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Dosimetric and biological comparison of treatment plans between LINAC and robot systems in stereotactic body radiation therapy for localized prostate cancer

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► ***Original article***

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ABSTRACT

***Background*:** The aim of this study was to make a comparison of plan quality between MLC-based EDGE and the cone-based CyberKnife systems in SBRT of localized prostate cancer. ***Materials and Methods*:** Ten patients with target volumes from 34.65 to 82.16 cc were included. Treatment plans were created for both systems using the same constraints. Dosimetric indices including target coverage, conformity index (*CI*), homogeneity index (*HI*), gradient index (*GI*) were applied for target, while the sparing of critical organs was evaluated with special dose-volume metrics and integral dose. Meanwhile, the delivery time and monitor units (MUs) were also estimated. The radiobiological indices such as equivalent uniform dose (*EUD*), tumor control probability (*TCP*) and normal tissue complication probability (*NTCP*) were also analyzed. ***Results*:** Both plans produced similar target coverage, *HI* and *GI*. For EDGE, more conformal dose distribution as well as reduced exposure of critical organs were obtained together with reduction of 91% delivery time and 72% MUs. EDGE plans also got lower EUD for bladder, rectum, urethra and penile bulk, which associated with reduction of NTCPs. However, higher values of EUD and TCP for tumor were obtained with CK plans. ***Conclusion*:** It indicated that both systems were capable of producing almost equivalent plan quality and can meet clinical requirements. CyberKnife has higher target dose while EDGE system has more advantages in normal tissue sparing and delivery efficiency.

INTRODUCTION

Stereotactic Body Radiation Therapy (SBRT), or Stereotactic Ablative Radiotherapy (SABR) has grown up to be a significant treatment modality for several years, as an alternative of the conventional radiotherapy in prostate cancer [1-4]. Especially, SBRT has been recognized as an appropriate option in cases of localized prostate cancer [5-9]. The radiobiological rational for prostate SBRT is due to its relatively lower α/β ratio (been estimated at 1.5 Gy) than adjacent organs at risk (OARs), which implies the gains in cost effectiveness and biologically equivalent dose to large fractionated radiotherapy [10-12]. Trials have reported superior biochemical control outcomes for patients with prostate cancer by hypo-fractionation [1-4]. SBRT for prostate cancer was recommended as an alternative to conventionally fractionated regiments according to ASTRO model policy update of 2013, as well as National Comprehensive Cancer Network (NCCN) guidelines on prostate version 2.2014. There remains however the technical limitations in the delivery of such high doses due to the proximity of sensitive normal tissues and organs. Therefore, more conformal radiation and sharper dose fall-off outside the targets are necessary in order to deliver such high dose safely.

Currently, multiple techniques available are developed for SBRT treatments [13, 14], among which CyberKnife® (Accuray Inc., Sunnyvale, CA) system has been known as one of the predominant SBRT facilities applied in the treatment of prostate cancer [14]. CyberKnife (CK) is a frameless image-guided radiotherapy system involving a 6-MV FFF (Flattening Filter Free) linear accelerator mounted on a flexible robotic arm, which makes it capable of delivering radiation from hundreds of non-coplanar directions. Moreover, its fiducial tracking technique allows for real-time tumor position and motion corrections during prostate SBRT treatment. These capabilities would make it produce improved conformal isodose with high precision [15].

Meanwhile, LINAC, using multi-leaf collimator (MLC), can also be used for SBRT by either

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intensity-modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT) [16]. EDGE® (Varian Medical Systems, Palo Alto, CA), an update version of TrueBeam, is one of the typical LINAC-based SBRT system. This dedicated machine is equipped with the HD (high definition) 120 leaf MLC (Multi Leaf Collimator), with two modes of FF (Flattening Filter) and FFF beam delivery [17, 18]. The MLC leaf resolution improvement with 2.5 mm leaf widths which allows more conformal dose delivery to the target. This system is equipped with multiple imaging modalities for treatment localization.

In order to make it clear which technique is superior, many comparative studies have been carried out between the LINAC and CK system for prostate SBRT [16, 19-21]. However, there is no study directly comparing the characteristics of dose distribution of treatment plans between EDGE and CK.

