

# Estimation of the effects of normal tissue sparing using equivalent uniform dose-based optimization

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Received on: 30-01-2016    Review completed on: 04-03-2016    Accepted on: 28-03-2016

## ABSTRACT

In this study, we intend to estimate the effects of normal tissue sparing between intensity modulated radiotherapy (IMRT) treatment plans generated with and without a dose volume (DV)-based physical cost function using equivalent uniform dose (EUD). Twenty prostate cancer patients were retrospectively selected for this study. For each patient, two IMRT plans were generated (i) EUD-based optimization with a DV-based physical cost function to control inhomogeneity (EUD<sub>With DV</sub>) and (ii) EUD-based optimization without a DV-based physical cost function to allow inhomogeneity (EUD<sub>Without DV</sub>). The generated plans were prescribed a dose of 72 Gy in 36 fractions to planning target volume (PTV). Mean dose, D<sub>30%</sub>, and D<sub>5%</sub> were evaluated for all organ at risk (OAR). Normal tissue complication probability was also calculated for all OARs using BioSuite software. The average volume of PTV for all patients was 103.02 ± 27 cm<sup>3</sup>. The PTV mean dose for EUD<sub>With DV</sub> plans was 73.67 ± 1.7 Gy, whereas for EUD<sub>Without DV</sub> plans was 80.42 ± 2.7 Gy. It was found that PTV volume receiving dose more than 115% of prescription dose was negligible in EUD<sub>With DV</sub> plans, whereas it was 28% in EUD<sub>Without DV</sub> plans. In almost all dosimetric parameters evaluated, dose to OARs in EUD<sub>With DV</sub> plans was higher than in EUD<sub>Without DV</sub> plans. Allowing inhomogeneous dose (EUD<sub>Without DV</sub>) inside the target would achieve better normal tissue sparing compared to homogenous dose distribution (EUD<sub>With DV</sub>). Hence, this inhomogeneous dose could be intentionally dumped on the high-risk volume to achieve high local control. Therefore, it was concluded that EUD optimized plans offer added advantage of less OAR dose as well as selectively boosting dose to gross tumor volume.

**Key words:** Biological optimization; equivalent uniform dose; in-homogeneity; intensity modulated radiotherapy

## Introduction

With the advancement of radiotherapy, treatment plan should be optimized to produce desired dose distribution inside the tumor with reduced normal tissue dose. This could be achieved using intensity modulated radiotherapy (IMRT). Nowadays, most of the IMRT treatment planning systems (TPS) incorporate the dose volume (DV)-based physical cost functions for IMRT optimization. The major

drawback associated with the DV-based physical cost function used in IMRT optimization is that it does not represent the nonlinear response of tumor or normal tissues. Further IMRT plan score does not get affected by small cold spot inside the tumor when using DV-based physical cost functions in optimization. On the other hand, plan score for IMRT plan based on equivalent uniform dose (EUD) cost functions would be significantly diminished if there is cold spot inside the tumor.<sup>[1]</sup> Furthermore, a single DV-based physical cost function for tumor does not represent the real nature of dose response of tumor. However, it can be argued that adding multiple DV-based physical cost functions for tumor would represent the dose response nature of the tumor but to a lesser extent. Although EUD-based cost

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DOI:  
10.4103/0971-6203.181631

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**How to cite this article:** Senthilkumar K, Maria Das KJ, Balasubramanian K, Deka AC, Patil BR. Estimation of the effects of normal tissue sparing using equivalent uniform dose-based optimization. J Med Phys 2016;41:123-8.

functions are highly degenerative, it might also pose some clinically unaccepted problems.<sup>[2]</sup> For instance, it may lead to very inhomogeneous target dose distribution. This target dose inhomogeneity was controlled by adding DV-based cost functions by limiting the real potential of EUD dose distributions in clinical practice. In this study, we intend to compare the effects of dose distributions in organ at risk (OAR) estimated from IMRT treatment plans generated with and without inhomogeneous dose distributions using EUD-based cost functions.

