Original Article

PMP

Progress in Medical Physics 30(4), December 2019
https://doi.org/10.14316/pmp.2019.30.4.94
eISSN 2508-4453

Volumetric-Modulated Arc Radiotherapy Using Knowledge-Based Planning: Application to Spine Stereotactic Body Radiotherapy

Chiyoung Jeong[1], Jae Won Park[2], Jungwon Kwak[1], Si Yeol Song[1], Byungchul Cho[1]

[1]Department of Radiation Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, [2]Department of Radiation Oncology, Yeungnam University Medical Center, Daegu, Korea

Received 16 December 2019
Revised 24 December 2019
Accepted 24 December 2019

Corresponding author
Byungchul Cho
(bcho@amc.seoul.kr)
Tel: 82-2-3010-4437
Fax: 82-2-486-7258

Corresponding author
Si Yeol Song
coocoori@amc.seoul.kr
Tel: 82-2-3010-4431
Fax: 82-2-486-7258

Chiyoung Jeong and Jae Won Park contributed equally to this work.

Purpose: To evaluate the clinical feasibility of knowledge-based planning (KBP) for volumetric-modulated arc radiotherapy (VMAT) in spine stereotactic body radiotherapy (SBRT).

Methods: Forty-eight VMAT plans for spine SBRT was studied. Two planning target volumes (PTVs) were defined for simultaneous integrated boost: PTV for boost (PTV-B: 27 Gy/3fractions) and PTV elective (PTV-E: 24 Gy/3fractions). The expert VMAT plans were manually generated by experienced planners. Twenty-six plans were used to train the KBP model using Varian RapidPlan. With the trained KBP model each KBP plan was automatically generated by an individual with little experience and compared with the expert plan (closed-loop validation). Twenty-two plans that had not been used for KBP model training were also compared with the KBP results (open-loop validation).

Results: Although the minimal dose of PTV-B and PTV-E was lower and the maximal dose was higher than those of the expert plan, the difference was no larger than 0.7 Gy. In the closed-loop validation, $D_{1.2cc}$, $D_{0.35cc}$, and D_{mean} of the spinal cord was decreased by 0.9 Gy, 0.6 Gy, and 0.9 Gy, respectively, in the KBP plans ($P<0.05$). In the open-loop validation, only D_{mean} of the spinal cord was significantly decreased, by 0.5 Gy ($P<0.05$).

Conclusions: The dose coverage and uniformity for PTV was slightly worse in the KBP for spine SBRT while the dose to the spinal cord was reduced, but the differences were small. Thus, inexperienced planners could easily generate a clinically feasible plan for spine SBRT by using KBP.

Keywords: Radiotherapy, Intensity-modulated, Radiotherapy planning, computer-assisted, Machine learning, Radiosurgery

Introduction

Intensity-modulated radiotherapy (IMRT) is widely used to increase the radiation dose to the tumor while reducing the dose to the surrounding organs. For inverse optimization of treatment planning, assignment of the appropriate dose constraints and priorities is important and needs to be optimized for each individual case. Therefore, the skills and experience of the planner significantly affect the duration of treatment planning as well as the plan quality.[1,2] Plan quality can be improved as planning time increases, but it then reaches a certain plateau, which may differ across planners; furthermore, it is difficult to assess whether a given plan is optimal.[3] To overcome such inter-planner variation in plan quality and to improve the efficiency of current treatment planning procedures, efforts have

been made to generate high-quality plans automatically and objectively, on the basis of the existing high-quality treatment plans.[4-6] Using these methods, a model by which achievable dose-volume constraints for both the target and the organs at risk (OARs) can be predicted is created by learning dosimetric features from various geometric relationships between the target and the surrounding normal organs in previous treatment plans. The clinical efficacy of knowledge-based treatment planning (KBP),[7] also known as model-based treatment planning, has been demonstrated for many cancer sites, including liver cancer,[8] prostate cancer,[9] lung cancer,[10] pancreatic cancer,[11] and head and neck cancer.[12] One such commercially available KBP system is the RapidPlan of the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA, USA).

Stereotactic body radiotherapy (SBRT) for spine metastases has mainly been conducted in patients with a longer life expectancy.[13,14] However, the low tolerance of the spinal cord to radiation is often a factor limiting the delivery of a sufficient tumor cell-killing dose.[15] According to the Quantitative Analyses of Normal Tissue Effects in the Clinic, the radiation dose limit of the spinal cord is usually 50 Gy in conventional fractionated irradiation, 20 Gy in three fractions, and 10 Gy in a single fraction.[16] The prescription doses for spine SBRT are from 18 Gy in a single fraction to 24–27 Gy in three fractions.[17] Spine SBRT has been delivered using linear accelerator-based methods of IMRT, TomoTherapy, and CyberKnife.

In most previous studies, KBP was focused on treatment plans with OARs in parallel rather than serial structures, and which overlapped with the target volume. However, the spinal cord is a representative serial organ where the high-dose region is more critical, while overall dose reduction is important in parallel organs. In addition, since the position of the spinal cord is usually located very close to the PTV and is sometimes surrounded by the PTV, most cases require a high-quality plan, which is technically very demanding. Therefore, in this study, we aimed to evaluate the clinical feasibility of using KBP in spine SBRT.

