

Image-Guided Stereotactic Body Radiation Therapy for Clinically Localized Prostate Cancer: Preliminary Clinical Results

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Stereotactic body radiotherapy (SBRT) is a new treatment modality for prostate cancer. The current study evaluates CyberKnife® SBRT and reports toxicity and early Prostate-Specific Antigen (PSA) kinetics. From June 2006 to August 2009, 45 low-and intermediate-risk prostate cancer patients received Cyberknife SBRT of 35 Gy in five fractions with 95% minimum target coverage. Median follow-up was 20-months (range 6-42-months). Seventeen patients received androgen-deprivation therapy also. Acute complications were mild, short-lived and no greater than Grade 2 by RTOG scale. Late toxicities consisted of one patient (2.2%) experiencing Grade 2 rectal, one patient (2.2%) Grade 3 and four patients (8.8%) with Grade 1 urinary toxicity. PSA in all patients progressively declined from a mean 4.7 ng/ml baseline to 1.48 ng/ml at three months, to 0.68 ng/ml at 12 months and to 0, 35 ng/ml at 24 months. The 28 hormon-naive patients had the mean PSA value of 1.1 ng/ml at one year from a mean 6.65 ng/ml baseline. There was a significant PSA value reduction in 11 hormone therapy patients with low baseline PSA value (≤ 1 ng/ml) from 0.37 down 0.14 ng/ml (p value 0.0068) at one year. Moreover, 14 low risk patients gave better results of mean PSA value than 17 Intermediate risk patients 0.43 ng/ml vs. 0.93 ng/ml (p value 0.02) at one year. No patient had biochemical failure at last follow-up. Hypofractionated SBRT appears to have potential against prostate cancer. Low toxicity and encouraging biochemical control support its use in early-stage prostate cancer. Results encourage further follow-up and larger studies.

Key words: Prostate cancer; Stereotactic body radiotherapy; Hypofractionation; PSA; Toxicity.

Introduction

The modern practice of radiotherapy (RT) offers certain choices of treatment, such as multi-field 3-D conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) (1) and stereotactic body radiotherapy (SBRT) (2).

Clinical, biologic and technological factors deeply influence the treatment of cancer patients with radiotherapy (1). In particular, technological advances in radiation therapy (3) have drastically changed the way patients with prostate cancer are treated these days.

Abbreviations: SBRT: Stereotactic body radiotherapy; PSA: Prostate-specific antigen; RTOG: Radiation Therapy Oncology Group; 3D-CRT: Three dimensional conformal radiotherapy; IMRT: Intensity-modulated radiotherapy; IGRT: Image-guided radiotherapy; TURP: Transurethral radical prostatectomy; TRUS: Transrectal ultrasound; ECOG: The Eastern Cooperative Oncology Group; AD: Androgen deprivation; PTV: Planning target volume; QoL: Quality of life; EBRT: External beam radiotherapy.

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In the current practice, the priority of radiation therapy has been found to adequately treat prostate cancer without damaging the rectum and the bladder, *i.e.*, keeping the dose to these organs within their respective levels of tolerance. Moreover, both recent analyses and reviews of clinical tumor control data support a low α/β ratio for prostate cancer, on the order of 1 to 3 Gy, which suggests that prostate cancer should be treated with fewer and larger doses of radiation — the hypofractionated approach (4, 5). There is increasingly convincing evidence that biochemical control, indicated by blood prostate-specific antigen (PSA) concentrations, improves with higher doses of radiation delivered per fraction, an observation noted by recent articles of publication (6-8). This fact introduces the challenge of delivering a very high dose to the prostate while keeping the dose to the surrounding organs at risk at acceptable levels.

CyberKnife® Robotic Radiosurgery System (Accuray Incorporated, Sunnyvale, California, U.S.A.) is one of the better-suited instruments to this end, with a 6-MV linear accelerator installed on a computer-controlled robotic arm that provides stereotactic targeting with flexibility; it allows for real-time organ positioning and motion correction during delivery. It also allows for non-isocentric inverse treatment planning, as it works with multiple non-coplanar beams shot from 1600 possible angles (2, 9). Accurate targeting is accomplished through *in-situ* orthogonal X-ray imaging and internal fiducials as reference markers used for alignment of the linear accelerator by the robotic arm (2, 10).

In this study, we set out to evaluate the feasibility, tolerability, early biochemical control and toxicity of CyberKnife SBRT as applied to the treatment of patients with low-and intermediate-risk prostate cancer.

