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Initial results of a randomized phase III trial of high dose image guided radiation with or without androgen deprivation therapy for intermediate-risk prostate cancer

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ABSTRACT

Background: Prior randomized studies have shown a survival benefit using combined androgen deprivation therapy (ADT) and radiation therapy for intermediate-risk prostate cancer. However, these studies either used low doses of radiation (66.6 Gy to isocenter) or imaged guidance was not available. This study reports the initial differences for high dose image guided radiation with or without ADT.

Methods: From 2012 to 2014, 56 patients were treated with and 60 patients without 6 months of ADT (N = 116) in our phase III randomized trial for intermediate-risk prostate cancer. The primary endpoints of the current analysis are Expanded Prostate Cancer Index Composite (EPIC) scores, International Prostate Symptom Score (IPSS) scores, and bowel or urinary adverse events (AEs, graded using CTCAE v4) with and without ADT. Treatment consisted of 81 Gy in 45 treatments (tx) or 100 Gy Pd-103 implant followed by 45 Gy in 25 tx with or without ADT. Cone-beam fiducial-based guidance was done. Statistical analysis included Fisher's exact test, chi-square test, and ANCOVA.

Results: Median follow-up for both groups was 2.6 years. Acute or chronic urinary and acute or chronic bowel toxicities were similar with or without ADT (acute urinary: 16 vs 25 G0-1, 39 vs 35 G2 and 1 vs 0 G3, p = 0.17; chronic urinary: 40 vs 45 G1 and 16 vs 15 G2 toxicities, p = 0.68; acute bowel: 56 vs 59 G1 and 0 vs 1 G2 toxicities, p = 0.99; chronic bowel: 56 vs 59 G1 and 0 vs 1 G2 toxicities, p = 0.99). One patient had grade 3 urinary AE (1/116 or 0.8%). No patient had grade 3 bowel AE. With the use of ADT, a temporary decline in the EPIC sexual (p = 0.004) and hormonal scores (p = 0.02) were seen for the first 3 to 6 months after the completion of radiation, but the scores recovered by 12 months. Brachytherapy plus external beam radiation was compared to external beam radiation alone; brachytherapy EPIC urinary irritative scores were temporarily lower at 3 months, 76 vs. 84 (p = 0.006), had higher IPSS scores at 3 months, 15 vs 12 (p = 0.01), and had increased acute urinary AEs (p < 0.001). No difference in failures were seen with or without ADT or associated with the use of brachytherapy.

Significance: Low toxicity and minimal temporary bother as measured by EPIC and IPSS were seen in both arms. ADT was well-tolerated and associated with temporary changes.

Introduction

Androgen deprivation therapy (ADT) and radiation therapy have shown a clinical benefit in several randomized trials including a survival benefit in RTOG 9408, which reported a 10-year absolute survival difference of 7% (HR 1.23) [1]. However, critics point to the lack of contemporary image guidance, relative low doses (66.6 Gy to isocenter), lack of intensity-modulated radiotherapy (IMRT), and relative high failure rate in the control group (41%). More recent randomized studies, including GETUG 14 [2], PCS III [3], EORTC 22991 [4], TROG 96.01 [5], have continued to show a benefit for ADT, however, the magnitude of the benefit has not translated into a survival benefit. EORTC 22991 showed an improvement in clinical progression free survival (HR 0.63) for a predominantly intermediate-risk

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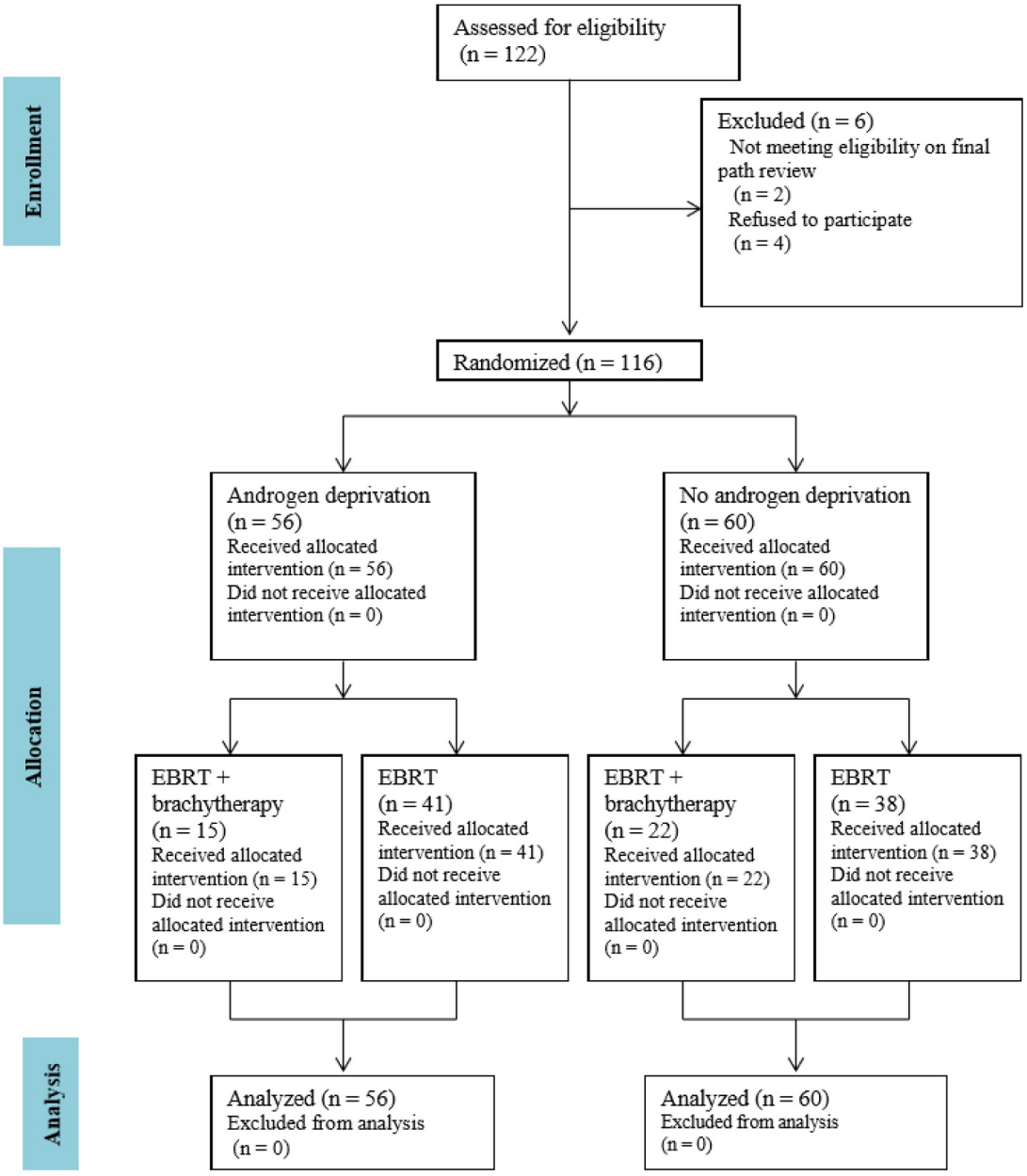

