ELSEVIER

Urologic Oncology: Seminars and Original Investigations 37 (2019) 813.e11−813.e19

UROLOGIC ONCOLOGY

Clinical-Prostate cancer

Survival after radiotherapy vs. radical prostatectomy for unfavorable intermediate-risk prostate cancer

Nikhil T. Sebastian, M.D.[a], Joseph P. McElroy, Ph.D.[b], Douglas D. Martin, M.D.[a], Debasish Sundi, M.D.[c], Dayssy Alexandra Diaz, M.D.[a,*]

[a] *Department of Radiation Oncology, The Ohio State University Comprehensive Cancer Center − Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus, OH*

[b] *Department of Biomedical Informatics, The Ohio State University College of Medicine, Columbus OH*

[c] *Department of Urology, The Ohio State University Comprehensive Cancer Center − Arthur G. James Cancer Hospital and Richard J. Solove Research Institute, Columbus OH*

Received 17 February 2019; received in revised form 8 April 2019; accepted 17 April 2019

Abstract

Background: The optimal treatment for unfavorable intermediate-risk prostate cancer is unknown. Given the lack of randomized evidence, large comparative studies may be useful in guiding clinical decision-making.

Methods: We queried the National Cancer Database for patients with unfavorable intermediate-risk prostate cancer, as defined by the National Comprehensive Cancer Network. We compared overall survival between patients treated with radical prostatectomy (RP), external beam radiation therapy (EBRT), brachytherapy, and EBRT plus brachytherapy (EBRT+BT) using Cox proportional hazards models and propensity score matching.

Results: A total of 10,439 patients were analyzed. There was no statistically significant difference in overall survival between RP and EBRT+BT (hazard ratio [HR] = 1.24; 95% confidence interval [CI] 0.58−2.65). RP was associated with higher survival when compared to EBRT (HR = 2.30, 95% CI 1.70−3.20) and brachytherapy (HR = 2.90, 95% CI 1.40−6.20). When accounting for androgen deprivation therapy (ADT), there was no statistically significant difference in survival between RP and brachytherapy with ADT (HR = 3.08; 95% CI 0.62 −15.27) or EBRT to a dose of ≥7920 cGy with ADT (HR = 2.6, 95% CI 0.50−13.20).

Conclusion: We found no statistically significant difference in survival between RP and EBRT+BT. EBRT and brachytherapy had higher mortality, respectively, compared to RP. When including only radiotherapy patients who received ADT and, in the case of EBRT, a total dose ≥ 7920 cGy, there was no statistically significant difference in survival when comparing RP to EBRT or brachytherapy. These findings should be prospectively studied.

Keywords: Prostatic neoplasms; Radiation; Brachytherapy; Combined modality therapy; Prostatectomy

1. Introduction

Prostate cancer accounts for nearly one-fifth of cancers in men in the United States, with over 160,000 men being diagnosed in 2018 [1]. Of these, the majority are classified as intermediate-risk based on criteria defined by the National Comprehensive Cancer Network (NCCN) [2]. Intermediate-risk prostate cancer represents a heterogeneous population [3] for which primary therapy can entail active surveillance, radical prostatectomy (RP), external beam radiation therapy (EBRT) with or without androgen deprivation therapy (ADT), brachytherapy with or without ADT, or external beam radiation therapy plus brachytherapy (EBRT+BT) with or without ADT [2,4,5].

In recognition of the prognostic heterogeneity of intermediate-risk prostate cancer, substratification schemes of "favorable" and "unfavorable" intermediate risk have been adapted into clinical practice guidelines [2,6−8]. This

Funding sources: None related to this work.

Conflict of interest disclosures: None.

*Corresponding author. Tel.: 614-293-3250; fax: 614-685-8894.

E-mail address: Dayssy.DiazPardo@osumc.edu (D.A. Diaz).

https://doi.org/10.1016/j.urolonc.2019.04.022

1078-1439/

subclassification proposes distinct treatment paradigms for each of these groups, with "unfavorable" patients requiring more aggressive therapy [6]. Nevertheless, there is little prospective evidence to guide treatment decisions for unfavorable intermediate-risk prostate cancer.

Although the results of the ProtecT trial suggest equivalence between RP and radiotherapy in low-to-intermediate risk prostate cancer, unfavorable intermediate-risk patients were likely poorly represented in this trial, in which only 21% of participants were intermediate risk [9]. Even within radiotherapy-based management, the relative role of EBRT, brachytherapy, and ADT are unclear. Recent data from the ASCENDE-RT trial, while underpowered for a survival endpoint, suggest superiority of low dose rate brachytherapy boost vs. conventionally dose-escalated EBRT in biochemical progression-free survival in the treatment of intermediate- and high-risk prostate cancer [10]. At the same time, initial reports of NRG Oncology/Radiation Therapy Oncology Group (RTOG) 0232 suggest equivalence between brachytherapy alone and EBRT with brachytherapy boost in a cohort of intermediate-risk patients in which the relative proportion of favorable and unfavorable patients is currently unknown [11]. Furthermore, although there is randomized evidence to suggest a survival benefit with addition of ADT to EBRT for intermediate-risk prostate cancer [12,13], the role of ADT in the modern era of dose-escalated radiotherapy is unclear and currently being prospectively evaluated [14].

Currently, there are no published randomized trials comparing EBRT (with or without brachytherapy boost) or brachytherapy with RP in unfavorable intermediate-risk prostate cancer. Comparative analysis of available patient data may help to inform patients and providers in treatment decision-making. To this end, we conducted a study comparing survival outcomes between RP, EBRT, brachytherapy, and EBRT+BT using the National Cancer Database (NCDB), a nationwide hospital-based registry that captures approximately 70% of newly diagnosed cancers in the United States. We additionally performed a secondary analysis of survival with stratification for receipt of ADT in radiotherapy cohorts.

