

FLEXIBILITY OF PROSTATE TREATMENT PLANNING AND DELIVERY FOR CYBERKNIFE® RADIOSURGERY

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I. INTRODUCTION

Accuray Incorporated has developed treatment planning tools for the treatment of prostate cancer that facilitate the construction and delivery of radiation distributions that emulate those employed in a highly effective radiation delivery technique, high-dose rate (HDR) brachytherapy. The flexibility also exists to allow the user to create a more homogeneous dose distribution, such as that seen with intensity-modulated radiation therapy (IMRT). In this white paper, we describe this HDR-like treatment planning utility, show how it is integrated into the current treatment planning system, and highlight new features of the CyberKnife® Robotic Radiosurgery System that will facilitate the rapid planning and delivery of treatment for prostate cancer.

II. BACKGROUND

Prostate cancer is the second most common cancer in men, with a worldwide incidence of 25.3 per 100,000.¹ It is the most commonly diagnosed malignancy in men in the United States, with an estimated 219,000 newly diagnosed cases in the United States in 2007.² With the advent of PSA screening and greater awareness of prostate cancer, a larger proportion of patients are being diagnosed with organ-confined disease.³ Treatment options for organ-confined prostate cancer include watchful waiting, laparoscopic or radical prostatectomy, external beam radiation therapy (EBRT), permanent source interstitial low dose rate brachytherapy, and HDR remote afterloading brachytherapy.

Although each treatment option has its advantages and disadvantages, HDR brachytherapy has rapidly gained popularity for treating organ-confined prostate cancer.⁴⁻¹⁶ In HDR brachytherapy, 14 to 18 transperineal catheters placed in the prostate are loaded with a high activity source that delivers a high dose of precisely targeted and conformal radiation in a few fractions. A heterogeneous distribution of dose, with large values of V_{125} and V_{150} in the peripheral zone of the prostate (V_{125} and V_{150} are the volume of the prostate that receives 125% and 150% of the prescription dose, respectively; see Figure 1), corresponds to the disproportionately greater number of cancer cells in the prostate periphery, as revealed on histologic examination.¹⁷ In addition, radiobiological studies suggest that the hypofractionated treatment regimen delivered by HDR brachytherapy is thought to be advantageous for prostate cancer in particular, which is characterized by a low α/β ratio (1.5 – 3.7 Gy).¹⁸⁻²⁰

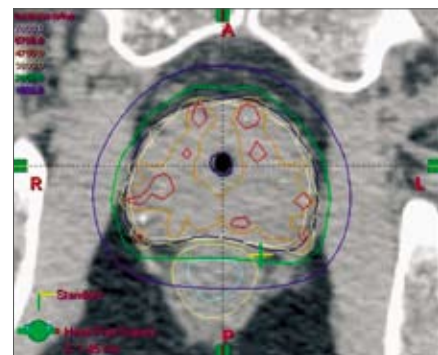


Figure 1. Axial view of a typical HDR brachytherapy dose distribution. Note that regions of high dose (indicated by the red and orange isodose lines) approximately correspond to the peripheral zone of the prostate. (Courtesy of Drs. Donald Fuller, Chad Lee, and Steve Hardy, Radiation Medical Group and CyberKnife Centers of San Diego.)

A growing body of clinical literature also attests to the efficacy, and the safety, of HDR brachytherapy for prostate cancer. As a boost in combination with EBRT, HDR brachytherapy has resulted in excellent local control rates and acceptable toxicity for low, intermediate, and high risk organ-confined prostate cancer.^{7,21-23} Recent reports of HDR as monotherapy for localized prostate cancer have also been promising, with biochemical disease-free survival (bDFS) at least as favorable as that obtained with LDR brachytherapy, conformal dose-escalated radiation therapy, or IMRT.^{4,5,11-14} A study from the California Endocurietherapy Cancer Center showed 97% bDFS at a median follow-up of 39 months in localized prostate cancer patients treated with 6-7.25 Gy for 6 fractions. No Grade 3 or higher gastrointestinal (GI) toxicities were reported, and only 3% of patients experienced Grade 3 or higher genitourinary (GU) toxicities.²⁴ Researchers at Texas Tech University reported 90% bDFS at 5 years in localized prostate cancer patients treated with 7.5 Gy for 6 fractions, with low levels of acute and chronic toxicity.²⁵ A prospective, non-randomized study comparing HDR monotherapy to LDR brachytherapy showed superior 5-year event-free survival (98% vs. 85%) and a trend towards improved freedom from cancer failure (98% vs. 92%).⁶ Levels of toxicity and quality of life were also more favorable in the HDR cohort.^{8,9} The rate of impotence 3 years after HDR was 16%, compared to 45% following LDR brachytherapy. Thus, HDR brachytherapy as a sole treatment modality for localized prostate cancer is feasible, well-tolerated, and highly effective in early (5-year) follow-up.

