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Clinical Investigation

Brachytherapy Improves Biochemical Failure—Free Survival in Low- and Intermediate-Risk Prostate Cancer Compared With Conventionally Fractionated External Beam Radiation Therapy: A Propensity Score Matched Analysis

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Summary

Propensity score matched analysis was used to assess the biochemical failure—free survival (bFFS) and overall

Purpose: To compare, in a retrospective study, biochemical failure-free survival (bFFS) and overall survival (OS) in low-risk and intermediate-risk prostate cancer patients who received brachytherapy (BT) (either low-dose-rate brachytherapy [LDR-BT] or high-dose-rate brachytherapy with external beam radiation therapy [HDR-BT+EBRT]) versus external beam radiation therapy (EBRT) alone.

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survival (OS) of prostate cancer patients treated with external beam radiation therapy (EBRT) or brachytherapy (BT). Low-dose-rate BT was compared with EBRT in low- and intermediate-risk matched cohorts, whereas combination high-dose-rate BT with EBRT was compared with EBRT in an intermediate-risk matched cohort. Our results demonstrated superior bFFS in all BT-treated patients, with no difference in OS.

Methods and Materials: Patient data were obtained from the ProCaRS database, which contains 7974 prostate cancer patients treated with primary radiation therapy at four Canadian cancer institutions from 1994 to 2010. Propensity score matching was used to obtain the following 3 matched cohorts with balanced baseline prognostic factors: (*1*) low-risk LDR-BT versus EBRT; (*2*) intermediate-risk LDR-BT versus EBRT; and (*3*) intermediate-risk HDR-BT+EBRT versus EBRT. Kaplan-Meier survival analysis was performed to compare differences in bFFS (primary endpoint) and OS in the 3 matched groups.

Results: Propensity score matching created acceptable balance in the baseline prognostic factors in all matches. Final matches included 2 1:1 matches in the intermediate-risk cohorts, LDR-BT versus EBRT (total n = 254) and HDR-BT+EBRT versus EBRT (total n = 388), and one 4:1 match in the low-risk cohort (LDR-BT:EBRT, total n = 400). Median follow-up ranged from 2.7 to 7.3 years for the 3 matched cohorts. Kaplan-Meier survival analysis showed that all BT treatment options were associated with statistically significant improvements in bFFS when compared with EBRT in all cohorts (intermediate-risk EBRT vs LDR-BT hazard ratio [HR] 4.58, $P = .001$; intermediate-risk EBRT vs HDR-BT+EBRT HR 2.08, $P = .007$; low-risk EBRT vs LDR-BT HR 2.90, $P = .004$). No significant difference in OS was found in all comparisons (intermediate-risk EBRT vs LDR-BT HR 1.27, $P = .687$; intermediate-risk EBRT vs HDR-BT+EBRT HR 1.55, $P = .470$; low-risk LDR-BT vs EBRT HR 1.41, $P = .500$).

Conclusions: Propensity score matched analysis showed that BT options led to statistically significant improvements in bFFS in low- and intermediate-risk prostate cancer patient populations. © 2015 Elsevier Inc.

Introduction

In Canada, external beam radiation therapy (EBRT) and brachytherapy (BT) are standard primary radiation therapy (RT) treatment options provided to patients with localized prostate cancer (1). The Genitourinary Radiation Oncologists of Canada (GUROC) prostate cancer risk-stratification system was established to help clinicians predict risk of disease recurrence and tailor appropriate therapies for patients (2, 3). Permanent seed low-dose-rate brachytherapy (LDR-BT) is generally given as an alternative to EBRT for low- or intermediate-risk patients, whereas high-dose-rate brachytherapy boost delivered concurrently with EBRT (HDR-BT+EBRT) has been explored for patients with intermediate- to high-risk prostate cancer (1).

To date, several phase 3 randomized, controlled trials have demonstrated the biochemical control benefits of dose-escalated EBRT (4-10). However, the number of definitive randomized studies directly comparing the effectiveness of EBRT versus BT treatment options is sparse (11, 12). The rapid adoption of new RT practices as well as patient preference toward more convenient BT treatments are proposed explanations for the lack of comparative RT trials (13). A large number of retrospective studies have attempted to compare the treatment effectiveness of 2 or more RT modalities (14-33). However, interpretation of this retrospective evidence can be challenging because very few studies make direct comparisons in homogenous GUROC low- or intermediate-risk patient populations. Additionally, unequal use of androgen deprivation therapy in compared RT treatment groups, which has demonstrated potential survival benefits for patients at high risk of disease recurrence (34-38), may also further confound results from these nonrandomized studies.

Propensity score (PS) matching is an analytical tool that has been demonstrated to reduce bias in observational studies by balancing known confounding variables in compared treatment groups (39-41). Propensity score analysis has been used in a variety of oncology research, including studies on cancers of the prostate, lung, breast, colon, and brain (20, 42-47). The goal of this study was to report the results of an EBRT versus BT, PS matched analysis. Low-dose-rate BT was compared with EBRT in separate low- and intermediate-risk matched cohorts, whereas combination HDR-BT+EBRT was compared with EBRT alone in an additional intermediate-risk matched cohort. The outcomes of biochemical failure−free survival (bFFS) and overall survival (OS) were compared.

