

Validation of RapidPlan Knowledge-Based Model for Volumetric-Modulated Arc Therapy in Prostate Cancer

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Abstract

Aims and Objectives: This study aims to investigate the viability of using RapidPlan (RP) knowledge-based (KB) treatment plans to initiate the new prostate volumetric-modulated arc therapy (VMAT) plans. **Materials and Methods:** The planning data for 120 prostate VMAT treatment plans were entered into the RP system's database. The database of previous VMAT plans was divided into four model groups for training in the RP system. The models were based on the numbers of 20, 60, and 120 prostate VMAT plans. The model of 120 plans used automated priority and manual priority for the optimization process. The models of 20 and 60 plans used only manual priority for optimization. Each model was validated on 15 cases of new prostate cancer patients by comparing RP model plans against manual clinical plans optimized according to the clinical dose constraints. **Results:** The RP models can estimate the dose comparable target volume to the manual clinical plan, which evaluated values of Dmax, D95%, D98%, HI, and CI and showed comparable results. For the normal organ doses of the bladder, rectum, penile bulb, and femoral head, all RP models exhibited a comparable or better dose than the manual clinical plan, except for the RP models using the automated priority for the optimization process, which cannot control the rectum dose below the dose constraints. **Conclusions:** The Varian RP KB planning can produce comparable doses or better doses with the clinical manual in a single optimization, although the RP model uses a minimum requirement of the planning number for the model training. The RP models can enhance the efficacy and quality of plans, which depend on the number of VMAT plans used in RP model training for prostate cancer.

Keywords: Knowledge-based planning, prostate cancer, RapidPlan Model, treatment planning, volumetric-modulated arc therapy

Received on: 16-11-2021

Review completed on: 17-05-2022

Accepted on: 18-05-2022

Published on: 08-11-2022

INTRODUCTION

Most prostate cancer patients are treated commonly by intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) in clinical treatments. These are the high-efficiency techniques to deliver the maximum dose to the target volume and the minimum dose to the normal organs that are the goal of radiotherapy treatments. These techniques result in good response for early-stage prostate cancer patients.^[1] At present, IMRT and VMAT plans use the inverse planning technique for optimizing and calculating the dose to the patient. A trial-and-error approach is utilized for the optimization process which consumes a long calculation time. The inverse planning technique takes several hours per case to create an acceptable final plan for clinical practice. After the plans are accepted and analyzed, the plan quality has a wide variation, which depends on the planners.^[2] The quality of the plan encourages

the planners to improve and minimizes the variation in any treatment plans. Knowledge-based (KB) treatment planning is the solution to improve a variety of plans' quality.^[3,4]

The RapidPlan (RP) system is a commercial system of KB treatment planning used to predict the dose distribution in patients. RP is a feature of the treatment planning system that takes the anatomical data of the patients and correlates these to the previously achieved data of dosimetry to create a suitable estimate of the achievable dose distribution for prospective cases and the automated creation of the optimization constraints. It can help the planner to improve plan quality by reducing

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Access this article online

Quick Response Code:



Website:
www.jmp.org.in

DOI:
10.4103/jmp.jmp_138_21

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How to cite this article: Ayuthaya II, Suriyapee S, Sanghangthum T. Validation of RapidPlan knowledge-based model for volumetric-modulated arc therapy in prostate cancer. *J Med Phys* 2022;47:250-5.

the variation in dosimetry of target and normal organs that has been investigated in many studies.^[5-8] Moreover, the RP system can reduce the planning time. Therefore, this study aims to investigate the viability of using RP KB treatment plans to initiate new prostate cancer cases using VMAT plans and find suitable cases to include in the database for learning and training in RP models. The RP KB software was evaluated before the treatment plans were approved for use in the clinical treatment.

MATERIALS AND METHODS

Knowledge-based learning library

A database of 120 prostate cancer VMAT cases was collected, all of them which were previously planned using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA) and delivered in clinical treatment. The prostate cancer cases from 2017 to 2020 did not include lymphatic nodes treated only the prostate gland. All cases were anonymized before including them in the database. The data information of each plan included the computed tomography image, normal organs, target volumes, and dose distributions. The VMAT technique by 6 MV photon beams with 2 full arcs rotation was used in all treatment plans. The prescription dose of the planning target volume (PTV) was 79.2 Gy in 44 fractions. The dose constraints of PTV and organs at risk (OARs) of bladder, rectum, femoral head, and penile bulb were defined in treatment planning for optimization and dose calculation. Then, the objective organs were analyzed for Dose Volume Histogram (DVH) constraints definition [Table 1].