The aim of this study was to make a further study on the properties about emerging treatment technology of EDGE system for making an appropriate option for individualized SBRT treatment. In this study, we performed a comprehensive evaluation of plan quality with the dose performance of EDGE compared to CK SBRT plans for prostate cancer. These comparison results were implemented by adopting both physical and radiobiological indices according to the dose volume histograms (DVHs) calculated on the evaluation software framework developed by our group. The final analyzed results can be used to find out virtues and shortcomings in optimized plans of each technique for making the most appropriate choice in prostate SBRT treatment. Besides, the monitor units (MUs) used and the beam-on times were also compared to examine the delivery efficiency for both systems.

MATERIALS AND METHODS

Case selection and volume definition

Ten patients with localized prostate cancer staged T1-T2b treated using CK SBRT at our institution between 2018 and 2019 were enrolled randomly. Each patient was scanned in head first-supine position, with a full bladder and an empty rectum. Computed tomography (CT) simulation was performed on a Brilliance™ Big Bore 16-slice CT scanner (Philips, Amsterdam, Netherlands) with a slice thickness of 1.5 mm. Clinical target volume (CTV) and critical structures were contoured jointly by oncologist and radiologist based on the fusion of CT and magnetic resonance (MR) images on the MultiPlan® system (Accuray Inc., Sunnyvale CA; version 4.02). CTV was defined as the whole prostate gland, with sizes of 59.15±15.63 cc (median, 61.48 cc). Planning Target Volume (PTV) was expanded from CTV with a 5 mm isotropic margin, except 3 mm posteriorly according to the literatures [1, 2] with sizes of 98.25±23.65 cc (median, 106.47 cc). Organs at risk (OARs) including bladder, rectum, small bowel, femoral heads, penile bulb, and urethra were contoured. The planning CT together with contours mentioned above were transferred to the Varian Eclipse® system (Varian Medical Systems, Palo Alto, CA; version 13.5) for EDGE planning. All methods were carried out in accordance with relevant guidelines and regulations. Informed consent was obtained from the patients for study participation. Consents for publication of data have been obtained from all patients. All the patients included in this study are above 18 years old.

Treatment planning

Two sets of plans were produced with the same CT images and delineated structures. For the purpose of comparison, all the plans were required to prescribe the same dose of 36.25 Gy delivered in 5 fractions and the prescription dose corresponds 100% non-normalized isodose. Dose constraints were set based on the criteria of the RTOG-0938 and previous studies [1, 3, 7, 22]. Required planning constraints are detailed in table 1. The CK plans were carried out with Multiplan® version 4.0.2 using sequential optimization method. A 6 MV FFF photon beam was employed with a dose rate of 800 MU/min and one or two cones with size of 20~30 mm. The plans were optimized with sequential process based on the ray tracing algorithm (RTA). Besides, 5 'shells' expanded isotropically from PTV were used to make steep dose fall-off gradient. At the end of the optimization, beams and time reduction were used to make the plan clinically practical. The VMAT plans were produced for EDGE system with the Eclipse version 13.5 using two full 360° arcs with the same isocenter located at the geometric center of PTV. The 10MV FFF photon beams at a high dose rate of 2400 MU/min was used in the optimization [17, 23]. The plans were optimized with progressive resolution optimizer (PRO) and calculated with the analytical anisotropic algorithm (AAA) with a grid size of 1.5mm.

Table 1. Dose targets and constraints for treatment planning.

Structure	Metrics	Objective
PTV	V_{100} (%)	≥95%
	PIDL (%)	≥75%
Bladder	V_{37Gy} (cc)	<10cc
	V_{100} (%)	<10%
	V_{50} (%)	<50%
Rectum	V_{36Gy}(cc)	<1cc
	V_{100} (%)	<5%
	V_{90} (%)	<10%
	V_{80} (%)	<20%
	V_{75} (%)	<25%
	V_{50} (%)	<50%
Femoral head	V_{40} (%)	<5%
Urethra	V_{37Gy} (%)	<50%
Penile bulk	$V_{29.5Gy}$ (%)	<50%

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Treatment efficiency

The delivery time and the MUs of two kinds of techniques were recorded to estimate the delivery efficiency. The delivery time includes beam-on time and operation interval.

