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On the use of radiobiological-based optimization functions in radiotherapy treatment planning for prostate and head and neck cases on Monaco and Eclipse TPS

Sobre el uso de funciones de costo basadas en radiobiología en la planeación de tratamientos de radioterapia para casos de próstata y cabeza y cuello en los TPS Monaco y Eclipse

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ABSTRACT: Introduction. Radiobiological-based optimization functions for radiotherapy treatment planning involve dose-volume effects that could allow greater versatility when shaping dose distributions and DVHs than traditional dose-volume (DV) criteria. Two of the most commercially available TPS (Monaco and Eclipse) already offer biological-based optimization functions, but they are not routinely used by most planners in clinical practice. Insight into the benefits of using EUD, TCP/NTCP-based cost functions in Monaco and Eclipse TPS was gained by comparing biological-based optimizations and physical-based optimizations for prostate and head and neck cases. **Methods.** Three prostate and three H&N cases were retrospectively optimized in Monaco and Eclipse TPS, using radiobiological-based cost functions vs DV-based cost functions. Plan comparison involved ICRU Report 83 parameters $D_{95\%}$, $D_{50\%}$, $D_{2\%}$ and TCP for the PTV, and NTCP and RTOG tolerance doses for OARs. **Results.** Although there were differences between Monaco and Eclipse plans due to their dissimilar optimization and dose calculation algorithms as well as optimization functions, both TPS showed that radiobiological-based criteria allow versatile tailoring of the DVH with variation of only one parameter and at most two cost functions, in contrast to the use of three to four DV-based criteria to reach a similar result. **Conclusion**. Despite the use of a small sample, optimization of three prostate and three head and neck cases allowed the exploration of optimization possibilities offered by two of the most commercially available TPS on two anatomically dissimilar regions. Radiobiological-based optimization efficiently drives dose distributions and DVH shaping for OARs without sacrifice of PTV coverage. Use of EUD-based cost functions should be encouraged in addition to DV cost functions to obtain the best possible plan in daily clinical practice.

KEYWORDS: Biological Optimization, EUD, TCP, NTCP.

INTRODUCTION

The main objective in radiotherapy (RT) treatment planning is to reach an optimum balance between local disease control and sparing of the surrounding normal tissue (Lyman & Wolbrast, 1989). In modern techniques such as IMRT and VMAT, Treatment Planning Systems (TPS) perform an inverse optimization process through cost-functions with underlying physical or radiobiological concepts. According to the AAPM Task Group Report 166 (Li *et al.*, 2012), Dose-Volume (DV) restrictions (based upon clinical studies that show a correlation between tumor control or normal tissue complications and a particular DV metric) are surrogate measures of biological outcome and do not appropriately reflect the non-linear response of tissue with radiation dose, especially when dealing with non-homogeneous dose distributions, and should therefore be replaced with biologi-

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cal indices that better relate to the clinical objectives of RT.

Contrastingly, concepts like the Equivalent Uniform Dose (EUD) and models of Tumor Control Probability (TCP) and Normal Tissue Complication Probability (NTCP) better describe the response of tissue with radiation and, in the case of the EUD, allow the representation of inhomogeneous dose distributions in one parameter (Niemierko, 1997). For tumors, it is desirable to maximize the TCP, which can be described by the Poisson Cell-Kill model (Joiner & van der Kogel, 2009):

$$TCP(D) = \exp\left(-N_0 e^{\alpha D}\right) \quad (1)$$

where N_0 is the initial clonogen number, α is the radio-sensitivity parameter and D is the absorbed dose. For normal tissues, NTCP should be minimized (Cozzie *et al.*, 2000, B. Serreta & G. Llorente, 2016):

$$NTCP(D) = \left[1 + \left(\frac{D_{50}}{D}\right)^{4\gamma}\right]^{-1} \quad (2)$$

where D_{50} is the tolerance dose that causes 50% complication probability within a given time period, γ quantifies the slope of the NTCP curve in a meaningful point (usually D_{50}) and D is the homogeneous absorbed dose. NTCP can also be described by the Lyman model (Lyman & Wolbrast):

$$NTCP(D,V) = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^{t} \exp\left(-\frac{1}{2} \cdot x^2\right) dx \quad (3)$$

where

$$t(D,V) = \frac{D - D_{50}(v)}{m \cdot D_{50}(v)} \quad (4)$$

involves the dose-volume dependence. *m* is a parameter inversely related with the slope of the NTCP curve, while D_{50} is related with volume (Lyman & Wolbrast):

$$D_{50}(v) = \frac{D_{50}(1)}{v^n} \quad (5)$$

where $D_{50}(v)$ is the dose that causes 50% complication probability when a fraction *v* of volume is irradiated, *n* is between zero and one and, as $n \rightarrow 1$, volume effect becomes more important. These parameters are determined by fitting the Lyman model to clinical data, as done by Burman *et al.* (1991). Since TCP and NTCP models assume a uniform dose distribution, DVH reduction methods, such as the Lyman-Kutcher-Burman (LKB) (Kutcher *et al.*, 1991) method, should be applied for their calculation (Hamilton *et al.*, 1992).

Conversely, the Equivalent Uniform Dose (EUD), introduced by Niemierko (Niemierko, 1997), is the dose that, if administered uniformly, would result in the same cell death as the corresponding non-uniform dose distribution. For targets, if the cell Surviving Fraction (SF) follows the linear part of the Linear-Quadratic (LQ) model:

$$EUD = -\frac{1}{\alpha} In\left[\frac{1}{N}\sum_{i}^{N} SF(D_i)\right] \quad (6)$$

where α is the sensitivity parameter, N is the number of sub-volumes in the structure and D_i is the corresponding homogeneous dose in each. To also consider organs at risk (OAR), the generalized equivalent uniform dose (gEUD) was defined by Niemierko as (Niemierko, 1999):

$$gEUD = \left(\frac{1}{N}\sum_{i} D_i^a\right)^{1/a} \quad (7)$$

where N is the number of voxels in the structure, D_i is the dose in the i^{th} voxel, while *a* describes the volume-effect and is related to parameter *n* in the Lyman NTCP model as $a = 1/n$. For $a \rightarrow -\infty$, gEUD approaches the minimum dose and therefore describes tumors, whereas for $a \rightarrow \infty$, gEUD approaches the maximum dose and thus describes serial normal tissues (Li *et al.*). For $a = 1$, gEUD represents the mean dose for parallel organs at risk (Wu *et al.*, 2002, Fogliata *et al.*, 2018). Since current TPS such as Monaco (Elekta Solutions AB, Stockholm, Sweden) and Eclipse (Varian Medical Systems, Palo Alto, CA) include gEUD, TCP and NTCP-based constraints with underlying dose-volume effects, shaping of the dose distribution (Fogliata *et al.*) and the resulting DVH can be achieved by proper use of the radiobiological-based cost functions parameters. The current work aimed to gain deeper insight into the benefits of using radiobiological-based cost functions as opposed to physical cost functions in Monaco 5.11 and Eclipse 15.1, optimizing Prostate and Head and

Neck (H&N) cases and comparing biological-based optimization (from here, BBO) with physical-based optimization (PBO) results.

