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Stereotactic radiotherapy for prostate cancer: A review and future directions

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Abstract

Prostate cancer affects over 200000 men annually in the United States alone. The role of conventionally fractionated external beam radiation therapy (RT) is well established as a treatment option for eligible prostate cancer patients; however, the use of stereotactic body radiotherapy (SBRT) in this setting is less well defined. Within the past decade, there have been a number of studies investigating the feasibility of SBRT as a potential treatment option for prostate cancer patients. SBRT has been well studied in other disease sites, and the shortened treatment course would allow for greater convenience for patients. There may also be implications for toxicity as well as disease control. In this review we present a number of prospective and retrospective trials of SBRT in the treatment of prostate cancer. We focus on factors such as biochemical progression-free survival, prostate specific antigen (PSA) response, and toxicity in order to compare SBRT to established treatment modalities. We also discuss future steps that the clinical community can take to further explore this new treatment approach. We conclude that initial studies examining the use of SBRT in the treatment of prostate cancer have demonstrated impressive rates of biochemical recurrence-free survival and PSA response, while maintaining a relatively favorable acute toxicity profile, though long-term follow-up is needed.

Key words: Stereotactic body radiotherapy; Prostate cancer; Radiation therapy; Hypofractionation; Toxicity; Stereotactic ablative radiotherapy

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Core tip: Initial studies examining the use of stereotactic body radiotherapy (SBRT) in the treatment of prostate cancer have demonstrated impressive rates of biochemical recurrence-free survival and prostate specific antigen response, while maintaining a relatively favorable acute toxicity profile. Here we review a number of recent

prospective and retrospective studies to evaluate the efficacy and toxicity of SBRT in the treatment of low, intermediate, and high-grade prostate cancer.

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INTRODUCTION

According to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database there were 220800 new cases of prostate cancer diagnosed in 2015 and an estimated 27540 deaths^[1]. Since the advent of routine prostate specific antigen (PSA) screening, the majority of cases are confined to the prostate and radiation therapy (RT) is often employed as an alternative to surgical resection. Currently, the National Comprehensive Cancer Network guidelines recommend a combination of observation, radical prostatectomy, conventionally fractionated external beam RT, and androgen deprivation therapy (ADT), depending on stage and risk profile. Stereotactic body radiation therapy (SBRT), which entails five or fewer fractions of at least 5 Gray (Gy), is not currently included in the national guidelines.

A number of studies have evaluated the efficacy of conventionally fractionated external beam RT. With follow up ranging from 5 to 20 years and total doses ranging from 78 to 86 Gy, reported biochemical control was greater than 80% for the favorable risk group compared to approximately 60% for the high risk group. Total dose was also a factor as biochemical control was approximately 60% at lower doses and greater than 80% for higher doses with an estimated overall risk reduction of 40%-50% with respect to biochemical failure^[2-5]. This review will examine the evidence for SBRT in comparison to conventional fractionation in the era of modern treatment, and the future direction of SBRT in the treatment of prostate cancer.

Stereotactic radiosurgery has already been applied with great success in other types of cancer, most notably malignancies of the lung and brain (*i.e.*, stereotactic radiosurgery). In the case of lung malignancies, SBRT offers an overall survival benefit as compared with conventionally fractionated RT and offers an alternative when patients are not surgical candidates. Recent work has sought to extend SBRT to prostate cancer with the goal of demonstrating improved outcomes. However, as described above, the threshold for proving non-inferiority is high given excellent results with conventionally fractionated radiation therapy, surgery, or even observation in low risk patients^[6].

In this review we present trials of SBRT in the

treatment of prostate cancer. Data from these studies are relatively immature with a maximum median follow-up time of 60 mo. Since overall survival at 60 mo or less is expected to be high even in the absence of intervention, we focus on factors such as biochemical recurrence-free survival (bRFS), PSA response, and toxicity. Here we attempt to provide a balanced perspective on the benefits and challenges associated with the use of SBRT in the treatment of prostate cancer.

