ORIGINAL ARTICLE

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External beam radiation therapy and a low-dose-rate brachytherapy boost without or with androgen deprivation therapy for prostate cancer

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ABSTRACT

Purpose: To assess outcomes with external beam radiation therapy (EBRT) and a low--dose-rate (LDR) brachytherapy boost without or with androgen deprivation therapy (ADT) for prostate cancer.

Materials and Methods: From January 2001 through August 2011, 120 intermediate--risk or high-risk prostate cancer patients were treated with EBRT to a total dose of 4,500 cGy in 25 daily fractions and a palladium-103 LDR brachytherapy boost of 10,000 cGy (n = 90) or an iodine-125 LDR brachytherapy boost of 11,000 cGy (n = 30). ADT, consisting of a gonadotropin-releasing hormone agonist ± an anti-androgen, was administered to 29/92 (32%) intermediate-risk patients for a median duration of 4 months and 26/28 (93%) high-risk patients for a median duration of 28 months.

Results: Median follow-up was 5.2 years (range, 1.1-12.8 years). There was no statistically-significant difference in biochemical disease-free survival (bDFS), distant metastasis-free survival (DMFS), or overall survival (OS) without or with ADT. Also, there was no statistically-significant difference in bDFS, DMFS, or OS with a palladium-103 vs. an iodine-125 LDR brachytherapy boost.

Conclusions: There was no statistically-significant difference in outcomes with the addition of ADT, though the power of the current study was limited. The Radiation Therapy Oncology Group 0815 and 0924 phase III trials, which have accrual targets of more than 1,500 men, will help to clarify the role ADT in locally-advanced prostate cancer patients treated with EBRT and a brachytherapy boost. Palladium-103 and iodine-125 provide similar bDFS, DMFS, and OS.

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INTRODUCTION

Phase III studies have shown a dose-response relationship for prostate cancer (1). As a result, the National Comprehensive Cancer Network (NCCN) recommends use of escalated-dose radiotherapy, i.e., either external beam radiation therapy (EBRT) and a brachytherapy boost or EBRT alone to ≥ 7,800 cGy, for locally-advanced prostate cancer (2). Phase III trials have also demonstrated an overall survival (OS) benefit with the addition of androgen deprivation therapy (ADT) to EBRT to 6,500-7,000 cGy, which constitutes low-dose radiotherapy by today's standards, for locally-advanced prostate cancer (1). Some have hypothesized that if escalated-dose radiotherapy is delivered, then the benefit to ADT may be lost (1,3).

Two Radiation Therapy Oncology Group (RTOG) phase III trials are currently evaluating the role of ADT in prostate cancer patients treated with dose-escalated radiotherapy (1). Mature results from these studies are years away. Consequently, the current role of ADT in intermediate-risk and high-risk prostate cancer patients treated with EBRT and a brachytherapy boost is unclear (1-3).

No phase III trials have evaluated outcomes with different low-dose-rate (LDR) brachytherapy sources when brachytherapy is used as a boost in combination with EBRT. A single prospective, randomized trial comparing palladium-103 LDR brachytherapy monotherapy with iodine-125 LDR brachytherapy monotherapy in patients with low--risk prostate cancer (2) demonstrated equivalent biochemical disease-free survival (bDFS) with slightly different toxicity profiles based on the brachytherapy source (4).

The primary goal of this retrospective study is to assess outcomes with EBRT and a LDR brachytherapy boost in intermediate-risk and high-risk prostate cancer patients (2), including results without and with ADT. A secondary goal of this study is to assess outcomes with EBRT and a palladium-103 versus (vs.) an iodine-125 LDR brachytherapy boost.

MATERIALS AND METHODS

Patient Characteristics

After obtaining investigational review board approval, we reviewed 171 cases of clinically--localized prostate cancer treated with EBRT and a LDR brachytherapy boost between January 2001 and August 2011. Patients were excluded if they had a low risk of recurrence as defined by the NCCN (2) or were treated with an EBRT dose other than 4,500 cGy in 25 fractions. One-hundred and twenty patients provided informed consent for treatment and were included in this analysis.