2. Methods

2.1. Study population

We identified 1,256,877 patients diagnosed with prostate adenocarcinoma between 2004 and 2014 using the NCDB. We selected for patients with pathologic confirmation in whom prostate cancer was their first cancer diagnosis ($n = 1,095,624$). We included only those patients diagnosed before 2012 to ensure adequate follow-up ($n = 863,153$). We included patients up to the age of 70, with a Charlson/Deyo comorbidity score of 0 to 1 ($n = 611,593$). Only patients with up to clinical stage T3N0M0 disease were included ($n = 431,036$) to exclude group stage IV disease. Only patients with a Gleason Score 6 to 10 were included while patients with unavailable or discordant primary/secondary Gleason scores and total Gleason scores were excluded.

Of the remaining 117,378 patients, we identified 47,364 patients as meeting one or more of the following NCCN criteria for intermediate-disease[2]: PSA 10 to 20 ng/ml, Gleason score of 7, T-stage T2b to T2c. We included only patients for whom there was available data on number of positive or total biopsy cores evaluated and for whom at least 10 cores were evaluated ($n = 22,741$). Of these, 11,834 patients met criteria for NCCN unfavorable intermediate-risk disease, characterized by primary Gleason pattern 4, number of positive biopsy cores ≥50%, and/or presence of >1 intermediate-risk factor [2,6,7]. Of these unfavorable intermediate-risk patients, 11,001 had treatment with either RP, EBRT, brachytherapy, or EBRT+BT. We limited the patients who received radiation to those who received a total dose between 70 and 90 Gy for patients who received EBRT alone and a regional dose between 40 Gy and 50.4 Gy for patients who received EBRT with or without a brachytherapy boost. A secondary analysis was performed that included stratification based on receipt of ADT. Additionally, on the basis of randomized evidence suggesting benefit in biochemical progression-free survival with dose-escalation [15–17] and retrospective evidence showing overall survival benefit [18,19], further analysis was performed specifically comparing RP to EBRT patients who received ADT and a total radiation dose ≥ 7920 cGy.

2.2. Statistical analyses

All analyses were performed using R. Univariable pairwise comparisons were visualized with Kaplan–Meier plots and tested with log-rank tests. Multivariable analyses were performed using Cox regression, and Analysis of Deviance was used for testing multilevel variable (n levels > 2) associations. Cases were matched (pairwise) 1:1 on the basis of age, race, year of diagnosis, T-stage, Gleason score, PSA, treatment facility type, distance to hospital, population density, and education, measured as the percentage of adults in the patient's zip code who graduated from high school. Nearest neighbor matching was used with propensity score logit distances, a caliper = 0.1, and exact matching on the basis of primary and secondary Gleason score. A mixed effects Cox model with a random effect for pair was used to analyze the matched data. Median follow-up times were calculated with the reverse Kaplan–Meier method. Due to multiple pairwise comparisons, Bonferroni adjusted significance thresholds (2-sided) were calculated and used to declare significance for the main hypothesis tests.

3. Results

Fig. 1 shows the schema for selection of the analyzed cohort and Table 1 shows the patient- and disease-specific characteristics per treatment cohort. Our final cohort

