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CyberKnife Radiotherapy For Localized Prostate Cancer: Rationale And Technical Feasibility

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Christopher R. King, Ph.D., M.D.[1*]
Joerg Lehmann, Ph.D.[1]
John R. Adler, M.D.[2]
Jenny Hai, Ph.D.[1]

[1]Department of Radiation Oncology
[2]Department of Neurosurgery
Stanford University School of Medicine
300 Pasteur Drive
Stanford, CA 94305, USA

There is a clear dose response for localized prostate cancer radiotherapy and there probably is a radiobiological rationale for hypo-fractionation. Combining the two should maximize tumor control and increase the therapeutic ratio. This study examines the rationale and technical feasibility of CyberKnife radiotherapy (a robotic arm-driven linear accelerator) for localized prostate cancer. Its ability to deliver non-coplanar non-isocentric arcs can yield maximally conformal isodoses. It is the only integrated system capable of target position verification and real-time tracking during delivery of conformal stereotactic radiotherapy.

Inverse planning with the CyberKnife is used to design a course of radiotherapy for localized prostate cancer. Fiducial markers within the gland are used to verify organ position and track organ motion via an orthogonal pair of electronic x-ray imaging devices and provide real-time feedback correction to the robotic arm during delivery. Conformal isodose curves and dose volume histograms (DVH) are used to compare with an optimized Intensity-Modulated Radiotherapy (IMRT) plan actually delivered to the study patient based upon CT scan-derived organ volumes.

The CyberKnife can produce superior DVHs for sparing of rectum and bladder and excellent DVHs for target coverage compared with IMRT, and possesses dose heterogeneities to the same degree as IMRT plans. Because of the significantly longer delivery times required it would be best suited for hypo-fractionated regimens. Such dose regimens might allow for biologically equivalent dose escalation without increased normal tissue toxicity. Since the CyberKnife can verify organ position and motion and correct for this in real-time it is the ideal means of achieving such excellent DVHs without a compromise in doses to normal tissues. These capabilities are essential if one contemplates hypo-fractionated regimens with large dose-per-fraction sizes (>5Gy to 10Gy) and dose-escalation.

Key words: Prostate cancer, Radiotherapy, Hypo-fractionation, CyberKnife.

Introduction

Increasing clinical evidence exists supporting the notion that radiotherapy dose-escalation results in improved prostate tumor control (1-3). There remains however the technical limitations in the delivery of such high doses due to the proximity of sensitive normal tissues and organs (i.e. rectum and bladder). Conformal techniques are of course necessary to deliver such high doses safely and currently several techniques are in clinical usage, such as multi-field 3D conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT), both of which have been well described. Improvements in the accuracy of delivery of conformal radiotherapy rely upon accurate target organ localization, such as trans-abdominal ultrasound systems, or the use of fiducial markers and elec-

* Corresponding Author:
Christopher R. King, Ph.D., M.D.
Email: christopher@reyes.stanford.edu

tronic portal imaging devices. The CyberKnife (Accuray Inc., Sunnyvale CA) is a 6MV linear accelerator (linac) mounted on a computer-controlled robotic arm and is capable of stereotactic radiosurgery of extra-cranial sites. It has recently been cleared by the FDA for the treatment of any anatomical site. It is equipped with an orthogonal pair of diagnostic quality digital x-ray imaging devices, and is the only integrated system that is designed to use real-time image-guidance during radiotherapy delivery. It improves upon other techniques in several important ways: i) it allows for real-time organ position and motion corrections during delivery, and ii) it allows for inverse optimization solutions and delivery with multiple non-isocentric, non-coplanar arcs. These capabilities would suggest that it might produce improved conformal isodose profiles and dose volume histograms (DVHs) than are currently achievable.

