Does CyberKnife improve dose distribution versus IMRT and VMAT on a linear accelerator in low-risk prostate cancer?

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Background. Hypofractionated stereotactic body radiation therapy (SBRT) for prostate cancer (PCa) can be delivered with the robot-assisted CyberKnife (CK) system or on a linear accelerator using dynamic intensity-modulated radiotherapy (IMRT) or volumetric arc radiotherapy (VMAT). This retrospective study was performed to determine whether CK offers better dose distribution than IMRT and/or VMAT.

Materials and methods. Treatment plans for three techniques were prepared using the same treatment parameters (36.35 Gy, 7.25 Gy/fr). We evaluated target coverage, conformity index (CI), homogeneity index (HI), gamma index (GI), and organs at risk (OAR) constraints.

Results. The mean planning target volume (PTV) dose for CK (39.58 Gy) was significantly greater than VMAT or IMRT (both 36.25 Gy). However, CK resulted in a wider dose range (31.48 to 45.89 Gy) vs. VMAT and IMRT (34.6–38.76 Gy). The volume of rectum (V36Gy, mm3) was significantly lower (p < 0.001) in the CK plans (219.78 vs. 519.59 and 422.62, respectively). The volume of bladder (V37Gy, mm3) was significantly greater for CK (3256 vs. 1090.75 for VMAT and 4.5 for IMRT (p < 0.001). CK yielded significantly better CI (1.07 vs. 1.17 and 1.25 for VMAT and IMRT, respectively; p < 0.01) and HI values (1.27 vs. 1.07 and 1.04; p < 0.01). GI values for the δd = 3mm, δ% = 3% criteria were 99.86 (VMAT), 99.07 (IMRT) and 99.99 (CK). For δd = 2mm, δ% = 2%, the corresponding values were 98.3, 93.35, and 97.12, respectively.

Conclusions. For most variables, CK was superior to both VMAT and IMRT. However, dynamic IMRT techniques, especially VMAT, do not differ significantly from CK plans and are therefore acceptable alternatives to CyberKnife.

Key words: prostate carcinoma; stereotactic radiotherapy; intensity-modulated radiotherapy, CyberKnife

Introduction

Radiotherapy is a mainstay treatment for prostate cancer (PCa).1–3 Technological improvements in the past decade have made it possible to deliver highly targeted, conformal radiotherapy beams to the prostate gland without harming adjacent healthy tissues or organs at risk (OAR). Intensity-modulated radiotherapy (IMRT) is the technique most commonly used to deliver conventional dose fractionation schemes (1.8–2 Gy/fr) in PCa. In recent years, however, there has been a growing interest in hypofractionated stereotactic body radiation therapy (SBRT), which greatly reduces overall treatment time while achieving comparable or better results than conventional fractionation schedules.

Various radiotherapy modalities can be used to deliver hypofractionated radiation, including dynamic IMRT and volumetric arc radiotherapy (VMAT), both of which are delivered through a conventional linear accelerator (linac). Another
common modality is the stand-alone robotic CyberKnife radiosurgery system, which is increasingly used to treat PCa due to its capacity to deliver highly conformal doses to the prostate while sparing the surrounding OARs, with excellent dose distribution characteristics. Dynamic IMRT and VMAT are also capable of delivering highly conformal SBRT with good dosimetric quality. However, it is not clear whether CyberKnife is superior to IMRT and VMAT in terms of target dose distribution. Numerous studies have compared VMAT to IMRT (among other techniques) for the treatment of PCa, and several studies have compared CyberKnife to SBRT. To our knowledge, none of the studies conducted to date have compared these three techniques using the same total dose and fractionation scheme (36.25 Gy and 7.25 Gy) and treatment plan criteria.

In this context, the aim of the present study was to compare hypofractionated treatment plans for CyberKnife, IMRT, and VMAT in a series of patients with low-risk PCa. We compared treatment plan parameters for all three techniques, including doses to the target and OARs, delivery quality assurance (DQA), gamma index (GI), and the homogeneity index (HI).

Materials and methods

This study was based on data (DICOM CT dataset) from 32 patients with low-risk PCa previously treated with CyberKnife at our institution using a hypofractionated SBRT protocol (total dose, 36.25 Gy; 7.25 Gy/fraction). The mean age of the patients was 72. The prostate gland was classified as small (< 30 cc; n = 10), medium (30–60 cc; n = 20), and large (≥ 60 cc; n = 4).

Figure 1 shows the dose distributions for a patient on a transversal scan showing the IMRT (Figure 1A) and VMAT (Figure 1B) treatment plans. Figure 1C shows the CyberKnife plan for the same patient.

