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Stereotactic Body Radiotherapy as Boost for Organ-confined Prostate Cancer

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Stereotactic body radiotherapy (SBRT) boost following external beam radiation therapy (EBRT) for advanced localized prostate cancer may reduce toxicity while escalating the dose. We present preliminary biochemical control and urinary, rectal and sexual toxicities for 73 patients treated with SBRT as a boost to EBRT. Forty-one intermediate- and 32 high-risk localized prostate cancer patients received 45 Gy EBRT with SBRT boost. Twenty-eight patients (38.3%) received a total SBRT boost dose of 18 Gy (3 fractions of 6 Gy), 28 patients (38.3%) received 19.5 Gy (3 fractions of 6.5 Gy), and 17 patients (23.2%) received 21 Gy (3 fractions of 7 Gy). Toxicity was assessed using the Radiation Therapy Oncology Group urinary and rectal toxicity scale. Biochemical failure was assessed using the Phoenix definition. The median follow-up was 33 months (range, 22 - 43 months). Less than 7% Grade II and no higher grade acute toxicities occurred. To date, one Grade III and no Grade IV late toxicities occurred. For the 97% of patients with 24 months minimum follow-up, 71.8% achieved a PSA nadir threshold of 0.5 ng/mL. Three intermediate-risk and seven high-risk biochemical failures occurred; one high-risk patient died of his cancer. Three-year actuarial biochemical control rates were 89.5% and 77.7% for intermediate- and high-risk patients, respectively. SBRT boost for prostate cancer treatment is safe and feasible with minimal acute toxicity. At 33 months late toxicity and biochemical control are promising. Long-term durability of these findings remains to be established.

Key words: Stereotactic body radiotherapy; Prostate cancer; Toxicity; Quality of life.

Introduction

Until the early part of this decade external beam radiation therapy (EBRT), at doses of 60-70 Gy, was considered a standard radiation treatment for localized prostate cancer, but the 10-year survival rates only ranged from 35-55% (1-5). Higher doses have been shown to improve biochemical control and cause-specific survival for EBRT treatments, particularly for intermediate- and high-risk localized prostate cancer patients (6, 7). However, increasing EBRT dose also increases the risk for rectal, urinary and sexual toxicities. Pollack *et al*. showed significant increases in both Grade 2 and Grade 3 rectal toxicities following an increase from 70 Gy to 78 Gy, delivered using three-dimensional (3D) conformal radiation therapy, in 306 stage T1-T3 patients (6). The use of intensity-modulated radiation therapy (IMRT) to increase dose to the prostate has shown promise. Zelefsky *et al*. reported decreased morbidity with IMRT to a total dose of 81 Gy for 772 stage T1-T3 patients compared to first generation 3D conformal techniques (8). However, as Zelefsky *et al*. show, even higher doses, with greater risks of toxicity, are likely needed for curative treatment of aggressive prostate cancer (8). In particular, intermediate- and high-risk prostate cancer patients' results, even with the use of IMRT, are not optimal (8).

It has been suggested that most high-risk prostate cancer patients develop PSA failure following local therapy due to microscopic distant metastases. A low-dose-rate

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(LDR) brachytherapy study that analyzed biologically effective dose (BED), however, found that dose response is an important factor in local control (9). Furthermore, a subsequent study by the same group concluded that patients with high-risk prostate cancer will benefit from delivery of a BED greater than 220 Gy (10). Although LDR boost results to date are promising, with 15-year follow-up data for low- to intermediate-risk prostate cancer patients that does not show late biochemical failures (11), such benefits are offset by increased short- and long-term toxicity and reductions in quality of life after LDR treatment.