METHODS

A. Clinical cases and evaluation parameters

Three prostate and three H&N VMAT cases were retrospectively optimized in Monaco 5.1 (Monte Carlo dose-calculation algorithm) and Eclipse 15.1 (Acuros dose-calculation algorithm). Although analysis was based upon dose distributions and ICRU 83 parameters, dosimetrically-equivalent Linacs, with geometrically similar MLCs and same arc geometry were employed to focus on the effect of each TPS's cost function effect. Contouring was performed by the same physician, with the following dose prescriptions: prostate and seminal vesicles to receive 56 Gy and a 20 Gy sequential boost to the prostate (total dose 76 Gy). H&N: two cases with lymph-node drainage up to 54 Gy and 59.4 Gy, and macroscopic disease up to 70 Gy (simultaneously integrated boosts). The third case involved 59.4 Gy and 70 Gy PTV dose levels.

Plan normalization was such that 95% of target volume received the prescription dose. The following parameters of the ICRU Report 83 (ICRU Report 83, 2010) were considered the most relevant for PTV evaluation: near-minimum dose ($D_{95\%}$), near-maximum dose ($D_{2\%}$), dose received by 50% of the PTV and TCP (for lower-dose PTVs, only $D_{95\%}$ and TCP were evaluated). NTCP and compliance with restrictions given by RTOG protocols (RTOG Foundation) were considered for rectum and bladder in prostate cases, and for spinal cord and parotid glands in H&N cases. Calculation of TCP and NTCP was performed in BioSuite (Uzan & Nahum, 2012), employing the LKB histogram reduction method based upon the Lyman NTCP and the Poisson TCP models (equations 1 and 3). The corresponding parameters for NTCP and TCP calculations (equations 1, 4 and 5) are shown in Table I.

B. Biological-based and physical-based optimizations (BBO and PBO)

B.1. Monaco Optimization

Monaco implements three biological cost functions: *Poisson statistics cell kill model* for the PTV, *Serial complication model* and *Parallel complication model* for OARs. For each function, a 3D dose distribution in a structure is reduced to one index, called *isoeffect*, that reflects the structure's biological response to radiation (Li *et al.*), (Elekta, Monaco Use Guide, 2016). For the PTV, *isoeffect* is calculated as (Li *et al.*):

$$D_{eff} = -\frac{1}{\alpha'} In\left[\frac{1}{\rho' V}\int \rho(\vec{x})\exp\left[-\alpha(\vec{x})D(\vec{x})\right]dx^3\right] \quad (8)$$

where α´ is the average cell sensitivity, ρ' is the clonogen average density, V is the organ's total volume, is the local clonogen density, is the cellular sensitivity in a given voxel and is the absorbed dose in such voxel. For the present time, = ρ' and = α', ρ' has been preset in 10^6 clonogens per voxel, while α' takes values from 0.1 to 1 Gy^{-1} (Li *et al.*). The *Poisson cell kill model* is equivalent to the EUD definition given by equation 6.

On the other hand, *isoeffect* for serial organs is described by an effective dose (Li *et al.*):

$$Deff = \left[\frac{1}{V}\int\left[D(\vec{x})\right]^k dx^3\right]^{1/k} \quad (9)$$

where *k* is the volume effect parameter, varying from 0 to 20, and *V* is the total voxel number. The *Serial complication model* cost function is equivalent to the gEUD definition given by equation 7. Although this function could describe parallel-like OARs when *k* = 1, Monaco has an additional cost function for this purpose, with *isoeffect* calculated in terms of mean organ damage (Li *et al.*):

$$veff = 100\% \times \frac{1}{V}\int\left[1+\left(\frac{d_0}{D(\vec{x})}\right)^k\right]^{-1} dx^3 \quad (10)$$

where *V* is the total voxel number and d_0 is the dose that results in a 50% complication rate. *k* varies from 0 to 4, determining the slope of the sigmoid curve. This *Parallel complication model* cost function is equivalent to the sigmoid NTCP model given by equation 2. The effect of *k* parameter on the DVH for the *Serial* and *Parallel* functions is shown in Figure 1.

B.1.a Physical cost functions in Monaco

Dose-volume constraints include *Overdose DVH* and *Underdose DVH* to act on a specific point

Table I. Parameters required for BioSiute TCP and NTCP calculations. α/β values were taken from [4] and *n*, *m* and TD_{50} were taken from [7].

Parameter	Tumor		OAR			
	Prostate	H&N	Rectum	Bladder	Spinal Cord	Parotid gland
α (Gy^{-1})	0.50	0.50	–	–	–	–
α/β (Gy)	1.20	10.5	3.00	5.00	3.30	3.00
n	–	–	0.12	0.50	0.05	0.70
m	–	–	0.15	0.11	0.18	0.18
TD_{50} (Gy)	–	–	80.0	80.0	66.5	46.0
Endpoint	–	–	Proctitis	Contracture	Myelitis	Xerostomy

