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Original Article

Dosimetric factors of stereotactic body radiation therapy for isolated spinal metastatic diseases: impact of distance from tumor target to spinal cord on planning dosimetry and low dose spillage restriction

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Abstract: Background: This study evaluated the impact of the distance from planning target volume (PTV) to spinal cord on planning dosimetry of stereotactic body radiation therapy (SBRT) in patients with isolated spine metastasis and established planning criteria and parameters to restricting low dose spillage. Methods: Six modified PTVs from each of 10 patients with isolated spinal metastasis were created by artificial uniform extension from clinical target volume (CTV) to ensure a minimum PTV-to-cord distance of 0, 1, 2, 3, 4 and 5 mm; respectively. The prescription dose (PD) was 22 Gy in a single fraction. PTV dosimetric parameters including V_{100}, D_{min}, D_{98}, D_{95}, D_1, conformity index (CI), $R_{50\%}$ (ratio of the 50% prescription isodose volume to the PTV), $D_{2\,cm}$ (maximum dose in percentage of PD at 2 cm from PTV in any direction), and cord dose were measured and compared. Results: PTV V_{100}, D_{min}, D_{98}, D_{95} were enhanced markedly along with the increase of the PTV-to-cord distance, with a significant difference. PTV CI, $R_{50\%}$, $D_{2\,cm}$, and cord dose were not statistically significant in different PTV-to-cord distances. A PTV-to-cord distance of 2 to 3 mm meet PTV D_{min}, D_{98}, D_{95}. $R_{50\%}$, and $D_{2\,cm}$ could restrict low dose spillage in SRS panning. Conclusions: PTV V_{100}, D_{min}, D_{98}, D_{95} are directly correlated with PTV-to-cord distance for spine SBRT in single fraction. A distance of 2 to 3 mm from PTV to spinal cord meets planning dose requirements. $R_{50\%}$ and $D_{2\,cm}$ can quantitatively restrict low dose spillage and improve plan quality.

Keywords: Spine metastasis, stereotactic body radiation therapy, distance, spinal cord, dose fall off

Introduction

Spine is the most common metastatic site in patients with bone metastasis, nearly one-third of skeletal metastases. Furthermore, autopsy studies have shown that as many as 70% of cancer patients have spinal metastases [1]. With technology development of contemporary radiation therapy, stereotactic body radiation therapy (SBRT) has become increasing mainstay and common treatment modality of spine metastasis, with preliminary outcome data demonstrating high rates of long-term local control and pain relief, with better efficacy than conventional palliative radiation therapy [2-4].

SBRT in single fraction allows delivery of a conformal high radiation dose to tumor target, and steep fall-off of dose gradient protects adjacent normal structures, especial spinal cord, which dose constraint requires a certain distance, and a too narrow distance between tumor and cord limits the dose fall-off, resulting in an under-dose in epidural space in where metastatic progression is the most common failure site [5-9]. Some research institutions and clinical trials, including RTOG 0631 trial, suggest a minimum distance of at least 2 to 5 mm from tumor to spinal cord to ensure a good dose distribution [10-14]. However the optimal distance between tumor volume and spinal cord with a

satisfied target dosimetry and cord dose constraint in patients undergoing spinal SBRT is unknown.

RTOG 0613 study has established detailed dosimetric quality control constraints for single fraction SBRT of localized spine metastases, such as target coverage, dose heterogeneity, high dose spillage (HDS), low dose spillage, and dose-volume constraints for spinal cord and organs at risk (OARs). However, the aim of RTOG 0613 study was to assess the feasibility and safety of single fraction spine SBRT with a dose of 16 Gy, and the primary endpoint was pain control, without quantitative guidance regarding the low dose spillage. More and more studies demonstrated that high dose (BED ≥ 70 Gy) is required for durable control of spine metastatic disease in selected patients, leading to improved survival [15-19].

In this study, we evaluated the impacts of different distances (0-5 mm) from tumor planning volume (PTV) to spinal cord on spine SBRT dosimetry in patients with isolated spine metastasis.