Treatment plans

Three different plans (IMRT, VMAT, and CyberKnife) were created for each patient. For all plans, we applied the same validation criteria for quality assurance verification (Table 1). In all cases, the planning target volume (PTV) was delineated on CT images. The PTV included the clinical target volume (CTV) with a 5 mm margin expanded laterally, inferiorly, and superiorly. The posterior margin was only 3 mm.

IMRT and VMAT

The Varian Eclipse treatment planning system (TPS) was used to prepare the two dynamic techniques (IMRT and VMAT) with an anisotropic analytical algorithm (AAA). The IMRT plans consisted of nine sliding window beams (0°, 40°, 80°, 120°, 160°, 200°, 240°, 280° and 320°). The VMAT plans had four partial arcs (235–125 collimator 30 and 330 clockwise arcs, 125–235 collimator 30 and 330 counterclockwise arcs). Both plans were calculated for 6 MV beam as it was only one output energy for CyberKnife. It was important to compare IMRT and VMAT under the most similar conditions to CK. Additional artificial structures were created to prepare a more suitable and conformal treatment plan.

Figure 1 shows the dose distributions for a patient on a transversal scan showing the IMRT (Figure 1A) and VMAT (Figure 1B) treatment plans. Figure 1C shows the CyberKnife plan for the same patient.

CyberKnife

The MultiPlan v. 4.6 software applying the ray-tracing dose calculation algorithm from Accuray
was used to calculate treatment plans for the CyberKnife system. Depending on the size of the PTV for each patient, four different sized Iris collimators (diameter: 20, 30, 40, or 50 mm) were used. For this technique, a dose is delivered to the edge of the PTV (prescribed dose = 78%–82% isodose of the maximum dose at the isocenter of the tumour). Acceptance criteria for the plan were conformity index (CI) ~1 and homogeneity index (HI) < 1.4.

**Plan evaluation**

The plans were compared according to the following PTV parameters: maximum, minimum, and mean doses, and PTV coverage. The OARs were as follows: rectum: V18Gy, V29Gy, V36.25Gy, V36Gy, bladder: V18Gy, V29Gy, V36Gy, V36.25Gy, V37Gy, femoral heads: V25Gy. The mean dose for the body was also compared. The CI and HI were calculated based on the ICRU 83 recommendations.23

The CI and HI were defined according to the following equations:

\[
CI = \frac{V_{RI}}{TV} \quad [1] \\
HI = \frac{I_{\text{max}}}{RI} \quad [2]
\]

where \(V_{RI}\) – is the volume of a prescribed dose for PTV, TV is a total volume of PT

\(I_{\text{max}}\) – maximum dose, RI is the prescribed dose.

**Delivery quality assurance**

All calculated treatment plans were verified. To evaluate the results, we used the Phantom Octavius T40054 or Octavius 4D (depending on the technique). Octavius Detector SRS 1000 and PTW Verisoft 6.4 software were used.

IMRT and VMAT were delivered on a Varian True Beam linear accelerator. The CyberKnife plans were delivered with an Accuray CyberKnife robotic arm accelerator.

**Gamma index**

The gamma index (GI) was calculated to compare differences between the measured and calculated dose distributions, which allowed us to compare three-dimensional (3D) dose distributions. The TPS-calculated dose distribution was used as the reference data. Following the methods described in previous studies24,25, we evaluated the following parameters: distance (depth and width of field), \(\delta d\) = 3mm, dose, \(\delta \% = 3\%\) and \(\delta d = 2\text{mm}\), and dose, \(\delta \% = 2\%\) (local normalization and threshold 5%).

**Statistical analysis**

The normality of the distribution of the study variables was checked with the Shapiro-Wilk test, which revealed a non-normal distribution. The Friedman test was used to compare the quantitative variables in the three groups, which showed statistically significant differences. A post-hoc analysis (Wilcoxon’s paired tests with Bonferroni correction) was performed to check for significant differences in the measurements. The cut-off for statistical significance was set at 0.05. All statistical analyses were performed with the R software, version 4.0.3.27

**Results**

**Treatment plan parameters: PTV**

For VMAT and IMRT, the mean dose (36.25 Gy) was constant. For CyberKnife, the dose was > 36.25 Gy in all patients. Table 2 presents all PTV-related parameters. The CyberKnife plan had a significantly higher mean maximum dose and lower mean minimum dose.
Treatment plan parameters: Body

The mean (±SD) doses to the whole body for the VMAT, IMRT and CyberKnife were 1.65±0.34, 1.8±0.35, and 2.06±0.39 Gy, respectively, a statistically significant (p < 0.001) difference. The mean dose with CyberKnife was significantly higher than the mean IMRT dose, which in turn was significantly higher than the mean VMAT dose.