Dosimetric evaluation

Common dose metrics

As is listed in table 2, the maximum, minimum and mean dose (D_{max}, D_{min} and D_{mean}) as well as coverage (V_{100}) of CTV and PTV were evaluated. Meanwhile V_{120}, V_{125} and V_{130} of PTV were also recorded to compare the details of hot spots in target volume. The volumes covered by 37 Gy, 100% and 50% of prescription isodose line (PIDL) for bladder, and that covered by 36 Gy, 100%, 90%, 80%, 75%, 50% of PIDL for rectum were categorized for plan evaluation. Meanwhile, D_{max} and D_{mean} were analyzed for all the OARs. To investigate the details of dose distribution outside PTV, V_{20}, V_{50} and V_{100} of normal tissue were also compared.

Integral dose

The Integral dose (ID) of radiation delivered to each volume was defined in equation (1) according to reference [24]:

$$ID[\mathrm{Gy}\cdot cc]=\overline{D}[Gy]\cdot V[cc]=\sum_{i=1} d_i[Gy]\cdot v_i \quad (1)$$

Where; $\overline{D}[Gy]$ is the mean dose delivered to volume *V[cc]* (where cc—cubic centimeter). v_i is the volume of voxels receiving dose d_i. ID formula was employed to calculate and compare the absorbed dose in target, OARs and the normal tissue, for both irradiation techniques. Since the dose distribution in each volume is heterogeneous，ID was calculated based on differential DVH.

CI, HI and GI

Additionally, conformity index (*CI*), new conformity index (*nCI*), homogeneity index (*HI*) and gradient index (*GI*) were also used to quantify the plan quality. The conformity index (*CI*) and new conformity index (*nCI*) describes how well the dose conforms to the boundary of the target volume and were defined in equations (2) and (3) [25, 26]:

$$CI=\frac{V^{Rx}}{V_{PTV}^{Rx}} \quad (2)$$

$$nCI=\left(\frac{V^{Rx}}{V_{PTV}^{Rx}}\right)\Big/\left(\frac{V_{PTV}^{Rx}}{V_{PTV}}\right) \quad (3)$$

Where; V^{Rx} is the prescription isodose volume while V_{PTV} and V_{PTV}^{Rx} are the volume of PTV and that covered by the PIDL. Smaller *CI* and *nCI* imply a more conformal plan and the ideal values for both indices are 1.0.

The homogeneity index (*HI*) evaluates the degree of uniformity of dose inside the target volume [27]. Mathematically, the index was calculated according to equation (4):

$$HI=\frac{D_2 - D_{98}}{D_P} \quad (4)$$

Where; D_2 (D_{98}) is the dose that covers 2% (98%) of the PTV, and D_P is prescription dose. Usually, *HI* >0, and *HI* = 0 means each voxel of target volume receives the same dose.

The gradient index (*GI*) is implemented to assess the degree of the dose fall-off outside the target [28]. This index was expressed in equation (5):

$$GI=\frac{V_{50}}{V_{100}} \quad (5)$$

Where; V_{50} and V_{100} are the volumes covered by 50% and 100% prescription dose, respectively. A smaller value of *GI* indicates steeper dose fall-off.

Radiobiological evaluation, EUD

The equivalent uniform dose (*EUD*), obtained with the DVH reduction method, is used to convert the inhomogeneous dose distribution into a simple uniform dose [29,30]. The *EUD* calculation was based on the phenomenological model suggested by Niemierko [29] and was defined in equation (6):

$$\begin{cases} EUD=\left(\sum_{i=1} v_i EQD_{2i}^{a}\right)^{1/a} \\ EQD_{2i}=d_i\times\dfrac{\left(\frac{\alpha}{\beta}+\frac{d_i}{n_f}\right)}{\left(\frac{\alpha}{\beta}+2\right)} \end{cases} \quad (6)$$

Where; v_i is the percentage of voxels receiving dose d_i. The v_i and d_i values are acquired from the DVHs and the sum of v_i over all voxels equals to 1. a is a parameter which reflects the dose response property of distinct organs, and in some literatures the parameter n is used with $a=1/n$. In clinical practice, a large negative value is employed to tumor, while large positive and small positive values are used for serial and parallel organs, respectively. a or n values in table 3 were used here for tumor [30], bladder [31], rectum [32], femoral head [28,29], urethra [33] and penile bulk [34]. DVH of different doses per fraction is converted into biologically equivalent physical dose of 2 Gy per fraction (EQD_2) using the linear quadratic (LQ) model according to reference [29]. In the formula of EQD_2, n_f is the number of fractions. The α/β is a parameter from the issue-specific LQ model of the certain organ, determining the fractionation sensitivity. α/β values in table 3 were used here for tumor [10-12], bladder [35],

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rectum [36], femoral head [37]. Since there was no clinical data of α/β values for urethra and penile bulk, $\alpha/\beta=3.0$ was applied here as was usually used for most OARs.