Fig. 1. CONSORT diagram.

population (75% of cases) using higher doses to isocenter but used no image guidance [4]. Nabid et al. have presented the results of the PCS III study, which again showed an improvement in biochemical control without a survival benefit at 10 years using higher doses without image guidance. Similarly, TROG 96.01 did not show a survival benefit for the intermediate-risk population, although the 10-year OS was improved for the high-risk population with 6-months of ADT [5]. Finally, GETUG 14, which used high doses (80 Gy), has shown an improvement in clinical progression free survival with ADT that has not yet translated into a survival benefit. RTOG 0815 is testing the use of more contemporary high-dose radiation and allows image guidance; however, the results are not yet available.

The collective evidence shows that ADT improves clinical results for intermediate-risk prostate cancer. However, as higher doses are delivered, as seen in the trials subsequent to RTOG 9408, the absolute advantage decreased [1–5]. With higher doses, MRI registration, rectal balloon, fiducial markers, IMRT, and daily volumetric image guidance, as done in the current study, the clinical benefit of ADT may decrease further.

We also allowed real-time intraoperatively planned brachytherapy boost. High doses delivered under ultrasound guidance with brachytherapy have shown very good results compared to non-image guided external beam radiation, with prior randomized trials showing improvement in biochemical control but not survival [6–8]. In our current trial, patients received all radiation treatments under image guidance. Thus, the differences in biochemical control favoring brachytherapy seen in prior studies may not be seen.

The median follow-up at the time of this analysis is not long enough to perceive potential differences in clinical control. However, initial differences in adverse events (AEs) and bother can be reported to evaluate the safety of our approach with and without ADT. Few randomized studies have been published comparing the effects of ADT in the context of contemporary techniques such as daily image guidance and rectal balloon. We believe that the current publication helps bridge this knowledge gap. Furthermore, few randomized studies have compared brachytherapy plus external beam to external beam radiation

Table 1
Patient characteristics (n = 116).

Patient characteristics	Androgen Deprivation	No Androgen Deprivation	P-value (Fisher's Exact)
Median age (years)	65.5	68.3	
Age range (years)	51 – 76	49 – 76	
T stage			0.58
T1c	29 (52%)	26 (43%)	
T2a	17 (30%)	19 (32%)	
T2b	10 (18%)	13 (22%)	
T2c	0 (0%)	2 (3%)	
Gleason score			0.57
6	4 (7%)	2 (3%)	
7 (3 + 4)	35 (63%)	36 (60%)	
7 (4 + 3)	17 (30%)	22 (37%)	
PSA			0.68
< 4	7 (12%)	11 (18%)	
≥ 4 to < 10	43 (77%)	42 (70%)	
≥ 10 to < 20	6 (11%)	7 (12%)	
Risk group			0.85
Intermediate favorable	21 (38%)	21 (35%)	
Intermediate unfavorable	35 (62%)	39 (65%)	
Follow-up in years			
Median	2.67	2.53	
Average	2.60	2.58	
Range	0.63 to 4.64	0.65 to 4.65	

alone in the context of contemporary image guidance. Although our brachytherapy analysis should be viewed as exploratory in nature, the randomization was stratified and blocked by the use of brachytherapy.

Material and methods

The present study was approved by the Baptist Health Institutional Review Board in Jacksonville, Florida (IRB number 12–21). All patients provided written informed consent.

Eligibility criteria

Eligible patients had histologically confirmed localized adenocarcinoma of the prostate with at least one intermediate-risk feature including T2b-T2c (International Union Against Cancer 2010 7th Edition Staging Criteria), prostate-specific antigen (PSA) ≥10 and < 20 ng/mL, or Gleason score 7. No high-risk features were allowed, including PSA ≥20 ng/ml, Gleason score 8–10, or T3-T4 disease. Staging included an MRI and bone scan for all cases. No previous hormonal therapy was allowed. The pathologic specimens were not centrally reviewed.

Brachytherapy patients included patients that were excellent brachytherapy candidates before ADT. In order to be brachytherapy eligible, the initial IPSS had to be < 17 if on alpha-blockers or < 20 without alpha-blockers, and prostate volume prior to any ADT had to be ≤50 cc.

Randomization and sample calculations

A total of 122 patients signed consent to participate in the trial, and a total of 116 patients were found eligible and treated per-protocol (CONSORT diagram, Fig. 1). The study was not blinded. Patients were randomly assigned in a 1:1 ratio between radiotherapy plus ADT (N = 56) versus primary radiotherapy alone (N = 60). Patients could elect treatment with IMRT alone or with a brachytherapy boost. The use of brachytherapy was used as a stratification factor to assign the use of ADT (Fig. 1).

