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Comparative Effectiveness of Radical Prostatectomy Versus External Beam Radiation Therapy Plus Brachytherapy in Patients with High-risk Localized Prostate Cancer

Sebastian Berg[a,b], *Alexander P. Cole*[a], *Marieke J. Krimphove*[a,c], *Junaid Nabi*[a], *Maya Marchese*[a], *Stuart R. Lipsitz*[d], *Joachim Noldus*[b], *Toni K. Choueiri*[e], *Adam S. Kibel*[a], *Quoc-Dien Trinh*[a,*]

[a] *Division of Urological Surgery and Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [b] *Department of Urology and Neurourology, Marien Hospital Herne, Ruhr-University Bochum, Herne, Germany;* [c] *Department of Urology, University Hospital Frankfurt, Frankfurt am Main, Germany;* [d] *Center for Surgery and Public Health, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;* [e] *Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA*

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Abstract

A previous study comparing external beam radiation therapy with/without brachytherapy (EBRT ± BT) and radical prostatectomy (RP) for high-risk localized prostate cancer (PCa) did not find a difference in overall survival (OS) between the treatments. However, this study was limited by short follow-up and assessment of OS in patients of divergent age and comorbidities. We therefore compared OS of EBRT + BT versus RP in comparatively young (≤65 yr) and healthy men (Charlson Comorbidity Index = 0) with high-risk localized PCa in the National Cancer Database. Inverse probability of treatment weighting (IPTW) adjustment was used to balance baseline characteristics. Median follow-up was 92 mo (interquartile range 78–108). Using IPTW-adjusted Cox regression analysis, EBRT + BT was associated with a higher risk of all-cause mortality compared with RP (hazard ratio = 1.22, 95% confidence interval 1.05–1.43). In young and healthy men presenting with high-risk localized PCa, RP showed statistically significant OS benefit compared with EBRT + BT.

Patient summary: In an analysis restricted to young and healthy men presenting with high-risk localized prostate cancer, initial radical prostatectomy is associated with an overall survival benefit compared with external beam radiation therapy plus brachytherapy.

* Corresponding author. Harvard Medical School, Division of Urological Surgery, Brigham and Women's Hospital, 45 Francis St, ASB II-3, Boston, MA 02115, USA. Tel. +1 617 525-7350; Fax: +1 617 525 6348.
E-mail address: qtrinh@bwh.harvard.edu (Q.-D. Trinh).

Radical prostatectomy (RP) and external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT) are standard of care options for high-risk localized prostate cancer (PCa) [1]. The ASCENDE-RT trial showed that brachytherapy (BT) as an adjunct to EBRT is associated with a recurrence-free survival benefit [2]. However, in the absence of randomized data comparing EBRT + BT with RP, the debate regarding the optimal management for these

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patients continues [3–6]. Recently, two observational studies with similar design and inclusion criteria found divergent results. Kishan et al. [6] demonstrated in a multi-institutional retrospective study that EBRT + BT was associated with better cancer-specific and metastasis-free survival compared with RP in patients with localized Gleason score (GS) 9–10 PCa. Conversely, Ennis et al. [5] did not find an overall survival (OS) difference between RP, EBRT (+ADT), and EBRT + BT (±ADT) in patients with high-risk PCa in the National Cancer Database (NCDB). However, the latter was limited by short follow-up and assessment of OS in patients of widely divergent age and comorbidities. To circumvent these limitations, we reanalyzed data from the aforementioned study [5] with importantly more restrictive inclusion criteria—specifically limiting our analysis to younger and healthier men who were diagnosed in the early study period to ensure sufficient follow-up—and compared the OS of EBRT + BT versus RP.

