

CLINICAL INVESTIGATION

Prostate

RADICAL PROSTATECTOMY, EXTERNAL BEAM RADIOTHERAPY <72 Gy, EXTERNAL BEAM RADIOTHERAPY ≥72 Gy, PERMANENT SEED IMPLANTATION, OR COMBINED SEEDS/EXTERNAL BEAM RADIOTHERAPY FOR STAGE T1–T2 PROSTATE CANCER

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Purpose: To review the biochemical relapse-free survival (bRFS) rates after treatment with permanent seed implantation (PI), external beam radiotherapy (EBRT) <72 Gy (EBRT <72), EBRT ≥72 Gy (EBRT ≥72), combined seeds and EBRT (COMB), or radical prostatectomy (RP) for clinical Stage T1–T2 localized prostate cancer treated between 1990 and 1998.

Methods and Materials: The study population comprised 2991 consecutive patients treated at the Cleveland Clinic Foundation or Memorial Sloan Kettering at Mercy Medical Center. All cases had pretreatment prostate-specific antigen (iPSA) levels and biopsy Gleason scores (bGSs). Neoadjuvant androgen deprivation for ≤6 months was given in 622 cases (21%). No adjuvant therapy was given after local therapy. RP was used for 1034 patients (35%), EBRT <72 for 484 (16%), EBRT ≥72 for 301 (10%), PI for 950 (32%), and COMB for 222 patients (7%). The RP, EBRT <72, EBRT ≥72, and 154 PI patients were treated at Cleveland Clinic Foundation. The median radiation doses in EBRT <72 and EBRT ≥72 case was 68.4 and 78.0 Gy, respectively. The median follow-up time for all cases was 56 months (range 12–145). The median follow-up time for RP, EBRT <72, EBRT ≥72, PI, and COMB was 66, 75, 49, 47, and 46 months, respectively. Biochemical relapse was defined as PSA levels >0.2 for RP cases and three consecutive rising PSA levels (American Society for Therapeutic Radiology Oncology consensus definition) for all other cases. A multivariate analysis for factors affecting the bRFS rates was performed using the following variables: clinical T stage, iPSA, bGS, androgen deprivation, year of treatment, and treatment modality. The multivariate analysis was repeated excluding the EBRT <72 cases.

Results: The 5-year bRFS rate for RP, EBRT <72, EBRT ≥72, PI, and COMB was 81%, 51%, 81%, 83%, and 77%, respectively ($p < 0.001$). The 7-year bRFS rate for RP, EBRT <72, EBRT ≥72, PI, and COMB was 76%, 48%, 81%, 75%, and 77%, respectively. Multivariate analysis, including all cases, showed iPSA ($p < 0.001$), bGS ($p < 0.001$), year of therapy ($p < 0.001$), and treatment modality ($p < 0.001$) to be independent predictors of relapse. Because EBRT <72 cases had distinctly worse outcomes, the analysis was repeated after excluding these cases to discern any differences among the other modalities. The multivariate analysis excluding the EBRT <72 cases revealed iPSA ($p < 0.001$), bGS ($p < 0.001$), and year of therapy ($p = 0.001$) to be the only independent predictors of relapse. Treatment modality ($p = 0.95$), clinical T stage ($p = 0.09$), and androgen deprivation ($p = 0.56$) were not independent predictors for failure.

Conclusion: The biochemical failure rates were similar among PI, high-dose (≥72 Gy) EBRT, COMB, and RP for localized prostate cancer. The outcomes were significantly worse for low-dose (<72 Gy) EBRT.
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Localized prostate cancer, Radiotherapy, Surgery, Relapse free survival.

INTRODUCTION

Patients with newly diagnosed localized prostate cancer face a bewildering number of choices among potentially curative

therapies. In the past 15 years, radical prostatectomy (RP), various forms of external beam radiotherapy (EBRT), and brachytherapy have all been promoted as reasonable options with acceptable toxicity and similar rates of biochemical con-

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trol and overall survival when patient selection factors have been accounted for. Additional confusion arises when considering the myriad variations of each basic therapeutic option: retropubic vs. perineal vs. laparoscopic vs. robotic RP; standard field vs. conformal vs. intensity-modulated EBRT; temporary vs. permanent brachytherapy; photons vs. protons; ^{125}I vs. ^{103}Pd ; and various combinations of therapies, including RP plus adjuvant EBRT, neoadjuvant hormones plus EBRT; and brachytherapy plus EBRT.

