

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

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Abstract

Aims: The aim of this study was to make a quantitative comparison of plan quality between MLC-based EDGE system and the cone-based CyberKnife system in stereotactic body radiation therapy (SBRT) for patients with localized prostate cancer.

Materials and methods: Ten patients with prostate volumes ranging from 34.65 to 82.16 cc were used for prostate SBRT. Treatment plans were created for both EDGE and CyberKnife G4 systems using the same dose-volume constraints. Dosimetric indices including Planning Tumor Volume (PTV) coverage, conformity index (C), new conformity index (nC), homogeneity index (HI), gradient index (G) were applied for target, while the sparing of critical organs, including bladder, rectum, femoral heads, urethra, penile bulk and normal tissue outside PTV), were evaluated in terms of various dose-volume metrics and integral dose (ID). Meanwhile, the required delivery time and number of monitor units (MUs) during irradiation were measured to estimate the treatment efficiency. The radiobiological indices such as equivalent uniform dose (EUD), tumor control probability (TCP) and the normal tissue complication probability ($NTCP$) were also analyzed.

Results: All dose constraints were achieved by both systems. It showed that the EDGE plans results were closest to the CK plans results in terms of PTV coverage, HI and G . For EDGE, more conformal dose distribution in the target as well as reduced exposure of critical organs were obtained together with reduction of 91% delivery time and 72% monitor units. 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.

Conclusions: Our study indicated that both systems were capable of producing almost equivalent plan quality and can meet clinical requirements. CyberKnife G4 system has higher target dose while EDGE system has more advantages based on the considerations of normal tissue sparing and delivery efficiency. With abundant clinical experience, CK provides accurate SBRT treatment with high quality. EDGE system also can be considered to be an option for SBRT treatment for localized prostate cancer treatment.

1. 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 rationale 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 multileaf collimator (MLC), can also be used for SBRT by either 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. Therefore, it is essential 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 our 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 some 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.

2. Materials And Methods

2.1 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, the 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 literature [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.

2.1 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 were 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 1.5 mm.

Table 1
Dose targets and constraints for treatment planning.

Structure	Metrics	Objective
PTV	$V_{100}(\%)$	$\geq 95\%$
	PIDL(%)	$\geq 75\%$
Bladder	$V_{37Gy}(cc)$	$< 10\text{ cc}$
	$V_{100}(\%)$	$< 10\%$
	$V_{50}(\%)$	$< 50\%$
Rectum	$V_{36Gy}(cc)$	$< 1\text{ cc}$
	$V_{100}(\%)$	$< 5\%$
	$V_{90}(\%)$	$< 10\%$
	$V_{80}(\%)$	$< 20\%$
	$V_{75}(\%)$	$< 25\%$
	$V_{50}(\%)$	$< 50\%$
Femoral head	$V_{40}(\%)$	$< 5\%$
Urethra	$V_{37Gy}(\%)$	$< 50\%$
Penile bulk	$V_{29.5Gy}(\%)$	$< 50\%$
<i>V_{xx}, percentage of PTV or OAR volume receiving at least xx% dose of 36.25 Gy; PIDL, Prescription isodose line; V_{xxGy}, volume of PTV or OAR receiving at least xxGy.</i>		

2.2 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.

2.3 Dosimetric evaluation

2.3.1 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.

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			

	EDGE ± SD	CK ± SD	p
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

	EDGE ± SD	CK ± SD	p
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

2.3.2 Integral dose

The Integral dose (ID) of radiation delivered to each volume was defined as follows according to reference[24]: (see Equation 1 in the Supplementary Files)

where \bar{d} 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 were calculated based on differential DVH.

2.3.3 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 was defined as follows [25, 26] : (see Equations 2 and 3 in the Supplementary Files)

where V^{Rx} is the prescription isodose volume while V_{PTV} and 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 the following equation: (see Equation 4 in the Supplementary Files)

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 as follows: (see Equation 5 in the Supplementary Files)

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

2.4 Radiobiological evaluation

2.4.1 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 as: (see Equation 6 in the Supplementary Files)

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], 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 of OARs,

Table 3
EUD, TCP and NTCP model parameters.

	$\alpha/\beta(\text{Gy})$	a	γ_{50}	TCD50(Gy)	Endpoint
Tumor	1.5	-10	1.4	57.3	5-year ASTRO free from recurrence
	$\alpha/\beta(\text{Gy})$	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

2.4.2 TCP

EUD based tumor control probability (TCP) proposed by Niemierko can be expressed with logistic equation [38]: (see Equation 8 in the Supplementary Files)

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 $\gamma_{50} = 1.4$ were used here with the endpoint of 5-year ASTRO free from recurrence according to reference[39].