HDR brachytherapy may be combined with EBRT to allow localized delivery of a higher overall dose with reported 5-year biochemical control rates of 77-93% and 5-year cause-specific survival rates of 96-98% (12-16). However, HDR brachytherapy is an invasive procedure that requires anesthesia, implantation of multiple catheters, pain control and hospitalization. Stereotactic body radiatiotherapy (SBRT) may be a less invasive alternative to HDR brachytherapy to boost the prostate dose after EBRT. SBRT that incorporates intrafraction image-guided correction of beam trajectory can deliver precisely targeted radiation to the prostate while sparing normal tissues. As a boost to EBRT for localized prostate cancer, SBRT has the potential to reduce treatment-related morbidity and maintain quality of life.

The purpose of this study was to assess the effects of using SBRT as a boost to EBRT for patients with intermediate- and high-risk prostate cancer. We report preliminary biochemical control and urinary, rectal and sexual toxicities for 73 patients treated with SBRT as a boost to EBRT.

Materials and Methods

Patient Population

From April 2006 through January 2008, 75 patients with clinically localized prostate cancer were treated with EBRT followed by SBRT boost at Winthrop University Hospital in Mineola, NY. Two of these patients were lost to follow-up at 10 and 15 months; their results have been excluded from this analysis. All patients had adenocarcinoma of the prostate; clinical stage was determined by physical exam, bone scan and CT scans. Patient risk categories were determined using the ASTRO definitions. Specifically, patients with a Gleason Score of ≥ 6 and ≤ 7 and a prostate-specific antigen (PSA) greater than 10 ng/ml but ≤ 20 ng/ml were identified as intermediate-risk; patients with a Gleason Score ≥ 8 or a PSA > 20 ng/ml were identified as high-risk. Thirty-six patients received hormone therapy for a median of 4.8 months (range, 1–13 months). We administered monthly Leuprolide injections to six patients; the remaining patients were administered hormone treatment by their referring physician with various treatment methods. Ten of the patients received hormone therapy after SBRT for a median 3 months (range, 1–9 months). All patients signed consent statements and were informed of the potential risks involved with this treatment. Patient characteristics are summarized in Table I.

Radiation Therapy and SBRT Treatment Planning and Delivery

EBRT was delivered to all patients using 15-MV photons at a total dose of 45 Gy. Treatment was delivered over consecutive work days in 25 fractions of 1.8 Gy each using a 3D conformal four-field box to include the prostate and pelvic nodes. Intermediate-risk patients received mini-pelvis treatment and high-risk patients received whole pelvis treatment. Image-guided SBRT boost was planned using MultiPlan® (Accuray, Inc., Sunnyvale, CA) inverse planning, and delivered using the CyberKnife (Accuray, Inc.) with motion tracking of internal fiducial seeds. A detailed description of the CyberKnife system can be found elsewhere (17).

Table I
Patient characteristics at time of diagnosis.

Age at diagnosis	Years	
Mean (range)	69.2 (48–83)	
Age at diagnosis	Number of Patients	Percent of Patients
40–49	1	1.3
50–59	22	29.3
60–69	23	33.3
70–79	23	30.6
80–89	4	5.3
PSA level at diagnosis	ng/mL	
Mean (range)	10.7 (1.3–52.4)	
Median	7.7	
PSA level at diagnosis	Number of Patients	Percent of Patients
<4 ng/mL	13	17.3
4–10 ng/mL	34	45.3
>10–20 ng/mL	17	22.6
>20 ng/mL	9	14.6
Clinical Stage		
T1cN0M0	69	94.6
T2aN0M0	4	5.4
Gleason Score		
6	4	5.3
3+4	16	21.3
4+3	25	36
8	20	26.7
9	8	10.7
Hormone Treatment		
No	6	49.4
Yes	37	50.6
Risk Assessment		
Intermediate-risk	0	54.7
High-risk	3	45.3

PSA – prostate-specific antigen.