Table 2. Comparison of dose-volume parameters and integral doses of target and OARs.

	EDGE±SD	CK±SD	p
CTV			
D_{max} (Gy)	47.64±0.40	46.57±0.32	<0.01
D_{min} (Gy)	35.31±0.80	32.84±2.23	<0.01
D_{mean} (Gy)	42.07±1.26	43.23±0.45	<0.01
V_{100}	99.75±0.36	99.50±0.60	0.34
ID (Gy·cc)	2410.33+649.46	2483.49+682.37	0.02
PTV			
D_{max} (Gy)	47.64±0.40	46.57±0.32	<0.01
D_{min} (Gy)	26.82±1.68	28.36±1.81	0.12
D_{mean} (Gy)	40.77±0.75	41.71±0.46	<0.01
V_{100} (%)	95.00±0.00	95.35±0.53	0.07
V_{120} (%)	24.45+10.02	41.04+12.22	<0.01
V_{125} (%)	7.91+5.94	4.97+4.21	0.11
V_{130} (%)	0.32+0.03	0.00+0.00	<0.01
ID (Gy·cc)	3928.84+871.05	4041.52+914.32	<0.01
Bladder			
D_{max} (Gy)	39.51±3.51	42.34±1.28	0.02
D_{mean} (Gy)	11.00±3.23	18.95±4.64	<0.01
V_{37Gy} (cc)	1.09±1.97	3.74±2.07	0.01
V_{100} (%)	0.92±1.33	3.55±2.27	0.01
V_{50} (%)	19.95±6.71	45.22±18.72	<0.01
ID (Gy·cc)	1720.11+913.09	3037.32+1873.76	<0.01
Rectum			
D_{max} (Gy)	35.61±1.28	38.94±0.91	<0.01
D_{mean} (Gy)	13.14±1.35	14.43±2.14	0.06
V_{36Gy} (cc)	0.07±0.18	0.73±0.33	<0.01
V_{100} (%)	0.01±0.12	0.79±0.45	<0.01
V_{90} (%)	0.91±0.89	4.39±1.60	<0.01
V_{80} (%)	4.57±1.62	9.47±2.89	<0.01
V_{75} (%)	7.08±1.96	11.40±3.41	<0.01
V_{50} (%)	29.95±3.82	30.48±8.04	0.86
ID (Gy·cc)	958.67+286.66	1086.39+367.92	0.02
LFH			
D_{max} (Gy)	14.80+2.10	13.63+1.15	0.12
D_{mean} (Gy)	7.83+1.34	8.47+1.30	0.19
ID (Gy·cc)	568.43+156.16	604.17+136.18	0.25
RFH			
D_{max} (Gy)	14.43+2.51	13.30+1.13	0.19
D_{mean} (Gy)	7.84+1.36	8.44+1.07	0.50
ID (Gy·cc)	577.59+149.27	605.45+104.07	0.38
Urethra			
D_{max} (Gy)	24.91+11.90	34.75+6.67	<0.01
D_{mean} (Gy)	4.09+2.04	14.97+2.13	<0.01
ID (Gy·cc)	152.82+246.74	410.03+406.72	<0.01
Penile bulk			
D_{max} (Gy)	9.34+11.82	23.17+10.02	<0.01
D_{mean} (Gy)	5.29+7.24	13.96+9.49	<0.01
ID (Gy·cc)	17.85+32.88	38.92+42.16	<0.01
Normal tissue			
V_{20} (cc)	1888.97+351.67	2749.98+714.67	0.02
V_{50} (cc)	280.83+51.54	331.44+71.43	0.13
V_{100} (cc)	6.87+1.31	23.64+6.16	<0.01
ID (Gy·cc)	41384.29+6323.47	60572.53+9831.61	<0.01

SD: standard deviation; Dmax: maximum dose; Dmin: minimum dose; Dmean: mean dose; Vxx: percentage of PTV or OAR volume receiving at least xx% dose of 36.25 Gy; VxxGy: volume of PTV or OAR receiving at least xxGy; ID: integral dose; LFH: left femoral head; RFH: left femoral head.