Materials and Methods

1. Contouring and treatment planning

Contouring was performed for 48 spinal metastases. For each patient the gross tumor volume (GTV) was contoured on a planning computed tomography scan, and the clinical target volume (CTV) was delineated according to the guidelines of the International Spine Radiosurgery Consortium (ISRC).[18] Two planning target volumes (PTVs) were defined for simultaneous integrated boost (SIB): PTV-B (PTV for boost: 27Gy/3fractions) and PTV-E (PTV for elective: 24Gy/3fractions). PTV-B was created with a 3-mm margin on the GTV, while maintaining a 2 mm–3 mm margin from the spinal cord when it was adjacent to the spinal cord. PTV-E was extended by a 3-mm margin to the CTV, while maintaining at least a 2 mm–3-mm margin from the spinal cord and with PTV-B subtracted. The prescription doses for PTV-B and PTV-E were 27 Gy and 24 Gy, each delivered in three fractions. As OARs, the spinal cord and esophagus were contoured 2 cm above and below the target volume, respectively.

The baseline treatment plans, called the “expert plan” hereafter, were generated by experienced dosimetrists. In spine SBRT, VMAT with dual arc beams has been demonstrated to be an efficient technique, providing plan quality comparable with that of conventional IMRT.[19] Therefore, in this study, all plans were generated using VMAT with two 6-MV arc beams. The first arc rotated in a counterclockwise direction, from 179 to 181 degrees, with a collimator angle of 45 degrees, while the second arc rotated in the clockwise direction, from 181 to 179 degrees, with a collimator angle of 45 degrees.

2. Knowledge-based planning

RapidPlan of Eclipse version 13.6 was used for KBP of spine SBRT. The three main components of the model generation process of RapidPlan were as follows:

1) The model creation and training algorithm, used to create a prediction model for the dose-volume histogram (DVH)

2) Model-based predictive tools, used to implement

dose-volume constraints for inverse planning (DVH prediction)

3) A new IMRT or VMAT optimization algorithm (photon optimizer)

Among the 48 spine SBRT plans, 26 cases were randomly selected for KBP model training. According to the geometric relationships between the target and OARs, the so-called "geometry-based expected dose" (GED) was computed and the contributing features, such as the volume-surface distance and geometric shape of a structure, were determined. These features consisted of a GED histogram, OAR volume, overlap volume with targets, out-field volume, and target volume. During training, the model was created through principal component analysis (PCA) and a PCA regression technique, the standard deviation for the OAR.

When the training was completed, the performance of the model was evaluated. Possible outliers which might be excluded from the model were determined based on the Cook's distance according to the PCA regression. The model was considered inaccurate if there were more than 4 outliers.

3. Model validation

The model was validated as follows:

1) Closed-loop validation

The 26 treatment plans that were used for training were re-optimized using the KBP-generated model. The KBP-generated plans were compared with the expert plans to evaluate the reproducibility of the model.

2) Open-loop validation

The remaining 22 treatment plans that were not used for training were re-optimized using the KBP-predicted model. The KBP-generated plans were compared with the expert treatment plans to evaluate the clinical applicability of the KBP plan (Fig. 1).

4. RapidPlan-based treatment planning process

The RapidPlan treatment planning process was carried out as follows. The generated model was applied to a new

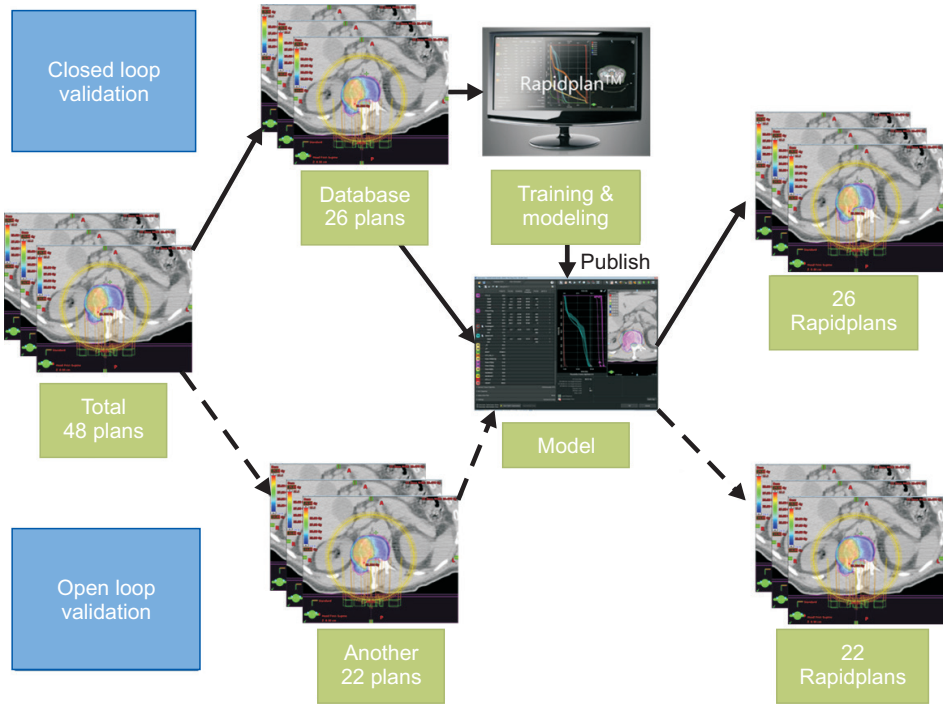

Fig. 1. Closed-loop validation and open-loop validation. All 26 plans used for the training were re-optimized using the estimated dose-volume histogram (DVH) in the model (closed-loop validation). Another 22 plans that were not used for the model were also re-optimized using the model-predicted DVH (open-loop validation). These plans were all compared with the expert plans.