Methods and Materials

Patient Eligibility

At our institution, from June 2006 to August 2009, 45-patients (Table I) with biopsy-proven prostate cancer were treated with CyberKnife SBRT. Eligibility of the patients was determined by a multidisciplinary tumor board consisting of a urologist, a medical oncologist and a radiation oncologist. The patients' advanced age and ineligibility for surgery were determinant factors in the indication of CyberKnife SBRT.

Clinical work-up consisted of a physical examination, including a digital rectal examination, and a PSA test, if the earlier test was conducted more than six weeks before the patient entered our care. Staging was performed according to the American Joint Committee on Cancer guidelines of 1997. Twenty-two patients had low-risk disease (T1c-T2a, Gleason score ≤ 6 , PSA < 10 ng/ml), and 23 had intermediate-risk

Table I
Patients characteristic, 45 Cyberknife -SBRT pts.

Median follow-up 20 months (6-42 months)			
RT group	28-pts		
RT+AD	17		
Average value PSA			
RT group	6.92 ng/ml Range [2.2-14]		
RT+AD group (at diagnosis)	8.07 ng/ml Range [2-20]		
RT+AD group (prior RT)	1.48 ng/ml Range [0.1-8.70]		
Gleason grade	5	(2+3, 3+2)	4 pts
	6	(3+3)	36
	7	(3+4)	5
Clinical stage	T1c		19 pts
	T2a		9
	T2b		5
	T2c		12
Risk	Low		22 pts
	Intermediate		23

pts = patients, RT = Radiotherapy, SBRT = Stereotactic Body Radiotherapy, AD = Androgen Deprivation Therapy.

disease (T2b-2c, Gleason score 7, PSA 10-20). Patients were divided into two groups: 28 received radiotherapy only (the RT group), and 17 received radiotherapy and androgen deprivation therapy (the RT + AD group). In the RT + AD group, three-patients received hormone therapy before radiotherapy; eleven patients received it for one year after radiotherapy and three-patients for two-years. Three patients had undergone transurethral resection (TURP) one, four, and five-years prior to SBRT. Median prostate volume calculated with transrectal ultrasound (TRUS) was 32.5 cc (range 16 – 69 cc); patients with larger than 70-cc prostate volume were excluded. Median age was 73-years (range 62 – 80 years). The older patients had 0 ECOG performance status, the cut-off for eligibility being 0-1. Transperineal endoscopic ultrasound-guided biopsies performed per patient ranged from six to 20 (mean 10.5). Clinical stages were T1c in 19 patients, T2a in nine-patients, T2b in five patients and T2c in 12-patients. Gleason score was 5 (2+3 or 3+2) in four-patients, 6 (3+3) in 36-patients and 7 (3+4) in five-patients. In all patients, mean PSA at diagnosis was 8.07 ng/ml. Immediately before the treatment, the PSA readings were 1.48 ng/ml in the RT + AD group, and 6.65 ng/ml in the RT group. No patient had a PSA level higher than 20 ng/ml.

Treatment

Four gold fiducials were implanted in the prostate, with transperineal ultrasound guidance. Two-weeks post-fiducial implantation, and two helical pelvic CT scans, were acquired in supine position with 1-mm slice thickness – one of the scans with bladder contrast and the other without - in order to be used in treatment planning. The week before the planning

CT acquisitions, the patients were put on a gas-minimizing diet. Both the planning CT and the treatment were performed with an empty rectum and a catheter-controlled bladder.

For treatment planning, the prostate gland, seminal vesicles, rectum, bladder, penile bulb and femoral heads were contoured. The planning target volume (PTV) included the prostate, with a 5-mm volumetric expansion, which was reduced to 3 mm toward the rectum. The treatment consisted of five fractions of 7 Gy for a total dose of 35 Gy in five consecutive days. The treatment plans contained the specific requirement of a minimum PTV coverage of 95% at the prescription dose, normalized to the 80% isodose line, and the dose to the organs at risk was constrained such that 5% of the rectal volume received no more than 38 Gy, 5% of the bladder no more than 40 Gy, and 5% of the urethra no more than 41 Gy and 25% of the penile bulb 29 Gy.

Results

Toxicity

All patients were able to complete the treatment. Median follow-up was 20-months (range 6-42 months). Toxicity was reported at the baseline, at ten-days, one-month and three-months, and every six-months after the treatment, using the RTOG acute and late toxicity criteria. Urinary and rectal toxicities are reported in Table II. In the majority of the patients, toxicity, in the form of urgency or urinary frequency, and rectal urgency or stool frequency, happened during either the first week or the following two to four weeks. Acute urinary toxicity occurred in 21-patients (46.6%), as Grade 1 toxicity in 16-patients (35.5%) and Grade 2 toxicity in 5-patients (11.1%). No Grade 3 or 4 acute toxicity was encountered.

