Equivalent normalized total dose estimates in cyberknife radiotherapy dose delivery in prostate cancer hypofractionation regimens

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ABSTRACT

As the α/β value of prostate is very small and lower than the surrounding critical organs, hypofractionated radiotherapy became a vital mode of treatment of prostate cancer. Cyberknife (Accuray Inc., Sunnyvale, CA, USA) treatment for localized prostate cancer is performed in hypofractionated dose regimen alone. Effective dose escalation in the hypofractionated regimen can be estimated if the corresponding conventional 2 Gy per fraction equivalent normalized total dose (NTD) distribution is known. The present study aims to analyze the hypofractionated dose distribution of localized prostate cancer in terms of equivalent NTD. Randomly selected 12 localized prostate cases treated in cyberknife with a dose regimen of 36.25 Gy in 5 fractions were considered. The 2 Gy per fraction equivalent NTDs were calculated using the formula derived from the linear quadratic (LQ) model. Dose distributions were analyzed with the corresponding NTDs. The conformity index for the prescribed target dose of 36.25 Gy equivalent to the NTD dose of 90.63 Gy (α/β = 1.5) or 74.31 Gy (α/β = 3) was ranging between 1.15 and 1.73 with a mean value of 1.32 ± 0.15. The D5% of the target was 111.41 ± 8.66 Gy for α/β = 1.5 and 90.15 ± 6.57 Gy for α/β = 3. Similarly, the D95% was 91.98 ± 3.77 Gy for α/β = 1.5 and 75.35 ± 2.88 Gy for α/β = 3. The mean values of bladder and rectal volume receiving the prescribed dose of 36.25 Gy were 0.83 cm3 and 0.086 cm3, respectively. NTD dose analysis shows an escalated dose distribution within the target for low α/β (1.5 Gy) with reasonable sparing of organs at risk. However, the higher α/β of prostate (3 Gy) is not encouraging the fact of dose escalation in cyberknife hypofractionated dose regimen of localized prostate cancer.

Key words: Cyberknife, hypofractionation, localized prostate, low α/β, normalized total dose

Introduction

Fractionation in radiotherapy is introduced based on the differential sensitive responses of the tumor and the normal cells to radiation. In radiobiological terminology, the early responding tumor cells and the late responding normal cells are characterized by the α/β value which is derived from the cell survival curve. Early responding cells have higher α/β values, while the late responding cells have lower α/β values. Classical tumors generally have a higher α/β value closer to 10 Gy, except the cancer of prostate. The α/β value for prostate cancer is very low. It is about 1.5 Gy and has greater fractionation sensitivity.[1-3] However, the in vitro and clinical studies by Carlson et al.[4] suggest that the prostate cancer cells have an α/β value about 3 or 4 Gy. The hypofractionation regimen was implemented in localized prostate cancer because of the low α/β value.[5] Late responding normal tissues have low α/β value, especially the rectum and the bladder. The α/β value of rectum for late rectal toxicity is estimated as 3 Gy by Marzi et al.[6] However, there is enough evidence available in the literature for higher α/β value of rectum in the range of 4–5 Gy.[7] According to Van der Kogel et al.,[8] the α/β for rectum is 4.1 Gy, while it is 4.6 Gy according to Brenner et al.[9] Similarly, from animal studies, the α/β of bladder is estimated as about 7 Gy.[7] This complex, nonuniform distribution of α/β in the pelvic region would be the matter of concern

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when the hypofractionation is applied. The effectiveness of prostate target dose escalation for a hypofractionated regimen from the conventional fractionation regimen can be estimated if the hypofractionated dose distribution is known in terms of conventional equivalent normalized total dose (NTD) distribution. The α/β value plays a major role in the conversion of hypofractionated dose to the NTD. The hypofractionation is attempted in several ways in the case of localized prostate cancer. The high dose rate (HDR) brachytherapy is one of the prime modes of hypofractionation.[10,11] Murali *et al.*[12] compared the intensity modulated radiotherapy (IMRT) conventional dose distributions with the hypofractionated HDR brachytherapy. There are trials to escalate the IMRT dose by hypofractionation for prostate cases as well.[13] The cyberknife (Accuray Inc., Sunnyvale, CA, USA) robotic radiosurgery unit is used to treat the localized prostate cancer in the hypofractionated dose regimen.[14,15] The hypofractionation regimen of 36.25 Gy in 5 fractions followed by King *et al.*[16] suggests a positive outcome after 5 years of review. The hypofractionated dose distribution within the prostate and the in the organs at risk (OARs) are known in the hypofractionated doses alone. Koukourakis *et al.*[17] found the escalated dose within the prostate target which was treated by the conformal hypofractionated accelerated dose regimen. The objective of the present study is to analyze the cyberknife hypofractionated dose distribution in the 36.25 Gy in 5 fractions regimen in terms of the conventional equivalent NTDs to evaluate the degree of dose escalation possible in the localized prostate cancer.