Initially, 144 patients were needed to show a freedom from failure difference of 15% with 80% power and a two sided p-value of ≤0.05. The study was closed early when the principal investigator changed institutions. The current study is not powered to show the expected difference in freedom from failure, and therefore close evaluation of the 95% confidence intervals will be necessary when the final analysis is done.

Patients were treated at a single institution in Jacksonville Florida, Terk Oncology, and enrolled from 2012 through 2014. No major protocol violations were seen in any patient, and therefore our current analysis is both intent-to-treat and per-protocol.

Radiation therapy volumes

Clinical target volume one (CTV I) included the prostate defined on MRI registration and the proximal 2 cm of the seminal vesicles. CTV II included the prostate only. Planning target volume one (PTV I) included CTV I with a 2 mm posterior expansion and 3 mm elsewhere. PTV II was created with the same expansions from CTV II.

D95% was 45 Gy in 25 treatments for PTV I and 36 Gy in 20 treatments for PTV II. Dose was specified as D95% = 100%. Minimum dose to PTV was > 90%. All treatments were planned to use an IMRT technique.

If brachytherapy was done, patients were first treated with intraoperatively planned brachytherapy to a pD90 of 100 Gy. External beam radiation was started 8 weeks after brachytherapy. PTV I, as described above, was treated to 45 Gy in 25 treatments with IMRT with daily cone-beam image guidance.

Daily cone-beam-based volumetric imaging was done prior to IMRT for all cases. Fiducial markers were used for initial alignment, followed by small corrections based on soft tissue anatomy from cone-beam, if needed. Rectal balloons were used for simulation, planning MRI, and daily treatments.

The rectum was defined from the ischial tuberosity to the sigmoid flexure. The whole bladder was contoured. Patients drank 12 ounces of

Table 2
International prostate symptom score (IPSS) mean values with or without androgen deprivation and with or without a brachytherapy boost.

	Androgen Deprivation	No Androgen Deprivation	Difference (95% CI)	P-value (ANCOVA)
Baseline	7.9 (5.1)	9.3 (6.7)	1.40 (−0.8, 3.6)	0.21
3 months	13.0	12.5	−0.52 (−3.1, 2.1)	0.69
6–9 months	8.7	8.8	0.13 (−2.1, 2.4)	0.91
12–15 months	7.8	9.9	2.10 (−1.1, 5.3)	0.20
18–24 months	6.9	8.6	1.80 (−1.0, 4.5)	0.20
30–36 months	6.8	7.6	0.76 (−2.2, 3.7)	0.61
	Brachytherapy	**No Brachytherapy**	**Difference (95% CI)**	**P-value (ANCOVA)**
Baseline	8.8 (5.3)	8.5 (6.4)	0.30 (−1.9, 2.5)	0.79
3 months	15.1	11.6	−3.5 (−6.2, −0.8)	**0.01***
6–9 months	9.8	8.3	−1.5 (−3.8, 0.9)	0.12
12–15 months	10.6	8.1	−2.5 (−6.1, 1.1)	0.18
18–24 months	7.2	7.9	0.7 (−2.2, 3.6)	0.64
30–36 months	7.0	7.4	0.5 (−2.5, 3.5)	0.75

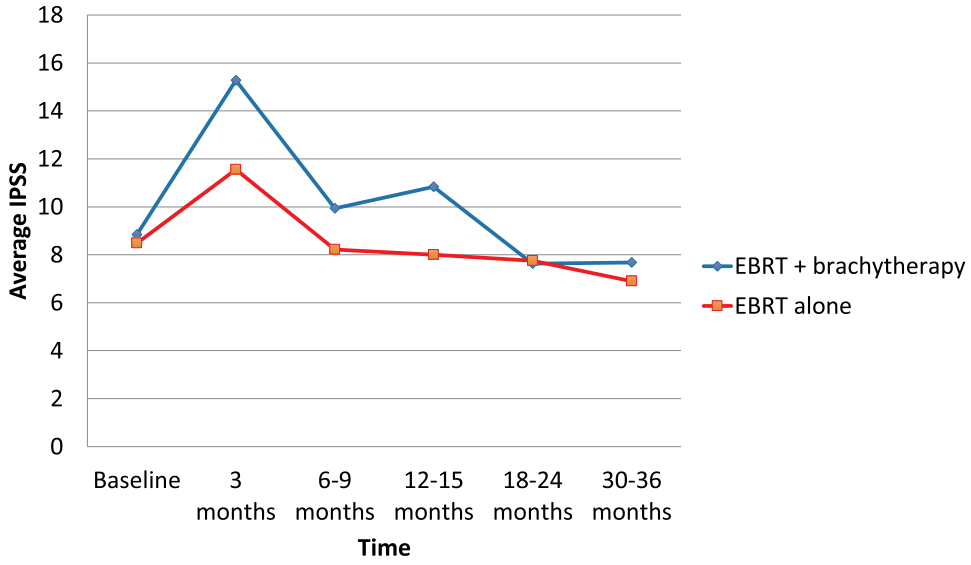

Fig. 2. IPSS for EBRT + Brachytherapy vs. EBRT Alone.

water about 60 min before treatment. If the bladder was still less than 2/3 full compared to the date of simulation, the patient was asked to get off the table and continue to drink an additional 12 ounces prior to treatment.

Procedures and endpoints

Prostate markers were used for all cases and placed prior to simulation and MRI acquisition. CT simulation was done with a rectal balloon for all cases followed by planning MRI with a rectal balloon, laser positioning, and flat table top. The MRI T2 TSE information was registered to the CT simulation using the prostate fiducial markers and soft tissue anatomy. IMRT was used for all patients.

ADT was done via luteinizing hormone-releasing hormone (LHRH) agonist injection for a total of 6 months starting 2 months prior to radiation or brachytherapy implant. Antiandrogens were allowed but were not used in the currently treated population.