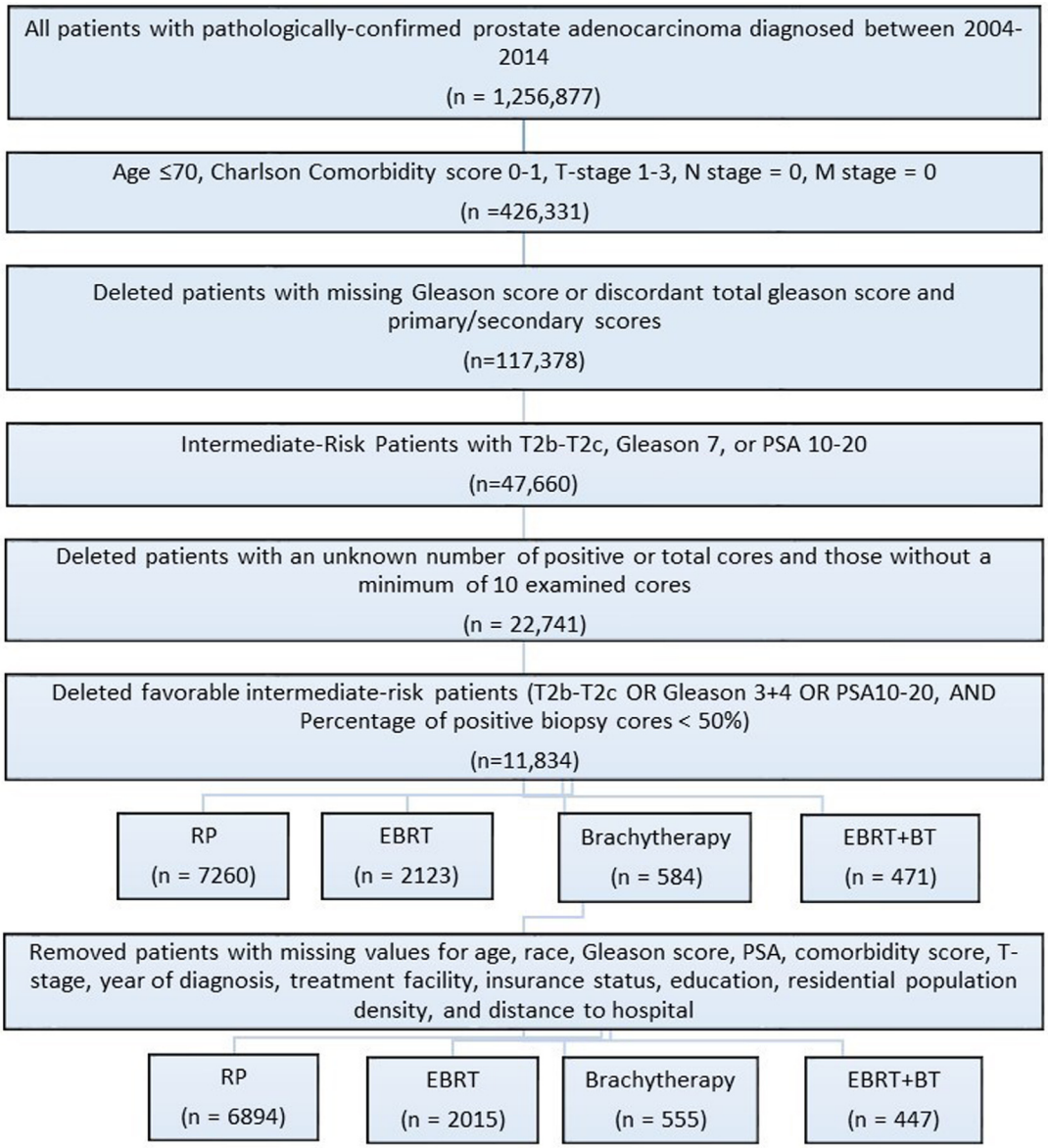

Fig. 1. Patient selection schema. Abbreviations: *RP*, radical prostatectomy; *EBRT*, external beam radiation therapy; *EBRT+BT*, external beam radiation therapy plus brachytherapy.

consisted of 10,439 patients, all of whom received either RP ($n = 7,260$), EBRT ($n = 2,124$), brachytherapy ($n = 584$), or EBRT+BT ($n = 471$) as their primary treatment. Median follow-up was 4.1 years. There was a statistically significant difference ($P < 0.05$) in all baseline characteristics between groups with the exception of year of diagnosis ($P = 0.064$) and T-stage ($P = 0.051$).

On Cox regression multivariate analysis (Table 2), predictors of overall mortality were lower education (HR = 1.38 [95% CI 1.03−1.84]; $P = 0.029$), Charlson comorbidity score of 1 (HR = 1.82 [95% CI 1.40−2.36]; $P < 0.001$), and PSA 10 to 20 ng/ml (HR = 1.35 [95% CI 1.04 −1.74]; $P = 0.023$). When compared to RP, predictors of overall mortality included treatment with EBRT (HR = 2.37 [95% CI 1.83−3.07]; $P < 0.001$) and treatment with brachytherapy (HR = 1.98 [95% CI 1.30−3.01]; $P = 0.001$).

After excluding patients with missing values for covariates, there were 6,894 patients who received RP, 2015 who received EBRT, 555 who received brachytherapy, and 447 who received EBRT+BT. The cohorts were well-balanced with regard to matching covariates (Supplementary Fig. 1). A Bonferroni adjusted P-threshold of $0.05/6 = 0.008$ was used for the 6 pairwise treatment comparisons. After propensity score matching, there was no statistically significant difference in survival between RP and EBRT+BT (HR = 1.24 [95% CI 0.58−2.65]; $P = 0.57$). RP was associated with statistically significant higher survival when compared to EBRT (HR = 2.30 [95% CI 1.70−3.20]; $P < 0.001$) and brachytherapy (HR = 2.90 [95% CI 1.40−6.20]; $P = 0.004$) (Fig. 2a−c). Overall survival difference did not reach statistical significance when directly comparing matched cohorts of EBRT+BT to brachytherapy alone

Table 1
Patient demographics and clinical characteristics of the study population.