spine SBRT plan to yield a generalized estimated DVH for the spinal cord and esophagus. The priority of dose constraint was assigned to this predictive DVH. Priorities for the upper and lower limits for the target volumes (PTV-B and PTV-E) were manually assigned on a case-by-case basis. For spine SBRT, the maximum dose or 1-cc dose to the spinal cord was considered important. Because the dose limit of the predicted DVH alone was difficult to achieve with the maximum dose constraint, an upper dose limit was additionally applied on a case-by-case basis (Fig. 2). The RapidPlan was used by two planners who had little experience with VMAT plan optimization.

To improve the dose distribution and uniformity in the treatment plan, the treatment planner often creates certain virtual volumes to assign dose-volume constraints for optimization. The virtual volumes included a ring structure surrounding the PTV to increase rapid dose fall-off outside the PTV and an expanded structure from the spinal cord to reduce the dose to the spinal cord. To analyze the effect of these virtual volumes on RapidPlan, statistical tests were performed with the KBP-generated plans generated with and without virtual volumes.

5. Statistical analysis

To evaluate the target dose coverage and uniformity, the minimum dose (D_{min}), mean dose (D_{mean}), and maximum dose (D_{max}) of the KBP-generated plans were compared with the expert plans. For OARs, $D_{0.35cc}$ and $D_{1.2cc}$ of the spinal cord and D_{5cc} of the esophagus were compared, as suggested by the RTOG0915 protocol.[20] Paired t-test was then used to evaluate the statistical difference between the expert plan and the corresponding KBP-generated plan. SPSS version 22.0 (IBM Corp., Armonk, NY, USA) was used and $P<0.05$ was considered statistically significant.

Results

Among the 48 patients, the tumor involved the cervical spine in 4 patients, thoracic spine in 36 patients, and lumbar spine in 8 patients. Only the spinal cord was considered as an OAR; therefore, we excluded the region be-

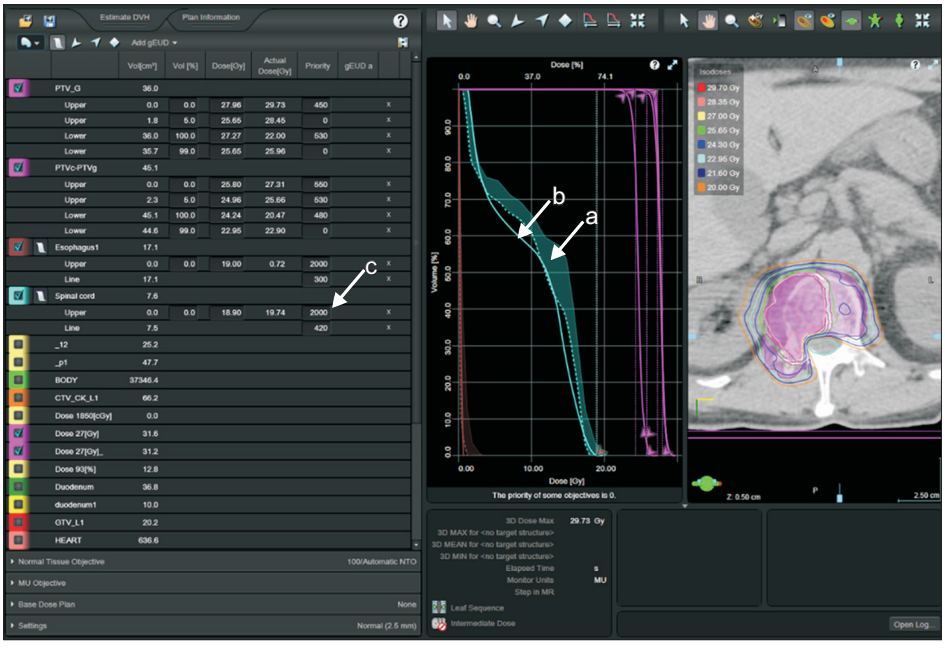

Fig. 2. A RapidPlan treatment plan window. (a) The dose-volume histogram (DVH) is estimated by the knowledge-based plan model considering a patient-specific geometric relationship between the target and the surrounding organs at risk (OARs). (b) The constraint objective for an OAR is generated using the estimated DVH. Priority can be given to each DVH objective, but the RapidPlan assigns a specific dose constraint to every volume point based on the estimated DVH, with equal weighting. (c) This constraint is expressed as a line in the DVH. Therefore, the upper constraint was used for each case, on an individual basis, because planning was difficult in a serial organ such as the spinal cord and esophagus.