Toxicity assessment

Protocol toxicity was measured using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Statistical calculations for toxicity used a two-sided $p \leq 0.05$ threshold for significance. In the present study, we used the strictest definition and any use of a prescription medication was considered a grade 2 (G2) AE. Use of CTCAE may also be misleading for grade 3 (G3) AE, since the definition usually includes the need for a medical intervention, transfusion, or hospitalization. However, given the ambiguity in hospitalization criteria across the United States, we define a G3 AE as any intervention or blood transfusion.

Quality-of-Life measures

Patients completed the EPIC and IPSS before treatment and during routine follow-up visits at 3, 6, and 12-months, and then yearly after completion of treatment. EPIC is a validated instrument that measures urinary, bowel, and sexual function and bother. The IPSS quantifies lower urinary tract symptoms.

Statistical analysis

To statistically evaluate change over time in EPIC scores, responses were grouped by system and assigned a numeric score. The difference in mean scores for EPIC and IPSS was assessed with ANCOVA. Multi-item scale scores were transformed linearly to a 0-to-100 scale following scoring instructions for EPIC. Lower numbers corresponded to worsening function and increased bother. To assess changes in health-related quality of life (QOL) from baseline, a clinically relevant difference was defined as a difference larger than the 95% CI and at least a 10-point change. A clinically relevant change in IPSS was defined as a change of 5 or more points. The cumulative incidence of gastrointestinal (GI) and genitourinary (GU) AEs were analyzed in the intent-to-treat population using Fisher's exact or chi-square tests. Statistical significance was considered as a 2-sided value $p \leq 0.05$. The primary endpoint of the overall study is freedom from failure, which will be reported at the time of the final analysis. All times were measured from the date of completion of external beam radiation with the exception of post-brachytherapy IPSS that was done 4-weeks after the implant and prior to the start of external beam radiation.

Results

Patient characteristics

All patients were considered to have intermediate-risk prostate cancer. Patients were well-balanced in terms of their age, T stage, Gleason score, PSA, and median follow-up time (Table 1). Unfavorable intermediate-risk patients were defined as Gleason score (4 + 3), T2c, or PSA ≥ 10. The proportion of unfavorable intermediate-risk patients was similar in both groups.

Urinary bother and urinary AEs with or without ADT

Prior to treatment or ADT, IPSS was similar for both groups ($p = 0.21$). At 3 months after the completion of radiation, IPSS had increased to 13 for both groups ($p = 0.69$). The IPSS increase was short-lived and values returned to normal within 6–9 months after the completion of external beam radiation in both groups (Table 2).

The urinary irritative/obstructive EPIC domain scores had a small decline at 3 months that recovered to baseline values at 6–9 months. The urinary irritative/obstructive EPIC scores were also similar

Table 3
Mean EPIC scores for the different domains with or without androgen deprivation and with or without a brachytherapy boost.

	Androgen Deprivation	No Androgen Deprivation	Difference (95% CI)	P-value (ANCOVA)
EPIC Total				
Baseline	84 (12.0)	84.6 (11.1)	−0.6 (−4.8, 3.6)	0.78
3 months	70.7	77.9	7.2 (3.4, 10.9)	< 0.001*
6–9 months	75.5	78.5	3.0 (−1.3, 7.3)	0.17
12–15 months	79	74.9	−4.1 (−15.8, 7.5)	0.46
≥18 months	82.3	80.1	−2.2 (−8.7, 4.3)	0.50
EPIC Incontinence				
Baseline	92.7 (13.9)	90.1 (13.8)	2.6 (−2.4, 7.6)	0.31
3 months	86.8	86.3	−0.5 (−6.4, 5.3)	0.86
6–9 months	91.3	89.2	−2.1 (−7.7, 3.5)	0.46
12–15 months	95.0	84.2	−10.8 (−23.4, 1.8)	0.09
≥18 months	97.9	90.8	−7.1 (−14.4, 0.2)	0.06
EPIC Irritative/Obstructive				
Baseline	87.4 (13.1)	90.3 (10.6)	−2.9 (−7.2, 1.4)	0.19
3 months	82.6	81.2	−1.5 (−6.9, 4.0)	0.59
6–9 months	90.7	87.0	−3.7 (−8.4, 1.0)	0.12
12–15 months	88.6	87.7	−0.9 (−10.0, 8.1)	0.83
≥18 months	94.6	91.0	−3.6 (−10.6, 3.5)	0.31
EPIC Bowel				
Baseline	94.8 (10.4)	96.8 (7.2)	−2.0 (−5.2, 1.2)	0.23
3 months	93.9	89.9	−4.0 (−9.0, 0.9)	0.11
6–9 months	93.7	90.3	−3.4 (−7.9, 1.2)	0.15
12–15 months	95.1	85.0	−10.1 (−24.0, 3.7)	0.14
≥18 months	93.6	93.8	0.2 (−6.0, 6.5)	0.94
EPIC Sexual				
Baseline	55.4 (33.1)	62.7 (67.6)	−7.3 (−26.9, 12.3)	0.47
3 months	22.0	48.5	26.5 (16.5, 36.5)	< 0.001*
6–9 months	26.7	43.6	16.9 (5.5, 28.3)	0.004*
12–15 months	36.8	36.6	−0.2 (−27.1, 26.7)	0.99
≥18 months	41.9	43.9	2.0 (−17.2, 21.1)	0.83
EPIC Hormonal				
Baseline	94.3 (9.1)	94.5 (13.9)	−0.2 (−4.5, 4.1)	0.93
3 months	76.8	91.0	14.2 (8.6, 19.8)	< 0.001*
6–9 months	83.3	92.1	8.8 (1.7, 15.8)	0.02*
12–15 months	90.6	89.9	−0.7 (−15.6, 14.1)	0.92
≥18 months	95.2	90.4	−4.8 (−12.9, 3.3)	0.24
	Brachytherapy	No Brachytherapy	Difference (95% CI)	P-value (ANCOVA)
EPIC Total				
Baseline	84.4 (12.4)	83.9 (10.0)	0.5 (−3.7, 4.7)	0.82
3 months	72.0	75.2	3.2 (−1.1, 7.4)	0.14
6–9 months	75.4	77.5	2.1 (−2.6, 6.7)	0.38
12–15 months	72.5	77.8	5.2 (−7.8, 18.3)	0.41
≥18 months	80.5	81.5	1.0 (−5.6, 7.6)	0.75
EPIC Incontinence				
Baseline	90.3 (15.0)	93.6 (11.2)	−3.3 (−8.2, 1.6)	0.19
3 months	85.4	87.0	1.6 (−4.7, 8.0)	0.61
6–9 months	90.7	89.9	−0.8 (−6.9, 5.3)	0.79
12–15 months	84.0	90.6	6.5 (−8.7, 21.7)	0.38
≥18 months	96.6	92.2	−4.4 (−11.9, 3.1)	0.24
EPIC Irritative/Obstructive				
Baseline	90.2 (12.2)	85.9 (11.4)	4.3 (−0.3, 8.9)	0.07
3 months	76.2	84.3	8.0 (2.4, 13.7)	0.006*
6–9 months	84.8	90.8	6.0 (0.9, 11.0)	0.02*
12–15 months	88.5	88.0	−0.5 (−11.1, 10.1)	0.92
≥18 months	89.4	94.9	5.5 (−1.5, 12.6)	0.12
EPIC Bowel				
Baseline	96.6 (6.7)	93.8 (12.6)	2.8 (−1.5, 7.1)	0.21
3 months	88.3	93.5	5.2 (−0.3, 10.6)	0.06
6–9 months	91.6	92.0	0.4 (−4.6, 5.4)	0.87
12–15 months	86.8	90.1	3.3 (−13.4, 20.0)	0.68
≥18 months	93.6	93.7	0.06 (−6.3, 6.4)	0.98
EPIC Sexual				
Baseline	53.0 (33.6)	70.6 (32.7)	−17.6 (−44.0, 8.8)	0.20
3 months	34.0	35.5	1.4 (−10.9, 13.8)	0.82
6–9 months	31.4	36.3	4.9 (−7.9, 17.6)	0.45
12–15 months	30.3	35.7	5.4 (−23.0, 33.8)	0.69
≥18 months	31.5	51.8	20.3 (3.2, 37.4)	0.02*
EPIC Hormonal				
Baseline	95.3 (8.3)	92.7 (16.7)	2.6 (−3.1, 8.3)	0.38
3 months	83.4	83.9	0.5 (−6.3, 7.4)	0.88
6–9 months	86.3	88.5	2.3 (−5.6, 10.1)	0.57
12–15 months	83.9	94.0	10.1 (−5.9, 26.0)	0.20
≥18 months	92.7	92.5	−0.1 (−8.6, 8.3)	0.97