A comparison of different therapies for localized prostate cancer should include issues of cancer control, morbidity, quality of life, salvage of primary treatment failure, late effects, and cost. Of these, cancer control is the most important, because most patients may be willing to endure some morbidity or sacrifice some quality of life for a more efficacious therapy. Such comparisons are best performed in randomized controlled trials, in which pretreatment factors, which potentially affect the outcome measures, are equally distributed among the study arms. A recently reported Scandinavian study of RP vs. observation demonstrated an advantage to RP in metastasis-free and disease-specific survival and no differences in overall survival or quality of life (1, 2). Previous randomized trials comparing RP vs. EBRT have been unsuccessful in determining which has a higher cure rate. A randomized trial published in 1982 showing an advantage to RP was never widely accepted because of randomization artifacts and worse-than previously reported RT results (3, 4). The Southwest Oncology Group closed a randomized study in the mid-1980s because of poor accrual. The American College of Surgeons Oncology Group has recently opened the Surgical Prostatectomy versus Interstitial Radiation Intervention Trial (SPIRIT) that randomizes RP vs. brachytherapy for patients with favorable risk features. This trial is powered for survival and includes parallel quality-of-life assessments, but since opening has accrued slowly and will not report meaningful results for >5 years.

Recognizing the limitations inherent in nonrandomized comparisons, sufficient data have been accumulated during the past decade with all available therapies for localized disease to report a meaningful comparison of cancer control outcomes in contemporaneously treated patients in whom known prognostic factors can be controlled for by multivariate analysis. In this study, we thus compiled the biochemical failure-free survival rates among nearly 3000 patients diagnosed and treated in the prostate-specific antigen (PSA) era with one of five commonly applied therapies for localized prostate cancer: RP alone, EBRT of <72 Gy, EBRT of >72 Gy, permanent brachytherapy implant (PI), and combination therapy with EBRT and permanent implantation (COMB). The goal of this report was to compile the available outcome data, so that patients can make informed decisions about the available treatment options.

METHODS AND MATERIALS

Patient population

The study cohort included 2991 consecutively treated patients with clinical Stage T1 and T2 adenocarcinoma of

the prostate treated with RP, EBRT <72 Gy, EBRT \geq 72 Gy, PI, or COMB at the Cleveland Clinic Foundation or Memorial Sloan Kettering at Mercy Medical Center between 1990 and 1998. Of the 2991 patients, 1973 were from the Cleveland Clinic Foundation (154, PI; 785, EBRT; and 1034, RP) and 1018 patients were from Memorial Sloan-Kettering at Mercy Medical Center (796, PI and 222, COMB). All patients had available pretreatment PSA (iPSA) levels and biopsy Gleason scores (bGSs). None received adjuvant androgen deprivation (AD) after local therapy, RT in the postoperative setting, or neoadjuvant AD for >6 months. All patients had a minimal follow-up of 12 months after therapy.

Staging and workup

The initial clinical evaluation included iPSA, bGS, and assignment of clinical stage using the 1997 American Joint Committee on Cancer classification. The diagnostic evaluation, including transrectal ultrasonography, bone scan, chest X-rays, and CT of the abdomen and pelvis, was at the discretion of the treating physician.

Treatment

Of the patients undergoing RP, 97% underwent radical retropubic prostatectomy and 3% underwent perineal prostatectomy. Fifty-five percent had either a bilateral or unilateral nerve-sparing procedure. For EBRT, megavoltage X-rays were used to deliver the treatment 5 days weekly. The median total dose was 68.4 Gy (range 63.0–83.0). For patients receiving EBRT <72 Gy, the median dose was 68.4 Gy (range 63.0–70.4), and for those receiving EBRT \geq 72 Gy, the median dose was 78 Gy (range 72.0–83.0). Any hormonal therapy used in combination with the local therapy was limited to \leq 6 months.

Of the patients undergoing PI or COMB, 471 (64%) received ^{103}Pd and 264 (36%) received ^{125}I . The treatment criteria were based on the American Brachytherapy Society recommendations, although patient self-selection and preference allowed for an overlap of treatment methods and risk factors (5). When PI alone was used, the doses for ^{125}I were prescribed to 144 Gy (Task Group 43) and the doses for ^{103}Pd were prescribed to 136 Gy (National Institute of Standards and Technology 1999 guidelines) (6). Treatment in the COMB group consisted of EBRT to 41.4 or 45 Gy and a ^{125}I or ^{103}Pd implant to 108 Gy or 102 Gy, respectively. These delivered doses were kept constant within this study cohort, which means that the written prescription doses have changed over time to account for changes in the air/water kerma strength for ^{125}I and a change in the calibration standard for ^{103}Pd that was identified in 1997 (6). A preimplant ultrasound volume was used to assess the prostate dimensions, and the total activity required was determined using an isotope-specific nomogram. Postimplant analysis consisted of stereo shift X-ray films and, as of late 1994, CT-based dosimetry at 3–4 weeks after implantation. D90 (the dose delivered to 90% of the prostate) was used to assess the quality of the implant. The D90 is an independent