2.4.3 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 (see Equation 9 in the Supplementary Files)

where (see Equation 10 in the Supplementary Files)

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.

2.5 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). A paired t-test was performed to analyze the difference between EDGE and CK plans, and a p value < 0.05 was considered to reveal statistical significance.

3. Results

3.1 Dose-volume metrics

All planning constraints detailed in Table 1 were met by both EDGE and CK plans. The comparison of isodose lines from 20–120% of the prescription dose for a selected case is illustrated in Fig. 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.

The averaged DVHs of CTV, PTV, bladder, rectum, left and right femoral heads, urethral as well as penile bulk are displayed in Fig. 2(a)-(h), respectively. The values of dose-volume parameters of target and OARs are detailed in Table 2. From both Fig. 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 and left femoral heads 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 volumes 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. Otherwise, the ID of OARs were much lower for bladder, urethral, penile bulk as well as normal tissue outside PTV for EDGE plans, while there were no much significant difference of ID for rectums and femoral heads.

3.2 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 Fig. 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 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.

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

	EDGE \pm SD	CK \pm 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

3.3 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.

4. 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. Both of the two techniques were able to produce clinically acceptable plans with adequate target irradiation and normal tissue sparing. Despite both systems were able to achieve excellent dose distribution according to the results above, EDGE had a little better performance in dosimetric results of conformity of PTV and better OAR sparing.

The EDGE plans were optimized using high definition HD120 MLCs (with minimum spatial resolution of 2.5 mm) on the X axis with even littler size of gap on the Y axis, while the CK plans were made by 1–2 circular cones with size of 20~30 mm. The high resolution of MLCs make it easier to reach more conformal dose distribution of PTV for EDGE, which will largely reduce the number of sub-fields.

The main reasons for the normal tissue sparing differences were due to the different characteristics of the two systems, which 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, several constraints could be set on the DVH curves of each OAR. This is one of the major reasons for superior OARs sparing of EDGE system. Further improvement for CK plan is feasible, if the optimization algorithm of Multiplan® evolves. Secondly, the beam arrangements in the process of planning optimization may play important roles for the dose distribution. CK offers superiority of highly flexible angles, which delivered noncoplanar beams from all directions moved by the robotic arm while EDGE rarely used noncoplanar beams in the region of abdomen due to mechanical and geometrical limitations. However, the 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, as displayed in Table 4. Lessening treatment time means less scatter dose, which may lower 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 10FFF mode delivering the maximum high dose rate of 2400 MU per minute which severely shortens the beam-on time [18, 23].

The radiobiological parameters in terms of EUD and TCP (NTCP) were calculated from DVHs, as showed in Table 5. The results indicated that the EDGE plans have slightly reduced CTV EUD than the CK plans, the results of which were in agreement with these of dosimetric evaluation. The mean EUD were lower for the OARs such as bladder, rectum, urethral and penile bulk in the EDGE plans in accordance with the calculated lower NTCP values consequentially. Both groups of plans were able to maintain high EUD to the tumors and yield good tumor TCP while low NTCP of normal structures were obtained in relation to late toxicity effects. For predicted clinical benefits, this two treatment modalities can be considered to be safe.

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 > 3 mm 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 1.8 mm in the anterior posterior direction and 1.4 mm 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]. Thus EDGE has similar performance against motion uncertainties. For this reason, we delineated target margins for EDGE system according to the same protocols used for the CK. For all that, EDGE is lack of practical experience clinically by Calypso 4D system compared to CK.

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.

5. Conclusion

A comparative quantitative assessment of the dosimetric and radiobiological indices of plans for both CyberKnife 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.

List Of Abbreviations

SBRT: stereotactic body radiation therapy; PTV: planning tumor volume; CI: conformity index; nCI: new conformity index; HI: homogeneity index; GI: gradient index; ID: integral dose; EUD: equivalent uniform dose; TCP: tumor control probability; NTCP: normal tissue complication; MUs: monitor units; SABR: Stereotactic Ablative Radiotherapy; OAR: organ at risk; NCCN: National Comprehensive Cancer Network; MLC: multileaf collimator; FF: Flattening Filter; FFF: Flattening Filter Free; DVH: dose volume histogram; CT: computed tomography; MR: magnetic resonance; AAA: analytical anisotropic algorithm; PIDL: prescription isodose line; LQ model: Linear Quadratic model; SD: standard deviation.

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board of our hospital.

Consent for publication

The consents for publication of data have been obtained from patients.

Availability of data and materials

Not applicable.

Competing interests

The authors state that they have no competing interests.

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Authors' contributions

Zhitao Dai: participation in the whole work; perception and design; generating CK plans; drafting of the article; data analysis;final approval of the version to be published.

