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Dosimetric Study

Evaluating dosimetric differences in spine stereotactic body radiotherapy: An international multi-institutional treatment planning study†

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Introduction: Stereotactic body radiotherapy (SBRT) planning for spinal metastases is a challenging task that involves complex target shapes and steep dose gradients proximal to the spinal cord. The aim of the present study is to investigate dosimetric variability among delivery systems and institutions doing spine SBRT.

Materials and Methods: Three institutions (in Japan, Canada, and the USA) participated in this retrospective treatment planning study. Computed tomography (CT) datasets for three patients including fully delineated targets and organs-at-risk (OAR) were distributed to all three institutions for planning. Delivery systems included the Clinac 21EX, Vero4DRT, Synergy S, and CyberKnife. All treatment plans were generated using a prescribed dose of 24 Gy in 2 fractions and met the following objectives: the evaluated planning target volume (PTV_{evl}, defined as the PTV minus spinal cord) should receive greater than 16.8 Gy in at least 95% of the volume (D_{95} > 16.8 Gy) and a maximum dose to the less than 140% of the prescribed dose (D_{max} < 33.6 Gy). The maximum dose of planning risk volume (PRV) cord or thecal sac was limited to 0.035 cm^3 receiving less than 17 Gy. Aside from minimum and maximum dose objectives for the PTV_{evl}, there were no criteria regarding the shape of the PTV_{evl} dose-volume histogram (DVH). For each completed treatment plan, the following DVH parameters were evaluated for the PTV_{evl}: D_{95}, D_{80}, D_{50}, D_2 and sigma-index (S-index, standard deviation of the differential DVH).

Results: The PTV_{evl} and OAR dose volume constraints were satisfied in all treatment plans. For Case 1, the mean PTV_{evl} D_{50} was 25.4 ± 1.5 Gy (range: 23.7 – 27.8 Gy), for Case 2 it was 26.7 ± 2.0 Gy (23.6 – 28.6 Gy), and for Case 3 it was 26.0 ± 1.3 Gy (24.1 – 27.3 Gy). The mean PTV_{evl} D_2 was 27.3 ± 2.2 Gy (24.4 – 30.2 Gy), 28.9 ± 3.0 Gy (24.5 – 31.4 Gy) and 28.7 ± 2.7 Gy (25.2 – 31.6 Gy) for Cases 1, 2, and 3, respectively. However, there were statistically significant variations in the DVH parameters of PTV_{evl} between apparatuses (CyberKnife versus non-CyberKnife) and among institutions (between 2 CyberKnife sites or between 2 conventional accelerator sites).

Conclusions: Although all institutions met the minimum prescribed objectives, inter-institutional and inter-apparatus target dose variations were observed. Further

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Table 1. Summary of treatment planning and delivery systems by institution.

Site	Treatment Planning and Delivery System	Description
A	MultiPlan version 5.3 + CyberKnife VSI (Accuray, Sunnyvale, CA, USA)	Fixed collimators
B	Pinnacle^3 version 9.6 (Phillips, Amsterdam, Netherlands) + Clinac 21EX (Varian Medical Systems, Palo Alto, CA, USA)	5 mm MLC
	iPlan RT Dose version 4.5.2 + Vero4DRT (MHI-TM200; Mitsubishi Heavy Industries, Ltd., Japan, and BrainLAB, Feldkirchen, Germany)	Ring-based linac with a 5 mm MLC
	MultiPlan version 4.6.0 + CyberKnife G4 (Accuray, Sunnyvale, CA, USA)	Iris collimator
C	Pinnacle^3 version 9.2 (Phillips, Amsterdam, Netherlands) + Synergy S (Elekta, Crawley, UK)	4 mm MLC

Abbreviation: MLC = multi-leaf collimator

study is necessary to determine target dose constraints that may minimize inter-institutional variations and lead to plan standardization.

