Technology in Cancer Research and Treatment
ISSN 1533-0346
Volume 9, Number 5, October 2010

CyberKnife Radiosurgery for Prostate Cancer

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Treatment of prostate cancer with SBRT is an area of significant controversy for many in the radiation oncology community despite radiobiologic data that strongly suggest the prostate would be an excellent SBRT target. Recently, new data have emerged that show promising outcomes with minimal toxicity for CyberKnife SBRT of prostate cancer. In the following we present the motivating factors for prostate cancer SBRT followed by a critical evaluation of the current literature and discussion of the future of prostate cancer treatment with SBRT.

Introduction

In recent years the lung, liver, spine, and kidney have become the poster children for stereotactic body radiation therapy (SBRT), with widespread use and favorable treatment outcomes (*e.g.,* (1-4); for review see (5)). Yet, treatment of prostate cancer with SBRT has become an area of significant controversy for many in the radiation oncology community. Indeed, this controversy has even prompted a 2008 position statement from the American Society for Therapeutic Radiology and Oncology (ASTRO) on SBRT for prostate cancer (6) and a subsequent report from their emerging technology committee (7). The irony of this acclamation for SBRT of lung, liver, spine, and kidney while eschewing SBRT for prostate is that radiobiologic discussions of the α/β ratio strongly suggest the prostate would be an excellent SBRT target. Furthermore, several publications since the release of the ASTRO statement present promising outcomes with minimal toxicity for CyberKnife SBRT of prostate cancer (8-12). In the following we present the motivating factors for prostate cancer SBRT followed by a critical evaluation of the current literature and discussion of the future of treatment of prostate cancer with SBRT.

The Evolution of SBRT for Prostate Cancer

Radiation therapy itself has been used for decades in the treatment of prostate cancer, with 5-year biochemical control rates of 60-85% for external beam radiation therapy (EBRT) at doses of 70-80 Gy (13) and 5-year biochemical control rates of 84-97% for intensity modulated radiation therapy (IMRT) at doses of 70-81 Gy (14, 15). Nevertheless, Zelefsky *et al*., have shown that even higher doses are likely needed, particularly for intermediate- and high-risk prostate cancer, even with the use of IMRT (15). Unfortunately, increasing the dose also increases the risk of toxicity.

The radiobiology of prostate cancer supports hypofractionated radiation delivery as an option to increase the dose while limiting toxicity. Specifically, there is a great deal of evidence that prostate cancer cells have a high degree of sensitivity to dose per fraction, as opposed to most other epithelial tumors (16, 17). This is not surprising since tumors with a low proportion of dividing cells are very

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sensitive to fractionation changes. The dose response of tumors and normal tissue to radiation can be calculated according to the α/β ratio which represents the overall radiation sensitivity of a cell to radiation (see (18) for a detailed discussion of the α/β ratio). If the α/β ratio is high (*e.g.,* around 10 Gy) there is little sensitivity to dose per fraction, as is the case in early responding normal tissues (such as mucosa and skin) and most tumors. A low α/β ratio, less than 5 Gy, would mean greater sensitivity to dose per fraction, as seen in late responding tissues. Since most tumors are not sensitive to fraction size but normal tissues are, many small doses of fractionated radiotherapy optimizes tumor control and minimizes risk of late normal tissue damage. Studies have suggested that the α/β ratio for prostate cancer is as low as 1.2 Gy, putting it below the ratio of around 3-5 Gy for late responding tissues (19). This would imply that a hypofractionated schedule of radiotherapy (*i.e.,* fewer fractions delivered with a larger dose) would increase the therapeutic ratio by driving up the biological equivalent dose for tumor control and decreasing the equivalent dose for late tissue response.

The first reported use of extreme hypofractionation (4-8 fractions) for prostate cancer was in England during the period of the late 1960s through the early 1980s (20), although its use was prompted by economic matters rather than a desire to escalate the prostate dose. Patients received a total dose of 36 Gy delivered in 6 fractions of 6 Gy over two weeks with large fields (this was prior to CT imaging and image guidance). The patients had good clinical response—the PSA response could not be assessed in this era—with overall survival curves similar to the unaffected population. In addition, there was surprisingly low morbidity considering that the volume of normal tissue treated was high relative to today's volumes. Nevertheless, the use of extreme hypofractionation was not pursued further for many years.