RapidPlan model configuration

In a model configuration, the geometric and dosimetric parameters of each plan were imported and trained in the RP algorithm.^[9] The minimum required number of training cases in the RP model was 20 cases. In this study, the model configuration was divided into four groups. The models are based on the number of 20, 60, and 120 prostate VMAT plans for training in the RP system. After importing and training each group, the RP system can generate dose constraints for automatic optimization in each group. A model can set the priority for dose constraint optimization by automatic and manual priority values, which may affect the optimization process and objective dose in the new plans. In the optimization process of Eclipse treatment planning, the priority values

determine the importance level of each organ, and PTV, which one is the important organ, must be set to the high values. The priority value for the RP model can be set automatically or manually. The automatic priority value settings should be investigated for the efficiency of the plans. In this study, the RP of 120 cases was divided into two groups for automatic and manual priority parameters (RP120A and RP120), while the RP of 20 and 60 cases (RP20 and RP60) only used the manual priority during the optimization procedure. The automatic priorities were created as the priority parameters for the optimization process by the RP from the KB calculation. In the optimization procedure, the treatment planning computes the plans until finalized. On the other hand, the manual priorities have adapted to the priorities during the optimization process. The model of RP was set up into four groups to investigate the doses in the new treatment plans. The new plans were the retrospective patients treated completely, but they were not the same as the cases with learning in the RP model.

Generating new treatment plans

Then, after each RP model was generated in a library, the 15 new prostate cancer cases that needed to be treated completely in clinical treatment but whose plans had never been used to collect data in an RP model were used to investigate each RP model. In each plan, the VMAT technique with 2 arcs and a 6 MV photon beam was used to plan. The dose prescription of 79.2 Gy was applied to PTV. In the optimization process, the RP models were selected to optimize and compute dose following the dose constraints created by each RP model. In each model, the RP system automatically generated dose objectives for PTV and OARs. The RP120 model used both manual and automatic optimization priorities during the optimization process. The DVHs of PTV and OARs were analyzed and compared to the dose following each parameter as shown in Table 1. Each RP model required 5–10 min of planning time per plan.

Dose comparison between each RapidPlan model and manually optimized plans

The manually optimized plans (MP) were created by using VMAT treatment with 2 arcs of 6 MV photon beams. The planner has more than 15 years of experience in doing manual plans. In the optimization process, the dose objectives and optimization priorities were set manually the same as in clinical treatment. All plans must be within the dose constraints [Table 1] that are used for accepted plans. Then, the doses of the MP were compared with the 4 models created by RP. The dosimetry parameters of PTV and OARs were collected from DVH as following the dose constraint. The comparison data of each plan were analyzed significantly by repeated ANOVA for a statistical test with a $P < 0.05$.

For the PTV, the conformity index (CI) was used to evaluate the treatment plans calculated by equation 1.^[10]

$$CI = \frac{PTV_p}{TV} \quad (1)$$

Table 1: Dose constraints for dose optimization and calculation

Organ	Dose constraints
PTV	$D_{max} \leq 107\%$, $D_{95\%} \geq 95\%$, and $D_{98\%} \geq 93\%$
Bladder	$V_{80Gy} \leq 15\%$, $V_{75Gy} \leq 25\%$, $V_{70Gy} \leq 30\%$, $V_{60Gy} \leq 40\%$ and $V_{40Gy} \leq 50\%$
Rectum	$V_{75Gy} \leq 15\%$, $V_{70Gy} \leq 20\%$, $V_{60Gy} \leq 30\%$, $V_{50Gy} \leq 40\%$ and $V_{40Gy} \leq 50\%$
Penile bulb	$V_{50Gy} \leq 10\%$ and $D_{mean} \leq 48$ Gy
Femoral head	$D_{mean} \leq 52.5$ Gy

PTV: Planning target volume

where PTV_p is the volume of the target receiving the prescription dose and TV is the target volume.^[10-12] CI is a parameter to explain the good dose conforming to PTV . The perfect conformity value is unity.