RESEARCH

Studies included in this review were identified by performing a search of existing literature appearing in the PubMed database, using the keywords "prostate" and "SBRT", which returned a total of 270 results. To qualify for inclusion, treatments must have been delivered in five fractions or fewer, with the exception of one study that employed SBRT as a boost upon conclusion of a conventionally fractionated course. Both prospective and retrospective studies were included. In addition, only those studies that provide detailed results for both PSA response and toxicity were considered for inclusion. Computed tomography and/or magnetic resonance imaging were used for treatment planning in all studies, and treatment positioning was achieved with either daily or real-time imaging. A total of 14 studies met these criteria and are presented here. The remaining 256 published works were excluded for a variety of reasons, including: Insufficient follow-up, lack of toxicity data, or irrelevance to the topics addressed in this review.

SBRT AS A DEFINITIVE THERAPY IN PROSTATE CANCER

SBRT is currently an evolving treatment approach, with no established standard fractionation schedule. There have been a number of single-institution experiences reported with promising results that show local control rates comparable to conventional fractionation, albeit with a much shorter length of follow-up. While hypofractionated radiation therapy has been used in the treatment of prostate cancer since the 1960's, it has historically been undertaken with 2D planning, as described in Lloyd-Davies *et al*^[7]. The emergence of advanced technologies, such as intensity modulated radiation therapy (IMRT) and image guided radiation therapy (IGRT), have greatly improved toxicity. However, this review of 209 patients treated with a six-fraction regimen over three weeks established the feasibility of hypofractionation with good local control and an absence of significant morbidity^[7].

Among the earliest published studies, Madsen *et al*^[8] reported initial findings from their SHARP trial in which forty enrolled patients were treated with five fractions of 6.7 Gy. The authors assumed an alpha/beta ratio of 1.5, similar to other prostate SBRT studies, resulting in a biologically equivalent dose of 78 Gy.

However, the advantage is that hypofractionated dose prescriptions produce an acute effect profile consistent with a significantly lower conventionally fractionated prescription. Enrolled patients were all categorized as low-risk with combined Gleason scores of six or less. All patients achieved a PSA nadir below 2.0 ng/mL and thirteen achieved a nadir below 0.5 ng/mL. There were three biochemical failures resulting in a bRFS rate of 90% at 48 mo. The group also reported an acute toxicity profile comparable to a conventionally fractionated trial conducted at the Cleveland Clinic^[9]. The five-year follow-up shows an overall survival of 75% with no prostate cancer related deaths and a resolution of all GU and GI toxicities; however, 50% of the twenty-six patients who were potent at the time of treatment subsequently became impotent^[10]. The median PSA nadir was 0.65 ng/mL at a median time of 24 mo.

Building upon past studies utilizing HDR brachytherapy as a monotherapy, King *et al.*^[11] enrolled 67 low- to favorable intermediate-risk patients in their phase II trial. All participants were treated in 5 fractions of 7.25 Gy^[12]. They report a four-year bRFS rate of 94% and a median PSA of 0.5 ng/mL at follow-up. There were, however, two biopsy proven failures, but neither of these patients were found to have metastatic disease. Furthermore, patients tolerated the treatment relatively well; there were no grade 3 or higher rectal toxicities, and the grade 3 urinary toxicity rate was 3.5% with no grade 4 urinary toxicities. The toxicity profile compared favorably to past conventionally fractionated dose-escalation and hypofractionated studies. The authors attribute this, in part, to the relatively narrow expansion margins that SBRT affords (in this study, 5 mm overall and 3 mm posteriorly). One unique feature of this trial is that the first twenty-two patients were treated QD (*i.e.*, five consecutive days) while the balance were treated every other day (QOD). Interestingly, the QOD cohort experienced fewer grade 1 to 2 urinary and rectal toxicities, with no change in the rate of grade 3 urinary toxicity.

Boike *et al.*^[13] conducted a multicenter dose escalation study, enrolling a total of forty-five stage T1-2 patients with Gleason scores of seven or less. Their dose prescriptions were based upon prior nude mouse xenograft studies and radiobiologic modeling of established high dose rate (HDR) brachytherapy^[14]. Patients were divided into three cohorts, each of which was treated in 5 fractions of 9, 9.5, or 10 Gy. The study began with the 9 Gy cohort and a ninety day observation period was enforced to evaluate for acute toxicity before the subsequent higher dose cohort was treated. PSA response was favorable in all cohorts with an overall mean nadir of less than 0.4 ng/mL. The authors were particularly focused on evaluating the toxicity associated with this protocol, as comparable preceding studies limited the total dose to 36.25 Gy or less^[15,16]. Acute toxicity was generally limited, with only grade 1 or 2 symptoms reported. A limited number of higher-grade late toxicities arose as follows: One case

of a grade 4 rectal ulcer, and one case each of grade 3 cystitis and dysuria.

