

Hypofractionated external beam radiation therapy in combination with HDR boost for localized prostate cancer: patient reported quality of life outcomes

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Abstract

Purpose: There is limited data to support the use of hypofractionated external beam radiation (HypoF) in combination with high-dose-rate brachytherapy (HDR). We report our quality of life (QOL) outcomes when treating intermediate and high-risk prostate cancer patients with external beam radiation (EBRT) plus HDR.

Material and methods: The charts of 54 patients with localized adenocarcinoma of the prostate treated with standard fractionation (SF) or HypoF EBRT plus HDR boost at a single institution between 2012 and 2015 were reviewed. All patients completed the American Urological Association Symptom Score (AUASS) and Expanded Prostate Index for Prostate Cancer – Clinical Practice (EPIC-CP) quality of life assessments prior to treatment and completed at least one follow-up survey. Linear mixed models were performed to test for significant changes and differences in each outcome over time.

Results: There was no significant difference in AUA score ($p = 0.98$), incontinence (urge) and urinary irritation/obstruction scores ($p = 0.81$ and $p = 0.62$, respectively), and bowel QOL ($p = 0.97$) between the two dosing groups over time or at any discrete time point. For both groups, AUA scores peaked at 0-2 months before improving. Likewise, sexual function, vitality score, and QOL scores were also not significantly different between the dose groups over time ($p = 0.59$, $p = 0.37$, and $p = 0.71$, respectively). All QOL categories, except sexual function, trended toward baseline with increasing time from intervention.

Conclusions: Our study suggests HypoF EBRT can be delivered in combination with HDR for patients with intermediate-risk and high-risk adenocarcinoma of the prostate without increasing toxicity compared to SF with an HDR boost.

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Purpose

Radiation dose escalation has long been associated with improved biochemical relapse-free survival in prostate cancer. Initially, dose escalation was achieved using external beam radiation therapy (EBRT) alone [1,2,3,4,5]. The advent of intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) allowed for more conformal treatments and decreased toxicity [6,7,8]. More recently, brachytherapy has been used as a means of dose escalation, given the rapid dose fall-off associated with the technique and improved sparing of

normal tissue. Three randomized trials including intermediate and high-risk prostate cancer patients have shown improvement in biochemical recurrence-free survival when escalation is achieved with a brachytherapy boost added to EBRT [9,10,11]. In one of the trials, the control arm consisted of modern external beam doses, leading to EBRT plus a brachytherapy boost to be considered a standard of care for intermediate and high-risk patients able to tolerate a procedure [11].

Given the importance of cost effective treatment strategies in combination with the low alpha/beta ratio associated with prostate cancer, hypofractionated treatment

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schedules have been investigated [12]. Four randomized trials have shown no difference in treatment efficacy when a hypofractionated EBRT treatment is delivered rather than a conventionally fractionated EBRT treatment [13,14,15,16]. This has become the new standard of care at many institutions, which improves resource utilization and is more convenient for patients. However, there is limited evidence on combining hypofractionated EBRT with a brachytherapy boost [17]. At our institution, EBRT plus a brachytherapy boost is delivered to unfavorable intermediate and high-risk prostate cancer patients whenever feasible. Since 2013, whenever possible, the external beam portion of the treatment has been delivered via a hypofractionated regimen, as discussed in the American College of Radiology (ACR) Appropriateness Criteria [18]. We report our quality of life (QoL) outcomes between patients receiving standard vs. hypofractionated EBRT and a high-dose-rate brachytherapy (HDR) boost.