Table 4
Adverse events with or without androgen deprivation and with or without a brachytherapy boost.

Bowel Adverse Events	Androgen Deprivation (n = 56)	No Androgen Deprivation (n = 60)	P-value (Fisher's Exact)
Acute < 180 days			0.99
G0-1	56 (100%)	59 (98%)	
G2	0 (0%)	1 (2%)	
G3	0 (0%)	0 (0%)	
Chronic > 180 days			0.99
G0-1	56 (100%)	59 (98%)	
G2	0 (0%)	1 (2%)	
G3	0 (0%)	0 (0%)	
Urinary Adverse Events			
Acute < 180 days			0.17
G0-1	16 (28%)	25 (42%)	
G2	39 (70%)	35 (58%)	
G3	1 (2%)	0 (0%)	
Chronic > 180 days			0.68
G0-1	40 (72%)	45 (75%)	
G2	16 (28%)	15 (25%)	
G3	0 (0%)	0 (0%)	
Bowel Adverse Events	**Brachytherapy (n = 37)**	**No Brachytherapy (n = 79)**	**P-value (Fisher's Exact)**
Acute < 180 days			0.99
G0-1	37 (100%)	78 (98.7%)	
G2	0 (0%)	1 (1.3%)	
G3	0 (0%)	0 (0%)	
Chronic > 180 days			0.99
G0-1	37 (100%)	78 (98.7%)	
G2	0 (0%)	1 (1.3%)	
G3	0 (0%)	0 (0%)	
Urinary Adverse events			
Acute < 180 days			< 0.001*
G0-1	2 (5%)	40 (51%)	
G2	34 (92%)	39 (49%)	
G3	1 (3%)	0 (0%)	
Chronic > 180 days			0.66
G0-1	28 (76%)	56 (71%)	
G2	9 (24%)	23 (29%)	
G3	0 (0%)	0 (0%)	

between the two groups at other time-points (Table 4).

Urinary incontinence EPIC bother showed a small decline at 3 months with or without ADT. However, patients treated with ADT showed an improvement in the scores that was not seen in patients without ADT. Over time, the difference in bother reached 11 points at 12 to 15 months after radiation and was borderline significant ($p = 0.09$). It is possible that smaller gland volumes after ADT were associated with a faster improvement in urinary incontinence EPIC scores.

Overall, only one grade 3 urinary AE was seen in the study. It occurred in a brachytherapy patient that also received ADT (Table 4 and Fig. 3a). The patient had persistent urinary retention symptoms and required a Foley catheter and transurethral incision of the prostate by a urologist with a long history of LDR brachytherapy patient management. The patient's symptoms improved soon after.

Urinary bother and urinary AEs with or without brachytherapy

One month after brachytherapy, IPSS scores increased 11 points ($p < 0.001$), from 9 at baseline to 20 at one-month (not presented in Table 2 or Fig. 2). However, IPSS scores for brachytherapy patients improved over time. By 3 months after treatment, a small 3.5-point difference favoring external beam radiation alone was statistically significant ($p = 0.006$) but did reach clinical relevance (≥ 5 points) (Table 2 and Fig. 2). Six to nine months after the completion of radiation the difference between patients with or without brachytherapy had disappeared and, IPSS values had returned to baseline.