Hannan *et al.*^[17] report the five-year follow-up results of Boike *et al.*^[13] and add a phase II portion consisting of 47 patients treated to 50 Gy in 5 fractions. This study achieved a remarkable collective five-year bRFS rate of 98.6%, which the authors acknowledge may be overestimated due to their follow-up protocol. This rate exceeded those previously reported by groups that employed other modalities, including: Intensity modulated radiation therapy, hypofractionated radiation therapy, and radical prostatectomy. The majority of acute grade 2 toxicities and all late grade 3 to 4 toxicities occurred in the 50 Gy arm. Three out of a total of four grade 4 toxicity events affected the rectum. Though the stoppage criteria for severe toxicity were not met, the authors ultimately concluded that doses less than 50 Gy are advisable.

Katz *et al.*^[18] recruited 304 low, intermediate, and high-risk patients. Expansion margins of 5 mm overall and 3 mm posteriorly were employed and patients were treated with five fractions of either 7 or 7.25 Gy. No acute grade 3 or 4 toxicity was reported, and of the 48 patients who reached the twelve-month follow-up at the time of publication, only one late grade 3 toxicity occurred. Quality of life (QOL) was measured using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. Patients reported an initial decrease in bowel and urinary QOL, but returned to baseline. However, sexual QOL decreased by approximately 10% and remained at that level. By twelve months, 28% of patients achieved a PSA nadir of less than 0.5 ng/mL. A total of four individuals failed biochemically. Long term follow-up revealed a seven-year biochemical disease free survival of 95.6%, 89.3%, and 68.5% for low, intermediate and high-risk cases, respectively^[19]. Minimal late toxicity was reported.

Jabbari *et al.*^[20] treated 20 low- or favorable intermediate-risk patients with four fractions of 9.5 Gy while another 18 intermediate- and high-risk patients were treated with EBRT and ADT combined with an SBRT boost consisting of two fractions of 9.5 Gy. Four patients received an integrated 1 Gy/fraction boost to the dominant intraprostatic lesion. Treatment was planned so as to mimic HDR brachytherapy in terms of dose heterogeneity and outside-of-target sparing. No acute grade 3 or higher toxicity was observed and two patients experienced late grade 3 toxicities. With a median follow-up of 18.3 mo, the median PSA nadir for the monotherapy group was 0.47 ng/mL and 0.10 ng/mL for the combined therapy group. No patients experienced biochemical failure at the time of publication. Though the results are generally favorable, the authors caution that additional accrual and follow-up is needed to ensure durable relapse-free survival. Bolzico *et al.*^[21] treated the spectrum of low- to high-risk patients and also stratified PSA response based upon ADT use. The authors note a trend towards lower nadirs with the addition of ADT (median nadir of 0.62

ng/mL vs 0.18 ng/mL at 3 years), though statistical significance was not reported. Oliai *et al.*^[22] undertook a dose escalation trial for low- to high-risk patients and also stratified PSA response by ADT use, reporting a mean PSA nadir that decreased from 0.4 ng/mL to less than 0.1 ng/mL with the addition of ADT.

The Naples and Stanford groups compiled a combined cohort of 41 patients with a median follow-up time of 5 years^[23]. The Stanford patients were treated with 5 fractions of 7.25 Gy and the Naples patients were treated with 5 fractions of 7 Gy. The reported five-year biochemical progression free survival rate was 92.7% with a mean PSA nadir of 0.35 ng/mL, though the Stanford subset had a mean nadir of 0.18 ng/mL, significantly lower than entire the cohort average. There were three biopsy proven failures. Treatment was generally well tolerated, though acute toxicities were not explicitly reported. There was one reported case of late grade 3 toxicity and no late grade 4 toxicities.