Treatment plan parameters: OARs

Table 3 shows the treatment plans for the three techniques. For the OARs, we evaluated the percentage volume of the bladder, rectum, and femoral heads corresponding to the constraint doses for the treatment plan. As that table shows, significant differences for rectal volume (p < 0.001) were observed for all doses except V29 Gy (p < 0.911). A 22.58% of the rectal volume was covered by the V18 Gy dose, a significantly higher percentage than observed for VMAT (15.33%) or IMRT (15.17%). In terms of high doses, CyberKnife had lower coverage of the rectum than the other techniques. Volume of bladder coverage by V18 Gy, V36.25 Gy and V37 Gy (measured in mm³) was significantly higher in the CyberKnife plans. The IMRT plan yielded significantly lower coverage of the bladder on the V36.25 Gy and V37 Gy doses. For IMRT, coverage of the right and left femoral heads with the V25 Gy dose was significantly compared to VMAT and CyberKnife. All these results met the constraints in the plans calculated in the TPS (Table 1).

Statistically significant differences between the techniques in terms of CI and HI values (p < 0.001 for both indices) were observed (Table 4). IMRT resulted in a significantly higher CI than the other two techniques, but with a lower HI than VMAT and CyberKnife.

Delivery quality assurance

Figure 2 shows the mean values for the GI calculated for two types of criteria: distance (depth and width of field), δd = 3mm, and dose, δ% = 3% and δd = 2mm, and dose, δ% = 2%. For the GI values, the acceptance criterion was > 95%. Significant differences (p < 0.001) were observed for IMRT, for which the mean GI values were lower than VMAT and CyberKnife. The GI values (3%/3mm criteria) were 99.86, 99.07 and 99.99 for VMAT, IMRT and CyberKnife, respectively. For the more restrictive criteria (2%/2mm), the corresponding values were lower (98.3, 93.35, and 97.12).

Given the significantly lower results for IMRT (2%/2mm criteria), we decided to determine these values individually for each patient (Figure 3). Only 10 of the 32 plans met the acceptance criteria (95%) for the treatment beams and seven plans were below the critical 90% threshold.

![Figure 2. Gamma index for verification plans.](image1)

![Figure 3. IMRT gamma index (2%/2mm) values for each patient.](image2)
The mean GI values (2%/2mm) for each beam direction are shown in Figure 4 (one bar represents each beam direction). The significantly lower GI values (p < 0.001) were as follows: 90.31%, 94.86% and 92.76% under the 95% acceptance level for beam directions 1200, 1600 and 2000, respectively.

**Discussion**

This study was performed to determine whether CyberKnife provides a superior dose distribution profile to linac-based IMRT and VMAT in patients who received hypofractionated SBRT for low-risk PCa. Our findings show that the dosimetric results for VMAT, IMRT, and CyberKnife are all acceptable and compliant with constraints (Tables 2 and 3). The mean dose to the PTV was the same (36.25 Gy) for the two isocentric techniques, but significantly higher (39.59 Gy) for CyberKnife. The PTV dose range was smaller for VMAT and IMRT (34.6–38.76 Gy), while CyberKnife was much more variable (31.48–45.89 Gy). The dose to the rectum (V36Gy, mm³) was significantly lower (p < 0.001) in the CyberKnife plans (219.78 ± 235.02 Gy) compared to the VMAT (591.59 ± 226.53 Gy) and IMRT (422.62 ± 236.64 Gy) plans. The mean bladder dose (V37Gy, mm³) was 3256 for CyberKnife, 1090.75 for VMAT, and 4.5 for IMRT (p < 0.001). The CI for VMAT, IMRT and CyberKnife (1.17, 1.25 and 1.07 respectively) were close to one and in line with TPS calculations. By contrast, HI values were higher for CyberKnife versus VMAT and IMRT (1.27 vs. 1.07 and 1.04, respectively).

An important difference between VMAT/IMRT and CyberKnife is that the first two are isocentric techniques while the latter is non-isocentric. Although CyberKnife was superior to both VMAT and IMRT for most parameters, the dosimetric results for all three techniques were comparable, in-
indicating that dynamic IMRT and VMAT are both acceptable alternatives to CyberKnife.