Material and methods

After institutional review board approval, the charts of 202 patients with biopsy proven localized adenocarcinoma of the prostate who received brachytherapy at our institution between 2012 and 2015 were retrospectively reviewed. Patients who were treated with standard or hypofractionated EBRT plus HDR boost were included in the analysis. Patients were excluded if their prostate cancer was previously treated. Patient reported outcomes (PRO) were collected at baseline and at regular intervals after treatment using the American Urological Association Symptom Score (AUASS) and Expanded Prostate Index for Prostate Cancer – Clinical Practice (EPIC-CP). The American Urological Association developed the AUASS to determine how bothersome men's urinary symptoms are. Each urinary symptom is given a score from 0-5. A score of 0 means the symptoms do not occur at all, while a score of 3 means men experience the symptoms about half the time. A score of 5 means the symptoms occur almost always. The AUASS consists of 7 urinary specific questions and is scored out of a total of 35 points. EPIC-CP is divided into subdomains, including urinary incontinence (incon), urinary irritability and obstructive symptoms (irr/obs), bowel QoL, sexual function, and vitality. Each subdomain consists of 3 questions and is scored out of a total of 12 points, while the overall EPIC-CP quality of life score is out of a total of 60 points. All patients completed the AUASS and EPIC-CP quality of life assessments prior to treatment and completed at

least one follow-up survey. This left 54 patients for analysis.

External beam radiation therapy

For all patients, EBRT was delivered prior to brachytherapy. The CTV standardly consisted of the prostate and seminal vesicles. However, pelvic lymph nodes were included in the CTV for 6 patients with high-risk disease. A 0.3-1 cm margin was added to the CTV to create the PTV. All patients treated with standard fractionation EBRT received 45 Gy in 25 fractions ($n = 38$). Hypofractionation regimens included 37.5 Gy in 15 fractions ($n = 14$), 42.5 Gy in 17 fractions ($n = 1$), and 40 Gy in 16 fractions ($n = 1$). Assuming an alpha/beta of 1.5 for prostate cancer, the biologically equivalent dose (BED) was calculated for each EBRT regimen and summed with the BED for each HDR regimen for the total BED (Table 1). All patients were treated with either intensity-modulated radiation therapy (IMRT) using a fixed gantry technique, or volumetric-modulated arc radiotherapy (VMAT) under daily image guidance.

High-dose-rate brachytherapy

HDR brachytherapy was carried out in an operating room. First, biplanar ultrasonography was performed in transverse and sagittal dimensions to identify the prostate and seminal vesicles, along with normal structures at risk, including the urethra, bladder, and rectum. A transperineal interstitial brachytherapy template was used to place 5 or 6-French HDR catheters into the prostate, under ultrasound guidance, at the appropriate depth circumferentially around the peripheral capsule of the prostate. Care was taken to avoid the urethra. After the catheters were placed and the template secured, the patient was transferred to the radiation oncology department where CT simulation was performed to verify brachytherapy catheter depth and for treatment planning. Treatment was delivered to the target volume using a remote after loaded Ir-192 source. Brachytherapy doses included 9.5 Gy \times 2 fractions ($n = 38$), 10 Gy \times 2 fractions ($n = 10$), 10.5 Gy \times 2 fractions ($n = 3$), or 15 Gy \times 1 fraction ($n = 4$). HDR dosimetry details are listed in Table 2.

Androgen deprivation therapy

Androgen deprivation therapy (ADT) was standardly delivered via an LHRH agonist with or without casodex to patients with unfavorable intermediate- and high-risk disease when feasible. ADT was typically given for

Table 1. Cumulative BED_{1.5} (Gy) for each combination of EBRT and HDR

EBRT dose (total dose in Gy/number of fractions)	45/25	37.5/15	42.5/17	40/16
HDR dose (dose per fraction in Gy \times number of fractions)				
9.5 \times 2	238.33	239.33	252.55	246
10 \times 2	252.33	253.33	266.66	260
10.5 \times 2	267	–	–	–
15 \times 1	264	265	278.33	271.67

EBRT – external beam radiation, BED_{1.5} – biologically equivalent dose at an alpha/beta of 1.5, HDR – high-dose-rate brachytherapy

