

Background

External beam radiotherapy (EBRT) is a standard treatment option for localized prostate cancer. High-dose-rate-brachytherapy (HDR-BT) uses iridium placed in the prostate to deliver radiation locally. HDR-BT combined with EBRT (HDR-BT+EBRT) is a relatively new technique in treatment of localized prostate cancer. HDR-BT+EBRT divides the total radiation dose between external beam radiation through the skin and internal radiation in the prostate gland. For this study, we compared HDR-BT plus EBRT to EBRT alone using two recently described surrogate markers of survival in prostate cancer - the time to PSA nadir (TTN) and the rate of PSA decline.

PURPOSE: To compare the biochemical control (TTN and PSA decline) and gastrointestinal (GI) and genitourinary (GU) toxicity of localized or locally advanced prostate cancer treated by HDR-BT plus EBRT versus EBRT alone.

Method

- 70 patients with T1c-T2a prostate cancer treated by EBRT alone (n=35) or HDR-BT+EBRT (n=35) were retrospectively identified at the Roger Maris Cancer Center (Fargo, ND).
- Toxicities were graded using the Common Toxicity Criteria version 3. Early toxicity occurred within 90 days of the completion of treatment. This grading system was selected to provide comparability of results with published Radiation Therapy Oncology Group (RTOG) studies.
- TTN was the time interval between the last day of treatment and the lowest PSA achieved.
- PSA decline was the linear regression of the PSA prior to treatment to the lowest PSA achieved:

$$PSA_{decline} = \frac{\text{initial PSA} - \text{nadir PSA}}{\text{initial PSA date} - \text{nadir PSA date}}$$

- PSA doubling time (PSADT) was a function of the nadir PSA and the first rise in PSA after the nadir PSA:

$$PSADT = \log(2) \frac{\text{rise PSA} - \text{nadir PSA}}{\log(\text{rise PSA}) - \log(\text{nadir PSA})}$$

- Since androgen ablation with hormone therapy reduces PSA, patients on hormone therapy were analyzed separately.

Statistics

The association of clinical, pathological and treatment related variables with any given event was analyzed using Pearson's chi-square and Fisher's exact test (2-tailed). Univariate and multivariate analysis were used to determine the association of PSA outcomes (nPSA, TTN, PSA decline) with treatment. Covariates were added to the model stepwise and included age, initial PSA, cancer stage, and Gleason score.

Method (cont.)

Common Toxicity Criteria v. 3

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhea	none	increase of < 4 stools/day over pre-treatment	increase of 4-6 stools/day, or nocturnal stools	increase of > 7 stools/day or incontinence	ICU care or hemodynamic collapse
Rectal bleeding/hematochezia	none	mild without transfusion or medication	persistent, requiring medication or radiation break	severe, requiring transfusion	colostomy
Rectal or perirectal pain (proctalgia)	none	mild pain not interfering with function	moderate pain: interfering with function, but not ADL	severe pain: severely interfering with ADL	colostomy
Dysuria (painful urination)	none	mild symptoms	symptoms relieved with therapy	symptoms not relieved despite therapy	
Urinary frequency/urgency	normal	increase in frequency or nocturia up to 2 x	increase > 2 x normal but < hourly	hourly or more with urgency, or requiring catheter	
Urinary retention	normal	hesitancy or dribbling, but no significant residual urine	hesitancy requiring medication or in/out catheterization (< 4 x per week)	requiring frequent in/out catheterization or (> 4 x per week) or urological intervention	bladder rupture
Incontinence	none	with coughing, sneezing, etc.	spontaneous, some control	no control (in the absence of fistula)	-

Abbreviation: ADL, activities of daily living.

Results

- Median follow-up was 10.7 months and 12.4 months for EBRT alone and HDR-BT+EBRT, respectively. Patient characteristics were balanced among groups.
- Those receiving EBRT alone had higher probability of early GI ($p < 0.02$), early GU ($p < 0.001$) and late GU ($p < 0.02$) toxicity.
- No patients developed biochemical relapse. Few patients had a PSA doubling time. On univariate analysis, shorter TTN and steeper PSA decline were found in the hormone HDR-BT+EBRT group v. hormone EBRT alone. On multivariate analysis, TTN ($p < 0.02$) and PSA decline ($p < 0.005$) retained significance. In patients not on hormone, TTN and PSA decline were equivalent between HDR-BT+EBRT and EBRT alone.