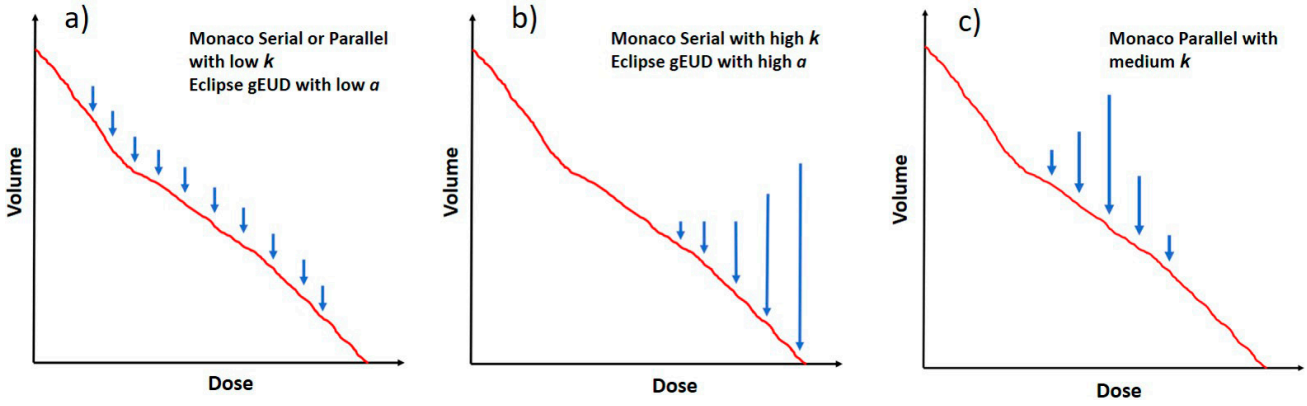

Figure 1. Influence of *k* and *a* parameters on the DVH for Serial and Parallel functions (Monaco) and gEUD function (Eclipse). a) Low *k* values in Monaco's Serial and Parallel functions and low *a* values for Eclipse Max gEUD function act along the entire DVH curve. b) DVH behavior for high *k* values in Monaco's Serial and high *a* in Eclipse's Max gEUD. Cost functions act upon higher doses. c) For intermediate to high *k* values in Monaco's Parallel function, priority is given to the specified dose (intermediate or high) with lesser influence on the surrounding doses.

on the DVH in order to penalize high or low dose points, respectively. Functions like *Quadratic Overdose (QoD)* and *Quadratic Underdose (QuD)* act upon the structure's voxels and impose a quadratic penalty for high and low doses, respectively. The *Target Penalty* function specifies the fraction of target volume that is to receive the prescription dose.

B.1.b Optimization cost functions and parameters

Biological Based Optimization (BBO)

The Target EUD function was used for PTV coverage with α values determined after several trials, assigning lower values for higher-prescription PTVs in integrated boosts (H&N cases), which allows to reduce high-dose regions within the PTV. An intermediate α value was assigned to the other PTVs and for prostate cases to assure appropriate coverage reducing hot spots. One QoD function was used to control hot spots further, since the Target EUD function has not explicit control over the maximum dose. One Underdose DVH function was used to improve coverage.

For OARs, Serial and Parallel cost functions were adjusted in order to comply with the RTOG dose restrictions and set to act upon the structure at 0.5 cm distance from the PTV *(shrink margin* = 0.3 cm). Serial cost functions used a lower k value, in order to act along the entire DVH, focusing on intermediate doses. Parallel cost functions, on the other hand, used higher k values and focused on higher doses in order to reduce high-dose regions on OARs. For parotid glands, an additional Quadratic Overdose function was used, since it has better control over the maximum and mean dose by acting over each voxel over the specified dose limit.

Physical Based Optimization (PBO)

PBO was performed using the Target Penalty function in place of Target EUD, and three to four Overdose DVH functions at convenient DVH values in place of Serial and Parallel. To ensure appropriate dose gradients, QoD functions at increasing distances from the PTV were employed in both biological and physical optimizations. Table II shows functions and parameter range used for both BBO and PBO.

B.2. Eclipse optimization

Starting from Eclipse 13.5 version, three biological cost functions based upon the gEUD concept (equation 7) were included in Photon Optimizer (PO) Varian Medical Systems, 2011):

- *Min EUD*: For targets, the objective is met when the EUD value is at least the specified value. For *a* < 1 up to –40, lower doses are given higher weight so that cold spots influence the EUD to a large extent. *a* = −1 represents the mean dose, so cold and hot spots are given the same weight.
- *Target EUD*: For targets, the objective is met when the EUD value is exactly the specified value. For *a* < 1 up to –40, lower doses are given higher weight and *a* = −1 represents the mean dose.
- *Max EUD*: For OARs and targets, the objective is met when the EUD value is at most the specified value. For *a* > 1 up to 40, high doses are given greater weight, so hot spots influence the EUD to a bigger extent. *a* = 1 represents the mean dose. Figure 1 shows the effect of *a* on the DVH curve for OARs.

B.2.a Physical cost functions in Eclipse

For targets, *Min dose* indicates the minimum dose for a given fraction volume of the structure. For OARs and targets, *Max dose* indicates the maximum dose received by a specified fraction of the structure's volume.

B.2.b Optimization cost functions and parameters.

BBO

For prostate targets, one Target EUD with the highest *a* value (–40) was used to ensure coverage. For H&N targets, one Min EUD with an intermediate *a* value was used in the lower-dose PTV to

Table II. Cost functions and parameters employed for BBO and PBO in Monaco.

Structure	BBO		PBO	
	Cost function	**Parameter**	**Cost function**	**Parameter**
Prostate PTV	Target EUD	α = 0.5	Target Penalty	$V_{100\%}$=95%
	QoD	Maximum dose	QoD	Maximum dose
	QuD	$D_{98\%}$ = 95%		
H&N PTVs	Target EUD	α = 0.25 (high-dose PTV)	Target Penalty	$V_{100\%}$=95%
		α = 0.5 (lower-dose PTVs)		
	QoD	Maximum dose	QoD	Maximum dose
	QuD	$D_{98\%}$ = 95%		
Rectum and Bladder	Serial	k: 4-5	Overdose DVH	3-4 functions with
	Parallel	k: 2-4		
Parotid glands	Serial	k: 4-5		appropriate
	Parallel	k: 2-4		DV values
	QoD	Max/mean dose		
Spinal cord	Serial	k = 20	Overdose DVH	V_{45Gy}=0
Patient (body)	QoD at 0.3 – 0.6 cm from PTV: maximum 95% of prescribed dose			
	QoD at 0.9 – 1.2 cm from PTV: maximum 70% of prescribed dose			
	QoD at 1.2 – 2.1 cm from PTV: maximum 50% of prescribed dose			

ensure coverage, and one Target EUD with also intermediate *a* values was used for higher-dose PTVs to get appropriate coverage while limiting hot spots. One Min Dose and one Max Dose were used in all PTVs (prostate and H&N alike) to help improve coverage and control the maximum dose, respectively.