McBride *et al.*^[24] reported on 45 patients who received 5 fractions of 7.25 to 7.5 Gy. Biochemical progression free survival at three years was reported as 97.7% and the median PSA nadir at twelve months was 0.91 ng/mL. One late grade 3 urinary obstruction and two late grade 3 proctitis events were noted. There was a statistically significant decrease in the Sexual Health in Men (SHIM) survey score, along with the EPIC bowel and sexual function scores. All three of the reported grade 3 toxicities resolved with corrective intervention.

In 2013, the American Society for Radiation Oncology (ASTRO) released a policy statement supporting the use of SBRT as an appropriate alternative to conventional RT for low- to intermediate-risk disease. This allowed researchers to begin focusing attention on addressing specific technical challenges associated with SBRT. Mantz *et al.*^[25] tried to control for prostate movement with the implementation of reliable organ tracking techniques to ensure adequate dose localization and to minimize toxicity to surrounding sensitive tissues. Towards this end, they enrolled 102 low-risk patients who were subsequently treated using a proprietary technology, the Calypso® System (Varian Medical Systems, Palo Alto, CA, United States) that uses implanted transponders to track the prostate in real-time during treatment. Patients are then treated on conventional linear accelerators. Other studies used a competing real-time tracking platform, CyberKnife® (Accuray, Inc., Sunnyvale CA), which is comprised of a 6 MV linear accelerator mounted to a robotic arm. Patients received five fractions of 8 Gy, and achieved a mean PSA of 0.27 ng/mL at 24 mo. The toxicity profile was among the best of the prostate SBRT studies with no grade 2 or higher rectal events and only two grade 3 urinary events, both acute. Twelve-month EPIC scores showed a return to near-baseline after an initial decline. These results suggest that real-time tracking may provide a means of reducing toxicity without compromising efficacy.

Recently, efforts have been made to expand the use of SBRT in the treatment of intermediate- and high-risk prostate cancer. Anwar *et al.*^[26] built upon the previously

discussed Katz study, delivering a two-fraction boost of either 9.5 or 10.5 Gy total to 50 patients who had already received a course of conventionally fractionated EBRT to doses of 45-50 Gy. The reported five-year bRFS for all patients was 83%, with a median PSA nadir of 0.05 ng/mL achieved at a median time of 26.2 mo. No grade 3 or higher toxicity was noted. Four cases of disease progression were recorded, all of which occurred outside of the field of radiation. By comparison, a multi-institutional analysis found five-year bRFS rates of 84% and 81% for intermediate- and high-risk patients, respectively^[27]. The results of this work compare favorably to HDR boost therapy, suggesting that SBRT boost may be a viable option for intermediate- and high-risk prostate cancer patients. Additionally, this work showed that SBRT resulted in an increased rate of PSA decline as compared to conventionally fractionated EBRT, which is a feature associated with improved clinical outcomes.

Davis *et al.*^[28] analyzed outcomes for a total of 437 localized prostate cancer patients treated with SBRT at one of seventeen centers in the United States and Australia. Patients were enrolled between 2006 and 2015 and all risk categories were represented. Two-year bRFS was found to be 99.0%, 94.5%, and 89.8% for low, intermediate and high-risk groups, respectively. Higher Gleason score was associated significantly with lower biochemical disease-free survival. Fifteen patients experienced biochemical failure. In general, the SBRT treatments were well tolerated; no patients experienced high-grade genitourinary or gastrointestinal toxicity. The authors corroborated an assertion others had made that SBRT does induce a rapid twelve-month decline in PSA, as observed across multiple studies. A similar pooled analysis by King *et al.*^[27] that included 1100 patients treated at eight institutions from 2003 to 2013 found collective bRFS rates of 95%, 84% and 81% for low-, intermediate- and high-risk patients, respectively. Patients were treated to a total dose of 35 to 40 Gy over five fractions. Biochemical failure at a median follow-up time of 36 mo was low, at 4.5%, and a subset of these patients were determined to have a PSA bounce that subsequently declined. Interestingly, neither total dose nor the use of ADT had a statistically significant effect on bRFS. The authors conclude that SBRT compares favorably to other definitive treatments and should be considered as an alternative therapy in low- and intermediate-risk prostate cancer. The relative paucity of high-risk patients prevented the authors from extending a similar recommendation to this subset.

