Original Article

# The Addition of Low-Dose-Rate Brachytherapy and Androgen-Deprivation Therapy Decreases Biochemical Failure and Prostate Cancer Death Compared With Dose-Escalated External-Beam Radiation Therapy for High-Risk Prostate Cancer

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**BACKGROUND:** The objective of this study was to determine whether the addition of low-dose-rate brachytherapy or androgen-deprivation therapy (ADT) improves clinical outcome in patients with high-risk prostate cancer (HiRPCa) who received dose-escalated radiotherapy (RT). **METHODS:** Between 1995 and 2010, 958 patients with HiRPCa were treated at Schiffler Cancer Center (n = 484) or at the University of Michigan (n = 474) by receiving either dose-escalated external-beam RT (EBRT) (n = 510; minimum prescription dose, 75 grays [Gy]; median dose, 78 Gy) or combined-modality RT (CMRT) consisting of $^{103}$Pd implants (n = 369) or $^{125}$I implants (n = 79) both with pelvic irradiation (median prescription dose, 45 Gy). The cumulative incidences of biochemical failure (BF) and prostate cancer-specific mortality (PCSM) were estimated by using the Kaplan-Meier method and Fine and Gray regression analysis. **RESULTS:** The median follow-up was 63.2 months (interquartile range, 35.4-99.0 months), and 250 patients were followed for >8 years. Compared with CMRT, patients who received EBRT had higher prostate-specific antigen levels, higher tumor classification, lower Gleason sum, and more frequent receipt of ADT for a longer duration. The 8-year incidence BF and PCSM among patients who received EBRT was 40% (standard error, 38%-44%) and 13% (standard error, 11%-15%) compared with 14% (standard error, 12%-16%; $P < .0001$) and 7% (standard error 6%-9%; $P = .003$) among patients who received CMRT. On multivariate analysis, the hazard ratios (HRs) for BF and PCSM were 0.35 (95% confidence interval [CI], 0.23-0.52; $P < .0001$) and 0.41 (95% CI, 0.23-0.75; $P < .003$), favoring CMRT. Increasing duration of ADT predicted decreased BF ($P = .04$) and PCSM ($P = .001$), which was greatest with long-term ADT (BF: HR, 0.33; $P < .0001$; 95% CI, 0.21-0.52; PCSM: HR, 0.30; $P = .001$; 95% CI, 0.15-0.6) even in the subgroup that received CMRT. **CONCLUSIONS:** In this retrospective comparison, both low-dose-rate brachytherapy boost and ADT were associated with decreased risks of BF and PCSM compared with EBRT. ***Cancer* 2013;119:681-90.** © *2012 American Cancer Society.*

**KEYWORDS:** prostatic neoplasms, brachytherapy, radiation, hormone therapy, treatment outcome.

## INTRODUCTION

Prostate cancer (PCa) is the most frequently diagnosed cancer in the United States and is the second leading cause of death.[1] Many patients with PCa have tumors with indolent behavior, but the risk of cancer-specific mortality can be high in those with high-risk disease,[2] and the management of these patients is controversial. Conventional-dose (<72 grays [Gy]) external-beam radiotherapy (EBRT), brachytherapy, and androgen-deprivation therapy (ADT) all have produced poor outcomes when used as monotherapies for high-risk PCa (HiRPCa).[4-7] In contrast, the combination of conventional-dose EBRT and ADT[6,7] has demonstrated improved overall survival in randomized clinical trials. However, a subgroup analysis of a randomized dose-escalation trial suggested that dose-escalated EBRT also reduced PCa-specific mortality (PCSM).[8] Nevertheless, the added utility of ADT after dose-escalated radiotherapy (RT) is unknown. Herein we retrospectively reviewed the results from patients with HiRPCa who were treated at 2 high-volume institutions and assessed the impact of ADT and/or low-dose-rate (LDR) brachytherapy in addition to dose-escalated EBRT on biochemical relapse and the risk of PCSM.

## MATERIALS AND METHODS

### *Patients*

An Institutional Review Board-approved, retrospective review was performed for patients with HiRPCa (defined as a prostate-specific antigen [PSA] level >20 ng/mL, or a Gleason sum of 8-10, or clinical T3-T4 tumors) who were treated

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at the Schiffler Cancer Center (SCC) or the University of Michigan (UM) with either dose-escalated EBRT or combined-modality RT (EBRT and LDR brachytherapy boost [CMRT]). Risk was also stratified using a modification of the University of California San Francisco Cancer of the Prostate Risk Assessment (CAPRA) tool, which gives points for PSA, T-classification, Gleason sum, and age. Unlike the original version,[9] the modified CAPRA score gives 0 points for any Gleason sum of 6, 1 point for any Gleason sum of 7, and 3 points for any Gleason sum of 8 to 10, with points from 0 to 9, because it does not include the "percentage positive biopsies" variable.[10]

### Treatment

The treatment techniques used by both institutions have been described elsewhere.[11,12] Briefly, all EBRT treatments used computed tomography planning with 3-dimensional or intensity-modulated RT to a minimum prescription dose of 75 to 81 Gy in fractions of 1.8 to 2.0 Gy. For EBRT, the clinical target volume typically consisted of the prostate gland and seminal vesicles with prophylactic pelvic radiotherapy. CMRT consisted of pelvic irradiation delivered either before or after permanent interstitial brachytherapy. The brachytherapy target volume was the prostate gland with or without the proximal 1.0 cm of seminal vesicles. Patients were implanted either with $^{103}$Pd (prescription dose, 73-100 Gy) or $^{125}$I (prescription dose, 108-110 Gy). ADT, consisting of a gonadotropin-releasing hormone analog alone or combined with antiandrogen, was used at the discretion of treating physicians.

