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SIMULATION AND OPTIMIZATION OF BRACHYTHERAPY HIGH DOSE RATE PLANS

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Abstract. *In this paper we are going to describe a brachytherapy planning system and the related optimization algorithms for optimization planning. Brachytherapy is an advanced cancer treatment. Radioactive sources are placed in or near the tumor itself, giving a high radiation dose to the tumor while reducing the radiation exposure in the surrounding healthy tissues.*
In addition, our scope is to present the scientific results of CEIROS EUROSTARS project and describe the mathematical and partly the physical background for the use of both DVH and gEUD concept for High Dose Rate (HDR) optimization. The concept of equivalent uniform dose (EUD) for tumors was introduced as the biologically equivalent dose that, if given uniformly, would lead to the same cell kill in the tumor volume as the actual non-uniform dose distribution. Later, it is extended to apply to normal tissues as well. Presently, most optimization systems use dose and/or dose–volume-based objective functions. Neither adequately represents the nonlinear response of tumors or normal structures to dose, especially for arbitrary inhomogeneous dose distributions. For instance, if a single voxel or a small number of voxels in a tumor receive a very low dose, it would not have a significant effect on the plan score. However, the tumor control probability would be greatly diminished as a result of the cold spot. Stated in a different way, for dose- or dose–volume-based objective functions, the penalty imposed for the failure to achieve the prescribed dose is proportional to the dose difference (or the square of the difference), rather than to the loss of tumor control, as would be more appropriate.

1 INTRODUCTION

Dose–volume constraints are simplified surrogates of the underlying biologic effects determining the outcome of treatment. Specifying a single dose–volume constraint is equivalent to stating that, if the volume above the tolerance dose is smaller than the critical volume, no complications will occur. This is a reduced subset and a special case of the critical volume dose–response model, in which a functional subunit is destroyed at exactly the tolerance dose and the response occurs when exactly the critical fractional number of the functional subunits is destroyed. One could argue that this inadequacy can be overcome by specifying the constraints on the entire dose–volume histogram (DVH) for the anatomic structure. However, there are multiple DVHs (in fact, an infinite number of them) that could lead to an equivalent dose response for a particular organ, but optimization based on each of these DVHs would, in general, lead to different dose responses in other organs and the tumor. Only one of these DVHs will be optimum so far as other organs and the tumor are concerned. Thus, constraining the search to a single DVH for an anatomic structure may miss the overall optimum solution.

That multiple DVHs correspond to the same dose response is an important advantage for dose–response-based objective functions. Mathematically speaking, one can state that dose–response functions are highly "degenerate" functions of dose–volume combinations and, therefore, of dose distributions. A dose–response index (e.g., tumor control probability [TCP], normal tissue complication probability [NTCP], EUD, or P_, the

probability of uncomplicated control) may be considered as a way of summarizing multiple DVHs into a single value similar to the way a DVH summarizes a three-dimensional dose distribution into a single curve. Dose–volume-based objective functions are also degenerate functions of dose distributions (i.e., multiplicity of dose distributions correspond to the same dose– volume constraint), but to a considerably lesser extent. The high degeneracy of dose–response functions makes a large space of biologically equivalent dose distributions for each organ equally acceptable, thus giving greater flexibility to the optimization process to reconcile competing requirements to find a better solution.

2 SIMULATION AND OPTIMIZATION APPLICATION

2.1 Oncentra Prostate™

Brachytherapy is a type of radiotherapy for cancer treatment. Brachytherapy works by precisely targeting the cancerous tumor from inside the body. The source of radiation is placed directly inside or next to the tumor. This tailored approach reduces the risk of any unnecessary damage to healthy tissue and organs that are close to the tumor, therefore reducing potential side effects.

In contrast to external beam radiotherapy (EBRT) that delivers radiation from outside the body. The radiation has to travel through healthy tissue to reach the tumor. As the technique is less targeted and precise than brachytherapy, more healthy tissues and organs can be exposed to harmful levels of radiation

Brachytherapy is commonly used as an effective treatment for cervical, prostate, breast and skin cancer and can also be used to treat tumors in many other sites of the body. Brachytherapy can be used to treat cancer on its own or in combination with other treatment methods, such as surgery, external beam radiotherapy or chemotherapy. The exact treatment(s) will depend on a number of factors, such as the location, shape and size of the tumor, and individual patient preferences.