Characteristic	RP	EBRT	Brachytherapy	EBRT+BT	P*
n (%)	7260 (100%)	2124 (100%)	584 (100%)	471 (100%)	
Age (Years)					
Median (Interquartile range)	61 (56-65)	64 (60-67)	64 (59-67)	63 (59-67)	<0.001
Race					
White	5914 (81.5%)	1519 (71.5%)	447 (76.5%)	337 (71.5%)	<0.001
Black	1057 (14.6%)	533 (25.1%)	119 (20.4%)	108 (22.9%)	
Other	192 (2.6%)	56 (2.6%)	12 (2.1%)	20 (4.2%)	
Unknown	97 (1.3%)	16 (0.8%)	6 (1.0%)	6 (1.3%)	
Year of diagnosis					
Median	2011	2011	2010	2011	0.064
Gleason score					
6	392 (5.4%)	91 (4.3%)	38 (6.5%)	18 (3.8%)	0.044
7	6868 (94.6%)	2033 (95.7%)	546 (93.5%)	453 (96.2%)	
PSA					
<10	5874 (80.9%)	1549 (72.9%)	460 (78.8%)	367 (77.9%)	<0.001
10−20	1386 (19.1%)	575 (27.1%)	124 (21.2%)	104 (22.1%)	
Clinical T-stage					
cT1	4891 (67.4%)	1410 (66.4%)	385 (65.9%)	289 (61.4%)	0.051
cT2	2369 (32.6%)	714 (33.6%)	199 (34.1%)	182 (38.6%)	
Charlson comorbidity score					
0	6048 (83.3%)	1848 (87.0%)	515 (88.2%)	425 (90.2%)	<0.001
1	1212 (16.7%)	276 (13.0%)	69 (11.8%)	46 (9.8%)	
Facility type					
Community cancer program	321 (4.4%)	232 (10.9%)	58 (9.9%)	30 (6.4%)	<0.001
Comprehensive community cancer program	2838 (39.1%)	918 (43.2%)	311 (53.3%)	234 (49.7%)	
Academic/Research program	3343 (46.0%)	721 (33.9%)	149 (25.5%)	116 (24.6%)	
Integrated network cancer program	754 (10.4%)	253 (11.9%)	66 (11.3%)	90 (19.1%)	
Other	4 (0.1%)	0 (0.0%)	0 (0.0%)	1 (0.2%)	
Distance to hospital					
≤ 50 miles	5989 (82.5%)	2004 (94.4%)	514 (88.0%)	445 (94.5%)	<0.001
> 50 miles	1240 (17.1%)	111 (5.2%)	67 (11.5%)	24 (5.1%)	
Education level†					
>79%	6275 (86.4%)	1736 (81.7%)	511 (87.5%)	388 (82.4%)	
≤ 79%	955 (13.2%)	378 (17.8%)	69 (11.8%)	82 (17.4%)	<0.001
Unknown	30 (0.4%)	10 (0.5%)	4 (0.7%)	1 (0.2%)	
County size					
Metro	5895 (81.2%)	1774 (83.5%)	466 (79.8%)	422 (89.6%)	<0.001
Urban	997 (13.7%)	266 (12.5%)	93 (15.9%)	34 (7.2%)	
Rural	82 (1.1%)	14 (0.7%)	4 (0.7%)	2 (0.4%)	
Unknown	286 (3.9%)	70 (3.3%)	21 (3.6%)	13 (2.8%)	
Insurance status					
Uninsured	153 (2.1%)	82 (3.9%)	13 (2.2%)	6 (1.3%)	<0.001
Private insurance	4854 (66.9%)	930 (43.8%)	314 (53.8%)	253 (53.7%)	
Medicaid	174 (2.4%)	91 (4.3%)	11 (1.9%)	19 (4.0%)	
Medicare	1929 (26.6%)	897 (42.2%)	225 (38.5%)	175 (37.2%)	
Other government insurance	91 (1.3%)	89 (4.2%)	15 (2.6%)	9 (1.9%)	
Unknown	59 (0.8%)	35 (1.6%)	6 (1.0%)	9 (1.9%)	

Abbreviations. *EBRT*, external beam radiation therapy. *EBRT+BT*, external beam radiation therapy plus brachytherapy; *RP*, radical prostatectomy.
* All statistical tests were two-sided. Reference threshold for significance = 0.05.
† Measured as the percentile of high-school graduates in patient's zip code.

(HR = 0.76 [95% CI 0.36−1.61; $P = 0.47$) or EBRT alone (HR = 0.66 [95% CI 0.34−1.26]; $P = 0.14$).

After matching cohorts based on stratification by use of concurrent ADT with radiotherapy, there was no statistically significant difference in any of the matching covariates for the various pairwise comparisons. Using a Bonferroni adjusted P-threshold of 0.05/27 = 0.0019, there was no statistically significant difference in survival between patients treated with RP compared to brachytherapy with ADT (HR = 3.08 [95% CI 0.62−15.27]; $P = 0.17$) or EBRT+BT with ADT (HR = 1.90 [0.35−10.37], $P = 0.46$). RP had higher survival compared to EBRT with ADT (HR = 2.80 [95% CI 1.70−4.60]; $P < 0.001$). The median dose of EBRT in this cohort was 7740 Gy (range

Table 2
Multivariable Cox proportional hazards analysis of covariate association with overall mortality.

Variable	Hazard ratio	95% Confidence interval	P*
Age	1.021	0.996 to 1.05	0.10
Race			
White	1.06	0.80 to 1.42	0.68
Black	0.57	0.23 to 1.40	0.22
Other	0.90	0.29 to 2.84	0.86
Year of diagnosis	1.08	0.91 to 1.29	0.36
Gleason score			
3+3			
3+4	1.07	0.62 to 1.82	0.82
4+3	1.03	0.60 to 1.79	0.91
PSA			
<10			
10–20	1.35	1.04 to 1.74	0.023
Clinical T-stage			
cT1			
cT2	0.90	0.70 to 1.15	0.38
Charlson comorbidity score			
0			
1	1.82	1.40 to 2.36	<0.001
Facility type			
Community cancer program			
Comprehensive community cancer program	0.97	0.64 to 1.48	0.90
Academic/Research program	0.77	0.49 to 1.20	0.25
Integrated network cancer program	0.84	0.50 to 1.41	0.51
Distance to hospital			
≤ 50 miles			
> 50 miles	.97	.65 to 1.46	0.90
Education level†			
>79%			
≤ 79%	1.38	1.03 to 1.84	0.029
County size			
Metro			
Urban	1.15	0.83 to 1.59	0.41
Rural	1.07	0.33 to 3.40	0.92
Insurance status			
Uninsured			
Private insurance	0.81	0.41 to 1.61	0.55
Medicaid	1.01	0.42 to 2.44	0.99
Medicare	1.10	0.55 to 2.23	0.79
Other government insurance	1.03	0.39 to 2.68	0.96
Treatment			
RP			
EBRT	2.37	1.83 to 3.07	< 0.001
Brachytherapy	1.98	1.30 to 3.01	0.001
EBRT+BT	1.43	0.83 to 2.45	0.20

Abbreviations: *EBRT*, external beam radiation therapy; *EBRT+BT*, external beam radiation therapy plus brachytherapy; *RP*, radical prostatectomy.
* All statistical tests were two-sided. Reference threshold for significance = 0.05.
† Measured as the percentile of high-school graduates in patient's zip code.