As a result the path to use of hypofractionation for prostate cancer has been long and comprised of small steps towards ever-larger degrees of hypofractionation. Mild hypofractionation schemes of 20-28 fractions were the first schemes designed to increase the biological equivalent dose through hypofractionation. Assuming an α/β ratio of 1.5 Gy, mild hypofractionation yields biologically equivalent doses of 70-85 Gy. These dosing schemes have been thus far successful, as measured by enhanced local control with no increase in morbidity. For instance, Kupelian *et al.,* delivered 70 Gy in 28 fractions using IMRT with 95% control at 7-years in low-risk patients and 85% control in intermediate-risk patients (14). If the α/β ratio were 10 Gy, this dose scheme would be the equivalent of 72 Gy and would not yield such high control rates. If the α/β ratio is 1.5 Gy, then the equivalent dose delivered is 84 Gy at 1.8 Gy per fraction. Cahlon *et al.,* report almost exactly the same control rates as Kupelian *et al.,* in all risk categories, with delivery of 86 Gy at 1.8 Gy per fraction, using so called ultra-high dose IMRT (21). The biologically equivalent dose (BED) for several studies of hypofractionated radiation therapy assuming different α/β values are shown in Table I.

Pursuit of extreme hypofractionation requires precise delivery of high doses of radiation to the target tissue which limits the use of EBRT. High-dose-rate brachytherapy (HDR) ensures such accuracy in dose delivery. In fact, excellent tumor control with low morbidity has been achieved with HDR brachytherapy as monotherapy for low-risk prostate cancers, using 4-8 high dose fractions. For instance, Martinez

Table I

Clinical results from various treatment modalities support the hypothesis of a low α/β ratio. Shown are the biologically equivalent doses at 1.8 Gy per fraction for α/β ratios of 10, 3 and 1.5 Gy.

Study	Treatment	BED α/β = 10 Gy	BED α/β = 3 Gy	BED α/β = 1.5 Gy	Biochemical Control Rate
Kupelian *et al.* (14)	IMRT, 70 Gy in 28 fractions	72 Gy	81 Gy	84 Gy	95% for low-risk; 85% for intermediate-risk patients at 7-years
Cahlon *et al.* (21)	IMRT, 86.4 Gy in 48 fractions	86.4 Gy	86.4 Gy	86.4 Gy	98%, 85% and 70% for low-, intermediate-, and high-risk patients at 5-years
Martinez *et al.* (22)	HDR, 38 Gy in 4 fractions or 42 Gy in 6 fractions	63 Gy	97 Gy	125 Gy	91% at 5-years
Demanes *et al*. (23)	HDR + EBRT, range of doses	58-85 Gy	70-95 Gy	87-120 Gy	87% and 69% for intermediate- & high-risk patients at 10-years
King *et al*. (8)	SBRT, 36.25 Gy in 5 fractions	52 Gy	78 Gy	96 Gy	100% at 33 months
Katz *et al*. (10)	SBRT, 35 Gy in 5 fractions	50 Gy	72 Gy	92 Gy	100% at 30 months
Katz *et al*. (38)	EBRT, 45 Gy in 25 fractions, plus SBRT 18-21 Gy in 3 fractions	69-76 Gy	77-89 Gy	88-98 Gy	92.5% for intermediate-risk 79% for high-risk

et al., reported a 5-year freedom from biochemical relapse rate of 91% using a total dose of 38 Gy in 4 fractions or 42 Gy in 6 fractions (22). For higher risk tumors, Demanes *et al.*, reported 10-year freedom from biochemical relapse rates in intermediate- and high-risk patients of 87% and 69%, respectively, using HDR brachytherapy as a boost following EBRT (23). These HDR treatments, although effective and safe, require hospitalization, anesthetic, urinary catheterization and are uncomfortable for patients. It should be noted that these dose regimens push the equivalent dose even higher to over 90 Gy if the α/β ratio is 1.5 Gy.

The first study on the use of SBRT to deliver HDR-like hypofractionated treatments came from Madsen *et al.,* (24). Forty low-risk patients were treated using 6 collimated non-coplanar beams, to deliver 33.5 Gy Dmax over 5 fractions. Treatment was well tolerated with no late Grade 3 toxicity reported. However, biochemical control rates were disappointing, with 4-year actuarial freedom from biochemical relapse rates of 70% and 90% using the ASTRO and Phoenix (nadir +2) definitions, respectively. It is important to note that the prostate was covered by only 90% of the prescribed dose, or 30 Gy in 5 fractions. Consequently, with an α/β ratio of 1.5 the biologically equivalent dose would have been 66 Gy, which likely accounts for the poor biochemical control rates.