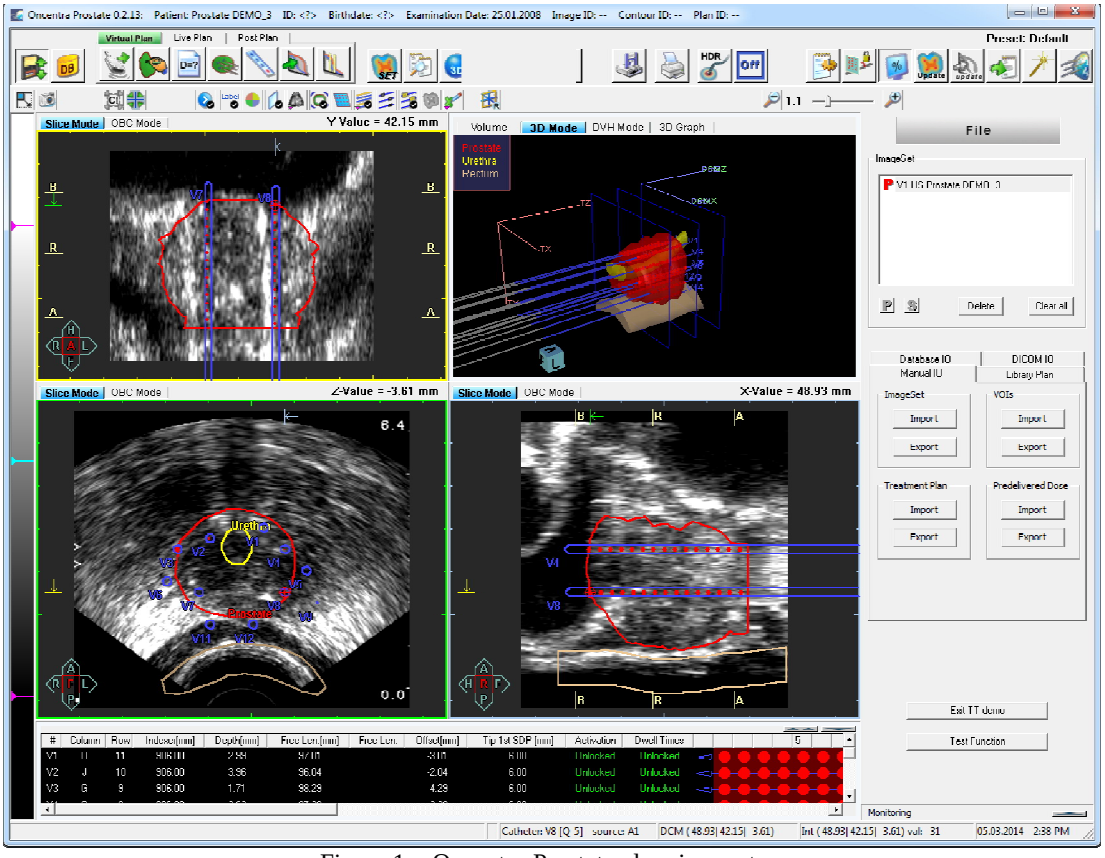

Figure 1. : Oncentra Prostate planning system

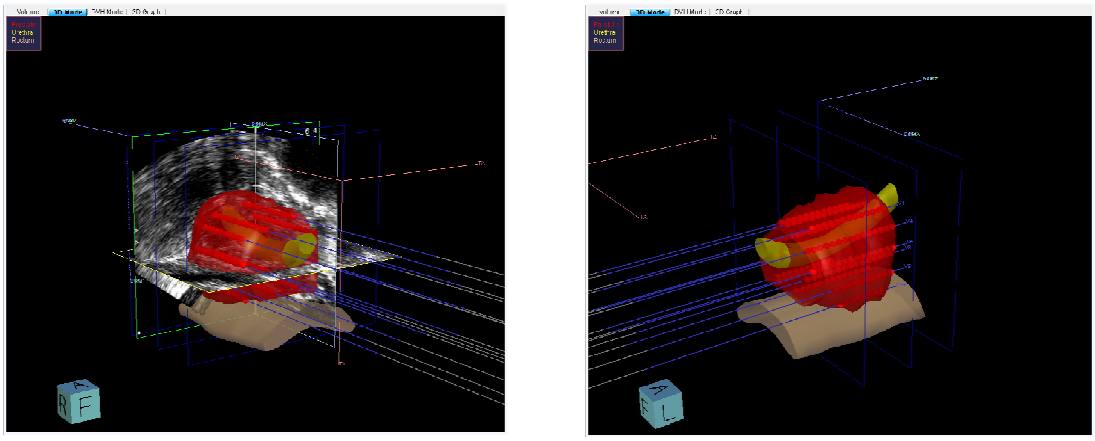

Figure 2. : Representation of radioactive sources inside the target/tumor

3 MATERIAL AND METHODS

3.1 Optimization problem in brachytherapy

The inverse problem in Brachytherapy is looking for a set of dwell times {t}, given the organ structure and the number of catheters, the placement settings in 3D space and a given clinical protocol (dose optimization settings).

A clinical protocol might be based on the GEC-ESTRO-EAU recommendation as illustrated below:

Organ	**Parameter**	**Value**
	Reference dose	11.5 Gy (=100%)
Prostate	D90	≥ 100 %
	V100	≥ 90%
	V150	≤ 35%
Urethra	D10	≤ 115%
	D0.1	≤ 120%
Rectum	D10	≤ 75%
	D0.1	≤ 80%
Bladder	D10	≤ 75%
	D0.1	≤ 80%

Table 1. : Clinical protocol

Numerical methods are used for the calculation of the dose inside the structures, since the analytical calculation is not possible. According to these methods, a large number of sampling points (ca. 10.000) is generated inside VOIs, the dose on these points is calculated and the information about the dose is taken using basic statistics.

