Dosimetric Comparison of Stereotactic Body Radiotherapy and Intensity-Modulated Radiotherapy to Deliver Hypofractionated Radiotherapy in Organ-Confined Prostate Cancer

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Abstract

We compared the dose conformity, homogeneity, dose to organs at risk, and remaining volume at risk of two radiotherapy techniques --stereotactic body radiotherapy and intensity-modulated radiotherapy (IMRT) to deliver hypofractionated radiotherapy in organ-confined prostate cancer. Eleven successive patients treated on the CyberKnife stereotactic robotic radiosurgical system were taken up for this study. The CT images, including the structures contoured, were imported through DICOM RT from the Multiplan (Accuray Inc., Sunnyvale, CA, USA) treatment planning system to the Plato Sunrise treatment planning system (Nucletron, The Netherlands) for creating IMRT treatment plans on the Linac. Treatment planning was done for five fractions, each fraction prescribed to a dose of 7.25 Gy to the planning target volume. Dose volume histograms were generated for the CyberKnife and Linac treatments for comparison. As per our protocol, a plan was considered adequate if at least 95% of planning target volume received the prescribed dose and satisfied the following constraints: a) volume of the rectum receiving 36Gy (V36) to < 1cc and b) volume of the bladder receiving 37Gy (V37) to < 10cc. Both the treatment techniques plans resulted in adequate planning target volume coverage (p value for D95, D90, D5, and V100% was 0.402, 0.97, 0.013, and 0.012, respectively). CyberKnife plans were more conformal (p value 0.001). Remaining volume at risk dose was significantly less in all CyberKnife plans at [V100% (p=0.01), V95% (p=.004), V90% (p=.001), V80% (p=0.02), V70 (p=0.03), V40% (p=0.021), and V30% (p=0.001)] dose levels. The mean dose to rectum was lower in the CyberKnife plans (The p value for V100%, V80%, V50% and V30% dose levels was 0.02, 0.0001, 0.0002, and 0.12, respectively).

Categories: Radiation Oncology, Urology
Keywords: prostate, cancer, imrt, cyberknife, sbrt, hypofractionation

Introduction

The treatment of organ-confined prostate cancer by external radiotherapy has evolved over a period of time from the conventional two-dimensional to high precision techniques, like 3D conformal radiotherapy, intensity-modulated, and image-guided radiotherapy. The main advantage of these high precision radiation techniques has been the potential for dose escalation in the range of 76-80 Gy without experiencing any undue rectal or bladder morbidity. There are several randomized Phase 3 trials demonstrating significant improvement in five years outcomes in organ-confined prostate cancer at these escalated doses [1-2].

The conventional fractionation used in intensity-modulated radiotherapy (IMRT) is usually 180-200 cGy/fraction, five fractions a week delivered over a period of around eight weeks. This has logistic implications in terms of work productivity and the cost of the treatment. Hypofractionation is an attractive concept in prostate cancer. The treatment is over in a short time, resulting in significant socioeconomic benefits for the patient. The radiobiologic rationale for hypofractionation in prostate cancer is the hypothesis that prostate cancer has a low α/β ratio (1.5-3), as suggested by various authors [3-5]. Hypofractionation in prostate cancer has been practiced as early as in 1993 when the present sophisticated radiotherapy techniques were not available. Two hundred and thirty-two prostate cancer patients were treated at London with a fractionation schedule of 6x6Gy with impressive results and without any undue morbidity [6]. Manchester reported their experience with a hypofractionated schedule of 15x 3.1 Gy [7]. Hypofractionation in prostate cancer can be delivered either by external radiotherapy, i.e. 3-D conformal radiotherapy, IMRT, stereotactic body radiotherapy (SBRT), or high dose rate (HDR) brachytherapy [8].