SBRT treatment planning began during EBRT treatment with transperineal implantation of four fiducial seeds; two seeds were placed at the prostate apex and two at the base. Treatment planning images were obtained one week after fiducial implantation to allow for possible seed migration. Treatment was planned on a CT volume (1.5-mm cuts) with MRI fusion images where feasible. All treatment planning images were obtained with the patient in the same position used for treatment delivery. The prostate was delineated to specify the gross target volume (GTV). The planning target volume (PTV) was created by adding a 5-mm margin to the GTV throughout except posteriorly by the rectum where a 3-mm margin was used. In all patients the bladder, prostate, rectum, seminal vesicles and penile bulb were contoured, but the urethra was not identified.

SBRT delivery occurred two weeks after EBRT was completed. The SBRT boost was delivered in three fractions over three consecutive days. Dose escalation was performed after at least 8 patients had 5 months of follow-up and no Grade 3 or higher toxicities were observed. The first 28 treated patients (38.3%) received a total SBRT boost dose of 18 Gy (3 fractions of 6 Gy each), the next 28 (38.3%) patients received 19.5 Gy (3 fractions of 6.5 Gy each) and the remaining 17 patients (23.2%) received 21 Gy (3 fractions of 7 Gy each). The initial dose of 18 Gy was based on HDR brachytherapy boost treatment. The dose was prescribed to the 83-87% isodose line to cover 95% of the PTV. The mean number of beams was 152 (range, 142–176). The average Dmax was 21.42 Gy, 23.21 Gy, and 24.99 Gy for the 18, 19.5 and 21 Gy doses, respectively. Typical V105 values ranged from 78-82% of the PTV. The V75 was typically less than or equal to 4 cc for the bladder and 3 cc for the rectum. The mean D50 to the bladder and rectum was 41% and 43% of the Dmax dose, respectively. When feasible, without compromising overall treatment plan quality, the mean D50 to the penile bulb and testes was kept to less than 40% and 15% of the Dmax, respectively.

The morning of each SBRT session patients had a bowel prep including Dulcolax® (Boehringer Ingelheim, Germany) and a Fleet® Enema (C.B. Fleet Company, Inc., Lynchburg, VA). In addition, at least 15–20 minutes before treatment all patients received 1500 mg of amifostine (MedImmune, LLC Gaithersburg, MD) mixed in saline instilled into the rectum.

Follow-up Schedule and Toxicity Assessment

All post-treatment time intervals were calculated from the time of SBRT boost completion. All patients were scheduled for follow-up three weeks after final treatment, four months later and then every six months thereafter. PSA tests were performed three months and six months after treatment, and every six months thereafter. Quality of life was assessed using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire (18) at every follow-up visit during the first year and at 24 months. EPIC scores were calculated as defined in Wei *et al*. (18). In addition, toxicity was assessed using the Radiation Therapy Oncology Group (RTOG) urinary and rectal toxicity scale (19) at every follow-up visit. Acute toxicity was defined as events that presented and resolved within the first 5 months following treatment. Biochemical failure was assessed using the Phoenix definition (20). Actuarial biochemical control and toxicity results were calculated using the Kaplan-Meier method. Statistical independence was assessed using the chi-square test. All statistical analysis was performed using Prism (GraphPad Software, Inc, La Jolla, Ca).

Results

Follow-up, PSA Response and Biochemical Control

The median follow-up was 33 months (range, 22-43 months). Three PSA failures occurred in the intermediate-risk group and seven PSA failures occurred in the high-risk group at a median of 15 months (range, 6-36 months). Twelve-core biopsies were performed on all of the patients with PSA failures except two who had overt bone metastasis. Of the 9 biopsied failures only one, in the high-risk group, was a local failure. The corresponding 3-year actuarial biochemical control rates (Figure 1) were 84.6%, 89.5% and 77.7% for the combined patient group, intermediate- and high-risk patients, respectively. One high-risk patient (Gleason 8, initial PSA 16 ng/ml), treated with a total dose of 19.5 Gy, died of his cancer at 26 months; one intermediate-risk patient died of a heart attack at 24 months.