Characteristics of the intermediate-risk (n = 92) and high-risk (n = 28) patients are shown in Table-1. Characteristics of intermediate-risk prostate cancer patients who did not or did receive ADT, including their percentage of positive prostate biopsy cores (5), are presented in Table-2. The only known, statistically-significant difference in characteristics between intermediate-risk patients who did not and did receive ADT was their American Joint Commission on Cancer (AJCC) clinical tumor stage (p = 0.01, Table-2) (6). There were no significant differences in baseline characteristics between patients treated with a palladium-103 versus an iodine-125 LDR brachytherapy boost.

EBRT and a LDR Brachytherapy Boost

In terms of the EBRT, 30 patients were treated with three-dimensional conformal radiation therapy and 90 patients were treated with intensity modulated radiation therapy (IMRT). Beginning in 2006, 4 fiducial gold markers were transrectally inserted under local anesthesia into the left and right mid lateral prostate and the prostatic base and apex prior to simulation (n = 91). The markers made it possible to determine the location of the prostate using electronic portal imaging immediately prior to each EBRT treatment and thereby deliver image-guided radiation therapy (7).

Patients were simulated with an empty rectum using a pelvic computed tomography (CT) scan with 0.3cm slices. Forty mL normal saline mixed with 10mL non-ionic contrast was injected into the bladder and urethra at the time of simulation in order to perform a cystogram and urethrogram, respectively. The clinical target volume (CTV) for EBRT consisted of the prostate and inferomedial 1.0cm of the seminal vesicles as defined by CT scan. In cases with extraprostatic extension on magnetic resonance imaging (MRI) or biopsy, the CTV for EBRT was expanded to include disease outside of the prostate based on CT-MRI fusion. The planning target volume (PTV) consisted of the CTV with 0.5cm expansion posteriorly, inferiorly, and superiorly and 0.7cm expansion anteriorly and laterally. The minimum allowable dose delivered to the PTV was 93% of the prescribed dose, and the maximum allowable dose delivered to the PTV was 115% of the prescribed dose. At least 98% of the PTV received ≥ 95% of the prescribed dose (8). Rectal and bladder dose-volume histograms (DVHs) were created. The dosimetric goals for EBRT were that no more than 15% of the rectal volume should receive > 4,100 cGy and no more than 15% of the bladder volume should receive > 4,000 cGy.

Table 1 - Characteristics of intermediate-risk and high-risk prostate cancer patients.

Characteristics	Intermediate-Risk and High-Risk Patients Combined, n (%)	Intermediate-Risk Patients, n (%)	High-Risk Patients, n (%)
Median Age (years, range)	65 (46, 82)	65 (46, 82)	66 (48, 77)
Race			
Caucasian	98 (82)	73 (79)	25 (89)
African American	11 (9)	10 (11)	1 (4)
Unknown	11 (9)	9 (10)	2 (7)
Median Pre-treatment Prostate-Specific Antigen (ng/mL, range)	6.5 (0.1, 118.0)	5.9 (0.1, 25.6)	7.8 (2.6, 118.0)
American Joint Committee on Cancer Clinical Tumor Stage			
T1c	55 (46)	50 (54)	5 (18)
T2a	31 (26)	23 (25)	8 (29)
T2b	22 (18)	15 (16)	7 (25)
T2c	8 (7)	4 (4)	4 (14)
T3a	3 (2)	0 (0)	3 (11)
T3b	1 (1)	0 (0)	1 (4)
Gleason Score			
6	9 (7)	9 (10)	0 (0)
3 + 4 = 7	62 (52)	61 (66)	1 (4)
4 + 3 = 7	26 (22)	22 (24)	4 (14)
8	12 (10)	0 (0)	12 (43)
9	10 (8)	0 (0)	10 (36)
10	1 (1)	0 (0)	1 (4)
Median Prostate Volume (mL, range)	31 (18, 71)	32 (18, 55)	31 (20, 71)
Low-Dose-Rate Brachytherapy Source			
Palladium-103	90 (75)	69 (75)	21 (75)
Iodine-125	30 (25)	23 (25)	7 (25)

Four to 6 weeks prior to a LDR brachytherapy boost, patients were evaluated by transrectal ultrasound to assess pubic arch interference and prostate volume. One month after receiving EBRT to 4,500 cGy, patients underwent a LDR brachytherapy boost according to American Brachytherapy Society consensus guidelines (9). Briefly, patients were placed under general anesthesia and 14-24 interstitial needles were advanced into the prostate. The CTV for the brachytherapy boost

Table 2 - Characteristics of intermediate-risk prostate cancer patients who underwent EBRT and a LDR brachytherapy boost without (n = 63) or with (n = 29) ADT.