There are reports of hypofractionation schedules with IMRT as well, showing the potential of delivering high doses per fraction without undue morbidity [9]. There has been also interest in SBRT in organ-confined prostate cancer, based mainly on the encouraging results obtained with high-dose-rate brachytherapy. Stereotactic body radiotherapy aims to deliver large doses per fraction to the target volume, while minimizing the dose to the surrounding critical normal structures. Improvements in image guidance tools, particularly frequent online tracking, have made delivery of stereotactic body radiotherapy feasible, reliable and safe.

The CyberKnife is one such machine among others available to deliver SBRT. Different institutions follow different image guidance protocols in the delivery of IMRT. At our institution, daily KV cone beam CT is done everyday before starting the radiotherapy. However, hypofractionation by no means can be considered the standard of care in the management of organ-confined prostate cancer. The ongoing PACE multi-institutional trial will probably be able to throw more light on this. This study is an international multicenter randomized study of organ-confined low and intermediate risk prostate cancer and is composed of two parallel randomization schemes based on applicability of surgery as a treatment for the patient. Patients for whom surgery is a consideration are randomized to either laparoscopic or da Vinci prostatectomy or CyberKnife prostate SBRT. Patients for whom surgery is not a consideration are randomized to either conventionally fractionated radiation therapy or CyberKnife prostate SBRT. Efficacy, toxicity and quality of life outcomes will be compared across the pairs in each randomization.

Materials And Methods

Traditionally, treatment planning systems for IMRT in prostate cancer use seven to nine isocentric non-opposed beams. The CyberKnife Multiplan treatment planning system uses non-isocentric beams that could be directed from innumerable different angles to deliver such treatments. Both types of planning system use inverse planning software. IMRT plans for the step-and-shoot technique were done using Plato Sunrise planning system, version 2.7v (Nucletron B.V, The Netherlands). The inverse planning optimization algorithm used is Konrad Optimization developed by MRC system, Heidelberg, Germany using gradient search method. The absolute dose calculation is based on the pencil beam dose calculation algorithm developed by Bortfield, et al. [10]. The algorithm calculates the dose using the percentage depth dose (PDD) for the field size at source to skin distance (SSD), the off-axis ratio (OAR) and the output factor. For in-homogeneity correction, equivalent path length method is employed. The CyberKnife plans done with Multiplan planning system version 3.5.4 (Ms. Accuray, Sunnyvale, USA) uses sequential optimisation programme. The sequential optimization programme differs from the conventional optimization, where multiple objectives are grouped in a single cost function and optimised simultaneously. The sequential optimization is executed sequentially

as a series of individual optimization steps. The optimization steps are meant for target conformality, minimisation of maximum or mean dose to the OAR and minimising MU. The multiplan dose calculation is based on a ray-racing algorithm, which basically uses beam parameters namely, tissue phantom ratio (TPR), off-centre ratio (OCR) and the output factor, that are stored in the system [11]. For in-homogeneity correction effective path length along the central axis is used. The dose calculation algorithm approach is the same for both the planning systems. Hence, it can be mentioned that the difference in final dose distribution is solely due to the optimization approach and the resultant beamlets (which again depends on the mechanical constraints of the treatment machine), as same goals are set for the target coverage and OAR, in both the planning systems.

For patients undergoing CyberKnife planning, four gold fiducials were placed in the prostate transperineally or transrectally. A week later, planning CT and MRI were done without a bladder catheter. Real time tracking during treatment was done with the help of roof-mounted x-ray imaging sources which take orthogonal images either for every beam or at some specified intervals set in the system for verifying the fiducials position. The position of these fiducials was automatically registered with the digitally reconstructed radiographs from the planning CT for online tracking of intrafractional translational and rotational movements of the prostate. A dose of 36.25Gy in five fractions was prescribed to the PTV. The PTV was defined as the prostate with 5 mm margin all around, excluding the seminal vesicles. The dose-volume constraints used were to limit

a) Volume of the rectum receiving 36Gy (V36) to < 1cc

b) Volume of bladder receiving 37Gy (V37) to < 10cc.