CyberKnife SBRT

The CyberKnife has unique features ideally suited for SBRT of prostate cancer including the use of several hundred non-coplanar beams from a Linac supported by a robotic arm, the delivery of highly conformal dose plans and the ability to track prostate motion in real-time (25). The first feasibility study on the use of the CyberKnife for hypofractionation in prostate cancer came from Stanford (26). This study demonstrated the superiority of CyberKnife treatment planning to the target, bladder and rectum when compared to IMRT by planning an identical case with both modalities. In addition to a high degree of conformality, the need for accuracy when delivering very high daily doses using SBRT is essential. CyberKnife SBRT employs fiducial markers, placed in the gland, to verify organ position in real time via a pair of orthogonal electronic x-ray imaging devices. This information is used to perform real-time corrections for position during the treatment by overlaying the images obtained on digitally reconstructed radiographs from the planning CT scan. The conformality and accuracy obtained with the CyberKnife is ideally suited for delivery of large hypofractionated doses (26). Since the CyberKnife provides intrafractional tracking, the amount of normal tissue included in the planning volume to cover the uncertainty of position can be reduced.

The conformality of treatment plans produced with the CyberKnife has also been shown to be superior to IMRT by Hossain *et al.,* who performed treatment planning for 8 patients with both the Accuray Multiplan system and a 9-field IMRT system (27). The CyberKnife plans had better conformality indices (1.18 vs. 1.44) than the IMRT plans, but they also had slightly higher dose inhomogeneity in the target volume. The fall-off of the dose was similar for the two plans. The need to track prostate motion and adjust for it has been studied by Hossain *et al.,* (28), who reviewed the dosimetric effect of intrafraction motion during a CyberKnife treatment of 9.5 Gy lasting 50-70 minutes. The effect of movement was found to be case dependent; although most cases did not have enough movement to affect the V100 substantially, sporadic intrafraction motion was seen which could reduce the V100 by 10%. The authors conclude that the online target motion monitoring and correction strategy, available with CyberKnife, is necessary to implement hypofractionated stereotactic radiotherapy. Xie *et al*., examined intrafraction motion of 21 prostate cancer patients treated with the CyberKnife at Stanford University (29). They conclude that reimaging approximately every 40 seconds, is sufficient in most cases to ensure sub-millimeter tracking, although they note that in certain cases sporadic motion was seen which would require more frequent sampling. They also examined deformation of the prostate by measuring the spatial relationship between three implanted seeds and found no evidence of significant deformation. These results highlight the importance of performing intrafraction motion tracking during prostate SBRT. To perform hypofractionation without motion tracking, it is necessary to expand the margin beyond what would be used with CyberKnife SBRT. However, it is important to note that such expanded margins exposes nearby critical structures to increased dose and may cause more normal tissue toxicity.

CyberKnife SBRT Clinical Outcomes

Since 2003, it is estimated that nearly 4,500 patients with early prostate cancer have been treated with the CyberKnife. While a variety of dosing schemes have been used, particularly in the early years of CyberKnife prostate treatment, most range from total doses of 35 Gy delivered in five fractions to 38 Gy delivered in 4 fractions. Recently, several reports on these treatments have been published with promising clinical outcomes (8-12). The following highlights these results while comparing and contrasting the treatment approaches and corresponding observed toxicities and biochemical control. Table II provides a summary of CyberKnife prostate treatment results with more than 12 months follow-up.

One of the earliest reports on CyberKnife SBRT for organ confined disease was an ASTRO abstract from a group in Korea (30) who delivered a total of 32-34 Gy in 4 fractions to 44 patients, the majority of which were intermediate- or high-risk. At a median follow-up of 13 months, overall toxicity was

Table II
Summary of published CyberKnife prostate treatment results with a median follow-up of more than 12 months.

Study	Median Follow-up (months)	PSA Freedom from Relapse (%)	Grade 3+ Late Urinary Toxicity	Grade 3+Late Bowel Toxicity	Erectile Function Preservation Rate
King *et al*. (8)	33	100%	5%	0%	40%*
Friedland *et al.* (9)	24	97%	0%	0%	82%
Katz *et al*. (10)	30	100%	0%	0%	87%
	17	98%	0.5%	0%	

*Wiegner *et al.* median 35.5 months follow-up.

mild. Although the 3-year actuarial biochemical freedom from failure rate was only 78%, the large proportion of intermediate- and high-risk patients likely explains this low biochemical freedom from failure rate.