## Materials and Methods

### Planning techniques

Twenty patients treated for prostate cancer were retrospectively selected for this study and all these patients underwent radiotherapy computed tomography (CT) scans of 3 mm slice thickness, extending from the second lumbar vertebrae to proximal third of femoral diaphysis. T2 weighted magnetic resonance imaging scans were fused to the CT images for delineation of gross target volume (GTV) which included visible prostate and clinical target volume (CTV). CTV includes prostate plus seminal vesicle. Planning target volume (PTV) was expanded nonuniformly from the CTV. The contours for OARs such as rectum, bladder, and femoral heads were delineated from the CT data.

For each patient, two IMRT plans were generated (i) EUD-based optimization with a DV-based physical cost function to control inhomogeneity ( $EUD_{\text{With DV}}$ ), a combination of cost functions for target which is widely used in day to day clinical practice and (ii) EUD-based optimization without a DV-based physical cost function to allow inhomogeneity ( $EUD_{\text{Without DV}}$ ), a combination of cost functions for target which we are proposing to estimate the effects of dose distributions in OAR. The generated plans were prescribed a dose of 72 Gy in 36 fractions to PTV. The treatment plan acceptance criterion was to deliver 95% of the prescribed dose to 95% volume of PTV. Treatment planning was generated using Monaco TPS version 5.0 (CMS Inc., St. Louis, MO, USA). Serial, parallel, and physical cost functions were used for OARs in all plans. To make both treatment plans identical, same kind of cost functions were used for both the plans for particular OAR. Both treatment plans used same beam energy, number of beams, beam angles, and isocenter. Monaco used 3 mm grid spacing for dose calculation. Monaco TPS is based on constrained optimization method.<sup>[3]</sup> For all Monaco plans, X-ray Volume Monte Carlo (XVMC) algorithm with 3% variance was used in the segment shape optimization phase.<sup>[4]</sup> All plans were corrected for tissue heterogeneities. The bladder and rectum dose reporting were done for entire organ. Iterative adjustment of isoconstraint values followed until the mandated dosimetric criteria was achieved.

### Biological optimization in Monaco TPS

The EUD concept was introduced by Niemierko for tumor and normal tissues as the biological EUD, if given uniformly, would result in same biological effect as the actual nonuniform dose distribution.<sup>[1]</sup> The phenomenological form of EUD,

$$EUD = \left( \frac{1}{N} \sum_i D_i^a \right)^{\frac{1}{a}} \quad (1)$$

The above equation applies to both tumors and normal tissues. In this equation,  $N$  is the number of voxels in the anatomical structure of interest,  $D_i$  is the dose in the  $i^{\text{th}}$  voxel, and  $a$  is the tumor or normal tissue specific parameter that describes the DV effect. This EUD formalism is based on the power law dependence which stimulus the response of complex biological system. The above expression is generalized mean of nonuniform dose distribution.<sup>[5]</sup> For  $a = \infty$ , the EUD is equal to the maximum dose, and for  $a = -\infty$ , the EUD is equal to minimum dose. For  $a = 1$ , the EUD is equal to arithmetic mean, and for  $a = 0$ , it is equal to geometric mean.

As stated by Wu *et al.*,<sup>[2]</sup> EUD-based cost function produces better normal structure sparing over DV-based cost function for the same minimal target dose in IMRT plans. The same has been demonstrated by several authors.<sup>[6-8]</sup> Further, EUD-based cost functions are insensitive to hot spots inside the tumor which leads to highly inhomogeneous target dose, if used alone.<sup>[2]</sup> In clinical practice, a physical cost function (DV-based) is added with EUD cost function to achieve homogenous dose distribution inside the tumor by accepting higher OAR dose.