Patient characteristics by treatment group

Characteristic	EBRT alone No Hormone	EBRT+HDR No Hormone	EBRT alone Hormone	EBRT + HDR Hormone
Age (y)	67 (39-78)	74 (62-78)	71 (50-88)	71 (57-81)
Gleason Score				
N (%)	13 (65%)	3 (18%)	1 (6%)	2 (10%)
6	5 (25%)	12 (71%)	6 (35%)	6 (30%)
7	2 (10%)	3 (18%)	2 (12%)	7 (35%)
8	0 (0)	1 (6%)	8 (47%)	5 (25%)
9				
Initial PSA (ng/mL)	6.6 (3.9-62.0)	6.1 (4.5-136.8)	10.7 (3.0-757.7)	11.5 (2.6-69.3)
Follow-up Time (months)	9.2 (0.6-43.2)	12.8 (5.1-24.0)	11.4 (0.4-23.9)	12.3 (2.1-23.8)

Values are Median (Range) except Gleason Score. Hormone is androgen ablation with luprolide. Hormone is androgen ablation with luprolide. Abbreviations: EBRT, external beam radiation therapy; HDR, high dose rate (brachytherapy).

Results

Post-treatment PSA Parameters by Treatment Group

PSA Parameter	EBRT alone No Hormone	EBRT+HDR No Hormone	EBRT alone Hormone	EBRT + HDR Hormone
Nadir PSA (ng/mL)	0.8 (0.0-2.6)	0.3 (0-36.7)	0 (0-1.7)	0 (0-0.2)
Time to PSA Nadir (days)	388 (87-867)	397 (75-706)	66 (12-378)	116 (27-354)
PSA Decline (ng/mL)	-0.013 (-0.33 to -0.004)	-0.013 (-0.40 to -0.0002)	-0.046 (-1.071 to -0.012)	-0.047 (-0.261 to -0.004)
PSA Doubling Time (days)	586 (272-1476) N=3	312 (112-702) N=5	86 (31-840) N=5	93 (60-183) N=5

Values are Median (Range). Hormone is androgen ablation with luprolide.

Abbreviations: PSA, prostate specific antigen; EBRT, external beam radiation therapy; HDR, high dose rate (brachytherapy). See Method for explanations.

Post-treatment toxicity grade by treatment group

Toxicity Grade (CTCv3)	EBRT alone	EBRT + HDR
Early GI		
0	11 (29%)	9 (23%)
1	13 (34%)	25 (64%)
2	14 (37%)	4 (10%)
3	0	1 (3%)
Grade < 2	24 (63%)	34 (87%)
Grade ≥ 2	14 (37%)	5 (13%) * ($p=0.018$)
Late GI		
0	29 (76%)	30 (77%)
1	3 (8%)	7 (18%)
2	3 (8%)	2 (5%)
3	2 (5%)	0
4	1 (3%)	0
Grade < 2	32 (84%)	37 (95%)
Grade ≥ 2	6 (16%)	2 (5%) ($p=0.154$)
Early GU		
0	5 (13%)	3 (8%)
1	8 (21%)	29 (74%)
2	20 (53%)	4 (10%)
3	5 (13%)	3 (8%)
Grade < 2	13 (34%)	32 (82%)
Grade ≥ 2	25 (66%)	7 (18%) * ($p < 0.001$)
Late GU		
0	25 (66%)	21 (54%)
1	3 (8%)	16 (41%)
2	7 (18%)	2 (5%)
3	3 (8%)	0
Grade < 2	28 (74%)	37 (95%)
Grade ≥ 2	10 (26%)	2 (5%) * ($p=0.013$)

Values are N (%). Hormone is androgen ablation with luprolide. * indicates statistical significance.

Abbreviations: CTCv3, Common Toxicity Criteria version 3; PSA, prostate specific antigen; GI, gastrointestinal toxicity; GU, genitourinary toxicity; EBRT, external beam radiation therapy; HDR, high dose rate

Discussion

- In this study, patients not on hormone therapy had equivalent biochemical control between groups. In patients on hormone therapy, HDR-BT plus EBRT achieved improved biochemical control, as assessed by time to PSA nadir and PSA decline.
- Recent studies suggest that PSA nadir¹, time to PSA nadir¹, and PSA decline² are early surrogate markers of disease-specific survival in localized prostate cancer. This study provides biochemical control data using these recently proposed surrogate markers.
- Early GI, early GU and late GU toxicity were less likely to occur in patients who received HDR-BT plus EBRT versus EBRT alone.
- Previous studies were performed at academic centers and have shown conflicting results regarding toxicity data in prostate HDR-BT. This study contributes additional toxicity data from a community practice new to HDR-BT.

Conclusion

- HDR-BT+EBRT had equivalent biochemical control without hormone therapy.
- HDR-BT+EBRT had superior biochemical control with hormone therapy.
- HDR-BT+EBRT produced less GI and GU toxicity.
- HDR-BT+EBRT is an attractive option for localized prostate cancer.

References

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- Choueiri TK, Xie W, D'Amico AV et al. Time to prostate-specific antigen nadir independently predicts overall survival in patients who have metastatic hormone-sensitive prostate cancer treated with androgen-deprivation therapy. Cancer. 2009 Mar 1; 115(5):981-7.

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