King *et al.*, performed a prospective Phase 2 clinical trial of low-risk, hormone naïve patients (8). Forty-one patients received 5 fractions of 7.25 Gy. The gross tumor volume (GTV) was delineated on CT images with a 5-mm margin in all directions, except posteriorly where the margin was 3 mm to create the planning target volume (PTV). The dose was prescribed to the 89-90% isodose line, yielding a homogeneous plan. At a median follow-up of 33 months, no biochemical failures were reported. The PSA response was encouraging; 78% of patients with a minimum of 12 months follow-up achieved a PSA nadir of less than 0.4 ng/mL and 29% of patients developed a benign PSA bounce. Late urinary toxicity rates were 24% for Grade 2 and 5% for Grade 3 with 15% Grade 2 late rectal toxicity. Late toxicity in the initial 21 patients led the investigators to treat the latter 20 patients with an every other day (QOD) schedule. Although the numbers are small, there is a suggestion that QOD treatments yield fewer late complications. For instance, 5 of 21 patients treated daily (QD) reported rectal quality of life (QOL) scores that indicated moderate to severe problems, while 0 of 20 patients treated QOD reported moderate problems. Four of 21 patients treated QD reported severe late urinary problems; two of the four developed urethral stricture. One of the 20 QOD patients reported severe problems, although this difference was not statistically significant. These results led King *et al.,* to tentatively recommend the QOD approach to treatment. The researchers concluded that CyberKnife radiosurgery yields a toxicity profile no worse than conventional treatment and that the observed PSA responses are highly encouraging. King *et al*., further note that if the α/β ratio is 10, then they are delivering only 52 Gy at 2 Gy per fraction, which would yield a failure rate of greater than 50%.

A group in Naples, Florida reported on CyberKnife treatment of 112 patients (102 low-risk, 9 intermediate-risk, and 1 high-risk patients) (9). Almost all patients received 35 Gy in 5 fractions over five consecutive days. MRI was obtained and fused to CT images to perform contouring. Twenty-one patients received hormonal ablation prior to CyberKnife treatment. For all patients the GTV was defined as the prostate and proximal 1 cm of seminal vesicles. The PTV expanded the GTV by 5 mm in all directions except posteriorly where the expansion was 3 mm. At a median follow-up of 24 months, the local control rate was 98% (3 patients experienced biochemical failure, with two having biopsy-proven recurrence, and the third patient developed bone metastases). PSA response was good with almost all patients who were followed for three years achieving a PSA of less than 1 ng/mL. In terms of toxicity, AUA scores increased in the first few months following treatment, but after 3 months returned to baseline. One patient required a TURP. No Grade 3 urinary complications were seen and only one patient developed significant rectal bleeding. Of those patients able to achieve erections prior to therapy 82% maintained their potency. The authors conclude that the early results are encouraging, but require more follow-up. They point out that a five day treatment course would yield social and economic benefits to patients. Freeman *et al*., recently presented an update of this data at the ASCO GU meeting (31). At a 30-month median follow-up including 152 patients, there were only 4 local failures, yielding a local control rate of greater than 97%. Toxicity remained low and potency was retained in 81% of patients that were potent prior to treatment.

The largest published series to date was reported by *Katz et al.*, (10) in which 304 patients were treated with the CyberKnife. A minority of patients received hormonal ablation prior to radiotherapy after which it was discontinued. The first 50 patients, most of whom were low-risk, received a total dose of 35 Gy delivered in 5 daily fractions, using homogeneous planning. The PTV was a 5-mm expansion of the prostate GTV, except 3 mm posteriorly. A typical treatment plan covered the PTV with the 83-87% isodose line using 140-170 beams and multiple collimator sizes. The penile bulb mean D50 was 18 Gy and the mean testicular D50 was 5 Gy. At a median 30 months follow-up, there were no biochemical failures and the median PSA was 0.22 ng/mL, with 97% of patients achieving a PSA nadir of less than 1 ng/mL. Toxicity was mild with 5% of patients experiencing Grade 2 acute rectal and urinary toxicity and no higher grade toxicities. Similarly, only 2% of patients had late Grade 2 urinary

toxicity. The subsequent 254 patients received a total dose of 36.25 Gy delivered in 5 daily fractions. Of these patients, 166 were low-risk, 76 were intermediate-risk and 12 were high-risk. The GTV included the proximal seminal vesicles if the patient had intermediate- or high-risk. Planning was otherwise unchanged from the first 50 patients. At a median follow-up of 17 months, there was one local failure in one of the 12 high-risk patients. Two of the 166 low-risk patients failed distantly, and two patients in the high-risk group failed distantly; no distant failures occurred in the intermediate-risk group. Urinary toxicity was slightly higher than in the 35-Gy group. Overall potency preservation was 87%. Quality of life assessment using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire found similar results with the mean EPIC sexual scores dropping by approximately 20%. Of note, all patients received intrarectally adminstered Amifostine (1500 mg) before each treatment fraction. The authors noted that the patients in the series enjoyed QOL scores as good if not better than those reported for other forms of treatment for prostate cancer (32). In a recent update of the 35-Gy group, at 36 months median follow-up no failures have occurred, the median PSA dropped to 0.15 ng/mL and no significant additional toxicity was noted (33).