Table 2. High-dose-rate dosimetry details

Variable	Standard fractionation (n = 38)	Hypofractionation (n = 16)	p-value
Mean prostate volume (cc)	44.2 (range, 21.58-84.1)	41.9 (range, 28.16-72.78)	0.583
HDR dose			0.775
9.5 Gy × 2 fractions	26 (68.4%)	11 (68.8%)	
10 Gy × 2 fractions	6 (15.8%)	4 (25.0%)	
10.5 Gy × 2 fractions	3 (7.9%)	0	
15 Gy × 1 fraction	3 (7.9%)	1 (6.3%)	
Median D ₉₀ (%)	104.85 (92.4-111.9)	105.01 (100.31-112.30)	
Median V ₁₀₀ (%)	94.3 (83.3-105.04)	95.21 (90.23-99.19)	
Median V ₂₀₀ (%)	13.0 (6.15-19.3)	12.22 (10.57-17.12)	
Mean rectal V _{75%} (cc)	0.058 (0.00-0.39)	0.044 (0.00-0.19)	
Mean bladder V _{75%} (cc)	0.070 (0.00-0.63)	0.03 (0.00-0.38)	
Mean urethral V _{125%} (cc)	0.006 (0.00-0.05)	0.008 (0.00-0.07)	

HDR – high-dose-rate brachytherapy, D₉₀ – the minimum dose to 90% of the CTV, V_{200%}, V_{125%}, V_{100%}, V_{75%} – target volume receiving at least 200, 125, 100, or 75% of prescription dose

6 months for those with unfavorable intermediate disease, and for 6-24 months for those with high-risk disease. Treatment details are listed in Table 3.

Statistical analysis

The groups analyzed included hypofractionated EBRT plus HDR boost vs. standard fractionation EBRT plus HDR boost. The univariate association of each covariate with the two groups, hypofractionation, and standard fractionation was assessed using the χ^2 test for categorical covariates and t test for numerical covariates. Outcomes include AUA score and EPIC-CP overall prostate cancer QoL score and subdomain scores – urinary incontinence (incon), irr/obs, bowel QoL, sexual function, and vitality. All outcome variables were treated as continuous variables. For descriptive statistics of each outcome, time points were set up as baseline, 0-2 months, 3-6 months, 7-12 months, 13-18 months, 19-24 months, 25-30 months, and >30 months. The mean and standard deviation of the outcomes of the different treatment groups at different measurement time points were calculated. Linear mixed models were performed to test whether there was any significant change over time for each outcome, and to detect whether there was any significant difference in each outcome among different treatments. The significance level was set at 0.05. SAS 9.4 was used for data analyses and management.

Results

Patient characteristics

Fifty-four patients with localized prostate adenocarcinoma were included in the analysis. Median age at treatment was 68 years (range, 55-82 years). Median follow-up for the standard fractionation and hypofractionation cohorts was 24 months (range, 2-51 months) and 19 months

(range, 2-40 months), respectively. A majority of patients had clinical T1c disease (n = 35), a Gleason score of 7 (n = 35), and a PSA < 10 (n = 39). Thirty-one patients had NCCN intermediate-risk disease and 23 had high-risk disease. Baseline characteristics were well-balanced between the 2 groups (Table 3).

Hypofractionated vs. standard fraction external beam radiation therapy

Urinary function

There was no significant difference in AUA score between the two dosing groups over time (p = 0.98), nor were there any significant differences at any discrete time point (Figure 1). Likewise, incon and irr/obs scores were not significantly different between the two groups over time (p = 0.81 and p = 0.62, respectively) (Figure 1). Incon and irr/obs scores did not differ between the two groups at any time point. For both groups, AUA and irr/obs scores peaked at 0-2 months before improving. Incontinence scores peaked at 3-6 months in the hypofractionation group, and at 19-24 months in the standard fractionation group. No patients in either group required temporary catheterization or developed a urethral stricture after treatment.

Bowel quality of life

Bowel toxicity peaked at 7-12 months in the hypofractionation group and at 0-2 months in the standard fractionation group. However, bowel QoL was not significantly different between either group over time (p = 0.97), or at any discrete time point (Figure 2).