To assess toxicity according to prostate volume, we divided the patients into two groups, a group with prostate volumes larger than or equal to 30 cc, and one of patients with volumes less than 30 cc. Acute urinary toxicity, evaluated based on prostate volume, was not different in the two groups of patients: 42.10% in the group with prostate volume < 30 cc

(19-patients) and 50% in the group with prostate volume ≥ 30cc (26-patients). No urinary toxicity difference occurred between the patients in the RT + AD group and those in the RT group, either. They were 47% (8/17 patients) and 46.4% (13/28 patients), respectively.

Acute rectal toxicity occurred in 22-patients (48.8%), 11 (24.4%) of whom had Grade 1, and 11 Grade 2. There were no Grade 3 or 4 rectal toxicities and no difference between patients with prostate volume < 30 cc and ≥ 30 cc, which were 47.3% (9/19 patients) vs. 50% (13/26 patients), respectively.

Late (six-months and later) urinary toxicities, as frequency or urgency, occurred in five patients (11%), four of whom had Grade 1 and one Grade 3 based on RTOG score. Of the three patients who had undergone TURP prior to treatment, two experienced late Grade 1 and Grade 3 urinary toxicity. Late rectal toxicities, *i.e.*, occasional bleeding, occurred in one patient out of 45 (2.2%).

PSA Response

Figure 1 shows mean PSA values after CyberKnife SBRT. In all patients, PSA decreased continuously, with a mean of 1.48 ng/ml at three months, 0.68 ng/ml at 12-months, and 0.35 ng/ml at 24-months.

In the RT + AD group (PSA value of 1.48 ng/ml prior RT) the mean PSA was 0.23 ng/ml, 0.23 ng/ml and 0.18 ng/ml at 3, 12, 24 months, respectively (Figure 2). In the RT group (PSA value of 6.65 ng/ml prior RT) the mean PSA was 2.24 ng/ml, 1.10 ng/ml and 0.47 ng/ml at 3, 12, 24 months post treatment, respectively (Figure 3).

In 11-patients of the RT + AD group with low baseline PSA value of ≤ 1 ng/ml (mean 0.37 ng/ml), PSA continued to decrease from 0.37 down to 0.14 ng/ml at one-year (p value 0.0068). By analyzing 31 low and intermediate risk patients at one year, a mean PSA of 0.43 ng/ml was found in 14 low risk patients, and of 0.97 ng/ml in 17 intermediate risk patients (p value 0.02).

Table II
Cyberknife-SBRT: toxicity in 45 patients.

	RTOG Grade			
	I	II	III	IV
Acute				
Urinary % (n° pts)	35.5% (16)	11.1% (5)	-	-
Rectal % (n° pts)	24.4% (11)	24.4% (11)	-	-
Late				
Urinary % (n° pts)	8.8% (4)	-	2.2% (1)	-
Rectal % (n° pts)	-	2.2% (1)	-	-

SBRT = Stereotactic Body Radiation Therapy, RTOG = Radiation Therapy Oncology.

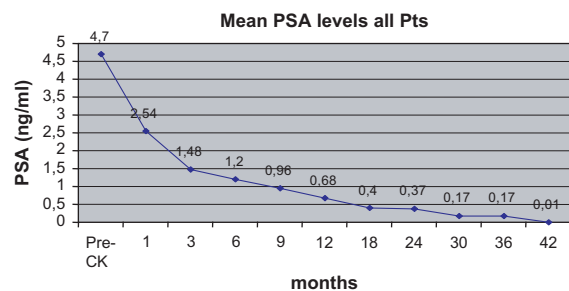


Figure 1: Mean PSA level (ng/ml), all patients.

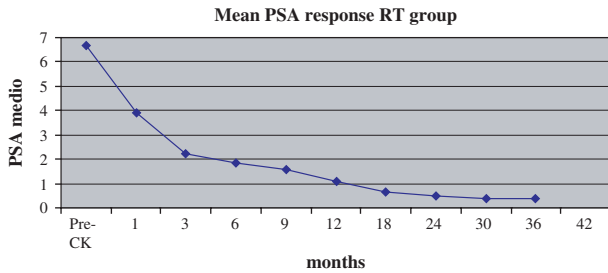


Figure 2: Mean PSA level (ng/ml), without hormone.