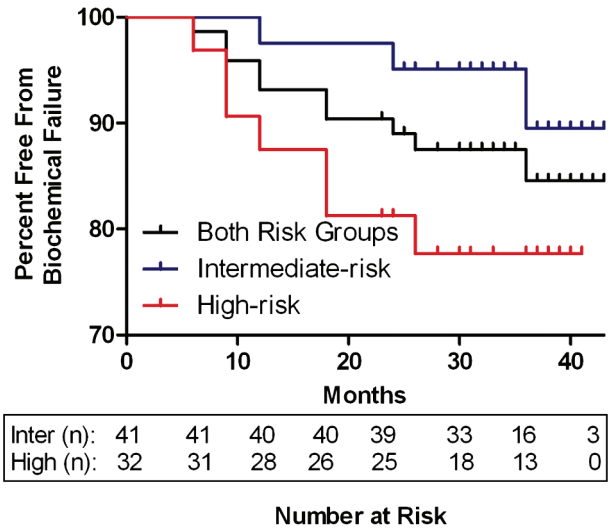

Figure 1: Actuarial biochemical control for the intermediate-risk group (blue), high-risk group (red) and for both risk groups (black). Median follow-up is 33 months.

All patients showed a trend toward decreasing PSA level after treatment. A PSA bounce (defined as an increased PSA > 0.2 ng/mL followed by a decreased PSA to previous value or lower) occurred in 17.8% (13/73) of the patients at a median of 17 months. The median magnitude of the bounce was 0.45 ng/ml (range, 0.25–0.89 ng/ml). PSA nadir thresholds of 0.5 ng/mL at 24 months follow-up and beyond were not significantly different between patients receiving and not receiving hormones (p = 0.91). For the 97% (71/73) of patients that reached 24 months follow-up, 71.8% (51/71) achieved a PSA nadir threshold of 0.5 ng/mL.

Toxicity

Tables II and III present the acute and late urinary and rectal toxicities on the RTOG scale. The majority of observed acute toxicities were Grade I with less than 7% Grade II toxicities and no Grade III or IV acute toxicities. At a median follow-up of 33 months, less than 14% of patients had any late rectal toxicity and less than 11% of patients had any late urinary toxicity. No Grade IV late toxicities occurred. The corresponding three-year actuarial late urinary and rectal RTOG Grade II and higher toxicity-free survivals are 94.5% and 91.8%, respectively (Figure 2).

The single Grade III late urinary toxicity occurred in a patient that received whole pelvis EBRT treatment and the 21 Gy SBRT dose. Four of the six late Grade II rectal toxicities received whole pelvis EBRT treatment. There was no statistically significant difference in toxicity between the SBRT treatment doses for urinary (p = 0.72) or rectal toxicity (p = 0.70). Similarly, there was no statistically significant difference between the patients receiving mini-pelvis and whole pelvis EBRT for either late urinary (p = 0.41) or late rectal (p = 0.19) toxicities.

The one Grade III late urinary toxicity consisted of bleeding for three months which resolved following hyperbaric oxygen therapy. For the three Grade II urinary toxicities, urgency and frequency occurred at months 10, 13, and 14 months. All symptoms resolved within four months. The six patients with late Grade II rectal toxicities had minor bleeding at 8, 10, 11, 12, 13 and 14 months. Three had resolution of symptoms at an average of four months; the symptoms persist for the other three patients.

Table II
Acute urinary and rectal toxicity using Radiation Therapy Oncology Group (RTOG) scoring after stereotactic body radiotherapy (SBRT) boost.

	RTOG Grade			
	0	I	II	III & IV
Acute Urinary	9.4% (7)	83.6% (61)	6.8% (5)	–
Acute Rectal	15.1% (11)	78.1% (57)	6.7% (5)	–

RTOG – Radiation Therapy Oncology Group.

Table III
Late urinary and rectal toxicity using Radiation Therapy Oncology Group (RTOG) scoring after stereotactic body radiotherapy (SBRT) boost.