Materials and Methods

Twelve localized prostate cases treated with cyberknife robotic radiosurgery unit were randomly and retrospectively selected for analysis in this study. The hypofractionated dose regimen used for all these cases was 36.25 Gy in 5 fractions (7.25 Gy per fraction). Planning Target Volume (PTV) was drawn with the help of magnetic resonance (MR) images after fusion in the dedicated cyberknife treatment planning system called Multiplan (Accuray Inc.). The PTVs were marked around the cancerous prostate with a margin of 5 mm in all the directions, except the anterior and posterior directions where the margin was only 3 mm to account for the rectum and the bladder. The average volume of the PTV was 71.7 cm³. The rectum was delineated from the anal verge to the sigmoid colon. Similarly, the entire bladder volume was contoured. The treatment plans were generated and evaluated.

Evaluation of the cyberknife treatment plan

The prostate cyberknife treatment plans were evaluated in terms of the dose conformity and homogeneity indices, while at the same time the dose spillage to the OARs was kept to the minimum. The target coverage was analyzed in terms of $D_{98\%}$, $D_{90\%}$, $D_{80\%}$, $D_{50\%}$, $D_{10\%}$ and $D_{5\%}$. Here, $D_{98\%}$

represents the dose received by 98% of the target volume. Similarly, the other doses represent the corresponding percentage of volumes involved. Furthermore, the volume receiving 100% of the prescribed dose, $V_{100\%}$, was evaluated in terms of percentage volume. The dose conformity and homogeneity were also analyzed using the values calculated by the treatment planning system. The formulae used by the treatment planning system to calculate the conformity index and the homogeneity index are given below:

conformity index (CI) = $(V_{RI} \times TV)/(TV_{RI})^2$,

where V_{RI} is the overall volume receiving the prescription isodose or more, TV is the total volume of the PTV, and TV_{RI} is the volume of the target which receives the prescription isodose or more.

Homogeneity index (HI) = D_{max}/D_{RI},

where D_{max} is the maximum dose in the target and D_{RI} is the prescription isodose.

For the OARs, rectum and the bladder, $V_{100\%}$, $V_{90\%}$, $V_{50\%}$, $V_{30\%}$ were evaluated in terms of the volume in cubic millimeters. The maximum dose received by the rectum and the bladder was estimated from $D_{2\%}$ and $D_{5\%}$. $D_{10\%}$ was also taken for the analysis.

Conversion of hypofractionated dose to normalized total dose

After analyzing the dose distribution, the doses were converted to the NTD distribution. NTD gives the dose in 2 Gy fractions that would result in equivalent biological effect in the fractionation of interest. In our case, the fractionation of interest is 7.25 Gy per fraction in 5 fractions (total dose of 36.25 Gy). The NTD[7,17,18] is given by

NTD = $D\{[1 + d/(\alpha/\beta)]/[1 + 2/(\alpha/\beta)]\}$,

where D is the total dose in the hypofractionation regimen and d is the dose per fraction. The α/β is the tissue/tumor sensitive value.

The prostate target, the rectum and bladder radiobiological effective doses were evaluated using their corresponding NTDs. The dose escalation in the target was compared with the doses reported in the literature for different modes of treatment for the localized prostate cancer. *P* values calculated using two-tailed Student's *t*-test are given in the tables.

