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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Radical Prostatectomy Versus External Beam Radiation Therapy for High-Grade, Clinically Localized Prostate Cancer: Emulation of a Target Clinical Trial

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AUA Virtual Presentation

Introduction

- The comparative effectiveness of surgery and radiation therapy for high-grade, clinically localized prostate cancer remains a seminal, open question in urology.
- There are no randomized controlled trials to inform management.
- Existing evidence base is comprised of exclusively observational studies of varying methodological rigor, many of which report contradictory results.

Introduction

- Since the conduct of a new trial in high-grade prostate cancer is impractical as an immediate source of evidence, we set out to **emulate a hypothetical target trial using observational data from the NCDB.**

Methods

Protocol Component	Hypothetical Target Trial of Surgery versus Radiotherapy for High Grade (Gleason Score 8-10) Prostate Cancer
Eligibility criteria	Adult patients age 55-69 with cT1-3 cN0 cM0 prostate cancer; Pretreatment PSA <20 ng/mL; Gleason Score 8-10; Charlson 0-1
Treatment strategies	Surgery versus EBRT (75-81 Gy) + ADT (18-36 months)
Assignment procedures	Un-blinded random assignment to treatments
Follow-up period	Starts at randomization; ends on date of last available data in observational dataset or at the occurrence of outcome event, loss to follow-up, or death (whichever is earlier)
Outcomes	Overall survival
Causal contrasts	Causal effect comparing point (non-time-varying) treatments

Methods

Patient Population

- We identified 26,806 men aged 55-69 years with cT1-3cN0cM0, PSA<20 ng/mL, Gleason 8-10 prostate adenocarcinoma treated with RP or 75-81 Gy EBRT with androgen deprivation therapy (ADT) from 2006-2015 in the National Cancer Database (NCDB.)

Statistical Analysis

- A propensity score (PS) for RP was estimated using baseline characteristics. The associations of treatment type with overall survival (OS) were estimated using Cox regression with stabilized inverse probability weights (IPW).

Results: Select Baseline Characteristics

	Overall (n = 26,806)	RP (n = 23,990)	EBRT+ADT (n = 2,816)	p-value
Patient Characteristics				
Age, yrs, median (IQR)	63 (60-66)	63 (60-66)	65 (61-67)	<0.001
PSA, median (IQR)	6.4 (4.8-9.3)	6.3 (4.7-9.1)	7.2 (5.1-10.8)	<0.001
Disease Characteristics				
cT stage, n (%)				<0.001
cT1	16,132 (60.2)	14,683 (61.2)	1,449 (51.5)	
cT2	9,129 (34.1)	8,063 (33.6)	1,066 (37.9)	
cT3	1,545 (5.8)	1,244 (5.2)	301 (10.7)	
Gleason score[1], n (%)				<0.001
8	16,609 (62.0)	14,970 (62.4)	1,639 (58.2)	
9	9,712 (36.2)	8,629 (36.0)	1,083 (38.5)	
10	485 (1.8)	391 (1.6)	94 (3.3)	