The Multiplan treatment planning system uses iterative or sequential optimization using either a combination of fixed collimators or the Iris variable aperture collimator (Accuray Incorporated, Sunnyvale, CA, USA) for generating a suitable treatment plan. The advantage of Iris collimator is that the field size can be varied automatically during treatment, and hence saves considerable time in contrast to the use of fixed collimators where the robotic manipulator has to pick up the desired collimator from the stand when multiple size collimators are used for planning. The plan quality, however, does not depend upon the whether iris collimator or fixed collimators are used. IMRT plans were done on the same CT slices (with the same contoured structures) that were used for CyberKnife plans. The comparative IMRT treatment plans were done using the same dose volume constraints and using seven co-planar non-opposed beams. The maximum number of segments allowed were 70 for the IMRT plans as per our institutional protocol.

The dose to the target volume, organs at risk (rectum and bladder), remaining volume at risk (RVR), conformation number, and homogeneity indices were compared for both the treatment techniques. Statistical analysis was performed using a paired two-tailed student t test to examine any statistically significant difference in the parameters examined. The p value < 0.05 was considered statistically significant.

Comparison parameters

For comparison purposes, all CyberKnife and IMRT plans were normalized, such that 95% of the planning target volume received at least 95% of the prescribed dose. Dose volume histograms were generated for each plan. The following dosimetric endpoints were evaluated for planning target volume coverage: V100%, D5, D90, D95. Vx is defined as the percentage of the normalized volume of the region of interest irradiated by x% of the prescribed dose. Dx is the dose coverage at x% of the PTV respectively.

Conformation number [12] and homogeneity index were used to evaluate the conformity and the homogeneity of target doses.

Conformation number (CN) is defined as:

$$CN = \frac{VT_{ref}}{VT} \times \frac{VT_{ref}}{V_{ref}}$$

Where VT ref = volume of target receiving a dose equal to or greater than the reference dose, VT = volume of target, V ref = volume receiving a dose equal to or greater than the reference dose (treated volume). The conformation number varies between 0 and 1. A higher value means a better conformality. This is in contrast to the conformity index that is a ratio of the prescription isodose volume over the tumor volume. The conformation number considers, in addition, the volume of normal tissue getting a dose equal to greater than the reference dose.

Homogeneity index (HI) was determined from the following equation:

$$\frac{D2\% - D98\%}{D50\%}$$

Ideal value is 0 for HI.

The *conformity difference ratio* (CN%) and *homogeneity difference ratio* (HI%) was calculated by the following equations respectively:

$$CN\% = \frac{CNCK - CNIMRT}{CNIMRT} \times 100$$

$$HI\% = \frac{HICK - HIIMRT}{HIIMRT} \times 100$$

These two parameters can be used to quantify the improvement or reduction in the CN & HI, respectively.

For the organs at risk (OAR's), the bladder and rectal exposure (V30%, V50%, V80%, V100%) of each patient in each plan was evaluated. In addition, the dose to the RVR was also evaluated.

Remaining volume at risk: As per ICRU (International Commission on Radiation Units and Measurements) report 83, RVR is defined by the difference between the volume enclosed by the external contour of the patient and that of the CTV and OAR's on the slices that have been imaged. This is a measure of all the normal tissues that could potentially receive significant radiation.

Comparing the mean value differences of the CK and IMRT plans, calculations of statistical significance were performed using the paired t test.

Results

Planning target volume coverage

Table *1* gives the dose volume parameters for clinical target volume taken from the DVH's (dose

Cureus

volume histograms) of the CyberKnife and corresponding IMRT plans for all the patients. The CyberKnife plans, in general, produced a better planning target volume coverage than the IMRT plans. The p value was statistically significant, (0.012 & 0.013), for the average V100% and D5. However, the p value for D90 and D95 was 0.97 and 0.42, showing no statistically significant difference in coverage at these levels.