Materials and methods

Patients

This study involved 10 patients with isolated spine metastases (single solitary spine metastasis involving one spine level, without epidural compression) and treated with image guided linear accelerator based SBRT, and selected to represent various spinal location at 3 spinal levels (2 cervical, 6 thoracic, and 2 lumbar). Patients were positioned in a stable supine position immobilized by thermoplastic mask. Before treatment planning, contrast enhanced planning CT scanning (Philips Medical Systems, Cleveland, OH, USA) with 1.5 mm slice thickness and contrast enhanced 3D planning MR imaging (SOMATOM Sensation Open CT scanner; Siemens, Munich, Germany) with FSPGR sequence and 1.2 mm slice thickness were performed for each patient.

Targets and OARs delineation

Planning CT and MR images were fused for gross tumor volume (GTV) and cord contouring. Clinical target volume (CTV) contours were consistent with International Spine Radiosurgery Consortium consensus guidelines [20], and included the entire vertebral body for lesions involving the vertebral body, or adjacent bony structures for lesions involving the lamina, pedicles, transverse or spinous process depending on lesion location and extent. For each patient 6 planning target volumes (PTVs) were created by artificial uniform extension from CTV to ensure the minimum distance between the spinal cord and PTV was 0, 1, 2, 3, 4 and 5 mm; respectively. OARs included pharynx, esophagus, lungs, kidneys and liver. Cord and esophagus were extended 6 mm above and below PTV in the cranio-caudal direction.

SBRT planning

Inversely optimized intensity-modulated radiation therapy (IMRT) planning, with single-isocenter, coplan, and 11 fields, was mandatory with Pinnacle system (Pinnacle^3 version 9.6, Phillips Medical Systems, Andover, Mass). Patients were treated with Elekta Synergy S system consists of a step-and-shoot IMRT function and a high-resolution multi-leaf collimator (MLC) with 40 leaf pairs with a leaf width of 4 mm (Beam modulator, Elekta, Crawley, UK). Volumetric image-guidance was performed with kV cone-beam CT CBCT technique (Elekta XVI, Crawley, UK). Informed consent was obtained from all patients before receiving treatment.

The PTV prescription dose (PD) was 22 Gy in one fraction, as biologically effective dose (BED) with an of 10 Gy of 70 Gy. Planning optimization was performed with established planning objectives to achieve satisfied target dose coverage, conformity, and dose falloff by using both RTOG 0631 and RTOG 0915 protocol criteria, and that of Hong et al. [21-23]. The constraints for spinal cord were as follows: < 1.2 cc receives > 7 Gy, < 0.35 cc receives > 10 Gy, and maximum point dose receives < 14 Gy [22, 24].

In this study, the 10 patients were initially planned with constraint of low dose spillage by $R_{50\%}$ and $D_{2\ cm}$ (restriction group); and subsequently replanned without constraint of low dose spillage, the planners would try their best to meet the cord constraints and get the best coverage that they deemed possible (no-restriction group).

Table 1. Summary of planning parameters based on different PTV-to-cord distances

Variable	PTV-to-cord distance						X^2	*P*
	0 mm	1 mm	2 mm	3 mm	4 mm	5 mm		
PTV								
Volume (cm^3)	41.4	41.0	40.4	39.7	38.8	37.9	0.02	1.000
V_{100} (%)	90.5	92.1	94.2	95.1	96.3	98.2	25.21	< 0.001
D_{min} (Gy)	10.4	12.6	14.4	16.1	17.7	19.2	24.50	< 0.001
BED D_{min} (Gy)	21.4	28.5	35.2	42.3	49.2	56.3		
D_{99} (Gy)	15.1	17.2	19.2	20.5	21.1	21.7	28.00	< 0.001
BED D_{99} (Gy)	37.9	46.7	56.0	62.7	65.8	68.6		
D_{98} (Gy)	16.8	18.8	20.5	21.3	21.6	22.0	27.99	< 0.001
BED D_{98} (Gy)	45.1	54.1	62.4	66.4	68.3	70.6		
D_{95} (Gy)	20.1	21.3	21.8	22.0	22.2	22.5	23.60	< 0.001
BED D_{95} (Gy)	60.7	66.4	69.4	70.5	71.5	72.9		
D_1 (Gy)	26.6	27.9	27.7	27.1	25.9	26.1	1.20	0.945
BED D_1 (Gy)	97.5	106.5	104.4	101.0	93.2	94.5		
CI	1.10	1.12	1.15	1.14	1.14	1.16	2.32	0.803
$R_{50\%}$	4.7	5.0	5.1	5.1	5.0	5.0	1.00	0.963
$D_{2\ cm}$ (%)	0.63	0.63	0.68	0.63	0.57	0.59	3.43	0.634
Cord dose (Gy)								
D_{max}	13.8	13.8	13.5	13.7	13.8	13.7	6.43	0.266
0.35 cc	9.7	9.7	9.5	9.6	9.6	9.7	0.67	0.984
1.2 cc	6.9	6.7	6.8	6.9	6.7	6.7	1.02	0.961