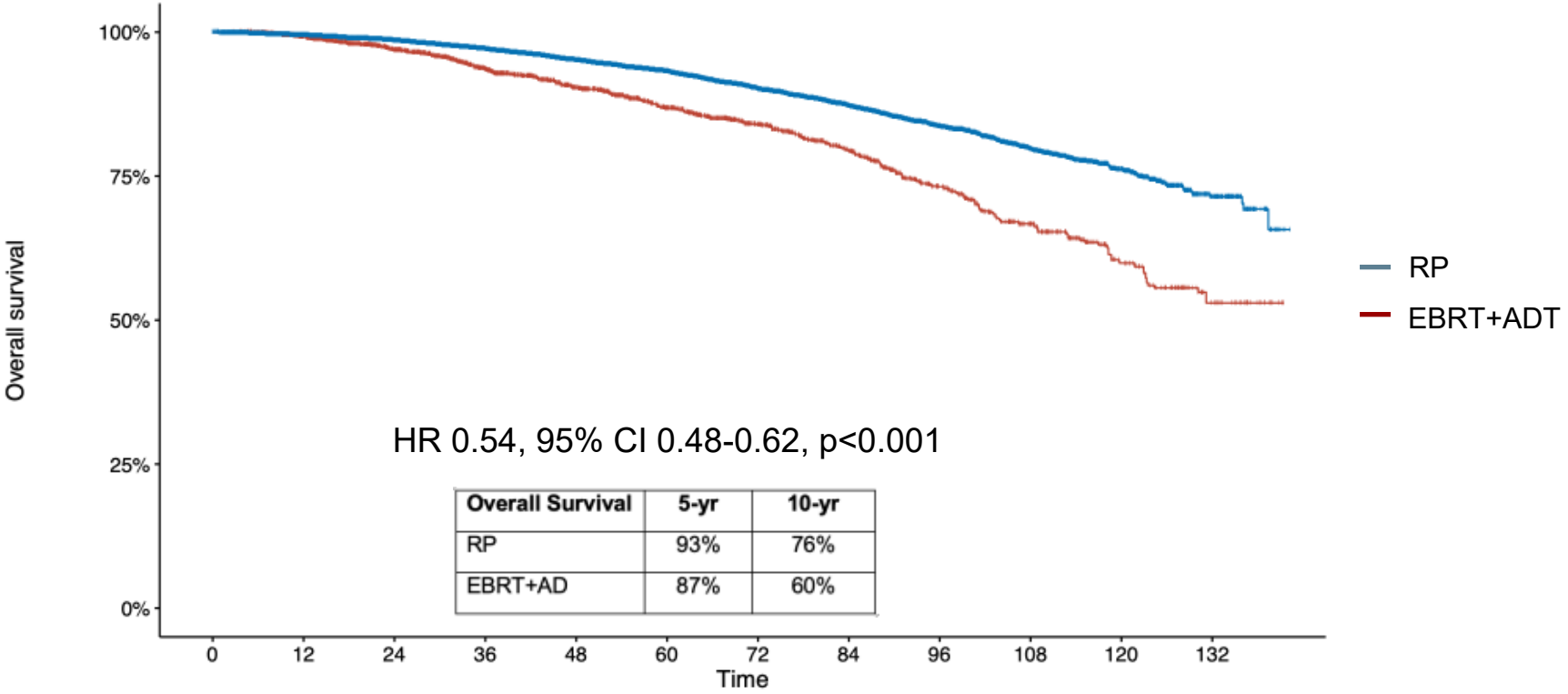
Results: PS Balance

	RP (n = 21,321)	EBRT+ADT (n = 2,478)	SD[1]
Patient Characteristics			
Age, yrs, median (IQR)	63 (60-66)	63 (60-66)	0.023
PSA, median (IQR)	6.4 (4.8-9.3)	6.6 (4.8-9.6)	0.011
Charlson Comorbidity Index, n (%)			0.0070
0	17,362 (81.4)	2,025 (81.7)	
1	3,959 (18.6)	453 (18.3)	
Disease Characteristics			
cT stage, n (%)			0.025
cT1	12,898 (60.5)	1,511 (61.0)	
cT2	7,213 (33.8)	816 (32.9)	
cT3	152 (6.1)	1,210 (5.7)	
Gleason score, n (%)			0.014
8	13,213 (62.0)	1,519 (61.3)	
9	7,718 (36.2)	914 (36.9)	
10	391 (1.8)	45 (1.8)	

Results: Follow-up

- Median follow-up for the cohort was 39.4 (IQR 22.3-59.8) months.
  -During follow-up, a total of 1,024 patients died of any cause.