### Follow-Up and Endpoints

Patients were followed with physical examinations and PSA measurements at 3-month to 6-months intervals for the first 5 years and every 6 months to 12 months thereafter. Biochemical failure (BF) was defined by the Phoenix definition.[13] PCSM was defined as death from PCa or death from any cause after the development of metastatic or castrate-resistant PCa.

### Statistical Analysis

Patients' clinical and treatment characteristics were compared using analyses of variance and chi-square tests. Univariate survival analysis was performed using with Kaplan-Meier method, and the cumulative incidence of failure was evaluated by a Fine and Gray regression analysis. Multivariate survival analysis used Fine and Gray regression analysis to account for competing causes of death and/or BF.[14] Statistical analysis was performed using MedCalc (version 11.5; MedCalc Software, Mariakerke, Belgium) or STATA (version 12.0; StataCorp; College Station, Tex).

## RESULTS

### Patients' Characteristics and Treatment

Clinical characteristics and treatment details are presented for 958 patients with HiRPCa who received treatment between 1995 and 2010 as either dose-escalated EBRT or CMRT at SCC (n = 484; EBRT, 154; CMRT, 330), or UM (n = 474; EBRT, 356; CMRT, 118) (Table 1). The median follow-up was 63.2 months (interquartile range, 35.4-99.0 months), which was not different between the EBRT and CMRT groups, and 250 patients were followed for >8 years. Patients who underwent EBRT were older and had higher pretreatment PSA levels and T-classification but lower GS compared with those who were treated with CMRT. Although the majority of patients in both groups had only 1 high-risk feature, patients in the EBRT group were twice as likely to have 2 or 3 high-risk features (32% vs 16%). Consequently, the CAPRA score was higher on average in those treated with EBRT as compared with CMRT (5.0 vs 6.0). The median prescription radiation dose to the prostate in the EBRT group was 78.3 Gy, whereas, among the patients who received CMRT, 369 received $^{103}$Pd implants, and 79 received $^{125}$I implants. There was more frequent use of ADT and for a longer duration in the EBRT group (85%; median duration, 22 months) versus those who received CMRT (76%; median duration, 12 months).

### Clinical Outcomes

BF was observed in 171 patients (18%), including 129 patients (25%) who received EBRT and 42 patients (9%) who received CMRT (chi-square statistic, 0.36; $P < .0001$). There were 261 deaths (27%), including 176 (35%) in the EBRT group and 85 (19%) in the CMRT group (chi-square statistic, 0.54; $P < .0001$); and 70 deaths (7%) were from PCa, with including 51 deaths (10%) in the EBRT group and 19 deaths (4%) in the CMRT group (chi-square statistic, 0.25; $P = .001$). The Cox proportional hazards model indicated that each point in the modified CAPRA score was related directly to an increasing risk of BF ($P < .0001$; HR, 1.51; 95% CI, 1.37-1.68) and PCSM ($P < .0001$; HR, 1.56; 95% CI, 1.33-1.82) without differences in the prognostic significance of the CAPRA score between the EBRT and CMRT groups.

### Association Between Outcomes and the Receipt of Brachytherapy

When we analyzed the treatment regimens without adjusting for other variables, there were significantly

**TABLE 1.** Patients' Clinical and Treatment Characteristics

| Characteristic | Overall, n = 958 (100%) | EBRT, n = 510 (53%) | CMRT, n = 448 (47%) | *P* |
|---|---|---|---|---|
| Follow-up, mo | | | | |
| Median [IQR], mo | 63.2 [35.4-99.0] | 62.9 [34.4-94.8] | 63.6 [38.8-103.7] | .22[a] |
| Median for those who remained alive [IQR] | 62.7 [35.3-99.8] | 62.7 [34.8-95.4] | 62.8 [38.1-105.6] | .89[a] |
| Median age [IQR], y | 70.0 [63.4-75.0] | 73.2 [67.4-78.6] | 66.0 [61.0-72.0] | < .001[a] |
| PSA | | | | |
| Median PSA [IQR], ng/mL | 13.4 [6.8-26.5] | 18.7 [8.7-30.5] | 9.9 [5.9-21.3] | < .001[a] |
| PSA level in ng/mL, % of patients | | | | |
| <10 | 40 | 31 | 50 | < .001[b] |
| 10-20 | 21 | 21 | 22 | |
| 20-50 | 31 | 37 | 24 | |
| >50 | 8 | 11 | 4 | |
| Tumor classification, % of patients | | | | < .0001[b] |
| T1-T2a | 56 | 49 | 64 | |
| T2b-T2c | 28 | 28 | 27 | |
| T3-T4 | 16 | 23 | 9 | |
| Gleason sum, % of patients | | | | < .0001[b] |
| 2-6 | 8 | 9.5 | 5 | |
| 7 | 18 | 22 | 14.5 | |
| 8 | 42 | 36.5 | 48 | |
| 9-10 | 32 | 32 | 32.5 | |
| No. of high-risk features, % of patients | | | | < .0001[b] |
| 1 | 75 | 68 | 84 | |
| 2 | 20 | 25 | 14 | |
| 3 | 5 | 7 | 2 | |
| Median modified CAPRA score [IQR] | 5 [4-6] | 6 [5-7] | 5 [4-6] | < .001[a] |
| ADT: No. of patients (%) | | | | .0002[b] |
| No | 180 (19) | 74 (15) | 106 (24) | |
| Yes | 778 (81) | 436 (85) | 342 (76) | |
| ADT duration, mo | | | | |
| Median [IQR] | 12 [8-24] | 22 [8-28] | 12 [8-24] | |
| <12 | | 140 (32) | 123 (36) | < .0001[b] |
| 12-<24 | | 91 (21) | 104 (30) | |
| ≥24 | | 202 (47) | 115 (34) | |
| Median EBRT dose [IQR], Gy | | 78.3 [77.0-80.0][c] | 45.0 [45.0-50.4][d] | |
| Pelvic radiotherapy: No. of patients (%) | 937 (98) | 488 (96) | 448 (100) | < .0001[b] |
| Brachytherapy boost | | | | |
| $^{125}$I implants: No. of patients (%) | | | 79 (17) | |
| Median prescribed dose [IQR], Gy | | | 108 [108-108] | |
| Median D90 [IQR], Gy | | | 112.6 [101.8-124.7] | |
| $^{103}$Pd implants: No. of patients (%) | | | 369 (83) | |
| Median prescribed dose [IQR], Gy | | | 100 [100-100] | |
| Median D90 [IQR], Gy | | | 120.4 [111.2-130.3] | |