The urinary irritative/obstructive EPIC domain showed a small decline at 3 months for both groups as compared to baseline (Table 3). However, a larger decline in urinary irritative/obstructive EPIC scores was seen for the first 9 months after brachytherapy ($p < 0.02$) that recovered by 12 to 15 months after the completion of radiation. Although the difference between brachytherapy and without brachytherapy was smaller than 10 points, it reached 8 points at 3 months ($p = 0.006$). The urinary irritative/obstructive EPIC scores were similar between the two groups after 12 months.

Urinary incontinence EPIC bother showed minimal decline at 3 months with or without brachytherapy and scores remained similar at other time-points (Table 3).

Acute GU AEs were more common in patients treated with brachytherapy than without it ($p < 0.001$). However, most of the AEs consisted of the use of alpha-blockers, and only one patient out of 37 (2.7%), as previously mentioned, had obstructive symptoms requiring a Foley catheter and a transurethral incision of the prostate. Chronic GU AEs were similar in both groups showing fast recovery of urinary symptoms after treatment as suggested by the IPSS and urinary EPIC scores (Fig. 3b).

Bowel bother and bowel AEs with or without ADT

A non-significant difference in bowel EPIC scores was seen favoring the use of ADT, which reached 10-points at 12–15 months after the completion of radiation. However, bowel EPIC scores were high for both groups at the different time-points.

Bowel AEs were minimal in either group with only one acute/chronic grade 2 AE seen in the whole study; the lack of AEs correlated well with the high bowel EPIC scores seen in both groups.

Bowel bother and bowel AEs with or without brachytherapy

A non-significant difference in bowel EPIC scores was seen favoring patients treated with external beam radiation alone. However, the difference only reached 5-points at 3 months after the completion of radiation. Bowel EPIC scores were high for both groups at all time-points.

Bowel AEs were minimal in either group with only one acute/chronic grade 2 AE seen in one patient treated with external beam radiation alone.

Sexual and hormonal bother with or without ADT

Sexual and hormonal EPIC scores declined with the use of ADT. The decline in the sexual domain was ≥ 17 points in the first 12 months when compared to patients treated without ADT. Similarly, ADT was also associated with a hormonal domain decline ≥ 9 points in the first 9 months after the completion of radiation. Patients received ADT for 6 months that started 2 months prior to the start of radiation. Sexual and hormonal bother started to improve 6 months after the completion of radiation and the difference between groups disappeared 12 to 15 months after the completion of radiation. Thus, on average, the effect of ADT lasted 6 months longer than the duration of the medication. As expected with an aging male population, sexual EPIC scores long-term were worse than at baseline.

Sexual and hormonal bother with or without brachytherapy

Sexual EPIC scores were similar with or without brachytherapy for the first 12 to 15 months post-treatment. At 18 months and after, a 20-point difference ($p = 0.02$) was observed between the two groups

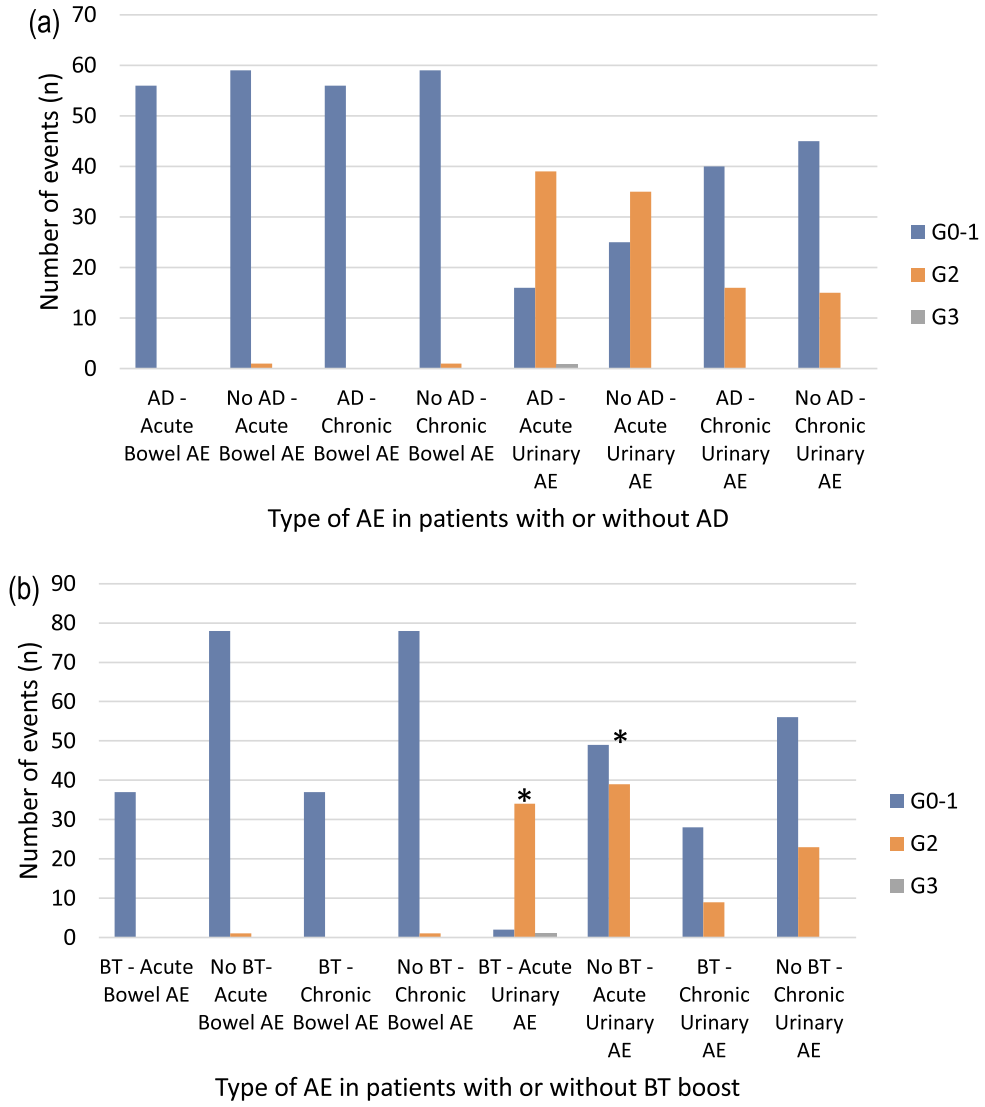

Fig. 3. (a) Bowel and urinary adverse events (AEs) with or without androgen deprivation (AD) (b). Bowel and urinary adverse events (AEs) with or without brachytherapy (BT) boost.