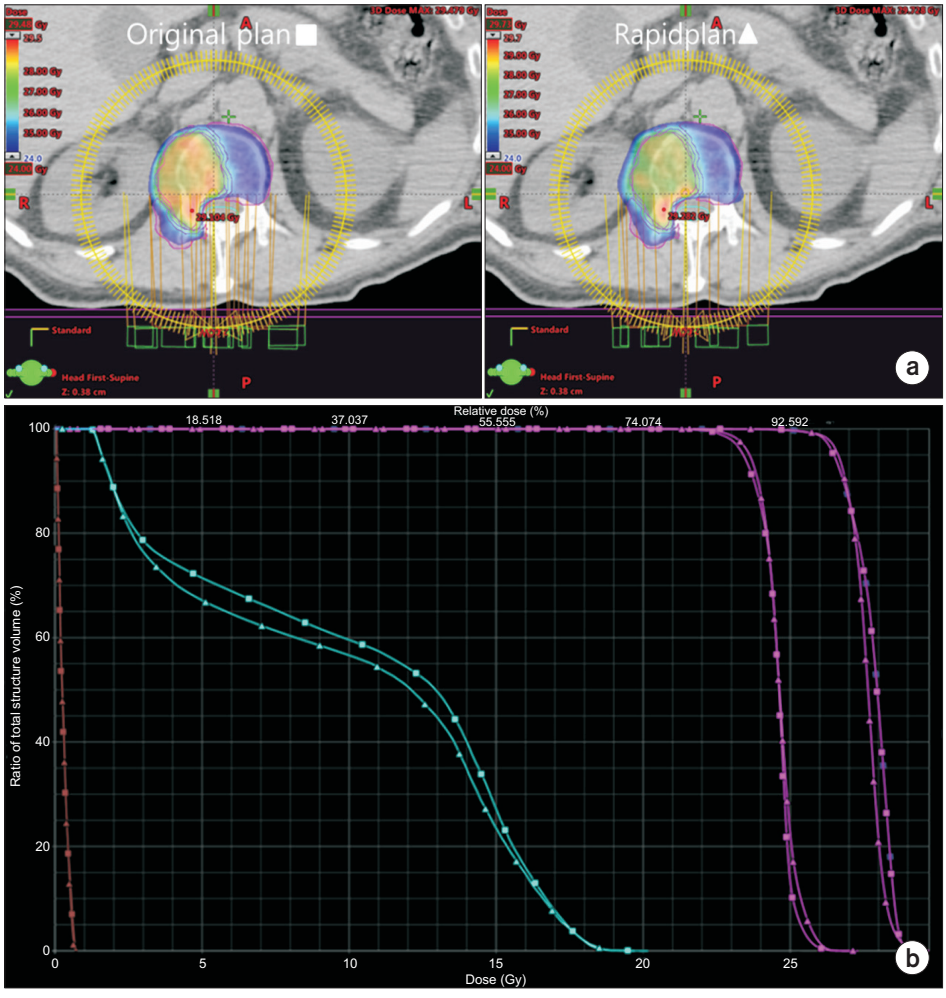

Fig. 3. A representative case of spine stereotactic body radiotherapy planning. (a) Dose distribution. (b) Dose-volume histogram for the expert plan and the RapidPlan.

low the second lumbar vertebra. The average volumes of PTV-B and PTV-E were 17.4 cm^3 (range: 3.0 cm^3–76.5 cm^3) and 23.8 cm^3 (range: 0.8 cm^3–98.4 cm^3), respectively. Fig. 3 shows a representative KBP plan. In terms of dose distributions and DVHs, the KBP plan was more suitable for clinical use than the expert plan. None of the expert plans were excluded in the KBP model as outliers. The goodness of fit for the spinal cord and esophagus was 0.999 and 1.0, respectively.

Table 1 summarizes comparisons of dosimetric parameters between the RapidPlans and the expert plans in the closed- and open-loop validations. In the closed-loop validation, the maximum dose to the target was higher in the KBP plans than in the expert plans. On the other hand, the minimum dose to the target was lower in KBP plans, although the difference did not exceed the maximum of 0.6 Gy. The maximum dose to the spinal cord and esophagus was significantly lower in the KBP plans. The dose to the target in the open-loop showed a similar pattern as that in the closed-loop, while the difference was not more than 0.7 Gy. However, no significant dose reduction was observed in the spinal cord and the esophagus in the KBP plans, in contrast to the closed-loop validation. Although the average dose reduction in the spinal cord and the esophagus was observed in the DVHs, the maximum dose was similar to that of the expert plans in both closed- and open-loop validations (Fig. 4).

Table 2 and Fig. 5 show the dosimetric parameters for the expert and KBP plans with and without use of virtual volumes. Virtual volumes were used in 38 of 48 expert treat-

Table 1. Result of the closed-loop validation and the open-loop validation (Gy)