Results

Treatment plan analysis in the hypofractionated regimen

The $D_{98\%}$, $D_{90\%}$, $D_{80\%}$, $D_{50\%}$, $D_{10\%}$ and $D_{5\%}$ values in the hypofractionated regimen of the target are shown in Table 1. A typical dose–volume histogram (DVH) of

hypofractionated dose distribution is shown in Figure 1. $D_{98\%}$ is a measure of the minimum dose within the target. The mean value of $D_{98\%}$ was 35.5 ± 1.01 Gy. The maximum and the minimum values of $D_{98\%}$ were 37.53 Gy and 33.43
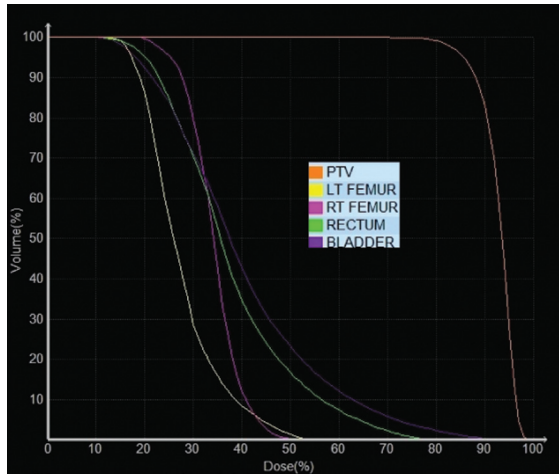

Figure 1: Dose–volume histogram of hypofractionated dose distribution in cyberknife radiosurgery

Gy, respectively. Similarly, $D_{5\%}$ is the measure of maximum dose within the target. $D_{5\%}$ was ranging between 38.59 Gy and 43.95 Gy. The mean value was 40.53 ± 1.69 Gy. The percentage volume of the prostate target receiving 100% of the prescribed dose, $V_{100\%}$, was $95.42 \pm 3.7\%$. The mean values of CI and the HI were 1.32 ± 0.15 and 1.14 ± 0.05, respectively. The conformity and homogeneity indices are shown in Table 2.

The $V_{100\%}$, $V_{90\%}$, $V_{50\%}$, $V_{30\%}$ volumes of the rectum and the bladder are tabulated in Table 3 and Table 4, respectively. The values of $V_{100\%}$, $V_{90\%}$ and $V_{50\%}$ of the rectum were 0.086 cm^3, 2.8 cm^3 and 20.5 cm^3, respectively. Similarly, the values of $V_{100\%}$, $V_{90\%}$ and $V_{50\%}$ of the bladder were 0.83 cm^3, 6.4 cm^3 and 38.9 cm^3, respectively.

Analysis of the treatment plan in terms of the normalized total dose

The NTD equivalents of the target doses were estimated for both α/β values of 1.5 Gy and 3 Gy. The NTDs corresponding to $D_{98\%}$, $D_{90\%}$, $D_{80\%}$, $D_{50\%}$, $D_{10\%}$ and $D_{5\%}$ are

Table 1: Hypofractionated dose to planning target volume from cyberknife robotic radiosurgery

Study number	Volume of PTV in cm³	PTV hypofractionated dose in Gy						
		$D_{98\%}$	$D_{95\%}$	$D_{90\%}$	$D_{80\%}$	$D_{50\%}$	$D_{10\%}$	$D_{5\%}$
1	48.4	34.9	36.7	38.0	39.3	41.1	42.4	42.8
2	71.6	35.9	36.3	36.7	37.1	37.9	39.5	39.9
3	85.8	34.4	36.7	38.1	39.4	41.7	43.5	44.0
4	107.3	35.9	36.3	36.3	36.6	37.4	38.6	39.0
5	44.5	36.3	36.6	36.6	37.0	37.4	38.2	38.6
6	75.2	35.5	36.3	36.6	37.0	37.8	38.6	39.0
7	51.3	37.5	38.4	39.7	40.5	41.4	41.8	42.2
8	91.0	35.8	36.7	37.1	37.9	38.7	40.0	40.4
9	55.2	35.9	36.7	37.1	37.9	38.7	39.5	39.9
10	146.2	35.0	36.7	37.5	38.4	39.7	40.9	41.4
11	44.1	33.4	34.6	35.4	36.7	37.9	39.1	39.5
12	39.5	35.9	36.7	37.5	37.9	38.7	39.5	39.9
P value		0.0001	0.0000	0.0001	0.0002	0.0012	0.0016	0.0016

Table 2: Conformity index, homogeneity index and the dose coverage of planning target volume