Methods and Materials

Creation of the ProCaRS database

The Prostate Cancer Risk-Stratification (ProCaRS) database provided the retrospective patient data for this study. The ProCaRS database contains primary RT outcome data on 7974 prostate cancer patients treated from 1994 to 2010 at four Canadian cancer institutions (Princess Margaret Hospital, Toronto, Canada; I'Université Laval, Quebec, Canada; McGill University, Montréal, Canada; and the British Columbia Cancer Agency, British Columbia, Canada). The

creation of the ProCaRS database was sanctioned by the GUROC in an attempt to advance research in prostate cancer risk stratification and outcomes (48, 49). Details of the ProCaRS database ethics approval, construction, quality assurance process, and results of recursive partitioning risk-stratification analysis and Cox multivariable regression outcome analysis have been previously described (48, 49).

Patient selection

The formation of analysis cohorts, including all patient inclusions and exclusions, were established as a result of the PS modeling process. The GUROC 3 risk-category system was used to stratify patients as low- or intermediate-risk (2). Treatment comparisons in the high-risk cohort were abandoned owing to low numbers of patients receiving BT (n = 21) compared with EBRT (n = 268) in the ProCaRS database (48, 49). Patients with T2b T stage with missing data on TNM staging year were removed before PS matching to ensure all T2b patients were properly identified with unilateral or palpable bilateral disease (50-52). Restricting RT start dates was viable in the low-risk cohort because all EBRT treatments (n = 104) occurred during the years 1999 to 2006, with ample LDR-BT treatments (n = 1716) given over that same time frame. A wide range of RT start dates made restricting treatment years impossible in the intermediate-risk matches (LDR-BT: 1996-2010; EBRT: 1999-2006; and HDR-BT+EBRT: 2001-2010). All intermediate-risk patients with Gleason totals ranging from 2 to 5 received BT and were removed to avoid difficulties in PS model convergence.

Because of the heterogeneity of RT treatment techniques and dose regimens provided by the various cancer institutions, only patients receiving adequate dose escalation in the EBRT cohort, with either 3-dimensional conformal therapy or intensity modulated radiation therapy, receiving either $\geq$70 Gy (low risk) or $\geq$74 Gy (intermediate risk) were eligible for PS matching. All matched LDR-BT patients were restricted to ^{125}I permanent seed implantation to a minimum dose of 144 Gy. The intermediate-risk HDR-BT+EBRT matched cohort was restricted to patients who received ^{192}Ir HDR-BT with concurrent EBRT using one of the 5 following dose regimens: (*1*) 10 Gy HDR-BT + 50 Gy EBRT; (*2*) 15 Gy HDR-BT + 40 Gy EBRT; (*3*) 15 Gy HDR-BT + 44 Gy EBRT; (*4*) 19 Gy HDR-BT + 45 Gy EBRT; and (*5*) 20 Gy HDR-BT + 44 Gy EBRT. All patients who received androgen deprivation therapy were excluded before PS matching and analysis. A detailed description of the prematch patient selection process is outlined in Figs. E1-E3 (available online at www.redjournal.com).

Endpoints

The outcome of bFFS was defined as the time from initiation of RT to the date of last follow-up or biochemical failure, whichever came first, according to the American Society for Radiation Oncology–Radiation Therapy Oncology Group Phoenix II definition of a prostate-specific antigen (PSA) rise by 2 ng/mL or more above the nadir PSA (53). This was the primary endpoint of the study. Technical biochemical failures due to benign PSA bounces were adjusted using a quality assurance procedure whereby patients with PSA levels that returned to an absolute level of 0.5 ng/mL or less without intervention were considered not to have had a biochemical failure (49, 54, 55). Patients with PSA levels >0.5 ng/mL after biochemical failure were still considered to have biochemically failed. Both external beam and brachytherapy patients were subjected to the same biochemical failure rules, to ensure consistent comparisons. Overall survival was defined as the time from initiation of RT to the date of last follow-up or death (any cause), whichever came first.

PS matching

Multivariable logistic regression was used to generate propensity scores for all match eligible patients (39), predictive of treatment assignment (LDR-BT vs EBRT or HDR-BT+EBRT vs EBRT), and adjusting for a priori identified baseline prognostic factors known to predict prostate cancer survival outcomes (age, baseline PSA, T stage, Gleason total) (1-3). All variables were included in the models as main effects with no interactions. The covariates age and baseline PSA were included as continuous variables, whereas the covariates T stage, Gleason total, and RT start year (used in the low-risk model only) were included in the models as categorical variables.

The PS-matched pairs were generated using nearest-neighbor matching methodology without replacement (39). One-to-one matches were explored before one-to-many matches. If a large discrepancy in sample size between RT groups existed, matched ratios up to 1:4 were explored. Maximum ratios beyond 1:4 were not attempted because the gain in statistical power has been shown to be insignificant (56). Currently no consensus recommendation for the most appropriate caliper width for PS matching exists (57-59). For this study, a previously validated caliper of 0.2 of the standard deviation of the logit of the PS was initially used to generate matches (60). These initial matches were compared concurrently with caliper matches on the PS scale, which included a narrow, previously utilized, caliper width of 0.025 (44), a moderate caliper width of 0.05, and a generous caliper width of 0.1. If a suitable match was not found using these initial calipers, a narrower caliper of 0.01 of the PS was explored.

After PS matching, baseline covariate balance was assessed statistically using the standardized difference (S.D.), which unlike standard *P* value testing has the advantage of being unaffected by sample size (61). For this study, a recommended S.D. cut-point of >0.10 (62) was used to indicate significant imbalance among baseline covariates. Optimal matches used in final analyses were chosen on the basis of both the balance assessment and the sample size (power). Detailed summaries of each caliper match explored are shown in Tables E1-E11 (available online at www.redjournal.com).