Abbreviations: PTV = planning target volume, V_x = volume within the target receiving ≥ x% of the prescription dose, D_{min} = minimum dose, BED = biologically effective dose, D_x = dose covering x% of the target volume, CI (conformity index) = ratio of the prescription isodose volume to the PTV volume, $R_{50\%}$ = ratio of the 50% prescription isodose volume to the PTV volume, $D_{2\ cm}$ = maximum dose in percentage of the prescription dose at 2 cm from PTV in any direction, D_{max} = maximum dose.

Planning evaluation

Dose distributions and dose volume histograms (DVHs) for all plans were evaluated with the following indices:

PTV coverage: V_x means the volume within the target receiving ≥ x% of the PD [25]. For example, V_{100} of PTV was used to describe the PTV coverage. In this study, PTV coverage required at least 90% of the target volume covered by the PD, coverage of 80%-90% was acceptable (minor deviation) and coverage < 80% was unacceptable (major deviation).

Dose parameters of PTV: D_x is defined as the dose covering x% of the target volume [26]. Maximum dose delivered to PTV was evaluated by using D_1 and maximum point dose (D_{max}). In addition, we also evaluated dose to 98% of the volume (D_{98}) and dose to 95% of the volume (D_{95}), which have been shown associated with local control [27]. The BED was calculated for all dosimetric data using a value of 10 Gy for tumor effect on PTV and a value of 2 Gy for spinal cord late effects.

Conformity index (CI): CI is the ratio of the prescription isodose volume (PIV) to the PTV volume. In this study, the CI constraint is no more than 1.2 (acceptable deviation: CI < 1.5).

Dose falloff: $R_{50\%}$ is the ratio of 50% prescription isodose volume (PIV) to the PTV volume, representing the falloff gradient beyond the PTV to extend into normal tissues. $D_{2\ cm}$ (%) is the D_{max} in percentage of PD at 2 cm from PTV in any direction, demonstrating the ability of a treatment technique to tightly conform the PD to the target. Appropriate conduct of treatment planning dosimetry for CI, $R_{50\%}$ and $D_{2\ cm}$ was based on RTOG-0915 study [21].

Statistics

All statistical analyses were performed with SPSS software (version 13.0, SPSS, Inc., Chicago, IL). Paired t-test was used to compare the dosimetric differences between limited group and non-limited group. A Wilcoxon signed rank test was used to determine the statistically significant difference for all the parameters with different distances from tumor to spinal cord. A two-tailed value of $P < 0.05$ was defined as having statistical significance.

Results

All together 120 SBRT plans were analyzed. **Table 1** summarizes variations of planning parameters based on different PTV-to-cord distances.