Abbreviations: ADT, androgen-deprivation therapy; CAPRA, Cancer of the Prostate Risk Assessment; CMRT, combined-modality radiotherapy; D90, minimal dose to 90% of the planned target volume; EBRT, external-beam radiotherapy; Gy, grays; IQR, interquartile range.
[a] This *P* value was determined using analysis of variance.
[b] This *P* value was determined using the chi-square test.
[c] This was the prescribed dose to the prostate gland.
[d] This was pelvic EBRT.

higher rates of BF and PCSM in the EBRT group. The 5-year and 8-year rates of BF were 27% (standard error, 24%-29%) and 40% (interquartile range, 36%-43%) in the EBRT group compared with 11% (standard error, 9%-13%) and 13% (standard error, 11%-15%) in the CMRT group ($P < .0001$; HR, 0.30; 95% CI, 0.22-0.40) (Fig. 1A); and the 5-year and 8-year PCSM rates were 6% (standard error, 5%-7%) and 14% (standard error, 12%-16%) in patients who received EBRT and 3% (standard error, 2%-4%) and 7% (standard error, 6%-9%) in patients who received CMRT ($P = .003$; HR, 0.39; 95% CI, 0.25-0.63) (Fig. 1B). The correlation between CMRT and better outcome also was present across the different definitions of high-risk disease (Table 2). Patients who received CMRT were younger and likely had less comorbid medical illness than those who received EBRT; therefore, the cumulative incidences of BF and PCSM also were evaluated as a function of treatment