Parameter	CK SBRT Plan(%)	IMRT Plan(%)	p value
D95	98.8+-2.74	97.7+-2.99	0.42
D90	101.6+-2.26	101.7+-2.45	0.97
D5	113.3+-3.96	110.1+-1.90	0.013
V100%	58.6+-18.73	56.69+-17.73	0.012

TABLE 1: Dose volume parameters for CK SBRT and IMRT for planning target volume

Statistically significant difference is displayed in bold (paired two-tailed t test) Abbreviations: CK=CyberKnife, IMRT=Intensity-modulated radiotherapy, SBRT= Stereotactic body radiotherapy. Dx is the dose coverage at x% of the PTV, Vx = percentage of the normalized volume of the region of interest irradiated by x% of the prescribed dose

Dose to organs at risk

Table 2 elucidates the dose volume parameters for rectum and bladder for the two treatment modalities. There is more efficient rectal sparing in the CyberKnife plans, which is statistically significant at V100%, V80%, and V50% dose levels. The p value was 0.02, 0.0001, and 0.0002, respectively.

	CK SBRT	IMRT	p value
Rectum			
V100%	0.07±0.07	1.2±1.34	0.02
V80%	3.4±2.75	9.2±4.79	0.0001
V50%	15.5±7.24	30.1±11.94	0.0002
V30%	32.7±12.34	35.7±12.02	0.12
Bladder			
V100%	1.3±2.28	2.6±2.3	0.08
V80%	10.4±6.84	10.3±6.10	0.92
V50%	38.6±16.54	33.8±15.02	0.23
V30%	85±30.55	53.7±25.04	0.006

TABLE 2: Dose volume parameters for OAR (organs at risk)

Statistically significant difference is displayed in bold (paired two-tailed t test). Abbreviations as in Table 1

In contrast, there is no appreciable difference in bladder sparing between the CyberKnife and the IMRT plans at these dose levels (V100%, V80%, and V50%) for which the corresponding p values were 0.08, 0.92, and 0.23, respectively. However, in the low dose regions of V30%, volume of bladder receiving this dose is higher in the CyberKnife plans as compared to the simulated IMRT plans (p=0.006). The lower dose to the rectum in the CyberKnife plans reflects a much sharper fall-off of dose posteriorly when compared to the IMRT plans. This could be because most of the beams in the CyberKnife plans are from anterior and lateral direction and the use of a large number of non-coplanar beams. This is a distinct advantage as rectal morbidity is one of the limiting factors in delivering hypofractionated radiotherapy. Our results are in accordance with a similar study done by Sabbir Hosaain, et al. and Ceylan, et al. [12-13] comparing these two modalities (CyberKnife and IMRT). However, in a study done by Shiu, et al. comparing CyberKnife and IMRT dose distributions, they found the dose to critical organs were less in the IMRT plans [14].
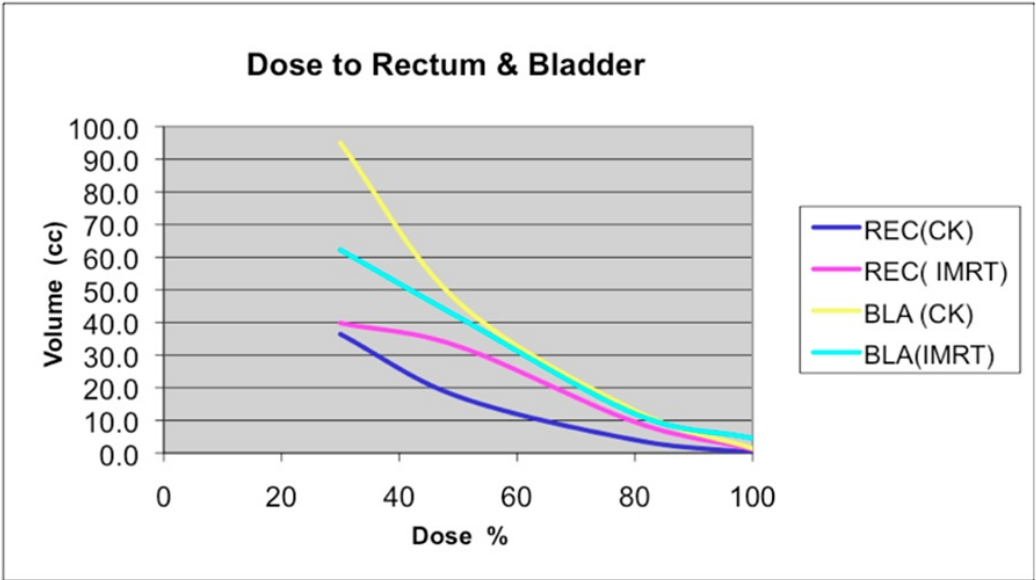
FIGURE 1: Dose to Rectum & Bladder