Characteristics	Intermediate-Risk Patients, n (%)	No Androgen Deprivation Therapy, n (%)	Androgen Deprivation Therapy, n (%)	p-Value
Median Age (years, range)	65 (46, 82)	64 (46, 79)	67 (50, 82)	0.06
Race				0.81
Caucasian	73 (79)	49 (78)	24 (83)	
African American	10 (11)	7 (11)	3 (10)	
Unknown	9 (10)	7 (11)	2 (7)	
Median Pre-treatment Prostate-Specific Antigen (ng/mL, range)	5.9 (0.1, 25.6)	5.8 (2.5, 25.6)	6.4 (0.1, 20)	0.58
American Joint Committee on Cancer Clinical Tumor Stage				0.01
T1c	50 (54)	39 (62)	11 (38)	
T2a	23 (25)	17 (27)	6 (21)	
T2b	15 (16)	6 (10)	9 (31)	
T2c	4 (4)	1 (2)	3 (10)	
Gleason Score				0.18
6	9 (10)	4 (6)	5 (17)	
3 + 4 = 7	61 (66)	45 (71)	16 (55)	
4 + 3 = 7	22 (24)	14 (22)	8 (28)	
> 50% Positive Prostate Biopsy Cores	27 (29)	17 (27)	10 (34)	0.46
Median Prostate Volume (mL, range)	32 (18, 55)	32 (18, 55)	32 (18, 53)	0.65
Low-Dose-Rate Brachytherapy Source				0.70
Palladium-103	69 (75)	48 (76)	21 (72)	
Iodine-125	23 (25)	15 (24)	8 (28)	

consisted of the prostate as defined by CT scan. In cases with extraprostatic extension on MRI or biopsy, the CTV was expanded to include disease outside of the prostate with a 0.3cm margin. The PTV was the same as the CTV. The PTV was treated with either a single palladium-103 (Pd-103) LDR brachytherapy boost of 10,000 cGy (n = 90) or a single iodine-125 (I-125) LDR brachytherapy boost of 11,000 cGy (n = 30). One to two months following a LDR brachytherapy boost, a pelvic CT scan with 0.3cm cuts was obtained for dosimetric calculations. Prostate doses were recorded as the minimum dose that covered more than 90% of the prostate volume expressed as a percentage of the prescription dose (prostate $D_{90,}$ goal > 90% and < 130%). Prostate volumes were recorded as the

fractional volume of the prostate that received 100% of the prescribed dose (prostate $V_{100,}$ goal > 90%), 150% of the prescribed dose (prostate $V_{150,}$ goal > 50%), and 200% of the prescribed dose (prostate $V_{200,}$ goal > 25%). The urethral volume was recorded as the fractional volume of the urethra that received 150% of the prescribed dose (urethra $V_{150,}$ goal < 10%).

ADT

ADT always consisted of a gonadotropin-releasing hormone agonist. In a minority of cases, ADT also included an anti-androgen. The median duration of a gonadotropin-releasing hormone agonist was 4 months for intermediate-risk disease and 28 months for high-risk disease. The median duration of an anti-androgen was one month starting two weeks prior to the gonadotropin-releasing hormone agonist. Twenty-nine of 92 (32%) intermediate risk patients and 26/28 (93%) high-risk patients received ADT.

Statistics

Statistical analysis was performed using Statistical Product and Service Solutions version 21.0 (SPSS®, Chicago, IL). Two or more nominal variables were compared using a two-sided Chi-squared test. A two-tailed Wilcoxon-rank sum test was used to compare two continuous variables. Biochemical disease-free survival, distant metastasis-free survival (DMFS), and OS were analyzed. Biochemical disease-free survival was defined according to the the RTOG-ASTRO Phoenix Consensus Conference as the time from EBRT start to prostate specific antigen (PSA) failure, i.e., a PSA increase ≥ 2.0ng/mL from the nadir value (10). Distant metastasis-free survival was defined as the time from the start of EBRT to distant metastasis or death, and overall survival was defined as the time from the start of EBRT to death. Biochemical disease-free survival, DMFS, and OS were calculated using the Kaplan-Meier method and differences in outcomes were calculated using the log-rank test. Since only two high-risk patients did not receive ADT, there was insufficient statistical power to compare bDFS, DMFS, and OS without vs. with ADT in this recurrence risk group. A Cox multivariate model was created using all pretreatment variables to look for independent associations between patient characteristics and bDFS, DMFS, and OS. An α (type I) error < 0.05 was considered statistically significant.