For all OARs, OTV structures were created at 0.5 cm from the PTV and optimization was performed over them. One Max gEUD with *a=1* ensured appropriate OAR sparing, since the function acts along the entire DVH. An additional Max gEUD with *a=5* was used for rectum OTV, to lower high-dose regions (around 80% isodose) without compromise of PTV coverage. Max Dose was used in OARs directly to avoid hot spots.

PBO

PBO involved one Min Dose and one Max Dose for targets. In prostate cases and in the lower-dose PTV in H&N cases, an additional Max Dose at 50% volume was used to improve homogeneity. OARs employed three to four Max Dose functions at convenient DVH points. Dose gradient was ensured by use of Max Dose functions in auxiliary rings at increasing distances from the PTV (an additional auxiliary structure in the posterior neck was employed in H&N cases to reduce the mean dose). Table III shows functions and parameter range used for both BBO and PBO.

RESULTS

A. PTV dose distributions and TCP

BBO and PBO yielded very similar dose distributions and DVH behavior for PTVs, in both Monaco BBO vs PBO and Eclipse BBO vs PBO optimizations, as shown in Figures 2-7 for two representative cases, that showed the greatest OAR DVH behavior differences. PTV ICRU parameters in Tables IV and V corroborate that target coverage, dose median and dose maximum differ at most 2%. On the other hand, TCP values (Tables VII and VIII) differ less than 1% for PTV56 in prostate cases (no difference for PTV76), and less than 1.1% in H&N cases, with a maximum difference of 1.8% for PTV59.4 in case 1. Furthermore, TCP values were around 1% lower in Eclipse optimization than Monaco optimization, for PTV56 in prostate cases and between 7% to 14% lower in H&N cases.

B. OAR dose distributions and NTCP

For OARs, better DVH behavior is achieved in BBO, as shown in Figures 2 and 3, and the re-

Table III. Cost functions and parameters employed in BBO and PBO in Eclipse.

Structure	BBO		PBO	
	Cost function	**Parameter**	**Cost function**	**Parameter**
Prostate PTV	Target EUD	*a* = –40	Min Dose	$V_{100\%}$ = 99%
	Max Dose	Maximum dose	Max Dose	M aximum dose
	Min Dose	$D_{100\%}$ = 99%		
	Min EUD	*a* = –20 (high-dose PTV)		
H&N PTVs	Target EUD	*a* = –20 (intermediate PTV)	Min Dose	$V_{100\%}$ = 99%
	Lower EUD	*a* = –20 (high/low-dose PTV)	Max Dose	Maximum dose
	Max Dose	Maximum dose	Max Dose	$D_{50\%}$ = 100%
	Min Dose	$D_{100\%}$ = 99%		
Rectum	Max EUD	*a* = 1 and *a* = 5	Max Dose	3-4 consecutive
Bladder	Max EUD	*a* = 1		functions with
Parotid glands	Max EUD	*a* = 1		working DV values
Spinal cord	Max Dose	V_{45Gy} = 0	Max Dose	V_{45Gy} = 0
Patient (body)	Max Dose at 0.5 cm from PTV: maximum 95% of prescribed dose. Max Dose at 2.0 cm from PTV: maximum 70% of prescribed dose. H&N: additional structure with Max EUD or Mean dose for posterior neck.			

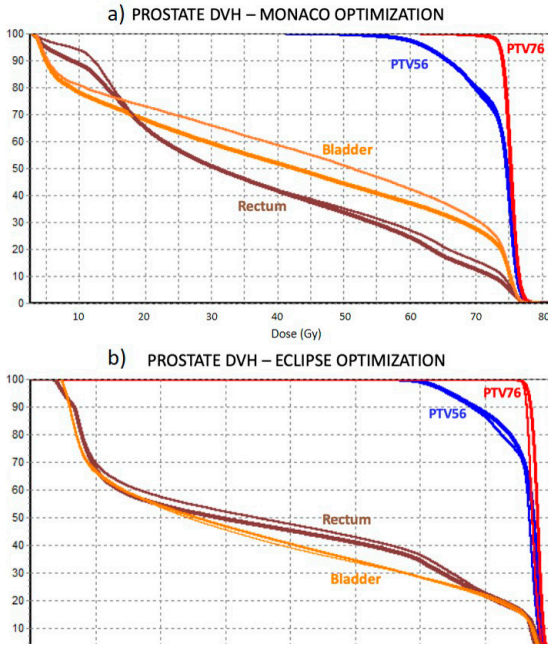

Figure 2. Prostate case BBO vs PBO DVH behavior. Resulting DVH for biological-based (thick line) and physical-based (thin line) optimizations for a representative prostate case in Monaco (a) and Eclipse (b). For rectum, Monaco Serial function defined at 35 Gy with k = 4 and Parallel function defined at 60 Gy – 30% with k = 3. Eclipse with gEUD defined at 14 Gy with *a* = 1 and another gEUD defined at 20 Gy with *a* = 5. For bladder, Monaco serial function defined at 50 Gy with k = 4. Eclipse with gEUD defined at 18 Gy with *a* = 1.

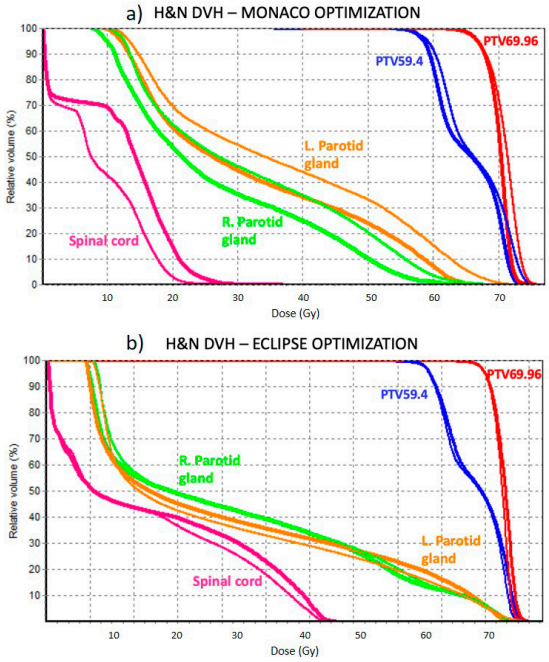

Figure 3. H&N case BBO vs PBO DVH behavior. Resulting DVH for biological-based (thick line) and physical-based (thin line) optimizations for a representative H&N case in Monaco (a) and Eclipse (b). For parotid glands, Monaco serial function defined at 20 Gy with k = 5, Parallel function defined at 30 Gy – 30% with k = 2 and QoD function defined at 20 Gy. Eclipse optimization with gEUD defined at 10 Gy with *a* = 1.