Lian Zhu: re-generating the EDGE plans and drafting the manuscript.

Tingting Cao: data analysis;drafting of the article.

Aihua Wang: re-generating the EDGE plans.

Xueling Guo: generating CK plans;data analysis.

Yongming Liu: generating CK plans.

Yayun Zhuang:re-generating the EDGE plans.

Peiyong Yang:executing plan on EDGE system.

Ning Li: drafting and final approval of the version to be published.

Huojun Zhang: perception and final approval of the version to be published.

Zuoling Xiang: final approval of the version to be published.

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Figures

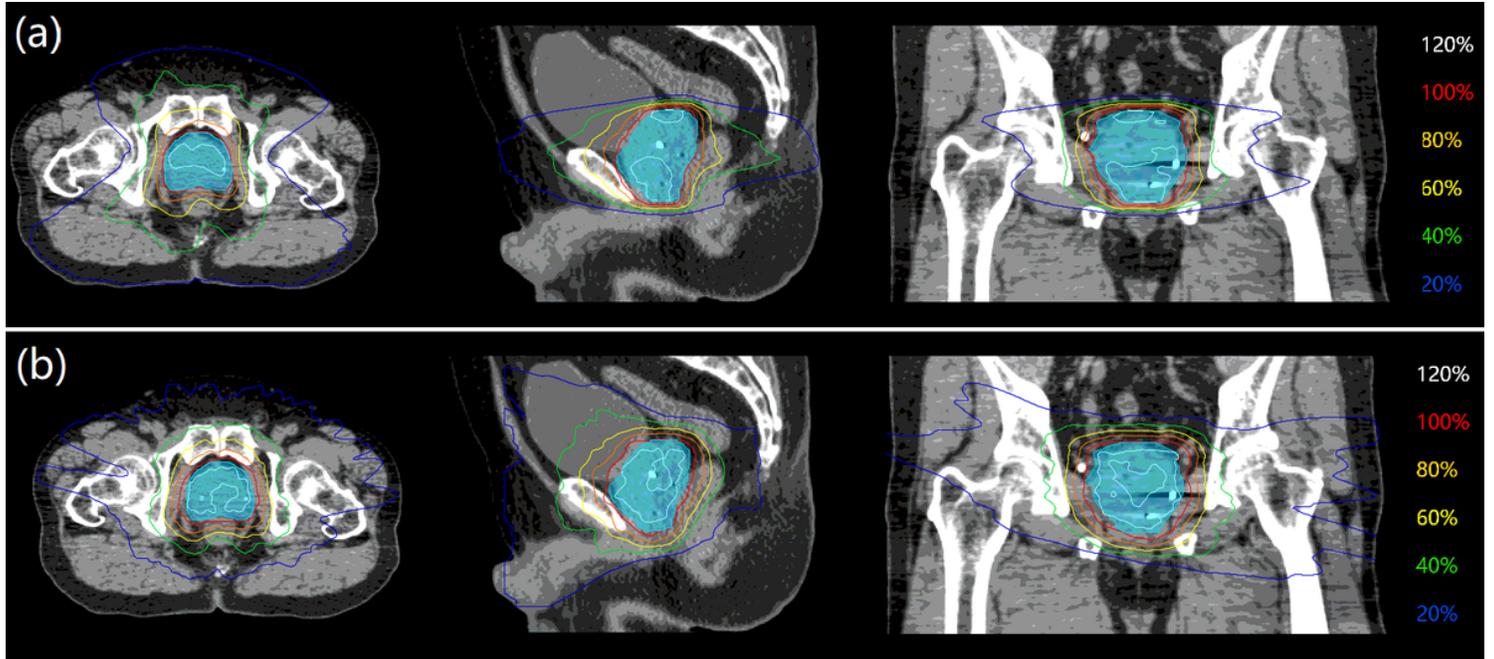


Figure 1

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.