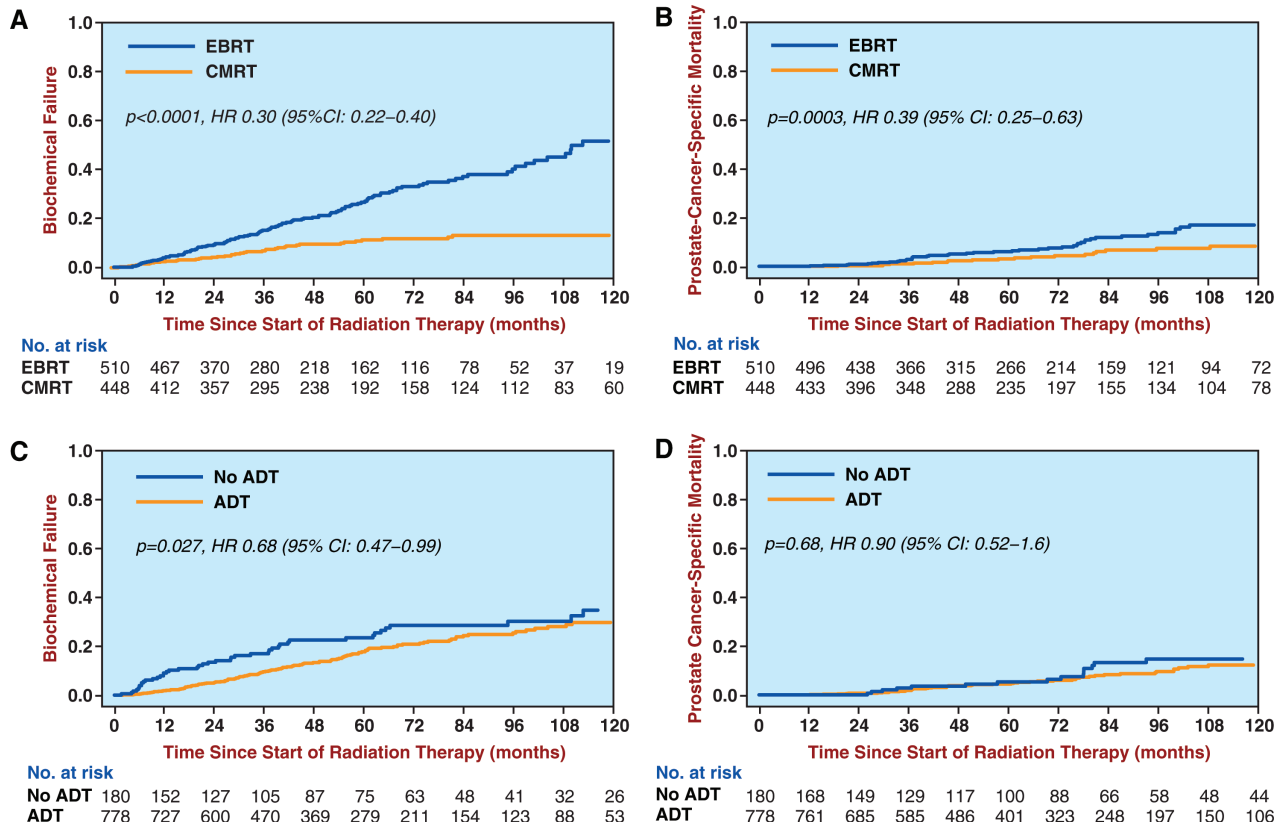


**Figure 1.** These Kaplan-Meier plots illustrate (A,C) biochemical failure and (B,D) prostate cancer-specific mortality as a function of radiotherapy regimen, including (A,B) dose-escalated external-beam radiotherapy (EBRT) versus combined modality radiotherapy (CMRT) and (C,D) the receipt of androgen-deprivation therapy (ADT) (none vs any). HR indicates hazard ratio; CI, confidence interval.

**TABLE 2.** Freedom From Biochemical Failure and Prostate Cancer-Specific Survival Across Different High-Risk Features

| | Rate (Range), % | | | | | |
|---|---|---|---|---|---|---|
| | T3-T4 Classification, n = 164 | | PSA >20 ng/mL, n = 373 | | Gleason Sum 8-10, n = 713 | |
| Regimen | 5-Year FFBF | 5-Year PCSS | 5-Year FFBF | 5-Year PCSS | 5-Year FFBF | 5-Year PCSS |
| EBRT | 59 (54-64) | 90 (87-93) | 69 (66-72) | 95 (93-97) | 71 (68-74) | 92 (90-94) |
| CMRT | 80 (73-87) | 97 (95-99) | 87 (83-91) | 98 (97-99) | 89 (87-91) | 96 (95-97) |
| *P* | .0031 | .05 | < .0001 | .01 | < .0001 | .0002 |
| HR [95% CI] | 0.33 [0.19-0.57] | 0.27 [0.11-0.65] | 0.29 [0.20-0.44] | 0.35 [0.18-0.68] | 0.32 [0.22-0.46] | 0.35 [0.20-0.60] |

Abbreviations: CI, confidence interval; CMRT, combined-modality radiotherapy; EBRT, external-beam radiotherapy; FFBF, freedom from biochemical failure; HR, hazard ratio; PCSS, prostate cancer-specific survival; PSA, prostate-specific antigen.

regimen using Fine and Gray regression adjusted for the competing risk of non-PCa death. The HRs obtained from the cumulative incidence analysis were 0.35 ($P < .0001$; 95% CI, 0.25-0.49) for BF and 0.45 ($P = .003$; 95% CI, 0.27-0.77) for PCSM, both of which were similar to the incidence observed in Kaplan-Meier analysis.

### *Association Between Outcomes and the Receipt of Androgen-Deprivation Therapy*

Unlike patients in the CMRT group, who generally had lower risk disease compared with patients in the EBRT group, those who received ADT, on average, had higher risk disease than those who did not receive ADT (CAPRA score, 5.0 vs 5.6; $P < .001$, chi-square test). Moreover, the

patients who received ADT for a longer duration had higher CAPRA scores than those who received ADT for shorter durations ($P < .0001$; data not shown). Despite this difference, the receipt of ADT was associated with a lower BF rate in Kaplan-Meier analysis: The 5-year and 8-year BF rates were in 23% (standard error, 20%-26%) and 31% (standard error, 27%-35%), respectively, without ADT compared with 18% (standard error, 16%-20%) and 26% (standard error, 24%-28%), respectively, with ADT ($P = .0027$; HR, 0.68; 95% CI, 0.47-0.99) (Fig. 1C). However, a trend (but no statistical difference) was observed in the PCSM rate with the receipt ADT, which was 5% (standard error, 3%-7%) at 5 years and 15% (standard error, 10%-20%) at 8 years without ADT compared with 4% (standard error, 3%-5%) at 5 years and 9% (standard error, 7%-11%) at 8 years with ADT ($P = .68$; HR, 0.90; 95% CI, 0.52-1.60) (Fig. 1D). The HRs derived from the Fine and Gray cumulative regression analysis adjusted for the competing risk of death were similar at 0.63 ($P = .008$; 95% CI, 0.44-0.89) for BF and 0.75 ($P = .30$; 95% CI, 0.44-1.29) for PCSM.