RESULTS

Median follow-up was 5.2 years (range, 1.1-12.8 years). Five patients experienced biochemical failure, 3 patients developed radiographic evidence of distant metastases, and 7 patients died. Median time to PSA failure was 4.4 years (range, 1.0-5.7 years) and median time to the development of distant metastasis was 6.8 years (range, 5.5-9.9 years).

Biochemical disease-free survival, DMFS, and OS for intermediate-risk patients who did not and did receive ADT are presented in Figure-1. Five-year bDFS, DMFS, and OS rates for intermediate-risk patients without vs. with ADT were 94% vs. 100% (p = 0.65), 96% vs. 100% (p = 0.59), and 96% vs. 100% (p = 0.48), respectively.

Biochemical disease-free survival, DMFS and OS for high-risk patients who did not and did receive ADT are presented in Figure-2. Five--years bDFS, DMFS, and OS rates for high-risk patients without vs with ADT were 100% vs. 88% (p = 0.62), 100% vs. 100% (p = 0.74), and 100% vs. 100% (p = 0.99), respectively.

There was no statistically-significant difference in bDFS or DMFS (p = 0.18 and p = 0.06, respectively) between patients treated with a palladium-103 compared with an iodine-125 LDR brachytherapy boost. Based upon a log-rank test, OS was longer in patients treated with an iodine-125 LDR brachytherapy boost (5-years OS rates: 100% vs. 96%, respectively; p = 0.048; Figure-3). However, on Cox multivariate-regression analysis, brachytherapy source was not significantly associated with OS (p = 0.95). Instead, age was the only variable significantly associated with OS (hazard ratio (HR) 1.26, 95% confidence interval (CI) 1.04-1.53, p = 0.02, and HR 1.29, 95% CI 1.05-1.57, p = 0.02, respectively).

Figure 1 - Kaplan-Meier estimates of bDFS (a), DMFS (b), and OS (c) in intermediate-risk prostate cancer patients treated with EBRT and a LDR brachytherapy boost without (__) or with (...) ADT.