HDR brachytherapy is an invasive procedure. During the implant procedure, the patient is administered spinal anesthesia through an epidural catheter for pain control. The catheters remain in place in the prostate for the 3-to-5 days required for treatment, during which, patients remain in the hospital. Catheters can shift position during this time, and if this occurs, the catheters need to be repositioned to maintain the accuracy of the treatment. The quality of the HDR implant is also dependant on the level of experience the physician has with the procedure. Despite the efficacy of HDR, a less invasive alternative with similar dosimetric characteristics could be of great value to clinicians and their prostate cancer patients.

III. PROSTATE RADIOSURGERY WITH THE CYBERKNIFE® SYSTEM

The CyberKnife System can deliver radiation to the prostate in a minimally invasive manner. High conformality and rapid dose fall-off outside the target volume, assured by the delivery of 100 to 200 uniquely angled, non-coplanar beams, provide excellent sparing of surrounding critical structures. Overall system accuracy has been documented in end-to-end phantom studies to be sub-millimeter for intracranial and spinal targets, and targets that move with respiration.²⁶⁻²⁸ Furthermore, the CyberKnife System has the unique ability to constantly track, detect and correct for any target or patient motion during treatment delivery. This is critical to safe prostate treatment. Significant motion of the prostate is common throughout delivery of radiation therapy or radiosurgery. In one study, substantial intrafraction prostate motion was detected with movement up to 2 mm, 6 mm and 7 mm in the left-right, anterior-posterior, and cranial-caudal direction, respectively.²⁹ A second study reported measuring intrafraction prostate motion greater than 1 cm over an 8-minute period, with some motion lasting longer than 1 minute.³⁰ Larger planning treatment volumes are required when using EBRT to compensate for this large intrafraction prostate motion, which increases the risk of delivering higher doses of radiation to adjacent structures including the bladder and rectum, thus increasing the risk of GU and GI toxicities.

Hypofractionated radiosurgery with the CyberKnife System for early-stage prostate cancer was described by researchers at Stanford University.³¹ In a presentation at the American Society for Therapeutic Radiation Oncology in 2006, PSA efficacy and acute and 18-month late toxicity in 33 low-risk patients treated with CyberKnife System were reported. No patient experienced Grade 3 or 4 acute toxicity, and only one patient experienced a Grade 3 late GU morbidity. The median normalized PSA declined to 0.12 at 18 months.³² To date, over 1000 patients have been treated for prostate cancer with the CyberKnife System. Most of these patients had early-stage, organ-confined disease and were treated in 4 or 5 fractions with prescription doses ranging from 35 to 38 Gy. The earliest prostate patients treated with the CyberKnife System are now approaching 36-month follow up. To date, PSA response and toxicity have been shown to be equal to or better than other modalities delivering hypofractionated treatment.³³ The feasibility of radiosurgery for early-stage prostate cancer delivered using the CyberKnife System has been demonstrated.