The preprocessing step of the plan optimization includes generation of the sampling points and calculation of all the Look Up Tables that are necessary for fast calculation of the dose contribution from each Source Dwell Position to each Sampling Point.

Finally, based on the above information, the objective functions are evaluated iteratively for sets of dwell times proposed by LBFGS, until the algorithm converges.

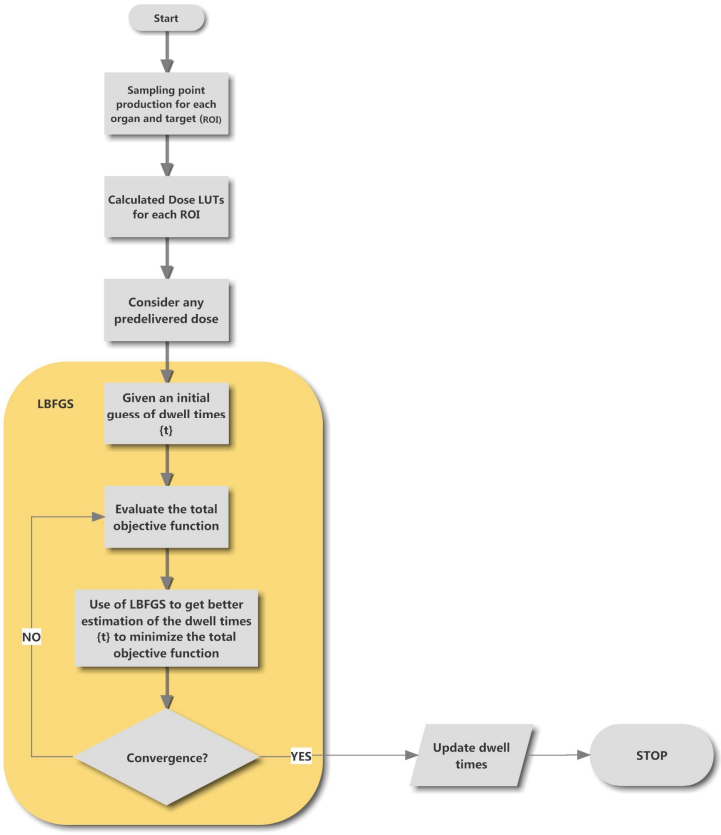

Figure 3. : Optimization process and workflow

3.2 gEUD-based objective function

The gEUD-based objective function suggested by Wu et al [1] for IMRT optimization is used as a biologically-based objective function for HDR brachytherapy optimization. In this concept, there are two types of objectives: the first type is the f_i^T objective corresponding to targets, aiming to cover the tumors with the desired dose and the second one f_i^{OAR} corresponds to OARs aiming to protect it from hot spots and overdose.