70000 cGy to 8900 cGy). When patients treated with EBRT with ADT were limited to those receiving a total dose of ≥ 7920 cGy, there was no statistically significant difference in survival between RP and EBRT with ADT (HR = 2.60 [95% CI 0.50–13.20]; $P = 0.25$). Table 3 includes hazard ratio estimates for overall mortality for radiotherapy groups with or without ADT when compared to RP. Table 4 shows hazard ratio estimates for overall mortality when comparing survival between radiotherapy groups stratified by use of ADT.

4. Discussion

The challenges in accruing to prospective trials with disparate modalities has prompted numerous retrospective studies comparing RP and radiotherapy. Prospective evidence for low-to-intermediate risk patients suggests equivalence between active surveillance, RP, and EBRT [9]. There is no randomized evidence, however, comparing RP to radiotherapy in unfavorable intermediate- or high-risk patients. While there are retrospective studies comparing

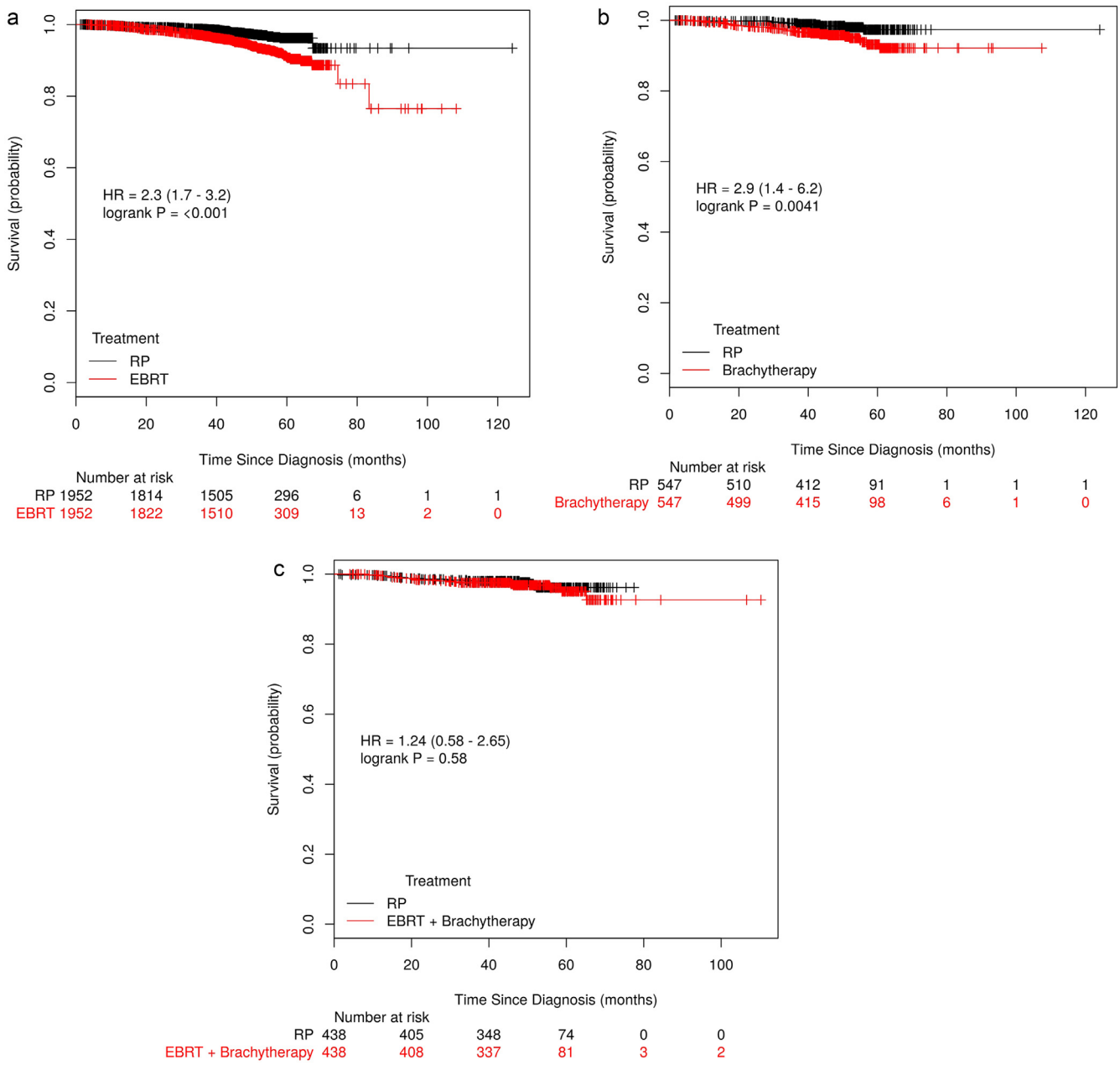

Fig. 2. Kaplan–Meier survival curves of matched cohorts comparing *P* to (a) EBRT, (b) Brachytherapy, and (c) EBRT+BT.

RP to EBRT or brachytherapy alone [20,21], there are no such studies comparing RP to EBRT+BT in intermediate-risk patients, despite evidence to suggest superiority of the latter compared to EBRT alone with regard to biochemical progression [10,22]. Moreover, to our knowledge, there are no studies comparing these treatments specifically in a cohort of unfavorable intermediate-risk patients, a prognostic group that likely requires distinct treatment paradigms [6].