Recent publications have also reported on the morbidity of CyberKnife SBRT for prostate cancer. Fuller *et al*., used a dose-planning approach modeled on the heterogeneous dose distribution common to HDR brachytherapy to treat 10 patients (34). In addition to showing dosimetric comparability, and in some instances superiority, to HDR dose distributions, Fuller *et al*., reported acute toxicity was primarily urinary which resolved within 2 months, and acute rectal toxicity was minimal (34). Townsend *et al.,* evaluated 50 patients, 37 of whom received monotherapy and 13 of whom received EBRT followed by a CyberKnife boost of 17.6-25 Gy delivered in 2-5 fractions (35). No acute Grade 2 or 3 rectal toxicity was observed; 10% Grade 2 and 6% Grade 3 acute urinary toxicity were observed. The authors concluded that CyberKnife radiosurgery was reasonably well tolerated in the acute phase, consistent with previous publications. Wiegner *et al.*, reported on sexual function in 32 patients who received CyberKnife monotherapy as part of the Stanford Phase II study (36). At baseline the erectile dysfunction (ED) rate was 38% and increased to 71% at a median 35.5 months. Age was a significant factor in observed ED rate; patients who were less than 70 maintained potency at a 60% rate as opposed to those older than 70 who maintained potency at rate of 12%. In this small number of patients, the penile bulb dose was not correlated with ED. The authors concluded that CyberKnife therapy yielded potency rates comparable with other radiotherapy modalities.

For intermediate- and high-risk disease, HDR brachytherapy as a boost to external beam radiotherapy is commonly used (23, 37). Since HDR brachytherapy is the biological model on which SBRT is based, use of SBRT as a boost to external beam radiotherapy has also been considered. In the first reported use of CyberKnife as a boost, Townsend *et al.*, (11) included 11 patients who received CyberKnife as a boost to IMRT. These patients primarily had mild and acceptable acute side effects, although one Grade 3 urinary toxicity occurred, no Grade 3 or higher rectal toxicities occurred.

More recently, Katz *et al*., reported on a study of biochemical control and toxicity outcomes using the CyberKnife as a boost to EBRT (38). In this study, 41 intermediate-risk patients and 34 high-risk patients were treated with EBRT to a dose of 45 Gy in 25 fractions over five weeks followed in two weeks by a CyberKnife SBRT boost of 18, 19.5 or 21 Gy in 3 fractions. Intermediate-risk patients received a mini-pelvis field and high-risk patients received whole pelvis with 4-field box technique. The CyberKnife boost was performed with the same dosimetric parameters as used in the Katz *et al.*, monotherapy study (10). All patients received Amifostine prior to each CyberKnife fraction and 36 patients received androgen deprivation therapy (ADT) for a median time of 4.8 months. At a median 33 months follow-up, 89.5% of intermediate-risk and 78% of high-risk patients were free of biochemical failure. Only one patient, with high-risk disease, failed locally. Of those patients with a minimum of 24 months follow-up, 71.8 % had a PSA nadir less than 0.5 ng/mL. Toxicity was mild with no Grade 3 or higher acute toxicities and one late Grade 3 urinary toxicity for a patient who received whole pelvis therapy. No significant difference in complications or outcomes was found among the three dose groups. The authors note that the observed biochemical control and toxicity rates are similar to those reported with HDR as a boost at 3-year follow-up and that QOL measures appeared to be as good or better than that reported by Sanda *et al.,* for EBRT plus brachytherapy boost (32). The overall impression of the authors was that since most late complications occur in the first 3 years with radiation therapy, the low observed toxicity rates show that this treatment is safe, but further follow-up is required to confirm the promising efficacy to date.

CyberKnife Treatment Future Considerations

The published results for CyberKnife SBRT for prostate cancer are highly encouraging while highlighting differences in the overall treatment approach including considerations on the use of QD versus QOD treatment, optimal dose of 35 vs 36.25 vs 38 Gy, homogeneous vs heterogeneous planning, the use of intrarectal Amifostine as a radioprotector, and the disparity in ED rates among the various studies. In the following, we briefly discuss these topics with a mind towards future studies aimed at optimizing CyberKnife SBRT for prostate cancer.