Keywords: Spine metastases, spine stereotactic body radiotherapy, dosimetric difference, target prescribed dose, apparatus dependence, international multi-institutional planning study

1. INTRODUCTION

Stereotactic body radiation therapy (SBRT) for spinal metastases is an emerging treatment technique (1). Its efficacy has been reported in a landmark Phase 2 trial by Wang et al. (2) with significant reductions in the severity of patient-reported pain, and impressive rates of complete pain relief and local tumor control. Recent reviews have since confirmed high rates of efficacy following SBRT in those spinal metastases patients that were previously radiated, un-irradiated, and post-operative (3, 4). Spine SBRT is currently being evaluated in a Phase 3 trial comparing 18 Gy in 1 fraction delivered with SBRT to 8 Gy in 1 fraction delivered with conventional palliative radiation, and in a Canadian randomized Phase 2 trial due to open in 2015 comparing 24 Gy in 2 fractions delivered with SBRT to 20 Gy in 5 fractions delivered with conventional palliative radiation.

As SBRT for spinal metastases is increasingly used in modern radiotherapy practice, standardized contouring of the target volume was in need, and the International Spine Radiosurgery Consortium (ISRC) Consensus Guideline was published in 2012. This consortium of experts proposed consensus target volume definitions using common scenarios for spinal stereotactic radiosurgery (5). However, there was no consensus on planning strategies with regard to the optimal prescribed dose, schedule and dose constraints for the target and normal structures. Without a consensus for planning strategies for spine SBRT, even if the same prescribed dose and constraints are defined in practice or multi-institutional clinical trials, inter-institutional variation may occur in target dose coverage and normal structure avoidance dose. Furthermore, since there is a range of apparatuses that can be used for spine SBRT (including CyberKnife and Vero4DRT), treatment plan standardization is a complex topic. As a preliminary step towards planning standardization for spine SBRT, the purpose of the present study was to investigate the potential for inter-institutional and inter-apparatus variations amongst experienced programs.

2. MATERIALS AND METHODS

2.1 Multi-institutional treatment planning study

Three institutions (Komagome Hospital, Tokyo, Japan; Odette Cancer Center, Sunnybrook Health Sciences Centre, Toronto, Canada; and the University of California San Francisco, San Francisco, CA, USA) participated in this planning study. As shown in Table 1,

5 apparatuses were included. All of the participants had implemented spine SBRT in practice. Three vertebral metastasis cases were chosen for this study as follows:

Case 1: 5th lumbar spine metastasis limited to the vertebral body (VB) with clinical target volumes (CTV) described as 'Paraspinal' category;
Case 2: 5th thoracic spine metastasis to the VB and the right side of the pedicle, with a CTV shape of 'Horseshoe' type, excluding the disk and posterior elements;
Case 3: 10th thoracic spine to the whole parts of the vertebra with a CTV shape of 'Donut' type encompassing a case with bilateral posterior involvement.

These target shapes were classified by reference to Weksberg's results (6). Figure 1 shows each target structure on one of the axial planes.

2.2 Target volume and critical structure definition

The target and organs-at-risk (OAR) were contoured by a single experienced radiation oncologist using non-contrast body CT images with a 1.0 mm slice thickness fused to axial thin slice T1 and T2 MR images. The CTVs were contoured according to ISRC guidelines (5). The spinal cord was contoured and a 1.5 mm planning organs-at-risk (PRV) uniform margin was applied as the dose constraining structure for the true cord. Other OARs consisted of the cauda equina (thecal sac contoured), esophagus, heart, and intestine. The planning target volumes (PTV) were defined as the CTV plus a 2 mm uniform expansion. To evaluate the target dose, the evaluated PTV (PTV_{evl}) was defined as the volume of the PTV excluding the PRV of the spinal cord or thecal sac at the level of the cauda equina. All CT images and structure datasets were anonymized and sent to each institution in DICOM-RT format.