Variable	Parameter	Closed-loop validation (n=26)			Open-loop validation (n=22)		
		Expert	RapidPlan	*P*-value	Expert	RapidPlan	*P*-value
PTV-B	D_{min}	24.7 (0.8)	24.3 (1.0)	0.007	24.7 (0.9)	24.1 (1.3)	0.003
	D_{mean}	28.1 (0.5)	28.1 (0.3)	0.778	27.9 (0.2)	28.0 (0.3)	0.015
	D_{max}	29.6 (0.8)	30.1 (0.7)	0.004	29.2 (0.5)	29.9 (0.8)	<0.001
PTV-E	D_{min}	20.8 (1.7)	20.5 (1.3)	0.376	21.1 (0.7)	20.4 (1.0)	0.003
	D_{mean}	25.1 (0.3)	25.1 (1.0)	0.029	24.9 (0.2)	25.2 (0.4)	0.007
	D_{max}	27.6 (0.9)	28.2 (1.0)	0.002	27.3 (0.7)	27.8 (0.8)	0.009
Spinal cord	$D_{1.2cc}$	12.2 (4.8)	11.3 (4.7)	0.010	12.9 (4.0)	12.6 (3.9)	0.409
	$D_{0.35cc}$	16.7 (1.2)	16.1 (1.0)	0.042	16.1 (1.6)	16.1 (1.2)	0.855
	D_{mean}	11.3 (1.7)	10.4 (1.6)	<0.001	9.4 (3.7)	8.9 (3.7)	0.041
Esophagus	D_{5cc}	6.7 (5.4)	6.1 (5.0)	0.047	4.9 (4.1)	4.6 (4.0)	0.282
	D_{mean}	4.5 (3.5)	4.0 (3.1)	0.003	3.2 (2.6)	3.0 (2.3)	0.077

Data are presented as number (standard deviation).
PTV, planning target volume; PTV-B, PTV for boost; PTV-E, PTV elective; D_{min}, minimum dose; D_{mean}, mean dose; D_{max}, maximum dose.

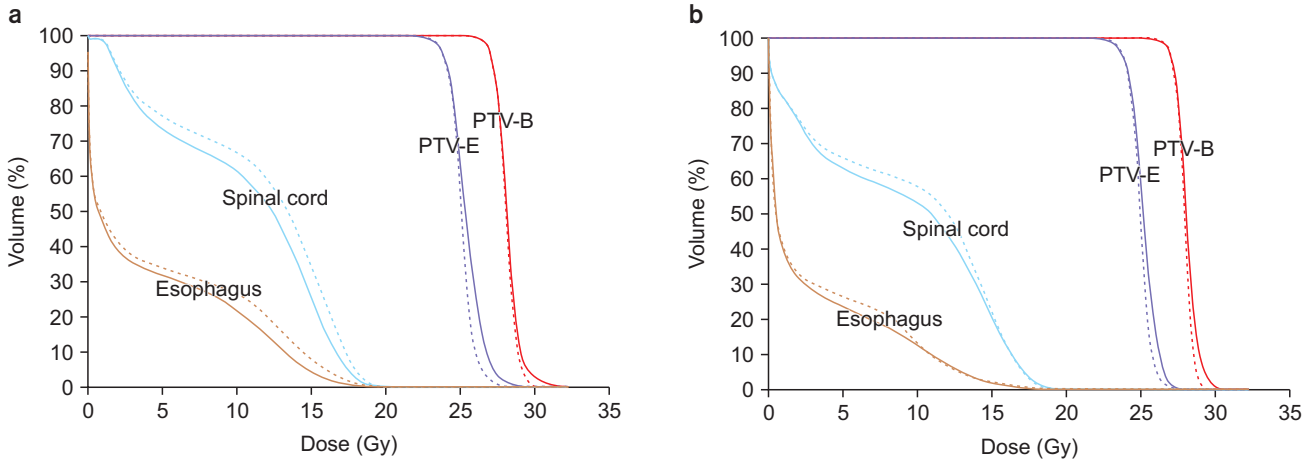

Fig. 4. Dose-volume histogram comparison between the expert plan (dotted line) and the RapidPlan (solid line). (a) Closed-loop validation. (b) Open-loop validation. PTV, planning target volume; PTV-E, PTV elective; PTV-B, PTV for boost.

Table 2. Dosimetric comparison between the expert plan and the RapidPlan, with and without use of a virtual volume (Gy)

Variable	Parameter	Plan with virtual volume (n=38)			Plan without virtual volume (n=10)		
		Expert	RapidPlan	*P*-value	Expert	RapidPlan	*P*-value
PTV-B	D_{min}	24.7 (0.9)	24.3 (1.2)	0.002	24.9 (0.6)	24.2 (0.9)	0.003
	D_{mean}	28.1 (0.4)	28.1 (0.3)	0.253	27.9 (0.2)	28.0 (0.1)	0.912
	D_{max}	29.5 (0.7)	30.2 (0.7)	<0.001	29.1 (0.5)	29.5 (0.5)	0.010
PTV-E	D_{min}	21.3 (1.2)	20.8 (1.5)	0.012	20.4 (2.6)	20.2 (1.0)	0.800
	D_{mean}	25.3 (0.9)	25.7 (1.1)	0.002	24.9 (0.3)	24.9 (0.3)	0.935
	D_{max}	27.8 (1.0)	28.4 (1.2)	<0.001	27.1 (0.5)	27.3 (0.6)	0.098
Spinal cord	$D_{1.2cc}$	12.8 (4.2)	12.3 (4.2)	0.053	11.3 (5.2)	10.5 (5.0)	0.080
	$D_{0.35cc}$	16.6 (1.4)	16.2 (1.0)	0.157	15.9 (1.2)	15.6 (1.2)	0.366
	D_{mean}	10.3 (2.9)	9.7 (2.8)	0.003	10.6 (3.3)	9.7 (2.9)	0.051
Esophagus	D_{5cc}	6.8 (4.9)	6.2 (4.6)	0.021	2.6 (3.4)	2.6 (3.5)	0.873
	D_{mean}	4.5 (3.5)	4.0 (3.1)	<0.001	3.1 (3.7)	2.7 (3.1)	0.201

Data are presented as number (standard deviation).
PTV, planning target volume; PTV-B, PTV for boost; PTV-E, PTV elective; D_{min}, minimum dose; D_{mean}, mean dose; D_{max}, maximum dose.