Dosimetry

The majority of published CyberKnife prostate results to date perform what is known as homogeneous planning (Figure 1). Typically, in homogeneous treatment the PTV is covered with 83-87% of the Dmax and 120-160 beams to achieve a fairly small dose gradient through the target volume. Since the hotspots created are not greater than 16-20%, identification of the urethra while planning is not essential. This method is easy to plan and treatment can be delivered in 45-50 minutes with older CyberKnife models. In newer CyberKnife models with a faster Linac and the IRIS variable collimator, which eliminates the need to manually change collimators during the treatment, treatment can be performed in 30-35 minutes. If the α/β ratio is indeed 1.5 Gy, then there is no need for HDR-like hotspots as the dose of 35 Gy should suffice to control the vast majority of cancers.

An alternative planning method, known as heterogeneous planning, involves using more beams to achieve a heterogeneous dose distribution throughout the prostate, simulating an HDR brachytherapy plan (34). The rationale for this method is that HDR success may stem not only from the hypofractionated dosing, but also from the higher doses applied to the posterolateral peripheral zone. By using heterogeneous dosing and treating with 4 fractions of 9.5 Gy each, HDR brachytherapy is more closely emulated. Using this treatment method the V125 is 28-55%, approaching the V125 achieved in HDR plans. Urethral doses are also lower with CyberKnife heterogeneous treatment than with HDR, suggesting an advantage in minimizing urethral complications. The number of beams necessary to accomplish heterogeneous treatment is 230-318 which leads to longer treatment times of approximately 90 minutes. A recent update of the heterogeneous treatment approach using the Iris Variable Collimator with Sequential Optimization Multiplan (Accuray Incorporated, Sunnyvale, CA) demonstrates that HDR-like plans can be achieved with fewer beams and monitor units, resulting in a 43% reduction in beam on time (12). Thus, heterogeneous treatment can be performed with equal or improved conformality, delivering higher intraprostatic maximum doses and lower urethral dose while maintaining bladder and rectal doses.

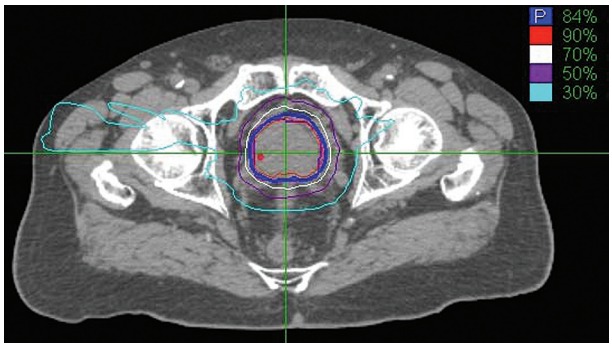

Figure 1: Sample homogeneous treatment planning images for CyberKnife SBRT. The planning target volume (thick blue line) is the 84% isodose line.

Reflecting these two planning methods, two national clinical studies are currently accruing patients. One uses heterogeneous treatment and delivers a total dose of 38 Gy in 4 fractions (39). The other covers the prostate homogeneously, delivering a total dose of 40 Gy in 5 fractions (40). Both clinical studies are entering patients with either low- or intermediate-risk. An initial report from the national homogeneous clinical study showed mild acute toxicity and no failures with up to 18 months follow-up (35). Further follow-up will be necessary to see if there is a difference in control and toxicity between these two treatment approaches.

Optimal Dose

Although long-term disease control, *i.e.,* longer than 3-5 years, has not yet been demonstrated, it may not be too early to speculate on the variables that will determine an optimal dose and fractionation regimen for CyberKnife-delivered prostate SBRT. To date CyberKnife researchers have used doses ranging from 35-40 Gy. Based on prostate cancer radiobiology, an α/β ratio of 1.5 Gy suggests that 35 Gy should maximize disease control rates by delivering a biological equivalent dose of 92 Gy at 1.8 Gy per fraction (Table I). Higher doses would be on the flat part of the sigmoid dose response curve (Figure 2) and yield no extra benefit, but since the α/β ratio for late complications is probably around 3-5 Gy