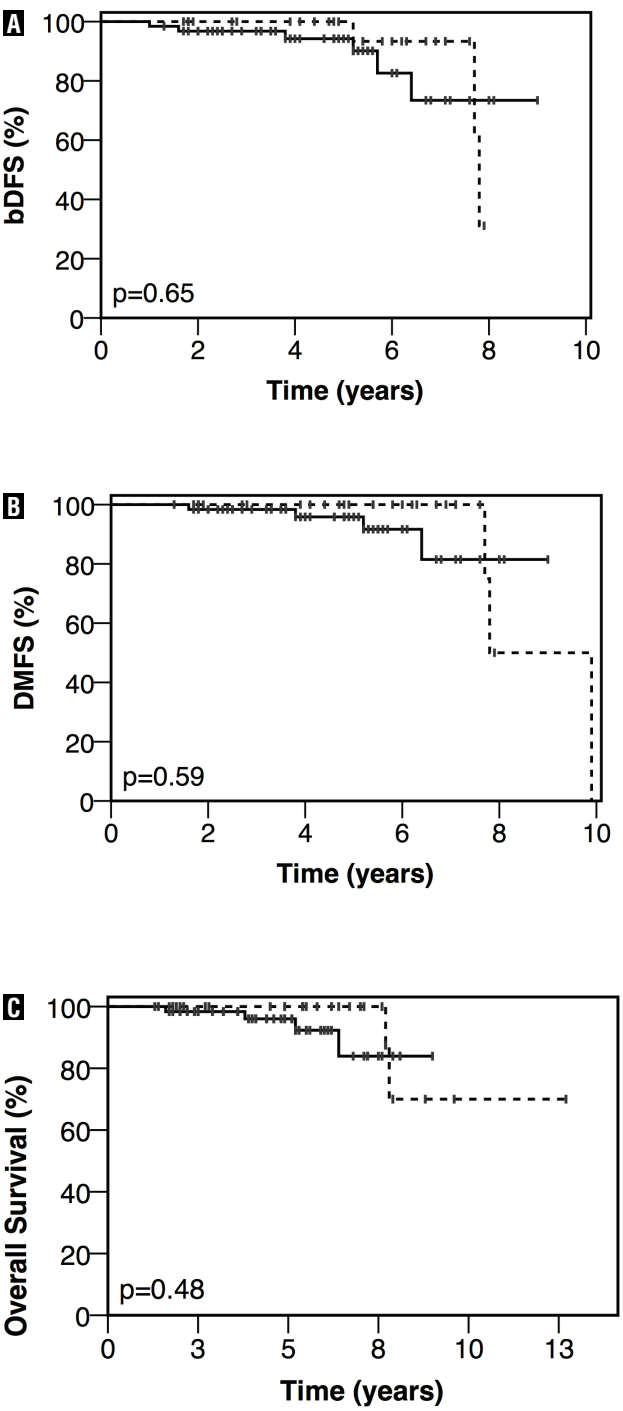


Figure 2 - Kaplan-Meier estimates of bDFS (a), DMFS (b), and OS (c) in high-risk prostate cancer patients treated with EBRT and a LDR brachytherapy boost without (__) or with (...) ADT.

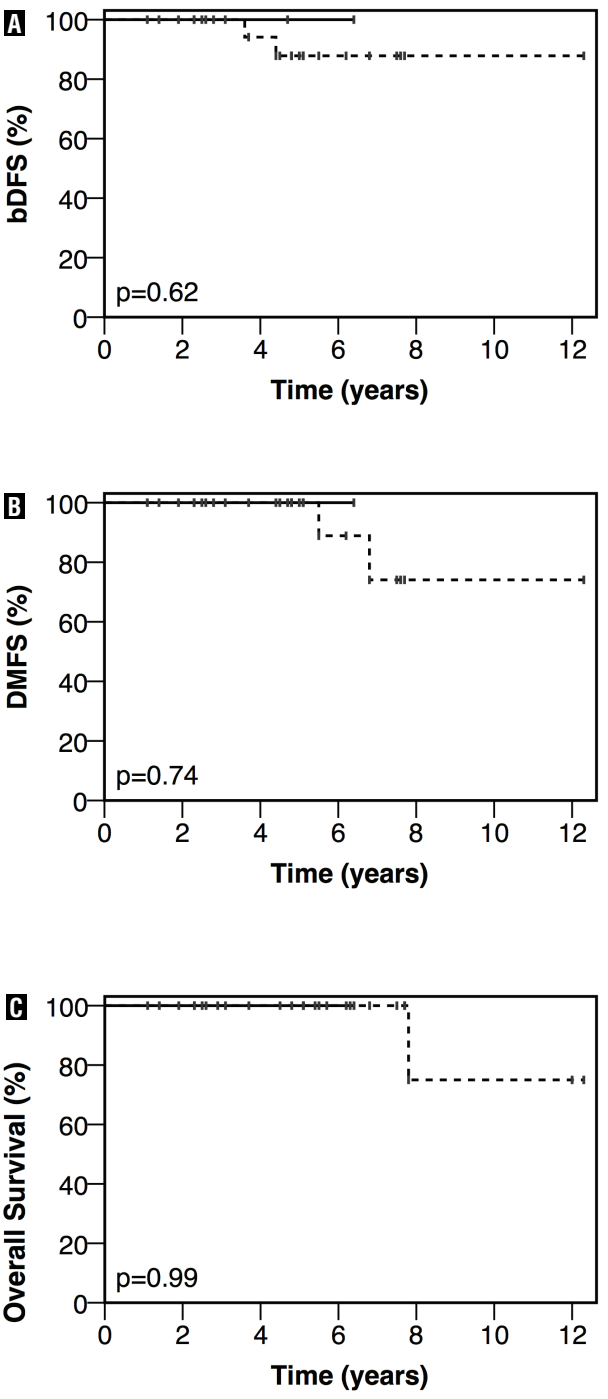
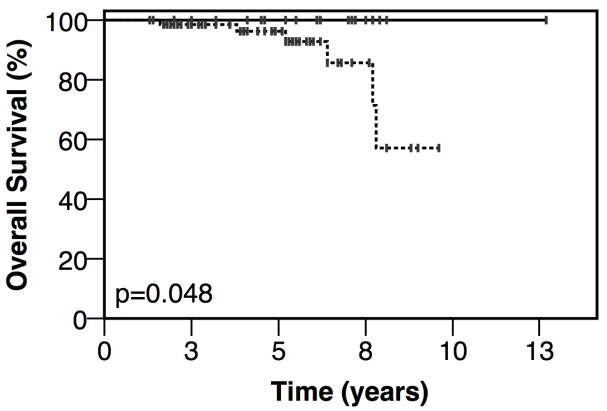