	RTOG Grade				
	0	I	II	III	IV
Late Urinary	89% (65)	5.5% (4)	4.1% (3)	1.4% (1)	–
Late Rectal	86.3% (63)	5.5% (4)	8.2% (6)	–	–

RTOG – Radiation Therapy Oncology Group.

Quality of Life

All patients completed the initial EPIC questionnaire prior to treatment. For subsequent time points, patients were given the questionnaire at follow-up visits. Figure 3 shows the EPIC scores for bowel, urinary and sexual quality of life (QOL) along with patient response rates. All QOL scores initially decreased. The bowel and urinary QOL scores subsequently returned to baseline values. For sexual QOL, an overall decrease of 9% in the mean QOL score was observed.

To further examine sexual QOL, we verbally screened those patients that were potent prior to treatment to determine if they remained potent. Prior to SBRT treatment 43 patients were potent, five of which were using erectile dysfunction medications. At 33 months median follow-up, 74% (32/43) of patients stated they maintained potency; 9 of those patients used erectile dysfunction medications.

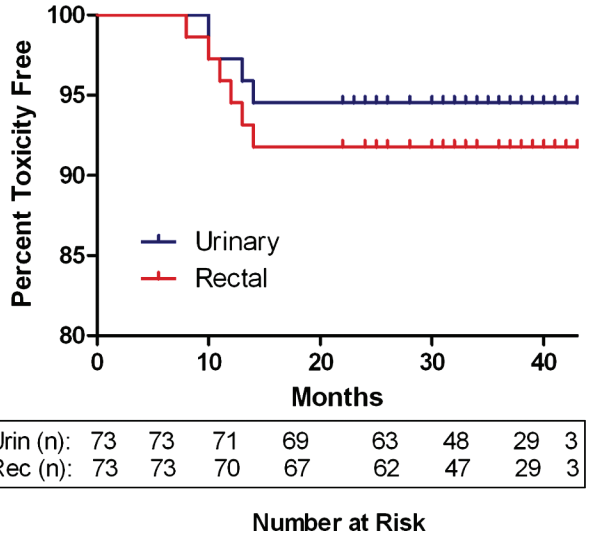

Figure 2: Actuarial late RTOG Grade 2 and higher urinary (blue) and rectal (red) toxicity-free survival.

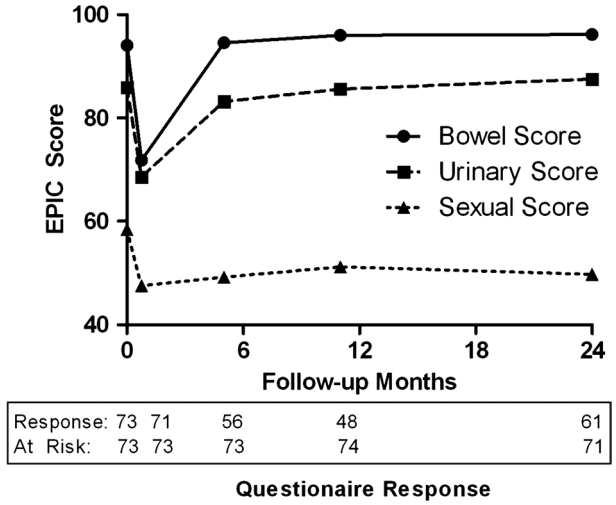

Figure 3: EPIC Quality of Life scores over time for bowel, urinary and sexual function. All patients initially completed the EPIC questionnaire, at 3 weeks 71 of 73 (97%) patients responded, at 5 months 56 of 73 (77%) responded, at 11 months 48 of 71 (68%) responded, and at 24 months 61 of 71 (86%) responded. Error bars represent 95% confidence intervals. Higher scores represent a better quality of life.