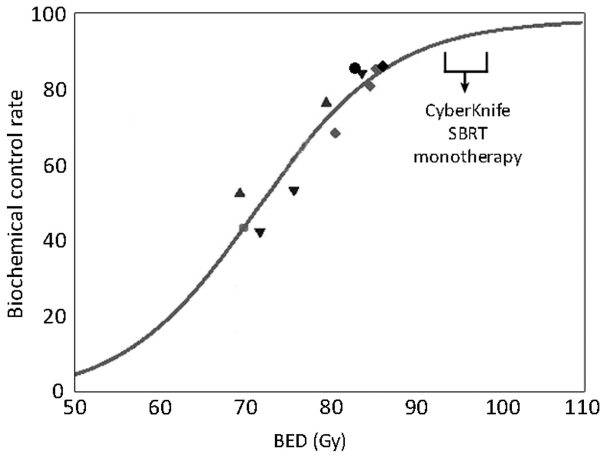

Figure 2: Dose-response curve highlighting biochemical control as a function of biologically equivalent dose (BED) of 1.8 Gy per fraction for an α/β ratio of 1.5. The symbols denote biochemical control rates from a variety of studies as follows (all of these studies reported biochemical control at 5 years for intermediate-risk patients): ◆Cahlon *et al*. (21), ● Kupelian *et al*. (14), ▼ Pollack (50), ▲ Zelefsky *et al.* (51), ◆ Hanks *et al.* (52). Adapted from Fowler *et al*. (18), which based the BED calculation on 2 Gy per fraction equivalents of EBRT results, by adjusting to a BED of 1.8 Gy per fraction, adding the biochemical control rates from recent IMRT publications and denoting the range of BEDs for published CyberKnife monotherapy results.

(41), higher doses could carry a higher risk of complications. In fact, the patients treated with a total dose of 36.25 Gy (8, 10) appear to have a slightly higher rate of toxicity in comparison to the patients treated with 35 Gy (9, 10). Although the lower rectal toxicity rate of Katz *et al.*, may be due to the use of rectally administered radioprotection, it is interesting that King *et al.,* (8) did note a higher risk of rectal complications with daily 7.25 Gy fractions that were ameliorated by going to QOD treatments. While a larger number of patients must be studied to confirm the underlying basis of these toxicities, one can infer from the current data that 35 Gy in five daily fractions is well tolerated and that additional rectal toxicity with 36.25 Gy may be lessened by use of either Amifostine or QOD fractionation.

Similarly, the risk of urinary complications for those patients treated with 35 Gy was very low (9, 10), but as the dose was increased to 36.25 Gy, Katz *et al.,* noted a slight increase, from 2% to 5.8%, in late urinary toxicity, which was mainly urethritis. Since there is no radioprotection for the urethra, the slightly higher rates of urethral complications for 36.25 Gy may be expected. The use of 38 Gy could then result in an additional increase in the risk of late complications. Long term follow-up by the on-going clinical studies is not yet available that would help address this assumption. In addition, if the 35 Gy dose continues to yield extremely high control rates, there may be no rationale for pursuing a higher dose.

Homogeneous planning, as used by Friedland *et al.,* and Katz *et al.,* has also thus far been successful, as the dose is probably optimal without needing hot zones. The higher peripheral doses achieved with heterogeneous planning (34) may not be necessary to eradicate prostate cancer cells. Use of homogeneous planning would simplify the planning process, with the use of fewer beams, shorter treatment times and no need to catheterize the urethra. Further control and toxicity data will clarify this issue.

Testicular Dose

King has cautioned (42) that CyberKnife plans can include beams that enter through the testicles and produce doses of up to 6.6 Gy in the testicles. King postulates that since other studies indicate a gonadal dose of 2-4 Gy can decrease testosterone levels that the low PSA levels observed in his studies could partially result from hypogonadism. Fuller responded (43) that they found no evidence of clinically significant reduction in either serum testosterone levels or in sexual desire. Fuller concluded that their median PSA of 0.4 ng/mL at two years was due to the radiation rather than a hormonal ablation effect. However, both agreed that as a precaution one should remove beams that traverse the testicles, which can be done without substantially degrading treatment plan quality. Katz *et al*., measured the mean dose delivered to the testicles and found this to be in the 5 Gy range (10). They noted that this also occurs with IMRT delivery and that no clinically significant reduction in testosterone has been reported in those cases (44). Although Katz *et al.*, did not measure testosterone level, no clinical signs of hypogonadism were observed in their patients (10). Overall, it appears this issued has been resolved and that the excellent PSA results seen thus far are due to the radiation rather than androgen deprivation.