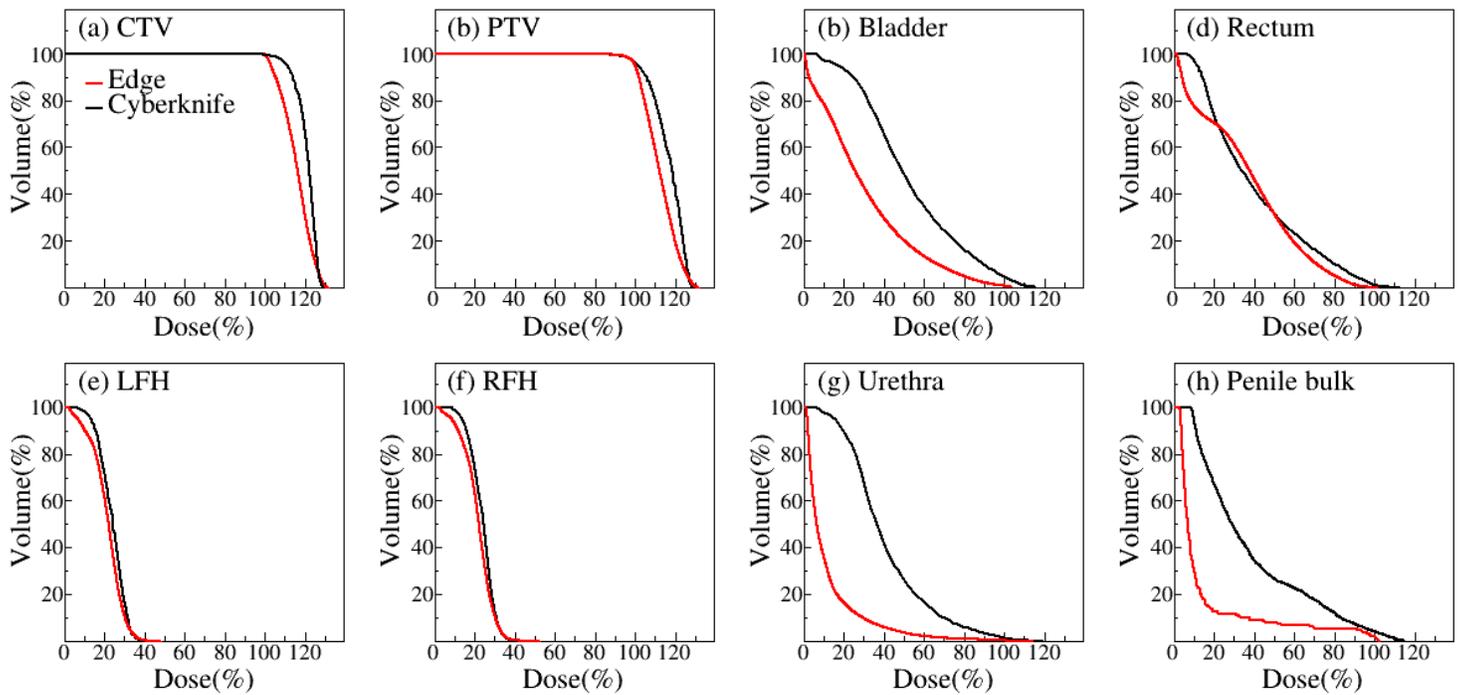


Figure 2

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.

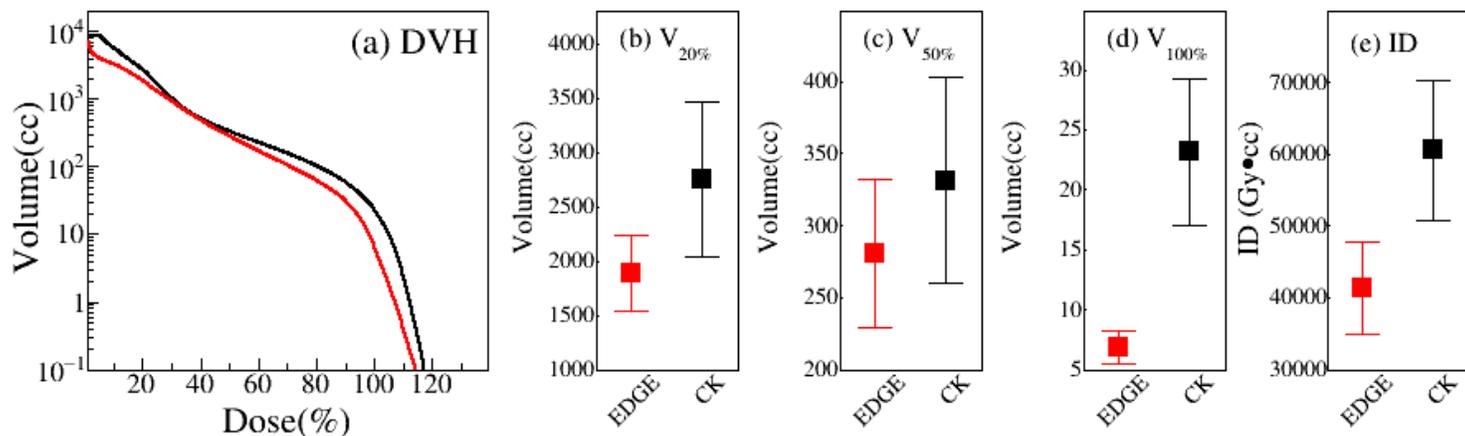


Figure 3

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.

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