In addition to dose-escalation there is increasing evidence that hypo-fractionation (i.e. the use of large dose-per-fraction sizes) might increase the therapeutic ratio. This evidence, suggested by a low α/β ratio for prostate cancer (which implies a high sensitivity to dose fraction size), comes from several directions. Radiobiological interpretation of clinical outcomes from different modalities (i.e. low dose-rate (LDR) brachytherapy, fractionated external beam, high dose-rate (HDR) brachytherapy) suggest an α/β ratio indistinguishable from normal tissue late-effects, that is, a value close to 3Gy rather than the value of 10Gy associated with most tumors (4-8). Such a low α/β ratio is consistent with other unique biological properties of prostate cancer such as very long PSA doubling times of untreated tumors (9), very long tumor potential doubling times and a very low proportion of proliferating cells in prostate tumors (10). The consequence of this is far reaching since it supports the use of large dose fraction sizes to achieve the same or even superior tumor control rates, similar normal tissue late-effects while minimizing acute toxicity. These advantages would also reduce overall cost and patient inconvenience. Such arguments in support of hypofractionated courses of radiotherapy have been eloquently given before (11) and several clinical series have shown excellent tolerances and outcomes from large fraction size regimens (12-15). The demands for high precision of delivery of large dose fractions require a system such as the CyberKnife that is capable of overcoming daily target position variations and potential organ motion to a high degree of precision while delivering conformal radiotherapy.

This study is the first to demonstrate that the CyberKnife can be used to generate excellent optimized plans compared with state-of-the-art conformal techniques for prostate cancer and that it would be technically capable of delivering such. This new technology could be exploited for dose-escalation studies with hypo-fractionated regimens.

Materials and Methods

As a test case for this study a patient who previously received IMRT at this institution to deliver 74Gy to the prostate was used. Planning was based upon a CT scan in the supine position (3mm thickness, 3mm indexing) of the pelvis with an urethrogram to help delineate the prostate apex. The GTV (i.e. prostate), seminal vesicles, bladder and rectum were outlined on each axial image.

The IMRT plan was generated using the Corvus 4.0 (Nomos Corp.) inverse planning system (which finds an optimized solution to minimize an objective 'cost function') with 6 coplanar fields to be delivered with the 'step and shoot' technique. Our optimal IMRT plans are achieved by an iterative process involving both the physician and physicist with the goal of minimizing dose heterogeneity, minimizing the maximum dose to rectum and bladder and avoiding placement of high-dose regions ('hot spots') near sensitive structures (e.g. prostatic urethra, rectal wall, urethra). The PTV margins (with respect to the GTV) are set at 10mm in all directions except for the posterior margin that is set at 8mm. Our IMRT plans seek to ensure that the minimum isodose coverage of the prostate is 74Gy in 2Gy per fraction (with 15MV photons) but the volume of prostate below 74Gy (but above 70Gy) is typically 1-2%. In this case this corresponded to the 89% isodose line. Our plans also seek to deliver 50Gy to the seminal vesicles by the end of the course, thus the nominal dose per fraction for the seminal vesicles is 1.35Gy.

With the CyberKnife, real-time correction due to target organ daily position changes or motion during radiation delivery is accomplished via an orthogonal pair of digital x-ray imaging devices monitoring the position of fiducial markers placed within the target organ. These fiducial markers consist of three gold 'seeds' placed within the prostate gland (base, mid and apex) under trans-rectal ultrasound guidance by the urologist. Since the planning CT scan is obtained with these seeds in place it is the relative position of the seeds with respect to the contoured organ that serves as reference points. The CyberKnife allows delivery with a precision of <0.5mm and a tracking error of <1mm. Collimator sizes range from 5mm to 60mm. Inverse planning with Accuray's system (which uses a non-optimized solution with a linear programming algorithm) was used to generate a treatment plan to be delivered with the CyberKnife, which is capable of non-coplanar, non-isocentric arc delivery. The optimal treatment plan consists of multiple arc segments, each of which is broken down into component 'step and shoot' beamlets. Since the CyberKnife can achieve such a very high degree of accuracy in target coverage the effective PTV margins are significantly reduced in every direction and coverage with the 100% prescription isodose is within 3-5mm from the contoured target. A minimum margin range of 3-5mm is necessary for complete coverage at

the prescription dose to account for the steep dose gradient. For the purposes of isodose and DVH comparisons a delivery of the same total dose to the same structures as the IMRT plan is calculated (that is, 74Gy total in 2Gy daily fractions).