Recently, some CyberKnife users have adjusted constraints set at the time of treatment plan optimization in order to arrange hotspots in the peripheral zone of the prostate to levels typically seen with HDR (while still meeting dose constraints to critical structures). Dr. Donald Fuller of the San Diego CyberKnife Center demonstrated that CyberKnife radiosurgery can produce a dose distribution comparable to that created by prostate HDR brachytherapy treatment.³⁴ Dr. Fuller has been treating patients with the CyberKnife System using a 9.5 Gy x 4 fractions schedule based on published prostate HDR brachytherapy monotherapy experience. The radiosurgery volume is made to resemble prostate HDR brachytherapy therapeutic volume as closely as possible, with similar dose limitation objectives to adjacent tissues, including the rectum, bladder and urethra.

Accuray Incorporated has developed several new features intended to facilitate efficient planning and delivery of treatments that emulate IMRT or HDR dose distributions; these features are specifically designed to reduce treatment delivery time and make treatment planning faster and more intuitive. These features will be described in this white paper, along with current treatment planning techniques for prostate. Typical HDR dose distributions will be examined and compared to those generated for the CyberKnife.

IV. CYBERKNIFE® TREATMENT PLANNING FOR PROSTATE

In addition to choosing dose constraints for targets and critical structures, CyberKnife users also routinely exploit the use of “shell” or “tuning” structures. These are pseudo structures created by the user at the time of treatment planning. Their purpose is to further sculpt the dose distribution around the target, potentially improving conformality or controlling dose received by critical structures. The MultiPlan® Treatment Planning System provides manual or automatic fusion tools. Automatic fusion is based on a mutual information algorithm. The ability to fuse 1.5T (and, more recently, 3T) MRIs to the treatment planning CT allows the user to more easily define both the capsule of the prostate and the internal zonal anatomy. Most prostate treatment plans developed by CyberKnife users have not included dose constraints or tuning structures specifically designed to increase the dose gradient within the prostate. The primary goal has been to simply achieve high conformality and rapid dose fall-off away from the target. In the absence of constraints designed to increase the dose gradient within the prostate, regions of high dose within the PTV tend to be only 10 to 15% greater than prescription dose. It is worth noting however, that these regions of high dose tend to naturally occur in the periphery of the prostate (Figures 2, 3).

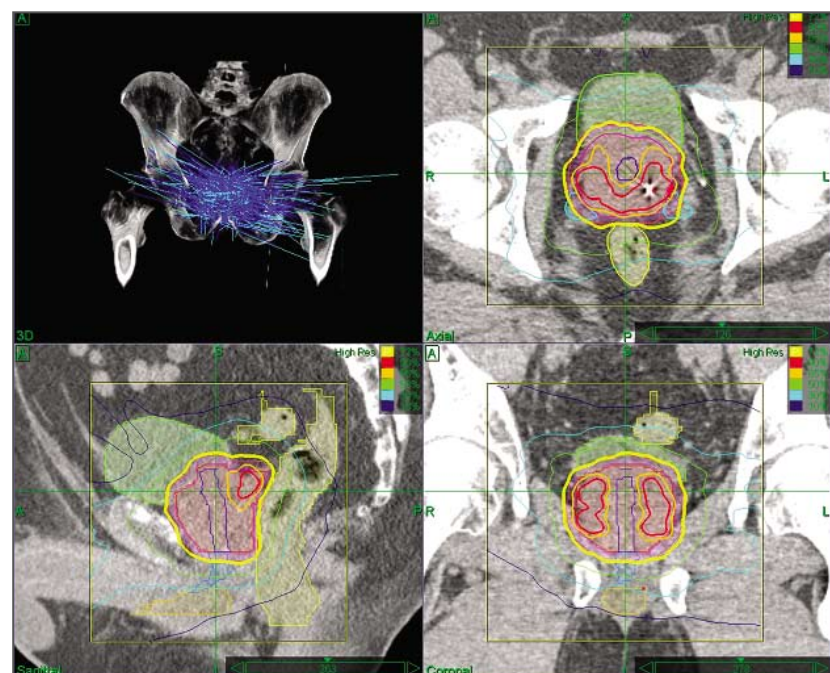


Figure 2. A CyberKnife treatment plan illustrating a prescription isodose line (shown in yellow) that is highly conformal to the planning target volume (PTV). Note sparing of the urethra and rectum. Note also that the regions of high dose within the prostate correspond approximately to the peripheral zone. In the case illustrated here, the dose gradient from prescription dose to the regions of high dose (shown in red) is approximately 15%. (Courtesy of Naples Community Hospital Healthcare System.)