Table 1. Patient characteristics

Characteristic	All (n = 2991; 100%)	RP (n = 1034; 35%)	EBRT <72 Gy (n = 484; 16%)	EBRT ≥72 Gy (n = 301; 10%)	COMB (n = 222; 74%)	PI (n = 950; 32%)
Mean age (y)	67	63	70	68	69	70
Age (y)						
<65	1191 (40%)	689 (67%)	133 (27%)	93 (31%)	72 (32%)	204 (21%)
≥65	1800 (60%)	345 (33%)	351 (73%)	208 (69%)	150 (68%)	746 (79%)
Race						
White	2687 (90%)	932 (90%)	368 (76%)	228 (76%)	221 (99%)	938 (99%)
Black	304 (10%)	102 (10%)	116 (24%)	73 (24%)	1 (1%)	12 (1%)
Stage						
T1a	5 (0.2%)	4 (0.4%)	1 (0.2%)	0 (0%)	0 (0%)	0 (0%)
T1b	32 (1.1%)	7 (0.7%)	16 (3.3%)	4 (1.3%)	0 (0%)	5 (1%)
T1c	1413 (47.2%)	489 (47%)	164 (34%)	140 (47%)	113 (51%)	507 (53%)
T2a	1335 (44.6%)	482 (47%)	236 (49%)	137 (46%)	95 (43%)	385 (41%)
T2b	206 (7%)	52 (5%)	67 (14%)	20 (7%)	14 (6%)	53 (6%)
iPSA (ns/mL)						
Mean	11	9.56	15.29	11.22	14.18	9.56
Range	0.2–276	0.2–210	0.4–276	1–56.5	1–66	0.4–112
≤4	243 (8%)	121 (12%)	44 (9%)	11 (4%)	7 (3%)	60 (6%)
>4 and ≤10	1718 (57%)	622 (60%)	210 (43%)	172 (57%)	85 (38%)	629 (55%)
>10 and ≤20	725 (24%)	215 (21%)	142 (29%)	79 (26%)	84 (38%)	205 (22%)
>20	305 (10%)	76 (7%)	88 (18%)	39 (13%)	46 (21%)	56 (6%)
Gleason score						
≤6	2069 (69%)	765 (74%)	321 (66%)	173 (57%)	87 (39%)	723 (76%)
7	728 (24%)	211 (20%)	114 (24%)	99 (33%)	105 (47%)	199 (21%)
≥8	194 (6%)	58 (6%)	49 (10%)	29 (10%)	30 (14%)	28 (3%)
Treatment dates						
1990–1994	890 (30%)	372 (36%)	309 (64%)	6 (2%)	31 (14%)	172 (18%)
1995–1998	2101 (70%)	662 (64%)	175 (36%)	295 (98%)	191 (86%)	778 (82%)
Follow-up (mo)						
Median	56	66	75	49	46	47
Range	12–145	12–145	13–140	12–125	15–99	12–111
PSA follow-up measurements (n)						
Median	8	6	10	9	10	9
Range	1–36	1–36	1–34	1–28	5–16	2–19
Total	25,768	7106	5140	2710	2152	8660
Neoadjuvant hormones ≤6 mo	622 (21%)	175 (17%)	25 (5%)	118 (39%)	79 (36%)	225 (24%)

Abbreviations: RP = radical prostatectomy; EBRT = external beam radiotherapy; COMB = combined seeds and EBRT; PI = permanent seed implantation; iPSA = pretreatment prostate-specific antigen (level).

Data presented as the number of patients, with the percentage in parentheses, unless otherwise/noted.

predictor of implant quality, independent from the isotope used and the treatment intention (7–9).

Follow-up

Follow-up information always included PSA level, and 25,768 PSA levels (mean 8.6/patient) were available for analysis. The frequency of follow-up visits was determined by physician preference, but typically, PSA levels were obtained every 6 months. The median follow-up for all patients was 56 months (range 12–145). The numbers of patients with fewer than three follow-up PSA levels were as follows: EBRT <72, 20 (4%); EBRT ≥72, 7 (2%); COMB, 0 (0%); PI, 3 (1%); and RP, 121 (12%). The median follow-up intervals and mean number of PSA levels for each treatment modality are shown in Table 1. The median follow-up interval was the longest for EBRT <72 (6 years), followed by RP (5 years). EBRT ≥72,

PI, and COMB cases had similar median follow-up intervals (4 years). Of the patients who were still alive at last follow-up, 82% had been evaluated within the prior 18 months from the time of analysis.

Statistical analysis

The study end point was biochemical relapse-free survival (bRFS). For EBRT, PI, and COMB patients, the American Society for Therapeutic Radiology and Oncology (ASTRO) consensus definition for bRFS was used: three consecutive rising PSA levels after a nadir (10). The time to failure was calculated to be midway between the time of nadir and the first PSA increase. For RP patients, failure was defined as two consecutive detectable PSA levels (>0.2 ng/mL). The time to failure was considered as the time of the initial detectable level. Because all clinical relapses were associated with, or preceded

Table 2. Pathologic findings in 1034 prostatectomy patients

Finding	n (%)
Organ confined	598 (58)
Specimen confined	172 (17)
Positive margins	162 (16)
Seminal vesicle invasion	86 (8)
Lymph node metastasis	16 (2)

by, an elevated PSA level, biochemical failures included both PSA increases and clinical failures.

To study the effect of treatment on bRFS, Kaplan-Meier curves were generated, and the log-rank statistic was used to determine the differences between the curves. Cox proportional hazards regression multivariate analysis was performed on the entire patient cohort using T stage, bGS, iPSA, treatment modality (EBRT <72 vs. EBRT ≥72 vs. PI vs. COMB vs. RP), age, race, AD, and year of therapy.

