A Prospective Pilot Study of Single 19 Gy Fraction High-Dose-Rate Brachytherapy for Favorable-Risk Adenocarcinoma of the Prostate

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Abstract

Objective: To evaluate the acute genitourinary (GU) and gastrointestinal (GI) toxicities, health-related quality of life (HRQOL) factors, biochemical control rates, and technical feasibility of high-dose-rate (HDR) brachytherapy as monotherapy for prostate cancer delivered in a single fraction.

Methods: A single-institution, prospective pilot study evaluating 6 patients with low- and intermediate-risk prostate cancer treated in 2013. Patients received a single 19 Gy fraction as HDR monotherapy. Patients were assessed according to the Common Terminology Criteria for Adverse Events version 4.0, the International Index of Erectile Function (IIEF-5), the International Prostate Symptom Score (IPSS), the Expanded Prostate Cancer Index Composite–Bowel Assessment (EPIC-Bowel), a Quality of Life (QOL) Assessment, and an institutionally designed quality of care (QOC) questionnaire. Biochemical failure was defined as a prostate-specific antigen (PSA) nadir plus 2 ng/ml.

Results: Patients tolerated the implant well and were all discharged home the same day by approximately 4 pm. Median follow-up was 9 months. No grade 3, 4 or 5 toxicities were observed. Two of the 6 patients (33%) experienced grade 2 GU toxicity. One patient (17%) experienced grade 2 GI toxicity. HRQOL bowel and urinary assessments revealed a majority of complaints at 3 months, which returned to baseline at 6 months.

Conclusion: HDR brachytherapy as monotherapy for favorable-risk prostate cancer using one implant delivered in a single 19 Gy dose has acceptable acute toxicities and HRQOL reports similar to alternative treatment options.

Keywords: Acute toxicity; High-dose-rate; HDR brachytherapy; Prostate cancer; Quality of life

Introduction

Adenocarcinoma of the prostate has multiple effective treatment options for low- and intermediate-risk disease including radical prostatectomy, external beam radiotherapy (EBRT), low dose rate (LDR) or high dose rate (HDR) brachytherapy, or active surveillance. Given that no specific treatment has been shown to be significantly superior over another [1], the treatment choice is often influenced by physician bias, patient preference, and cost. Regarding radiotherapy, one option of increasing interest is that of high-dose-rate (HDR) brachytherapy with iridium-192. In recent years, there has been a trend to further develop HDR brachytherapy techniques and implement its use for the treatment of prostate cancer because of its excellent clinical outcomes and radiobiologic and dosimetric advantages [2]. HDR brachytherapy has many attractive advantages over low-dose-rate (LDR) brachytherapy. These advantages include no radiation exposure to family or staff, pre-treatment delivery of an optimized dose plan, and a more favorable side effect profile [3-5]. The major HDR advantages over external beam radiotherapy include time-related convenience and cost benefits to the patient. Furthermore, given the growing body of knowledge concerning the radiobiology of prostate cancer suggestive of a low alpha-beta ratio, hypofractionated schedules have gained considerable interest amongst investigators [6-8].

Prada et al. recently published the first report of HDR brachytherapy as monotherapy in one fraction for patients with low-and intermediate-risk prostate cancer [9]. Patients were treated with 19 Gy in a single fraction and excellent biochemical control rates were reported. Additionally, Prada et al. performed transperineal hyaluronic acid injections into the perirectal fat to minimize rectal toxicity. This single fraction HDR brachytherapy was well tolerated by all patients with minimal to no genitourinary or gastrointestinal toxicity.

Given the promising results of Prada’s report, a prospective pilot study was initiated to evaluate single-fraction HDR brachytherapy used as monotherapy for favorable-risk prostate cancer. The purpose
of which was to determine the technical feasibility, toxicity, and efficacy of this single-fraction approach without the use of the transperineal hyaluronic acid injections. The present article is a report of technical feasibility, acute toxicity, patient satisfaction, and biochemical control rates.

**Materials and Methods**

**Study design**

We conducted a single-institution prospective pilot study after approval of the appropriate internal review board. A total of 6 male patients were enrolled and treated with high-dose-rate brachytherapy as monotherapy for low- and intermediate-risk adenocarcinoma of the prostate. Treatment was given as a single implant delivered in one 19 Gy fraction. Patient disease was staged using the 7th edition AJCC staging manual and stratified into risk categories of low, intermediate, and high risk according to the version 2.2012 National Cancer Cooperative Network (NCCN) risk factors.