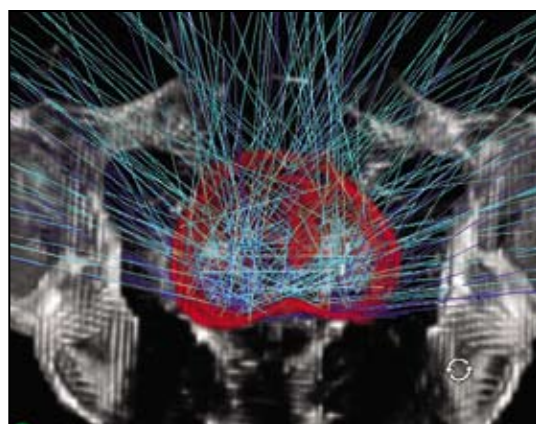


Figure 3. Three-dimensional rendering of a non-coplanar beam arrangement developed for a CyberKnife prostate treatment plan. The concentration of beams targeted to the peripheral zone of the prostate is clearly visible. (Courtesy of Drs. Donald Fuller, Chad Lee, and Steve Hardy, Radiation Medical Group and CyberKnife Centers of San Diego.)

V. REPRODUCING HDR BRACHYTHERAPY DOSIMETRY FOR THE PROSTATE IN CYBERKNIFE® TREATMENT PLANS

Users of the CyberKnife Robotic Radiosurgery System have successfully created extremely heterogeneous dose distributions within a target volume. Specifically, they have reproduced the hotspots within the peripheral zone of the prostate, typically associated with HDR brachytherapy. Treatment plans with values for V_{125} and V_{150} on the order of 50% and 25%, respectively, have been created. In a study by Fuller et al. at the San Diego CyberKnife Center, HDR brachytherapy treatment plans were developed using the planning CT data for patients previously treated using CyberKnife.³⁴ In all cases CyberKnife dosimetry compared favorably with that generated using the HDR treatment planning system. V_{125} and V_{150} levels comparable to HDR were achieved without increasing urethral and rectal D_{max} values (Figure 4).

Treatment plans that emulate HDR brachytherapy plans were initially developed using a single collimator. This resulted in a correspondingly high value for total monitor units (MU) and, therefore, a longer-than-average treatment time. The use of multiple collimators has resulted in improved conformality and an overall reduction in total MU.

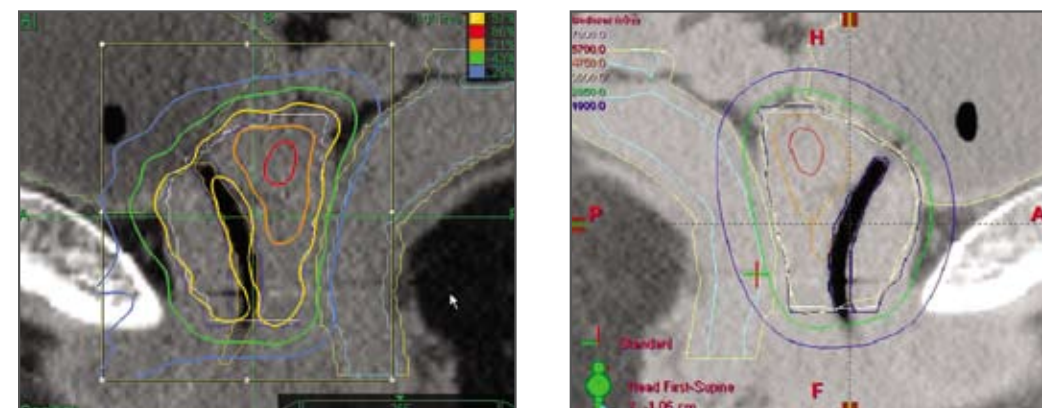


Figure 4. Sagittal views of CyberKnife (left) and HDR brachytherapy (right) treatment plans. V_{50} , V_{25} , V_{100} , V_{125} , and V_{150} are displayed. (Courtesy of Drs. Donald Fuller, Chad Lee, and Steve Hardy, Radiation Medical Group and CyberKnife Centers of San Diego.)