Statistical analysis

Once final matches were obtained in each of the compared cohorts, pre- and postmatch descriptive statistics for baseline patient, tumor, and treatment characteristics were assessed. Kaplan-Meier survival curves stratified by treatment group were generated for bFFS and OS. Owing to the lack of independence in the PS matched cohorts, Cox proportional hazard regression adjusted for clustering (stratified by matched pairs) was used to generate the reported P values, instead of the log−rank test. For cases of violation of the proportionality assumption, comparisons were made using an extended Cox model incorporating a time-dependent covariate.

Power and sample size

The sample sizes for each comparison were determined through the PS match selection process and were not considered before matching. Once final matches were obtained, the minimum hazard ratios required for a statistical power $\geq$0.8 for each match were calculated. All power calculations used literature-reported 5-year and $\geq$7-year bFFS actuarial percentages for prostate cancer patients treated with EBRT and assumed that BT options would provide superior biochemical control. Table E12 (available online at www.redjournal.com) shows the minimum hazard ratios in favor of BT required for statistical power $\geq$0.8 in each final matched comparison. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary NC), using 2-sided statistical testing at the .05 significance level.

Results

Propensity score matching brought adequate balance to all variables included in each matching procedure. Before matching, we identified 1716 LDR-BT patients and 104 EBRT patients eligible for low-risk PS matching; and 231 LDR-BT patients, 265 EBRT patients, and 390 HDR-BT+EBRT patients eligible for intermediate-risk PS matching. Final PS matched cohorts included 2 1:1 intermediate-risk matches, LDR-BT versus EBRT (total n=254) and HDR-BT+EBRT versus EBRT (total n=388); and a 4:1 (LDR-BT:EBRT) low-risk match (total n=400). Matched low-risk EBRT patients (n=80) received total doses of 70 Gy (21.3%), 72.5 Gy (1.3%), 74 Gy (18.8%), 75.6 Gy (3.8%), and 79.8 Gy (55%). Matched intermediate-risk EBRT patients received total doses of 74 Gy (13.4%), 75.6 Gy (11.8%), 76 Gy (0.8%), 78 Gy (0.8%), and 79.8 Gy (73.2%) in the LDR-BT versus EBRT matched comparison (n=127) and 74 Gy (17%), 75.6 Gy (12.4%), 76 Gy (1.0%), 78 Gy (0.5%), and 79.8 Gy (69.1%) in the HDR-BT+EBRT versus EBRT matched comparison (n=194). Intermediate-risk HDR-BT+EBRT matched patients (n=194) received the following dose regimens: 10 Gy HDR-BT + 50 Gy EBRT (26.8%), 15 Gy HDR-BT + 40 Gy EBRT (15.0%), 15 Gy HDR-BT + 44 Gy EBRT (4.6%), 19 Gy HDR-BT + 45 Gy EBRT (4.1%), and 20 Gy HDR-BT + 44 Gy EBRT (49.5%). All low- and intermediate-risk LDR-BT matched patients received a minimum ^{125}I implant dose of 144 Gy.

Median follow-up varied among PS matched treatment groups. Low-risk matched LDR-BT patients had a median follow-up of 6.8 years, whereas low-risk matched EBRT patients had a median follow-up of 7.3 years. In the intermediate-risk matched LDR-BT versus EBRT cohort, median follow-up was 4.1 years versus 6.9 years, respectively. In the intermediate-risk matched HDR-BT+EBRT versus EBRT cohort, median follow-up was 2.7 years versus 6.8 years, respectively. The descriptive statistics for all patients before matching as well as after PS matching are shown in Tables 1-3.

Low-risk LDR-BT versus EBRT match

Kaplan-Meier curves comparing both bFFS and OS for low-risk, PS matched, LDR-BT versus EBRT patients are displayed in Figure 1A and B. Low-dose-rate BT was associated with a statistically significant improvement in bFFS when compared with EBRT (EBRT vs LDR-BT hazard ratio 2.90, 95% confidence interval [CI] 1.40-5.99, P=.004). The 5-year actuarial percentage for bFFS was 95.8% (95% CI 94.7-96.8%) after LDR-BT versus 86.6% (95% CI 76.4-92.6%) after EBRT. In total, 17 of 320 (5.3%) LDR-BT patients and 10 of 80 (12.5%) EBRT patients experienced a biochemical failure. No significant difference was found comparing OS in the low-risk LDR-BT versus EBRT match (LDR-BT vs EBRT hazard ratio 1.41, 95% CI 0.52-3.86, P=.500). The 5-year actuarial percentage for OS was 96.6% (95% CI 95.6-97.4%) for LDR-BT patients and 93.8% (95% CI 86.8-97.2%) for EBRT patients. Number of posttreatment PSA tests per year was 2.25 (Standard Deviation 0.75) and 1.64 (Standard Deviation 0.59) for LDR-BT and EBRT, respectively (P<.0001).