RESULTS

Pretreatment/treatment characteristics

Table 1 summarizes the pretreatment clinical characteristics of the 2991 patients by treatment modality. The patients treated with RP were significantly younger, had a higher proportion of white patients, and had more favorable tumor characteristics. Neoadjuvant androgen deprivation (AD) was used for ≤6 months in 622 patients (21%), predominantly in patients treated by EBRT, PI, or COMB.

Pathologic parameters in RP patients

Table 2 represents the pathologic findings of the 1034 patients who underwent RP. Most patients had organ-confined disease and only 2% had lymph node metastases.

Treatment results

For the entire cohort of 2991 patients, the 5- and 7-year bRFS rate was 76% and 72%, respectively (Fig. 1). When

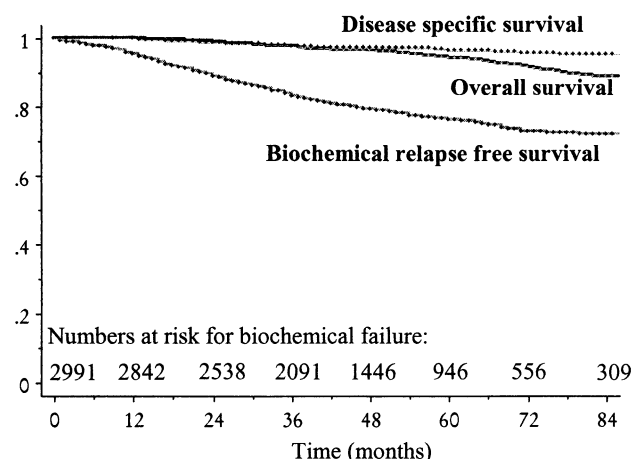


Fig. 1. Biochemical relapse-free survival, disease-specific survival, and overall survival for all 2991 patients. Symbols represent censored events.

stratifying by treatment modality, the 5-year bRFS rate was 81% for RP, 51% for EBRT <72 Gy, 81% for EBRT ≥72 Gy, 83% for PI, and 77% for COMB ($p < 0.001$). The 7-year bRFS rate for the same groups was 76%, 47%, 82%, 76%, and 77%, respectively (Fig. 2a). However, when the EBRT <72 group was removed from analysis, no difference was found in the bRFS by treatment modality (Fig. 2b). Similar comparisons were made for patients with favorable (Fig. 3) and unfavorable (Fig. 4) tumors.

In the univariate model, age (<65 years vs. ≥65 years), clinical T stage (T1-T2a vs. T2b), bGS (≤6 vs. ≥7), use of AD (yes vs. no), and year of therapy (1990–1994 vs. 1995–1998) were treated as dichotomous variables. iPSA was stratified by ≤4, >4 but ≤10, >10 but ≤20, and >20 ng/mL, and each therapeutic modality was considered an independent variable. Log-rank analysis revealed that higher T stage ($p < 0.001$), higher iPSA ($p < 0.001$), bGS ≥7 ($p < 0.001$), lack of hormone use ($p = 0.004$), low radiation doses ($p < 0.001$), and earlier year of therapy ($p < 0.001$) were predictors of a worse outcome. When the EBRT <72 group was excluded, hormone use ($p = 0.91$) and type of therapy ($p = 0.18$) were no longer predictors of outcome, and higher T stage ($p < 0.001$), higher iPSA ($p < 0.001$), bGS ≥7 ($p < 0.001$), and year of therapy ($p = 0.005$) remained predictive of worse outcome.

In the proportional hazards multivariate model, AD, treatment modality, T stage, iPSA, bGS, and year of therapy were analyzed. All factors, except AD and treatment modality, were analyzed as continuous variables. For the entire study sample, treatment modality, iPSA, bGS, and year of therapy were independent predictors of bRFS (Table 3). A trend was found for improved bRFS with lower T stage ($p = 0.08$). Use of AD was not a significant predictor. When the EBRT <72 Gy subset was excluded, treatment modality was no longer a predictor of bRFS (Table 3). The findings were similar when patients receiving AD were excluded (Table 3). When considering only unfavorable tumors, treatment modality does tend to have more of an impact, favoring COMB and EBRT ≥72, even when excluding the EBRT <72 population (Fig. 4).