favoring EBRT alone. Although the results are thought provoking, suggesting a long-term improvement in patients treated with external beam radiation alone, an effect not seen in brachytherapy patients, it will need to be confirmed with longer follow-up. Hormonal EPIC scores were similar for both groups at different time-points.

Erectile function with or without ADT

Self-assessed erectile function (EF) was similar at baseline (Table 5). However, with ADT a decline was seen at 3 months ($p = 0.06$) and 6 to 9 months ($p = 0.05$) after treatment when compared to patients treated without ADT. EF recovered about 12 to 15 months after ADT, with no difference between the two groups ($p = 0.2$) thereafter. At baseline, about 60% of all patients had erections suitable for intercourse ($p = 0.99$), and at 12 to 15 months, about 55% of the patients treated with ADT had erections suitable for intercourse ($p = 0.2$).

Erectile function with or without brachytherapy

Self-assessed EF was similar at baseline with or without brachytherapy. At 3 months, EF was lower in patients treated with brachytherapy (59% vs. 40% erections suitable for intercourse, $p = 0.006$). At all other time-points, values were similar between the two groups.

Freedom from failure

Five events were seen in the current study. Based on the ADT randomization, 3 failures occurred with ADT and 2 without ADT ($p = 0.67$). Based on the stratification by use of brachytherapy, 2 failures occurred with brachytherapy and 3 without brachytherapy ($p = 0.65$).

Discussion

The role of ADT for intermediate-risk prostate cancer continues to evolve. With the techniques and doses used in RTOG 9408, ADT was responsible for a large absolute benefit in survival [1]. However, as radiation techniques and dose continue to progress, the absolute benefit of ADT for intermediate-risk prostate cancer may be decreasing, with more recent trials showing a benefit in freedom from failure but not survival [2–5]. With continued improvements in technique and dose escalation, the benefit in freedom from failure for ADT may further decrease [9–13]. Although our follow-up is still very short for any meaningful interpretations of the freedom from failure rates, other events such as toxicity, QOL, and EF can be compared between the two groups.

In general, ADT was well-tolerated. Hormonal, sexual and EF

Table 5
Self-reported erectile function (EF) scores with or without androgen deprivation and with or without a brachytherapy boost. EF Scores (3-normal, 2-partial erections but sufficient for sex, 1-partial erections but insufficient for sex, 0-no erections).

EF Score	Androgen Deprivation	No Androgen Deprivation	Total	P-value (Fisher's Exact)
Baseline				0.99
0	7 (12.5%)	8 (13.3%)	15 (12.9%)	
1	14 (25.0%)	15 (25.0%)	29 (25.0%)	
2	12 (21.4%)	14 (23.3%)	26 (22.4%)	
3	21 (37.5%)	22 (36.7%)	43 (37.1%)	
Total	54	59	113	
3 months				0.06
0	14 (46.7%)	6 (18.8%)	20 (32.3%)	
1	4 (13.3%)	5 (15.6%)	9 (14.5%)	
2	9 (30.0%)	11 (34.4%)	20 (32.3%)	
3	3 (10.0%)	10 (31.3%)	13 (21.0%)	
Total	30	32	62	
6–9 months				0.05
0	12 (42.9%)	3 (10.3%)	20 (35.1%)	
1	3 (10.7%)	4 (13.8%)	9 (15.8%)	
2	6 (21.4%)	10 (34.5%)	20 (35.1%)	
3	7 (25.0%)	12 (41.4%)	13 (22.8%)	
Total	28	29	57	
12–15 months				0.28
0	4 (36.4%)	1 (8.3%)	5 (21.7%)	
1	1 (9.1%)	0 (0.0%)	1 (4.3%)	
2	4 (36.4%)	8 (66.7%)	12 (52.2%)	
3	2 (18.2%)	3 (25.0%)	5 (21.7%)	
Total	11	12	23	
	Brachytherapy	**No Brachytherapy**	**Total**	**P-value (Fisher's Exact)**
Baseline				0.16
0	1 (2.7%)	14 (17.7%)	15 (12.9%)	
1	11 (29.7%)	18 (22.8%)	29 (25.0%)	
2	9 (24.3%)	17 (21.5%)	26 (22.4%)	
3	15 (40.5%)	28 (35.4%)	43 (37.1%)	
Total	36	77	113	
3 months				0.006
0	8 (40.0%)	12 (28.6%)	20 (32.3%)	
1	4 (20.0%)	5 (11.9%)	9 (14.5%)	
2	4 (20.0%)	16 (38.1%)	20 (32.3%)	
3	4 (20.0%)	9 (21.4%)	13 (21.0%)	
Total	20	42	62	
6–9 months				0.66
0	7 (35.0%)	8 (21.6%)	15 (26.3%)	
1	1 (5.0%)	6 (16.2%)	7 (12.3%)	
2	6 (30.0%)	10 (27.0%)	16 (28.1%)	
3	6 (30.0%)	13 (35.1%)	19 (33.3%)	
Total	20	37	57	
12–15 months				0.39
0	0 (0.0%)	5 (27.8%)	5 (21.7%)	
1	1 (20.0%)	0 (0.0%)	1 (4.3%)	
2	3 (60.0%)	9 (50.0%)	12 (52.2%)	
3	1 (20.0%)	4 (22.2%)	5 (21.7%)	
Total	5	18	23	

changes due to ADT were temporary and recovered at about 12 months after the completion of radiation. Hormonal and sexual bother associated with ADT, although clinically relevant ($\geq$10-point change), was temporary.