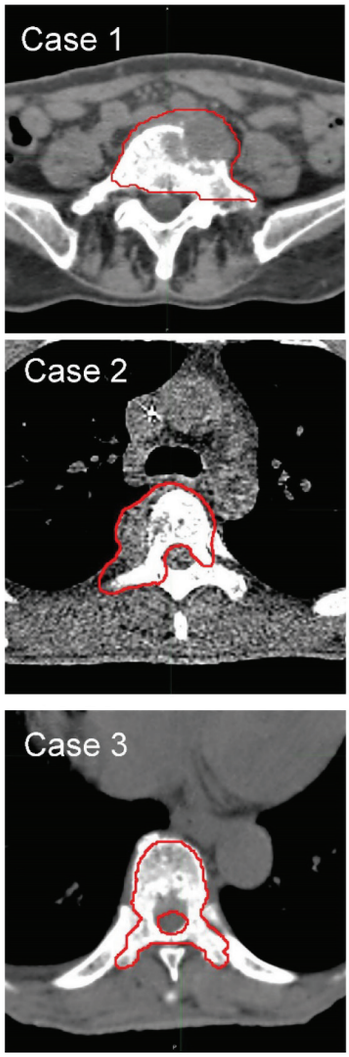


Figure 1. An axial CT image with clinical target volume (red line) for each case. Case 1, tumor at 5th lumbar spine; Case 2, tumor at 5th thoracic spine; Case 3, tumor at 10th thoracic spine.

2.3 Dose volume constraints and treatment plans

Table 2 shows the target and OAR dose volume constraints applied to all plans. In this study, for all cases, the target prescribed dose was 24 Gy in 2 fractions, which encompassed at least 95% of the PTV_{evl} volume, with two constraints: (1) the point maximum dose was within 140% of the prescribed dose ($D_{max} \leq 33.6$ Gy); and (2) the minimum dose to 95% of the PTV_{evl} volume was greater than 70% of the prescribed dose ($D_{95} \geq 16.8$ Gy). The maximum point dose, defined as a dose to a volume of 0.035 cm^3 or less (7), to the spinal cord PRV or thecal sac was no more than 17 Gy.

Commercially available treatment planning systems (TPSs) with an inverse optimization feature: Pinnacle^3 (Phillips, Amsterdam, Netherlands), iPlan (BrainLAB, Feldkirchen, Germany) or Multiplan (Accuray, Sunnyvale, CA, USA) were used for each linear accelerator devices. All plans were calculated by Monte Carlo or convolution/superposition technique, and heterogeneity corrections were applied. Each dose distribution was calculated with a 2 mm or less calculation grid resolution as recommended by the AAPM Task Group 101 (7), except for the Vero4DRT plans using iPlan, which were calculated using a 3 mm dose grid size due to the inherent limitation of 32-bit machine providing poor performance. As to planning strategies (e.g. beam arrangement, col-

Table 2. Dose volume constraints for each structure.

Prescribed dose: 24 Gy in 2 fractions (encompass at least 95% PTV_{evl} volume)	
Structure	Dose volume constraints
PTV_{evl}	Maximum dose ≤ 33.6 Gy Minimum dose to 95% volume ≥ 16.8 Gy
PRV cord or Thecal sac	Maximum dose ≤ 17 Gy
Esophagus Intestine	No more than 1.0 cc to receive ≥ 20 Gy
Heart	Mean dose ≤ 4 Gy (if possible)

Abbreviations: PTV_{evl} = evaluated planning target volume; PRV = planning organs-at-risk.

limator size, etc.) were not specified in this study since each institution has its own established methodology.

Following submission of the final treatment plans, DICOM-RT datasets were imported into MIM version 6.2.6 (MIM software, Cleveland, OH, USA), and a dose–volume histogram (DVH) analysis was performed for all regions of interest. For PTV_{evl}, the following dose metrics were extracted to evaluate plan quality: D_{95}, D_{80}, D_{50}, D_2, and sigma-index (S-index), which was described as the standard deviation of the differential DVH to quantify the degree of dose inhomogeneity within the PTV_{evl} (8). For the OAR, D_{1cc} and $D_{0.5cc}$, which were the dose that covered volumes of 1 cc and 0.5 cc of the volumes, respectively, were evaluated. The mean dose was compared for the heart. Student's t-test or Welch's t-test was used to compare each dosimetric parameter, and a p value of < 0.05 was considered statistically significant.