Study number	CI	HI	Prescription isodose line with respect to Dmax	Percentage of PTV receiving 100% dose, $V_{100\%}$
1	1.43	1.2	83	95.9
2	1.37	1.11	90	96.2
3	1.36	1.25	80	95.7
4	1.3	1.09	92	93.0
5	1.24	1.08	93	99.2
6	1.15	1.09	92	95.5
7	1.73	1.18	85	99.1
8	1.27	1.14	88	96.2
9	1.19	1.11	90	96.5
10	1.23	1.18	85	95.9
11	1.24	1.11	90	84.9
12	1.32	1.11	90	97.2
P value	0.1608	0.0034	0.0031	0.0009

CI: Conformity index, HI: Homogeneity index

Table 3: The rectal dose volumes

Study number	Volume of rectum in cm³	Rectum dose volumes in cm³			
		$V_{100\%}$	$V_{90\%}$	$V_{50\%}$	$V_{30\%}$
1	117.2	0.4	1.4	11.2	26.9
2	51.9	0.0	8.0	27.3	36.2
3	76.1	0.0	1.1	21.4	44.0
4	86.2	0.2	10.8	53.8	70.6
5	70.1	0.0	2.2	14.2	29.4
6	74.3	0.1	3.6	23.1	38.2
7	91.7	0.0	1.7	17.3	32.5
8	140.3	0.1	2.9	28.0	50.8
9	81.1	0.0	0.8	14.6	32.2
10	69.5	0.0	0.2	19.3	58.9
11	58.5	0.0	0.0	6.5	17.3
12	45.2	0.1	1.0	9.1	21.3
P value		0.8907	0.8855	0.7814	0.6792

Table 4: The bladder dose volumes

Study number	Volume of bladder in cm³	Bladder dose volumes in cm³			
		$V_{100\%}$	$V_{90\%}$	$V_{50\%}$	$V_{30\%}$
1	54.3	2.0	4.0	15.7	35.4
2	81.0	1.0	6.4	31.9	65.4
3	136.0	1.0	5.1	41.2	92.2
4	131.7	1.9	29.1	118.3	131.7
5	282.9	0.3	4.0	25.1	80.5
6	54.7	0.1	7.7	49.2	54.7
7	141.7	1.3	5.3	24.1	48.7
8	236.4	0.4	2.9	34.2	77.3
9	139.0	0.2	3.5	46.4	118.9
10	105.9	1.3	3.4	37.3	88.7
11	114.3	0.2	1.8	17.3	48.5
12	296.0	0.3	3.4	26.0	66.1
P value		0.8369	0.8829	0.8088	0.6593

Table 5: Planning target volume dose in terms of equivalent normalized total dose for α/β = 1.5 Gy of prostate

Study no	PTV NTD dose in Gy for α/β = 1.5						
	$D_{98\%}$	$D_{95\%}$	$D_{90\%}$	$D_{80\%}$	$D_{50\%}$	$D_{10\%}$	$D_{5\%}$
1	84.7	92.6	98.8	105.1	113.9	120.7	123.0
2	88.8	90.6	92.5	94.3	98.1	106.0	108.0
3	82.5	92.7	99.1	105.7	117.2	126.8	129.2
4	88.8	90.6	90.6	92.4	96.1	101.8	103.7
5	90.6	92.4	92.4	94.2	96.1	99.8	101.6
6	87.1	90.6	92.4	94.3	98.0	101.8	103.7
7	96.6	100.6	106.9	111.2	115.5	117.7	120.0
8	88.8	92.5	94.4	98.3	102.3	108.4	110.4
9	88.8	92.5	94.3	98.1	102.0	106.0	108.0
10	84.9	92.6	96.6	100.6	106.9	113.3	115.5
11	78.2	83.4	87.0	92.5	98.1	104.0	106.0
12	88.8	92.5	96.2	98.1	102.0	106.0	108.0
P value	0.0066	0.0014	0.0075	0.0149	0.0396	0.0473	0.0476

shown in Tables 5 and 6 for α/β = 1.5 Gy and α/β = 3 Gy, respectively. The dose covering almost the entire target was estimated in this study by the doses $D_{98\%}$ and $D_{95\%}$. The mean NTD value $D_{98\%}$ for α/β = 1.5 Gy was 87.38 ± 4.54 Gy, while it was 71.85 ± 3.58 Gy for α/β = 3 Gy. Similarly, the mean NTD of $D_{95\%}$ was 91.98 ± 3.8 Gy for α/β = 1.5 Gy and 75.35 ± 2.9 Gy for α/β = 3 Gy. The maximum dose within the target was estimated by the $D_{5\%}$. The mean NTD