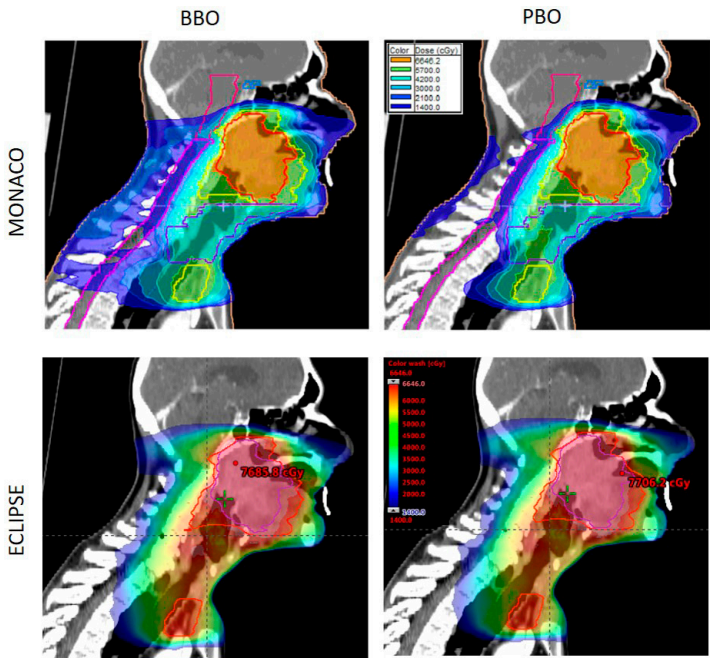

Figure 4. Monaco prostate dose distributions in BBO and PBO. Representative dose distribution in Monaco for prostate cases in a) biological optimization and b) physical optimization. Dose range shown: 7.6 Gy - 72.2 Gy.

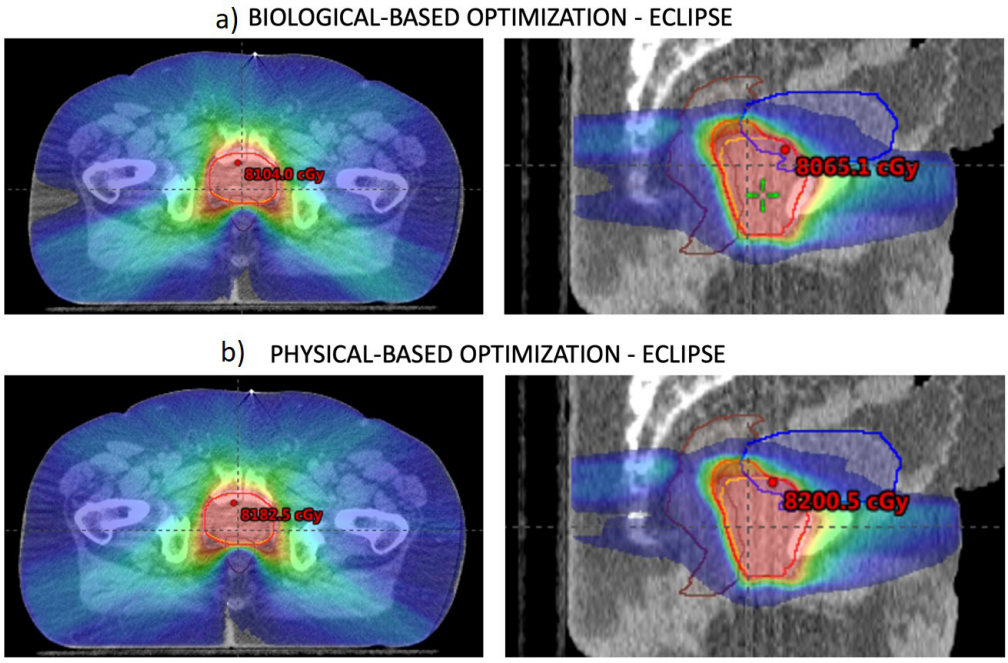

Figure 5. Eclipse prostate dose distributions in BBO and PBO. Representative dose distribution in Eclipse for prostate cases in a) biological optimization and b) physical optimization. Dose range shown: 7.6 Gy - 72.2 Gy.

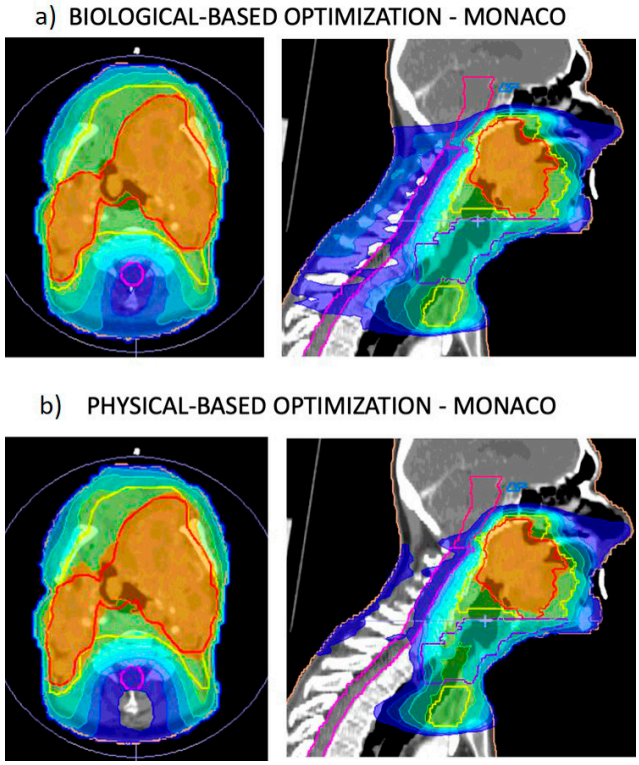

Figure 6. Monaco H&N dose distributions in BBO and PBO. Representative dose distribution in Monaco for H&N cases in a) biological optimization and b) physical optimization. Dose range shown: 14.0 Gy - 66.5 Gy.