Intermediate-risk LDR-BT versus EBRT match

Kaplan-Meier curves comparing both bFFS and OS for intermediate-risk, PS matched, LDR-BT versus EBRT patients are displayed in Figure 1C and D. Low-dose-rate BT was associated with a statistically significant improvement in bFFS when compared with EBRT (EBRT vs LDR-BT hazard ratio 4.58, 95% CI 1.82-11.51, P=.001). The 5-year actuarial percentage for bFFS was 92.5% (95% CI 85.8%-96.2%) after LDR-BT versus 75.3% (95% CI 68.9%-80.5%) after EBRT. In total, 5 of 127 (3.9%) LDR-BT patients and 41 of 127 (32.3%) EBRT patients experienced a biochemical failure. No significant difference was found comparing OS in the intermediate-risk LDR-BT versus EBRT match (EBRT vs LDR-BT hazard ratio 1.27, 95% CI 0.40-4.10, P=.687). The 5-year actuarial percentage for OS was 95.8% (95% CI 91.2%-98.0%) for

Table 1 Baseline characteristics for all low-risk patients (n = 1820) and patients matched on propensity scores (n = 400), stratified by treatment type (LDR-BT vs EBRT)

	All patients (n = 1820)				Matched patients (n = 400) Caliper: 0.2 × 1 SD [Logit] Ratio: 4 LDR:1 EBRT			
Variable	Total sample (n = 1820)	LDR (n = 1716)	EBRT (n = 104)	S.D. (*P*)	Total sample (n = 400)	LDR (n = 320)	EBRT (n = 80)	S.D. (*P*)
Age (y)*								
Mean ± SD	63.32 ± 7.07	62.97 ± 6.96	68.98 ± 6.59	0.886	66.93 ± 5.49	66.94 ± 5.39	66.87 ± 5.91	0.012 (.92)†
Median	63.00	63.00	70.00	(<.01)†	68.00	68.00	67.00	
(range)	(43.00-84.00)	(43.00-83.00)	(51.00-84.00)		(51.00-80.00)	(51.00-79.00)	(51.00-80.00)	
Baseline PSA (ng/mL)*								
Mean ± SD	5.44 ± 2.12	5.40 ± 2.10	6.06 ± 2.36	0.295 (<.01)†	5.88 ± 2.14	5.89 ± 2.06	5.86 ± 2.44	0.013 (.91)†
Median	5.40	5.34	6.23		5.90	5.90 (0.50-9.80)	5.92 (0.26-10.00)	
(range)	(0.26-10.00)	(0.30-10.00)	(0.26-10.00)		(0.26-10.00)			
Gleason total*								
2-5	136 (7.5)	129 (7.5)	7 (6.7)	0.031 (.77)‡	25 (6.3)	19 (5.9)	6 (7.5)	0.062 (.61)§
6	1684 (92.5)	1587 (92.5)	97 (93.3)		375 (93.7)	301 (94.1)	74 (92.5)	
T stage*								
T1	1112 (61.1)	1051 (61.3)	61 (58.7)	0.053 (.60)‡	234 (58.5)	185 (57.8)	49 (61.3)	0.070 (.58)§
T2	708 (38.9)	665 (38.8)	43 (41.4)		166 (41.5)	135 (42.2)	31 (38.8)	
RT start year*								
1999	67 (3.7)	59 (3.4)	8 (7.7)	0.186	25 (6.3)	19 (5.9)	6 (7.5)	0.062
2000	138 (7.6)	120 (7.0)	18 (17.3)	0.320	54 (13.5)	42 (13.1)	12 (15.0)	0.054
2001	197 (10.8)	192 (11.2)	5 (4.8)	0.237	25 (6.3)	20 (6.3)	5 (6.3)	0.000
2002	236 (13.0)	208 (12.1)	28 (26.9)	0.380	95 (23.8)	77 (24.1)	18 (22.5)	0.037
2003	312 (17.1)	284 (16.6)	28 (26.9)	0.254	116 (29.0)	94 (29.4)	22 (27.5)	0.042
2004	314 (17.3)	307 (17.9)	7 (6.7)	0.345	38 (9.5)	31 (9.7)	7 (8.8)	0.032
2005	275 (15.1)	269 (15.7)	6 (5.8)	0.324	25 (6.3)	19 (5.9)	6 (7.5)	0.062
2006	281 (15.4)	277 (16.1)	4 (3.9)	0.419 (<.01)‡	22 (5.5)	18 (5.6)	4 (5.0)	0.029 (.99)‡
Percent positive cores								
<50%	860 (80.1)	800 (81.1)	60 (69.0)	0.282 (<.01)‡	189 (76.5)	147 (80.3)	42 (65.6)	0.336 (.02)§
>50%	214 (19.9)	187 (19.0)	27 (31.0)		58 (23.5)	36 (19.7)	22 (34.4)	
[Missing]	[746]	[729]	[17]		[153]	[137]	[16]	
Center								
1	536 (29.5)	495 (28.9)	41 (39.4)	0.224	124 (31.0)	91 (28.4)	33 (41.3)	0.271
2	687 (37.8)	624 (36.4)	63 (60.6)	0.500	170 (42.5)	123 (38.4)	47 (58.8)	0.415
3	597 (32.8)	597 (34.8)	0	1.033 (<.01)‡	106 (26.5)	106 (33.1)	0	1.000 (<.01)‡

Abbreviations: EBRT = external beam radiation therapy; LDR = low dose rate brachytherapy; PSA = prostate-specific antigen; RT = radiation therapy; S.D. = standardized difference.

Values are number (percentage) unless otherwise noted.

* Variable(s) used in propensity score computation procedures (if no asterisk [*] shown, then not used in propensity score model).

† Calculated *P* value using paired *t* test.

‡ Calculated *P* value using χ^2 test.

§ Calculated *P* value using McNemar test.

LDR-BT patients and 96.3% (95% CI 93.0%-98.1%) for EBRT patients. Number of posttreatment PSA tests per year was 2.49 (SD 0.89) and 1.86 (SD 0.71) for LDR-BT and EBRT, respectively ($P<.0001$).