Monaco TPS is the first commercial IMRT TPS that incorporated biological-based optimization features. It offers three biological-based cost functions namely; Poisson statistics cell kill model for target; serial complication model and parallel complication model for OAR. Monaco also offers several physical DV-based cost functions. The biological cost functions incorporated into Monaco TPS were developed by Alber and Reemtsen.<sup>[9]</sup> Detailing the full mathematics of their work is beyond the scope of this paper. For each cost function, a three-dimensional dose distribution is reduced to a single index called isoeffect.<sup>[10]</sup> On the other hand, clinical goals specified by the user are referred to as isoconstraint.

Isoeffect for target calculated using Poisson cell kill model is as follows:

$$D_{\text{eff}} = -\frac{1}{\alpha'} \ln \left[ \frac{1}{V \rho'} \int_V f(D(\vec{x})) dx^3 \right] \quad (2)$$

Where  $\alpha'$  is the average cell sensitivity,  $\rho'$  is the average clonogen density,  $V$  is the total volume of the organ, and  $f(D(\vec{x}))$  is a biological response function given by,

$$f\left(D(\bar{x})\right)=\rho(\bar{x}) \exp\left[-\alpha(\bar{x})D(\bar{x})\right] \quad (3)$$

Where  $\rho(\bar{x})$  is the local density of clonogenic tumor cells,  $\alpha(\bar{x})$  is the cell sensitivity for particular voxel, and  $D(\bar{x})$  is the absorbed dose in the particular voxel. At present, user can only specify the parameter cell sensitivity ranges from 0.1 to 1.0 Gy<sup>-1</sup>. Equation (3) conceptually represents the EUD formalism which was discussed earlier.

### Physical dose evaluation indices

The cumulative DV histograms (DVH) parameters were reported for the following:

- Rectum - Mean dose,  $D_{30\%}$ , and  $D_{5\%}$
- Bladder - Mean dose and  $D_{5\%}$
- Left femur head -  $D_{5\%}$
- Right femur head -  $D_{5\%}$ .

The treatment time and total monitor units (MU) were also compared.

### Biological dose evaluation indices

Normal tissue complication probability (NTCP) values were calculated using BioSuite software proposed by Nahum and Uzan.<sup>[11]</sup> Lyman-Kutcher-Burman NTCP model was used for calculation of NTCP.<sup>[12,13]</sup> Although BioSuite software offers a list of endpoints with default parameters extracted from literature, it is possible for users to use their own experimental data. We used the default BioSuite endpoints for all our cases to calculate NTCP. Differential DVH for OAR for both the plans was exported from Monaco TPS and was converted to a BioSuite compatible format. BioSuite plan was generated with same planning parameters used in Monaco TPS including total dose, fraction size, and number of fractions. Differential DVHs were imported into the BioSuite software and corresponding endpoints were associated with respective DVHs. NTCP values were calculated for OARs for all patients.

### Statistical analysis

To determine the statistical significance, two-tailed paired *t*-tests were performed with  $P < 0.05$  considered to be statistically significant. All calculations were performed using the online statistical packages software called VassarStats (Vassar College, Poughkeepsie, NY, USA).

## Results

The average volume (mean  $\pm$  standard deviation) of PTV for all patients was  $103.02 \pm 27.03$  cm<sup>3</sup>. The PTV mean dose for EUD<sub>With DV</sub> plans was  $73.67 \pm 1.7$  Gy, whereas for EUD<sub>Without DV</sub> plans was  $80.42 \pm 2.7$  Gy. The PTV volume receiving dose more than 107% of the prescription dose in EUD<sub>With DV</sub> plans was  $2.1 \pm 0.6$  cm<sup>3</sup> while for EUD<sub>Without DV</sub> plans was  $40.6 \pm 3.8$  cm<sup>3</sup> (40.8%). Similarly, PTV volume receiving dose more than 115% of the prescription dose in

EUD<sub>With DV</sub> plans was negligible, whereas for EUD<sub>Without DV</sub> plans was  $27.9 \pm 1.7$  cm<sup>3</sup> (27%). Table 1 shows the target volume (X) receiving the dose (Y). Figure 1 (a) to (e) shows the cumulative DVH curves of a typical prostate cancer patient.