**Selection criteria**

Patient accrual was accomplished by informing referring physicians in the community of the study by letter. Patients felt to be eligible for enrollment on the study were referred to radiation oncology for a pre-study evaluation to determine eligibility. Please see Table 1 for inclusion and exclusion criteria.

| Inclusion Criteria |
|--------------------|
| Male patient diagnosed with prostate adenocarcinoma, confirmed by histopathology |
| Age ≥ 50 years old |
| Low- and Intermediate-risk prostate carcinoma as defined by the NCCN version 2.2012 |
| • Low-risk: ≤ csT2a, Gleason ≤ 6, PSA ≤ 10 |
| • Intermediate-risk: = csT2b-c, Gleason 7, PSA=10-20 |

**Surgical clearance**

ECOG performance status of 0-1

No pubic arch interference or anatomical variants that would preclude a satisfactory implant as determined by pre-operative radiologic assessment (CT, MRI, ultrasound as indicated)

Pre-operative approval by primary care provider, cardiologist or other qualified clinician

**Exclusion Criteria**

History of prior radiotherapy to prostate or pelvis

Prior prostate surgery such as transurethral resection of the prostate (TURP)

History of prior chemotherapy for prostate cancer

Significant pelvic CT/MRI artifact distortion due to prior surgical implants (e.g. hip implants)

High-risk prostate carcinoma: >csT3, Gleason 8-10, PSA >20

Prostate volume >60 cm³

History of autoimmune disorders (e.g. inflammatory bowel disease, CREST syndrome, scleroderma, lupus)

Clinical, radiological or pathological confirmed/suspected T3b, N1, or M1 per 7th ed. AJCCC staging manual

**Pre-existing rectal fistula**

Medically contraindicated for surgery or anesthesia

Determined to be unfit for procedure by primary care provider, cardiologist, or other qualified clinician

| Abbreviations: PSA : Prostate Specific Antigen; NCCN : National Cancer Cooperative Network; ECOG : Eastern Cooperative Oncology Group |

Table 1: Patient selection criteria.

**Pre-brachytherapy evaluation**

Once enrolled on the protocol, each patient was cleared surgically by his primary care provider or cardiologist and evaluated in the pre-op anesthesia clinic to obtain anesthesia clearance. Complete history and physical examination findings including a digital rectal exam were documented for all patients. The pre-op evaluation included routine labs, ECG, and a chest X-ray. For additional information, a CT or MRI of the pelvis was done to rule out potential pubic arch interference. Baseline serum PSA levels were drawn within one month prior to the
procedure. Baseline patient questionnaires were completed by each patient that included the International Index of Erectile Function (IIEF-5), the International Prostate Symptom Score (IPSS), the Expanded Prostate Cancer Index Composite – Bowel Assessment (EPIC-Bowel), a Quality of Life (QOL) Assessment, and an institutionally designed quality of care (QOC) questionnaire. The perceived quality of life (QOL) assessment was a one page scale marked at 0=worst possible state of health and 100=best possible state of health, and the patient drew a line at the level of their perceived overall quality of life. The quality of care (QOC) questionnaire included 5 levels of care: 1=very dissatisfied with care plan, 2=dissatisfied with care plan, 3=neutral (no impact) regarding care, 4=satisfied with care plan, 5=very satisfied with care plan. Pre-op instructions included a prescription for a polyethylene glycol electrolyte solution to be taken the evening prior to the procedure, clear liquid diet for 24 hours, NPO after midnight, and a sodium phosphate rectal enema to be administered the morning of the procedure.