Intermediate-risk HDR-BT + EBRT versus EBRT match

Kaplan-Meier curves comparing both bFFS and OS for intermediate-risk, PS matched, HDR-BT+EBRT versus EBRT patients are displayed in Figure 1E and F. High-dose-rate BT+EBRT was associated with a statistically significant improvement in bFFS when compared with EBRT (EBRT vs HDR-BT+EBRT hazard ratio 2.08, 95% CI 1.13-3.82, $P=.007$). The 5-year actuarial percentage for bFFS was 87.6% (95% CI 81.7%-91.6%) after HDR-BT+EBRT versus 75.2% (95% CI 68.9-80.5%) after EBRT. In total, 13 of 194 (6.7%) HDR-BT+EBRT patients and 64 of 194 (33.0%) EBRT patients experienced a biochemical failure. No significant difference was found comparing OS in the intermediate-risk HDR-BT+EBRT versus EBRT match (EBRT vs HDR-BT+EBRT hazard ratio 1.55, 95% CI 0.47-5.13,

Table 2 Baseline characteristics for all patients (n=496) and patients matched on propensity scores (n=254), stratified by treatment type in intermediate-risk LDR-BT versus EBRT comparison

	All patients (n=496)			
Variable	Total sample (n=496)	LDR (n=231)	EBRT (n=265)	S.D. (*P*)
Age (y)*				
Mean ± SD	68.31 ± 6.82	65.88 ± 7.24	70.42 ± 5.64	0.700 (<.01)†
Median (range)	69.00 (45.00-83.00)	67.00 (46.00-83.00)	71.00 (45.00-82.00)	
*Baseline PSA (ng/mL)				
Mean ± SD	8.24 ± 3.94	7.49 ± 3.39	8.89 ± 4.26	0.361 (<.01)†
Median (range)	7.46 (0.46-19.97)	7.00 (0.46-18.00)	7.83 (1.13-19.97)	
Gleason total*				
6	146 (29.4)	95 (41.1)	51 (19.3)	0.491 (<.01)‡
7	350 (70.6)	136 (58.9)	214 (80.8)	
T stage*				
Any T1	212 (42.7)	110 (47.6)	102 (38.5)	0.185
Low T2	211 (42.5)	79 (34.2)	132 (49.8)	0.320
High T2	73 (14.7)	42 (18.2)	31 (11.7)	0.183 (<.01)‡
Percent positive cores				
<50%	240 (59.0)	119 (70.8)	121 (50.6)	0.423 (<.01)‡
>50%	167 (41.0)	49 (29.2)	118 (49.4)	
[Missing]	[89]	[63]	[26]	
Gleason pattern				
3 + 3	110 (24.8)	59 (33.2)	51 (19.3)	0.320
3 + 4	251 (56.7)	100 (56.2)	151 (57.0)	0.016
4 + 3	82 (18.5)	19 (10.7)	63 (23.8)	0.352 (<.01)‡
[Missing]	[53]	[53]	[0]	
RT start year				
1996	1 (0.2)	1 (0.4)	0	0.093
1997	2 (0.4)	2 (0.9)	0	0.132
1998	0	0	0	0.000
1999	16 (3.2)	11 (4.8)	5 (1.9)	0.161
2000	23 (4.6)	6 (2.6)	17 (6.4)	0.185
2001	47 (9.5)	13 (5.6)	34 (12.8)	0.251
2002	94 (19.0)	13 (5.6)	81 (30.6)	0.685
2003	80 (16.1)	16 (6.9)	64 (24.2)	0.489
2004	44 (8.9)	19 (8.2)	25 (9.4)	0.043
2005	56 (11.3)	33 (14.3)	23 (8.7)	0.177
2006	72 (14.5)	56 (24.2)	16 (6.0)	0.525
2007	15 (3.0)	15 (6.5)	0	0.373
2008	20 (4.0)	20 (8.7)	0	0.435
2009	15 (3.0)	15 (6.5)	0	0.373
2010	11 (2.2)	11 (4.8)	0	0.316 (<.01)‡
Center				
1	130 (26.2)	93 (40.3)	37 (14.0)	0.619
2	313 (63.1)	85 (36.8)	228 (86.0)	1.173
3	53 (10.7)	53 (22.9)	0	0.777 (<.01)‡

Abbreviations as in Table 1.

Values are number (percentage) unless otherwise noted.

* Variable(s) used in propensity score computation procedures (if no asterisk [*] shown, then not used in propensity score model).

† Calculated *P* value using paired *t* test.

‡ Calculated *P* value using χ^2 test.

§ Calculated *P* value using McNemar test.

P=.470). The 5-year actuarial percentage for OS was 99.4% (95% CI 97.7-99.8%) for HDR-BT+EBRT patients and 96.3% (95% CI 93.0-98.1%) for EBRT patients. Number of posttreatment PSA tests per year was 3.17 (SD 1.04) and 1.86 (SD 0.71) for HDR-BT+EBRT and EBRT, respectively (*P*<.0001).

Table 2 Baseline characteristics for all patients (n = 496) and patients matched on propensity scores (n = 254), stratified by treatment type in intermediate-risk LDR-BT versus EBRT comparison (*Continued*)