Discussion

Biochemical Control and PSA

While considerable additional follow-up is required to confirm these findings, a recent analysis by Zelefsky *et al.* suggests that PSA values at as early as two-years from treatment are predictive of long-term disease control (21). In the current study, 71.8% of patients that reached a minimum of 2 years' follow-up achieved a PSA nadir threshold of 0.5 ng/mL with no significant difference in PSA nadir threshold between patients who received and those who did not receive hormone therapy. This, combined with our 3-year actuarial biochemical control rates of 89.5% for intermediate-risk and 77.7% for high-risk patients suggests the potential for long-term disease control in our patients. These results are also comparable to results obtained in studies of HDR boost treatment, where 3-year biochemical control rates for intermediate- and high-risk patients range from 90-95% and 75-92%, respectively (12, 13, 15, 16, 22-24). As with the current results, all but two of the HDR studies (12, 15) included some patients who received hormone therapy. We note, however, that the patients in the HDR studies have an overall longer follow-up time and the durability of the outcomes has been established.

Acute Toxicity

Several studies have published acute RTOG urinary toxicity results for EBRT followed by HDR (25-27), HDR followed by EBRT (28), and proton followed by EBRT (29) treatments (Table IV). Our acute urinary toxicity results are comparable or slightly better than those obtained for EBRT+HDR boost (25-28). Specifically, in most HDR boost studies Grade III acute urinary toxicity was observed, but none was observed in this study. For Grade II acute urinary toxicity, the observed rate of 6.8% is lower than most HDR boost studies and substantially less than reported for proton+EBRT boost (29).

Published acute rectal RTOG toxicity results for EBRT+HDR (25, 27) and proton+EBRT (29) treatments are shown in Table V. Our observed rate of 6.7% Grade II acute rectal toxicity is substantially less than the acute rectal toxicity reported in the proton+EBRT studies (29) and slightly higher than the rectal toxicity observed in the EBRT+HDR studies (25). We note that in this study rectally administered amifostine was used, which has been shown to reduce RTOG Grade II rectal toxicity incidence due to EBRT (30). Given the absence of prior published clinical results for prostate cancer treatment using EBRT+SBRT boost we elected to proceed cautiously and included rectal administration of amifostine prior to each SBRT treatment fraction.

Late Toxicity

At a median follow-up of 33 months, our preliminary late toxicity results require additional follow-up. However, late rectal toxicity has been shown to occur less frequently as time progresses, with comparable toxicity-free survival at 3 versus 5 years (29, 31). Given that the most recent rectal toxicity event occurred at 14 months, the observed 3-year actuarial rate of 91.8% for Grade II or higher rectal toxicity-free survival is promising.

In a study of prostate SBRT treatment alone (without EBRT), we delivered a total SBRT dose of 35 Gy, and observed no

Table IV

Acute urinary Radiation Therapy Oncology Group (RTOG) toxicity results for published external beam radiation therapy (EBRT) prostate cancer treatments with a high-dose-rate brachytherapy or proton boost.

	RTOG Grade				
Study	0	I	II	III	IV
Current Study	9.4%	83.6%	6.8%	0%	0%
Ares (25)	76%	18%	4%	1%	1%
Ishiyama[†] (28)	30%	58%	6%	6%	0%
Kalkner[‖] (26)	29%	29%	22%	18%	2%
Soumarova (27)	47.5%	37.5%	15%	0%	0%
Zeitman[§] (29)	17%	40%	42%	1%	0%
Zeitman[§] (29)	14%	35%	49%	1%	1%

[†]HDR+EBRT.
[‖]Grades extrapolated from plot.
[§]Proton+EBRT.
EBRT – external beam radiation therapy; HDR – high-dose-rate; RTOG – Radiation Therapy Oncology Group.

Table V
Acute rectal Radiation Therapy Oncology Group (RTOG) toxicity results for published external beam radiation therapy (EBRT) prostate cancer treatments with a high-dose-rate brachytherapy or proton boost.