The results of the recently published ASCENDE-RT trial suggest a benefit with brachytherapy-based dose-escalation when compared to EBRT alone in a cohort of intermediate-to-high risk patients. In this trial, intermediate- and high-risk prostate cancer patients were randomized to dose-escalation using EBRT alone or in combination with low-dose-rate prostate brachytherapy. Both arms entailed pelvic irradiation to 46 Gy with 12 months of ADT followed by dose-escalation via either EBRT or brachytherapy. At a median follow-up of 6.5 years, biochemical progression free-survival was 94% for intermediate-risk patients who received brachytherapy. Multivariate analysis indicated biochemical failure as a risk factor for mortality. While there was no statistically significant difference in overall survival between the arms, the trial was underpowered for this endpoint [10]. Simultaneously, early results of NRG Oncology/RTOG 0232 suggest that, for intermediate-risk

Table 3
Hazard ratio estimates (95% CIs) for overall mortality for propensity-score matched analysis of radiotherapy with stratification for use of ADT, compared to RP.

	*n**	HR (95% CI)	*P*†
RP			
EBRT without ADT	1032	3.9 (2.3–6.8)	< 0.001
EBRT with ADT	933	2.8 (1.7–4.6)	<0.001
EBRT > 7920 cGy with ADT	130	2.6 (0.5–13.2)	0.26
Brachytherapy without ADT	398	2.5 (1.1–5.7)	0.029
Brachytherapy with ADT	143	3.08 (0.62–15.27)	0.17
EBRT+BT without ADT	291	1.39 (0.56–3.45)	0.48
EBRT+BT with ADT	143	1.90 (0.35–10.37)	0.46

Abbreviations. *ADT*, androgen deprivation therapy; *CI,* confidence interval; *EBRT*, external beam radiation therapy. *EBRT+BT*, external beam radiation therapy plus brachytherapy; *HR,* hazard ratio; *RP*, radical prostatectomy.

* Per matched treatment group.

† All statistical tests were two-sided. Reference Bonferroni significance threshold = 0.05/27 = 0.0019.

patients, addition of EBRT to brachytherapy does not confer superior progression-free survival vs. brachytherapy alone. This trial included 588 intermediate-risk patients with T1c-T2b prostate cancer and either Gleason score 2 to 6 and PSA ≥ 10 and <20; Gleason score 7 and PSA < 10; or prostate volume < 60 cm^3. Patients were randomized to treatment with 45 Gy EBRT followed by Pd-103 or I-125 interstitial brachytherapy boost, or Pd-103 or I-125 monotherapy. Five-year progression-free survival was 85% for combined therapy and 86% for the brachytherapy alone arm, while overall grade ≥3 toxicity was 12% and 7%, respectively [11]. While the relative number of favorable and unfavorable patients in this study is currently unknown, these results suggest brachytherapy monotherapy may be a reasonable alternative to combined EBRT and brachytherapy and may spare excess treatment-related morbidity associated with combined modality therapy [23].

Unlike ASCENDE-RT or RTOG 0232, our study does not evaluate biochemical or disease progression and is thus unable to provide validation for the primary endpoints and findings of these studies. But similar to these trials, our study did not reveal statistically significant difference in survival between matched cohorts treated with EBRT+BT when compared to those treated with EBRT or brachytherapy alone. However, these trials were not statistically powered to show a survival difference and our study's power is similarly limited by low patient numbers in the comparisons between radiotherapy cohorts. For this reason, our findings are insufficient to explicitly confirm the presence or absence of overall survival benefit with combination radiotherapy compared to radiation monotherapy.

Two trials have shown a survival benefit with the addition of ADT to radiotherapy for patients with intermediate-risk cancer, albeit in the setting of standard-dose radiotherapy. D'Amico et al. reported a 10% absolute survival benefit after a median follow-up of 8 years with the addition of 6 months of ADT to 70 Gy of conventional radiotherapy [12]. Additionally, RTOG 9408, which contained low- and intermediate-risk patients, showed a 7% overall survival benefit at 10 years with the addition of 4 months of ADT to 66.6 Gy for the subset of patients with intermediate-risk disease [13]. The benefit of ADT in the era of dose-escalated radiotherapy is currently being evaluated in RTOG 0815 [14]. In comparison to the aforementioned studies, when evaluating radiotherapy groups who did and did not receive ADT, we found no statistically significant

Table 4
Hazard ratio estimates (95% CIs) for overall mortality for propensity-score matched analysis comparing radiotherapy groups with *stratification for use of ADT*.

	*n**	HR (95% CI)	*P*†
EBRT without ADT vs. EBRT with ADT	801	0.94 (0.63–1.39)	0.74
EBRT without ADT vs. Brachytherapy without ADT	380	0.88 (0.47–1.62)	0.67
EBRT without ADT vs. Brachytherapy with ADT	141	0.67 (0.26–1.73)	0.41
EBRT without ADT vs. EBRT+BT without ADT	285	0.87 (0.39–1.93)	0.72
EBRT without ADT vs. EBRT+BT with ADT	146	0.49 (0.15–1.63)	0.24
EBRT with ADT vs. Brachytherapy without ADT	359	1.00 (0.53–1.90)	0.99
EBRT with ADT vs. Brachytherapy with ADT	139	0.67 (0.22–2.06)	0.66
EBRT with ADT vs. EBRT+BT without ADT	270	1.25 (0.52–3.04)	0.62
EBRT with ADT vs. EBRT+BT with ADT	145	0.43 (0.13–1.39)	0.16
Brachytherapy without ADT vs. Brachytherapy with ADT	137	0.90 (0.33–2.48)	0.85
Brachytherapy without ADT vs. EBRT+BT without ADT	246	0.73 (0.32–1.64)	0.42
Brachytherapy without ADT vs. EBRT+BT with ADT	128	0.41 (0.13–1.33)	0.14
Brachytherapy with ADT vs. EBRT+BT without ADT	125	1.01 (0.33–3.15)	0.98
Brachytherapy with ADT vs. EBRT+BT with ADT	96	0.62 (0.10–3.73)	0.60
EBRT+BT without ADT vs. EBRT+BT with ADT	130	0.31 (0.08–1.13)	0.076

Abbreviations. *ADT*, androgen deprivation therapy; *CI,* confidence interval; *EBRT*, external beam radiation therapy. . *EBRT+BT*, external beam radiation therapy plus brachytherapy; *HR,* hazard ratio.