### HDR brachytherapy

Patients were given IV antibiotics, typically gentamicin and metronidazole, just prior to the procedure. Compression stockings were used for lower extremity venous thromboembolism prophylaxis. Dissimilar to the Prada method [9], hyaluronic acid injection into the posterior prostatic space was not utilized. Prada et al. used this method to displace the rectum posteriorly away from the prostate in an attempt to protect the rectum. This technique is not FDA approved in the United States and may not be necessary for rectal sparing. No intentional positioning to displace bowel superiority was done during simulation and delivery of dose due to targeted DVH constraints being met without such interventions. After general and/or epidural anesthesia, the patient was placed in the dorsal lithotomy position in stirrups, cleaned and prepped in the usual sterile fashion, and a 3-way Foley catheter placed into the bladder. ProGuide needles (Nucletron, Veenendaal, The Netherlands) were used for lower extremity venous thromboembolism prophylaxis. Once ideal positioning was obtained the template was tightened to prevent catheter movement. The catheters were positioned at the bladder-prostate interface avoiding bladder wall puncture. The patient was then transferred to the CT simulation suite in the cancer center. Prior to the first CT scan, 25 ml of contrast was placed within the bladder. The first CT scan was limited to the distal catheters to confirm correct depth positioning at the prostate-bladder interface. As needed, catheters were advanced cranially or withdrawn caudally as needed. Once ideal positioning was obtained the template was tightened to prevent catheter movement. The catheters were marked at the catheter-template interface to confirm that no movement of the catheter had occurred away from the template prior to the treatment. CT images were then obtained through the entire bladder down to the outer edge of the template. Images were transferred to an Oncentra planning station (Nucletron NV, The Netherlands) for contouring and isodose plan development. The treatment plan was typically completed within 2 hours of the simulation during which the patient remained in the same position on the Slessinger board with legs held in position with velcro straps to limit lower extremity movement and to provide patient support. Please see Table 2 for treatment parameters and Table 3 for patient dose-volume-histogram constraints. HDR brachytherapy was given in the designated HDR suite under camera surveillance using an iridium-192 stepping source unit (MicroSelectron, Nucletron NV, The Netherlands). At the conclusion of the treatment, the template and catheters were pulled out in one movement. Once the patient urinated, the patient was discharged home at approximately 4 pm the same day. The patient was typically discharged on tamsulosin, pain medications, and antibiotics for 7 days.

### Table 2: Treatment parameters.

| Patient 001 | Patient 002 | Patient 003 | Patient 004 | Patient 005 | Patient 006 |
|-------------|-------------|-------------|-------------|-------------|-------------|
| **Urethra** |             |             |             |             |             |
| V100        | 67.31%      | 63.55%      | 60.48%      | 50.36%      | 36.34%      | 60.56%      |
| V125        | 0.03%       | 0.08%       | 0.5%        | 0%          | 0%          | 0%          |
| **Bladder** |             |             |             |             |             |
| V85         | 0%          | 0.80%       | 0.14%       | 0.67%       | 0.08%       | 0.08%       |

Abbreviations: V100=Percentage of the structure volume receiving 100% of the prescription dose (19 Gy).
Table 3: Patient dose-volume-histogram constraints.

Table 4: Patient characteristics.

Acute toxicity

Data for acute toxicity is based on a median follow-up of 9 months for the 6 patients under evaluation. Genitourinary and gastrointestinal toxicities are reported in Figure 1. There were minimal low-grade toxicities observed, of which none persisted to the next follow-up appointment. No grade 3, 4, or 5 toxicities were observed.

Results

A total of 6 patients met inclusion criteria and were enrolled in this pilot study between December 2012 and August 2013. Please see Table 4 for patient characteristics. The median age was 76 years old. The most common T stage was T1c, and the most common Gleason score was 7. The pre-brachytherapy PSA mean was 7.8, median 8.5, and range 4.4-10.5. Only one patient received androgen deprivation therapy prior to radiotherapy. All patients received 19 Gy in a single fraction. Every patient was discharged home before 4 PM on the same day of brachytherapy. Median follow-up for the group was 9 months (range, 6-12).
month follow-up appointment, which had resolved at the 9-month follow-up appointment, and the other patient had grade 2 GU toxicities consisting of urinary tract pain, cystitis, and urinary urgency at the 1 week check-up and urinary retention at the 6-month check-up which all resolved at the next follow-up appointment. The second patient also experienced grade 2 GI toxicities in the form of proctitis and rectal pain at his 1-week check-up both of which had resolved at his 3-month follow-up.

Health-related quality of life and care

Please see Table 5 for quality of life data. Prior to treatment and at every follow-up visit, all 6 patients (100%) had completed the questionnaires concerning bowel, urinary, and sexual quality of life. Overall perceived quality of life and quality of care questionnaires were also completed by all patients. Bowel complaints were highest at 3 months with the average score dropping to 91.9 from a baseline of 96.7 on the EPIC questionnaire; however, bowel quality of life did trend toward baseline at the 6-month follow-up and returned to baseline at the 9-month follow-up. Urinary complaints, as determined by the IPSS, reached a zenith within 3 months with an average 3.2 points above the baseline IPSS and then partially recovered by the 6-month follow-up.

