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Early toxicity and health-related quality of life results of high-dose-rate brachytherapy as monotherapy for low and intermediate-risk prostate cancer

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ABSTRACT

PURPOSE: To determine the acute toxicity and effect on health-related quality of life of a two-fraction regimen of high-dose-rate (HDR) prostate brachytherapy.

METHODS AND MATERIALS: Patients with low- or intermediate-risk prostate cancer were treated with HDR brachytherapy as monotherapy in two implants of 13.5 Gy spaced 7−14 days apart. Patients completed International Prostate Symptom Score (IPSS) and Expanded Prostate Index Composite (EPIC) questionnaires at 1, 3, 6, 9, 12, 16, 20, and 24 months after brachytherapy. Proportion of patients in each IPSS category (mild = 0−7, moderate = 8−18, severe = 19+) was evaluated at each of the intervals above. Paired *t* tests with baseline values were done for IPSS and EPIC scores.

RESULTS: Thirty patients were accrued to the study. Median prostate-specific antigen was 8,7 (range 4.1−17.5). T stages were T1c = 65%, T2a = 21%, and T2b = 14%. Twenty-seven percent of patients had a Gleason score of 6 and 73% had a Gleason score of 7. IPSS categories at baseline, 1, 3, 6, 12, and 24 months were mild (81%, 43%, 58%, 62%, 76%, 64%), moderate (19%, 32%, 29%, 30%, 20%, 29%), and severe (0%, 25%, 13%, 7%, 4%, 6%), respectively. There was a significant decrease in EPIC sexual summary scores at 1, 3, 6, and 12 months of 0 points ($p < 0.001$), 17 points ($p = 0.01$), 18 points ($p = 0.02$), and 17 points ($p = 0.01$), respectively.

CONCLUSIONS: This is the first report of this cohort of patients treated with two-fraction HDR monotherapy. This regimen shows rates of toxicity and health-related quality of life that appear acceptable as compared to other treatment modalities. These results are also comparable with other reports with similar treatment regimens.

Keywords: Prostate; HDR; Brachytherapy; Monotherapy; Health-related quality of life

Introduction

Multiple radiation treatment modalities including intensity-modulated radiotherapy (IMRT), stereotactic body radiotherapy, and brachytherapy have been shown to be effective for the treatment of localized prostate cancer (1). Brachytherapy for prostate cancer was initially developed in the 1980s using permanent implant low-dose-rate (LDR) brachytherapy with ultrasound guidance (2,3). Large series with long-term data have reported very favorable outcomes with LDR brachytherapy as monotherapy in cases of low- and intermediate-risk prostate cancer (4). With the widespread adoption of high-dose-rate (HDR) afterloader

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technology, HDR brachytherapy has gained widespread acceptance for the treatment of localized prostate cancer. However, the vast majority of initial studies of HDR prostate brachytherapy were done using an HDR boost combined with external beam radiotherapy (5,6).

Many institutions in the United States, the United Kingdom, and Germany have since developed protocols for HDR prostate brachytherapy as monotherapy (7−12). These groups have since reported mature results of their series. However, most of these patients were treated with HDR monotherapy treatment regimens involving multiple implants and multiple fractions (up to 10). These fractionation schedules made this procedure less accessible than procedures such as LDR brachytherapy despite theoretical advantages such as radioprotection and cost.

More recent studies have evaluated hypofractionated HDR monotherapy schedules with one to two fractions (13−15). Long-term data concerning these strategies are emerging, and it was felt that this technique could be implemented at our center in the context of a clinical trial documenting outcomes for these patients. The objectives of the present study were to evaluate acute toxicity and health-related quality of life (HrQOL) for a cohort of patients treated with a two-implant two-fraction regimen of HDR prostate monotherapy. Similar early data for two-fraction HDR monotherapy have already been reported for much larger series in large academic centers like the study reported by Morton *et al.* (16). Nonetheless, an underlying objective of the present study was to demonstrate that similar results could be obtained in a smaller community center.

Methods and materials

Patients for the study referred to one center for curative treatment of localized prostate cancer were offered the possibility of treatment with HDR brachytherapy as monotherapy if they were eligible for the present study. Patients were considered eligible if they had biopsy-proven adenocarcinoma of the prostate, Gleason Score 6 or 7, Stages T1c−T2b, serum prostate-specific antigen (PSA) less than 20 ng/mL, and no evidence of nodal or distal metastases. Patients were deemed ineligible if they had a history of previous pelvic radiotherapy, collagen vascular disease, inflammatory bowel disease, bilateral hip prosthesis, or an International Prostate Symptom Score (IPSS) of 19 or more. Patients were permitted to have androgen deprivation therapy (ADT) according to the discretion of their treating physician.

Brachytherapy treatment

High-dose-rate (HDR) brachytherapy treatment consisted of two separate implants of 13.5 Gy, each given 7−14 days apart. Transrectal ultrasound guidance was used for catheter placement. A template-based technique was used unless significant pubic arch interference was encountered in which case a freehand technique was used. Between 15 and 21 catheters were inserted. Cystoscopy was then obtained with assistance from a urologist to ensure no needles punctured the bladder. Treatment planning was CT based similar to previously reported techniques (5,17,18). Target volume included the entire prostate. Planning objectives were the following: prostate $V_{100} > 95\%$, prostate $V_{150} < 35\%$, prostate $V_{200} < 15\%$, and prostate $D_{90} > 90\%$ of prescription dose; bladder $V_{75} < 1$ cc, rectum $V_{75} < 1$ cc, urethra $V_{125} = 0$ cc, and $D_{10} < 120\%$. Fig. 1 shows a typical implant and dose distribution.

Clinical followup included visits at 1, 3, 6, 9, 12, 16, 20, 24, 30, 36 months, and every year thereafter until 10 years. At each followup visit, patients underwent a physical examination including digital rectal examination, PSA and completed IPSS, and Expanded Prostate Index Composite (EPIC-50) questionnaires (19−22). The EPIC questionnaire used in French has since been validated by Vigneault *et al* (21). Clinical toxicity was also evaluated according to Common Terminology Criteria for Adverse Events v4.0.

Study was approved by CISSS de l'Outaouais Research Ethics Board and registered on clinicaltrials.gov (NCT02077335). All patients provided written consent.

Study sample size was based on primary hypothesis, which was that biochemical disease free survival (bDFS) in HDR monotherapy would be similar. With previous data from our center, it was determined that 50 patients would be required to be able to demonstrate a 20% difference in bDFS at 5 years with a power of 80% and alpha error equal to 0.05. This publication reports on a secondary objective of toxicity and HrQOL. With the analyses completed, the power to detect clinically significant differences in EPIC scores as of 10 for urinary scores and sexual scores (23) with the actual population of 30 patients was approximately 80%.

The present study's objective was to determine clinically significant differences in IPSS and EPIC scores over time. Planned statistical analyses were to compare proportion of patients in IPSS categories over time with χ^2 tests. IPSS severity category was described as mild (0−7), moderate (8−19), or severe (≥20). Mean intrapatient differences from baseline in EPIC scores were compared using paired *t* tests. All statistical analyses were considered statistically significant if bilateral *p*-value was less than 0.05 except for repeated paired *t* tests to which we applied a simplified Bonferroni correction and considered *p*-value to be statistically significant less than 0.00625.

All statistical analyses were completed with SPSS v25 software (Armonk, NY).

Results

Thirty-four patients were screened for eligibility between June 2014 and February 2016. Two patients declined participation. One patient was excluded because