Although several studies have compared these three techniques, it is difficult to directly compare our results given the heterogenous parameters used in those studies (number of beams; wide range of prescribed [1.8 Gy to 7.25 Gy/fraction]; and variable constraint protocols). In addition, most previous studies focused mainly on early and late grade toxicity of the different techniques and many evaluated results for standard and high dose fractions, but not all techniques with hypofractionated doses. Nevertheless, to the extent that it is possible, we compare our findings to those reported by other authors.

The mean dose to the PTV was the same for the two isocentric techniques, but significantly higher for CyberKnife. Similarly, the dose range to the PTV was more uniform for VMAT and IMRT, with a greater range observed for CyberKnife. These results are consistent with previous reports and with comparisons among conventional doses calculated on the percentage of minimum and maximum doses. Scobioala et al. defined these differences in PTV homogeneity as lower sensitivity of the Multiplan- CyberKnife planning system to dose constraints. The Eclipse VMAT and IMRT planning system is more flexible with regard to changing organ priorities when calculating the plan. Each change in priority or dose constraints is entered in real time. This advantage of the Eclipse system allows for better control of treatment plan outcomes compared to Multiplan.

The CI values for VMAT, IMRT and CyberKnife (Table 4) were close to one and in line with previous studies that used the same formula. However, these CI values were higher than those obtained for IMRT and CyberKnife (0.94 and 1.23) in a similar study that applied the same formula. Other studies have used other formulas to calculate the CI, which can raise or lower the CI. The lack of a standardized formula makes it difficult to compare the findings between different studies. CyberKnife yielded the best CI value, indicating better target conformity than VMAT and IMRT. The good CI obtained with CyberKnife can be attributed to the way the dose is built at the PTV with Multiplan, where the prescribed dose is delivered to the edge of the target volume. This provides better coverage of the target area with the prescribed dose. Similarly, this approach to dose building results in a higher dose at the “isocenter” of target, where the dose accumulates from all the beams. HI values for CyberKnife (1.27) in our study were significantly higher than those observed for VMAT and IMRT (Table 4). Other studies that have used the same formula to calculate the HI have reported similar results.

Our data suggest that CyberKnife is superior to both IMRT and VMAT in protecting the rectum, mainly by avoiding high doses. For example, with the CyberKnife plan, only 0.24% of the rectum received the prescribed dose (36.25 Gy) compared to 0.54% and 0.32% for VMAT and IMRT, respectively. Nevertheless, the results for all three techniques were good, with doses well below the constraint parameters. It should be noted, however, that the CyberKnife plan resulted in a substantially greater V18 percentage in the rectum (22.58%) compared to VMAT and IMRT (15.33% and 15.17%), respectively. Scobioala et al. reported a similar trend, with 29.62% of the rectum receiving 18 Gy with CyberKnife versus only 10.40% and 8.34% for VMAT and IMRT. Although the volume for CyberKnife was higher than in the isometric techniques, it still met the dose constraints (V18 Gy < 50% Vol). We found no significant differences between VMAT and IMRT in terms of the mean rectal dose, consistent with the findings described by Kopp et al., who reported no significant differences between the techniques (except for V95%). In our study, the V50% was 30% (VMAT) and 34% (IMRT) of the rectal volume, which compares to the 28% and 34% reported by Hardcaste et al. Seppala and colleagues reported the mean dosimetric parameters for the rectum using the same constraint criteria as in our study. Those authors observed substantially lower results for V18Gy < 50%Vol: 10% vs. 15.33% (VMAT); 11.6% vs. 15.17% (IMRT); and 12% vs. 22.58% (CyberKnife).

In terms of the DVH values for IMRT and CyberKnife, we obtained significantly lower volume of rectum than Ceylan and colleagues for all constraints with IMRT. For example, V18 Gy was 15.17% in our study versus 30% for Ceylan et al. This trend was also maintained for high doses (near the prescribed dose), as follows: V36.25 Gy < 5% Vol: 0.32% vs. 3%. Ceylan and colleagues reported lower volumes for CyberKnife: V18 Gy < 50% Vol: 22.58% vs. 12% and V36.25 Gy < 5% Vol: 0.24% vs. 0%, respectively. By contrast, those authors observed significantly higher rectal doses. Similar findings have been observed in other studies. The superiority of CyberKnife in terms of minimizing high doses to the rectum is due to the technique itself, in which (due to technical impediments) the dose is built by a large number of beams delivered from the front of the patient. This ap-
proach protects the rectum from high doses while, at the same time, building the prescribed dose at the target.