3. RESULTS

Typical dosimetric parameters with standard deviation (SD) were summarized in Table 3. The target and all other OAR dose volume constraints were satisfied in all treatment plans. The mean PTV_{evl} D_{50} ± SD was 25.4 ± 1.5 Gy (range: 23.7 – 27.8 Gy) (Case 1), 26.7 ± 2.0 Gy (23.6 – 28.6 Gy) (Case 2), and 26.0 ± 1.3 Gy (24.1 – 27.3 Gy) (Case 3). The mean PTV_{evl} D_2 ± SD was 27.3 ± 2.2 Gy (24.4 – 30.2 Gy), 28.9 ± 3.0 Gy (24.5 – 31.4 Gy), and 28.7 ± 2.7 Gy (25.2 – 31.6 Gy), for Cases 1 to 3, respectively. However, as shown in Figure 2, the PTV DVHs exhibit qualitative differences in shape between the various treatment machines and institutions.

3.1 Inter-apparatus variations

There were statistically significant differences in D_{80}, D_{50}, and D_2 for the PTV_{evl} DVHs between the two CyberKife plans (sites A, B) and those of the conventional apparatuss (sites B, C). The mean D_{80} ± SD was 25.3 ± 1.3 Gy versus 24.1 ± 1.0 Gy ($p = 0.04$), the mean D_{50} ± SD was 27.4 ± 1.2 Gy versus 25.2 ± 1.2 Gy ($p < 0.001$), and the D_2 ± SD was 30.3 ± 1.6 Gy versus 27.0 ± 2.2 Gy ($p < 0.001$) for CyberKnife versus conventional apparatus, respectively.

The S-index ± SD of CyberKnife plans was 11.4 ± 3.2, significantly greater than with conventional linacs, (7.4 ± 2.3: $p = 0.01$).

3.2 Inter-institutional variations

3.2.1 Two CyberKnife systems in sites A and B

There were statistically significant differences in PTV_{evl} D_{95}, D_{80}, and D_2. For $D_{95,}$ the mean ± SD was 22.9 ± 1.4 Gy versus 19.4 ± 1.1 Gy ($p < 0.001$); for D_{80}, the mean ± SD was 26.2 ± 0.8 Gy versus 24.4 ± 1.1 Gy ($p = 0.03$); and for D_2, the mean ± SD was 30.6 ± 0.5 Gy versus 30.0 ± 2.3 Gy ($p < 0.001$), for site A versus B, respectively.

The S-index ± SD of site A plans was 9.7 ± 1.7 and statistically greater than that of site B, 13.1 ± 3.7 ($p < 0.001$).

3.2.2 Conventional apparatuses in sites B (Clinac 21EX and Vero4DRT) and C (Synergy S)

A significant variation between sites B and C was observed only in the PTV_{evl} D_2 ± SD, 25.8 ± 1.3 Gy for site B versus 29.3 ± 1.9 Gy for site C ($p = 0.03$).

4. DISCUSSION

In this study, variations of the plan metric among not only the radiotherapy apparatuses but also among institutions were investigated using CT datasets of patients with spinal metastasis. Although prior studies have been reported (9), this is the first to evaluate the Vero4DRT as an emerging technology for SBRT.

In these results, there were significant variations in the parameters for PTV_{evl} DVHs. The CyberKnife plans tended to be the most heterogeneous, as indicated by the significantly higher S-index values when compared with non-CyberKnife delivery apparatuses, which were the Clinac 21EX, Vero4DRT, and Synergy S in this study. These results were consistent with Ma's results (9). The present study also confirmed statistically significant inter-institutional differences in the average

Table 3. Summary of the dose indices for each case

Case 1

	PTV_{evl}					Thecal sac		Intestine	
Site_Modality	D_{95}	D_{80}	D_{50}	D_2	S	$D_{0.1cc}$	D_{1cc}	$D_{0.1cc}$	D_{1cc}
A_CyberKnife	23.8	26.5	27.8	30.2	8.48	16.2	13.9	21.8	19.9
B_CyberKnife	20.4	23.8	25.2	27.3	8.93	15	12.4	20.9	18.8
B_21EX	21.1	23.2	23.7	24.4	4.99	15.5	14.3	20.8	19.5
B_Vero	22.7	24.7	25.2	26.1	5.11	15.7	13.5	19.8	18.8
C_SynergyS	22.9	24.2	25	28.6	7.33	14.9	13.2	19.8	18.7
1SD	1.4	1.3	1.5	2.2	1.85	0.5	0.7	0.8	0.5