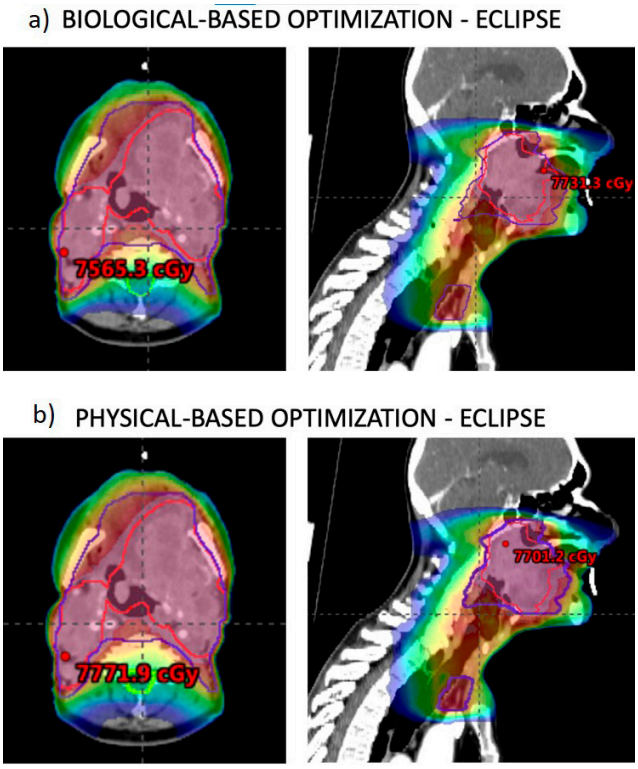

Figure 7. Eclipse H&N dose distributions in BBO and PBO. Representative dose distribution in Eclipse for H&N cases in a) biological optimization and b) physical optimization. Dose range shown: 14.0 Gy - 66.5 Gy.

Table IV. ICRU $D_{98\%}$, $D_{50\%}$ and $D_{2\%}$ parameters for prostate targets in Monaco and Eclipse optimizations.

Monaco optimization for prostate PTVs					
Case		**PTV 76**			**PTV 56**
		$D_{98\%}$ (Gy)	**$D_{50\%}$ (Gy)**	**$D_{2\%}$ (Gy)**	**$D_{98\%}$ (Gy)**
1	BBO	73.8	75.7	77.6	59.1
	PBO	73.5	75.5	77.4	58.7
2	BBO	73.5	75.5	77.4	62.2
	PBO	73.3	75.4	77.3	62.5
3	BBO	72.9	75.4	77.4	58.9
	PBO	73.0	75.4	77.3	58.9
Eclipse optimization for prostate PTVs					
Case		**PTV 76**			**PTV 56**
		$D_{98\%}$ (Gy)	**$D_{50\%}$ (Gy)**	**$D_{2\%}$ (Gy)**	**$D_{98\%}$ (Gy)**
1	BBO	75.8	78.2	80.2	59.6
	PBO	75.9	77.7	79.7	60.9
2	BBO	76.0	77.4	78.7	63.6
	PBO	76.0	77.4	79.3	66.2
3	BBO	76.3	78.1	79.6	61.6
	PBO	76.0	77.3	79.1	61.6

Table V. ICRU $D_{98\%}$, $D_{50\%}$ and $D_{2\%}$ parameters for H&N targets and combined parotid gland dose for 20 cc in Monaco and Eclipse optimizations.

Monaco optimization for H&N PTVs							
Case		**PTV 69.96**			**PTV 59.4**	**PTV 54**	**Parotid glands**
		$D_{98\%}$ (Gy)	**$D_{50\%}$ (Gy)**	**$D_{2\%}$ (Gy)**	**$D_{98\%}$ (Gy)**	**$D_{98\%}$ (Gy)**	**D_{20cc} (Gy)**
1	BBO	66.5	70.8	73.4	57.9	51.9	23.3
	PBO	66.5	70.6	72.7	56.4	51.4	19.5
2	BBO	64.9	70.3	73.3	55.9	52.5	18.5
	PBO	64.9	71.2	74.4	55.8	52.5	15.8
3	BBO	65.4	70.5	72.9	57.3	–	19.6
	PBO	65.4	71.5	74.6	57.4	–	15.3
Eclipse optimization for H&N PTVs							
Case		**PTV 69.96**			**PTV 59.4**	**PTV 54**	**Parotid glands**
		$D_{98\%}$ (Gy)	**$D_{50\%}$ (Gy)**	**$D_{2\%}$ (Gy)**	**$D_{98\%}$ (Gy)**	**$D_{98\%}$ (Gy)**	**D_{20cc} (Gy)**
1	BBO	69.6	71.5	73.6	58.4	53.7	14.3
	PBO	69.7	71.3	73.0	58.9	54.5	17.9
2	BBO	69.1	73.0	75.2	58.0	53.9	24.7
	PBO	69.2	72.7	74.7	54.4	54.6	25.2
3	BBO	68.9	73.2	75.6	60.1	–	8.6
	PBO	69.0	72.7	74.8	60.2	–	9.9

Table VI. Rectum and bladder DV parameters for Monaco and Eclipse optimizations.