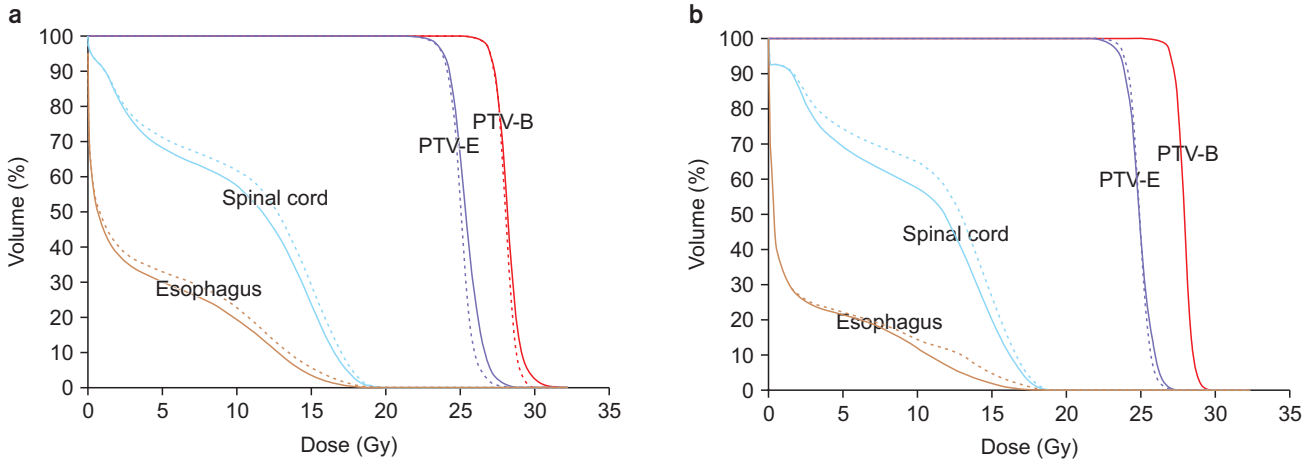

Fig. 5. Dose-volume histogram comparison between the expert plan (dotted line) and the RapidPlan (solid line) with or without use of a virtual volume. (a) Plan with a virtual volume. (b) Plan without a virtual volume. PTV, planning target volume; PTV-E, PTV elective; PTV-B, PTV for boost.

Table 3. Homogeneity index (maximum dose/prescribed dose; Gy)

Planning	PTV-B			PTV-E		
	Expert	RapidPlan	*P*-value	Expert	RapidPlan	*P*-value
Validation						
Closed-loop	1.10 (0.03)	1.12 (0.03)	0.004	1.15 (0.04)	1.17 (0.04)	0.002
Open-loop	1.08 (0.02)	1.11 (0.03)	<0.001	1.13 (0.03)	1.15 (0.03)	0.009
Virtual volume (VV)						
With VV	1.09 (0.03)	1.12 (0.03)	<0.001	1.15 (0.04)	1.17 (0.04)	<0.001
Without VV	1.08 (0.02)	1.09 (0.02)	0.010	1.13 (0.02)	1.14 (0.02)	0.098

Data are presented as number (standard deviation).
PTV, planning target volume; PTV-B, PTV for boost; PTV-E, PTV elective.

ment plans. Regardless of the use of the virtual volume in the dose parameters for PTV-B, the KBP plans significantly increased the maximum dose and reduced the minimum dose, compared with the expert plans. There was no significant difference in the dose variables for PTV-E, regardless of whether the virtual volume was used.

For the OARs, a significant dose reduction was observed only in the esophagus when a RapidPlan was used with a virtual volume. In the DVH, the KBP plan without the virtual volume showed similar results to those of the expert plan.

The dose homogeneity of the target was slightly, yet statistically significantly, worse in RapidPlans for both open- and closed-loop validations. The difference in uniformity reached 0.03 between the expert and KBP plans with virtual volumes but was less than 0.01 between the expert and KBP plans without virtual volumes (Table 3).

Discussion

The basic concept of KBP is to learn, from previous high-quality plans, the achievable dose distributions by analyzing the geometric relationship between targets and OARs in these plans, and then to apply this knowledge to manage the quality of the treatment plan and to achieve a high level of plan quality, regardless of the experience of the treatment planners.

This geometric relationship is analyzed using the overlapping volume histogram (OVH)[5] and the distance to the target histogram (DTH).[21] In previous KBP studies on patients with pancreatic cancer,[11] prostate cancer,[5] lung cancer,[9] liver cancer,[8] and head and neck cancer,[22] the dose of the OAR could be reduced while maintaining the dose distribution to the target. However, there have been only a few studies on KBP for spine SBRT.

Because this study was conducted on spine SBRT, there are some differences from previous studies. Firstly, because the spinal cord and esophagus are both serial OARs, the reduction of the higher dose region is more important than the average organ dose reduction. Secondly the application of SIB treatment with VMAT is another unique feature of this study. Finally, the spine varies from the cervical spine to the lumbar spine, and according to the outline drawing guidelines proposed by the IRSG, the shape of the target varies greatly, depending on the location of the tumor.