	Matched patients (n = 254) Caliper: 0.01 Ratio: 1 LDR:1 EBRT		
Total sample (n = 254)	LDR (n = 127)	EBRT (n = 127)	S.D. (*P*)
68.63 ± 6.33 69.00 (45.00-83.00)	68.72 ± 6.56 69.00 (46.00-83.00)	68.54 ± 6.12 69.00 (45.00-82.00)	0.029 (.82)†
7.78 ± 3.40 7.12 (1.30-18.00)	7.87 ± 2.99 7.41 (1.30-18.00)	7.70 ± 3.77 6.80 (1.48-17.00)	0.050 (.69)†
57 (22.4) 197 (77.6)	30 (23.6) 97 (76.4)	27 (21.3) 100 (78.7)	0.057 (.65)§
109 (42.9) 118 (46.5) 27 (10.6)	56 (44.1) 56 (44.1) 15 (11.8)	53 (41.7) 62 (48.8) 12 (9.5)	0.048 0.095 0.077 (.70)‡
140 (62.8) 83 (37.2) [31]	77 (72.6) 29 (27.4) [21]	63 (53.9) 54 (46.2) [10]	0.398 (<.01)§
47 (20.0) 145 (61.7) 43 (18.3) [19]	20 (18.5) 73 (67.6) 15 (13.9) [19]	27 (21.3) 72 (56.7) 28 (22.1) [0]	0.069 0.226 0.214 (.18)‡
0 0 0 3 (1.2) 12 (4.7) 23 (9.1) 41 (16.1) 35 (13.8) 24 (9.5) 33 (13.0) 59 (23.2) 5 (2.0) 11 (4.3) 3 (1.2) 5 (2.0)	0 0 0 2 (1.6) 2 (1.6) 3 (2.4) 6 (4.7) 5 (3.9) 12 (9.5) 23 (18.1) 50 (39.4) 5 (3.9) 11 (8.7) 3 (2.4) 5 (3.9)	0 0 0 1 (0.8) 10 (7.9) 20 (15.8) 35 (27.6) 30 (23.6) 12 (9.5) 10 (7.9) 9 (7.1) 0 0 0 0	0.000 0.000 0.000 0.073 0.300 0.480 0.653 0.596 0.000 0.308 0.827 0.286 0.436 0.220 0.286 (<.01)‡
83 (32.7) 152 (59.8) 19 (7.5)	65 (51.2) 43 (33.9) 19 (15.0)	18 (14.2) 109 (85.8) 0	0.859 1.250 0.593 (<.01)‡

Discussion

A statistically significant difference in bFFS in favor of the BT treatment options was found in all low-risk and intermediate-risk matched cohorts (Fig. 1A, C, E). This matched analysis successfully adjusted for the baseline prognostic factors of age, PSA, Gleason total, and T stage, which are the primary factors used to risk-stratify patients

Table 3 Baseline characteristics for all patients (n=655) and patients matched on propensity scores (n=388), stratified by treatment type in intermediate-risk HDR-BT+EBRT versus EBRT comparison

	All patients (n=655)			
Variable	Total sample (n=655)	HDR+EBRT (n=390)	EBRT (n=265)	S.D. (*P*)
Age (y)*				
Mean ± SD	67.59 ± 6.62	65.66 ± 6.55	70.42 ± 5.64	0.779 (<.01)†
Median (range)	69.00 (45.00-82.00)	66.00 (47.00-81.00)	71.00 (45.00-82.00)	
Baseline PSA (ng/mL)*				
Mean ± SD	8.51 ± 4.06	8.26 ± 3.91	8.89 ± 4.26	0.155 (.05)†
Median (range)	7.41 (0.37-19.97)	7.23 (0.37-19.96)	7.83 (1.13-19.97)	
Gleason total*				
6	93 (14.2)	42 (10.8)	51 (19.3)	0.239 (<.01)‡
7	562 (85.8)	348 (89.2)	214 (80.8)	
T stage*				
Any T1	344 (52.5)	242 (62.1)	102 (38.5)	0.485
Low T2	263 (40.2)	131 (33.6)	132 (49.8)	0.334
High T2	48 (7.3)	17 (4.4)	31 (11.7)	0.273 (<.01)‡
Percent positive cores				
<50%	173 (53.9)	52 (63.4)	121 (50.6)	0.260 (.05)‡
>50%	148 (46.1)	30 (36.6)	118 (49.4)	
[Missing]	[334]	[308]	[26]	
Gleason pattern				
3 + 3	65 (18.5)	14 (16.3)	51 (19.3)	0.078
3 + 4	202 (57.6)	51 (59.3)	151 (57.0)	0.047
4 + 3	84 (23.9)	21 (24.4)	63 (23.8)	0.015 (.83)‡
[Missing]	[304]	[304]	[0]	
RT start year				
1999	5 (0.8)	0	5 (1.9)	0.196
2000	17 (2.6)	0	17 (6.4)	0.370
2001	44 (6.7)	10 (2.6)	34 (12.8)	0.392
2002	102 (15.6)	21 (5.4)	81 (30.6)	0.694
2003	84 (12.8)	20 (5.1)	64 (24.2)	0.559
2004	54 (8.2)	29 (7.4)	25 (9.4)	0.072
2005	50 (7.6)	27 (6.9)	23 (8.7)	0.066
2006	47 (7.2)	31 (8.0)	16 (6.0)	0.075
2007	55 (8.4)	55 (14.1)	0	0.573
2008	98 (15.0)	98 (25.1)	0	0.819
2009	73 (11.2)	73 (18.7)	0	0.679
2010	26 (4.0)	26 (6.7)	0	0.378 (<.01)‡
Center				
1	37 (5.7)	0	37 (14.0)	0.570
2	228 (34.8)	0	228 (86.0)	3.511
3	303 (46.3)	303 (77.7)	0	2.640
4	87 (13.3)	87 (22.3)	0	0.758 (<.01)‡

Abbreviations as in Table 1.
Values are number (percentage) unless otherwise noted.
* Variable(s) used in propensity score computation procedures (if no asterisk [*] shown, then not used in propensity score model).
† Calculated *P* value using paired *t* test.
‡ Calculated *P* value using χ^2 test.
§ Calculated *P* value using McNemar test.