Table 3. EUD, TCP and NTCP model parameters.

	α/β Gy)	a	γ_{50}	TCD50 (Gy)	Endpoint
Tumor	1.5	-10	1.4	57.3	5-year ASTRO free from recurrence
	α/β Gy)	**n**	**m**	**TD50(Gy)**	
Bladder	7.5	0.06	0.195	72.5	RTOG grade 2 acute genitourinary
Rectum	5.4	0.09	0.13	76.9	Grade≥2 late rectal toxicity
LFH	6.0	0.25	0.12	65	Necrosis
RFH	6.0	0.25	0.12	65	Necrosis
Urethra	3.0	0.3	0.37	70.7	clinical stricture/ perforation
Penile bulk	3.0	0.74	0.86	70.1	erectile dysfunction≥1

TCP

EUD based tumor control probability (TCP) proposed by Niemierko can be expressed with logistic equation according to equation (8) [38]:

$$TCP = \frac{1}{\left(1+\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (8)$$

Where; TCD_{50} is the dose for achieving a 50% probability of tumor control as the tumor is irradiated homogeneously, and γ_{50} is the slope of sigmoidal dose response curve of tumor. TCD_{50}=57.3 Gy and γ_{50}=1.4 were used here with the endpoint of 5-year ASTRO free from recurrence according to reference [39].

NTCP

The normal tissue complication probability (NTCP) were calculated based on the Lyman-Kutcher-Burman (LKB) model [29, 30], in which NTCP for an organ to equivalent uniform dose (EUD) is given by equation (9):

$$NTCP = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{x} e^{-t^2/2}dt \quad (9)$$

Where;

$$x = (EUD - TD_{50})/(m \cdot TD_{50}) \quad (10)$$

m is a dimensionless parameter and TD_{50} is the whole organ dose for which NTCP is 50%. TD_{50} and m for bladder [31], rectum [32], femoral head [29,30], urethra [33] and penile bulk [34] with definitive clinical endpoints were listed in table 3.

Statistical analysis

All the parameters were calculated from the DVHs with an in-house program based on C++. Statistical analyses were carried out using IBM SPSS Statistics version 21 (SPSS Inc.Armonk, NY). All statistical data are evaluated in terms of x±s. Before comparison, Shapiro-Wilk (S-W) test was carried out for each data set, and p>0.05 conforms to the normal distribution. The data conforming to the normal distribution

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adopts the paired t-test, while the data not conforming to the normal distribution adopts the Wilcoxon rank sign and non-parametric test. A p value <0.05 was considered to reveal statistical significance.

RESULTS

Dose-volume metrics

All planning constraints detailed in table 1 were met by both EDGE and CK plans. The comparison of isodose lines from 20% to 120% of the prescription dose for a selected case is illustrated in figure 1. Obviously, both plans are very conformal and provide adequate coverage of PTVs. Besides, we can find that the 100% PIDL (with red color) of EDGE plan is closer to PTV boundary than that of CK plan.

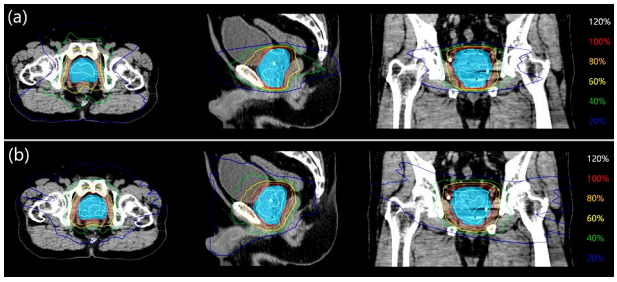

Figure 1. Dose distribution of EDGE **(a)** and Cyberknife **(b)** plans for a selected case. The 100% isodose line of both plans were normalized to 36.25 Gy.

The averaged DVHs of CTV, PTV, bladder, rectum, left and right femoral heads, urethral as well as penile bulk are displayed in figure 2(a)-(h), respectively. The values of dose-volume parameters of target and OARs are detailed in table 2. From both figure 2(a)-(h) and table 2, CTV and PTV coverage of EDGE and the CK plans were found to be of similar levels and showed no obvious difference. The mean dose (D_{mean}) of CTV and PTV are higher for CK, indicating larger ablation effect within target.