Remaining volume at risk dose

Table 3 gives the dose volume histogram values for remaining volume at risk.

RVR	CK (cc)	IMRT (cc)	p value
V100%	11.5±6.6	17.2±6.4	0.011
V95%	24.4±11.01	33.4±11.03	0.004
V90%	39.2±14.32	50.6±15.42	0.001
V80%	67.4±22.26	79.7±22.42	0.02
V70%	99.7±30.04	118.2±35.76	0.03
V60%	146.8±45.81	178±54.42	0.012
V50%	230±79.27	289.9±102.41	0.008
V40%	431.3±163.5	596.7±231.6	0.01
V30%	877.5±316.4	1514.8±576.46	0.0005
V20%	1793±630.25	2075.9±683.6	0.1

TABLE 3: Comparison of dose volume statistics of remaining volume at risk in CK SBRT and IMRT plans

Statistically significant difference is displayed in bold (paired two-tailed t test) Abbreviations: RVR= Remaining volume at risk, other abbreviations as in Table1

RVR is less in all CyberKnife plans compared to the simulated IMRT plans reaching statistical significance at V100%(p=0.01), V95%(p=0.004), V90%(p=0.001), V80%(p=0.02), V70%(p=0.03), V60%(p=0.01), V50%(p=0.01), V40%(p=0.02), and V30%(p=0.001) levels indicating lower non-clinical target volume, non-organ at risk tissue exposure at these dose levels. This has important clinical implications. When IMRT started gaining popularity in clinical use, one of the major concerns was that, even though there was significant dose reduction to the critical structures, larger volumes of normal tissue were exposed to the low-dose regions which could have the potential of inducing second malignancies [15-16]. This is thought to be mainly due to the increased monitor units and more number of fields used in IMRT. The second malignancies are a concern in long-term survivors. One would expect a majority of the organ-confined prostate cancer patients to be cured completely, and hence would probably live for a reasonably long time. Therefore, it is desirable to keep the normal volume low-dose radiation regions as less as possible. In this respect, the CyberKnife plans with lower remaining volume at risk doses have a slight edge over the IMRT plans.

Dose to testes

The mean dose to the testes was evaluated retrospectively. The testes were not contoured at the time of planning, and hence no attempt was made to limit the dose to testes. The mean dose was 142.5 cGy and 45 cGy in the CyberKnife and IMRT plans respectively, which was statistically significant (p=0.001)

Conformation number, homogeneity index, conformity

difference ratio, and homogeneity difference ratio

Table 4 lists the mean and standard deviation of the conformation number, homogeneity index, conformity difference ratio, and homogeneity difference ratio values for each patient in the CyberKnife and IMRT plans.