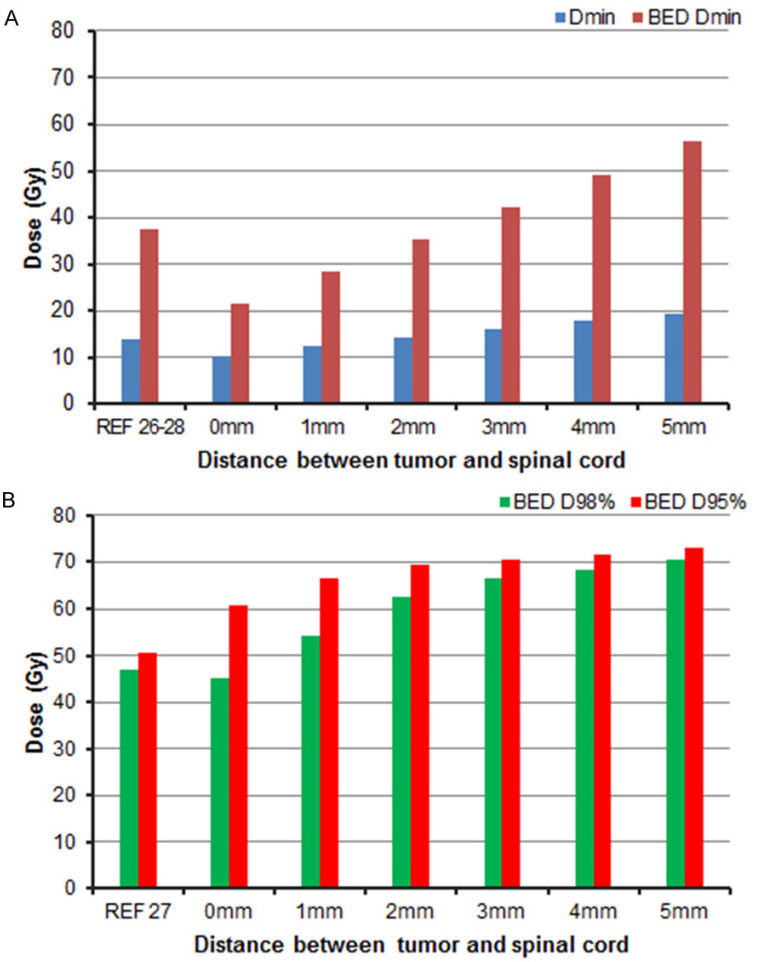

Figure 1. A. Mean PTV D_{min} and BED D_{min} with a PTV-to-cord distance varying from 0 to 5 mm, and a BED D_{min} of 33.6 Gy or more corresponded with a reduced local recurrence based on References 26-28. B. Mean PTV BED D_{95} and BED D_{98} with different PTV-to-cord distances. And 48.1 Gy and 50.5 Gy were the corresponded BED D_{95} and BED D_{98} above which local recurrence could be reduced based on Reference 26).

PTV coverage

PTV V_{100} increased with the increase of PTV-to-cord distance, and was 90.5, 92.1, 94.2, 95.1, 96.3 and 98.2% as the distance increased from 0 to 5 mm, respectively ($P < 0.001$).

PTV dosimetry

PTV D_{min} and BED D_{min} were enhanced significantly along with the increase of PTV-to-cord distance ($P < 0.001$). Several studies showed that D_{min} might be an important risk factor for local failure and recommend a PTV D_{min} above 14 Gy in 1 fraction (BED = 33.6 Gy) [27-29], or 15 Gy in 1 fraction (BED = 37.5 Gy) [30]. Based on the results of this study, a PTV-to-cord distance between 2 mm (BED = 35.2 Gy) and 3 mm (BED = 42.3 Gy) could meet the above PTV D_{min} constraints. Additionally, D_{95}, BED D_{95}, D_{98} and BED D_{98} increased significantly along with the increase of PTV-to-cord distance ($P < 0.001$). Bishop et al. [27] showed a local failure reduction when BED D_{98} and BED D_{95} were not less than 47.1 and 50.4 Gy, corresponding to 1 and 0 mm of PTV-to-cord distance in this study; respectively. **Figure 1** shows PTV D_{min}, BED D_{min}, BED D_{95} and BED D_{98} with different PTV-to-cord distances.

CI and dose falloff

Average values PTV CI with different PTV-to-cord distances are shown in **Table 1** ($P = 0.803$). For $R_{50\%}$ and $D_{2\ cm}$, no significant value was detected with the variation of PTV-to-cord distance (for $R_{50\%}$, $P = 0.963$; for $D_{2\ cm}$, $P = 0.634$; respectively).

Spinal cord dose

No significant difference was detected for cord D_{max}, or dose received by 0.35 cc and 1.2 cc of spinal cord ($P = 0.803$).