The mean dose for rectum in EUD<sub>With DV</sub> plans was 5.6 Gy higher than EUD<sub>Without DV</sub> plans. The same correlation continues in  $D_{30\%}$  also. For bladder, the mean dose in EUD<sub>With DV</sub> plan was higher than EUD<sub>Without DV</sub> plans. For rectum and bladder,  $D_{5\%}$  dose difference was not statistically significant between both the plans. The  $D_{5\%}$  dose for right femur in EUD<sub>With DV</sub> was 5.01 Gy higher than EUD<sub>Without DV</sub> plans ( $p < 0.002$ ). Similarly, the  $D_{5\%}$  dose for left femur in EUD<sub>With DV</sub> was 4.8 Gy higher than EUD<sub>Without DV</sub> plans ( $p < 0.002$ ). Table 2 summarizes the dosimetric values of all OARs evaluated.

The calculated NTCP for rectum was  $4.4 \pm 0.25\%$  for EUD<sub>With DV</sub>, whereas for EUD<sub>Without DV</sub> it was  $3.3 \pm 0.24\%$  with  $P = 0.0028$ . For bladder, the calculated NTCP was  $1.25 \pm 0.19\%$  for EUD<sub>With DV</sub> plans, whereas for EUD<sub>Without DV</sub> was  $0.84 \pm 0.16\%$  with  $P = 0.0017$ . The calculated NTCP for left femur was  $0.28 \pm 0.11\%$  for EUD<sub>Without DV</sub> plans, whereas for EUD<sub>With DV</sub> was  $0.70 \pm 0.15\%$  with  $P = 0.001$ . For right femur, the calculated NTCP was  $0.27 \pm 0.10\%$  for EUD<sub>Without DV</sub> plans, whereas for EUD<sub>With DV</sub> was  $0.64 \pm 0.15\%$  with  $P = 0.001$ . The calculated NTCP values are shown in Table 3.

The mean treatment delivery time was  $7.2 \pm 2.3$  min for homogenous plans (EUD<sub>With DV</sub>), whereas for inhomogeneous (EUD<sub>Without DV</sub>) plans, it was  $9.12 \pm 1.9$  min. The calculated mean MU was  $456 \pm 39$  for homogenous plans (EUD<sub>With DV</sub>) and  $610 \pm 42$  for inhomogeneous plans (EUD<sub>Without DV</sub>).

## Discussion

Plans generated without DV cost function in the EUD-based optimization resulted in inhomogeneous dose distribution inside the PTV. It was found that the PTV volume receiving dose more than 107% of prescription dose was around 40% and the PTV volume receiving dose more than 115% of the prescription dose was around 28% in EUD<sub>Without DV</sub> plans. This inhomogeneous dose could be deliberately dumped to high-risk volume to achieve high local control. This opens up the possibility of selectively boosting the substantial volume of the tumor using EUD-based cost function for IMRT optimization.

Mean dose for both rectum and bladder was high in EUD<sub>With DV</sub> plans compared to EUD<sub>Without DV</sub> plans. For both femoral heads,  $D_{5\%}$  was high in EUD<sub>With DV</sub> plans compared to EUD<sub>Without DV</sub> plans. It was found that by allowing inhomogeneous dose (EUD<sub>Without DV</sub> plans) inside the target,