As it shown in the bibliography and confirmed in our preliminary runs, it is a good practice to assign two objectives (i.e. f_i^T and f_i^{OAR}) at each target. This way, the dose is restricted within a given range in the target volumes.

Furthermore, in addition to the contoured OARs, an extra objective called normal tissue (NT), is defined. This corresponds to an area surrounding all contoured volumes and considered as health tissue that should be protected. This is a practice successfully used in dose based optimization.

The calculation of the objective functions is based on the gEUD values. In turn, the gEUD values are calculated making use of the dose values in each voxel. In order to calculate these voxel doses, we generate sampling points inside the volume of each VOI (only inside and not on the surface as in the case of dose based optimization), using an advanced method (e.g. Halton sequence) which ensures the uniform distribution and the coverage of all parts of the volume. Given this, and a relatively high number of points, we can assume that the dose at each sampling point corresponds to the dose in a voxel. The dose calculations are based on the TG-43 protocol and the use of predefined look-up tables.

The optimization (minimization) of the objective function is based on the standard L-BFGS algorithm [2] (alternative implementation in BFGS gives equally good results) with a run time of ~0.5min for a standard case (5 objectives) on a Intel i5 processor with 4GB RAM, Win 7. Although the proposed objective is not convex, thus multiple minima are theoretically expected [3].

Aggregate objective function

The aim of this method is to maximize the product of all the objectives or, alternatively, to minimize:

$$F = -\ln\left(\prod_{i=1}^{N_{obj}^{T}} f_i^{T} \cdot \prod_{i=1}^{N_{obj}^{OAR}} f_i^{OAR}\right) = -\left(\sum_{i=1}^{N_{obj}^{T}} \ln f_i^{T} + \sum_{i=1}^{N_{obj}^{OAR}} \ln f_i^{OAR}\right) \quad (1)$$

Where the objectives for targets and OARs are

Target and OAR objective functions

$$f_i^{T}(\mathbf{t}) = \frac{1}{1+\left(\frac{gEUD_{0,i}^{T}}{gEUD_i^{T}}\right)^{n_i^{T}}} \quad (2)$$

$$f_i^{OAR}(\mathbf{t}) = \frac{1}{1+\left(\frac{gEUD_i^{OAR}}{gEUD_{0,i}^{OAR}}\right)^{n_i^{T}}} \quad (3)$$

The gEUD values are calculated as follows:

$$gEUD_i^{T} = \left(\frac{1}{N_i^{T}} \sum_{k=1}^{N_i^{T}} \left(d_k^{T,i}\right)^{a_i^{T}}\right)^{\frac{1}{a_i^{T}}} \quad (4)$$

$$gEUD_i^{OAR} = \left(\frac{1}{N_i^{OAR}} \sum_{k=1}^{N_i^{OAR}} \left(d_k^{OAR,i}\right)^{a_i^{OAR}}\right)^{\frac{1}{a_i^{OAR}}} \quad (5)$$

The dose at a sampling point *k* is calculated using the TG-43 dose kernels:

$$d_k^{T,i}(\mathbf{t}) = \sum_{m=1}^{N^{ASDP}} t_m \tilde{d}_{jm}^{T,i}$$

$$d_k^{OAR,i}(\mathbf{t}) = \sum_{m=1}^{N^{ASDP}} t_m \tilde{d}_{jm}^{OAR,i}, \quad \mathbf{t} = \left\{t_1, t_2, ..., t_{N^{ASDP}}\right\}$$

Where:

N_{obj}^{T}: Number of Target objectives

N_{obj}^{OAR}: Number of OAR objectives

N_i^{T}: Number of dose sampling points for the *i*-th Target.

N_i^{OAR}: Number of dose sampling points for the *i*-th OAR.

$d_k^{T,i}, d_k^{OAR,i}$ The dose at the *k*-th sampling point of the *i*-th Target or OAR.