Figure 3 - Kaplan-Meier estimates of OS in intermediate-risk prostate cancer patients treated with EBRT and a palladium-103 (...) or an iodine-125 (__) LDR brachytherapy boost.



DISCUSSION

Two retrospective studies have examined outcomes with ADT in combination with EBRT to total doses ≥ 7,560 cGy. Castle et al. (11) found a freedom-from-failure benefit with the addition of ADT to EBRT to 7,560-7,800 cGy in "unfavorable" (Gleason score 4+3=7 or AJCC clinical T2c disease) intermediate-risk patients. There was no benefit to ADT in "favorable" (Gleason score 6 and ≤ clinical T2b disease or Gleason score 3+4 and ≤ clinical T1c disease) intermediate-risk patients. Zumsteg et al. (12) demonstrated an improvement in bDFS, DMFS, and prostate-cancer specific mortality with the addition of ADT to EBRT to ≥ 8,100 cGy in intermediate-risk patients. They did not separate intermediate-risk patients into unfavorable and favorable subgroups.

Outcomes with EBRT and ADT may not be comparable to those with EBRT, a LDR brachytherapy boost, and ADT. Assuming an α/β ratio of 1.5 for prostate cancer (13), the biologically effective doses ($BED_{1.5}$) with EBRT to a total dose of 8,100 cGy in 45 fractions, EBRT to a total dose of 4,500 cGy in 25 fractions in combination with a Pd-103 LDR brachytherapy boost of 10,000 cGy, and EBRT to a total dose of 4,500 cGy in 25 fractions in combination with an I-125 LDR brachytherapy boost of 11,000 cGy are 17,820 cGy, 19,000 cGy, and 20,000 cGy, respectively. As a result, EBRT and a LDR brachytherapy boost deliver approximately a 7-12% higher $BED_{1.5}$ than EBRT alone.

A brachytherapy boost offers a potential radiobiological benefit over conventionally-fractionated EBRT by delivering hypofractionated treatment, which may increase the sensitivity of prostate cancer to radiation therapy by favorably affecting the α/β ratio (14-16). This may, in part, explain why some have observed improved bDFS with EBRT and a brachytherapy boost compared with EBRT alone, though there is a greater risk of late urinary, e.g., urethral, toxicity (17).

Koontz et al. (18) assessed outcomes with EBRT to 4,600 cGy and a LDR brachytherapy boost (10,000 cGy for Pd-103 and 12,000 cGy for I-125) in 199 patients with low-risk (20%), intermediate--risk (47%), or high-risk (33%) prostate cancer. Forty-five percent of patients received ADT. They reported a 5-year bDFS rate of 87% for all patients and 81% in high-risk patients. Their study did not assess the role of ADT. Fang et al. (19) observed a 5-years bDFS rate of 92% with EBRT to 4,500 cGy and a 9,000-10,000 cGy palladium-103 LDR brachytherapy boost without or with ADT in high-risk patients. In the current study, the 5-years bDFS rates were 96% and 89%, respectively, in intermediate-risk patients (Figure-1A) and high--risk patients (Figure-2A).

In high-risk patients who undergo LDR brachytherapy ± EBRT, it is unclear whether the addition of ADT improves bDFS. Merrick et al. (20) observed a bDFS, but no cause-specific survival or OS, benefit to ADT in high-risk patients treated with LDR brachytherapy ± EBRT (95% of patients received EBRT). Similarly, Stone et al. (21) reported a bDFS, but no DMFS or OS, benefit to ADT in patients with a Gleason score 7-10 who underwent LDR brachytherapy ± EBRT (58% of patients received EBRT). However, many other retrospective studies have found no bDFS, DMFS, or OS benefit to ADT in intermediate-risk or high-risk patients treated with EBRT and a brachytherapy boost (19,22-26). Similarly, in this study, there was no significant bDFS, DMFS, or OS benefit to ADT in intermediate-risk patients treated with EBRT and a LDR brachytherapy boost (Figure-1). There were too few high-risk patients treated without ADT (n = 2) to do a meaningful comparison of outcomes

without vs. with ADT (Figure-2). Vargas et al. (27) observed worse DMFS, prostate-cancer specific survival, and OS in patients with a Gleason score 8-10, palpable disease, and a PSA ≥15 ng/mL who received ADT. It is possible that patients who received ADT may have had a history of congestive heart failure or myocardial infarction, accounting for the poor outcomes with ADT in that report (28).

