

# VIRTUAL HDR CYBERKNIFE RADIOSURGERY FOR LOCALLY RECURRENT PROSTATIC CARCINOMA: A PHASE II STUDY

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## INDEX SCHEMA

### Eligibility:

- History of prior pelvic radiation therapy for prostate cancer;
- No complication higher than grade I from their prior course of radiotherapy
- Histologically confirmed, locally recurrent adenocarcinoma of the prostate;
- Clinical stages T1 - T3 (AJCC 6<sup>th</sup> Edition, see Appendix III);
- Greater than 2 years since the original radiotherapy course
- No distant metastases, no clinically or pathologically involved lymph nodes;
- No major medical or psychiatric illness;
- Hormonal therapy is not encouraged, but will not represent a study exclusion either
- No history of inflammatory bowel disease
- Signed study-specific informed consent form prior to study entry

### Required Sample Size: 20

## 1.0 INTRODUCTION

### 1.1 Background

Patients with locally recurrent adenocarcinoma of the prostate following prior radiotherapy present a challenging clinical problem, with no universally accepted safe and effective local retreatment option. Though cure appears possible in some of these patients, they may suffer serious complications following any of the radiation, surgical or thermal ablative local retreatment options.<sup>1-14</sup> In fact, the risk of serious complications following local retreatment is substantial enough that local salvage is often not attempted in patients with locally recurrent disease following radiotherapy, relegating them to palliative rather than curative measures.<sup>13</sup> Too, only selected patients with favorable prognostic indicators seem to enjoy a successful disease control outcome following local retreatment, while those who present more adverse prognostic indicators have a far lower salvage cure rate.<sup>1,2,7,9,10,11</sup>

Radical prostatectomy as a post-radiotherapy salvage method has been described by several investigators.<sup>1,2</sup> In a series of 100 post-radiotherapeutic salvage prostatectomy patients described by Bianco et al., a 5-year disease-free survival rate of 55% was observed, improving to 86% for men who were surgically treated when their PSA level was less than 4 ng/ml.<sup>1</sup> Some of these patients were continuously disease-free beyond 10 years following their salvage prostatectomy, and the authors concluded that long-term surgical control of post-radiotherapeutic recurrence was possible when salvage prostatectomy was performed early in the course of their recurrent disease. A similar conclusion was reached by Sanderson et al., who reported a 47% overall 5-year disease-free survival rate after salvage prostatectomy, and a substantially higher success rate in men with a PSA level lower than 5 ng/ml at the time of salvage surgery.<sup>2</sup>

Although there is a respectable long-term success rate in selected patients treated with salvage prostatectomy following failure of therapeutic radiation, the presence of post-radiotherapeutic tissue changes also contributes to a significant complication rate, including urethral strictures, urinary incontinence and erectile dysfunction. A 30% anastomotic stricture rate was reported by Stephenson et al., and a frequent need for artificial urinary sphincters was reported by both Sanderson et al. and Stephenson et al.<sup>1,3</sup> Rectal injury following salvage prostatectomy has also been reported, though this now appears to be an unusual complication, with only a 2% rate reported in men treated since 1993 in the Stephenson et al. series compared with 15% for patients treated prior to 1993.<sup>3</sup> In summary, although complication rates have come down, even in the most experienced surgical hands urinary tract complications appear to occur at least 30%

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of the time when radical prostatectomy is applied for radiorecurrent prostate cancer, and less experienced urologic surgeons may not perform the salvage prostatectomy procedure at all, due to its difficulty.

Thermal ablative maneuvers have also been applied for radiorecurrent prostate cancer.<sup>4-8</sup> Favorable PSA-based response rates measuring 90% or greater have been observed following cryosurgery for radiorecurrent prostate cancer, though inconsistent definitions of biochemical relapse, and shorter follow-up compared with salvage prostatectomy precludes any definitive conclusion about the effectiveness of this modality for the long-term salvage of prostate cancer that recurs following radiotherapy.<sup>4,5</sup> Significant complications have also been described following cryosurgery, including rectal or perineal pain, scrotal edema, hematuria, obstructive symptoms, incontinence, and occasionally, complications that require major surgery to correct.<sup>4-7</sup> Post-cryosurgery complications are more frequent in the setting of prior radiotherapy.<sup>7</sup>

More recently, heat destruction in the form of high-intensity focused ultrasound (HIFU) has been applied against radiorecurrent prostate cancer, creating a PSA-nadir value < 0.5 ng/ml in 61%, a negative prostate biopsy in 80%, and a short-term PSA-relapse free survival rate of 44% in patients who typically harbored Gleason score 7 or greater recurrent lesions.<sup>8</sup> Again the complications of this method were not trivial, with a 6% rate of rectourethral fistula, a 7% rate of grade III incontinence and a 17% rate of bladder neck stenosis, though the authors concluded that this modality had salvage potential with lower complication rates compared with other post-radiotherapy salvage modalities of therapy.<sup>8</sup> Longer follow-up will be required before any definitive efficacy assessment of this modality may be made.