The bladder DVH indices (D_{max}, D_{mean}, V_{37Gy}, $V_{100\%}$ and $V_{50\%}$) from the EDGE plans were also statistically lower than the CK plans, presenting a distinct reduction of irradiation. The EDGE plans achieved slightly better rectum protection with respect to D_{max}, V_{36Gy}, $V_{100\%}$, $V_{90\%}$, $V_{80\%}$ and $V_{75\%}$. The irradiation dose of right (RFH) and left femoral heads (LFH) for both systems were very low and showed no significant difference in terms of D_{max} and D_{mean}. Moreover, D_{max} and D_{mean} of urethra and penile bulk were much lower for EDGE plans. The DVH of normal tissure outside PTV were displayed in figure 3(a). As were shown in figure 3(b)-(d), the volumes of normal tissue covered by 20%, 50% and 100% PIDL were all lower for EDGE plans, which were associated with better conformity and steeper dose fall-off gradient. Meanwhile, the integral dose of target volumes were a little larger for CK plans as were shown in figure 3 (e). Otherwise, the ID of OARs were much lower for bladder, urethral, penile bulk as well as normal tissure outside PTV for EDGE plans, while there were no much significant difference of ID for rectums and femoral heads.

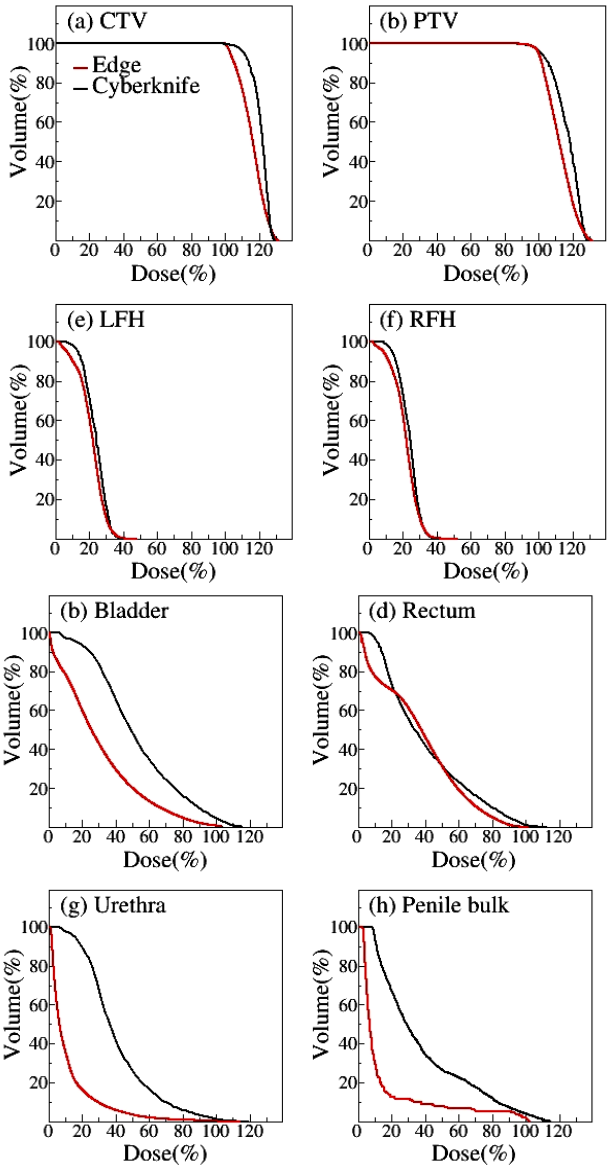

Figure 2. Averaged DVH comparison of **(a)** CTV, **(b)** PTV, **(c)** bladder, **(d)** rectum, **(e)** left femur, **(f)** right femur, **(g)** urethral and **(h)** penile bulk between EDGE and CK plans collected from 10 patients. The red curves are for EDGE plans and the black ones are for the CK plans.