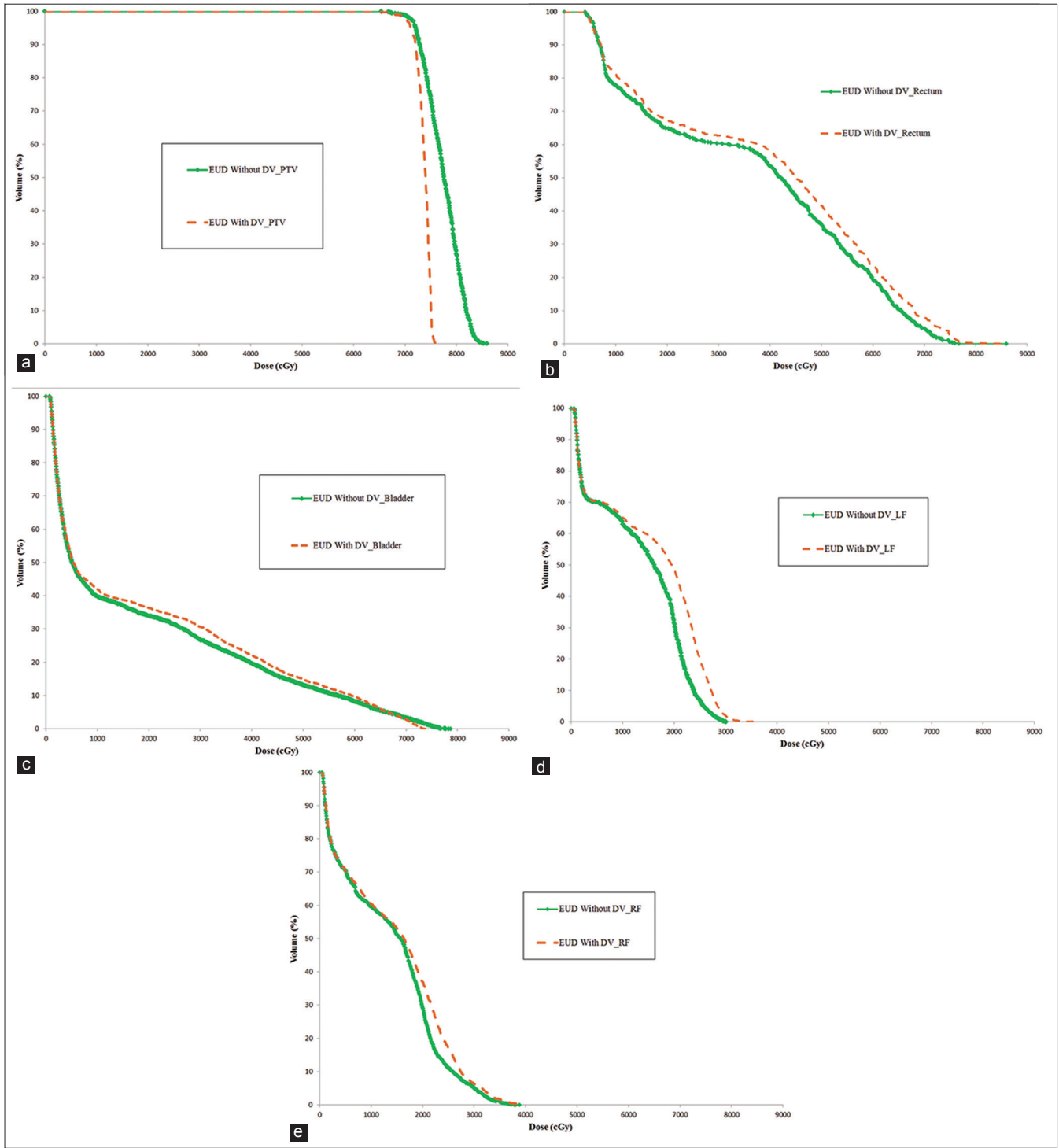


Figure 1: Comparison of the dose volume histograms between EUD<sub>With DV</sub> plan and EUD<sub>Without DV</sub> plan for (a) PTV\_72Gy (b) Rectum (c) Bladder (d) Left femoral head and (e) Right femoral head of a typical prostate cancer patient

Table 1: Target volume (X) (cm<sup>3</sup>) receiving dose (Y) (Gy)

	Mean±SD					
	70.56 Gy (98%)	72 Gy (100%)	75.6 Gy (105%)	77.04 Gy (107%)	79.2 Gy (110%)	82.8 Gy (115%)
EUD <sub>With DV</sub> plans	98.4±2.3	97.3±2.0	32.3±3.2	2.1±0.6	-	-
EUD <sub>Without DV</sub> plans	99.4±1.8	98.2±1.6	68.9±3.2	40.6±3.8	31.4±2.7	27.9±1.7