* Per matched treatment group.

† All statistical tests were two-sided. Reference Bonferroni significance threshold = 0.05/27 = 0.0019.

difference in survival. However, the small size of these cohorts, short patient follow-up, and unavailability of data on hormone therapy duration undermine assessment of the influence of ADT on survival.

While there is prospective evidence to inform decision making between radiotherapy-based modalities, there is no such randomized evidence comparing RP to radiotherapy in patients with unfavorable intermediate-risk prostate cancer. In our study, there was no statistically significant difference in survival between RP and EBRT+BT. RP had statistically significant higher overall survival compared to EBRT or brachytherapy. However, when analyzing radiotherapy with or without ADT, there was no statistically significant difference between RP and brachytherapy with ADT or EBRT $\geq$ 7920 cGy with ADT. Several randomized trials have demonstrated benefit of dose-escalation in improving biochemical recurrence and while none have demonstrated a survival benefit, this may be due to short follow-up and insufficient patient numbers [15−17]. Furthermore, the contemporary dosing derived from these trials is arguably a precondition for evaluating EBRT within a risk-group classification derived in the context of dose-escalated radiotherapy [6]. Nevertheless, due to the low number of patients in this subset analysis in our study, these findings should be clarified using larger patient cohorts.

There are several advantages to our study. Namely, as the NCDB provides information regarding radiation dose, fractionation, and use of ADT, we were able to select for patients who received adequate standard-of-care radiation treatment and exclude those who received palliative or non-standard dosing. Although our total radiation dose cutoff inherently excludes common hypofractionation regimens, which recent clinical trials have deemed largely equivalent to conventional fractionation [24,25], it is unlikely that this cohort of patients in our study, treated prior to 2012, were treated with these more recently established regimens. Additionally, given the established equivalence of hypofractionation with conventional fractionation with regard to survival, it is unlikely our results would be significantly different with the inclusion of these regimens. Finally, due to the availability of positive and total biopsy cores, we were able to ensure adequate pathologic evaluation.

Despite the advantages of using a large, statistically robust data set, we must acknowledge several limitations of this study. First, it should be noted that the treatment groups were significantly different for most baseline patient and disease characteristics. Despite accounting for several relevant socioeconomic variables and comorbidity, as well as the use of propensity score matching, it is impossible to eliminate all potential confounders due to the study's retrospective design. This is especially important when considering comparisons between radiotherapy and surgery, as it is well-established that prostate cancer patients treated with radiotherapy are older and have more comorbidities than those treated with RP [26]. Another significant limitation of this study is that the short median follow-up of 4.1 years is restricting in a cohort of patients generally typified by a median survival exceeding 10 years [10]. Along these lines, as previously noted, the analysis of radiotherapy with or without ADT was limited in power due to the fewer number of analyzable patients. Additionally, the NCDB does not capture information regarding cancer-specific mortality, biochemical progression, or treatment-related morbidity, which are relevant endpoints considering the long natural history of prostate cancer and the risk of competing comorbidities [27]. Finally, while NCCN criteria were utilized to define unfavorable intermediate-risk in this study, separate American Urological Association criteria have been proposed, with the primary difference being the inclusion of percentage of positive biopsy cores in NCCN criteria [8]. Although these more stringent criteria were used for this study due to evidence showing the utility of biopsy core information in refining prognostication [28,29], we acknowledge this may limit the applicability of this data to alternate definitions of the unfavorable intermediate-risk classification.

In summary, we observed no statistically significant difference in overall survival between unfavorable intermediate-risk patients treated with RP or EBRT+BT. RP was associated with higher survival when compared to EBRT and to brachytherapy alone. In a subset analysis, there was no statistically significant difference in survival when comparing RP to brachytherapy with ADT or standard-of-care, dose-escalated EBRT with ADT, although this analysis was limited by low patient numbers. While randomized prospective comparison between surgery and radiotherapy-based modalities is warranted, these findings may be useful in guiding clinical decision-making in a multidisciplinary approach that emphasizes differences in treatment-related morbidity.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.urolonc.2019.04.022.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68(1):7–30. https://doi.org/10.3322/caac.21442.

[2] Mohler JL, Armstrong AJ, Bahnson RR, et al. Prostate cancer, version 1.2016. J Natl Compr Cancer Netw 2016;14(1):19–30. https://doi.org/10.6004/jnccn.2016.0004.

[3] Reese AC, Pierorazio PM, Han M, Partin AW. Contemporary evaluation of the national comprehensive cancer network prostate cancer risk classification system. Urology 2012;80(5):1075–9. https://doi.org/10.1016/j.urology.2012.07.040.

[4] Mottet N, Bellmunt J, Bolla M, et al. EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 2017;71(4):618–29. https://doi.org/10.1016/j.eururo.2016.08.003.

[5] Chin J, Rumble RB, Kollmeier M, et al. Brachytherapy for patients with prostate cancer: American Society of Clinical Oncology/Cancer

Care Ontario Joint Guideline Update. J Clin Oncol 2017;35 (15):1737–43. https://doi.org/10.1200/JCO.2016.72.0466.