Sexual function

While sexual dysfunction was not significantly different between the dose groups over time (p = 0.59) (Figure 2),

Table 3. Patient, disease, and treatment characteristics

Variable	Standard fractionation (n = 38)	Hypofractionation (n = 16)	p-value
Median age (years) (range)	68 (55-82)	67 (60-77)	0.776
Clinical T stage			0.901
T1c	25 (65.8%)	10 (62.5%)	
T2a	6 (15.8%)	3 (18.8%)	
T2b	1 (2.6%)	1 (6.3%)	
T2c	2 (5.3%)	1 (6.3%)	
T3a	2 (5.3%)	1 (6.3%)	
T3b	1 (2.6%)	0	
PSA			0.583
< 10	26 (68.4%)	13 (81.3%)	
10-20	10 (26.3%)	2 (12.5%)	
> 20	2 (5.3%)	1 (6.3%)	
Gleason score (sum)			0.685
7	23 (60.5%)	12 (75.0%)	
8	7 (18.4%)	3 (18.8%)	
9	7 (18.4%)	1 (6.3%)	
10	1 (2.6%)	0	
NCCN risk group			0.274
Intermediate	20 (52.6%)	11 (68.8%)	
High	18 (47.4%)	5 (31.3%)	
ADT			0.766
Yes	17 (44.7%)	6 (37.5%)	
No	21 (55.3%)	10 (62.5%)	
Median duration of ADT (months) (range)	6 (4-25)	6 (6-12)	
Pelvic lymph node radiation therapy			0.163
Yes	6 (15.8%)	0	
No	32 (84.2%)	16 (100%)	

PSA – prostate specific antigen, NCCN – the National Comprehensive Cancer Network, ADT – androgen deprivation therapy

sexual dysfunction was significantly associated with time from intervention ($p = 0.041$), peaking at > 30 months for both dose groups.