**Table 5**: Health-related quality of life scores and biochemical control.

| Domain                        | Baseline | 1 week | 3 months | 6 months | 9 months |
|-------------------------------|----------|--------|----------|----------|----------|
| Bowel (EPIC)                  | 96.7 (92.9-100) | 97.6 (92.9-100) | 91.9 (73.2-100) | 93.3 (82.1-100) | 96.4 (92.9-98.2) |
| Urinary (IPSS)                | 6.3 (1 to 12) | +4.2 (-1 to +15) | +3.2 (-2 to +14) | +2.5 (0 to +4) | +2 (0 to +4) |
| Bother (IPSS)                 | 1.8 (0 to 5) | +0.8 (-2 to +4) | +0.3 (0 to +1) | -0.5 (-1 to 0) | 0 (-1 to +1) |
| Perceived Quality of Life     | 74 (60.5 to 91) | +7.8 (-5 to +29.5) | +2.8 (-11 to +21.5) | -2.9 (-11.5 to +11) | +3 (-10.5 to +21.5) |
| Perceived Quality of Care     | 4.3 (1-5) | 5 | 4.8 (4.5) | 5 | 5 |
| Prostate Specific Antigen     | 7.8 (4.4-10.5) | N/A | 1.9 (0.6-4.8) | 1.1 (0.5-1.9) | 1.4 (0.4-2.7) |

**Discussion**

The major findings of this report can be summarized as follows. First, we demonstrated the technical feasibility of a single-19 Gy fraction of HDR brachytherapy used as monotherapy in favorable-risk adenocarcinoma of the prostate. This is the first reported pilot study to investigate this single-fraction method in the United States, and the first-ever to do so without transperineal hyaluronic acid injections into the perirectal fat to displace the rectum. Second, our preliminary results suggest there is minimal to no acute low-grade GU or GI toxicity with this treatment and that quality of life measures are comparable to other common treatment modalities [11-14]. Furthermore, there were no acute high-grade GU or GI toxicities (Grade ≥3). Third, biochemical control rates have been encouraging with good biochemical response to therapy and no biochemical relapses at a median follow-up of 9 months; however, it is far too early to report on this method’s durable biochemical control rate. Finally, the cost of this treatment is substantially less than current alternative options. The actual cost for this single fraction therapy, reported by our institution’s Southwest Cancer Center, is $15,096.00. Likewise, a typical prostate cancer intensity-modulated radiation therapy treatment reportedly costs Medicare $31,574 [15]. While the drastic difference in cost is easily appreciated, similar ranges exist when comparing any brachytherapy treatment to IMRT. Reason would follow that a single fraction of HDR brachytherapy would cost less than multiple fractions over a period of days. The economics of single-fraction HDR brachytherapy coupled with the convenience to the patient makes this an attractive treatment option, especially if durable control rates prove to be non-inferior to the current alternatives.

Prada et al. were the first to report on this HDR brachytherapy method using a single-19 Gy fraction as monotherapy for prostate cancer [9]. At a median follow-up of 9 months, their report had no Grade 2 or greater acute GI or GU toxicity and no chronic toxicities were observed. Chronic toxicity was defined as symptoms persisting or appearing beyond 6 months. Similar to Prada’s results, we also found that this treatment had minimal acute GI or GU toxicities wherein we did not observe any Grade 3 or above adverse sequelae. One major difference between our pilot study and the trial performed by Prada was that we did not use the transperineal hyaluronic acid injections into the perirectal fat to displace the rectum. It was felt that this technique was unnecessary to minimize the dose to the rectum and prevent GI toxicity. In contrast to Prada’s study, however, we did observe one patient (16.7%) with temporary acute Grade 2 proctitis and rectal pain. Whether or not the hyaluronic acid injections would

**Sexual function assessment**

The International Index of Erectile Function (IIEF-5) questionnaire given before HDR brachytherapy revealed that all 6 patients had significant erectile dysfunction at baseline. Five of the six patients (83%) reported baseline IIEF-5 scores of ≤4, where a score of ≥21 is suggestive of erectile dysfunction. The other patient had a baseline IIEF-5 score of 10, yet was potent before HDR brachytherapy despite some dysfunction and disinterest. Sexual potency was preserved in the one patient who was potent preoperatively. Potency was defined as being able to achieve an erection sufficient for intercourse.