### *The Influence of Treatment on Outcomes Adjusted for the Number of High-Risk Features*

The EBRT group had twice as many patients who had >1 high-risk feature compared with the CMRT group, whereas the number of these features was prognostic for both BF and PCSM (Fig. 2A,B). In an exploratory subgroup analysis, after adjusting for the number of high-risk features by clustering into a "low" high-risk group (a single high-risk feature) and a "high" high-risk group (>1 high-risk feature), we observed that CMRT had a lower BF rate in both groups ("low" high-risk group: HR, 0.44; $P < .0001$; 95% CI, 0.28-0.69; "high" high-risk group: HR, 0.41; $P = .004$; 95% CI, 0.22-0.75) (Fig. 2C,E). CMRT, however, was not associated with significantly lower PCSM in either the "low" high-risk group ($P = .17$; HR, 0.61; 95% CI, 0.30-1.23; crude PCSM, 5%; 33 of 722 patients) nor the "high" high-risk group ($P = .21$; HR, 0.57; 95% CI, 0.24-1.38; crude PCSM, 16%; 37 of 237 patients) (Fig. 2D,F).

### *Multivariate Analysis for Biochemical Failure and Prostate Cancer-Specific Mortality: Demonstrated Improvements With Combined-Modality Radiotherapy and Androgen-Deprivation Therapy*

Given the imbalance of clinical risk features as well as competing causes of death (because more men died of causes other than PCa), multivariate Fine and Gray cumulative regression analysis was performed controlling for age, PSA, T-classification, Gleason sum, RT regimen, and both the receipt and duration of ADT (Table 3). Models initially were carried out for all patients and then were run separately in those who received EBRT and those who received CMRT. Older age led to decreased risks of both BF and PCSM; whereas increasing PSA, T-classification, and Gleason sum all were associated with worse BF and PCSM, with the greatest risk associated with a Gleason sum of 9 or 10 (Table 3). The receipt of brachytherapy was correlated with a 65% relative reduction in BF ($P < .0001$; HR, 65; 95% CI, 0.23-0.52) and a 59% relative reduction in PCSM ($P = .004$; HR, 0.41; 95% CI, 0.23-0.75). Similarly, the receipt of ADT was correlated with lower BF, and a more favorable HR was observed with each incremental increase in ADT duration (<12 months, 12-<24 months, and ≥24 months) that was statistically significant for each group but greatest for those who received ≥24 months of ADT ($P < .0001$; HR, 0.33; 95% CI, 0.21-0.52). Increasing duration of ADT also was associated with lower PCSM; however, only those who received ADT for ≥24 months demonstrated a statistically significant reduction in PCSM ($P = .001$; HR, 0.30; 95% CI, 0.15-0.60). Graphic representations are presented for the adjusted impact of CMRT on BF (Fig. 3A) and PCSM (Fig. 3B), and the impact of ADT duration is illustrated for BF (Fig. 3C) and PCSM (Fig. 3D). Repeating these analyses with ADT as a continuous variable revealed that each 1-month increase in the duration of ADT was associated with lower BF (HR, 0.98; $P = .04$; 95% CI, 0.97-1.0) and PCSM (HR, 0.97; $P = .001$; 95% CI, 0.95-0.99). In further subgroup analyses, long-term ADT (≥24 months) was associated with both reduced BF (HR, 0.37; $P < .0001$; 95% CI, 0.21-0.64) and reduced PCSM (HR, 0.25; $P = .001$; 95% CI, 0.11-0.56) for those who received EBRT, and it was associated with reduced BF (HR, 0.21; $P = .003$; 95% CI, 0.08-0.58) in those who received CMRT. However, there was not a statistically significant reduction in PCSM in the subgroup of patients who received CMRT with the addition of ADT assessed either as a categoric variable (HR, 0.54; $P = .42$; 95% CI, 0.12-2.2) or as a continuous variable (HR, 0.97; $P = .20$; 95% CI, 0.92-1.02), although the HRs were very similar to those observed for EBRT.

Finally, to control for potential institutional differences, treating institution was included as a variable. Differences between institutions were not statistically significant ($P \geq .1$ for BF and PCSM; data not shown); and, when treating institution was included in the multivariate analyses, the HRs favoring CMRT for BF ($P = .0008$; HR, 0.43; 95% CI, 0.26-0.70) and PCSM ($P = .038$; HR, 0.47; 95% CI, 0.23-0.95) were similar to