DISCUSSION

This study represents the largest published series comparing the most frequently used therapies for clinically localized prostate cancer in the PSA era in a contemporaneously treated cohort of patients. The results suggest that except for EBRT <72 Gy, bRFS at 7 years is determined more by the intrinsic tumor characteristics at the time of therapy rather than a specific treatment modality. This observation holds for patients with either favorable or unfavorable tumor characteristics. We have previously observed similar outcomes in a large single-institution series comparing RP to EBRT alone (11), and the results of the present study extend this observation in a larger cohort and suggest similar efficacy for PI and COMB approaches as currently practiced. Together, these studies suggest that EBRT <72

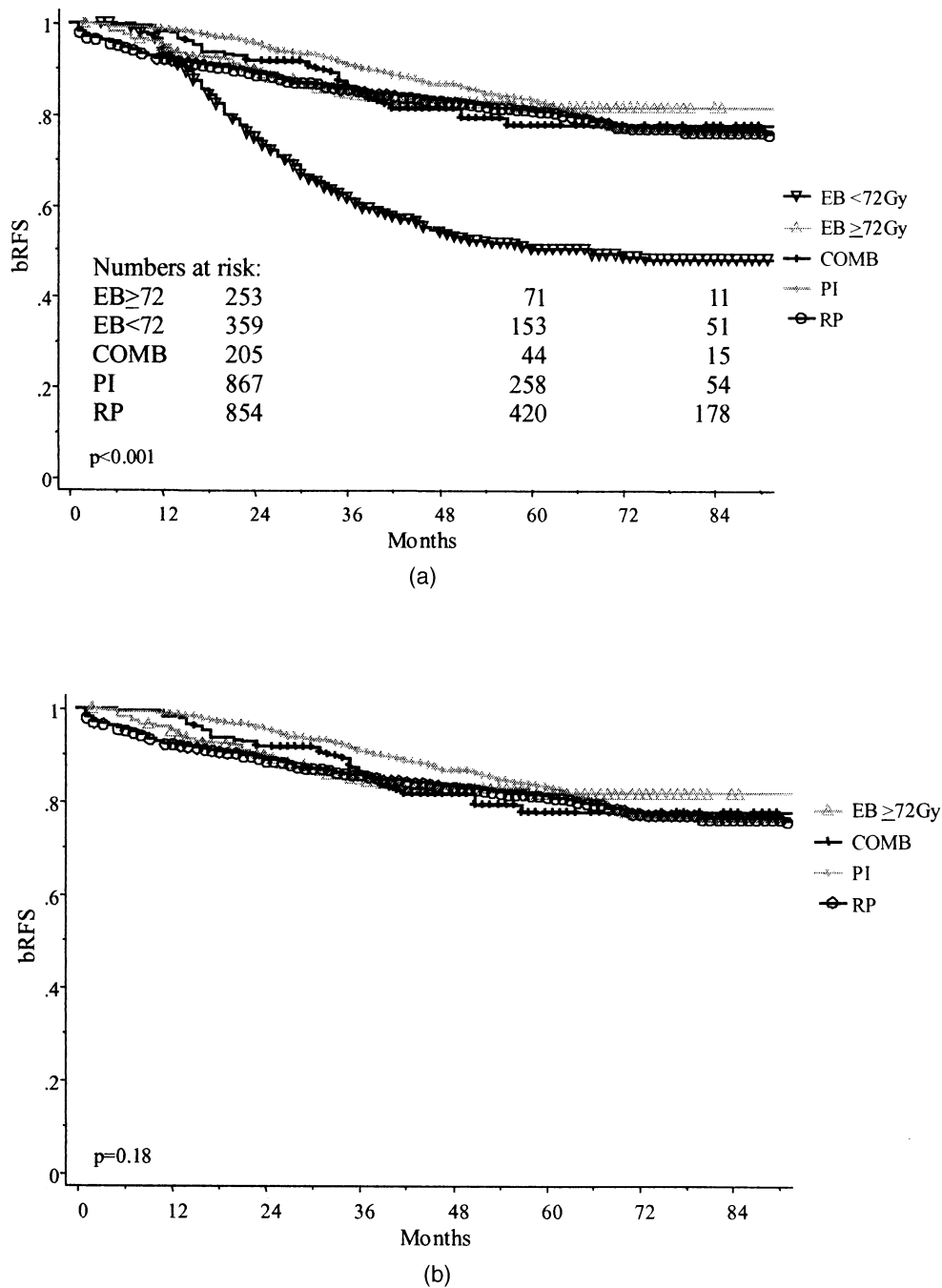


Fig. 2. Biochemical relapse-free results by treatment modality. (a) All cases: RP, EBRT <72 Gy, EBRT \geq 72 Gy, PI, or COMB. (b) Excludes EBRT <72 Gy. RP = radical prostatectomy; EBRT = external beam radiotherapy; PI = permanent seed implantation; COMB = combined seeds and EBRT.

Gy is inadequate to cure even favorable risk tumors, independent of the use of short-course AD, an observation also consistent with previously published cohort studies (12, 13). One randomized trial has confirmed these observations in unfavorable risk tumors (14).