Table 6: Planning target volume dose in terms of equivalent normalized total dose for α/β = 3 Gy of prostate

Study no	PTV NTD dose in Gy for α/β = 3 Gy						
	$D_{98\%}$	$D_{95\%}$	$D_{90\%}$	$D_{80\%}$	$D_{50\%}$	$D_{10\%}$	$D_{5\%}$
1	69.8	75.9	80.6	85.4	92.1	97.2	99.0
2	72.9	74.3	75.7	77.2	80.1	86.0	87.5
3	68.1	75.9	80.8	85.8	94.5	101.8	103.7
4	72.9	74.3	74.3	75.7	78.5	82.8	84.3
5	74.3	75.7	75.7	77.1	78.5	81.3	82.7
6	71.6	74.3	75.7	77.1	79.9	82.8	84.3
7	78.9	82.0	86.7	90.0	93.3	95.0	96.6
8	72.9	75.8	77.2	80.2	83.2	87.8	89.4
9	72.9	75.7	77.2	80.1	83.0	86.0	87.5
10	69.9	75.8	78.9	82.0	86.7	91.6	93.3
11	64.8	68.8	71.5	75.7	80.1	84.5	86.0
12	72.9	75.7	78.6	80.1	83.0	86.0	87.5
P value	0.0044	0.0009	0.0050	0.0104	0.0299	0.0363	0.0366

Table 7: The rectal volume doses

Study no	Rectal volume doses in Gy					
	α/β = 3 Gy			α/β = 4 Gy		
	$D_{2\%}$	$D_{5\%}$	$D_{10\%}$	$D_{2\%}$	$D_{5\%}$	$D_{10\%}$
1	55.7	37.5	23.6	51.5	35.3	22.6
2	71.5	68.8	66.1	65.5	63.1	60.7
3	60.7	52.4	44.6	56.0	48.6	41.7
4	71.6	68.9	65.0	65.6	63.2	59.7
5	66.4	57.6	43.0	60.9	53.2	40.1
6	67.6	62.4	53.8	62.0	57.5	49.9
7	60.1	51.0	38.2	55.4	47.4	35.9
8	61.9	50.6	38.2	57.0	46.9	35.9
9	55.9	45.3	33.9	51.6	42.3	32.0
10	53.6	46.2	37.1	49.6	43.0	34.9
11	44.2	34.9	25.7	41.3	32.9	24.6
12	62.2	52.2	39.9	57.2	48.4	37.4
P value	0.2092	0.4208	0.5949	0.4027	0.1932	0.5791

Table 8: The bladder volume doses

Study no	Bladder volume doses in Gy					
	α/β = 3 Gy			α/β = 4 Gy		
	$D_{2\%}$	$D_{5\%}$	$D_{10\%}$	$D_{2\%}$	$D_{5\%}$	$D_{10\%}$
1	78.9	55.7	44.4	72.0	51.5	41.5
2	72.9	67.4	58.3	66.7	61.8	53.8
3	68.1	57.8	45.8	62.4	53.4	42.7
4	72.9	71.5	68.9	66.7	65.5	63.1
5	57.6	38.8	22.0	53.2	36.4	21.2
6	71.5	68.9	64.9	65.5	63.1	59.7
7	68.4	56.1	38.2	62.8	51.9	35.9
8	56.7	41.4	30.2	52.4	38.7	28.7
9	63.4	53.4	42.0	58.3	49.4	39.3
10	68.4	56.1	45.0	62.8	51.9	41.9
11	59.5	46.4	31.9	54.9	43.2	30.2
12	55.8	36.86	21.6	51.6	34.6	20.8
P value	0.1543	0.4544	0.6418	0.1402	0.4366	0.6285

Table 9: Comparative dose analysis of the IMRT and HDR doses reported by Murali *et al*.[12] with the present cyberknife doses in terms of equivalent NTDs

Dose index	IMRT dose in Gy	NTD of brachytherapy dose in Gy		NTD of cyberknife dose in Gy	
		α/β = 1.5 Gy	α/β = 3 Gy	α/β = 1.5 Gy	α/β = 3 Gy
D98%	70.9	83.4	66.6	87.4	71.8
D90%	77.9	103.0	81.4	95.1	77.7
D80%	79.5	119.3	93.5	98.8	80.5
D50%	81.9	163.0	125.9	103.9	84.4
D10%	84.6	464.9	345.7	109.3	88.6
D5%	85.4	845.7	619.6	111.4	90.2

IMRT: Intensity modulated radiotherapy, HDR: High dose rate, NTD: Normalized total dose

of $D_{5\%}$ was 111.41 ± 8.66 Gy for α/β = 1.5 Gy and 90.15 ± 6.57 Gy for α/β = 3 Gy.