DISCUSSION

Initial results and follow-up duration

The use of SBRT for prostate cancer has received considerable attention in recent years and multiple studies have demonstrated short-term outcomes comparable to established therapies. Currently, 8.8% of low-risk patients treated with RT at academic centers are receiving SBRT^[29]. Advantages include the potential for

Table 1 Summary of stereotactic body radiotherapy prostate trials and retrospective analyses

| Study | No. of patients | Dose | Median follow-up | Biochemical RFS | Overall survival | PSA response | BF ¹ | PSA bounce |
|----------------------------------|-------------------|--|-----------------------------|--|---|--|-----------------|------------|
| Madsen (IJROBP, 2007) | 40 | 6.7 Gy × 5 Fx | 41 mo | 90% at 48 mo | | 18 mo time to nadir | 3 | "Few" |
| Pham (IJROBP, 2010) | 40 | 6.7 Gy × 5 Fx | 60 mo | 93% at 60 mo | 75% at 60 mo | Median nadir of 0.65 ng/mL at median time of 24 mo | | 22.50% |
| Boike (JCO, 2011) | 15/15/15 (45 tot) | 9/9.5/10 Gy × 5 Fx | 30/18/12 mo | 100% at median follow-up | 100% at median follow-up | Mean < 0.4 ng/mL at 12 mo for all cohorts | 0 | "Multiple" |
| Katz (BMC Urol, 2010) | 50/254 (304 tot) | 7/7.25 Gy × 5 Fx | 30/17 mo | 35 Gy: 88% < 1 ng/mL PSA at 30 mo 36.25 Gy: 81% < 1 ng/mL PSA at 24 mo ² | 94%/99% at median follow-up. No deaths due to prostate cancer | 28.1% < 0.5 ng/mL at 12 mo | 4 | 37 |
| Jabarri (IJROBP, 2012) | 20/18 (38 tot) | 9.5 Gy × 4/2 Fx | 18.1/23.5 mo | 100% at median follow-up | | Median of 0.35 ng/mL at 18.3 mo | 0 | |
| King (IJROBP, 2012) | 67 | 7.25 Gy × 5 Fx | 2.7 yr | 94% at 4 yr | | Median of 0.50 ng/mL at follow-up | 2 | |
| McBride (Cancer, 2012) | 34/10/1 (45 tot) | 7.5/7.25 Gy × 5 Fx, 1 received "other regimen" | 44.5 mo | 95.5%/97.5% at 3 yr | 97.7% at 3 yr | Median of 0.2 ng/mL at follow-up | 0 | 9 |
| Anwar (Rad Oncol, 2016) | 24/26 (50 tot) | 9.5/10.5 Gy boost in 2 Fx | 42.7 mo | 95%/95%/90% at 3/4/5 yr | | Median nadir of 0.05 ng/mL at median time of 26.2 mo | 4 | 2 |
| Mantz (Fontiers Rad Oncol, 2014) | 102 | 8 Gy × 5 Fx | Min. of 5 yr | 99% at 6 yr | | Mean of 0.27 ng/mL at 24 mo | 1 | 15 |
| Hannan (Eur J Cancer, 2016) | 92 | 9/9.5/10 Gy × 5 Fx | 54 mo (pooled phase I / II) | 98.6% at 5 yr | 94%/89.7% at 3/5 yr | Median of 0.125 ng/mL at 42 mo | 1 | 19 |
| Freeman (Rad Oncol, 2011) | 41 | 7-7.25 Gy × 5 Fx | 5 yr | 93% at 5 yr | | Median nadir of 0.3 ng/mL at follow-up | 3 | |
| Davis (Cureus, 2015) | 437 | 7-7.4 Gy × 5 Fx, 9.5 Gy × 4 Fx, 19.5-29 Gy boost | 20 mo | 96.1% combined at 2 yr 99.0%/94.5%/89.8% for low/intermediate/high-risk at 2 yr | | Median of 0.4 ng/mL at 24 mo | 15 | 35 |

¹Biochemical failure; ²Values reflect only patients who did not receive hormone therapy.