Other published comparative series have come to mixed conclusions about the relative efficacy of each of these therapies, and all of them have various weaknesses that limit their interpretation. Many compared therapies performed in the pre-PSA era and therefore lack important prognostic information

(such as the pretreatment PSA level) known to predict relevant outcomes; many included EBRT performed in the era in which 66–70 Gy was standard and thought to be curative. For example, data from the Henry Ford Health System suggests a better overall survival with RP than EBRT, even for patients with similar comorbidities (15). However, in that series, information on pretreatment PSA, dose of EBRT, and use of AD was not available. A selection bias toward more patients with unfavorable tumors treated with EBRT is suggested by the observation that 7% of those treated with EBRT died within 2 years of

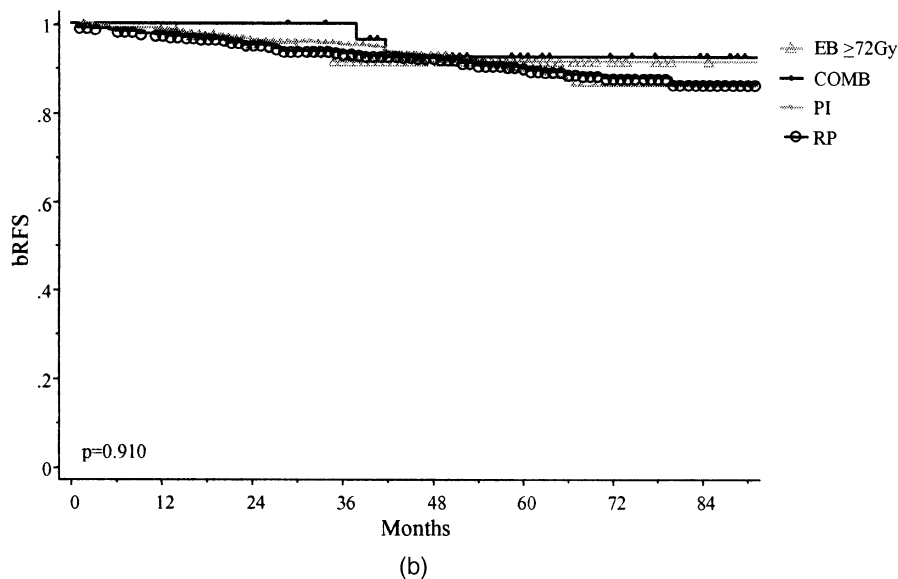
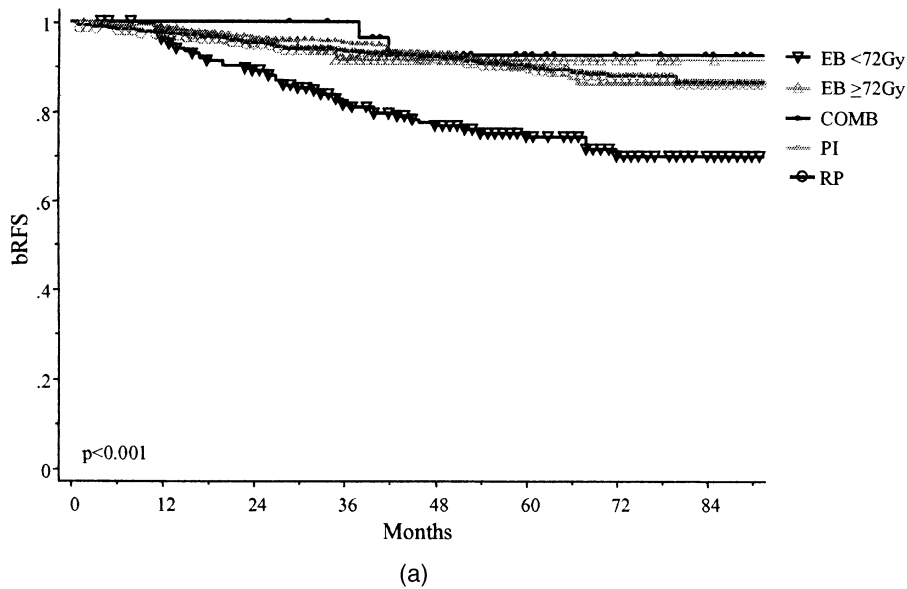


Fig. 3. Biochemical relapse-free results for favorable-risk (Stage T1-T2a, iPSA ≤ 10 ng/mL, and bGS ≤ 6) patients by treatment modality. (a) All favorable cases: RP, EBRT < 72 Gy, EBRT ≥ 72 Gy, PI, or COMB. (b) Excludes EBRT < 72 . Abbreviations as in Fig. 2.

therapy, signifying the likelihood that a substantial proportion of them had occult metastatic disease at presentation. Another more recent PSA-era comparison of RP and EBRT concluded that RP resulted in better bRFS only for patients with low- and intermediate-risk tumor characteristics but the study was limited by the use of conventional RT doses (mean 70 Gy) (16). Two prior reports from these authors concluded that RP, EBRT, and PI with or without AD had equivalent short-term bRFS rates for all modalities (17, 18). Beyer *et al.* (19) and Brachman *et al.* (20) have published a comparison of EBRT

with permanent seed implantation showing similar results between the two modalities for low-risk patients, although EBRT was advantageous for the higher risk patients. Two studies have compared bRFS with RP to early PI series by Ragde *et al.* (21), who in 1997, reported a 78% likelihood of biochemical cure (defined as PSA level < 0.5 ng/mL) at 7 years in patients undergoing brachytherapy with ^{125}I . In a comparative study, the Johns Hopkins group reported a markedly better biochemical cure rate (98%, with cure defined as PSA < 0.2 ng/mL) in a cohort of patients from their contemporaneous RP series