Nevertheless, RapidPlan, the commercially available KBP software used in this study, makes it possible to create a clinically usable treatment plan easily, rapidly, and by less experienced treatment planners. If high-quality plans are available, it is also easy to generate the KBP model rapidly. According to a study by Chung et al.,[1] which compared the treatment plans for IMRT for gastric cancer at the National University Hospital of Singapore and the University of California-San Francisco, the mean dose to the right kidney, V20%, and the mean dose to the left kidney, the maximal dose to the spinal cord, and the mean dose to the liver were all smaller at the University of California-San Francisco Hospital, which has more experience in this technique. This indicates that the quality of the IMRT plan may vary according to experience. In contrast, the present study demonstrated that KBP plans can maintain good plan quality regardless of the experience of the planners.

In this study, using the RapidPlan, the dose coverage and uniformity of the target were slightly inferior to those of the expert plans. However, the dose to the spinal cord in $D_{1.2cc}$ was decreased by 0.9 Gy, by 0.8 Gy in $D_{0.35cc}$, and by 0.6 Gy in the esophagus in the closed-loop test. In the open-loop test, $D_{1.2cc}$ of the spinal cord and D_{5cc} of the esophagus was decreased by 0.3 Gy without statistical significance from the expert plan. The mean dose of the spinal cord was statistically significantly decreased. According to Fogliata et al.,[8] RapidPlan was successfully modeled and applied to liver cancer, but no dose reduction was observed to the normal liver. Later, when applied to lung cancer and prostate cancer, the overall doses to OARs were reduced, except for an increased dose to the bladder in the open-loop validation.[9] The bladder volume receiving more than 70 Gy was relatively increased in the open-loop validation, similar to the observation in this study. Although a decrease in the maximum dose or in hot spots is more important in serial organs, such as the spinal cord, RapidPlan may limit the predicted dose as a DVH line, and since the weights for the points on the DVH line are all equal, an average dose decrease is likely to be more common. This is not an effective approach for serial organ, where reduction of the maximum dose is more important. To overcome this limitation, a normal tissue complication probability model[23] or generalized equivalent uniform dose[24] can be used, because these models incorporate the biological effect of the radiation on each organ.

In this study, the closed-loop and open-loop tests showed that the minimum dose of the target was decreased while the maximum dose were increased in the RapidPlans compared with the expert plans, but the difference in dose was less than 0.7 Gy for both PTV-B and PTV-E. The difference in the homogeneity index was as small as 0.02. While the improvement in target dose uniformity were reported in head and neck cancer, liver cancer, and lung cancer, in prostate cancer studies, the D99% (99% volume dose) was decreased by 0.6 Gy in the closed-loop test. (1 standard deviation: 0.7 Gy), and by 0.7 Gy (1 standard deviation: 1.1 Gy) in the open-loop test. Therefore, the improvement of target dose homogeneity in the KBP plan is not universal and may be a consequence of the target dose distribution that is affected by surrounding OARs. RapidPlan only provides the expected dose for the OARs; therefore, the target dose must be passively imposed, and as a result, the uniformity of the target can be affected by the imposed target dose constraints.

In this study, we evaluated the effect of virtual volume on KBP plan quality. For IMRT plan optimization, virtual volumes are widely generated and used to increase the minimum dose or decrease the maximum dose to the target, or to decrease the dose of the OARs. In the expert plans, virtual volumes were used in 38 of the 48 cases, while the RapidPlan did not use any virtual volumes. Consequently, the maximum dose of PTV-B was significantly lower in the expert plans utilizing the virtual volumes and the difference was 0.7 Gy. However, the difference was reduced to 0.4 Gy when virtual volumes were not used in the expert plans. In addition, for PTV-E, there was no statistically significant

difference for plans in which virtual volumes were not used. Wu et al. reported that imposing a dose constraint on the virtual volume improved the dose uniformity of the target.[25] Therefore, the inclusion of clinically used virtual volumes in the KBP model should be studied in future in order to improve plan quality further.

Conclusions

The dose coverage and uniformity for PTV was slightly worse in the KBP for spine SBRT while the dose to the spinal cord was reduced, but the differences were not clinically significant, demonstrating non-inferior plan quality. Even less-skilled treatment planners can easily create clinically feasible treatment plans with the RapidPlan, which can mitigate the difficulty associated with designing treatment plans or the effect of the treatment planners' skill on plan quality.

Acknowledgements

This study was supported by a grant (2019-7049) from the Asan Institute for Life Sciences, Asan Medical Center, Seoul, Korea.

Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

All relevant data are within the paper and its Supporting Information files.