Patient no.	PTV in cc	CK	CN IMRT	!CN%	CK	HI IMRT	!HI%
1	37.86	0.6729	0.5479	22.81	0.2309	0.2272	1.6
2	44.15	0.8242	0.7878	4.62	0.1516	0.2148	-29.4
3	45.37	0.7597	0.6876	10.48	0.1976	0.1374	43.81
4	56.87	0.7866	0.6485	21.29	0.1789	0.1194	49.83
5	70.32	0.7866	0.6951	13.23	0.2061	0.1436	43.52
6	75.2	0.8726	0.7481	16.64	0.0933	0.1192	-21.7
7	75.9	0.7239	0.676	7.08	0.1691	0.1923	-12.1
8	77	0.7355	0.681	8	0.1433	0.1414	1.34
9	90.08	0.9365	0.762	22.9	0.1269	0.174	-27.1
10	91.2	0.8289	0.7977	3.91	0.198	0.1203	64.58
11	167	0.9144	0.8222	11.21	0.2416	0.1554	55.47
Mean	75.54	0.804	0.714	12.6	0.1761	0.1586	11.03
SD	35.37	0.081	0.079	2.53	0.045	0.0384	17.2
p value			0.0001			0.305	

TABLE 4: Conformation number and homogeneity index values for each patient

Statistically significant difference is displayed in bold (paired two-tailed t test) Abbreviations: CN= conformation number, !CN%= Conformity difference ratio, HI= Homogeneity index, !HI%= Homogeneity difference ratio, SD= Standard deviation, no.=number

The average clinical target volume in cc was 75.54 ± 35.37. The conformation number values for the CyberKnife plans was 0.804±0.081, and for corresponding IMRT plans was 0.71±0.079. The CyberKnife plans had a higher conformation number than the corresponding IMRT plan in all of the 11 patients, indicating better conformality of the CyberKnife plans (p=0.0001). The conformation number values were also analyzed for clinical target volumes less than and greater than 75 cc to see whether size has any impact on the conformation number in the two techniques. The p value for clinical target volume <75 cc and >75 cc was 0.007 and 0.01, respectively indicating the superiority of the CyberKnife plans over the IMRT plans even for larger target volumes. The mean of the conformity difference ratio in CyberKnife plans was 12.6 ± 2.53. Three patients (27%) had a >20% and eight patients (66%) >10% improvement in conformation number in the CyberKnife plans when compared to the corresponding IMRT plans.

The average homogeneity index value and standard deviation for the CyberKnife plans was 0.1768 ± 0.045 and 0.159 ± 0.039 for the IMRT plans, suggesting that CyberKnife plans are slightly more inhomogenous than the IMRT plans but statistically not significant (p=.305). The average homogeneity difference ratio value was 11.03 ± 17.2. In five patients, the IMRT plans were more inhomogenous than the CyberKnife plans, and in the remaining seven patients, the CyberKnife plans were more inhomogenous when compared with the corresponding IMRT plans [14].

Discussion

N/A

Conclusions

IMRT and CyberKnife SBRT can be used to deliver hypofractionated schedules in organ-confined prostate cancer satisfying the specified constraints for organs at risk. Both treatment techniques provide adequate PTV coverage. In our study, CyberKnife plans delivered reduced doses to rectum and remaining volume at risk, which was statistically highly significant. CyberKnife plans are more conformal than IMRT plans, which was statistically significant. Though the CyberKnife plans are more inhomogenous than the IMRT plans, it does not reach statistical significance. Both these techniques are viable alternatives to HDR brachytherapy to deliver a hypofractionated schedule in a non-invasive way. However, precise image guidance tools are required to deliver these hypofractionated regimens. Randomized trials comparing conventional fractionation and hypofractionation are necessary to determine the ideal fractionation schedule. The results of the ongoing PACE study may provide more insight into this issue. Hence, long-term data is required before stereotactic body radiotherapy can be considered as an alternative to conventional fractionation in organ-confined prostate cancer.

Additional Information

Disclosures

Human subjects: All authors have confirmed that this study did not involve human participants or tissue. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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