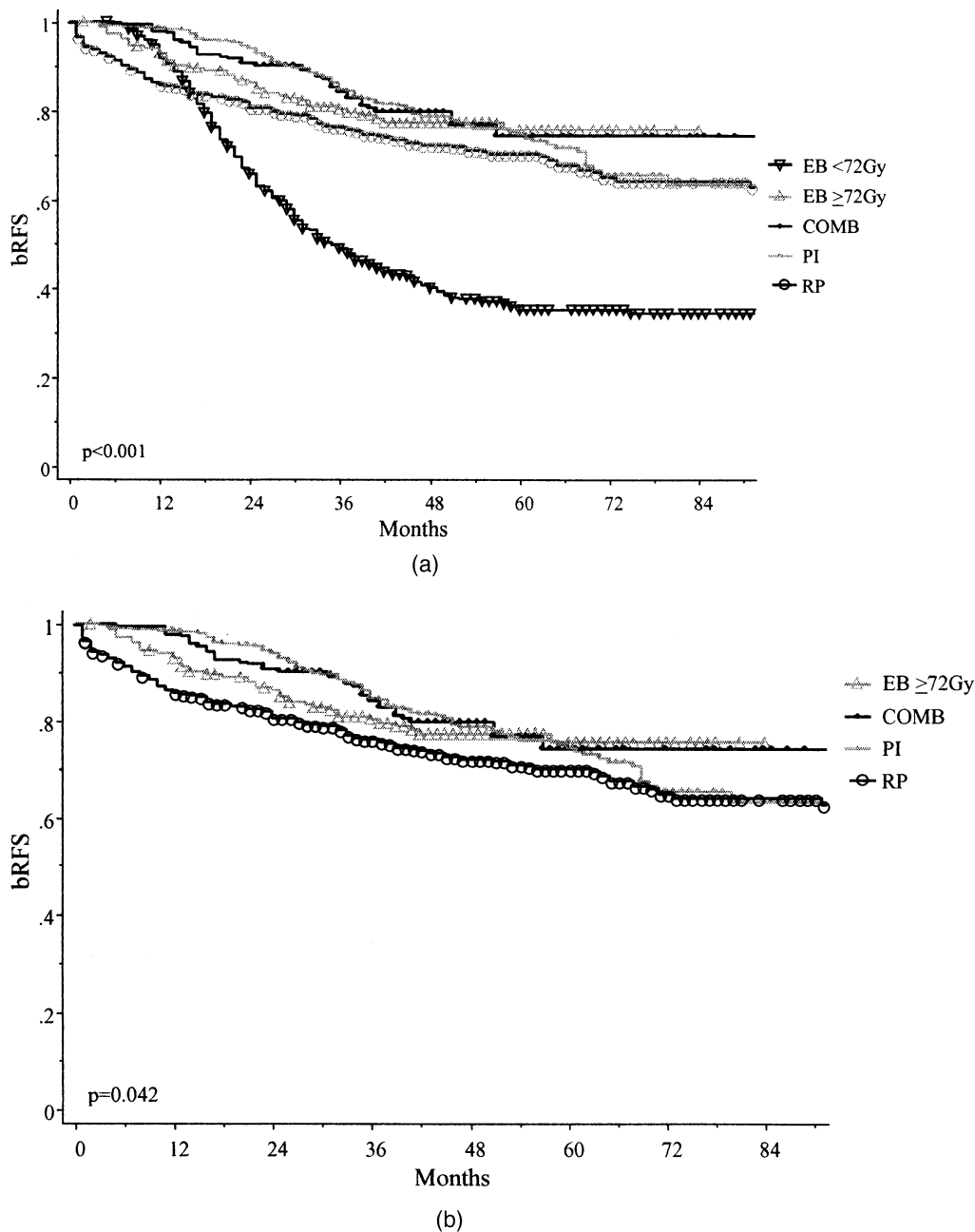


Fig. 4. Biochemical relapse-free results for unfavorable-risk (Stage T2b, iPSA >10 ng/mL, or bGS ≥ 7) patients by treatment modality. (a) All unfavorable cases: RP, EBRT <72 Gy, EBRT ≥ 72 Gy, PI, or COMB. (b) Excludes EBRT <72. Abbreviations as in Fig. 2.

matched for grade and stage and concluded that RP had a superior rate of cancer control (22). No match to iPSA was done. In an identical analysis, Ramos *et al.* (23) reported an 84% biochemical cure rate in similarly matched patients from their radical prostatectomy series at Washington University, and concluded that this result was not statistically different from the results of Ragde *et al.* with brachytherapy. Our present study did not attempt to match patients, but, by using Cox proportional hazards analysis, we identified no difference in biochemical outcome relative to treatment approach, except for the low-dose EBRT group.