Discussion

The present study adds to the evidence in the literature on the benefits of hypofractionation, a relatively recent phenomenon, in the treatment of prostate cancer (7, 9, 11, 12). According to the theory of radiobiology, larger fraction doses should cause higher damage to prostate cancer cells than to normal tissue cells surrounding them, because of the low α/β ratio of prostate cancer cells (5, 13-15). With advanced computer-aided technologies, the prostate target volume can be treated with higher radiation dose levels (1, 4, 8).

SBRT, combined with enhanced technologies, including the CyberKnife, allows the beams to be targeted more precisely to the prostate, while exposing the rectum and the bladder to the smallest possible doses of radiation (9, 10, 16). In this way, advanced SBRT techniques should theoretically obtain better disease control with fewer side effects. The 35/5 dose was applied, as many clinic studies support the efficacy and safety of larger doses (5, 6, 7, 8, 12).

According to King *et al.*, (10) 89% of the 41-patients treated with CyberKnife had no quality of life (QoL) problems as far as rectal health, and 90% reported a QoL score below 3 as far as urinary problems following the treatment. Friedland *et al.*, (9), in one series of 100-patients treated with CyberKnife, reported no cases of urinary stricture or incontinence; only one patient had Grade 3 rectal toxicity. The results in our series were similar: no patient had late rectal Grade 3 toxicity, only one-patient had Grade 3 urinary urgency. The latter patient had undergone TURP before entering our trial. This may or

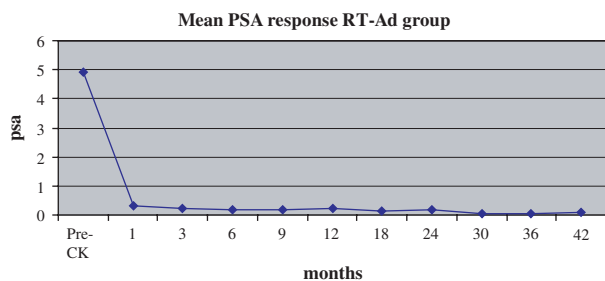


Figure 3: Mean PSA level (ng/ml), with hormone.

may not have contributed to the relatively serious toxicity this patient experienced. Literature reports an increased risk of acute and severe radiation toxicities in patients who had had TURP before external beam radiation therapy (EBRT), but it also stresses that overall incidence of long-term toxicity is low and not persistent.

When comparing other prognostic factors, *i.e.*, hormone therapy and prostate volume in relation to acute and late toxicities, no differences were seen. With regard to the hormone therapy group, we had the same genito-urinary acute toxicity rates: 47% (8/17 patients) and 46.6% (13/28 patients), respectively, in the RT + AD and the RT groups, contrary to the results in the literature for 3-D radiation therapy (17). As for acute rectal toxicity, there was no difference between the RT + AD and the RT group – 35% (6/17 patients) and 57% (16/28 patients).

As for toxicity, we evaluated prostate volume as a prognostic factor of acute toxicity. There was no difference between the two groups with plus or equal to 30 cc and less. In the ≥ 30 cc. group, 3/26 patients (11.5%) had acute Grade 2 genito-urinary toxicity and 7/26 patients had acute Grade 2 rectal toxicity. In the group with less than 30 cc prostate volume, 2/19 patients (10.5%) had grade 2 genitourinary toxicity and 4/19 patients (21%) had acute Grade 2 rectal toxicity.

Within the confines of the limited experience that so far has made it to press, CyberKnife SBRT has demonstrated promising biochemical control. King *et al.*, have observed a median PSA nadir of 0.32 ng/ml at 33 months (10); Friedland *et al.*, have reported that 44% of the patients treated with hormone therapy in addition to CyberKnife obtained a PSA nadir below 1.0 ng/ml at 1-year (9). In our series, the PSA readings continuously decreased down to a value of 0.40 ng/ml in 31 of the 45-patients at 18-month medium follow-up. The 28-patients treated without hormone therapy attained a PSA level of 0.84 ng/ml at one year. Paralleling the 2009 King *et al.*, study on SBRT with CyberKnife (10), in our series also, no patient had PSA failure at last follow-up, regardless of the definition of biochemical failure (18).

There was a significant PSA value reduction in patients with low baseline PSA value, (≤ 1 ng/ml), who had hormone therapy (p value 0.0068).

Literature reports a better biochemical control rate and a better PSA free survival in patients with different risk factors. In fact, our 14 low risk patients gave better results of mean PSA value at one year than the 17 intermediate risk patients - 0.43 ng/ml vs. 0.93 ng/ml (p value 0.02).

Although all these results seem promising as far as biochemical response and complications, it is well known that prostate

cancer is a slow-progressing ailment and monitoring its outcome requires extended amounts of time measured in years rather than months. The results of the current study can only be considered preliminary, calling for further follow up and other more extensive studies to test the possibilities of high-precision SBRT against prostate cancer.