**Short-term biochemical control**

Biochemical relapse was defined as a PSA nadir plus 2 ng/mL [10]. The mean baseline PSA was 7.8 ng/mL (range, 4.4-10.5). Mean PSA levels gradually decreased from 7.8 at baseline to 1.4 at 9 months, and there have been no cases of biochemical failure (Table 5).
have prevented this single case of temporary acute GI toxicity is difficult to determine but is unlikely to warrant transperineal hyaluronic acid injections.

Actuarial biochemical control rates in Prada’s study were 100% and 88%, respectively, for low- and intermediate-risk prostate cancer groups at 32 months. Although it is far too early to conclude anything concerning the durable biochemical control rates in the present study, there has been 100% biochemical control at a median follow-up of 9 months.

There is a paucity of literature concerning health-related quality of life (HRQOL) data for HDR monotherapy. There are, however, a few prospective multicenter cohort studies that have utilized validated HRQOL questionnaires to measure quality of life issues after LDR brachytherapy, external beam radiotherapy, and prostatectomy [11-14]. It appears that all of these treatment modalities commonly affect three major HRQOL domains – sexual, urinary, and bowel – in similar fashion. The greatest impact of HRQOL in these previously cited studies occurs within the first 6 months. There is typically an initial decline in quality of life within the first 3 months and then there is an appreciable recovery which typically plateaus after 1 year. Barkati et al. an Australian group studying HDR monotherapy, used the patient-reported modified EPIC questionnaire [16]. They showed that urinary and bowel domains were affected similarly with the majority of symptoms reported within the first 3 months after treatment. Similarly, we observed the most significant decrease in urinary and bowel quality of life at 3 months after treatment and then appreciated a return towards baseline thereafter. While it is known that radiation complications have variable responses over time, it is important to remember that an absence of complications does not rule out late toxicity. Clinicians have demonstrated that late complications can arise even though the patient was asymptomatic weeks and months earlier [17]. Of interest, the sexual domain was the most commonly affected in Barkati’s study and the impact persisted beyond 1 year after treatment. Of our 6 patients, only one was sexually potent before treatment and has remained so 6 months after brachytherapy with no change in his IIEF-5 score of 10.

Ghilezan et al. treated favorable-risk prostate cancer with HDR monotherapy to 24-27 Gy delivered in two fractions within 1 day. Their results were encouraging given the minimal acute (<6 months) and chronic (>6 months) toxicities and the fact that, like our study, the entire treatment was delivered in 1 day. Similar to their study, urinary frequency and urgency were the most common acute GU toxicities our patients experienced. Although acute GI toxicities were essentially non-existent in the Ghilezan report, they did appreciate a few chronic GI toxicities, however, the percentage of patients experiencing grade 2 or above was only 1% [18].

There are two major advantages of this treatment that we would like to highlight. First, it is arguably the most convenient and most time conserving treatment option for the patient. All 6 of our patients tolerated the procedure with minimal discomfort and were able to return home by 4 PM the same day. The second major advantage is that it is arguably the least expensive treatment option available and deals with the economics of prostate cancer. Currently, in the United States, a major goal of health reform is to reduce the growth rate of healthcare expenses while simultaneously maintaining or improving the quality of care [18]. Prostate cancer treatment is an important area for comparative effectiveness research because its cost to healthcare in the United States is an estimated $4.5 billion for the initial treatment alone [19]. To drive home this issue’s relevance, the Institute of Medicine’s Committee on Comparative Effectiveness Research recently identified the treatment of favorable-risk prostate cancer as a top research priority [20]. Thus, it would be prudent to develop effective and affordable treatments, such as the present treatment method, to provide risk-adverse patients with a low-cost alternative to active surveillance.

This study does have limitations, the first of which being its limited follow-up period (median 9 months). As data matures, we will report the outcomes of chronic toxicity, disease free survival, overall survival, and biochemical control rates. However, given the pressing need for affordable and effective treatments in a cost-conscious healthcare system, we felt the study would add positively to the prostate cancer community discussion and be hypothesis generating.

We conclude that HDR brachytherapy delivered in a single-19 Gy fraction and used as monotherapy for favorable-risk prostate cancer is technically feasible with excellent patient satisfaction. No grade 3, 4 or 5 acute GI or GU toxicities were observed. Biochemical control appears to be comparable to other radiotherapy treatments (although the data is too immature to comment on durable biochemical control rates). The cost and convenience advantages of this treatment method make it an attractive option although our findings need to be confirmed in a larger prospective trial.

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