$\tilde{d}_{jm}^{T,i}, \tilde{d}_{jm}^{OAR,i}$ The [j,m] entry of the dose kernel matrix (TG-43 Look up tables) for the *i*-th target or OAR

N^{ASDP} Number of ASDPs (active source dwell positions)

t Dwell times vector

Indices:

T: Target

OAR: Organ at risk

i: The index of the Target or the OAR (i.e. denoting the *i*-th target or the *i*-th OAR). Thus, for Targets, the index $i = 1,..., N_{obj}^{T}$ while for OARs $i = 1,..., N_{obj}^{OAR}$.

j or *k*: The index of the sampling point. For Targets, the index $j = 1,..., N_i^T$ while for OARs $j = 1,..., N_i^{OAR}$

Parameters:

- a_i^T, a_i^{OAR}: It is a structure-specific parameter which is usually negative for tumors and positive for organs-at-risk a is small and close to 1 for organs displaying parallel behaviour and large for organs of serial structure.

- n_i^T, n_i^{OAR}: Parameter *n* is akin to the weight or penalty that indicates the importance of the structure-specific end point. This corresponds to the importance factors used for the dose-based optimization (e.g. DVHO).

- N_i^T, N_i^{OAR}: These are the total number of voxels (or equivalently sampling points) belonging to the *i*-th target and *i*-th OAR.

- $d_k^{T,i}$, $d_k^{OAR,i}$: It is the dose to a *k*-th voxel in the *i*-th target or OAR objective. For the reasons explained above, we can assume that the dose at a voxel corresponds to the dose at a sampling point

- $gEUD_{0,i}^{T}$: It is the desired dose parameter for the *i*-th target volume.
- $gEUD_{0,i}^{OAR}$: It is the maximum tolerable uniform dose for *i*-th OAR.

2.2 Optimization algorithm

Limited-memory BFGS (L-BFGS or LM-BFGS) is an optimization algorithm [3][4] in the family of quasi-Newton methods that approximates the Broyden–Fletcher–Goldfarb–Shanno (BFGS) algorithm using a limited amount of computer memory. It is a popular algorithm for parameter estimation in machine learning [5].

Like the original BFGS, L-BFGS uses an approximation to the inverse Hessian matrix to steer its search through variable space, but where BFGS stores a dense n×n approximation to the inverse Hessian (n being the number of variables in the problem), L-BFGS stores only a few vectors that represent the approximation implicitly. Due to its resulting linear memory requirement, the L-BFGS method is particularly well suited for optimization problems with a large number of variables [6]. Instead of the inverse Hessian H_k, L-BFGS maintains a history of the past m updates of the position x and gradient $\nabla f(x)$, where generally the history size m can be small (often m<10). These updates are used to implicitly do operations requiring the H_k-vector product.

2.3 gEUD based optimization run

For running the our gEUD optimization algorithm, we used the following structures: (a) prostate gland as the PTV (target) and (b) OAR (prostate-OAR) and the (c) urethra, (d) bladder, and (e) rectum as the OARs. Having generated the clinically accepted HDR brachytherapy plans for the twelve prostate cancer patient cases using the HIPO in Ocentra Prostate application [8], the gEUD values for all the structures were calculated

using the DVH data results from the optimization. These gEUD values for each structure were used as the $gEUD_0$ values for the corresponding gEUD-based optimization, for this part of the study. Using this technique the ability of the biologically-based optimization model to reproduce the treatment plans generated by the HIPO optimization method was tested, as a benchmarking method. For the prostate-OAR structure, the limiting $gEUD_0$ value was set to 150% of the calculated target gEUD value, allowing for 50% overdose. The values for the rest of the optimization parameters are shown in Table 2, below. The optimized plans generated by the two different methods for each patient were compared based on the resulting DVHs and final gEUD values for each structure.

3 RESULTS

The ability of the gEUD-based optimization to reproduce the clinically accepted plans generated by the HIPO algorithm was tested at this point, by using the HIPO calculated final gEUD values as the $gEUD_0$ goal for the gEUD-based optimization. Figure 4 shows the resulting DVH comparison graph from a representative case. For a similar target coverage, as shown by the overlapping DVH plots up to the 100% of the dose, small decrease in the dose range between 100% and 150% of the reference dose is noticed for the target accompanied by a more obvious decrease in the maximum doses received by the OARs, especially the urethra and the rectum. Comparison of the DVH evaluation parameters (Table 2) for the total of cases under study showed a statistically significant decrease in the mean PTV dose for somewhat smaller coverage of the PTV (<1% average difference for the V 100 parameter). This result is accompanied by a non-significant difference in the D_{100} value (p-value = 0.26), indicative of the target coverage, while the V_{150} and V_{200} parameters were decreased for the gEUD-optimized plans. The comparison for the OARs showed a statistically significant decrease in the D_{10} evaluator by 3.3% for the urethra, 3.1% for the bladder, and 1.9% for the rectum.