The homogeneity index (HI) of the PTV is defined as equation 2.^[13]

$$HI = D_{2\%} - D_{98\%} / D_p \quad (2)$$

where $D_{2\%}$ = minimum dose to 2% of the target volume, indicating the “maximum dose,” $D_{98\%}$ = minimum dose to 98% of the target volume, indicating the “minimum dose,” and D_p = prescribed dose. The ideal value is zero, and it increases as homogeneity decreases.

RESULTS

The results of MP and RP models calculated in 15 new patient plans are shown in Table 2. The example of DVHs in each plan model is shown in Figure 1. The dosimetric comparisons of PTV in each plan model comparable to MP were not statistically different on $D_{2\%}$, $D_{95\%}$, and $D_{98\%}$. Thus, the average HI of each planning model was in the range of 0.07–0.08. As shown in Table 3, the average CI of all planning models was 0.96. All RP models can optimize and compute the target doses with the same quality as MP and can slightly decrease the maximum dose of PTV .

For the rectum, the average dose volume of 15 patient plans for $V_{75Gy} \leq 15\%$, $V_{70Gy} \leq 20\%$, $V_{60Gy} \leq 30\%$, $V_{50Gy} \leq 40\%$, and $V_{40Gy} \leq 50\%$ is shown in Table 4, which is a readout from the DVH. The RP120A model showed the highest mean doses of the rectum for all dose constraints, for which there was a statistical difference significantly with the MP by $P < 0.05$. When using the RP20, RP60, and RP120 models to calculate the dose, the rectum achieved was lower than calculated by the MP for all dose constraints. There were statistical differences significantly with the MP by $P < 0.05$, except that in the RP20 model, the mean doses of the rectum were less than the MP, but there were no statistical differences significantly. All models can calculate the rectum dose within

the limit of the dose constraints, except the RP120A model, which cannot achieve the dose requirement at $V_{40Gy} \leq 50\%$

Table 2: Average dose of the planning target volume for 15 new prostate cancer volumetric modulated arc therapy plans in each dose parameters and planning models

Organ	Dose parameters	Model	Mean (Gy)±SD	P
PTV	$D_{95\%}$	MP	79.4±0.1	Reference
		RP20	79.4±0.1	0.62
		RP60	79.4±0.1	0.62
		RP120	79.4±0.2	0.32
		RP120A	79.4±0.1	0.99
	$D_{98\%}$	MP	78.0±0.4	Reference
		RP20	78.2±0.3	0.02
		RP60	78.1±0.2	0.22
		RP120	78.1±0.3	0.14
		RP120A	78.2±0.3	0.1
	D_{max}	MP	84.8±1.4	Reference
		RP20	84.1±0.7	0.02
		RP60	84.4±0.6	0.21
		RP120	84.5±0.4	0.31
		RP120A	84.3±0.9	0.12

PTV: Planning target volume, SD: Standard deviation, MP: Manually optimized plans, RP: RapidPlan

Table 3: The conformity index and homogeneity index values of planning target volume for each planning model

Parameters	Model	Mean
CI	MP	0.96
	RP20	0.96
	RP60	0.96
	RP120	0.96
	RP120A	0.96
HI	MP	0.08
	RP20	0.07
	RP60	0.08
	RP120	0.08
	RP120A	0.07

CI: Conformity index, HI: Homogeneity index, MP: Manually optimized plans, RP: RapidPlan

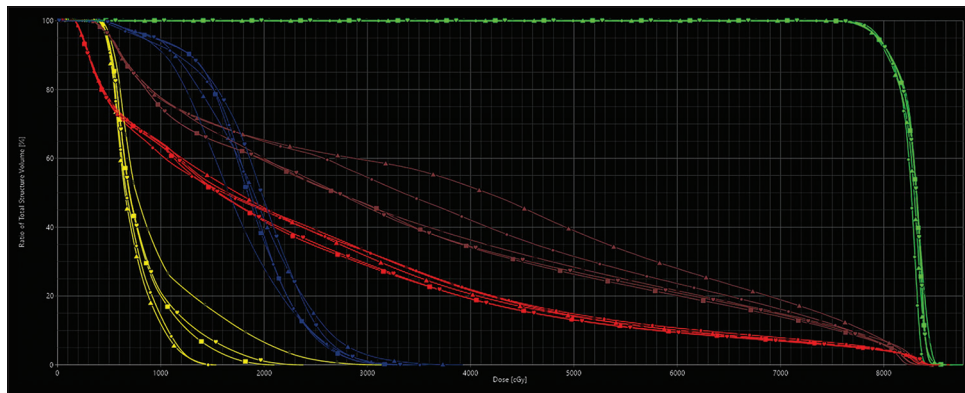


Figure 1: The DVHs of each plan model for PTV (green), rectum (brown), bladder (red), femoral head (blue), and penile bulb (yellow). Each plan model of each contouring as the black dot is MP, the circle dot is RP20 model, the square dot is RP60, the heart shape dot is RP120, and the triangular dot is RP120A. DVH: Dose volume histogram, PTV : Planning target volume, MP: Manually optimized plans