Potency Preservation

There is a disparity in the approximately 80% potency preservation rates reported by Friedland *et al*., and Katz *et al*., versus the 40% rate reported by Stanford. While one cannot make any definitive conclusions due to the small number of patients analyzed by Stanford and the relatively short follow-up, one postulation would be that the higher dose delivered by Stanford is a factor. Yet, Katz *et al.*, saw no difference in the potency rates between 35-Gy and 36.25-Gy groups. Examination of the treatment methodology does indicate another difference. In particular, Katz *et al.,* and Friedland *et al.*, fused MRI scans into the planning CT scans for treatment planning whereas the Stanford study used only CT scans. It is known that MRI scans provide more detailed views of the prostate. Indeed, Sannazzari *et al.*, found that the use of MRIs in treatment planning decreases prostate volume by 34% (45). Perhaps the smaller GTVs result in lower doses to the neurovascular bundles and subsequently higher potency rates. One would have to analyze the GTV contours generated by the various sites to elucidate this theory. Further follow-up with larger numbers of patients will also be helpful in this regard.

Hormonal Therapy

Hormonal therapy has generally not been recommended by any authors who have reported using it. In particular, Martinez *et al.*, indicated no benefit to ADT when used with hypofractionated HDR (46). Based on this and the significant toxicity from ADT, it was judged to be inadvisable to use hormonal therapy. The excellent results reported for the CyberKnife SBRT do not appear to be skewed by the few patients who did receive ADT, as the follow-up is long enough to have seen normalization of testosterone levels. If the benefit of ADT disappears with SBRT hypofractionated regimens, this would be an advantage to SBRT as the toxicity associated with ADT would be avoided.

CyberKnife SBRT as a Boost

Although the use of CyberKnife SBRT as a boost has, thus far, appeared to be effective (38), the EBRT component of the boost treatment approach does increase the duration of treatment by at least a month. Recent studies do not reveal a

clear benefit from the use of pelvic nodal radiation (47, 48); therefore, it is likely that the radiation dose to the prostate and immediate periprostatic tissues is the determinant of success in biochemical control. Consideration of the BED also shows little difference, with CyberKnife boost treatment yielding a BED of 89-98 Gy and CyberKnife alone yielding a BED of 92-96 Gy, assuming a α/β ratio of 1.5 (Table I). It is therefore unlikely that EBRT plus SBRT boost will add significant benefit, especially if the seminal vesicles and extracapsular tissues can be adequately included with monotherapy, as appears to be the case. In fact, with the current data available, no benefit to the addition of a boost to EBRT is discernible over SBRT monotherapy. For intermediate-risk patients, Katz *et al.*, reported slightly better results with CyberKnife treatment alone than with CyberKnife boost therapy (100% biochemical control at 30 months vs. 89.5% at 33 months). Similarly, for high-risk patients they observed an 83% biochemical control rate at 17 months for patients treated with CyberKnife alone versus a 79% biochemical control rate at 33 months for those treated with CyberKnife as a boost to EBRT. Of course, the follow-up with the boost therapy is longer and the number of patients treated in the two studies differs, so it is possible that boost therapy will yield higher control rates with further follow-up.

Conclusions

Although long-term follow-up is necessary to further validate CyberKnife SBRT for prostate cancer, much can be learned from the available data. Thus far, the local control rates for all risk groups have been highly promising and the low PSA values at 2-3 years are highly suggestive of a potent biological effect of a total dose of 35 to 36.25 Gy delivered in 5 fractions. A recent publication has suggested that low PSA values at 2 years are highly correlated with low long-term failure rates (49). This suggests that excellent long terms results, as seen with hypofractionated HDR, can be reasonably expected for CyberKnife SBRT, although long-term follow-up is needed to confirm this is the case. In addition, the low PSA values seen with CyberKnife SBRT in this time frame make the thesis that the α/β ratio is 10 Gy untenable, as that would mean a biological equivalent dose of 52 Gy, which is clearly inadequate. Rather, the clinical results for multiple treatment modalities strongly support the low α/β ratio hypothesis (Table I). The low level of observed side effects is probably multifactorial, including the dosing schedule, the conformality of the treatment plans and the reduced target volumes possible as a result of the real-time tracking abilities of the CyberKnife. Real-time tracking allows for 5-mm margins around the prostate, which are significantly lower than the 8-10 mm margins used in IMRT or proton therapy. We eagerly await long-term follow-up to further validate the efficacy and minimal toxicity of CyberKnife SBRT for prostate cancer.

Conflicts of Interest

Dr. Katz has received speaker's honoraria from Accuray, Inc., Sunnyvale CA.

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Received: April 30, 2010; Revised: June 18, 2010;
Accepted: June 30, 2010