improved therapeutic control and a reduced number of patient visits. However, the lack of long-term toxicity data combined with a relatively small number of patients enrolled in prospective trials prevents SBRT from superseding conventionally fractionated RT at the present time. Clinical results, discussed above and compiled in Tables 1-3, have demonstrated consistently favorable outcomes over the short-term using a variety of SBRT fractionation schedules for definitive and boost treatment. Overall, five fractions of 6.7 to 10.5 Gy per fraction were utilized. With range of follow-up varying from 18 to 60 mo, biochemical recurrence free survival was excellent, as later trials reported rates of greater than 93%.

Conventionally fractionated RT often requires long courses of treatment consisting of eight or more weeks of daily visits. The accelerated schedule that SBRT offers improves the logistic feasibility of treatment. While these initial SBRT reports are encouraging, longer follow up will be required to confirm that bRFS and an acceptably low rate of late toxicity can be maintained over the long term. Most current studies have yet to report data beyond five years and thus are not sufficient to allow for an unequivocal endorsement of SBRT in the

treatment of prostate cancer.

Toxicity and dose per fraction

While continued follow-up and additional large-scale prospective studies are needed, certain conclusions can be inferred from the body of existing literature. Firstly, increasing per fraction dose beyond approximately 8 Gy appears to worsen toxicity without offering significantly improved progression-free survival. High-grade toxicity has not been reported in studies with doses between 7 and 8 Gy. Beyond 8 Gy per fraction, reports of both low- and high-grade toxicities increase measurably. Though rectal toxicity and early urinary toxicity are comparable to those seen with conventional fractionation, late urinary toxicity remains a concern^[27,30]. The majority of studies evaluated here reported at least one instance of late grade 3 or higher urinary toxicity, often requiring instrumentation or transurethral resection of the prostate (TURP). This flare phenomenon has been found to peak between 12 and 18 mo post-treatment, though symptoms resolve by 24 mo in a majority of cases^[31]. However, this trend remains a concern and should be further elucidated prior to large-scale adoption of SBRT

Table 2 Summary of genitourinary toxicities for included stereotactic body radiotherapy trials

| Study | Acute | | | Late | | | Clinical notes |
|---|--|-----------------------|--------------|---|-----------------------|---------|---|
| | Gr. 1 | Gr. 2 | Gr. ≥ 3 | Gr. 1 | Gr. 2 | Gr. ≥ 3 | |
| Madsen (<i>IJROBP</i> , 2007) | 28% | 21.50% | 1 tot | 25% | 20% | 0% | Gr. 3 event was urinary obstruction that resolved |
| Pham (<i>IJROBP</i> , 2010) | | | | 22.50% | 12.50% | 2.50% | All toxicities resolved |
| Boike (<i>JCO</i> , 2011) ¹ | 28.80% | 22.20% | 0% | 13.30% | 8.80% | 2 tot | Gr. 3 events due to dysuria and cystitis |
| Katz (<i>BMC Urol</i> , 2010) ¹ | 74.60% | 4.60% | 0% | 4.70% | 5.10% | 1 tot | |
| Jabbari (<i>IJROBP</i> , 2012) | 29% | 42% | 0% | 1 tot | 8% | 2 tot | One case each of urge incontinence and irritation requiring catheterization |
| King (<i>IJROBP</i> , 2012) ¹ | Not reported | Not reported | Not reported | 22.80% | 5.30% | 2 tot | Gr. 3 patients both underwent repeated urologic instrumentation for post-SBRT dysuria |
| McBride (<i>Cancer</i> , 2012) | 59% | 19% | 0% | 17% | 17% | 1 tot | Gr. 3 event was urinary obstruction requiring TURP |
| Anwar (<i>Rad Oncol</i> , 2016) | 48% | 37% | 0% | 21% | 25% | 1 tot | Gr. 3 event was urinary obstruction |
| Mantz (<i>Frontiers Rad Oncol</i> , 2014) | 32.3% frequency, 16.6% dysuria, 7.8% retention | | 2 tot | 19.6% frequency, 2.9% dysuria, 4.9% retention | | 0% | Gr. 3 events were urinary frequency |
| Hannan (<i>Eur J Cancer</i> , 2016) ¹ | 48.40% | 22.00% | 0% | 24.20% | 20.90% | 5.50% | 1 late Gr. 4 event (cystitis requiring ureteroileal diversion) |
| Freeman (<i>Rad Oncol</i> , 2011) | Not reported | Not reported | Not reported | 25% | 7% | 1 tot | Gr. 3 event after repeated urologic instrumentation |
| Davis (<i>Cureus</i> , 2015) | 19%/3%/3% ² | 2%/1%/1% ² | 0% | 25%/4%/5% ² | 8%/2%/2% ² | 0% | |