Case 2

	PTV_{evl}					PRV cord		Spinal cord		Esophagus	
Site_Modality	D_{95}	D_{80}	D_{50}	D_2	S	$D_{0.1cc}$	D_{1cc}	$D_{0.1cc}$	D_{1cc}	$D_{0.1cc}$	D_{1cc}
A_CyberKnife	23.6	26.7	28	30.5	8.93	15.6	11.9	11.8	8.4	26.8	20.3
B_CyberKnife	19.5	25.6	28.6	31.0	14.36	12.3	9.4	9.0	6.9	24.6	19.8
B_21EX	19.5	22.4	23.6	24.5	6.35	15.5	14.3	14.0	13.0	19.2	17.7
B_Vero	22.3	24.9	25.8	27.1	6.21	16.5	13.8	13.4	11.0	22.0	18.3
C_SynergyS	20.5	25.3	27.5	31.4	12.61	14.8	13.1	12.6	11.4	18.6	17.3
1SD	1.8	1.6	2.0	3.0	3.68	1.6	2.0	2.0	2.5	3.5	1.3

Case 3

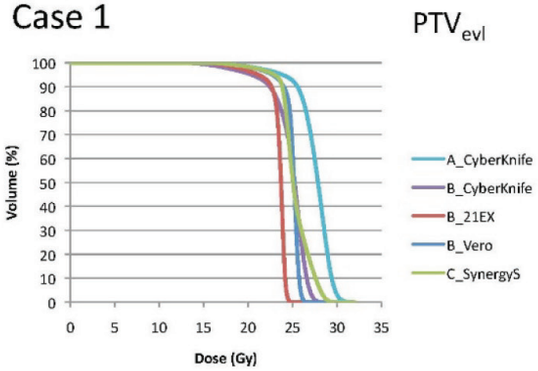
	PTV_{evl}					PRV cord		Spinal cord		Esophagus		Heart
Site_Modality	D_{95}	D_{80}	D_{50}	D_2	S	$D_{0.1cc}$	D_{1cc}	$D_{0.1cc}$	D_{1cc}	$D_{0.1cc}$	D_{1cc}	D_{mean}
A_CyberKnife	21.3	25.3	27.3	31.2	11.68	16.8	14.6	13.8	12.1	21.8	18.7	4.0
B_CyberKnife	18.2	23.7	27.2	31.6	16.12	15.3	12.9	13.2	11.2	19.2	17.5	3.9
B_21EX	19.2	22.8	24.1	25.2	7.52	14.2	13.1	12.4	11.5	19.7	18.2	3.9
B_Vero	21.6	24.8	25.9	27.5	7.71	14.3	11.5	10.5	7.9	21.5	18.4	3.5
C_SynergyS	20.6	24.3	25.6	27.9	8.64	15.4	14	13.8	12.1	18	16.4	4.9
1SD	1.4	1.0	1.3	2.7	3.64	1.1	1.2	1.4	1.8	1.6	0.9	0.5

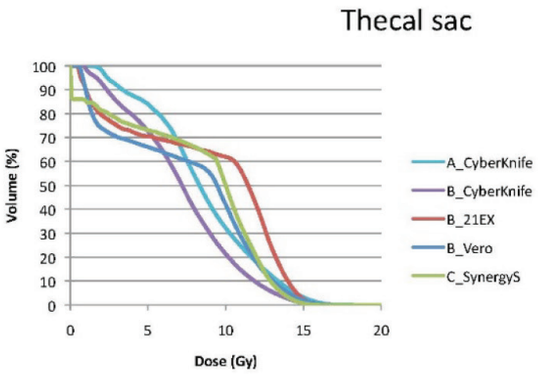
Abbreviations: PTV_{evl} = evaluated planning target volume; PRV = planning organs-at-risk; D = dose; S = S-index; 21EX = Clinac 21EX; Vero = Vero4DRT; SD = standard deviation.