The bladder is a key OAR in PCa due to the risks of early and late toxicity. Of the three techniques, IMRT resulted in the lowest volume (1.22%, Table 3) receiving high doses (V36.25Gy). These findings compare favourably with those described by Hardcaste et al., who reported that 9% of the bladder volume received the prescribed dose for both techniques (VMAT and IMRT). Scobioala et al. reported the best results for bladder protection with VMAT to date. Our results for V18 Gy were significantly lower than those obtained by Hardcaste et al., as follows: 11.98% vs. 36% (VMAT) and 14.93% vs. 40% (IMRT). For CyberKnife, our results were also lower than those reported by Scobioala et al. (15.52% vs. 15.46%). The bladder dose volumes in our study were also lower than those reported in several other studies. For example, Ceylan et al. compared CyberKnife to IMRT, finding a V18 Gy of 22% vs. 14.93% and V36.25Gy of 2.5% vs. 1.22%. The CyberKnife results in that study were also lower than in ours: V18Gy: 10.8% vs. 19.25%, and V36.25Gy: zero vs. 2.16%. Although our results were higher than those reported by Ceylan et al., they still met the dose constraints. IMRT plans resulted in a lower bladder dose due to the nine uniform beams positioned around the patients. In this technique, the dose is spread to each beam to meet OAR constraints. In CyberKnife, most beams are delivered from the front, and thus it is impossible to avoid the bladder while simultaneously providing good target coverage, which is exactly the opposite of what happens with high doses to the rectum in CyberKnife.

Finally, using the criteria of distance (depth and width of field), δd = 3mm, and dose, δ% = 3%, all three techniques presented similar GI values (99.86%, 99.07% and 99.99% for VMAT, IMRT and CyberKnife, respectively). For all three techniques, these results are excellent. However, when more restrictive GI criteria were applied for distance (depth and width of field), δd = 2mm, and dose, δ% = 2%, the GI values fell: 98.3%, 93.35% and 97.12%, respectively. The only technique that did not meet the accepted conditions (GI > 95%) was IMRT. For the more restrictive criteria (GI 2%/2mm), for three of the nine beam directions (1200, 1600 and 2000), only six, 18, and 14 IMRT plans, respectively, yielded acceptable GI values. Beams from directions 1200, 1600 and 2000 passed through the table what can give weak individual results of GI for these beams. Unfortunately, we cannot compare our data to other reports because no similar studies have compared these techniques with GI results.

The results from DQA provide more information about the beam delivered to the target. Based on the treatment protocol at our centre, many of the patients in this retrospective cohort would not be eligible for IMRT because the more restrictive GI criteria (2%/2mm) were not achievable (<95%). In our sample, three of the nine IMRT beams had unacceptably low GI values, indicating a need to eliminate weak beams in order to improve the DQA for IMRT.

The imaging is one way and the immobilization of prostate using a rectal balloon another to eliminate intrafraction prostate motion during delivery of SBRT. An imagining and positioning of fiducials is checked by real time treatment, delivered from CyberKnife. Digital reconstructed radiograph DRR’s image are taken before each treatment beam for IMRT and VMAT additional patients are treated with full bladder. As Ceylan et al. presented that CK has the advantage for accurate target localization by real time tracking and it can treat the patient with lower dose to the bladder and rectum.

The main limitation of this study is the limited sample size and retrospective study design. As Scobiola et al. observed, results for small groups cannot be extrapolated for all treated cases, as the individual anatomy of each patient could play a significant role in determining the superiority of a given technique. For example, organ size and proximity play a significant role in treatment selection for individual patients. By contrast, the main strength of this study is the large number of dosimetric comparisons between the three modalities (VMAT, IMRT and CyberKnife) under the same treatment conditions (SBRT).

Conclusions

In this study, we compared the dose distribution for SBRT plans delivered with CyberKnife, IMRT, and VMAT for patients with low-risk PCa. Our findings show that dynamic IMRT and VMAT are both capable of delivering SBRT on a standard linac for patients with low-risk PCa, with dosimetric results that are largely comparable to those achieved with CyberKnife. Using the same treatment plan acceptance criteria originally established for CyberKnife, treatment plans for both VMAT and IMRT had good dosimetric parameters with acceptable PTV coverage of the prescribed dose and OAR protection.
These findings suggest that VMAT and IMRT can be used to safely administer SBRT, thus offering the possibility of completing treatment in only two weeks versus the seven weeks typically required for conventional VMAT or IMRT treatments. This offers another treatment option for patients for whom daily treatment is not feasible or accessible.

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