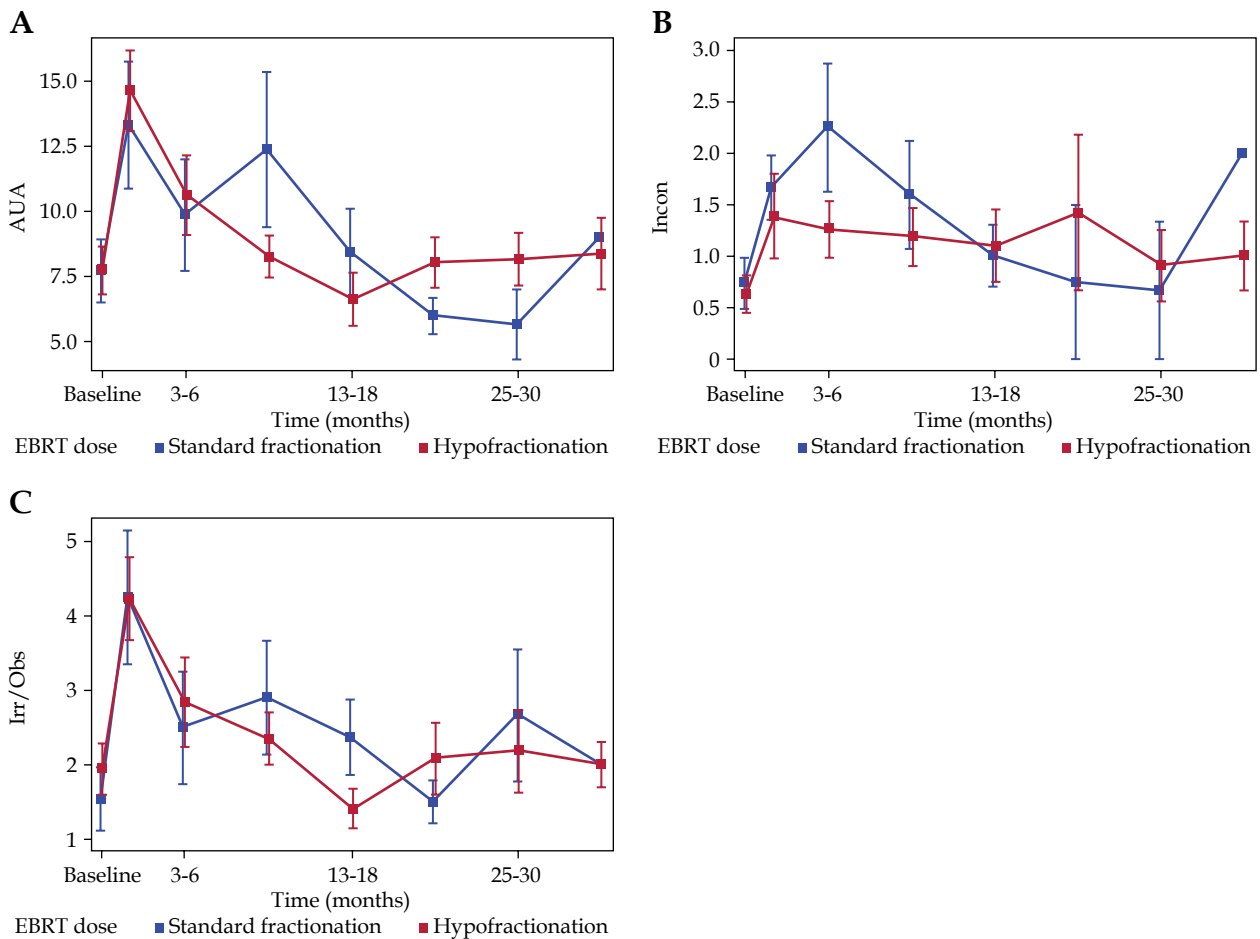
Vitality/quality of life

Vitality score was not significantly different between the two groups over time ($p = 0.37$), or at any time-point after intervention (Figure 2). Also, QoL scores were not significantly different between the dosing groups with time ($p = 0.71$) (Figure 2). QoL scores peaked at the 0-2 months' time point in the hypofractionation group, and at 3-6 months in the standard fractionation group. Vitality scores peaked at 3-6 months in both groups.

Discussion

The results in our study suggest hypofractionated EBRT is feasible in combination with an HDR brachytherapy boost. There was no increase in acute or late toxicity as measured by AUASS and EPIC-CP for a hypofractionated EBRT regimen combined with HDR brachytherapy boost, compared to standard fractionation EBRT plus HDR boost.

When treating intermediate and high-risk prostate cancer with RT, EBRT with dose escalation via brachytherapy has been found to improve biochemical progression-free survival compared to dose escalation via EBRT (DE-EBRT). In the ACSCENDE-RT trial by Morris *et al.*, all patients were randomized to receive 46 Gy to the pelvis with a conformal EBRT boost to a total of 78 Gy or the same pelvic dose of 46 Gy plus an LDR brachytherapy boost. The 9-year biochemical progression-free survival (b-PFS) in the DE-EBRT group was 62%, compared to 83% for the EBRT plus LDR group. This improvement in b-PFS was at the cost of higher late grade 3 genitourinary toxicity in the LDR boost group. Additionally, a multi-institutional retrospective cohort study of 1,809 men with localized Gleason 9 and 10 prostate cancer compared clinical outcomes in men treated with EBRT plus a brachytherapy boost and ADT vs. EBRT plus ADT vs. radical prostatectomy [19]. Five-year prostate cancer-specific mortality was significantly lower in the EBRT plus brachytherapy boost and ADT group. Furthermore, this group was found to have a longer time to distant metastasis compared to the EBRT and ADT and radical prostatectomy groups. Moreover, acceptable toxicity rates have been shown using this



Patient survey completion rates

Number of patients who completed the survey	Baseline	0-2 months	3-6 months	7-12 months	13-18 months	19-24 months	25-30 months	> 30 months
Standard fractionation	38	26	20	26	19	16	11	16
Hypofractionation	16	12	8	10	10	5	4	4

Fig. 1. Average urinary function symptom scores over time by group **A)** American Urological Association Symptom Score (AUASS), **B)** urinary incontinence (incon) score, **C)** irritability and obstructive symptoms (irr/obs) score

approach [20,21]. These results have led to a push for combination treatment in those with NCCN high-risk prostate cancer, along with select intermediate risk patients. An additional benefit of a brachytherapy boost is shortened overall treatment time for patients.