ADT causes significant impairment of health-related quality of life (29). The detrimental effect of ADT on quality of life needs to be considered since the benefit of ADT is unclear in prostate cancer patients undergoing EBRT and a brachytherapy boost (1,3,29).

No phase III trials evaluating the role of ADT in locally-advanced prostate cancer patients treated with EBRT and a brachytherapy boost have been reported to date, though two trials are ongoing (1). These trials will help to define the role of ADT in intermediate-risk and high-risk patients treated with EBRT and a brachytherapy boost. RTOG 0815 randomizes intermediate-risk patients to dose-escalated radiotherapy alone vs. dose-escalated radiotherapy combined with 6 months of ADT consisting of a gonadotropin-releasing hormone agonist and an anti-androgen. Dose escalation can be achieved with EBRT alone or EBRT and a brachytherapy boost. The hypothesis of the study is that ADT will improve the 5-years OS rate from 90.0% to 93.3%. Based on a power of 85% and a one-sided log-rank test with a significance of 0.025, the required sample size is 1,520 patients. The projected year of accrual completion for RTOG 0815 is 2016. RTOG 0924 randomizes unfavorable intermediate-risk and favorable high-risk patients to ADT with EBRT to the prostate and seminal vesicles vs. ADT with EBRT to the whole pelvis followed by a boost to the prostate and seminal vesicles. The boost can be delivered with IMRT or brachytherapy. ADT is given for 6 months or 32 months. The target accrual is 2,580 patients, and the projected year of accrual completion for RTOG 0924 is 2024.

In this study, there was no statistically-significant difference in bDFS, DMFS, or OS on multivariate analysis between patients treated with a palladium-103 compared with an iodine-125 LDR brachytherapy boost. These findings are in accordance with the literature (30).

The current study is limited by its retrospective nature, which gave rise to selection bias. Specifically, intermediate-risk patients were more likely to receive ADT if they had a more advanced clinical tumor stage (Table-2). Nevertheless, this one feature, by itself, should not lead to worse outcomes in patients with an intermediate risk of recurrence (31). Another weakness of the present study is that it was not powered to detect a 3% improvement in the 5-years OS rate due to ADT (more than 1,500 men would be required). Also, the duration of follow up was limited. Pending the results of RTOG 0815 and 0924, use of ADT should be based upon an informed discussion of possible risks and benefits with prostate cancer patients who undergo EBRT and a brachytherapy boost (1-3).

CONCLUSIONS

EBRT and a LDR brachytherapy boost provided excellent outcomes in intermediate-risk and high-risk prostate cancer patients. There was no statistically significant difference in bDFS, DMFS, or OS without or with ADT, though the power was limited. The RTOG 0815 and 0924 phase III trials, which have a target accrual of over 1,500 men, will help to clarify the role ADT in locally-advanced prostate cancer patients treated with EBRT and a brachytherapy boost. There was no statistically-significant difference in bDFS, DMFS, or OS with a palladium-103 vs an iodine-125 LDR brachytherapy boost.

ABBREVIATIONS

ADT = androgen deprivation therapy
AJCC = American Joint Commission on Cancer
bDFS = biochemical disease-free survival
BED = biologically effective dose
CI = confidence interval
CT = computed tomography
CTV = clinical target volume
DMFS = distant metastasis-free survival
DVH = dose-volume histogram
EBRT = external beam radiation therapy
HR = hazard ratio
I-125 = iodine-125
IMRT = intensity modulated radiation therapy

LDR = low-dose-rate
MRI = magnetic resonance imaging
OS = overall survival
Pd-103 = palladium-103
PSA = prostate-specific antigen
RTOG = Radiation Therapy Oncology Group
vs. = versus

CONFLICT OF INTEREST

None declared.

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