under the dose constraint. The average dose of the V_{40Gy} parameter was 47.

For the bladder, the average dose volume of $V_{80Gy} \leq 15\%$, $V_{75Gy} \leq 20\%$, $V_{70Gy} \leq 30\%$, $V_{60Gy} \leq 40\%$, and $V_{40Gy} \leq 50\%$ is shown in Table 5. All RP models display the bladder dose lower than the MP in all dose constraints, except the RP20 model at $V_{40Gy} \leq 50\%$. For all dose constraints, the average doses of the bladder calculated by the RP60 and RP120 models were less than calculated by the MP with a statistical significance of $P < 0.05$. All models can be optimized and calculate the doses within the dose objectives.

For the femoral head, the average doses of D_{max} and mean dose are shown in Table 6. The D_{max} and the mean dose calculated by all RP models were less than those calculated by the MP. However, the doses were not statistically different significance. All models can be optimized and calculate the doses within the dose objectives.

For the penile bulb, the average doses of D_{max} and mean dose are shown in Table 7. The D_{max} and the mean dose calculated by all RP models are less than those calculated by the MP. The doses are statistically different significance by $P < 0.05$. The D_{max} and the mean dose of the RP120A are the lowest. All models can be optimized and calculated dose within the dose objectives.

Table 4: Average dose of the rectum for 15 new prostate cancer volumetric modulated arc therapy plans in each dose constraint and planning model

Organ	Dose constraints	Model	Mean (%) ± SD	P
Rectum	$V_{75} < 15\%$	MP	11.7 ± 3.1	Reference
		RP20	11.4 ± 2.6	0.300
		RP60	10.6 ± 2.5	0.002
		RP120	10.5 ± 2.4	0.002
		RP120A	12.7 ± 2.9	0.003
	$V_{70} < 20\%$	MP	15.6 ± 3.9	Reference
		RP20	15.1 ± 3.2	0.320
		RP60	14.0 ± 3.2	0.001
		RP120	14.1 ± 3.2	0.001
		RP120A	17.3 ± 4.0	<0.001
	$V_{60} < 30\%$	MP	22.4 ± 5.2	Reference
		RP20	22.0 ± 4.4	0.610
		RP60	20.3 ± 4.4	0.008
		RP120	20.4 ± 4.8	0.009
		RP120A	25.5 ± 5.7	<0.001
	$V_{50} < 40\%$	MP	29.9 ± 6.8	Reference
		RP20	29.4 ± 5.4	0.700
		RP60	26.6 ± 5.3	0.007
		RP120	27.1 ± 5.5	0.010
		RP120A	35.3 ± 8.1	<0.001
$V_{40} < 50\%$	MP	39.0 ± 7.9	Reference	
	RP20	38.7 ± 6.7	0.890	
	RP60	34.2 ± 5.8	0.007	
	RP120	35.0 ± 6.0	0.010	
	RP120A	47.0 ± 10.2	<0.001	

SD: Standard deviation, MP: Manually optimized plans, RP: RapidPlan

DISCUSSION

The VMAT plan uses the inverse planning process for optimization. It complicates treatment planning to achieve a good quality plan. The process requires the experience of planners and a trial-and-error approach. Sometimes, the planner must spend a long time on VMAT planning in the optimization and calculation process. By automating inverse planning procedures, RP KB can reduce planning time and variation in plan quality, as previously reported.^[7,14] Before using the model in clinical treatment, its performance should be compared to that of a manually optimized plan. A suitable model can be applied to the clinic to increase the efficiency of the plans.