Within the NCDB (2004–2015), 1 380 357 men with PCa were identified. The final study was derived using the following exclusion criteria: diagnosis after 2010, age ≥66 yr, histology other than adenocarcinoma of the prostate (International Classification of Diseases for Oncology, third edition, C61), unknown/confirmed clinical T stage 0, unknown/confirmed clinical lymph node positive or metastatic diseases, unknown prostate-specific antigen (PSA), unknown GS, and Charlson Comorbidity Index >0. We included only those patients who received either upfront RP (regardless of adjuvant/salvage therapy) or EBRT + BT. RP was defined based on the *surgery of the primary site codes 50–80* and EBRT + BT as EBRT (≥40 Gy) in combination with radioactive implants/radioisotopes. In concordance with the main analysis by Ennis et al. [5] and to maintain sufficient sample size, we did not account for ADT use in our treatment groups. Furthermore, we restricted our analyses to high-risk disease defined as clinical T stage ≥3, GS ≥8, or PSA >20 ng/dl. Patient- and provider-level covariates included age, race, insurance status, income, education, GS, PSA, clinical T stage, county type, and distance to treating hospital.

To address inherent selection biases, we conducted an inverse probability of treatment weighting (IPTW) propensity score analysis. Specifically, a binomial logistic regression model—including the covariates above—was used to predict each patient's probability of receiving RP versus EBRT + BT, and each patient was weighted by the inverse of their probability of receiving RP. Balance was evaluated using standardized differences, which revealed <10% imbalance for all covariates. Testing for the proportional-hazard assumption revealed no violation. Therefore, IPTW-adjusted Kaplan-Meier curves were used to compare OS between the two groups. Furthermore, IPTW-adjusted Cox regression model was fit to compare risk of overall mortality between the groups [7]. All statistical analyses were performed using Stata version 14, and two-sided statistical alpha was set at $p < 0.05$. The study was performed under a general IRB for research using the NCDB to assess comparative effectiveness of cancer treatments.

Overall, the final study population comprised 13 985 men (Supplementary Fig. 1). In total, 12 283 (88%) patients underwent RP versus 1702 (12%) patients who underwent EBRT + BT. Among RP patients, 1835/12 283 (15%) received additional medical ADT, while 1176/1702 (69%) patients within the EBRT + BT group received ADT. Adjuvant radiation therapy was performed in 1797/12 283 (15%) patients of the RP group, whereas no men within the EBRT + BT group received a salvage prostatectomy. Unweighted and weighted baseline characteristics of the patients are depicted in Table 1. The median follow-up was 91 mo (interquartile range [IQR] 77–107) in the RP versus 101 mo (IQR 84–117) in the EBRT + BT group. In the IPTW-adjusted Cox regression analysis, EBRT + BT was associated with a higher risk of overall mortality compared with RP (hazard ratio = 1.22, 95% confidence interval 1.05–1.43). The OS curves derived from the Kaplan-Meier analysis are shown in Figure 1.

In contrast to recently published results, our study in a relatively young and healthy population of men with high-risk localized PCa suggests a survival benefit for RP. These findings—interpreted within the limitations of the study design—should serve as a counterargument to recent efforts, suggesting the superiority of EBRT + BT [6]. Our results are linked to a former study emphasizing decreased OS after EBRT or BT [8]. Another study comparing RP versus radiation therapy for locally advanced PCa failed to demonstrate a difference in cancer-specific survival, due to insufficient power [9], while Boehm et al. [10] comparing EBRT + BT versus RP in cT1–T2 stages did not find a difference in 5-yr OS rates.

Our study has limitations that are inevitable, given the retrospective design. Unmeasured confounders such as missing information on biological effective dose for radiation treatment and potential selection bias may limit generalizability of our conclusions. The most important limitation of the NCDB is the absence of information on cause of death. However, there are important strengths of our study: we used IPTW, which allowed for more