	RTOG Grade				
Study	0	I	II	III	IV
Current Study	15.1%	78.1%	6.7%	0%	0%
Ares (25)	78%	19.5%	2.5%	0%	0%
Soumarova (27)	60%	40%	0%	0%	0%
Zeitman[§] (29)	27%	31%	41%	1%	0%
Zeitman[§] (29)	18%	25%	57%	0%	0%

[§]Proton+EBRT
EBRT – external beam radiation therapy; RTOG – Radiation Therapy Oncology Group.

Grade II or higher late rectal toxicity, and no higher grade late rectal toxicity, at a median 30-month follow-up (32). In comparison, in the current study we observed an 8.2% rate of Grade II rectal toxicity at a median 33-month follow-up. In both studies SBRT was performed similarly, including the use of rectally administered amifostine, yet the SBRT-only treatment, which delivered a higher dose (35 Gy vs up to 21 Gy), has resulted in a substantially lower rectal toxicity rate to date. We suggest, therefore, that the increased rectal toxicity in the current results, at a median 33 months, was due to the EBRT portion of the treatment.

Quality of Life

A study by Sanda *et al*. examined QOL in prostate cancer patients using EPIC and other measures for the two years following treatment by techniques including radical prostatectomy (n = 603), EBRT (n = 292), brachytherapy (BT) alone (n = 306) or BT with EBRT boost (n = 20) (33). While the number of patients that received EBRT+BT boost in the Sanda *et al*. study is small, a comparison of the 24-month EPIC responses for all of the treatment modalities reveals that EBRT treatment with hypofractionated SBRT boost results in an overall similar or slightly better QOL (33). Specifically, our urinary QOL returned to baseline while the Sanda *et al.* results showed sustained decreased urinary QOL for all treatment modalities (33). Our bowel QOL returned to baseline while the Sanda *et al*. study found a slight decrease in QOL for the 20 EBRT+BT patients and an approximate 10% decrease in QOL for those receiving only EBRT or BT treatment (33). Lastly, our sexual QOL results are comparable to EBRT+BT, EBRT alone, and BT alone whereas radical prostatectomy resulted in a substantial loss of sexual QOL.

The potency preservation rate in the current study was 74% at a median 33 months follow-up. Published potency preservation rates following EBRT with HDR boost vary from 59-73% (12, 34-37) over a variety of follow-up times ranging from 1–10 years. While it is unknown how long potency preservation rates decline, Duchesne *et al*. observe in their study that erectile dysfunction developed within the first 24 months (31) suggesting the retained potency rate in this study may remain durable.

Dosimetry

Although HDR dosing and fractionation provided the general clinical basis for our SBRT boost approach, it important to note that the characteristic dose heterogeneity of HDR was not emulated in this study; rather a more homogeneous, IMRT-like distribution was employed. Nevertheless, the feasibility of delivering HDR-like distributions using the CyberKnife has been demonstrated (38). Indeed Fuller *et al.* observed dosimetric comparability, and in some instances superiority, to HDR dose distributions (38). 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. The difference in these approaches becomes relevant when examining dosimetry values such as the V125 of the target. Specifically, in HDR-like distributions the V125 ranges from 25-50% (38) whereas in our treatments the V125 is essentially 0%. Further follow-up will be necessary to see if there is a difference in control and toxicity between these two treatment approaches.

Dosimetry differences between our approach and HDR can be seen when comparing the V75 of the bladder and rectum. In typical HDR studies, the V75 is limited to 1 cc due to the smaller margin expansion of the PTV, but in our study the V75 to the bladder and rectum was up to 4 cc and 3 cc, respectively. As our observed toxicity rates indicate, however, this does not seem to have impacted toxicity.

Conclusions

Based upon the clinical outcomes of HDR brachytherapy as a boost to EBRT, we have used less invasive SBRT as a boost to EBRT. As reported by Xie *et al.* (39), accurate SBRT dose delivery from an external radiation source requires frequent, automated image-guided correction of beam aim during a treatment fraction. Using such a system, preliminary results suggest that SBRT as a boost for prostate cancer treatment is safe and feasible, although the long-term durability of these results needs to be substantiated.

Conflicts of Interest Statement

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

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