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Original Article

# Long-term Toxicity and Health-related Quality of Life after Single-fraction High Dose Rate Brachytherapy Boost and Hypofractionated External Beam Radiotherapy for Intermediate-risk Prostate Cancer

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## Abstract

*Aims:* To report health-related quality of life (HRQOL) and toxicity in prostate cancer patients treated with single-fraction high dose rate (HDR) brachytherapy boost and external beam radiotherapy (EBRT).

*Materials and methods:* Patients with intermediate-risk prostate cancer were accrued to a phase II clinical trial of 15 Gy HDR boost and EBRT to a dose of 37.5 Gy in 15 fractions. HRQOL (Expanded Prostate Cancer Index Composite [EPIC]), urinary symptoms (International Prostate Symptom Score [IPSS]), erectile function (International Index of Erectile Function [IIEF]) and toxicity (Common Terminology Criteria for Adverse Events [CTCAE], version 3.0) were monitored prospectively. Univariate and multivariate logistic regression analysis was used to investigate associations between HRQOL/toxicity and baseline covariates.

*Results:* The median follow-up time was 5.2 years. The change in the median EPIC scores from baseline to year 5 in the urinary domain was from 91 to 85 ($P = 0.0028$), in the bowel domain was from 98 to 96 ($P = 0.03$), in the sexual domain was from 63 to 35 ($P < 0.0001$) and the hormonal domain remained unchanged at 95 ($P = 0.93$). Fifty-nine per cent and 46% of the patients with normal erectile function at baseline remained potent at year 1 and year 5, respectively. Late genitourinary toxicity grade 1, 2 and ≥3 occurred in 29, 59 and 4% of patients, respectively. The rates of late gastrointestinal toxicity grade 1, 2 and ≥3 were documented as 45, 19 and 0%, respectively. On multivariate logistic regression analysis, patients with larger prostates were more likely to develop a urinary late toxicity grade ≥2 ($P = 0.01$). The dose to 10% of the urethra was the only factor associated with a decline in the EPIC urinary domain score ($P = 0.012$). Prostate volume >43 ml was associated with higher late genitourinary toxicity grade ≥2.

*Conclusions:* Single 15 Gy HDR brachytherapy with EBRT has a low rate of late genitourinary and gastrointestinal toxicities. Late urinary morbidity may be minimised by limiting the dose to the urethra, particularly for patients with larger prostates.



*Key words:* Brachytherapy; health-related quality of life; prostate cancer; toxicity

## Introduction

External beam dose escalation for the treatment of prostate cancer has been shown to improve biochemical disease-free survival [1]. Brachytherapy delivers a higher dose to the prostate than that achievable with any form of external beam radiotherapy (EBRT) while sparing the adjacent normal structures due to the rapid dose fall-off. Combining EBRT with brachytherapy provides a means of further dose escalation, with sparing of adjacent organs [2,3]. This combination has been shown to improve biochemical control and recurrence-free survival compared with EBRT alone [4–9].

Several treatment options are available to prostate cancer patients, including radical prostatectomy, EBRT, brachytherapy or a combination of EBRT and brachytherapy, with or without the use of adjuvant androgen deprivation

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therapy. All of these treatments have been reported to cause urinary, bowel or sexual dysfunction with different levels of severity, frequency and duration [10–12].

We have previously reported the long-term cancer control outcomes of intermediate-risk prostate cancer patients treated radically with a novel brachytherapy boost protocol using single-fraction high dose rate (HDR) brachytherapy of 15 Gy followed by 37.5 Gy EBRT in 15 fractions [13,14]. With a median follow-up of 74 months, patients who were treated with this protocol had a 5 year biochemical relapse-free survival of 97% [13]. Early changes in health-related quality of life (HRQOL) and toxicity were reported after 24 months of follow-up [15]. At 2 years, grade 2 urinary toxicity was seen in 23% of the patients and 5% had developed grade 2 bowel toxicity. Only one patient developed grade 3 or higher urinary toxicity. With regards to HRQOL, 57, 65, 51 and 30% of the patients reported a clinically significant decline in the urinary, bowel, sexual and hormonal domain scores, respectively, at 12 months. Since then, this protocol has been widely adopted due to its convenience, high disease control rates and favourable early toxicity rates.