[6] Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. Eur Urol 2013;64(6):895–902. https://doi.org/10.1016/j.eururo.2013.03.033.

[7] Zumsteg ZS, Zelefsky MJ. Short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer undergoing dose-escalated radiotherapy: the standard of care. Lancet Oncol 2012;13 (6):e259–69. https://doi.org/10.1016/S1470-2045(12)70084-0.

[8] Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. J Urol 2018;199(3):683–90. https://doi.org/10.1016/j.juro.2017.11.095.

[9] Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med 2016;375(15):1415–24. https://doi.org/10.1056/NEJMoa1606220.

[10] Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT Trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol 2017;98(2):275–85. https://doi.org/10.1016/j.ijrobp.2016.11.026.

[11] Prestidge BR, Winter K, Sanda MG, et al. Initial report of NRG Oncology/RTOG 0232: a phase 3 study comparing combined external beam radiation and transperineal interstitial permanent brachytherapy with brachytherapy alone for selected patients with intermediate-risk prostatic carcinoma. Int J Radiat Oncol Biol Phys 2016;96(2):S4. https://doi.org/10.1016/j.ijrobp.2016.06.026.

[12] D'Amico AV, Chen M-H, Renshaw A, Loffredo M, Kantoff PW. Long-term follow-up of a randomized trial of radiation with or without androgen deprivation therapy for localized prostate cancer. JAMA 2015;314 (12):1291–3. https://doi.org/10.1001/jama.2015.8577.

[13] Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. N Engl J Med 2011;365(2):107–18. https://doi.org/10.1056/NEJMoa1012348.

[14] Radiation Therapy Oncology Group 0815. A Phase III prospective randomized trial of dose-escalated radiotherapy with or without short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer. Version date 4/21/15. https://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?action=openFile&FileID=13149.

[15] Michalski JM, Moughan J, Purdy J, et al. Effect of standard vs dose-escalated radiation therapy for patients with intermediate-risk prostate cancer: the NRG oncology RTOG 0126 randomized clinical trial. JAMA Oncol 2018;4(6):e180039. https://doi.org/10.1001/jamaoncol.2018.0039.

[16] Beckendorf V, Guerif S, Le Prisé E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol 2011;80(4):1056–63. https://doi.org/10.1016/j.ijrobp.2010.03.049.

[17] Dearnaley DP, Jovic G, Syndikus I, et al. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: long-term results from the MRC RT01 randomised controlled trial. Lancet Oncol 2014;15(4):464–73. https://doi.org/10.1016/S1470-2045(14)70040-3.

[18] Kalbasi A, Li J, Berman AT, et al. Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. JAMA Oncol 2015;1(7):897. https://doi.org/10.1001/jamaoncol.2015.2316.

[19] Amini A, Jones B, Jackson MW, et al. Survival outcomes of dose-escalated external beam radiotherapy versus combined brachytherapy for intermediate and high risk prostate cancer using the national cancer data base. J Urol 2016;195(5):1453–8. https://doi.org/10.1016/j.juro.2015.11.005.

[20] Marsh S, Walters RW, Silberstein PT. Survival outcomes of radical prostatectomy versus radiotherapy in intermediate-risk prostate cancer: a NCDB study. Clin Genitourin Cancer 2018;16(1):e39–46. https://doi.org/10.1016/j.clgc.2017.07.029.

[21] Goy BW, Soper MS, Burchette RJ, Chang TC, Cosmatos HA. Ten year treatment outcomes of radical prostatectomy vs external beam radiation therapy vs. brachytherapy for 1,503 patients with intermediate risk prostate cancer. J Clin Oncol 2018;36(6_suppl). https://doi.org/10.1200/JCO.2018.36.6_suppl.47:47-47.

[22] Helou J, D'Alimonte L, Loblaw A, et al. High dose-rate brachytherapy boost for intermediate risk prostate cancer: Long-term outcomes of two different treatment schedules and early biochemical predictors of success. Radiother Oncol 2015;115(1):84–9. https://doi.org/10.1016/j.radonc.2015.02.023.

[23] Rodda S, Tyldesley S, Morris WJ, et al. ASCENDE-RT: an analysis of treatment-related morbidity for a randomized trial comparing a low-dose-rate brachytherapy boost with a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. Int J Radiat Oncol 2017;98(2):286–95. https://doi.org/10.1016/j.ijrobp.2017.01.008.

[24] Dearnaley D, Syndikus I, Mossop H, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol 2016;17(8):1047–60. https://doi.org/10.1016/S1470-2045(16)30102-4.

[25] Catton CN, Lukka H, Gu C-S, et al. Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol 2017;35(17):1884–90. https://doi.org/10.1200/JCO.2016.71.7397.

[26] Cancela M, de C, Comber H, Sharp L. Age remains the major predictor of curative treatment non-receipt for localised prostate cancer: a population-based study. Br J Cancer 2013;109(1):272–9. https://doi.org/10.1038/bjc.2013.268.

[27] Daskivich TJ, Chamie K, Kwan L, et al. Comorbidity and competing risks for mortality in men with prostate cancer. Cancer 2011;117 (20):4642–50. https://doi.org/10.1002/cncr.26104.

[28] D'Amico AV, Whittington R, Malkowicz SB, et al. Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer. J Clin Oncol Off J Am Soc Clin Oncol 2000;18 (6):1164–72. https://doi.org/10.1200/JCO.2000.18.6.1164.

[29] D'Amico AV, Keshaviah A, Manola J, et al. Clinical utility of the percentage of positive prostate biopsies in predicting prostate cancer-specific and overall survival after radiotherapy for patients with localized prostate cancer. Int J Radiat Oncol Biol Phys 2002;53(3):581–7.