With a need for cost-effective, convenient, and effective treatments, hypofractionated EBRT is becoming increasingly utilized. Hypofractionated EBRT has been shown to be safe and efficacious when applied as monotherapy, with multiple randomized studies addressing this question. While RTOG 0415 included only patients with low-risk disease, PROFIT consisted of patients with intermediate-risk disease, and CHHiP and HYPRO included both intermediate- and high-risk patients [13,16]. In RTOG 0415, late grade 2 and 3 GI and GU toxicity was significantly higher in the hypofractionated group [16]. In HYPRO, cumulative grade 3 or worse late GU toxicity was significantly higher in the hypofractionation group than in

the standard fractionation group. However, there was no significant difference in cumulative grade 3 or higher GI toxicity between the 2 groups [13]. However, in CHHiP, there was not a significant difference in grade 2 or higher GI or GU toxicity in the hypofractionation group and in PROFIT, there was no significant difference in grade 3 or higher GI or GU toxicity [14,15]. Together, these studies have proven the safety and efficacy of hypofractionated EBRT as prostate cancer monotherapy.

While less robust data exists for hypofractionated EBRT plus brachytherapy boost, an early report by Sathya *et al.* compared EBRT alone to EBRT plus a brachytherapy boost. In the EBRT alone group, a dose of 66 Gy in 33 fractions was delivered; in the combination group, patients received an EBRT dose of 40 Gy in 20 fractions plus an iridium implant delivering 35 Gy over 48 hours to the prostate. This study did report similar rates of acute and late toxicity between the groups [9]. Similar to our