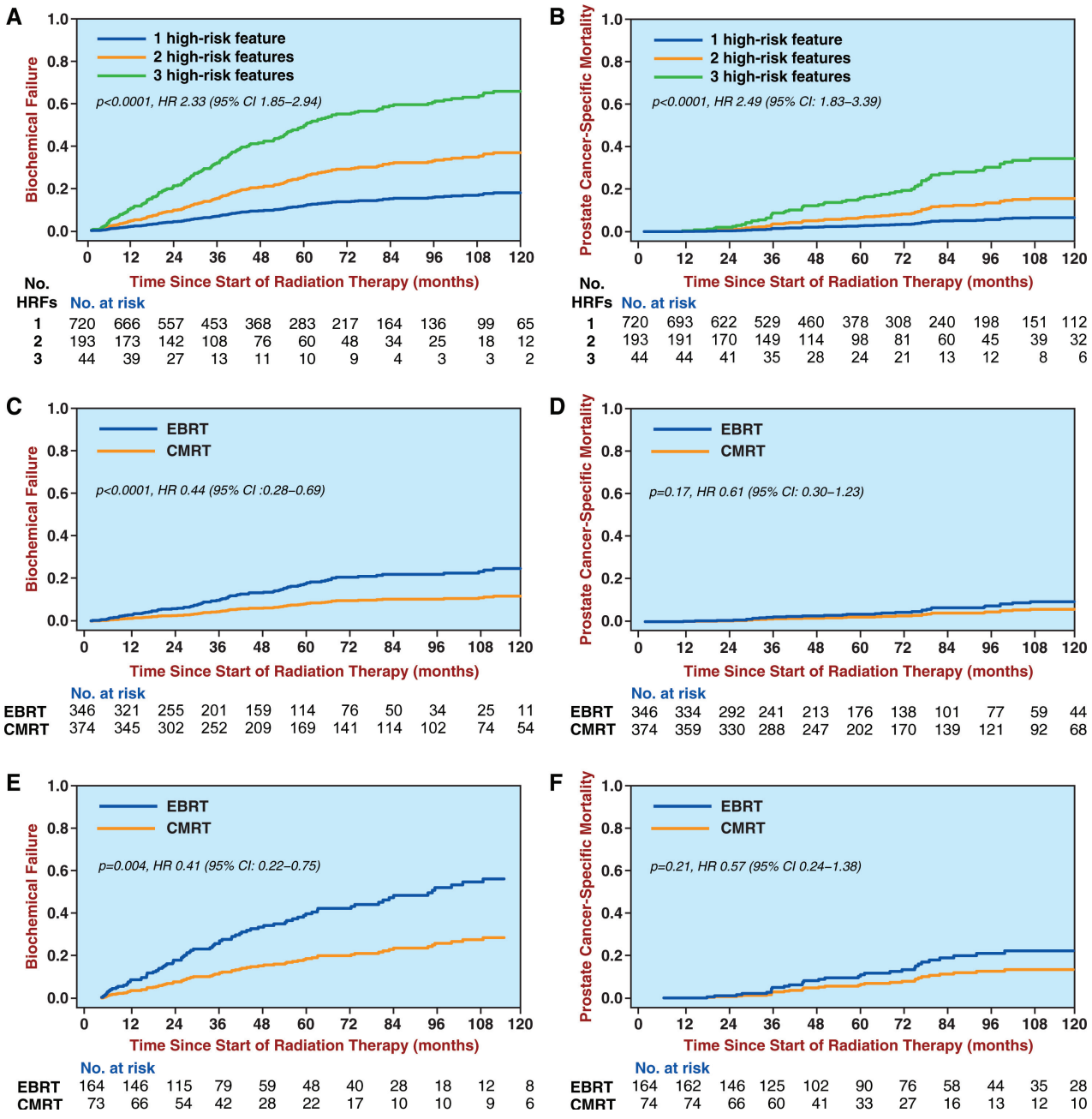


**Figure 2.** These plots illustrate the cumulative incidence of (A,C,E) biochemical failure and (B,D,F) prostate cancer-specific mortality according to (A,B) the number of high-risk features (HRFs) and for (C,D) "low" high-risk patients (with 1 HRF) and (E,F) "high" high-risk patients (with 2 or 3 HRFs). EBRT indicates external-beam radiotherapy; CMRT, combined-modality radiotherapy; HR, hazard radio; CI, confidence interval.

the HRs observed in the analyses that did not control for the treating institution.

## DISCUSSION

In patients with HiRPCa, randomized trials have demonstrated that long-term ADT added to conventional-dose EBRT improves relapse-free survival, PCSM, and overall survival.[6,7] In separate trials, dose-escalated RT demonstrated better biochemical recurrence-free survival[8,15] and, recently, in an unplanned subgroup analysis, better disease-specific survival in patients with HiRPCa.[8] However, it remains unclear whether ADT still improves outcomes after dose-escalated EBRT or whether further escalation of the RT

**TABLE 3.** Multivariate Analysis of Clinical Outcomes in All Patients With High-Risk Prostate Cancer

| | Biochemical Failure | | | Prostate Cancer-Specific Mortality | | |
|---|---|---|---|---|---|---|
| Variable | HR | 95% CI | *P* | HR | 95% CI | *P* |
| Age (continuous) | 0.97 | 0.95-0.99 | .001 | 0.97 | 0.95-0.99 | .016 |
| PSA (log) | 2.8 | 1.8-4.5 | <.0001 | 2.5 | 1.4-4.4 | .001 |
| Tumor classification | | | | | | |
| T1-T2a | Reference | | | Reference | | |
| T2b-T2c | 1.3 | 0.90-2.0 | 0.16 | 2.2 | 1.2-4.1 | .016 |
| T3-T4 | 2.1 | 1.5-3.2 | <.0001 | 2.5 | 1.2-4.7 | .014 |
| Gleason sum | | | | | | |
| 2-6 | Reference | | | Reference | | |
| 7 | 2.0 | 1.1-3.6 | .028 | 5.6 | 0.75-41 | .092 |
| 8 | 2.7 | 1.4-5.1 | .003 | 8.9 | 1.2-64 | .03 |
| 9-10 | 3.4 | 1.7-6.7 | <.0001 | 28 | 3.9-195 | .001 |
| Regimen[a] | | | | | | |
| EBRT | Reference | | | Reference | | |
| CMRT | 0.35 | 0.23-0.52 | <.0001 | 0.41 | 0.23-0.75 | .004 |
| ADT duration, mo[a] | | | | | | |
| None | Reference | | | Reference | | |
| <12 | 0.60 | 0.39-0.92 | .019 | 0.56 | 0.30-1.1 | .079 |
| 12-<24 | 0.44 | 0.25-0.74 | .002 | 0.53 | 0.25-1.2 | .11 |
| ≥4 | 0.33 | 0.21-0.52 | <.0001 | 0.30 | 0.15-0.60 | .001 |

Abbreviations: ADT, androgen-deprivation therapy; CI, confidence interval; CMRT, combined-modality radiotherapy; EBRT, external-beam radiotherapy; HR, hazard ratio; PSA, prostate-specific antigen..