Dosimetric indexes and delivery efficiency

The average of dosimetric indexes including *CI*, *nCI*, *HI* and *GI* are listed in table 4. It was apparent that EDGE plans are more conformal with *CI* (*nCI*) value of 1.07±0.03 (1.13±0.03) compared to that of the CK plans with 1.20 ±0.03 (1.25±0.04), which was consistent as shown in figure 1. The higher average HI value of 0.26±0.03 for the EDGE plans compared to that of CK with 0.24±0.03 (table 4) means the hot point is smaller in CK plans than that in EDGE. A slightly steeper GI was achieved in EDGE plans but there was no significant difference. In addition, the

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delivery efficiencies were quantified in terms of monitor units (MUs) and delivery time. It indicated that the average MUs and delivery time were reduced by 72% and 91% using EDGE compared to CK. This means less additional irradiation and higher treatment efficiency by utilizing EDGE.

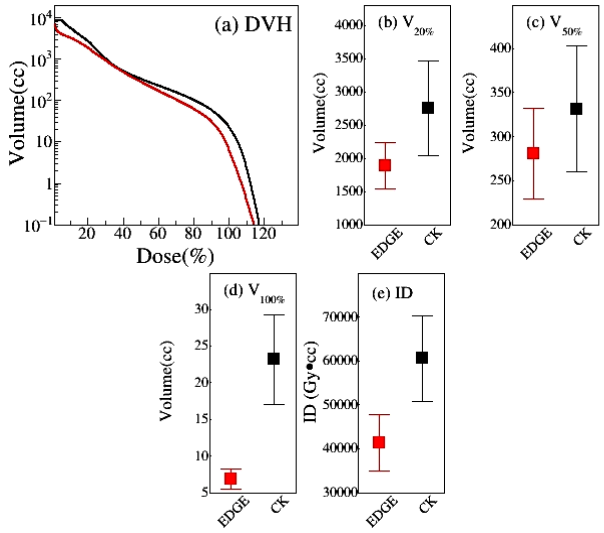

Figure 3. Comparisons of dose distribution outside PTV. **(a)** Avergae DVH comparison of normal tissue; **(b)-(d)** Normal tissue volumes covered by 20%, 50% and 100% of prescription isodose lines; **(e)** Integral dose of normal tissue outside PTV. The red lines are for EDGE plans and the black ones are for the CK plans.

Table 4. Average values of CI, nCI, HI and GI, MUs and delivery time per fraction between the EDGE and the CyberKnife plans.

	EDGE±SD	CK±SD	p
CI	1.07±0.03	1.20±0.03	<0.01
nCI	1.13±0.03	1.25±0.04	<0.01
HI	0.26±0.03	0.24±0.03	0.09
GI	3.70±0.30	3.87±0.21	0.09
MUs	2602.07±330.41	9419.55±1619.01	<0.01
Delivery time(min)	4.10±0.09	46.35±3.87	<0.01

CI: conformity index; nCI: new conformity index; HI: homogeneity index; GI: gradient index; MUs: monitor units.

Radiobiological comparison

The radiobiological parameter EUD extracted from DVHs for CTV, bladder, rectum, left and right femoral heads, urethral and penile bulk, as well as TCP of CTV and NTCP of all these OARs were compared between the EDGE and the CK plans. The average values, standard deviation (SD), and *p* values were detailed in table 5. The CK plans provided a slightly greater *EUD* and comparatively higher TCP than the EDGE plans. However, the larger *EUD* for bladder, rectum, urethral and penile bulk in CK plans were obtained, which indicated dramatically increasing *NTCP* of CK compared to EDGE plans for the four organs, respectively. The NTCP of femoral heads were too small to be considered, and showed no significant difference.

Table 5. Comparison of radiobiological parameters (EUD, TCP and NTCP) between the EDGE and the CK plans.

	EUD (Gy)			TCP/NTCP (%)		
	EDGE±SD	CK±SD	p	EDGE± SD	CK±SD	p
CTV	113.04± 6.83	119.81± 2.99	0.02	97.69± 0.82	98.40± 0.22	0.03
Bladder	38.79± 5.15	46.47± 3.85	<0.01	0.29± 0.18	1.93±1.30	<0.01
Rectum	38.01± 2.21	44.76± 1.91	<0.01	3.93± 0.84	7.27±1.29	<0.01
LFH	9.23± 1.05	9.01±1.38	0.71	<0.0001	<0.0001	0.94
RFH	9.16± 1.21	8.94±1.10	0.72	<0.0001	<0.0001	0.96
Urethra	12.03± 5.80	24.99± 4.60	<0.01	1.41± 0.93	4.24±1.54	<0.01
Penile bulk	7.41± 14.83	20.84± 20.67	<0.01	15.55± 7.26	21.76± 11.18	<0.01

SD: standard deviation; EUD: equivalent uniform dose; TCP: tumor control probability; NTCP: normal tissue complication probability.