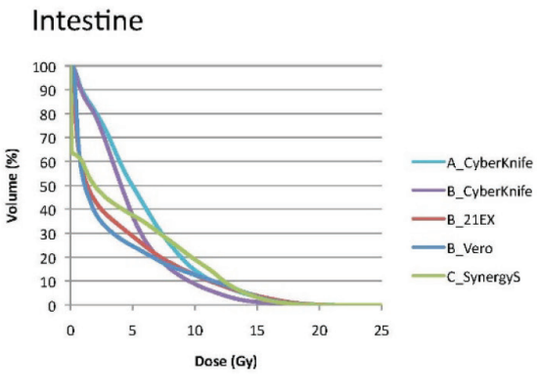
PTV D_{95}, D_{80}, and D_2 for CyberKnife systems. Furthermore, among non-CyberKnife apparatuses, there was inter-institutional D_2 variation. However, in site B, the PTV_{evl} DVH was also different between Clinac 21EX and Vero4DRT, as shown in Figure 2. The reason for this might come from the variation of dose normalization with TPS.

We hypothesize that one of the reasons for these variations might be a deficiency of strict dose constraints a priori for PTV coverage. To eliminate these inter-institutional or apparatus-dependent variations, the results of the present study indicate the need for consensus or guidelines for dose prescription in spine SBRT. Eaton et al. also suggested a similar proposal for prostate SBRT (10). As ICRU report 83 discusses, there is a need for more refined prescription and reporting for state of the art techniques such as SBRT (11). Although no specific dose-volume recommendations are made, ICRU report