EUD: Equivalent uniform dose, DV: Dose volume, SD: Standard deviation

**Table 2: Comparison of evaluated dosimetric values for all organs at risk**

Organs at risk	Parameter	EUD <sup>†</sup> With DV plans (Gy)	EUD Without DV plans (Gy)	P
Rectum	Mean dose	46.34±0.20	40.68±0.30	0.001
	D <sub>30%</sub>	56.19±0.44	51.72±0.57	0.002
	D <sub>5%</sub>	70.35±0.16	70.79±0.36	0.452
Bladder	Mean dose	26.32±0.58	23.11±0.95	0.001
	D <sub>5%</sub>	70.23±0.12	70.45±0.23	0.561
Left femoral head	D <sub>5%</sub>	36.43±0.17	31.59±0.11	0.001
	D <sub>5%</sub>	35.51±0.23	30.48±0.12	0.002

<sup>†</sup>EUD: Equivalent uniform dose

**Table 3: Calculated normal tissue complication probability values for all organs at risk**

Organs at risk	Normal tissue complication probability (%)		P
	EUD <sup>†</sup> With DV Plans	EUD Without DV Plans	
Rectum	4.4±0.25	3.3±0.24	0.0011
Bladder	1.25±0.19	0.84±0.16	0.0021
Left femoral head	0.70±0.15	0.28±0.11	0.0015
Right femoral head	0.64±0.15	0.27±0.10	0.0023

<sup>†</sup>EUD: Equivalent uniform dose

it was possible to achieve reduced OAR dose compared to homogenous dose distribution (EUD<sub>With DV</sub> plans). Even calculated NTCP values for all OARs substantiate the reduced OAR dose with inhomogeneous dose inside the target. Therefore, it was noted that EUD-based IMRT optimized plans offer added advantage of less OAR dose as well as selectively boosting dose to gross tumor volume. It was already stated by Wu *et al.*<sup>[2]</sup> that introducing a DV-based physical cost function with EUD-based optimization to get homogenous dose would degrade the dose distributions in OARs. In this study, we estimated the effects of dose distributions in OARs using EUD-based IMRT optimization.

At the same time, for both rectum and bladder, there was no statistically significant difference between EUD<sub>With DV</sub> and EUD<sub>Without DV</sub> plans in D<sub>5%</sub> doses. It is obvious that D<sub>5%</sub> dose was evaluated for full organ, i.e., some part of the rectum and bladder was inside the PTV. Although we tried to prevent the overlapping OAR volume from receiving more than the prescription dose, still for EUD<sub>Without DV</sub> plans, D<sub>5%</sub> dose was slightly high compared to EUD<sub>With DV</sub> because of increased dose inhomogeneity inside the target.

Total treatment time was significantly high in inhomogeneous dose (EUD<sub>Without DV</sub>) plans because of more total energy required to deliver such high dose.

Consequently, treatment time was also high to deliver inhomogeneous dose to the target. One should note that the absolute treatment time may vary depending on how efficient the sequencing of the segments and therefore be TPS dependent.

In clinical practice, there is a concern for accepting inhomogeneous dose inside the tumor. Goitein and Niemierko<sup>[14]</sup> stated that inhomogeneous dose can be accepted if it is not due to treatment delivery methods. However, further study is needed on how much tumor volume can be selectively boosted by EUD-based cost functions optimized plans. The hypothesis of this study should also be tested where we practice simultaneous integrated boosts such as in the treatment of head and neck cancer.

## Conclusion

This study demonstrated that by allowing inhomogeneous dose (EUD<sub>Without DV</sub>) inside the target one can achieve better normal tissue sparing as compared to homogenous dose distribution (EUD<sub>With DV</sub>). Hence, this inhomogeneous dose could be intentionally dumped on the high-risk volume to achieve high local control. Therefore, it is concluded that EUD optimized plans offer added advantage of less OAR dose as well as selectively boosting dose to gross tumor volume.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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