and tailor their RT (1-3). Observational studies directly comparing LDR-BT versus EBRT in strictly low-risk patients have reported comparable American Society for Radiation Oncology Phoenix II defined bFFS (23, 27, 28, 31, 33). Results from our matched analysis of LDR-BT versus EBRT in low-risk patients demonstrated 5-year bFFS actuarial percentages of 96% LDR-BT versus 89% EBRT (*P*=.004) (Fig. 1A). In a separate, Canadian matched-pair study, Pickles et al (23) reported superior bFFS in patients treated with LDR-BT compared with

Table 3 Baseline characteristics for all patients (n = 655) and patients matched on propensity scores (n = 388), stratified by treatment type in intermediate-risk HDR-BT+EBRT versus EBRT comparison (*Continued*)

Matched patients (n = 388) Caliper: 0.2 × 1 SD [Logit] Ratio: 1 HDR:1 EBRT			
Total sample (n = 388)	HDR+EBRT (n = 194)	EBRT (n = 194)	S.D. (*P*)
69.19 ± 5.25 70.00 (55.00-82.00)	69.20 ± 5.03 70.00 (57.00-81.00)	69.17 ± 5.48 70.00 (55.00-82.00)	0.006 (.95)†
8.77 ± 4.06 7.79 (1.00-19.76)	8.92 ± 4.01 8.00 (1.00-19.76)	8.62 ± 4.13 7.60 (1.48-19.60)	0.074 (.47)†
57 (14.7) 331 (85.3)	27 (13.9) 167 (86.1)	30 (15.5) 164 (84.5)	0.044 (.67)§
184 (47.4) 179 (46.1) 25 (6.4)	92 (47.4) 90 (46.4) 12 (6.2)	92 (47.4) 89 (45.9) 13 (6.7)	0.000 0.010 0.021 (.98)‡
121 (54.5) 101 (45.5) [166]	30 (62.5) 18 (37.5) [146]	91 (52.3) 83 (47.7) [20]	0.207 (.21)§
39 (15.9) 145 (59.2) 61 (24.9) [143]	9 (17.7) 29 (56.9) 13 (25.5) [143]	30 (15.5) 116 (59.8) 48 (24.7) [0]	0.059 0.060 0.017 (.91)‡
4 (1.0) 15 (3.9) 31 (8.0) 74 (19.1) 50 (12.9) 36 (9.3) 35 (9.0) 28 (7.2) 25 (6.4) 50 (12.9) 28 (7.2) 12 (3.1)	0 0 6 (3.1) 12 (6.2) 12 (6.2) 16 (8.3) 15 (7.7) 18 (9.3) 25 (12.9) 50 (25.8) 28 (14.4) 12 (6.2)	4 (2.1) 15 (7.7) 25 (12.9) 62 (32.0) 38 (19.6) 20 (10.3) 20 (10.3) 10 (5.2) 0 0 0 0	0.205 0.409 0.367 0.694 0.408 0.071 0.090 0.160 0.544 0.833 0.581 0.363 (<.01)‡
35 (9.0) 159 (41.0) 142 (36.6) 52 (13.4)	0 0 142 (73.2) 52 (26.8)	35 (18.0) 159 (82.0) 0 0	0.664 3.014 2.337 0.856 (<.01)‡

EBRT in their intermediate-risk subgroup analysis. The results from our PS matched analysis comparing LDR-BT versus EBRT in intermediate-risk patients are agreeable, with a hazard ratio of 4.58 (95% CI 1.82-11.51, $P = .001$) in favor of LDR-BT (Fig. 1C). Recent phase 3 trial evidence has demonstrated improved biochemical control in predominately intermediate- to high-risk patients after HDR-BT+EBRT when compared with either conventionally fractionated 66 Gy EBRT (11) or hypofractionated EBRT (12). Our results comparing HDR-BT+EBRT with