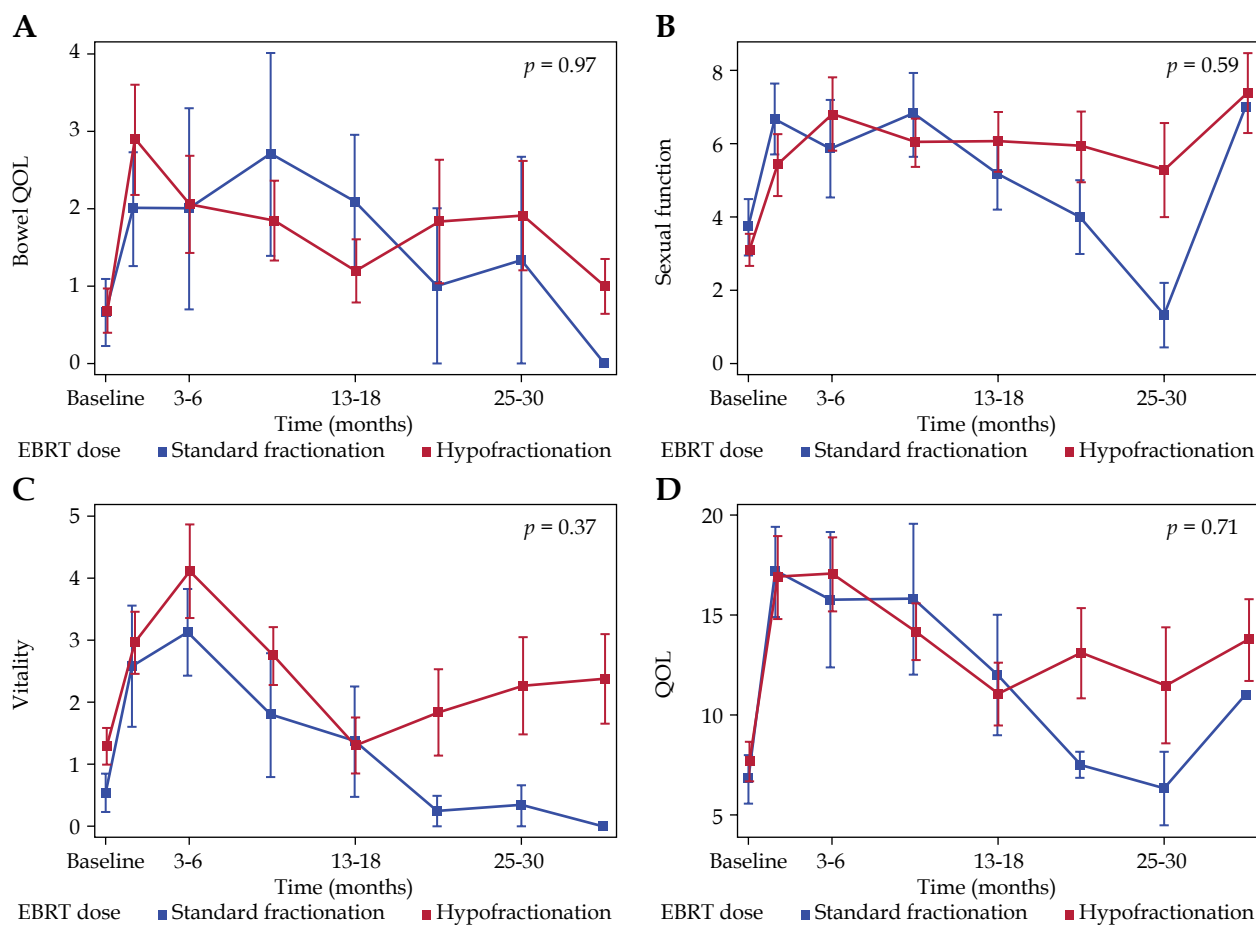


Fig. 2. Average bowel, sexual function, vitality, and quality of life (QoL) symptom scores over time by group: **A)** bowel QoL score, **B)** sexual function score, **C)** vitality score, **D)** overall Expanded Prostate Index for Prostate Cancer - Clinical Practice (EPIC-CP) QoL score

study, a more modern series by Morton *et al.* included patients receiving EBRT to 37.5 Gy in 15 fractions plus HDR boost to 15 Gy in 1 fraction [17]. This group was compared to patients receiving 45 Gy in 25 fractions with an HDR boost of 10 Gy in 2 fractions. While late urinary and bowel toxicity was similar between the two groups, the differing HDR dosing makes it difficult to compare the two EBRT dose groups in terms of toxicity. Morton *et al.* and Shahid *et al.* reported on the acute and long-term toxicity and health-related QoL of intermediate-risk prostate cancer patients who received an HDR boost of 15 Gy in 1 fraction, followed by hypofractionated EBRT to 37.5 Gy in 15 fractions in a single-institution phase II trial as mentioned above [22,23]. Both the IPSS and EPIC questionnaires were used for assessment. In this study, IPSS scores rose by 7 points acutely before improving, which mirrors what was seen in our study for both groups. Also, similar to our study, the greatest decline was seen in the EPIC sexual subdomain score, which continued to decline over time. The EPIC urinary, bowel, and vitality subdomain scores showed worsened function acutely before improving, with small absolute changes. The authors noted a majority of the decline occurred over the first 12 months. Again, this is comparable to our own study, in which function worsened acutely with small absolute changes in subdomain scores

before improving. It is also important to note that changes in the incon subdomain score reflect urge incontinence rather than the stress incontinence commonly seen after prostatectomy. When there was a difference, the hypofractionation group generally experienced an earlier peak in subdomain scores in our study. We expect this is due to the slightly higher BED in this group. With the exception of sexual function, all EPIC subdomain scores showed absolute changes of < 3 points over time for both groups in our cohort.

Though limited by its retrospective nature and small sample size, our study does offer a direct comparison of two fractionation schedules of EBRT in combination with an HDR brachytherapy boost in terms of patient-reported toxicity outcomes. This adds to the limited toxicity data regarding the use of a hypofractionated EBRT regimen in this field. Brachytherapy boost doses were not uniform in our study. The doses used represent the evolution of our practice to a higher dose per fraction with the 2-fraction regimen, and ultimately to a single fraction regimen for patient convenience. However, multiple studies have compared HDR fractionation schedules similar to our own showing no clinically significant differences in toxicity between varying regimens [17,24,25,26]. Furthermore, the cumulative BEDs used in our cohort have been associated with excellent oncologic outcomes [27].

In conclusion, our study suggests a hypofractionated regimen of EBRT can be delivered in combination with an HDR boost for patients with intermediate- and high-risk adenocarcinoma of prostate without increasing toxicity compared to standard fractionation EBRT with an HDR boost. This further supports current ACR guidelines, and has important implications in terms of patient convenience and resource utilization. A clinical trial comparing these two fractionation schemes with a brachytherapy boost is warranted to confirm these results.

Disclosure

The authors report no conflict of interest.

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