For this study, the optimization objective at 95% of the dose to target must receive the prescription dose and control the maximum dose following the dose constraints used in the optimized process. Thus, the target dose comparisons are not significantly different for each planning model, including the HI and CI indexes, because the PTV is the first-order priority during the optimization process. Both indexes exhibit the same quality of the plans. All final plans achieve the dose constraint for PTV. Kubo *et al.*^[14] reported the planning from the RP comparison with the clinical manual optimization, in which their results showed a value of $D_{95\%}$, $D_{2\%}$, HI, and CN

Table 5: Average dose of the bladder for 15 new prostate cancer volumetric modulated arc therapy plans in each dose constraint and planning model

Organ	Dose constraints	Model	Mean (%) ± SD	P
Bladder	$V_{80} < 15\%$	MP	6.7 ± 2.5	Reference
		RP20	6.4 ± 2.5	0.007
		RP60	6.1 ± 2.4	<0.001
		RP120	6.2 ± 2.5	<0.001
		RP120A	6.4 ± 2.6	0.004
	$V_{75} < 25\%$	MP	8.9 ± 3.1	Reference
		RP20	8.8 ± 3.0	0.420
		RP60	8.3 ± 2.9	<0.001
		RP120	8.3 ± 3.1	<0.001
		RP120A	8.6 ± 3.2	0.02
	$V_{70} < 30\%$	MP	10.7 ± 3.6	Reference
		RP20	10.6 ± 3.4	0.820
		RP60	10.0 ± 3.4	0.002
		RP120	9.90 ± 3.5	<0.001
		RP120A	10.1 ± 3.6	0.070
	$V_{60} < 40\%$	MP	14.2 ± 4.7	Reference
		RP20	14.1 ± 4.5	0.850
		RP60	13.3 ± 4.4	0.003
		RP120	13.4 ± 4.8	0.001
		RP120A	13.6 ± 4.8	0.140
$V_{40} < 50\%$	MP	25.9 ± 8.1	Reference	
	RP20	26.0 ± 7.8	0.900	
	RP60	24.4 ± 8.0	0.050	
	RP120	23.9 ± 7.8	0.008	
	RP120A	25.3 ± 8.2	0.410	

SD: Standard deviation, MP: Manually optimized plans, RP: RapidPlan

Table 6: Average dose of the femoral heads for 15 new prostate cancer volumetric modulated arc therapy plans in each dose constraint and planning model

Organ	Dose constraints	Model	Mean (Gy) ±SD	P
Femoral heads	D _{mean} <52.5 Gy	MP	17.5±3.3	Reference
		RP20	16.8±2.3	0.15
		RP60	16.4±2.0	0.06
		RP120	16.7±2.5	0.12
		RP120A	16.4±2.8	0.06
	D _{max}	MP	34.2±5.1	Reference
		RP20	33.5±3.4	0.35
		RP60	32.9±3.4	0.12
		RP120	33.6±3.0	0.37
		RP120A	32.9±3.3	0.14

SD: Standard deviation, MP: Manually optimized plans, RP: RapidPlan

Table 7: Average dose of the penile bulb for 15 new prostate cancer volumetric modulated arc therapy plans in each dose constraint and planning model

Organ	Dose constraints	Model	Mean (Gy) ±SD	P
Penile bulb	D _{mean} <48 Gy	MP	18.57±10.8	Reference
		RP20	15.25±8.50	<0.001
		RP60	15.46±9.22	<0.001
		RP120	15.49±9.11	<0.001
		RP120A	14.97±8.92	<0.001
	D _{max}	MP	32.45±14.9	Reference
		RP20	31.90±14.2	0.001
		RP60	32.21±14.0	<0.001
		RP120	30.72±14.7	<0.001
		RP120A	38.49±15.0	<0.001

SD: Standard deviation, MP: Manually optimized plans, RP: RapidPlan

were significantly similar. On the other hand, Hussein *et al.*^[7] reported that the RP model can produce better conformity plans than the original manual optimization plans.