As far as the OARs are concerned, two α/β values (3 Gy and 4 Gy) were considered for estimating the NTD in this study as the literature suggests different α/β values for rectum and the bladder. The comparisons between the hypofractionated dose and the NTD dose for the rectum and the bladder are given in Tables 7 and 8, respectively. The mean NTD for $D_{2\%}$ of the rectum was 60.94 ± 7.9 Gy for α/β = 3 Gy, while it was 56.14 ± 7.01 Gy for α/β = 4 Gy. Similarly, the NTD for $D_{2\%}$ of the bladder was having a mean value of 66.22 ± 7.4 Gy for α/β = 3 Gy, while it was 60.82 ± 6.6 Gy for α/β = 4 Gy.

Discussion

The NTD dose within the target shows a better dose escalation for α/β = 1.5 Gy when compared with the α/β = 3 Gy. The NTDs for α/β = 1.5 Gy in the target range from 87.38 ± 4.54 Gy ($D_{98\%}$) to 111.41 ± 8.66 Gy ($D_{5\%}$). This shows the existence of fair dose escalation in the cyberknife hypofractionation regimen. Wolff *et al*.[19] compared the volumetric modulated arc radiotherapy (VMAT) with the serial tomotherapy, the step and shoot IMRT and the 3D conformal radiotherapy (3DCRT) of prostate cancer. According to that study, the $D_{95\%}$ values of the PTV were 71.59 ± 0.53 Gy, 71.70 ± 0.63 Gy, 70.51 ± 0.91 Gy, 69.79 ± 3.52 Gy, and 73.42 ± 0.37 Gy for VMAT 1X, VMAT 2X, IMRT, tomotherapy, and 3DCRT, respectively. The NTD equivalent of $D_{95\%}$ of PTV in our cyberknife hypofractionation regimen for α/β = 1.5 Gy was 91.98 ± 3.77 Gy and for α/β = 3 Gy it was 75.35 ± 2.88 Gy. This comparison shows a higher degree of dose escalation when the α/β of the prostate is 1.5 Gy. However, the present hypofractionation is very much comparable with the conventional fractionation regimen adopted in the above-said modes of prostate radiotherapy when the α/β of the prostate is taken as 3 Gy. The NTD equivalent doses of the cyberknife hypofractionated doses were also compared with the IMRT conventional fractionation doses and the hypofractionated HDR doses reported by Murali *et al*.[12] The HDR brachytherapy hypofractionation regimen taken in that study was 30 Gy in 3 fractions and

the IMRT conventional fractionation regimen was 76 Gy in 38 fractions. The doses were reported in terms of the percentage in that study. The doses were converted to the absolute doses and then the HDR doses were converted to the NTDs. The comparison is shown in Table 9. The result shows a dose escalation of about 20 Gy in the cyberknife hypofractionation for α/β = 1.5 Gy when compared with IMRT. However, not much difference is observed between the IMRT dose and the cyberknife NTD dose for α/β = 3 Gy. A huge difference between the NTD doses of HDR and the cyberknife dose is observed especially in the $D_{10\%}$ and $D_{5\%}$ doses for obvious reasons. However, the values of $D_{98\%}$ and $D_{90\%}$ are comparable between HDR and the cyberknife NTD doses. All the 12 cyberknife plans of the localized prostate cancer taken for the study are showing a better homogeneity and conformity. Also, the NTDs of the OARs, the rectum and the bladder, are very much within the acceptable tolerance for both the α/β values of 3 Gy and 4 Gy.

The clinical correlation may be the further scope of this study to ensure the dose escalation in cyberknife hypofractionation regimen of 36.25 Gy in 5 fractions.

Conclusion

Dose escalation is definitely there in the hypofractionated regimen of 36.25 Gy in 5 fractions if the α/β of the prostate is 1.5 Gy. However, an appreciable dose escalation is not prompted when the α/β of the prostate is taken as 3 Gy. Clinical correlations should be made to ensure the dose escalation in cyberknife hypofractionated dose regimen for localized prostate cancer.

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