[a] The interaction terms between receipt of ADT (yes vs. no) and treatment regimen (EBRT vs CMRT) as well as ADT duration and treatment regimen also were evaluated in biochemical failure and prostate cancer-specific mortality models. In all analyses, the interaction terms were not statistically significant (data not shown) and were not included in the final models.

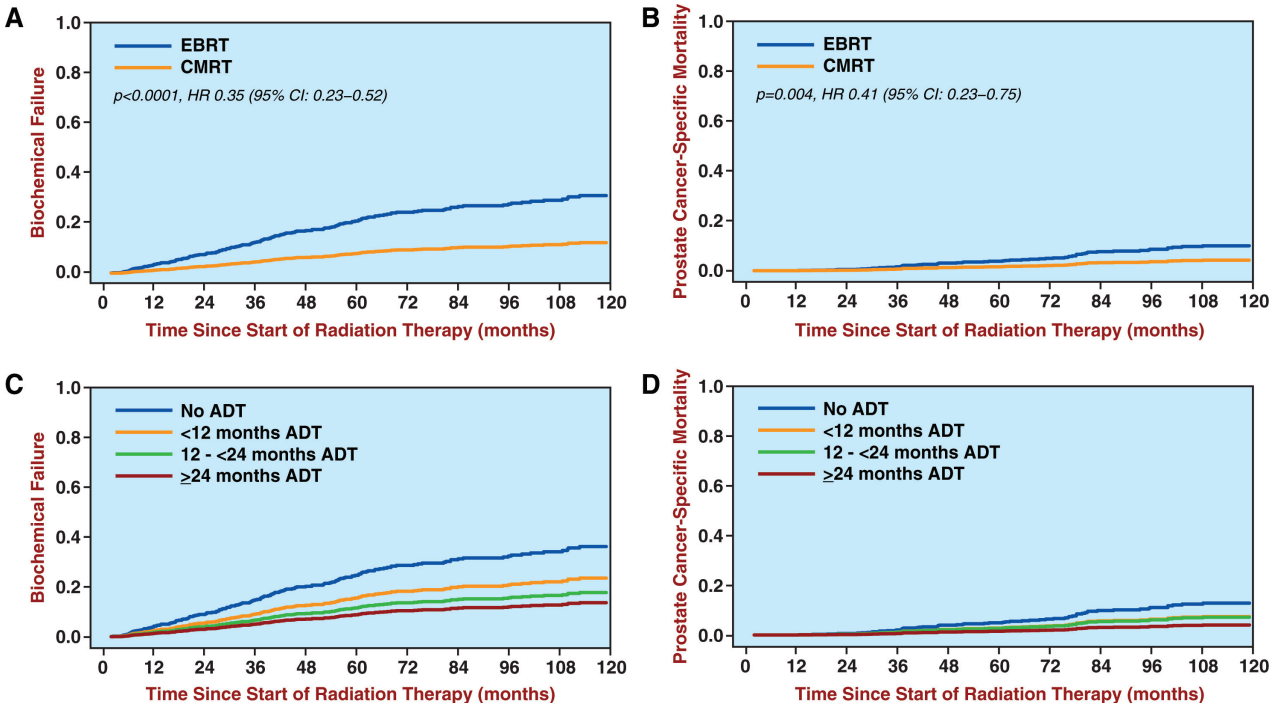


**Figure 3.** These plots illustrate cumulative incidence according to the multivariate model for (A) biochemical failure (BF) and (B) prostate cancer-specific mortality (PCSM) for all patients and all durations of androgen-deprivation therapy (ADT) and controlling for ADT duration for (C) BF and (D) PCSM for all patients. EBRT indicates external-beam radiotherapy; CMRT, combined-modality radiotherapy; HR, hazard radio; CI, confidence interval.

dose through the addition of brachytherapy to dose-escalated EBRT provides any benefit.

The current retrospective analysis is one of the largest to date investigating patients with HiRPCa who received dose-escalated RT or CMRT. The treatments were not allocated randomly, which is a significant limitation. Consequently, the patients who received EBRT were older, had more advanced disease, and received ADT more frequently and for a longer duration than the patients who received CMRT. The CAPRA score for the EBRT group was 1 point higher than for the CMRT group, which would translate into approximately 1.5-fold higher rates of both BF and PCSM.[10] In reality, the BF and PCSM rates were 2.9-fold and 2.2-fold higher in the EBRT group, suggesting that, after adjusting for risk factors, the type of RT received may explain the difference.

One possible explanation for better efficacy of CMRT is the higher biologically effective dose of RT that can be achieved with a brachytherapy boost. For example, the 2-Gy per fraction equivalent dose of combining 45 Gy EBRT and 112 Gy of $^{125}$I is 106 Gy,[16] and meta-analysis of EBRT dose-escalation trials revealed that every added 1 Gy yielded a 2.2% gain in the 8-year rate of freedom from BF.[17] Assuming a linear dose-response relation for doses $>$80 Gy, an additional 12 to 13 Gy on top of the median 78 Gy would be required to account for the 27% difference in the 8-year freedom from BF rate observed between the 2 subsets of patients in our study, which fits within the presumed additional dose delivered by LDR brachytherapy.