Monaco optimization - rectum and bladder DV parameters									
Case		Rectum					Bladder		
		$\%V_{50Gy}$	$\%V_{60Gy}$	$\%V_{65Gy}$	$\%V_{70Gy}$	$\%V_{75Gy}$	$\%V_{65Gy}$	$\%V_{70Gy}$	$\%V_{75Gy}$
1	BBO	17.6	12.0	9.3	6.4	2.8	16.6	13.0	6.9
	PBO	19.8	13.8	10.6	7.5	3.5	18.5	14.6	6.8
2	BBO	25.5	17.9	13.3	7.6	3.4	20.0	16.1	7.4
	PBO	28.5	20.6	15.1	9.9	2.4	19.5	15.5	6.8
3	BBO	33.7	24.4	17.7	12.6	5.2	32.7	27.2	12.0
	PBO	35.3	27.2	21.1	15.6	7.1	36.7	30.5	12.8
Eclipse optimization - rectum and bladder DV parameters									
Case		Rectum					Bladder		
		$\%V_{50Gy}$	$\%V_{60Gy}$	$\%V_{65Gy}$	$\%V_{70Gy}$	$\%V_{75Gy}$	$\%V_{65Gy}$	$\%V_{70Gy}$	$\%V_{75Gy}$
1	BBO	16.8	12.4	8.9	6.8	5.0	10.5	8.8	7.2
	PBO	14.6	11.1	10.0	7.7	5.3	12.5	10.3	8.0
2	BBO	28.2	23.3	22.1	13.3	8.7	15.4	13.0	9.9
	PBO	32.2	26.2	18.8	15.1	9.1	15.7	13.4	10.3
3	BBO	40.9	28.4	27.8	21.8	16.3	25.2	21.4	16.2
	PBO	42.9	28.4	29.7	22.9	17.5	25.7	21.4	16.2

Table VII. TCP and NTCP values for prostate PTV56, PTV76 and rectum.

TCP and NTCP - Prostate cases				
Monaco Optimization				
Case		TCP (%)		NTCP (%)
		PTV56	PTV76	Rectum
1	BBO	97.6	99.0	1.7
	PBO	98.5	99.0	2.1
2	BBO	98.5	99.0	2.3
	PBO	98.7	99.0	2.9
3	BBO	97.0	99.0	4.2
	PBO	96.6	99.0	5.3
Eclipse Optimization				
Case		TCP (%)		NTCP (%)
		PTV56	PTV76	Rectum
1	BBO	96.6	98.9	2.7
	PBO	97.1	98.9	2.7
2	BBO	97.8	98.9	5.3
	PBO	98.4	98.9	6.1
3	BBO	97.3	98.9	10.6
	PBO	97.4	98.9	10.5

sulting dose-restrictions in Tables V and VI. NTCP values for rectum and for parotid glands are shown in Tables VII and VIII, respectively. Rectum NTCP values were lower for BBO than PBO in Monaco, similar for both optimizations in Eclipse, and almost twice as low in Monaco than in Eclipse for two of the three cases. Parotid gland NTCP values were nearly identical in both optimizations, except for case 3 (in which around 13.5% of parotid gland volume was inside the PTV), where BBO in Monaco yielded much lower values than PBO, and generally lower values than Eclipse. Conversely, NTCP values for bladder and spinal cord were zero since dose levels were widely below their RTOG restrictions, for both PBO and BBO.

C. Monitor Units and optimization time considerations

Monitor Unit ratio for BBO vs PBO was between 0.8 and 1.0 for Monaco, and between 1.1 and 1.3 for Eclipse prostate optimizations. For H&N optimizations, ratio was 1.0 in both TPS. Optimization time ratio, on the other hand, was between 1.0 and 1.7 for prostate and H&N plans, thus taking them longer in both Monaco and Eclipse, except for Monaco prostate cases (ratio between 0.6 and 0.8).

Table VIII. TCP and NTCP values for H&N PTVs and parotid glands.

TCP and NTCP - H&N cases						
Monaco Optimization						
Case		**TCP (%)**			**NTCP (%)**	
		PTV69.96	**PTV59.4**	**PTV54**	**R. Parotid**	**L. Parotid**
1	BBO	91.0	86.1	81.7	0.2	0.2
	PBO	90.7	84.3	80.3	0.1	0.1
2	BBO	90.2	83.9	82.2	0.2	0.1
	PBO	90.3	83.9	82.3	0.1	0.1
3	BBO	90.4	86.3	–	0.4	2.4
	PBO	90.4	86.5	–	1.9	9.2
Eclipse Optimization						
Case		**TCP (%)**			**NTCP (%)**	
		PTV69.96	**PTV59.4**	**PTV54**	**R. Parotid**	**L. Parotid**
1	BBO	83.5	71.5	67.9	0.2	0.2
	PBO	83.3	72.0	69.0	0.1	0.4
2	BBO	80.3	71.5	66.8	0.3	0.3
	PBO	80.3	69.5	65.7	0.4	0.4
3	BBO	79.5	72.7	–	3.0	3.2
	PBO	79.4	72.8	–	3.5	2.0

DISCUSSION

BBO allows replacing DV constraints with biological functions that show greater versatility when shaping the DVH and that have better association with treatment outcome than DV criteria (Li *et al.*). Radiobiological cost functions in Monaco directly relate to concepts like the EUD and the Poisson model for targets, the gEUD concept for serial organs and the logistic NTCP model for parallel-like organs. Similarly, the gEUD concept is involved in Eclipse's biological cost-functions, allowing the description of tumors and normal tissues with one parameter (*a*). Implementation of the EUD concept (equations 6 and 7), makes dose values in each structure's voxel become important to determine the corresponding EUD or gEUD values desired by the user, thus having a larger effect on the DVH than traditional DV constraints. Moreover, since biological cost functions inherently involve dose-volume effects in parameters *k* and *a*, shaping of the DVH for OARs is possible by variation of only one parameter. Consequently, at most two biological cost functions were necessary to obtain the desired DVH behavior for OARs, as opposed to the use of three to four physical cost functions to obtain a similar result, with comparable monitor unit number, and thus actual treatment execution time, with reasonably longer optimization times.

It should be noted that Target EUD and Target gEUD functions do not impose a maximum dose limit, so inclusion of at least one Overdose DVH or Max Dose function for targets is necessary. As previously demonstrated by Wu *et al.* (2002), cold spots influence the gEUD to a larger extent than hot spots for targets, which will result in undesired high dose regions for the PTV if no additional (physical) restriction is made. Consequently, it is not possible to generate a purely biological-based plan. Nonetheless, variation of α or *a* parameters permits proper coverage of high-dose PTVs surrounded by lower-dose PTVs (like in H&N cases) by allowing the former to have more high-dose voxels and the latter to have a more homogeneous dose.