DISCUSSION

In this study, we compared the plan quality of EDGE and CK in terms of dosimetric properties, delivery efficiency and predicted biological outcomes for prostate SBRT treatment. Despite both systems were able to achieve excellent dose distribution according to the results, EDGE was a little superior in terms of target conformity and OAR sparing. The high resolution of MLCs make account for the more conformal dose distribution of PTV for EDGE. The main reasons for OAR sparing differences could be explained in two aspects. First and foremost, the plan optimization processes of the Multiplan version 4.0.2 and Eclipse 13.5 are very different. In the Multiplan, we could only set the maximum doses of OARs as constraints and optimize the mean doses of OARs, while in the Eclipse, more constraints could be set on the DVH curves of each OAR. Secondly, the beam arrangements in planning optimization may play important roles for the dose distribution. CK offers superiority of highly flexible beam angles, which delivered noncoplanar beams from more directions while EDGE rarely used noncoplanar beams in the region of abdomen due to mechanical limitations. However, CK did not benefit from this advantage in this study because the beams of CK were mainly distributed in directions perpendicular to cranio-caudal (CC) direction in these plans, as the final results of beam-angle optimization in light of the anatomical position of the prostates. The most beneficial beam angles were similar to those from two full 360 rotation arcs (178 segments for each plan) of EDGE which were rotated around CC direction.

As noted above, EDGE had the shortened average delivery time and the fewer MUs largely. Lessening MUs means less scatter dose, which may lower

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the probability of secondary malignancies. On the other hand, decreased delivery time of EDGE can potentially reduce the effects of intra-fractional motion, and make the patients more comfortable. The VMAT technique, which delivers from a large number of angles with fewer control points, has been showed to decrease the number of MUs significantly, along with even lower MUs for dual-arc VMAT plans under the same condition as reported by Quan *et al.* [40]. Moreover, EDGE system has 10 FFF mode delivering the maximum high dose rate of 2400 MU per minute which severely shortens the beam-on time [18. 23].

Additionally, there also exists a concern for tumor and adjacent organs position variations throughout the course of treatment after the online match per fraction [41-43]. The intra-fraction prostate displacements were reported to be >3mm and >5 mm were 24% and 5% of fractions respectively [43]. In this case, the target localization and real-time tracking systems are necessary to improve confidence in radiation dosimetry. Previous studies showed that CK has the competitive in light of target localization to deliver accurately in comparing conventional linear accelerator [44]. For the CK, two kilovoltage X-ray generators and two hereafter cameras are incorporated to finish fiducial tracking for prostate motion [45]. Very small set-up errors were observed with 1.8mm in the anterior posterior direction and 1.4mm in the superior inferior direction [46]. However, EDGE system, designed for SBRT or SRS, has been improved to integrate Calypso 4D system capable of monitoring target position on the basis of radiographic transponder locations. Calypso system was reported to present a treatment accuracy of average 3D difference of 1.5 mm in dose delivery [47].

Several limitations should be recognized in this investigation. Firstly, because the representative version of CyberKnife G4 system with the fixed cone is most commonly used, it was selected to compare to the latest EDGE system in our study. The latest generation of CK system M6™, with IRIS collimator and InCise MLC, may increase the output rate and conformal dose distribution as well as to reduce delivery time. Otherwise, the radiobiological parameters presented in this study are highly dependent on the model and related parameters. Therefore, the radiobiological responses could only be regarded as references when making clinical decisions. Further studies on clinical trials are required to collect practical experience and find out which is the valuable option for localized prostate cancer.

CONCLUSION

A comparative quantitative assessment of the dosimetric and radiobiological indices of plans for both CybkerKnife and EDGE systems was made in this study. We confirm that radiotherapy systems with different characteristics should be investigated and utilized to help radiation oncologists choose a proper SBRT method for each individual patient to get better therapeutic effects. EDGE system can be used as an option for prostate cancer, especially for patients who cannot remain lying in bed for a long time.

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