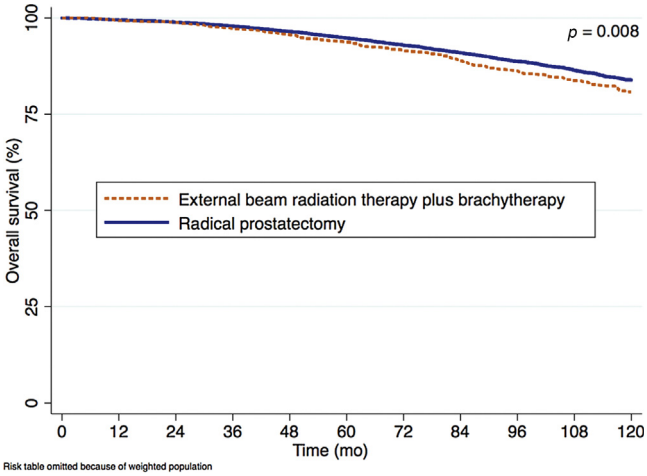

Fig. 1 – Inverse probability of treatment weighting-adjusted Kaplan-Meier analysis of overall survival after radical prostatectomy versus external beam radiation therapy plus brachytherapy.

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Table 1 – Demographic, socioeconomic, and clinical characteristics of 13 985 patients undergoing radical prostatectomy or external beam radiation therapy plus brachytherapy within the National Cancer Database from 2004 to 2015

	Unweighted population				Weighted population			
	Overall	RP	EBRT + BT	SDF [a]	Overall	RP	EBRT + BT	SDF [a]
Patients, *n* (%)	13 985 (100)	12 283 (88)	1702 (12)	–	13 985 (100)	12 283 (88)	1702 (12)	–
Mean age (yr)	58.15	58.00	59.27	0.25	58.13	58.15	58.12	−0.005
Age group, *n* (%)								
≤50	1310 (9.4)	1227 (10)	83 (5)	−0.20	9.6	9.4	10	0.017
51–55	2691 (19.2)	2415 (20)	276 (16)	−0.090	19	19	19	0.007
56–60	4478 (32)	3956 (32)	522 (31)	−0.033	32	32	32	−0.008
61–65	5506 (39)	4685 (38)	821 (48)	0.20	39	39	39	−0.008
Race, *n* (%)								
White	11 448 (82)	10 230 (83)	1218 (72)	−0.28	82	82	82	0.005
Black	1861 (13)	1490 (12)	371 (22)	0.26	13	13	13	−0.008
Other/unknown	676 (5)	563 (5)	113 (7)	0.089	4.8	4.8	4.9	0.003
Insurance status, *n* (%)								
Private	11 330 (81)	10 031 (82)	1299 (76)	−0.13	80	81	80	−0.033
Medicare	1649 (12)	1368 (11)	281 (17)	0.16	12	12	12	0.018
Medicaid/other government	542 (3.8)	467 (3.8)	75 (4.4)	0.030	4.1	3.9	4.3	0.022
Not insured	275 (1.9)	248 (2.0)	27 (1.6)	−0.033	2.3	1.9	2.5	0.039
Unknown	189 (1.3)	169 (1.3)	20 (1.2)	−0.018	1.2	1.3	1.0	−0.026
Income, *n* (%) [b]								
>$63 000	5280 (38)	4614 (38)	666 (39)	0.032	37	38	37	−0.021
$48 000–62 999	3661 (26)	3245 (26)	416 (24)	−0.045	26	26	25	−0.025
$38 000–47 999	2946 (21)	2631 (21)	315 (19)	−0.073	22	21	23	0.038
<$38 000	1949 (14)	1673 (14)	276 (16)	0.073	14	14	15	0.019
Unknown	149 (1.0)	120 (0.9)	29 (1.7)	0.063	1.0	1.0	0.9	−0.012
Education level, *n* (%) [c]								
>21%	1916 (14)	1626 (13)	290 (17)	0.10	14	14	14	0.007
13–20.9%	3218 (22)	2801 (23)	417 (25)	0.040	23	23	24	0.015
7–12.9%	4524 (32)	4004 (33)	520 (31)	−0.044	32	32	32	0.002
<7%	4184 (30)	3738 (30)	446 (26)	−0.094	29	30	30	−0.020
Unknown	143 (1.0)	114 (0.9)	29 (1.7)	0.068	9.8	1.0	9.4	−0.008
Gleason score, *n* (%)								
≤6	1959 (14)	1757 (14)	202 (12)	−0.072	14	14	15	0.027
7	3843 (27)	3449 (28)	394 (23)	−0.11	28	27	28	0.005
8	4494 (32)	3777 (31)	717 (42)	0.23	32	32	32	−0.006
9	3543 (25)	3184 (26)	359 (21)	−0.11	25	25	24	−0.020
10	146 (1.0)	116 (0.9)	30 (1.7)	0.071	1.0	1.0	1.0	−0.000
PSA (ng/dl), *n* (%)								
<10	6827 (49)	6032 (49)	795 (47)	−0.048	49	49	49	−0.002
10–20	1823 (13)	1550 (13)	273 (16)	0.098	13	13	13	−0.001
>20	5335 (38)	4701 (38)	634 (37)	−0.021	38	38	38	0.003
Clinical T stage								
T1	7136 (51)	6391 (52)	745 (44)	−0.16	50	51	50	−0.026
T2	4308 (31)	3697 (30)	611 (36)	0.12	31	31	31	−0.003
T3	2451 (18)	2111 (17)	340 (20)	0.072	18	18	19	0.032
T4	90 (0.64)	84 (0.68)	6 (0.35)	−0.046	0.58	0.64	0.51	−0.017
Travel distance (miles), *n* (%) [d]								
<12.4	6519 (47)	5546 (45)	973 (57)	0.24	47	47	46	−0.004
12.5–49.9	4852 (35)	4354 (35)	498 (29)	−0.13	35	35	35	0.001
>50	2475 (17)	2270 (18)	205 (12)	−0.18	18	18	17	0.006
Unknown	139 (0.99)	113 (0.92)	26 (1.5)	0.055	9.3	0.99	0.88	−0.011
County type								
Metro	11 431 (82)	9989 (81)	1442 (85)	0.091	82	82	82	−0.004
Urban	1834 (13)	1673 (14)	161 (9.4)	−0.13	13	13	13	0.001
Rural	279 (1.9)	244 (1.9)	35 (2.0)	0.005	1.9	2.0	1.9	−0.001
Unknown	441 (3.1)	377 (3.0)	64 (3.7)	0.038	3.2	3.1	3.2	0.007