There is also experience with permanent source brachytherapy salvage of post-radiotherapeutic local prostate cancer treatment failures, using both <sup>125</sup>Iodine and <sup>103</sup>Palladium isotopes, with or without neoadjuvant/adjuvant hormonal-based therapy.<sup>9-12</sup> Local control and 5-year disease-free survival rates of up to 100% and 83%, respectively, have been described in this setting if patient selection factors including initial relapse-free interval greater than 2 years, prostate-specific (PSA) antigen level less than 10 ng/ml, PSA-doubling time greater than 9 months at the time of relapse and a Gleason score of ≤ 6 are followed.<sup>9,10,11</sup> Unfortunately, the majority of these brachytherapy investigators also report a significant level of urinary tract complications, including hematuria, urinary incontinence and stricture.<sup>9,10,11</sup> At least one investigator has also reported substantial rates of lower gastrointestinal toxicity following salvage brachytherapy, with grade II and III GI complications reported in 29% and 6% of their salvage brachytherapy cases, respectively.<sup>9</sup> Thus, while local salvage appears feasible in a fairly high percentage of selected post-radiotherapeutic recurrence patients with the use of permanent source brachytherapy, a substantial percentage of them also appear destined to develop significant urinary tract complications, sometimes also accompanied by serious lower GI complications.

More recently, High Dose Rate (HDR) interstitial brachytherapy has been successfully applied for patients with radiorecurrent prostate cancer, reported by the USCF group.<sup>14</sup> Using an HDR dose of 36 Gy in 6 fractions over the course of 2 interstitial catheter applications separated by a week, a 2-year biochemical control rate of 89% was achieved in this study, with a median follow-up of 18.9 months. This result seems more impressive considering the fact that 18/21 patients had a Gleason score of 7 or greater and nearly half (9/21) had T3 lesions at the time of their recurrence, though the follow-up duration remains too short to fully assess the long-term efficacy of this salvage method. Only two patients had a documented relapse at the time of this report. Morbidity in this series also seems acceptable, with 3/21 patients developing grade 3 urinary tract toxicity, none developing incontinence and no rectal toxicity higher than grade 2.<sup>14</sup> Though follow-up remains relatively short, the authors concluded that salvage HDR brachytherapy appears safe and effective, pending longer term confirmation in more patients.

Although this HDR brachytherapy experience seems very encouraging, possibly suggesting a therapeutic ratio superior to that achieved with salvage permanent source brachytherapy, the

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procedure is invasive, typically requiring an operating room, hospitalization, and pain control. Fibrotic pelvic tissues may also be more difficult to implant in a geometrically optimal HDR fashion. As such, there is room for further improvement.

The use of hypofractionated CyberKnife® stereotactic therapeutic radiation as a modality of treatment for early-stage prostate cancer has also been described.<sup>15</sup> The CyberKnife® is a unique noninvasive radiosurgical system capable of treating any part of the body from any of approximately 1600 different targeting angles, which create a very conformal three-dimensional radiosurgical treatment volume. A linear accelerator that delivers highly collimated radiation is mounted on a robotic arm guided by continuously updated stereoscopic X-ray-based targeting feedback with automated targeting adjustment, resulting in a real-time target volume tracking process that continuously reacquires sub-millimeter accuracy throughout the radiosurgical treatment.<sup>16</sup> Though therapeutic radiation is generated externally rather than by a brachytherapy approach, the CyberKnife® effectively limits the volume of adjacent tissue receiving high dose radiation, creating dose fall-off of comparable magnitude to brachytherapy. The result is a non-invasive modality of radiation delivery that could be used to salvage radiorecurrent cancers of the prostate.

Due to the unique CyberKnife® dose delivery methodology that targets small segments of the target volume with a very large number of noncoplanar beams, this device is also capable of molding the dose internally within the target volume creating similar morphology to HDR brachytherapy (which we refer to here as “Virtual HDR”), allowing HDR-like dose escalation within the peripheral zone of the prostate while limiting the urethral and rectal dose comparably to HDR brachytherapy.<sup>17</sup>

In this protocol, the CyberKnife® prostate target volume morphology will be designed similarly to that described in the UCSF salvage HDR brachytherapy study<sup>14</sup>, including the prostate and any identified contiguous disease extension with no added margin as the planning target volume, similarly limiting the dose to bladder, urethra and rectum, while radiobiologically adapting their fractionation schedule to a 5 treatment SBRT regimen.