The main limitation of the present study was the reliance on biochemical failure rather than metastasis-free or overall survival as the end point. We have previously reported that the likelihood of being alive 10 years after RP is unrelated to biochemical relapse and recently published a similar observation for EBRT (24, 25). Pound *et al.* (26) reported that the median time to clinically apparent metastases after biochemical failure in untreated patients after RP is 8 years and that the median time to death was an additional 5 years. Iselin *et al.* (27) reported that PSA predicted death after perineal RP with a 10-year lead time, but only for high-

Table 3. Multivariate analysis of factors predictive of bRFS

Factor	P	Risk ratio	95% CI
All Cases			
Treatment	<0.0001		
RP	RV	RV	RV
EBRT <72 Gy	<0.0001	2.24	1.83–2.73
EBRT ≥72 Gy	0.63	1.08	0.78–1.50
PI	0.72	0.96	0.76–1.21
COMB	0.67	1.08	0.76–1.54
T stage	0.084	1.11	0.99–1.25
iPSA	<0.0001	1.01	1.01–1.01
bGS	<0.0001	1.33	1.23–1.44
AD	0.26	1.14	0.91–1.44
Year of therapy	<0.0001	0.88	0.84–0.92
All cases, excluding EBRT <72			
Treatment	0.948		
RP	RV	RV	RV
EBRT ≥72 Gy	0.89	1.02	0.73–1.43
PI	0.62	0.74	0.74–1.19
COMB	0.85	0.97	0.67–1.38
T stage	0.09	1.15	0.98–1.35
iPSA	<0.0001	1.02	1.02–1.03
bGS	<0.0001	1.47	1.33–1.64
AD	0.56	1.29	0.99–1.67
Year of therapy	0.001	0.92	0.87–0.97
All cases excluding those receiving AD			
Treatment			
RP	RV	RV	RV
EBRT <72Gy	<0.0001	2.51	2.02–3.11
EBRT ≥72 Gy	0.60	1.11	0.75–1.66
PI	0.56	1.08	0.84–1.39
COMB	0.27	1.25	0.84–1.88
T stage	0.07	1.12	0.99–1.23
iPSA	<0.0001	1.01	1.008–1.014
bGS	<0.0001	1.31	1.21–1.43
Year of therapy	<0.0001	0.88	0.94–0.92

Abbreviations: bRFS = biochemical relapse-free survival; CI = confidence interval; bGS = biopsy Gleason score; AD = androgen deprivation; RV = reference variable; other abbreviations as in Table 1.

grade tumors (Gleason score 8–10). With up to 22 years of follow-up in that series, the median time to death had not been reached for lower grade tumors. Together, these observations emphasize the long natural history of treated prostate cancer, made longer by the lead-time bias and stage migration effects of PSA measurement. It is noteworthy that even 21 years after RP was repopularized (28) and 15 years after PSA measurement came into widespread use (29), we presently are still unable to tell patients which of the various treatments for localized disease results in the best metastasis-free or overall survival.

A second limitation of this study was use of the ASTRO definition of biochemical failure for EBRT, PI, and COMB. The adequacy of the ASTRO definition has come into question because of the statistical artifact (i.e., larger

denominator of patients at risk) introduced by backdating the time of failure to midway between the first and second PSA rises (30), although Kattan *et al.* (31) reported insignificant changes in bRFS estimates when modifying this definition by early censoring of nonrecurrent patients with rising PSA levels, cumulative rather than consecutive rises (without a decrease) as evidence of recurrence, both of the above, and waiting 2 years before data analysis. Others have suggested that the use of a nadir definition is more appropriate, and recently published data support nadir PSA as a good surrogate for metastasis-free survival (32). We noted that in our prior report comparing RP and EBRT, the 8-year bRFS rates were similar using either the ASTRO definition or achievement and maintenance of a nadir PSA of <0.5 ng/mL (11). Until consensus is reached on the best definition of failure after RT, two observations seem relevant. First, the issue of whether surgical or radiation-based approaches cure more patients will not be approximated until nonrandomized PSA-era series mature further or randomized trials powered for survival are actually completed. Second, biochemical failure will remain an important clinical end point even in the absence of data validating it as a surrogate for survival because of its anxiety-provoking effects in both patients and physicians and its use as a trigger for potentially curative salvage therapies or prolonged AD.

CONCLUSION

In a contemporaneously treated cohort in the PSA era, bRFS rates at 7 years after therapy for localized prostate cancer were similar for RP, EBRT with a minimal dose of 72 Gy, permanent PI, and a combination of PI and EBRT. bRFS was inferior for EBRT of <72 Gy in all prognostic subsets and was not improved by the use of AD. The need to define outcomes using biochemical failure rather than metastasis-free or overall survival and the lack of randomized trials make comparative predictions on mortality rates for each modality impossible. We believe that the accumulated experience with each of the modalities examined here should be shared with newly diagnosed patients who face a decision on how to be treated, along with a discussion of other relevant considerations not addressed in this report, including acute and chronic toxicities, quality-of-life issues, salvage of primary treatment failure, risk of late local recurrence with therapies that leave the prostate *in situ*, other late treatment-related effects, and cost. Ultimately the “best” treatment choice is one made by an informed patient who is comfortable with, and committed to, whichever he chooses.

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