For normal organs, the RP120A model used the automated priority for optimization that could not control the rectum dose less than the MP because it estimated the unsuitable priority value for the optimization process. The dose difference was significantly higher. The RP120A model exhibited the dose to the bladder less than the MP, but it was not significantly different, including the dose of the femoral head. The other 3 RP models showed the bladder and rectum doses were lower than the MP significantly, except the RP20 model, which showed no significant difference. However, all RP models showed significantly higher performance for the penile bulb dose than the MP model. For the femoral head, all RP models exhibited doses slightly lower than the MP. The RP20 model can perform a dose to normal organs comparable to the MP. On the other hand, the RP60 and RP120 models exhibited significantly better results than the MP. For the RP120A, the results showed poor quality plan comparison with the MP in rectum overlapping with PTV. When the RP model is used in the automated priority function for optimization, it may not

be enough to create the best plan. The rectum doses are not controlled within the dose constraint. Kubo *et al.*^[14] proposed manually adjusting the RP optimization procedure to improve organ dose. The number of plans for training in the RP system led to poor conformity, coverage, and efficiency compared to clinical plans.^[7]

At least the 20 patient plans for prostate cancer are used to model in the RP system following a vendor recommendation, which means it can create a dose comparable with the manually clinical plan. If the number of the plans increases, the efficiency and performance of the RP model can be enhanced, especially in bladder and rectum dose reduction. The prostate cancer plans of 60–120 cases used in the RP model are suitable for VMAT treatment planning. The results showed better efficacy and high performance than the MP for normal organ dose. The RP model is a tool to help the planner improve the normal organ dose sparing as low as possible compared to the clinical manual planning without changing the target coverage.

CONCLUSIONS

The Varian RP KB planning can produce comparable doses or better doses with the clinical manual in a single optimization, although the RP model uses a minimum requirement of the planning number for the model training. The RP models can enhance the efficacy and quality of plans, which depend on the number of VMAT plans used in RP model training for prostate cancer. The automated priority function for optimization cannot control some normal organ doses below the dose constraint. The manual adjustment can improve the efficiency of plans.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Cahlon O, Hunt M, Zelefsky MJ. Intensity-modulated radiation therapy: Supportive data for prostate cancer. *Semin Radiat Oncol* 2008;18:48-57.
- 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.
- Chanyavanich V, Das SK, Lee WR, Lo JY. Knowledge-based IMRT treatment planning for prostate cancer. *Med Phys* 2011;38:2515-22.
- Schubert C, Waletzko O, Weiss C, Voelzke D, Toperim S, Roeser A, *et al.* Intercenter validation of a knowledge based model for automated planning of volumetric modulated arc therapy for prostate cancer. The experience of the German RapidPlan Consortium. *PLoS One* 2017;12:e0178034.
- Delaney AR, Tol JP, Dachele M, Cuijpers J, Slotman BJ, Verbakel WF. Effect of dosimetric outliers on the performance of a commercial knowledge-based planning solution. *Int J Radiat Oncol Biol Phys* 2016;94:469-77.
- 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;113:385-91.
- Hussein M, South CP, Barry MA, Adams EJ, Jordan TJ, Stewart AJ,

- et al.* Clinical validation and benchmarking of knowledge-based IMRT and VMAT treatment planning in pelvic anatomy. *Radiother Oncol* 2016;120:473-9.
8. Wu H, Jiang F, Yue H, Zhang H, Wang K, Zhang Y. Applying a RapidPlan model trained on a technique and orientation to another: A feasibility and dosimetric evaluation. *Radiat Oncol* 2016;11:108.
 9. Marks LB, Yorke ED, Jackson A, Ten Haken RK, Constone LS, Eisbruch A, *et al.* Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76:S10-9.
 10. Feuvret L, Noël G, Mazeron JJ, Bey P. Conformity index: A review. *Int J Radiat Oncol Biol Phys* 2006;64:333-42.
 11. Huchet A, Caudry M, Belkacémi Y, Trouette R, Vendrely V, Causse N, *et al.* Volume-effect and radiotherapy [II]. Part II: Volume-effect and normal tissue. *Cancer Radiother* 2003;7:353-62.
 12. Shaw E, Scott C, Souhami L, Dinapoli R, Kline R, Loeffler J, *et al.* Single dose radiosurgical treatment of recurrent previously irradiated primary brain tumors and brain metastases: Final report of RTOG protocol 90-05. *Int J Radiat Oncol Biol Phys* 2000;47:291-8.
 13. Kataria T, Sharma K, Subramani V, Karrthick KP, Bisht SS. Homogeneity Index: An objective tool for assessment of conformal radiation treatments. *J Med Phys* 2012;37:207-13.
 14. Kubo K, Monzen H, Ishii K, Tamura M, Kawamorita R, Sumida I, *et al.* Dosimetric comparison of RapidPlan and manually optimized plans in volumetric modulated arc therapy for prostate cancer. *Phys Med* 2017;44:199-204.