VI. FACILITATING FASTER TREATMENT PLANNING AND TREATMENT DELIVERY TIMES

Accuray has announced the availability of a number of new technologies that are focused on reducing both treatment planning time and the time required for treatment delivery. These technologies also make the plan optimization process more intuitive, allowing the user to specify specific clinical objectives such as conformality and homogeneity. Individually or in combination, the new technologies should provide the user with improved capability to deliver treatments in a shorter time with either a homogeneous or heterogeneous dose gradient within the prostate.

The new system features include:

800 MU/minute Linac

– The dose rate of the CyberKnife® linear accelerator has been increased to 800 MU/minute. Previously, the dose rate was 600 MU/min. Therefore, a 30% reduction in beam-on time is expected for comparable treatment plans.

Optimized Path Traversal

– Currently, during treatment delivery, the robot and CyberKnife linac must traverse through every node on a given path, even those nodes from which no dose is to be delivered. Robot traversal through zero-dose nodes adds to overall treatment time. Optimized path traversal gives the robot the ability to skip zero-dose nodes whenever doing so will not result in traversal through the patient “safe zone.”

Xchange™ Robotic Collimator Changer

– It has been demonstrated that the use of multiple collimators can result in both improved conformality and an overall reduction in MU.³⁵ The reduction in treatment time as a result of reduced beam-on time can be lost, however, due to the time taken to manually change collimators. If the patient needs to be repositioned due to motion when distracted by the operator entering the treatment room, treatment time is lengthened further.

Xchange allows the CyberKnife robot to automatically swap collimators when this is called for by a treatment plan. The Xchange table houses all 12 collimators. The exact locations of the table and collimator are “taught” to the robot. As necessary, the robot moves to the Xchange table, unlocks and places on the table the collimator in use. The next collimator required can then be picked up and locked before resuming treatment. Xchange makes it more likely that overall treatment time will be reduced when plans employ multiple collimators.

Iris™ Variable Aperture Collimator

– The Iris Collimator allows any of 12 available aperture settings to be delivered during a single traversal of the treatment workspace by the robot.
– The Iris Collimator consists of two banks of 6 tungsten leaves, offset by 30 degrees.
– Extensive testing has shown that both the penumbra and radiation transmission through the device are comparable to the existing fixed collimators for the CyberKnife system.
– The Iris Collimator allows users to fully exploit the improved conformality and reduced beam-on time associated with multiple-collimator treatment plans.

Sequential Optimization

– This new optimization tool was designed to both improve the ease of creating quality treatment plans and make the treatment planning process more intuitive. It introduces a new treatment planning approach: sequential optimization. With this approach, the system optimizes specific clinical objectives (homogeneity, coverage, conformality, organ at risk protection) in a sequence. This approach allows the user to build up the treatment plan one clinical objective at a time. The user has the ability to specify clinical objectives such as homogeneity, conformality, total MU, and dose to critical structures.

VII. CONCLUSION

The efficacy of HDR brachytherapy for early-stage carcinoma of the prostate has been demonstrated. Based partly on the low α/β ratio for prostate cancer, there is a consensus in the radiation oncology community that hypofractionated treatment for prostate cancer should result in improved long-term local control for early-stage disease. Conventional linear accelerators can not deliver a dose gradient within the prostate that is of the magnitude as that seen with HDR brachytherapy. Users of the CyberKnife Robotic Radiosurgery System have delivered hypofractionated treatment to the prostate both with and without the high-dose regions commonly associated with HDR brachytherapy. With the new technologies discussed above, it is the intention of Accuray to further enhance the ability of CyberKnife users to deliver either type of dose distribution.

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The information provided in this report is intended for background and educational purposes only as it relates to the CyberKnife System. The information contained herein is not intended, nor should it be construed, as advocating the acquisition or purchase of a CyberKnife System. Please direct any questions or comments to the contact information below.



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