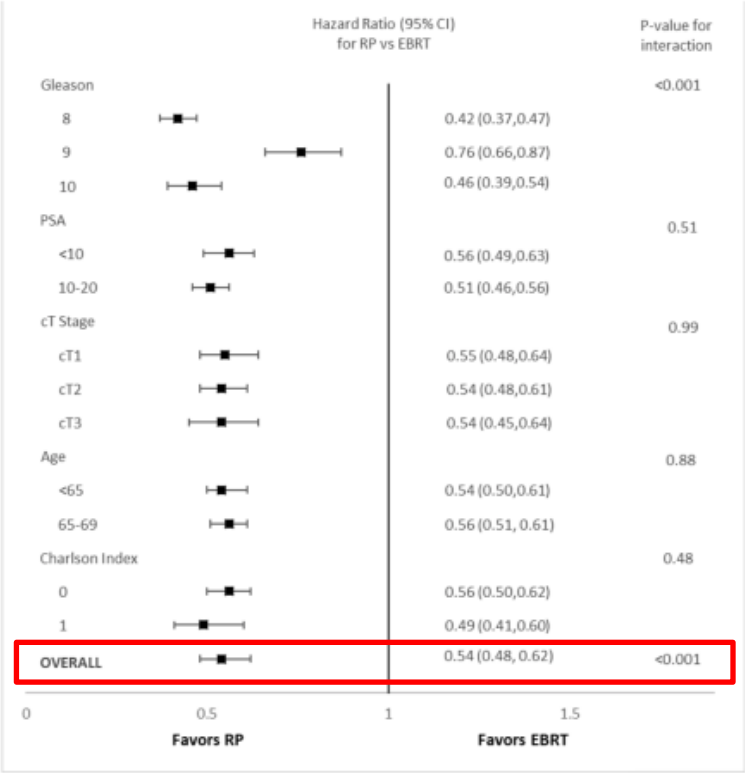
Results: Main Treatment Effect



HR 0.54, 95% CI 0.48-0.62, p<0.001

Overall Survival	5-yr	10-yr
RP	93%	76%
EBRT+AD	87%	60%

Results: Heterogeneity of Treatment Effect



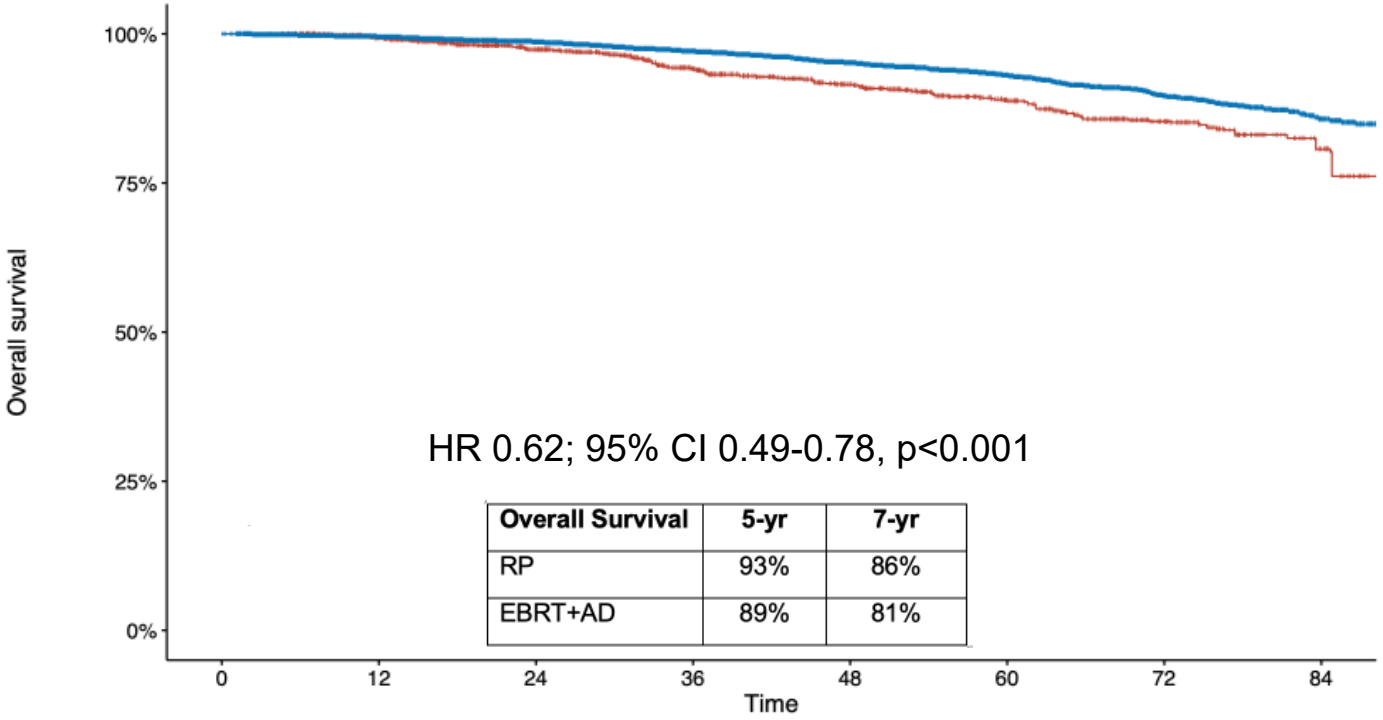
Results: Sensitivity Analysis

- Prior to 2010, the summary Gleason score was non-specific and reflected either biopsy Gleason score or prostatectomy Gleason score.
- Similarly, data regarding number of biopsy cores examined and number of positive biopsy cores were not routinely reported prior to 2010.

Results: Sensitivity Analysis

	RP (n = 11,345)	EBRT+ADT (n = 1,365)	SD[1]
Disease Characteristics			
Biopsy Gleason score, n (%)			0.02
8	7,271 (64.1)	872 (63.9)	
9	3,867 (34.1)	465 (34.1)	
10	208 (1.8)	28 (2.1	
Biopsy cores examined, median (IQR)	12 (12-12)	12 (12-12)	0.005
% Biopsy cores positive, median (IQR)	50.0 (26.7-66.7)	50.0 (25.0-66.7)	0.03

Results: Sensitivity Analysis



HR 0.62; 95% CI 0.49-0.78, p<0.001

Overall Survival	5-yr	7-yr
RP	93%	86%
EBRT+AD	89%	81%

Strengths

- Emulation framework

Limitations

- Non-randomized
- NCDB only captures OS
- No EBRT+brachytherapy arm
- Unable to quantify duration or type of ADT utilized in EBRT arm

Conclusion

In observational analyses designed to emulate a target clinical trial of men with high-grade, clinically localized prostate cancer, RP was associated with improved OS compared with EBRT+ADT.

Questions/Discussion