The optimum CyberKnife plan for this patient resulted in a total of 107 beamlets, 87 with a 30mm collimator aperture and 20 with a 20mm collimator aperture. This plan would require about 45 minutes to deliver a dose of 5 to 10Gy per fraction (most of which is consumed by robotic arm motion and target localization).

Results

Among techniques that yield radiotherapy plans with a certain inherent degree of heterogeneity, such as IMRT and CyberKnife, there are several ways to normalize the isodoses in order to compare plans: one way is to use the equal average tumor dose, another is to use equal maximum target dose. Each will produce slightly different comparisons since both modalities have different heterogeneity profiles. In this study we have decided to show plans that would have been selected to be delivered to a patient in clinical practice. As such these plans are chosen so that the isodose encompassing the entire target (prostate) will be assigned the 100% prescription dose (i.e. 74Gy in this case). For the IMRT this corresponded to the 89% isodose line yielding a maximum dose of 83.1Gy and for the CyberKnife this corresponded to the 90% isodose line yielding a maximum dose of 82.2Gy.

In Figure 1 several isodoses for the CyberKnife plan and the IMRT plan are shown in the same prostate mid-axial plane. Both plans are very conformal and the 74Gy isodose provides complete coverage of the target and minimal overlap with the rectum. Just how much sparing of normal tissues (rectum and bladder) can best be measured via DVHs. In Figure 2 comparison between CyberKnife and IMRT DVHs are shown. The bladder and rectum DVHs show significantly improved sparing with the CyberKnife as compared to the IMRT plan. The GTV coverage is similar for both IMRT and CyberKnife although one can see that CyberKnife would deliver a slightly higher mean dose to the prostate. Considering the improved normal tissue sparing the CyberKnife compared with IMRT, the CyberKnife could allow further dose-escalation while keeping normal tissue under current tolerances.

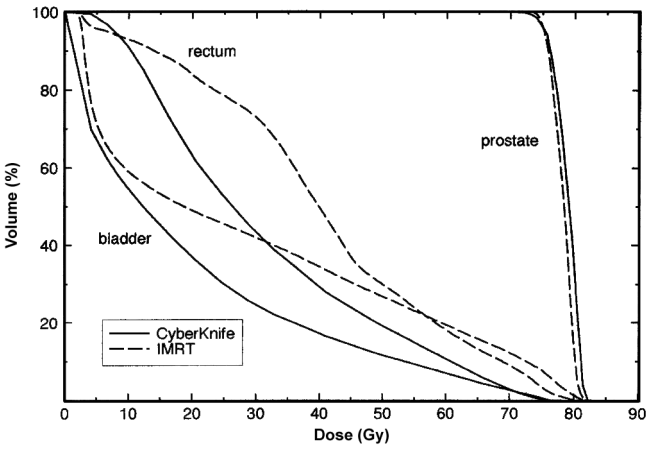

Figure 2: Cumulative dose volume histogram (DVH) comparison between the CyberKnife and IMRT plans for the same patient for the target organ (prostate) and normal tissues (rectum and bladder). The solid curves are for the CyberKnife plan and the dashed curves are for the IMRT plan. Both plans were normalized to deliver 74Gy via the isodose that completely encompassed the target organ.

Discussion

Clearly one of the means of exploiting the virtues of the CyberKnife is with hypo-fractionation. There are several studies that suggest that prostate cancer may behave radiobiologically more like late-reacting normal tissues based upon evidence that the α/β ratio is quite low, perhaps 3Gy or even lower (4-8). If true, the implications are clear: that a hypofractionated regimen would yield high tumor control rates while maintaining an equivalent dose to normal tissues for