On the other hand, TCP values were calculated by use of the Poisson model, which depends on the radio-sensitivity parameter α and on the uniform dose D. Since DVH behavior for PTVs was very similar both in BBO and PBO, this uniform dose D, calculated by the LKB reduction method

must be nearly the same, thus yielding very close TCP values. Greater differences in H&N cases relate to their PTV and dose distribution complexity. Although both Monaco and Eclipse used equivalent functions in biological and physical optimizations (EUD or gEUD-based cost functions and DV-based cost functions), that allowed proper target coverage and ICRU parameters, TCP slight differences are observed between the two. This might be attributed to dose-calculation algorithms used (Monte Carlo vs Acuros), since physical interaction and dose deposition modeling are different, thus obtaining dissimilar dose distributions within the PTV and the resulting DVH. Also, care must be given to DVH grid resolution, which will directly affect the LKB calculation (in the present case, Monaco grid resolution was 0.5 cGy and Eclipse resolution was 0.1 cGy).

Upon histogram reduction for OARs, larger variations in DVH behavior result in dissimilar NTCP values. As observed in DVH and NTCP results for rectum (Figure 2 and Tables VI and VII), the lower the DV points, the lower the NTCP values for OARs. Additionally, NTCP values for rectum were always lower in Monaco Optimization than in Eclipse Optimization. Besides the fact of using contrasting dose-calculation algorithms, BBO differences might be due to the fact that two distinct biological cost functions (Serial and Parallel) were used in Monaco, while Eclipse used the same gEUD cost function with two *a* values. Although gEUD and Serial cost functions are conceptually and mathematically equivalent, gEUD and Parallel cost functions are not identical and have a different effect on the resulting DVH (Figures 1 and 2, Tables V and VI), where higher doses are more effectively controlled by the Parallel cost function in Monaco (with high k), whereas low and intermediate doses reach better values with the gEUD function with low *a* in Eclipse. Better high-dose control (with dose values 2-3 fold lower than Eclipse) with high-k Parallel cost function in Monaco thus results in a NTCP twice as low. However, given the versatility in DVH shaping for biological cost functions, proper adjustment of parameters *k* and *a* could result in similar results for OARs in Monaco and Eclipse optimizations. Specifically, the gEUD function in Eclipse could be adjusted around high-dose values with an *a* value near 20-30 to lower high doses.

Finally, for H&N case number 3, a large portion of the parotid glands was inside PTV69.96. The much lower NTCP values in BBO in Monaco could be explained by the fact that an additional Quadratic Overdose function was added to help lower mean dose, while only Overdose DVH functions were utilized in PBO. Thus, it might be advisable to include an additional Quadratic Overdose function in cases where a large portion of the parotid gland is inside the Target Volume. Contrastingly, since gEUD in Eclipse with $a = 1$ acts as mean-dose already, effective lowering of parotid-gland dose is achieved with one function (see Figure 3 and Table V), obtaining close NTCP values in both parotid glands, in contrast to the dissimilar values observed for Monaco optimization (Table VIII). Corresponding Max Dose functions in PBO were adjusted to resemble the BBO DVH behavior, subsequently achieving similar NTCP values.

CONCLUSION

BBO in Monaco and Eclipse provides an efficient optimization method for RT treatment planning, being advantageously associated to radiobiological concepts like the EUD and gEUD, inherently involving dose-volume effects and thus driving dose distributions with one cost function and one parameter. Although both Monaco and Eclipse involve similar radiobiological concepts in their models, differences in DVH behavior and NTCP values can be attributed to non-identical cost function form and parameter range, and their subsequent influence on the DVH, whereas differences in TCP values could also relate to dissimilar dose-calculation algorithms and DVH grid size for the LKB reduction method. Nonetheless, both TPS show that for nearly the same target coverage and TCP, more efficient OAR sparing and NTCP can be achieved with variation of only one parameter in BBO, as opposed to the use of several DV criteria in PBO to attain a similar result. Even so, addition of DV criteria for OARs and targets should be considered, for they could yield even better results. Knowledge, use and experimentation of radiobiological-based cost functions should be encouraged in the treatment planning process to obtain the best possible RT plan in terms of target coverage, dose distribution, TCP, compliance with DV-constraints and NTCP.

CONFLICT OF INTEREST

No conflicts of interest.

RESUMEN: Introducción. Las funciones de optimización basadas en radiobiología para la planificación del tratamiento de radioterapia implican efectos dosis-volumen que podrían permitir una mayor versatilidad a la hora de dar forma a las distribuciones de dosis y DVH que los tradicionales criterios dosis-volumen (DV). Dos de los TPS más disponibles comercialmente (Mónaco y Eclipse) ya ofrecen productos de funciones de optimización de base biológica, pero la mayoría de los planificadores no las utilizan de forma rutinaria en la práctica clínica. El conocimiento de los beneficios del uso de las funciones de costos basadas en EUD, TCP/NTCP en Mónaco y Eclipse TPS se obtuvo comparando optimizaciones de base biológica y optimizaciones físicas para casos de próstata y cabeza y cuello. **Métodos**. Tres próstatas y tres casos de H&N en Mónaco y Eclipse TPS fueron optimizadas retrospectivamente usando funciones de costos basadas en radiobiología vs funciones de costos basadas en DV. La comparación de planes involucró los parámetros del Informe ICRU 83 $D_{95\%}$, $D_{50\%}$, $D_{2\%}$ y TCP para el PTV, y dosis de tolerancia NTCP y RTOG para OAR. **Resultados**. Aunque hubo diferencias entre los planes Mónaco y Eclipse, debido a sus diferentes algoritmos de optimización y cálculo de dosis, así como funciones de optimización, ambos TPS demostraron que el criterio basado en radiobiología permiten una adaptación versátil del DVH con variación de un solo parámetro y como máximo dos funciones de costos, en contraste con el uso de tres o cuatro criterios basados en DV para alcanzar un resultado similar. **Conclusión**. A pesar del uso de una muestra pequeña, la optimización de tres casos de próstata y tres de cabeza y cuello permitió la exploración de las posibilidades de optimización que ofrecen dos de los TPS más disponibles comercialmente en dos regiones anatómicamente diferentes. La optimización basada en radiobiología impulsa de manera eficiente las distribuciones de dosis y la configuración de DVH para OAR sin sacrificar Cobertura de PTV. Se debe fomentar el uso de funciones de costos basadas en EUD además de las funciones de costos DV para obtener el mejor posible plan en la práctica clínica diaria.

PALABRAS CLAVE: Optimización Biológica, EUD, TCP, NTCP.

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