Dosimetric comparison between restriction and no-restriction groups

No difference in PTV V_{100}, D_{min}, D_{99}, D_{98}, D_{95}, D_1, CI, $D_{2\ cm}$ and spinal cord D_{max} was detected between restriction and no-restriction groups. However, $R_{50\%}$ increased significantly from 5.1 in restriction group to 5.6 in non-restriction group ($P < 0.001$). **Figure 2** compares $V_{50\%}$ in DVH and $R_{50\%}$ between restriction and no-restriction groups. Additionally mean V_{30}, representing low dose distribution, was 598.4 cm^3 and 628.8 cm^3 in restriction group and no-restriction group, respectively ($P < 0.001$). **Table 2** summarizes mean $R_{50\%}$ and V_{30} in the two groups with different PTV-to-cord distances, and **Figure 3** compares V30 between the two groups.

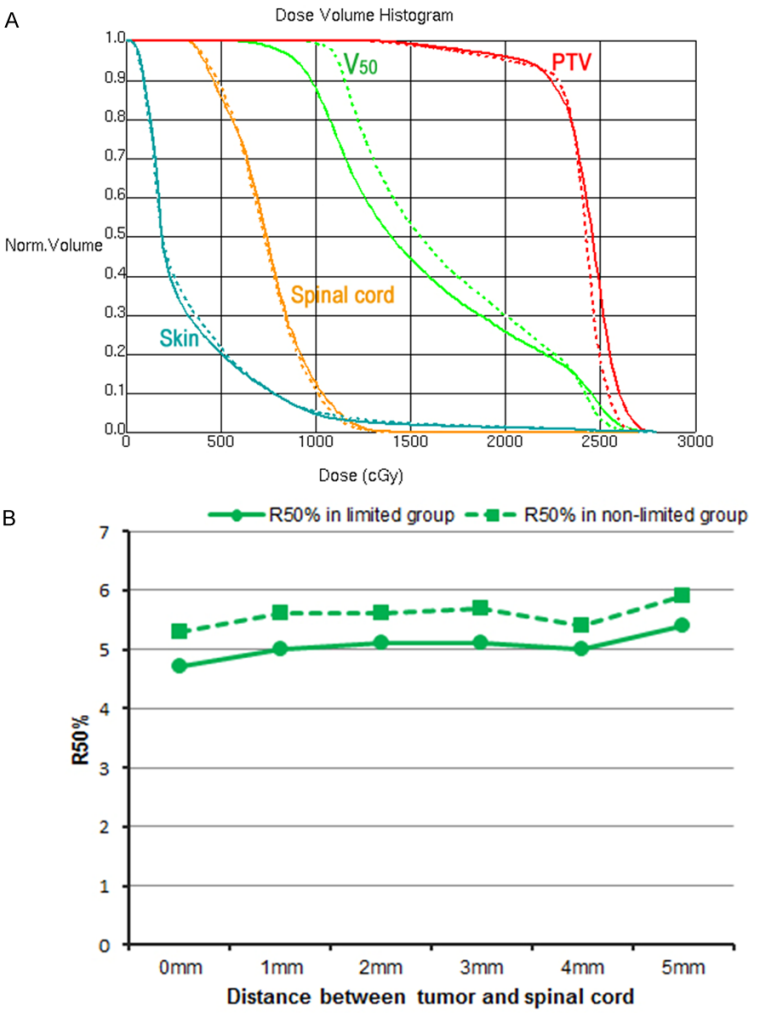

Figure 2. A. Comparison of V_{50} in dose-volume histogram between restriction and no-restriction groups. B. Comparison of $R_{50\%}$ between restriction and no-restriction groups. (Solid line: restriction group, dashed line: no-restriction group).

Discussion

A survey of clinical practice in the United States characterized the adoption of SBRT showed spine was the second most common disease site treated with SBRT (67.5% of the SBRT users) [31]. This technique, which can be used as definitive local treatment or post-surgical adjuvant treatment, improves clinical outcomes and local control for patients with spine metastases, by delivering a higher dose than conventional radiation therapy.

SBRT in single fraction require not only a high ablative dose delivered to the tumor, but also a sharp dose falloff outside the target. However, the distance between target and spinal cord is the major factor influencing on dose fall-off, and a too narrow distance causes an under-dose in the epidural space. Several clinical studies suggest a minimum target-to-cord distance of at least 2 to 5 mm to reduce epidual failure [10-14]. Therefore, SBRT remains a relative contra-indication for patients with tumor abutting or compressing the spinal cord, and the target-to-cord distance is a special factor in the choice of treatment strategies. The aim of this study is to evaluate the impact of the PTV-to-cord distance on SBRT dosimetry in patients with isolated spine metastasis and to establish planning criteria and parameters for limiting low dose spillage.