¹Aggregate values for all cohorts; ²Notation as follows: urinary frequency/urinary retention/cystitis. TURP: Transurethral resection of the prostate.

for low- and intermediate-risk prostate cancer.

Relatively few studies attempt to rigorously evaluate the impact of prostate volume on outcomes, and the overall conclusions are equivocal. A subset includes maximum volume cutoffs in the exclusion criteria, while others simply note the range of organ volumes among those enrolled. Chen *et al*^[30] prospectively collected quality of life data for 204 prostate cancer patients treated with SBRT, with median follow up time of 3.9 years. Patients were treated to a dose of 35-36.25 Gy in 5 fractions. At 3 years post SBRT, EPIC-UI (Urinary Incontinence) score declined significantly; however, this was of borderline clinical significance. Notably, prostate volume was associated with UI score. Similarly, a second study evaluated 515 patients treated with SBRT to a dose of 35-36.25 Gy in 5 fractions. Of 336 patients with available prostate volumes, there was a higher incidence of grade 2 and 3 urinary toxicity with prostate volumes greater than 60 cc that trended towards statistical significance^[19]. Conversely, a third study evaluated 216 patients treated with 35-36.25 Gy in 5 fractions, and found no correlation between urinary symptoms and prostate volume at the 2 year mark^[31]. It is important to note that the mean prostate volumes for the first two studies were 39 cc and 65.3 cc, respectively; median prostate volume for the third study was 38 cc. For men with prostate volumes greater than 50 cc, Janowski *et al*^[32] conducted a retrospective review of 57 patients with a median prostate volume of 62.9 cc (range 50-138.7cc). All patients were treated to 35-36.25 Gy in 5 fractions, and followed for a median of 2.9 years. The rate of grade 3 urinary toxicities was

low, occurring in two patients. As there is limited data regarding toxicity with SBRT in the setting of larger volume prostates (> 100 cc), caution should be used when treating these patients.

Similar to large prostate volume, prior TURP may predict for worse toxicity, although large-scale data are unavailable. Bolzicco *et al*^[21] prospectively accrued 100 patients for treatment with SBRT, to a dose of 35 Gy in 5 fractions. Of seven patients with prior TURP, three had late urinary toxicities (1% Grade 1, 1% Grade 2, 1% Grade 3). Also of note, there was only one patient with Grade 3 late urinary toxicity, and this patient had undergone urologic tests including cystoscopy and urethral dilatation. Similarly, Chen *et al*^[33] report a single case of Grade 3 late urinary toxicity, in a patient with a large prostate and two prior TURP procedures.

Real-time tracking of the prostate

The role of improved technology cannot be overstated. Though rigorous evaluations of prostate movement are limited, it is commonly accepted that translation of 5 mm or more during a single treatment session is likely^[34]. Real-time tracking of the prostate has the potential to markedly improve dose delivery to tumor tissue and minimize the exposure of surrounding non-involved structures. The majority of studies presented here made use of either CyberKnife or Calypso, and while there are no marked differences in toxicity, the prevailing sentiment among authors strongly favors real-time tracking. Furthermore, catheterization during treatment simulation improves urethral contour accuracy and may be advisable.