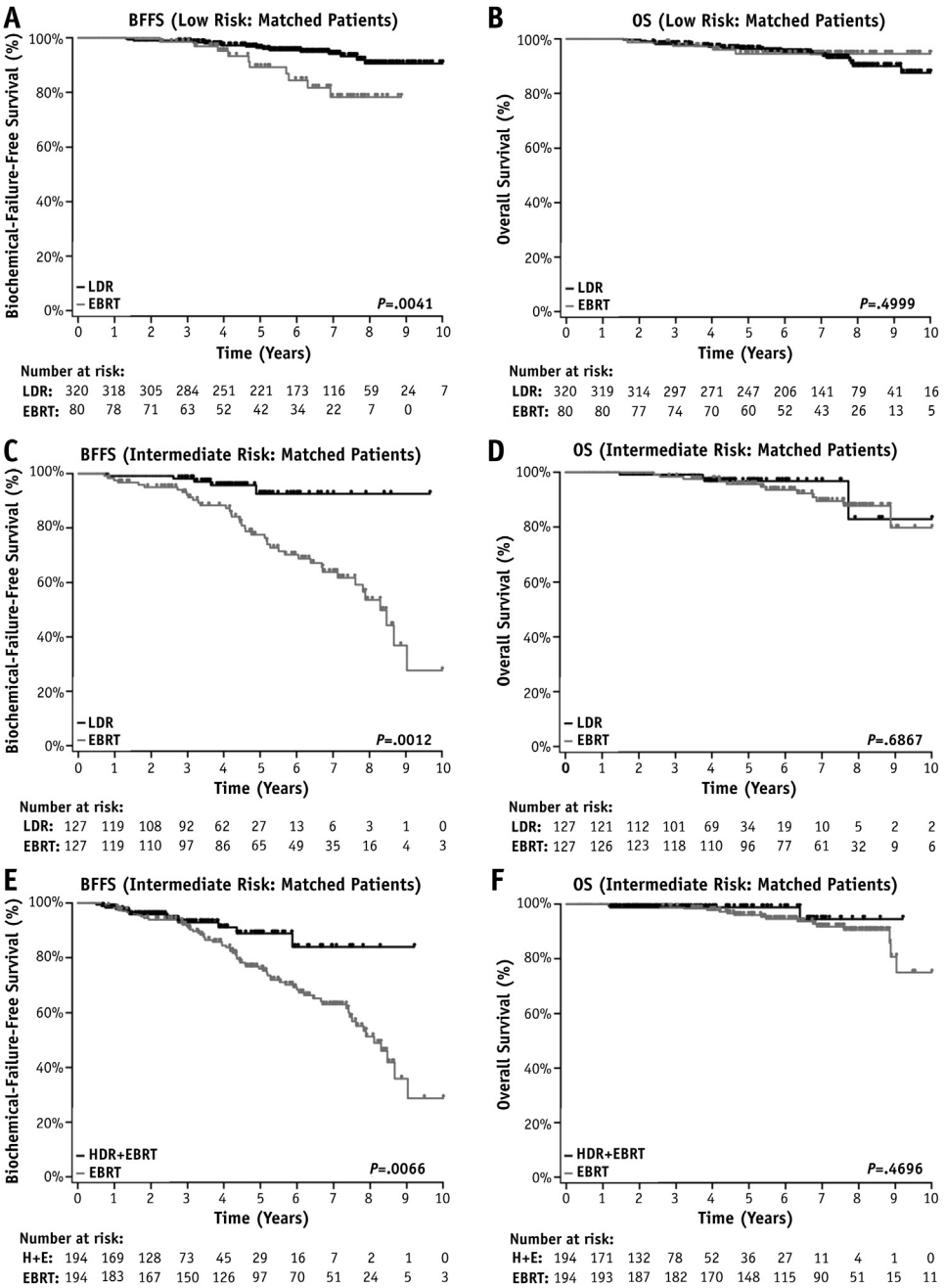

Fig. 1. Biochemical failure-free survival (BFFS) (A, C, E) and overall survival (OS) (B, D, F) Kaplan-Meier curves comparing propensity score−matched patients receiving external beam radiation therapy (EBRT) versus brachytherapy (BT) options for (A, B) low-risk patients receiving low-dose-rate (LDR)-BT (n = 320) versus EBRT (n = 80); (C, D) intermediate-risk patients receiving LDR-BT (n = 127) versus EBRT (n = 127); and (E, F) intermediate-risk patients receiving high-dose-rate (HDR)-BT+EBRT (n = 194) versus EBRT (n = 194).

conventionally fractionated (1.8-2.0 Gy) EBRT doses of ≥74 Gy in strictly intermediate-risk patients showed superior bFFS after combination therapy (Fig. 1E).

Propensity score matched analysis found no difference in OS comparing BT options with EBRT in any matched comparison (Fig. 1B, D, F). Prospective randomized data comparing OS in intermediate- to high-risk patients receiving HDR-BT+EBRT versus EBRT alone have reported 5-year OS percentages of 94% versus 92% ($P = .54$), respectively (11). Our PS matched analysis was agreeable with the literature, demonstrating no OS survival difference between HDR-BT+EBRT- and EBRT-compared treatment groups (Fig. 1F). Currently, no definitive evidence exists favoring either LDR-BT or EBRT with respect to OS of patients with low- or intermediate-risk prostate cancer. Our results comparing LDR-BT versus EBRT in low-risk and intermediate-risk matched cohorts found no OS difference in either comparison (Fig. 1B and D).

This investigation had several limitations. The analysis performed was limited by the treatment and outcome data available in the ProCaRS database. For example, no toxicity data were available, which would have allowed for both mortality and morbidity assessment (48, 49). Matching was restricted to patients with complete data for all variables included in the PS models (logistic regression models) and based on specific sets of exclusion criteria used to create homogenous comparison groups. This resulted in a reduction in sample size and power in our matched comparisons. Variable eligibility for inclusion in the PS models was also restricted to those readily available in the database and of sufficient level of completeness. For example, information on both percent positive core biopsy and Gleason 7 subpattern (3 + 4 vs 4 + 3) was generally incompletely entered and could not be controlled for in our analysis (48, 49). The variation in RT management of prostate cancer across different treatment centers could potentially impact outcomes (63); however, the method of data collection from the various cancer institutions made it impossible to include a "treatment center" variable in the PS models (48, 49). Finally, any conclusions regarding OS should be made cautiously given the limited median follow-up, ranging from 2.7 to 7.3 years depending on the cohort being assessed. In particular, there is significant uncertainty for 10-year survival estimates given the limited number of patients that have been followed to that time period. Additionally, comparison of treatment selection on late bFFS and OS endpoints should be considered hypothesis-generating given the lack of late (>10 year) follow-up as well as differential follow-up between BT and EBRT cohorts.

Propensity score matched analysis demonstrated that BT options significantly improved bFFS in low- and intermediate-risk prostate cancer patients but did not lead to an observed difference in OS. To our knowledge, this was the first Canadian, multi-institutional, PS matched study comparing primary BT versus EBRT survival outcomes in separate GUROC low- and intermediate-risk prostate cancer patients. The results of this study add to an increasing amount of evidence favoring BT over EBRT with respect to biochemical control in the treatment of localized prostate cancer.

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