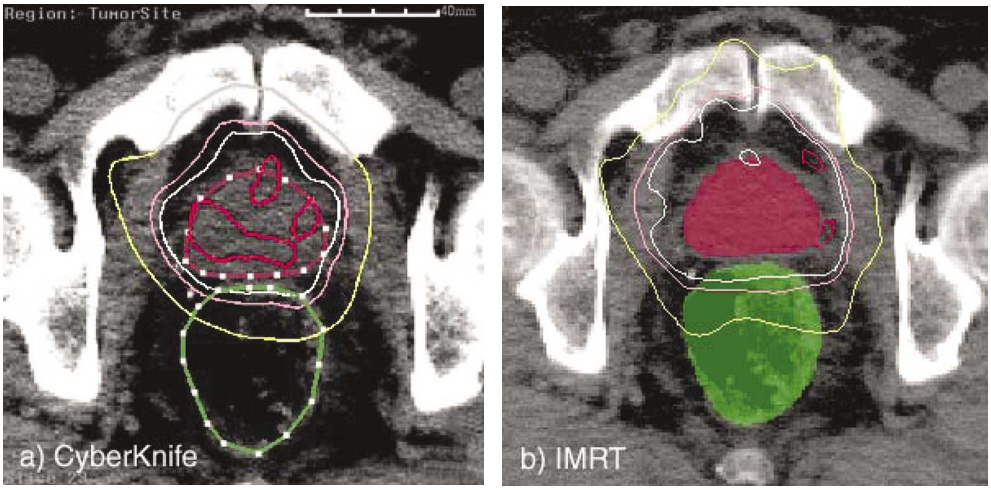

Figure 1: Isodose comparison between (a) CyberKnife and (b) IMRT plans in the same prostate mid-axial plane (small differences in the appearance between CT slices are artifacts due to differences between each system's graphic software). The isodoses shown are, from lowest to highest: 50Gy, 70Gy, 74Gy and 81Gy. Prostate and rectum are shown by the dot-solid lines for CyberKnife and color wash for the IMRT. Note that the 74Gy isodose (100% prescription) encompasses the prostate.

late-effects and reduce acute effects. The basis for conventional fractionated radiotherapy lies in the fact that the α/β ratio for most tumors and normal tissue late-effect are quite different (10Gy for tumors and 3Gy for late-effects). As such the tumor BED is maximized while keeping late-effects at tolerance doses when smaller dose-per-fraction are used. If normal tissue late-effects and tumor have the same α/β ratio then this rationale for small fractions disappears.

There are already several clinical series that support the safety and efficacy of larger dose-per-fractions. First, an older British study using 6Gy per fraction for a total of 36Gy (13) produces long-term outcomes and morbidity that are as good as historical cohorts from the same era. More recently a study using IMRT to deliver 70Gy in 2.5Gy per fraction has been reported with excellent acute and long-term morbidity (12). Much higher dose per fraction has been used with HDR brachytherapy as monotherapy and with excellent results so far (15). That series used 8.5Gy to 10.5Gy per fraction with 4 fractions total using Ir-192 HDR brachytherapy. The acute toxicity is within acceptable range while the long-term tumor control awaits maturation of the data but so far is very encouraging.

Several hypofractionated regimens that would produce a similar 'biological equivalent dose' (BED = $D[1+d/(\alpha/\beta)]$ is a relationship derived from the linear-quadratic model of cell survival, where D is the total dose and d the dose per fraction) as would a 'conventional' course at 2Gy per fraction to 74Gy are summarized in Table I. One should note that while similar BED are achieved for tumor control, the normal tissue late-effects doses are not increased and the early-effects doses are in fact *reduced*. Hypofractionated dose regimens would also allow significant biologically effective dose escalation while keeping normal tissue toxicity at current levels (see Martinez et al.'s HDR brachytherapy regimen in Table I). An additional benefit of such regimens is the significantly reduced number of treatments required which translate into convenience for the patient, economy of resources and cost reduction.

Table I

Comparison between various fractionation regimens resulting in roughly equivalent BED† for tumor control and normal tissue late-effects (assuming that tumor and normal tissue late-effects have a similar α/β ratio). Note how the acute (early) reactions would be *reduced* with larger fraction sizes. Several hypo-fractionated clinical series are noted.