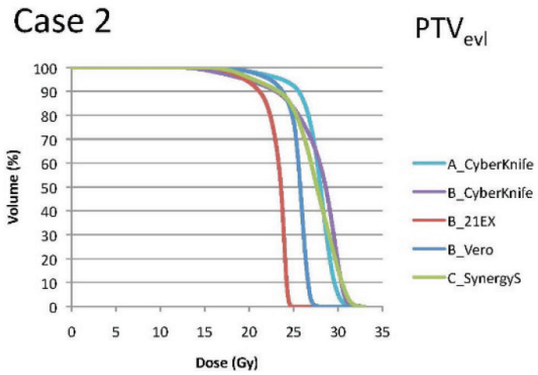
Case 1

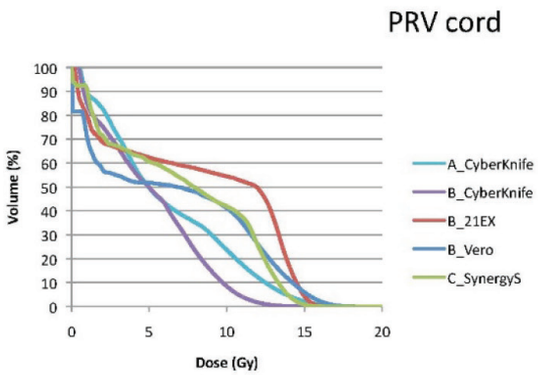


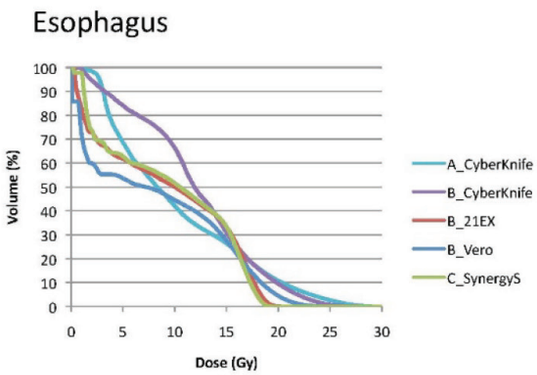




Case 2







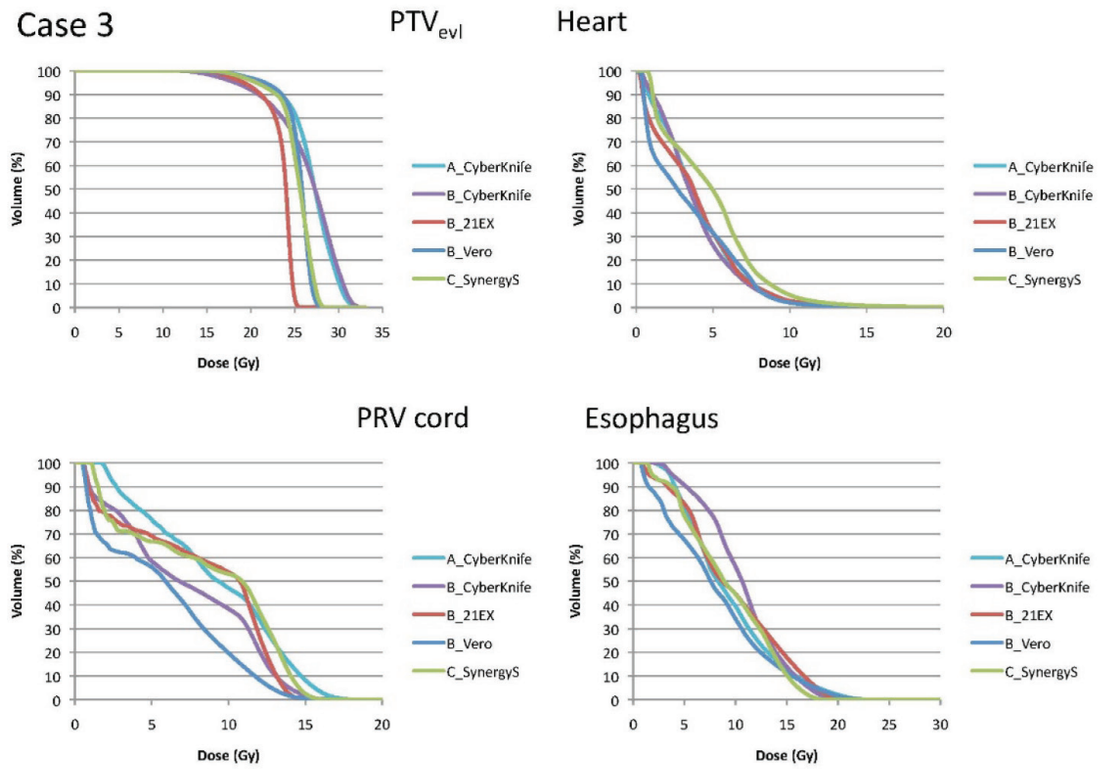


Figure 2. Dose volume histograms for each evaluated planning target volume and normal tissues of five machines in three institutions (A, B, and C). PTV_{evl} = evaluated planning target volume; PRV = planning organs-at-risk; 21EX = Clinac 21EX; Vero = Vero4DRT.

83 discusses the utility of the D_{50} being largely representative of the typical absorbed dose in the PTV. In the present study, even though all sites met the same minimum and maximum dose constraints for the PTV_{evl}, the shape of the DVHs, as represented by D_{50}, varied substantially among sites and apparatuses. Incorporating PTV_{evl} D_{50} as an additional dose constraint for the target in spine SBRT planning might decrease dosimetric variations among treatment machines.

This is the first planning study for spine SBRT including the Vero4DRT. The Vero4DRT is an emerging image guided radiotherapy system allowing dynamic tumor-tracking irradiation(12). As shown in Figure 2, the Vero4DRT tends to consistently produce higher target dose homogeneity and lower mean doses to all of the OARs compared to all other apparatuses. Such a result suggests that the Vero4DRT is a feasible delivery system for spine SBRT.

It should be noted that in the present study, the results of pre-treatment quality assurance (QA) for each system were excluded from consideration. Pre-treatment QA is a vital component of any spine SBRT program to ensure the effective and safe delivery of the planned absorbed dose distribution within the patient. All of the participating sites in the present study clinically treat spine SBRT with a range of QA approaches including ion chamber, film, and diode arrays.

Another point to consider is what, if any, clinical impact the inter-institutional dose variations may have. Sahgal et al. cautioned that a total dose of ≥ 20 Gy/fraction increased the risk of vertebral compression fracture from results based on multi-institutional clinical datasets (1). However, the term "20 Gy/fraction" might not sufficiently depict the prescribed dose for the target, as indicated by the large variation in DVH parameters for the PTV. Without more refined guidelines regarding dose prescription with respect to the DVH, the correlation of treatment outcomes or toxicity may be confounded by the resulting variation amongst institutions and apparatuses.

In this study, substantial inter-institutional target dose variations were observed, which is likely caused by a simplified set of target dose constraints. A further planning study is warranted to determine what target dose constraints may reduce inter-institutional variations.

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