The purpose of this study was to determine longer term data on late toxicities and changes in HRQOL after single 15 Gy HDR brachytherapy and hypofractionated EBRT, and to determine clinical and treatment-related predictors of patient-reported outcomes.

## Materials and Methods

### *Patient Characteristics*

A prospective phase II clinical trial to assess single-fraction HDR brachytherapy in combination with EBRT for the treatment of prostate cancer was conducted at Sunnybrook Odette Cancer Center. The clinical trial was approved by the Sunnybrook Research Ethics Board and it was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

This study accrued 125 men with intermediate-risk prostate cancer between 2005 and 2007. All patients provided informed consent before participation in the clinical trial. The inclusion criteria, exclusion criteria and treatment details were previously described [14,15].

Eligible patients had a histological diagnosis of adenocarcinoma of the prostate with clinical stage T1c–T2b. They either had a Gleason score 6 and a serum prostate-specific antigen (PSA) level of 10–20 ng/ml or a Gleason score 7 and a PSA level <20 ng/ml. Eastern Cooperative Oncology Group (ECOG) performance status score was 0–1. Patients were excluded if they had a prostate volume > 60 ml assessed by trans-rectal ultrasound, previous pelvic radiotherapy, previous trans-urethral resection of the prostate or androgen deprivation therapy.

### *Treatment Details*

The protocol consisted of single-fraction 15 Gy HDR brachytherapy followed 2 weeks later by 37.5 Gy in 15 fractions of daily EBRT delivered over 3 weeks. The brachytherapy was carried out under spinal anaesthesia as an out-patient procedure. The patients were placed in the dorsal lithotomy position and with trans-rectal ultrasound guidance, a median of 17 (between 14 and 18) afterloading catheters were inserted into the prostate. Computed tomography with 50 ml diluted bladder contrast was then carried out and images transferred to the Nucletron PLATO planning system, version 14.3.2 (Nucletron BV, Veenendall, the Netherlands). The prostate (as the planning target volume), rectum, bladder and urethra were contoured. Dwell time optimisation was carried out using inverse planning with simulated annealing. Before treatment delivery, fluoroscopic imaging was obtained to assess and correct any catheter displacement. The dosimetric constraints for the target and organs at risk were as follows: prostate V100 > 95%, prostate V200 < 11%, urethra D10 < 118% and rectum V80 < 0.75 ml.

EBRT was carried out 2 weeks after the HDR brachytherapy to a dose of 37.5 Gy in 15 fractions delivered daily over 3 weeks. Patients underwent a computed tomography simulation before the start of the EBRT. The prostate gland and the proximal 2 cm of seminal vesicles were contoured as the clinical target volume. The planning target volume was described as a 1 cm uniform margin beyond the clinical target volume to be covered by at least 95% of the prescription dose using a four-field conformal technique. No specific normal tissue dosimetric constraints were mandated for EBRT.

### *Patient Follow-up and Outcome Measures*

Outcome measures were documented before the start of radiation therapy (baseline) and again 1 month after brachytherapy, every 3 months for the first year, every 6 months for the second year and once a year thereafter. At each visit, a digital rectal examination was carried out and PSA/testosterone were checked. Treatment-related toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. The CTCAE grade was assigned by a clinical research assistant. Patient-reported outcomes including HRQOL data were collected for the first 5 years. Lower urinary tract symptoms and erectile function was documented at each follow-up visit using International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) questionnaires, respectively. Prostate cancer-specific HRQOL was measured using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire. EPIC has four domains: urinary, bowel, sexual and hormonal. Each domain is then categorised into two subdomains describing function and bother within each specific domain.

### *Statistical Analysis*

A data analysis was carried out using Statistical Analysis System software, version 9.4 (SAS Institute, Cary, NC, USA). Demographics and dosimetric data were summarised as mean, standard deviation, median and range for continuous variables and proportions for categorical variables. The

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