When converting the 6 x 6 Gy regimen described in the UCSF HDR salvage regimen<sup>14</sup> to a 5 fraction SBRT regimen, it should be noted that although the alpha/beta ratio for de novo prostate cancer has most commonly been postulated as 1.5 – 5 Gy, the specific value has yet to be definitively established. In fact, while a recent very large study suggested an alpha/beta ratio of 3.7 Gy for prostate cancer, the 95% confidence interval was 1.1 to infinity Gy, and the authors admitted that due to difficulties interpreting the complex data base, considerable uncertainty remains regarding the alpha/beta ratio for prostate cancer.<sup>18</sup> They also noted that if HDR-based heterogeneity is introduced into the calculation, the alpha/beta ratio increases.<sup>18</sup> Too, it is entirely possible that recurrent prostate cancers, which are often characterized by a higher Gleason score than de novo prostate cancers, could harbor a higher alpha-beta ratio.

As such, if tumor control is the primary objective, it would seem prudent to design the fractionation conversion considering the possibility that the alpha/beta ratio of the post-radiotherapeutic recurrent lesion could be as high as 10 Gy, yielding an equivalent 5 fraction regimen of 34 Gy in 5 fractions of 6.8 Gy/fraction. This figure is also remarkably close to the “SHARP” prostate cancer dose fractionation schedule of 33.5 Gy in 5 fractions of 6.7 Gy/fraction described by the Virginia Mason Group, even though their dose was arrived at by a different calculation method than ours, and applied to de novo rather than recurrent prostate cancers.<sup>19</sup> In the SHARP study, the incidence of acute and chronic grade 3 complications was zero, with the authors contemplating an escalated radiation dose to reduce the late biochemical failure rate, which measured 30% per ASTRO biochemical relapse criteria and 10% per “nadir + 2” biochemical relapse criteria, in a favorable prognosis patient group.

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Considering the above, balancing the need to deliver adequate dose while maintaining a reasonable safety expectation, the dose fractionation regimen used in this protocol will be 34 Gy in 5 fractions of 6.8 Gy per fraction, with further internal prostate dose escalation accomplished using “HDR-like” peripheral zone dose molding, while creating sharp dose gradients that limit dose to adjacent critical bladder, urethra and rectum.

Patients selected for inclusion in this study will have clinically localized, biopsy-proven recurrent prostate cancer following a prior course of definitive prostate cancer radiotherapy, with no evidence of significant preexisting radiation injury from their original treatment course. To minimize the chance of incorrect recurrence biopsy diagnosis, and to reduce their chance of receiving potentially toxic local retreatment only to then rapidly fail with distant metastatic disease, the interval since their original radiation treatment will be at least two years. They shall not have any radiographic evidence of lymphatic or hematogenous metastatic disease, and their recurrent lesion shall not have a T-stage higher than T3b. Their disease-free survival and complication rate following Virtual HDR CyberKnife salvage treatment will be assessed. Initially the sample size will be limited to 20 cases, with additional cases potentially enrolled thereafter, pending confirmation of reasonable safety of this treatment method in the initial 20 patient cohort.

### **2.0 OBJECTIVES**

#### **2.1 Primary Objectives**

The primary objective of the study will be to establish the pattern of PSA decline following Virtual HDR CyberKnife treatment for locally recurrent prostate cancer, and to evaluate the biochemical and clinical relapse-free survival thereafter, using the ASTRO and Phoenix definitions of biochemical relapse. The second primary objective of this study will be to evaluate the incidence of grade III or higher normal tissue toxicity.

#### **2.2 Secondary Objective**

The secondary objective will be to evaluate quality of life, relative to other commonly used methods of treatment for recurrent prostate cancer. EPIC long-form, IPSS and IIEFF scoring will be used in the QOL evaluation.