Table 3 Summary of gastrointestinal toxicities for included stereotactic body radiotherapy prostate trials

| Study | Acute | | | Late | | | Clinical notes |
|---|-----------------------|-----------------------|--------------|-----------------------|--------|--------------|---|
| | Gr. 1 | Gr. 2 | Gr. \geq 3 | Gr. 1 | Gr. 2 | Gr. \geq 3 | |
| Madsen (<i>IJROBP</i> , 2007) | 26% | 13% | 0% | 30% | 7.50% | 0% | Gr. 2 events were proctitis All toxicities resolved Gr. 4 event due to rectal ulcer |
| Pham (<i>IJROBP</i> , 2010) | | | | 22.50% | 7.50% | 0.00% | |
| Boike (<i>JCO</i> , 2011) ¹ | 33% | 22.50% | 0% | 22.20% | 2 tot | 1 tot | |
| Katz (<i>BMC Urol</i> , 2010) ¹ | 74.90% | 3.60% | 0% | 5.10% | 2.30% | 0% | Gr. 3 events were proctitis requiring ablation |
| Jabarri (<i>IJROBP</i> , 2012) | 21% | 11% | 0% | 2 tot | 1 tot | 0% | |
| King (<i>IJROBP</i> , 2012) ¹ | Not reported | Not reported | Not reported | 14.00% | 1 tot | 0% | |
| McBride (<i>Cancer</i> , 2012) | 31% | 7% | 0% | 7% | 7% | 2 tot | |
| Anwar (<i>Rad Oncol</i> , 2016) | 42% | 10% | 0% | 12.50% | 0% | 0% | |
| Mantz (<i>Frontiers Rad Oncol</i> , 2014) | 0% | 0% | 0% | 3 tot | 0% | 0% | Toxicity was rectal bleeding 1 acute and 2 late Gr. 4 events (one rectal bleed) |
| Hannan (<i>Eur J Cancer</i> , 2016) ¹ | 37.40% | 20.90% | 2 tot | 25.30% | 13.20% | 6.60% | |
| Freeman (<i>Rad Oncol</i> , 2011) | Not reported | Not reported | Not reported | 13% | 1 tot | 0% | |
| Davis (<i>Cureus</i> , 2015) | 4%/1%/1% ² | 1%/0%/0% ² | 0% | 4%/3%/3% ² | 0% | 0% | |

¹Aggregate values for all cohorts; ²Notation as follows: Diarrhea/constipation/proctitis.

Future directions

Ongoing clinical trials seek to address some of the concerns discussed above. The SMART trial, initiated in 2009, is a phase II study for stage T1-T2c prostate cancer using Calypso for real-time tracking and IMRT plan reoptimization. Patients are treated to 37 Gy in five fractions with a primary endpoint of urinary and gastrointestinal toxicity at 3 years, placing the focus on late complications. Enrollment has closed, though no results have been published to date. RTOG 0938 is a phase II trial comparing 36.25 Gy delivered in 5 fractions to 51.6 Gy delivered in 12 fractions. This work builds upon RTOG 0415, an equivalence study comparing 70 Gy in 28 to a conventionally fractionated course of 73.8 Gy in 41 fractions. RTOG 0938 includes patients with T1-2a disease and mandates the use of intrafraction motion tracking. The primary endpoint is QOL at 1 year post-treatment, assessed by EPIC score. Again, the importance of toxicity is highlighted.

To date, the field has emphasized the role of SBRT in treating early stage, low- to intermediate-risk disease. A subset of studies presented here included high-risk patients and reported favorable results. Katz *et al.*^[18] noted a 7-year bRFS of 68.5% for high-risk cases while Anwar *et al.*^[35] reported 81% bRFS at 5 years. Additionally, Oliai *et al.* report a 3-year freedom from biochemical failure of 77.1% for their high-risk cohort. These results, among others, suggest that SBRT may offer improved biochemical control as compared with conventionally fractionated RT and should be explored further in this context.

CONCLUSION

Initial studies examining the use of SBRT in the treatment of prostate cancer have demonstrated impressive rates of biochemical recurrence-free survival and PSA response,

while maintaining a relatively favorable acute toxicity profile. Doses of 8 Gy or less per fraction have lower reported rates of toxicity with similar biochemical control rates compared to higher doses per fraction. Though we are cautiously optimistic that SBRT has the potential to serve as an alternative to conventionally fractionated RT in the treatment of prostate cancer, long-term follow-up is needed in order to evaluate whether biochemical control, overall survival, and late toxicity are maintained, or improved, as compared to the current standard of care.

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