The most significant differences in EPIC scores were within the sexual and hormonal EPIC domains. In our study, the largest decline for patients treated with ADT was 3-months after the completion of radiation, but scores improved at 12 months and were no longer significantly different than without ADT. In RTOG 9408, EF at 1-year was lower for patients treated with ADT [1]. However, at 3-months after treatment, testosterone levels declined even in patients treated without ADT. The authors suggested that the incidental dose to the testicles from the field used in the study was responsible for the decline [14]. Other studies have also shown a decline in testosterone associated with radiation [15]. Although a decline in hormonal bother, sexual activity, and sexual function was seen during the first year in EORTC 22,991, values recovered with additional follow-up [4]. In our study, we also saw a decline in sexual and hormonal bother scores within the first year associated with ADT. However, in our study, sexual and hormonal recovery was faster than previously published. Major reasons for the difference could be related to the timing of ADT – in EORTC 22,991, 6 months of ADT were given starting with the first radiation treatment, whereas we started ADT 2 months before radiation. Therefore, the difference in recovery may all be related to the timing of ADT. Alternatively, in both RTOG 9408 and EORTC 22,991 antiandrogens were given, which may have prolonged sexual and hormonal recovery. No patients received antiandrogens in the present trial. Lastly, differences in radiation scatter to the testicles may account for the difference in sexual and hormonal recovery. Our study used daily image guidance and tight margins, which could have minimized delivery errors and scattered dose to the testes compared to older techniques. Prior studies also suggest the median time to normal testosterone recovery occurs within 7 months, which would match our findings [16]. Even in patients with 3 years of ADT, 75% of the patients recovered testosterone levels within 12 months of the completion of ADT [17].

Maximum decline in EF with ADT occurred 3 months after radiation. At 6 months, some improvement was seen, and at one year, there was no longer a difference between ADT and no ADT. The results in patient-reported EF were similar to the differences in sexual and hormonal EPIC scores, showing a recovery at about 12 months. Similar to the results in EORTC 22,991, sexual scores were comparable to baseline after 12 months. Although sexual bother and erectile function scores are difficult to measure due to large confidence intervals, minimal deterioration in sexual function was seen in this study with or without ADT, similar to the results of EORTC 22,991 study.

Brachytherapy was used in 37 patients in our study. Although the numbers are small, some comparisons with patients treated with external beam radiation alone are possible. Four weeks after the implant, a significant change in the IPSS score was seen. However, 6 months after the completion of external beam radiation, scores were close to baseline. Acute urinary AEs, EF, and irritative EPIC scores were worse with brachytherapy but were also temporary. In our study, well-selected patients treated with brachytherapy had temporary changes compared to external beam radiation alone. In other trials, brachytherapy was associated with larger changes, with rates of grade 3 urinary toxicity of 18% and grade 3 rectal toxicity of 8% and high persistence of toxicities at 5 years [7]. In our current trial, only one temporary grade 3 AE was seen. Our use of intraoperative planning and strict selection criteria for brachytherapy candidates may be responsible for our low toxicity rates with brachytherapy. Intraoperatively planned brachytherapy has been associated with low toxicity rates even in the retreatment setting [18]. The low toxicity rates seen in our study were associated with small temporary changes in EPIC and IPSS scores.

Low AE rates correlated with small changes in EPIC and IPSS scores seen in our study. Low toxicity rates for external beam radiation may be a reflection of current radiation standards when using IMRT, rectal balloon, and daily image guidance with fiducial markers and cone-beam CT. Low toxicity rates for brachytherapy plus external beam may also be a reflection of intraoperative planning and strict patient selection. Our results compare very favorably to older studies with external beam radiation with or without brachytherapy boost [5,7,9,10,12,13,19,20]. Based on the current published literature that shows an improvement in failure rates among intermediate-risk prostate cancer patients treated with ADT [1–4], a short-lived ADT-related increase in bother is likely justified, and the use of ADT with radiation remains the standard of care.

Conclusion

IMRT with cone-beam fiducial-based image guidance and rectal balloon with or without intraoperatively planned brachytherapy is associated with low toxicity and minimal temporary bother with or without ADT. ADT was well-tolerated and associated with temporary symptoms. Given the clinical benefits of ADT seen in other trials for intermediate-risk prostate cancer, ADT remains the standard of care.

Clinical practice points

Androgen deprivation therapy (ADT) and radiation therapy have shown a clinical benefit in several randomized trials including a survival benefit in RTOG 9408, which reported a 10-year absolute survival difference of 7% (HR 1.23). However, critics point to the lack of contemporary image guidance, relative low doses (66.6 Gy to isocenter), lack of intensity-modulated radiotherapy (IMRT), and relative high failure rate in the control group (41%). More recent randomized studies, including GETUG 14, PCS III, EORTC 22,991, TROG 96.01 have continued to show a benefit for ADT, however, the magnitude of the benefit has not translated into a survival benefit. The collective evidence shows that ADT improves clinical results for intermediate-risk prostate cancer. However, as higher doses are delivered, as seen in the trials subsequent to RTOG 9408, the absolute advantage decreased. With higher doses, MRI registration, rectal balloon, fiducial markers, IMRT, and daily volumetric image guidance, as done in the current study, the clinical benefit of ADT may decrease further. Although our follow-up is still very short for any meaningful interpretations of the freedom from failure rates; other events such as toxicity, quality of life, and erectile function (EF) can be compared between the two groups. In general, ADT was well-tolerated. Hormonal, sexual and EF changes due to ADT were temporary and recovered at about 12 months after the completion of radiation. Given the clinical benefits of ADT seen in other trials for intermediate-risk prostate cancer, ADT remains the standard of care.

Conflict of interest form

We have no conflicts of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2019.100119.

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