Kaplan-Meier analysis of local control.

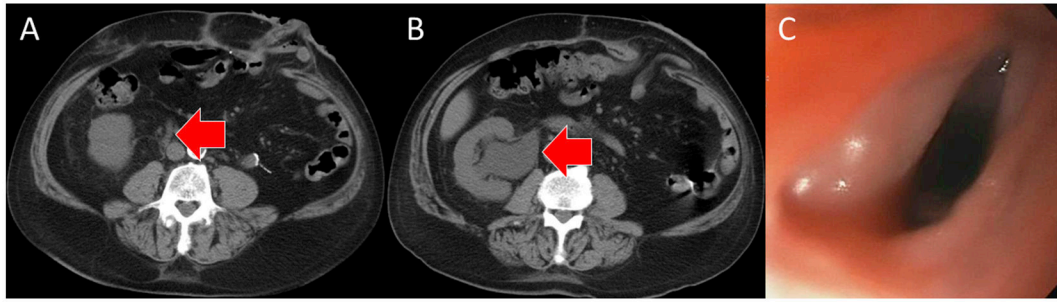


Fig. 2.

(A) Grade 3 radiation-induced right ureteral stricture at 5 years after stereotactic radiosurgery, causing hydronephrosis as shown in (B), requiring a chronic ureteral stent. (C) Grade 3 radiation-induced esophageal stricture at 53 months after stereotactic radiosurgery.

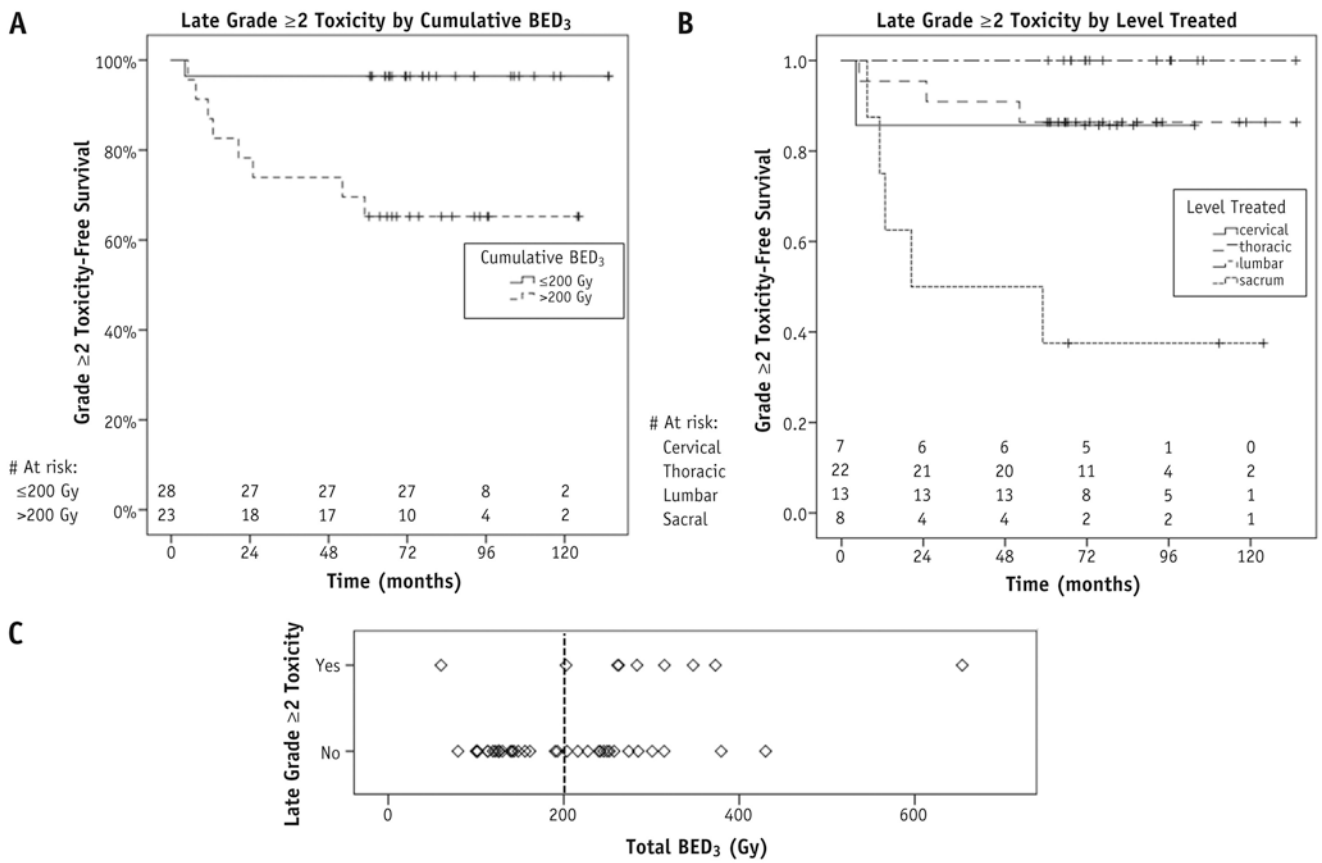


Fig. 3. (A, B) Grade ≥ 2 late toxicity by cumulative biologically effective dose (BED₃) and by spine level treated, respectively. (C) Cumulative biologically effective dose cut-off point of 200 Gy, above which the vast majority of late toxicities occurred.