Dose/dpf/n*	BED (Gy)		notes
	α/β=10Gy (early effects)	α/β=3Gy (tumor control/ late effects)	
74 / 2 / 37	88.8	123.3	'conventional' RT
70 / 2.5 / 28	87.5	128	Kupelian et al. (12)
60 / 3 / 20	78	120	
56 / 3.5 / 16	75.6	121.3	
52 / 4 / 13	72.8	121.3	
49.5 / 4.5 / 11	71.7	123.7	
44 / 5.5 / 8	68.2	124.6	
36 / 6 / 6	57.6	108	Lloyd-Davis et al. (13)
34 / 8.5 / 4	62.9	130.3	Martinez et al. (15)
38 / 9.5 / 4	74.1	158.3	*ibid*
42 / 10.5 / 4	86.1	189.0	*ibid*

†BED = $D[1+d/(\alpha/\beta)]$, where D is the total dose, d is the dose-per-fraction, and α/β is the radiobiological parameter that describes sensitivity to dose-per-fraction of a particular tumor or tissue; *Dose / dpf / n: total dose / dose-per-fraction / number of fractions

From a radiobiological standpoint an increase in the therapeutic ratio for the larger dose-per-fraction sizes would be amplified further should the α/β ratio be even lower than that of normal tissue late-reactions. The clinical data available so far would suggest that anywhere from 2.5Gy to 10.5Gy per fraction are nearly equivalent in toxicity and tumor control, however longer follow-up than is currently available is still needed to confirm this.

A significant attribute of the CyberKnife is accurate target localization. There have been several studies defining the extent of organ motion and daily set-up errors present in modern radiotherapy for prostate cancer. A recent study (16) using fiducial markers implanted within the prostate and portal imaging has shown that set-up errors are generally very small, 1.8mm in the (anterior posterior) AP direction and 1.4mm in the (superior inferior) SI direction (values are one standard deviation). Similar set-up errors were noted in another study (17) where one standard deviation for the (medial lateral) ML, SI and AP directions were 2.0, 1.7 and 1.9mm respectively. Prostate internal organ motion/position is substantially larger that set-up errors with 5.8mm in the AP direction and 3.3mm in the SI direction (one standard deviation) (16). In another such study (18) the combined set-up and internal motion errors were measured as 6.1mm AP and 3.6mm ML (one standard deviation). With these values in mind the optimum PTV margins required to ensure a 95% dose coverage (two standard deviations) are ~12mm in the AP direction and ~7mm in the ML and SI directions. These should be considered conservative values since patients in some of these studies (16) were uniformly instructed on control of bladder and rectal filling prior to the scan and daily treatments. Such large margins, while necessary when no corrections are made for organ position changes, can result in both potentially risky overdosage to normal tissues and equally risky underdosage of target organ with large dose fraction sizes. This is particularly the case for the AP direction with the rectum in such close proximity. Hypo-fractionation regimens would be much less forgiving of errors than conventional fractionation would be. The CyberKnife's capabilities for real-time tracking are essential for hypo-fractionation schedules in order to reduce the PTV margins to ensure coverage while minimizing normal tissue exposure.

While the CyberKnife has many attributes that would make it an excellent tool in the delivery of conformal

radiotherapy for localized prostate cancer, the relatively longer daily treatment times would make it inefficient for conventional fractionation (i.e. 2Gy) but very well suited for hypo-fractionated regimens. Such trials are being contemplated.

At first, one might argue that treating only 8 patients per day (assuming 1 hour per patient) with the CyberKnife would be quite limiting. However, consider for example a hypofractionated regimen of 8 daily fractions of 5.5Gy each (corresponding to the same BED as 74Gy in 37 fractions of 2Gy each, see Table I). On a conventional linac one can treat around 32 patients a day (assuming 15 minute time slots). So over a period of 37 days one can complete conventional radiotherapy on 32 patients. Over that same 37 day time period the CyberKnife could complete 37 days/8 day course = 4.6 treatment courses, and with 8 patients per day it would complete treatment on 8x4.6 = 37 patients. Thus the patient throughput of the CyberKnife would be equivalent to that of linacs.

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