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## REFERENCES

1. Bianco FJ Jr, Scardino PT, Stephenson AJ, Diblasio CJ, Fearn PA, Eastham JA. Long-term oncologic results of salvage radical prostatectomy for locally recurrent prostate cancer after radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005 Jun 1;62(2):448-53
2. Sanderson KM, Penson DF, Cai J, Groshen S, Stein JP, Lieskovsky G, Skinner DG. Salvage radical prostatectomy: quality of life outcomes and long-term oncological control of radiorecurrent prostate cancer. *J Urol*. 2006 Nov;176(5):2025-31
3. Stephenson AJ, Scardino PT, Bianco FJ Jr, DiBlasio CJ, Fearn PA, Eastham JA. Morbidity and functional outcomes of salvage radical prostatectomy for locally recurrent prostate cancer after radiation therapy. *J Urol*. 2004 Dec;172(6 Pt 1):2239-43
4. Pisters LL, von Eschenbach AC, Scott SM, Swanson DA, Dinney CP, Pettaway CA, Babaian RJ. The efficacy and complications of salvage cryotherapy of the prostate. *J Urol*. 1997 Mar;157(3):921-5
5. Ghafar MA, Johnson CW, De La Taille A, Benson MC, Bagiella E, Fatal M, Olsson CA, Katz AE. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy: the Columbia experience. *J Urol*. 2001 Oct;166(4):1333-7
6. Izawa JI, Ajam K, McGuire E, Scott S, von Eschenbach AC, Skibber J, Pisters LL. Major surgery to manage definitively severe complications of salvage cryotherapy for prostate cancer. *J Urol*. 2000 Dec;164(6):1978-81
7. Chin JL, Lim D, Abdelhady M. Review of primary and salvage cryoablation for prostate cancer. *Cancer Control*. 2007 Jul;14(3):231-7
8. Gelet A, Chapelon JY, Poissonnier L, Bouvier R, Rouviere O, Curiel L, Janier M, Vallancien G. Local recurrence of prostate cancer after external beam radiotherapy: early experience of salvage therapy using high-intensity focused ultrasonography. *Urology*. 2004 Apr;63(4):625-9
9. Wong WW, Buskirk SJ, Schild SE, Prussak KA, Davis BJ. Combined prostate brachytherapy and short-term androgen deprivation therapy as salvage therapy for locally recurrent prostate cancer after external beam irradiation. *J Urol*. 2006 Nov;176(5):2020-4.
10. Beyer DC. Permanent brachytherapy as salvage treatment for recurrent prostate cancer. *Urology*. 1999 Nov;54(5):880-3
11. Beyer DC. Salvage brachytherapy after external-beam irradiation for prostate cancer. *Oncology (Williston Park)*. 2004 Feb;18(2):151-8.
12. Grado GL, Collins JM, Kriegshauser JS, Balch CS, Grado MM, Swanson GP, Larson TR, Wilkes MM, Navickis RJ. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. *Urology*. 1999 Jan;53(1):2-10.
13. Huang WC, Lee CL, Eastham JA. Locally ablative therapies for primary radiation failures: a review and critical assessment of the efficacy. *Curr Urol Rep*. 2007 May;8(3):217-23
14. Lee B, Shinohara K, Weinberg V, Gottschalk AR, Pouliot J, Roach M 3rd, Hsu IC. Feasibility of high-dose-rate brachytherapy salvage for local prostate cancer recurrence after radiotherapy: the University of California-San Francisco experience. *Int J Radiat Oncol Biol Phys*. 2007 Mar 15;67(4):1106-12
15. King CR, Lehmann J, Adler JR, Hai J. CyberKnife radiotherapy for localized prostate cancer: rationale and technical feasibility. *Technol Cancer Res Treat*. 2003 Feb;2(1):25-30.

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16. Chang SD, Main W, Martin DP, et al. An analysis of the accuracy of the CyberKnife: a robotic frameless stereotactic radiosurgical system. *Neurosurgery*. 2003;52(1):140-146

17. Fuller DB, Lee CL, Hardy S, Jin H, Virtual HDR<sup>sm</sup> CyberKnife Prostate Treatment: Toward the Development of Non-Invasive HDR Dosimetry Delivery and Early Clinical Observations. *International Journal of Radiation Oncology, Biology, Physics*, 69(3S), Abstract 2279. October 2007.

18. Williams SG, Taylor JM, Liu N, Tra Y, Duchesne GM, Kestin LL, Martinez A, Pratt GR, Sandler H. Use of individual fraction size data from 3756 patients to directly determine the alpha/beta ratio of prostate cancer. *Int J Radiat Oncol Biol Phys*. 2007 May 1;68(1):24-33.

19. Madsen BL, Hsi RA, Pham HT, Fowler JF, Esagui L, Corman J. Stereotactic hypofractionated accurate radiotherapy of the prostate (SHARP), 33.5 Gy in five fractions for localized disease: first clinical trial results. *Int J Radiat Oncol Biol Phys*. 2007 Mar 15;67(4):1099-105.