Is it reasonable to assume that LDR brachytherapy also would improve PCSM? Two recent phase 3 studies demonstrated that improved local control by adding EBRT to life-long ADT improved freedom from BF, PCSM, and OS in patients with locally advanced PCa.[5,18] In addition, 3 randomized trials of adjuvant EBRT after radical prostatectomy for PCa with high-risk features also demonstrated a 50% relative reduction in BF[19-21] and a 9% improvement in 10-year OS in the study with the longest follow-up.[19] Thus, even for HiRPCa in 5 randomized trials, improvements in local control with the addition of RT demonstrated improved BF, and 3 of these trials demonstrated improvements in PCSM and OS. Consequently, is it possible that the local failure rate after dose-escalated RT is decreased with a brachytherapy boost? Two additional randomized studies did demonstrate significant improvements in BF with prostate brachytherapy added to EBRT (although the control arm was not dose-escalated RT).[22,23] In addition, the positive biopsies percentages after conventional-dose EBRT have been as high as 50%, which are reduced with either dose-escalated EBRT or with ADT added to EBRT, but still are in excess of 20%.[24] In contrast, biopsy-proven local failure rates after combined ADT, EBRT, and LDR brachytherapy have been $<$10%, even in patients with HiRPCa.[25] Thus, the improvement in PCSM observed with CMRT in the current study is plausible within the context of previous improvements observed with RT in localized or locally advanced PCa.

In addition, in the current analysis, the receipt of ADT also was associated with lower BF, which became greater with increasing duration of ADT and was consistent across both RT modalities. Longer duration ADT ($\geq$24 months) also improved PCSM in all patients and in those who received EBRT alone, but not when ADT was analyzed separately in the CMRT group. However, the low absolute PCSM in this group (19 deaths; 4%) makes it difficult to demonstrate an improvement, especially because 76% of patients in the CMRT group had already received ADT for a median of 12 months. In any case, in this series, we observed no evidence of the worse outcomes from ADT combined with brachytherapy that have been reported by others.[26] The reduction in PCSM with ADT observed in the current study translates into a 40% relative improvement in PCSM (95% CI, 0.3%-1.1%) for short-duration ADT ($<$12 months) and 70% improvement (95% CI, 0.15%-0.60%) for long-duration ADT ($\geq$24 months), both of which are similar in magnitude to what was observed with ADT duration in a meta-analysis of 4128 patients who received treatment in the 1980s and 1990s on 4 Radiation Therapy Oncology Group trials with conventional-dose RT.[27] However, the overall rates of PCSM were lower in the current study, which may reflect an improved outcome with dose-escalated EBRT and a lower overall risk of PCa in this contemporary cohort.

Although it is retrospective and nonrandomized in nature, this study comprises 1 of the largest series to date of patients with HiRPCa who received treatment using modern RT techniques and doses. Comorbid illnesses were not routinely or uniformly collected across all treatment sites and, as such, could not be evaluated. Given the younger age and likely lower comorbid illnesses in the brachytherapy group, we chose not to evaluate all-cause mortality, because we were not able to appropriately control for comorbid illness. Although we tried to take into account all measured confounders, including the treating institution, in the multivariate analysis, it is likely that other factors, such as prostate size, urinary function, and medical comorbidities, contributed to differences between groups that would temper our conclusions; nevertheless,

the outcomes in this study were similar to previous reports for either RT modality.[15,25,28] Moreover, a recent analysis of brachytherapy-based outcomes also demonstrated an association with decreased PCSM when both EBRT and ADT were added to LDR brachytherapy.[28] In addition, an analysis of the Surveillance, Epidemiology, and End Results (SEER) database revealed that the rates of CMRT use for the treatment of HiRPCa have increased 6-fold since 1988; however, only 19.4% of patients with HiRPCa received this treatment between 1988 and 2000; although in that SEER analysis, the PCSM rate was lower for those who received brachytherapy-based treatment.[29] In contrast, an analysis of treatment trends in >10,000 men with HiRPCa who were treated in academic and community urology-based practices revealed that the majority of patients received possibly less effective monotherapy approaches, including a high proportion that received primary ADT, with an increasing trend in the receipt of primary ADT (from 18% to 29%) over the 10-year study period, and brachytherapy rarely was used.[3] The current study also did not address the toxicity of these treatment; however results from the Radiation Therapy Oncology Group RTOG 00-19 study suggest a higher rate of genitourinary toxicity with the addition of brachytherapy to EBRT in a multi-institutional phase 2 study.[30]

In conclusion, the results from this multi-institutional, retrospective study suggest that, for patients with HiRPCa, the receipt of an LDR brachytherapy boost decreased the risk of BF and PCSM compared with dose-escalated EBRT. Furthermore, even with dose-escalated EBRT or combination therapy, ADT decreased BF and PCSM in a duration-dependent fashion, and the greatest benefit was observed for long-term ADT. Validation of these findings in the University of British Columbia Androgen Suppression Combined with Elective Nodal and Dose-Escalated RT trial, which is comparing dose-escalated EBRT (78 Gy) versus CMRT plus $^{125}$I LDR boost (both with 12 months of ADT), may significantly change the treatment standard for patients with HiRPCa.[31]

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## CONFLICT OF INTEREST DISCLOSURES

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