References

1. Chung HT, Lee B, Park E, Lu JJ, Xia P. Can all centers plan intensity-modulated radiotherapy (IMRT) effectively? An external audit of dosimetric comparisons between three-dimensional conformal radiotherapy and IMRT for adjuvant chemoradiation for gastric cancer. Int J Radiat Oncol Biol Phys. 2008;71:1167-1174.
2. Nelms BE, Robinson G, Markham J, Velasco K, Boyd S, Narayan S, et al. Variation in external beam treatment plan quality: an inter-institutional study of planners and planning systems. Pract Radiat Oncol. 2012;2:296-305.
3. Moore KL, Brame RS, Low DA, Mutic S. Quantitative metrics for assessing plan quality. Semin Radiat Oncol. 2012; 22:62-69.
4. Moore KL, Brame RS, Low DA, Mutic S. Experience-based quality control of clinical intensity-modulated radiotherapy planning. Int J Radiat Oncol Biol Phys. 2011;81:545-551.
5. Yang Y, Ford EC, Wu B, Pinkawa M, van Triest B, Campbell P, et al. An overlap-volume-histogram based method for rectal dose prediction and automated treatment planning in the external beam prostate radiotherapy following hydrogel injection. Med Phys. 2013;40:011709.
6. Zarepisheh M, Long T, Li N, Tian Z, Romeijn HE, Jia X, et al. A DVH-guided IMRT optimization algorithm for automatic treatment planning and adaptive radiotherapy replanning. Med Phys. 2014;41:061711.
7. Yang Y, Xing L. Clinical knowledge-based inverse treatment planning. Phys Med Biol. 2004;49:5101-5117.
8. Fogliata A, Wang PM, Belosi F, Clivio A, Nicolini G, Vanetti E, et al. Assessment of a model based optimization engine for volumetric modulated arc therapy for patients with advanced hepatocellular cancer. Radiat Oncol. 2014;9:236.
9. Fogliata A, Belosi F, Clivio A, Navarria P, Nicolini G, Scorsetti M, et al. On the pre-clinical validation of a commercial model-based optimisation engine: application to volumetric modulated arc therapy for patients with lung or prostate cancer. Radiother Oncol. 2014;113:385-391.
10. Kavanaugh JA, Holler S, DeWees TA, Robinson CG, Bradley JD, Iyengar P, et al. Multi-institutional validation of a knowledge-based planning model for patients enrolled in RTOG 0617: implications for plan quality controls in cooperative group trials. Pract Radiat Oncol. 2019;9:e218-e227.
11. Campbell WG, Miften M, Olsen L, Stumpf P, Schefter T, Goodman KA, et al. Neural network dose models for knowledge-based planning in pancreatic SBRT. Med Phys. 2017;44:6148-6158.
12. Fogliata A, Cozzi L, Reggiori G, Stravato A, Lobefalo F, Franzese C, et al. RapidPlan knowledge based planning: iterative learning process and model ability to steer planning strategies. Radiat Oncol. 2019;14:187.
13. Agarawal JP, Swangsilpa T, van der Linden Y, Rades D, Jer-

emic B, Hoskin PJ. The role of external beam radiotherapy in the management of bone metastases. Clin Oncol (R Coll Radiol). 2006;18:747-760.
14. Prasad D, Schiff D. Malignant spinal-cord compression. Lancet Oncol. 2005;6:15-24.
15. Sahgal A, Ma L, Fowler J, Weinberg V, Gibbs I, Gerszten PC, et al. Impact of dose hot spots on spinal cord tolerance following stereotactic body radiotherapy: a generalized biological effective dose analysis. Technol Cancer Res Treat. 2012;11:35-40.
16. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S42-S49.
17. Chawla S, Schell MC, Milano MT. Stereotactic body radiation for the spine: a review. Am J Clin Oncol. 2013;36:630-636.
18. Cox BW, Spratt DE, Lovelock M, Bilsky MH, Lis E, Ryu S, et al. International Spine Radiosurgery Consortium consensus guidelines for target volume definition in spinal stereotactic radiosurgery. Int J Radiat Oncol Biol Phys. 2012;83:e597-e605.
19. Wu QJ, Yoo S, Kirkpatrick JP, Thongphiew D, Yin FF. Volumetric arc intensity-modulated therapy for spine body radiotherapy: comparison with static intensity-modulated treatment. Int J Radiat Oncol Biol Phys. 2009;75:1596-1604.
20. Videtic GM, Hu C, Singh AK, Chang JY, Parker W, Olivier KR, et al. A randomized phase 2 study comparing 2 stereotactic body radiation therapy schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer: NRG Oncology RTOG 0915 (NCCTG N0927). Int J Radiat Oncol Biol Phys. 2015;93:757-764.
21. Yuan L, Ge Y, Lee WR, Yin FF, Kirkpatrick JP, Wu QJ. Quantitative analysis of the factors which affect the interpatient organ-at-risk dose sparing variation in IMRT plans. Med Phys. 2012;39:6868-6878.
22. Wu B, McNutt T, Zahurak M, Simari P, Pang D, Taylor R, et al. Fully automated simultaneous integrated boosted-intensity modulated radiation therapy treatment planning is feasible for head-and-neck cancer: a prospective clinical study. Int J Radiat Oncol Biol Phys. 2012;84:e647-e653.
23. Källman P, Agren A, Brahme A. Tumour and normal tissue responses to fractionated non-uniform dose delivery. Int J Radiat Biol. 1992;62:249-262.
24. Miften MM, Das SK, Su M, Marks LB. Incorporation of functional imaging data in the evaluation of dose distributions using the generalized concept of equivalent uniform dose. Phys Med Biol. 2004;49:1711-1721.
25. Wu Q, Mohan R, Niemierko A, Schmidt-Ullrich R. Optimization of intensity-modulated radiotherapy plans based on the equivalent uniform dose. Int J Radiat Oncol Biol Phys. 2002;52:224-235.