Bishop et al. [27] treated 332 patients with spinal metastases using SBRT, 44 patients (13%) had local recurrences, and detected PTV dosimetric parameters including D_{min}, D_{98} and D_{95} as factors associated with local relapse, and recommend maintaining a PTV D_{min} above 14 Gy in 1 fraction (BED = 33.6 Gy) or 21 Gy in 3 fractions (BED = 35.7 Gy). Additionally, they recommended PTV BED D_{98} and BED D_{95} not less than 47.1 Gy and 50.4 Gy to maintain a local control, respectively. Similar findings were reported by Lovelock et al. [30], who observed a correlation of D_{min}, D_{98}, and D_{95} with local failure in 91 consecutively treated spine lesions in 79 patients, and no local failure was detected with a D_{min} above 15Gy (BED = 37.5 Gy). In the study of Ryu et al. [29, 32]. A prescription dose of ≥ 14 Gy had a strong trend to increase pain control, although without reaching statistical significance. This study delivered relatively high dose (BED = 70 Gy) to improve local control and showed a PTV-to-cord distance of 2 mm (BED = 35.2 Gy) to 3 mm (BED = 42.3 Gy) could meet these constraints

Table 2. Mean $R_{50\%}$ and V_{30} in restriction and no-restriction groups with different PTV-to-cord distances

PTV-to-cord distance	$R_{50\%}$			V_{30} (cm^3)		
	Restriction group	No-restriction group	*P*	Restriction group	No-restriction group	*P*
0 mm	4.7	5.4	0.040	616.7	641.6	0.025
1 mm	5.0	5.6	0.025	610.5	645.2	0.019
2 mm	5.1	5.7	0.038	614.6	649.6	0.013
3 mm	5.1	5.6	0.024	586.2	618.8	0.012
4 mm	5.0	5.4	0.006	589.7	616.6	0.019
5 mm	5.4	5.9	0.029	572.6	601.2	0.029
Average	5.1	5.6	0.001	598.4	628.8	0.001

Abbreviations: $R_{50\%}$ = ratio of the 50% prescription isodose volume to the PTV, V_{30} = volume within the target receiving ≥ 30% of the prescription dose.