Conclusions

SBRT is a new technique, so follow up is relatively short. In our series, this technique seems to have high potential for the therapy of prostate cancer; its use is facilitated and enhanced by technological advances. Low toxicity and encouraging biochemical control support the use of SBRT in early-stage prostate cancer. In our series, urinary and rectal complications were acceptable, with a sharp PSA response. Although the results seem very encouraging both for PSA response and for low complications, longer-term follow-up analysis will be necessary. The results of the present study will have to be confirmed in 2-3 years.

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Conflicts of interest

None.

References

1. Levitt, S. H., Perez, C. A., Hui, S., Purdy, J. A. Evolution of computerized radiotherapy in radiation oncology: potential problems and solutions. *Int J Radiat Oncol Biol Phys* 70, 978-986 (2008).
2. Wurm, R., Okunieff, P. Intracranial and Extracranial Stereotactic Radiosurgery and Radiotherapy. *Int J Radiat Oncol Biol Phys* 66, S1-S2 (2006).
3. Ling, C. C., Yorke, E., Fuks, Z. From IMRT to IGRT: frontierland or neverland? *Radiother Oncol* 78, 119-122 (2006).
4. Ritter, M. Rationale, conduct, and outcome using hypofractionated radiotherapy in prostate cancer. *Semin Radiat Oncol* 18, 249-256 (2008).
5. Fowler, J., Chappell, R., Ritter, M. Is alpha/beta for prostate tumors really low? *Int J Radiat Oncol Biol Phys* 50, 1021-1031 (2001).
6. Zelefsky, M. J., Fuks, Z., Hunt, M., Yamada, Y., Marion, C., Ling, C. C., Amols, H., Venkatraman, E. S., Leibel, S. A. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 53, 1111-1116 (2002).
7. King, C. R., Lehmann, J., Adler, J. R., Hai, J. CyberKnife radiotherapy for localized prostate cancer: rationale and technical feasibility. *Technol Cancer Res Treat* 2, 25-29 (2003).
8. Kupelian, P. A., Willoughby, T. R., Reddy, C. A., Klein, E. A., Mahadevan, A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys* 68, 1424-1430 (2007).
9. Friedland, J. L., Freeman, D. E., Masterson-McGary, M. E., Spellberg, D. M. Stereotactic body radiotherapy: an emerging treatment approach for localized prostate cancer. *Technol Cancer Res Treat* 8, 387-392 (2009).
10. King, C. R., Brooks, J. D., Gill, H., Pawlicki, T., Cotrutz, C., Presti, J. C., Jr. Stereotactic body radiotherapy for localized prostate cancer: interim results of a prospective phase II clinical trial. *Int J Radiat Oncol Biol Phys* 73, 1043-1048 (2009).
11. Fuller, D. B., Naitoh, J., Lee, C., Hardy, S., Jin, H. Virtual HDR CyberKnife treatment for localized prostatic carcinoma: dosimetry comparison with HDR brachytherapy and preliminary clinical observations. *Int J Radiat Oncol Biol Phys* 70, 1588-1597 (2008).
12. Madsen, B. L., Hsi, R. A., Pham, H. T., Fowler, J. F., 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* 67, 1099-1105 (2007).
13. Brenner, D. J. Toward optimal external-beam fractionation for prostate cancer. *Int J Radiat Oncol Biol Phys* 48, 315-316 (2000).
14. Fowler, J. F., Ritter, M. A., Chappell, R. J., Brenner, D. J. What hypofractionated protocols should be tested for prostate cancer? *Int J Radiat Oncol Biol Phys* 56, 1093-1104 (2003).
15. Brenner, D. J., Martinez, A. A., Edmundson, G. K., Mitchell, C., Thames, H. D., Armour, E. P. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys* 52, 6-13 (2002).
16. Zelefsky, M. J., Chan, H., Hunt, M., Yamada, Y., Shippey, A. M., Amols, H. Long-term outcome of high dose intensity modulated radiation therapy for patients with clinically localized prostate cancer. *J Urol* 176, 1415-1419 (2006).
17. Peeters, S. T., Heemsbergen, W. D., van Putten, W. L., Slot, A., Tabak, H., Mens, J. W., Lebesque, J. V., Koper, P. C. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy. *Int J Radiat Oncol Biol Phys* 61, 1019-1034 (2005).
18. Roach, M., 3rd, Hanks, G., Thames, H., Jr., Schellhammer, P., Shippey, W. U., Sokol, G. H., Sandler, H. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 65, 965-974 (2006).

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