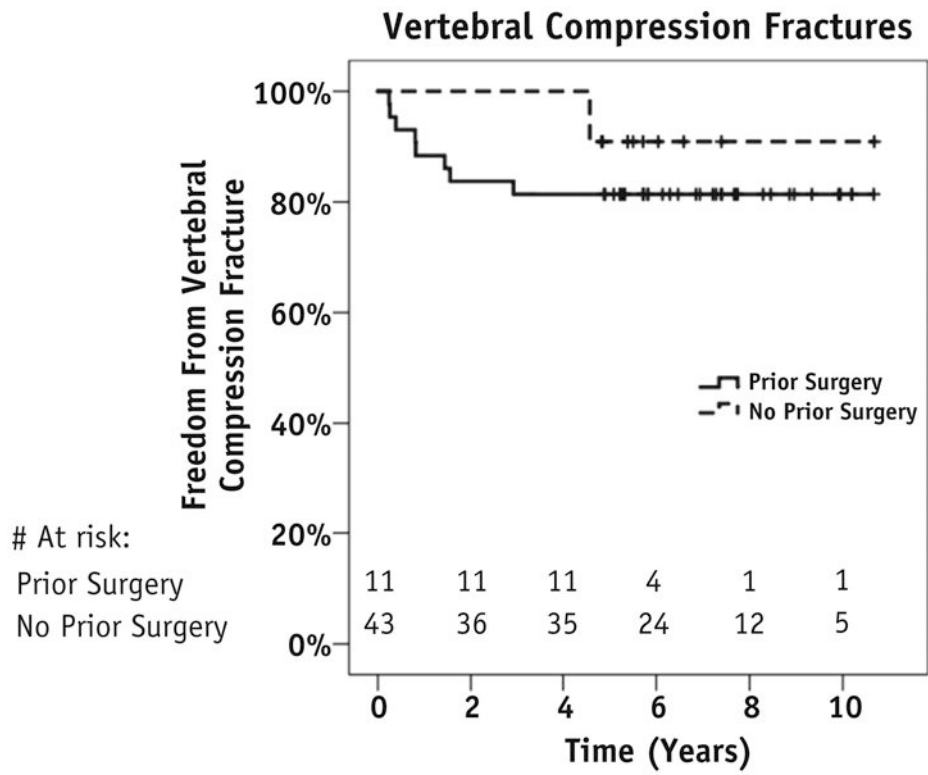


Fig. 4. Kaplan-Meier analysis of long-term risk of vertebral compression fractures.

Table 1

Baseline characteristics

Characteristic	n	% or range	Grade 2 late toxicity			Vertebral compression fracture		
			No (%)	Yes (%)	HR (95% CI)	No (%)	Yes (%)	HR (95% CI)
Age (y)								
<60	32	59.3	84.4	15.6		81.3	18.8	
60	22	40.7	81.8	18.2	1.2 (0.3-5.1)	86.4	13.6	0.5 (0.1-2.6)
Sex								
Male	23	42.6	82.6	17.4		87.0	13.0	
Female	31	57.4	83.9	16.1	0.9 (0.2-3.9)	80.6	19.4	1.3 (0.3-6.2)
Primary tumor histology								
Breast	22	40.7	77.3	22.7		86.4	13.6	
Renal	11	20.4	81.8	18.2	0.8 (0.1-4.7)	81.8	18.2	1.4 (0.2-10.0)
NSCLC	5	9.3	100.0	0.0	-	100.0	0.0	-
Other	16	29.6	87.5	12.5	0.5 (0.1-2.9)	75.0	25.0	1.9 (0.3-11.2)
Level treated								
Cervical	9	16.7	88.9	11.1		88.9	11.1	
Thoracic	24	44.4	87.5	12.5	1.1 (0.1-12.7)	83.3	16.7	-
Lumbar	13	24.1	100.0	0.0	-	76.9	23.1	-
Sacral	8	14.8	37.5	62.5	13.3 (1.1-166.4)	87.5	12.5	-
Prior EBRT	30	55.6	-	-	-	-	-	-
Median reirradiation interval after EBRT (mo)	12.7	0.9-145.0	-	-	-	-	-	-
Median prior EBRT BED ₃ (Gy)	60	27-131	-	-	-	-	-	-
Lesion type								
Sclerotic	9	16.7	-	-	-	77.8	22.2	
Lytic	23	42.6	-	-	-	82.6	17.4	0.4 (0.1-2.2)
Mixed	7	13.0	-	-	-	100.0	0.0	
Pre-existing fracture								
No	45	83.3	-	-	-	84.4	15.6	
Yes	9	16.7	-	-	-	77.8	22.2	1.7 (0.3-10.3)
Single-fraction SRS dose (Gy)								
			-	-	-	-	-	-

Characteristic	n	% or range	Grade 2 late toxicity			Vertebral compression fracture		
			No (%)	Yes (%)	HR (95% CI)	No (%)	Yes (%)	HR (95% CI)
16	38	56.7	-	-	-	86.8	13.2	
>16	29	43.3	-	-	-	86.2	13.8	1.1 (0.3-4.3)
Cumulative BED ₃ (Gy)								
<200	31	57.4	96.8	3.2		83.9	16.1	
200	23	42.6	65.2	34.8	16.0 (1.8-140.0)	82.6	17.4	1.3 (0.3-5.7)

Abbreviations: BED = biologically equivalent dose; CI = confidence interval; EBRT = external beam radiation therapy; HR = hazard ratio; NSCLC = non-small cell lung cancer.

Table 2

Late toxicities

Toxicity	Grade 2		Grade 3		Grade 4	
	n	%*	n	%*	n	%*
Neuropathy	4	7.4	3	5.6	0	0.0
Esophageal stricture	0	0.0	1	1.9	0	0.0
Skin	0	0.0	0	0.0	1	1.9
Ureteral stricture	0	0.0	1	1.9	0	0.0

* Percentage is out of a total of 54 treated spine sites.

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