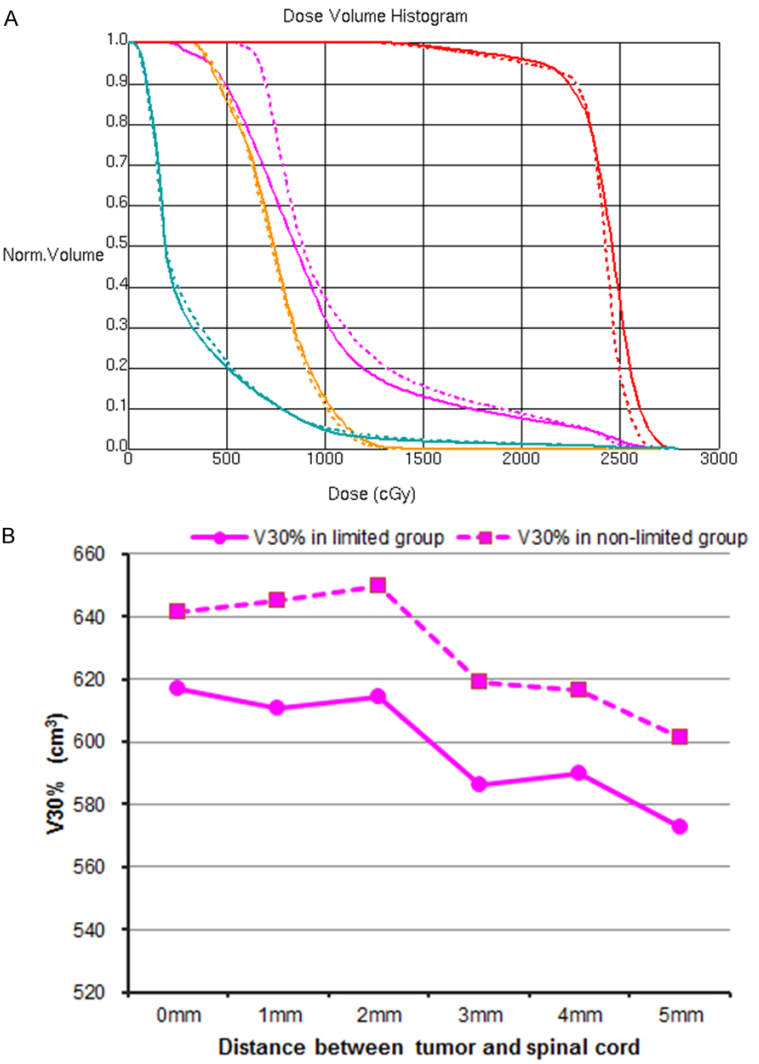

Figure 3. V_{30} in restriction group and no-restriction group. A. Comparisson of V_{30} the dose-volume histogram between restriction and no-restriction groups. B. Comparison of V_{30} between restriction and no-restriction groups. (Solid line: restriction group, dashed line: no-restriction group).

of BED D_{min}, D_{98} and D_{95} for spine SBRT in single fraction.

The indication of spine SBRT in single fraction in patients with epidural compression (with a motor strength of four or less out of five) and metastatic tumors within 2 to 3 mm to the spinal cord is controversial [33], and is not in the contents of this study. Based on radiobiological principle, there is a tendency to employ multisession or hypofractionated (> 5 fractions) radiation therapy which can deliver higher BED to tumor target than single-fractional protocols, particularly when tumor is close to spinal cord [6, 11, 34, 35]. In addition, multisession or hypofractionated treatment can reduce under-dose in epidural space and avoid failures in the region.

To the best of our knowledge, few studies reported target coverage as a predictor of local failure following SBRT for spinal tumors. Jawad et al. [36] treated 67 spinal tumors with SBRT, and with a median prescription dose of 18 Gy in 1-5 fractions, and found a higher local failure rate when absolute volume of PTV received < 80% of the prescription dose (P = 0.003). Bishop et al. [27] showed that approximately half of the recurrences occurred at the margin of the prescription isodose line, corresponding with a poorer PTV coverage than those without relapse (86% vs. 91%, P = 0.002). In this study, PTV coverage reached 90.5% even with a PTV-to-cord distance of 0 mm, might be relevant to large PTV volumes (minimum PTV volume

is 37.9 in this study vs. 17.2 cm^3 in the study of Bishop et al. [27]).

Based on spine SBRT planning objectives of RTOG spine and lung protocols used by Hong et al. [21]. We established $R_{50\%}$ and $D_{2\ cm}$ as parameters to restrict low dose spillage. Average $R_{50\%}$ dropped more than 0.5 (5.6 vs. 5.1, $P < 0.001$) and average V_{30} dropped more than 30.4 cm^3 (628.8 vs. 598.4 cm^3, $P < 0.001$) when low dose spillage was restricted, suggesting a potential usage of SBRT in patients who went through ever radiation therapy. For example, radiation pulmonary fibrosis is a frequent side effect in post-radiation patients with lung or breast cancer, and can be aggravated by spine SBRT. And as the steep falloff gradient of the target dose with negligible skin and muscle dose, spine SBRT can be given to these previously irradiated patients. Moreover, spine SBRT will be associated with a significant skin dose and potential toxicity that is rarely observed in conventionally fractionated radiotherapy [37]. Therefore, it is essential to quantitatively restrict low dose spillage of normal tissue outside target volumes and improve plan quality by $R_{50\%}$ and $D_{2\ cm}$.

Conclusions

PTV coverage, D_{min}, D_{98}, and D_{95} are directly correlated with PTV-to-cord distance in spine SBRT in single fraction. Based on this study, a distance of 2 mm (BED = 35.2 Gy) to 3 mm (BED = 42.3 Gy) from PTV to spinal cord can meet planning dose requirements. $R_{50\%}$ and $D_{2\ cm}$ can quantitatively restrict low dose spillage and improve plan quality.

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Disclosure of conflict of interest

None.

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