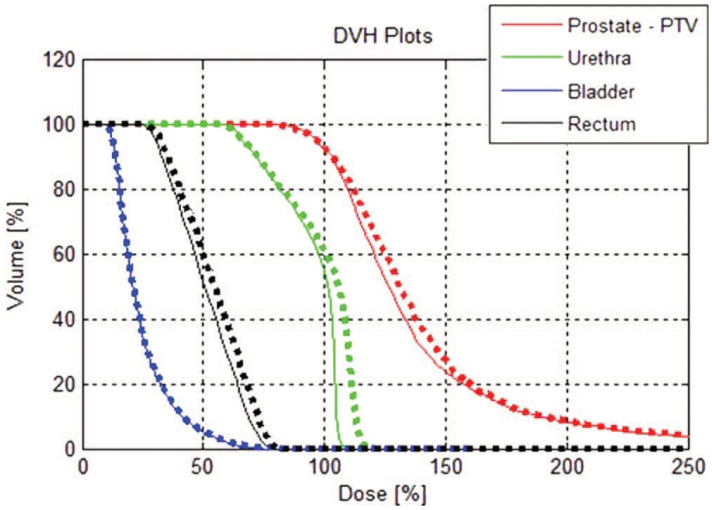

Figure 4. : DVH comparison of HIPO (dashed lines) and gEUD (solid lines) based optimization.

Organ	Opt. type	Control point	Mean	Std. Dev.	p-value
PTV	HIPO	D_{90}	103.8	1.34	< 0.01
	gEUD	D_{90}	102.8	1.44	
	HIPO	D_{100}	75.5	1.78	0.26
	gEUD	D_{100}	76.6	1.67	
	HIPO	V_{100}	93.2	1.14	< 0.01
	gEUD	V_{100}	92.4	1.34	
	HIPO	V_{150}	29.1	1.34	< 0.01
	gEUD	V_{150}	26.9	1.58	
	HIPO	V_{200}	8.2	1.0	< 0.01
	gEUD	V_{200}	7.4	0.83	
	HIPO	Total gEUD (Gy)	12.9	0.44	0.10
	gEUD	Total gEUD (Gy)	12.8	0.54	
Urethra	HIPO	D_{10}	112.4	1.48	< 0.01

	gEUD	D_{10}	109.1	1.89	
	HIPO	$D_{0.1cc}$	114.4	1.44	< 0.01
	gEUD	$D_{0.1cc}$	110.8	2.04	
	HIPO	Total gEUD (Gy)	11.8	0.54	< 0.01
	gEUD	Total gEUD (Gy)	11.6	0.63	
Bladder	HIPO	D_{10}	45.5	2.04	< 0.01
	gEUD	D_{10}	42.4	2	
	HIPO	$D_{0.1cc}$	72.3	1.41	< 0.01
	gEUD	$D_{0.1cc}$	66.7	1.92	
	HIPO	Total gEUD (Gy)	4.7	0.44	< 0.01
	gEUD	Total gEUD (Gy)	4.3	0.54	
Rectum	HIPO	D_{10}	68.6	2.12	< 0.01
	gEUD	D_{10}	66.7	2.28	
	HIPO	$D_{0.1cc}$	76.8	1.30	0.09
	gEUD	$D_{0.1cc}$	75.6	1.70	
	HIPO	Total gEUD (Gy)	6.5	0.70	< 0.01
	gEUD	Total gEUD (Gy)	6.3	0.70	

Table 2: HIPO and gEUD based optimization. Mean values and variance at specific control points

4 CONCLUSIONS

The gEUD-based optimization method for HDR brachytherapy treatment planning for prostate cancer was implemented in the research version of Oncentra Prostate. The comparison between dose based and biological-based optimized HDR plans showed significantly improved sparing of the organs at risk for the biological-based optimized plans. However, further investigation needs to be performed towards the dosimetric indices and clinical studies need to be performed.

5 AKNOWNLODGEMENT

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