EBRT + BT = external beam radiation therapy + brachytherapy; PSA = prostate-specific antigen; RP = radical prostatectomy; SDF = standardized difference.
[a] By convention, <0.10 standardized difference between treatment arms indicates well-balanced cohorts.
[b] Income was defined based on equally proportioned income ranges among all US ZIP codes.
[c] Education level was defined as percentage of people in a specific ZIP code who did not graduate from high school.
[d] Travel distance describes the shortest distance (based on ZIP codes) between the patient's residence and the location of the hospital; percentages may not add up to 100% because they are rounded.

balanced baseline characteristics and a reduction in selection bias. By restricting our analysis to younger and healthier patients, we sought to minimize other-cause mortality. Finally, inclusion of only patients diagnosed from 2004 to 2009 secured longer follow-up compared with earlier studies.

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Our results, showing that young and healthy men presenting with high-risk localized PCa had better survival with RP compared with EBRT + BT, call into question other recent research suggesting better or equivalent outcomes with EBRT + BT. Clinicians and patients should continue to practice shared decision making, while awaiting more definitive practice-changing research findings.

Author contributions: Quoc-Dien Trinh had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Berg, Cole, Trinh.
Acquisition of data: Berg, Choueiri, Trinh.
Analysis and interpretation of data: Berg, Cole, Trinh.
Drafting of the manuscript: Berg, Cole, Krimphove.
Critical revision of the manuscript for important intellectual content: Nabi, Marchese, Lipsitz, Noldus, Choueiri, Kibel, Trinh.
Statistical analysis: Berg, Cole, Marchese, Lipsitz.
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Supervision: Noldus, Choueiri, Kibel, Trinh.
Other: None.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.032.

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