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Clinical Outcomes for Patients with Gleason Score 9–10 Prostate Adenocarcinoma Treated With Radiotherapy or Radical Prostatectomy: A Multi-institutional Comparative Analysis

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Abstract

Background: The long natural history of prostate cancer (CaP) limits comparisons of efficacy between radical prostatectomy (RP) and external beam radiotherapy (EBRT), since patients treated years ago received treatments considered suboptimal by modern standards (particularly with regards to androgen deprivation therapy [ADT] and radiotherapy dose-escalation]. Gleason score (GS) 9–10 CaP is particularly aggressive, and clinically-relevant endpoints occur early, facilitating meaningful comparisons.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.06.046.

Objective: To compare outcomes of patients with GS 9–10 CaP following EBRT, extremely-dose escalated radiotherapy (as exemplified by EBRT + brachytherapy [EBRT + BT]), and RP.

Design, setting, participants: Retrospective analysis of 487 patients with biopsy GS 9–10 CaP treated between 2000 and 2013 (230 with EBRT, 87 with EBRT + BT, and 170 with RP). Most radiotherapy patients received ADT and dose-escalated radiotherapy.

Outcome measurements and statistical analysis: Kaplan-Meier analysis and multivariate Cox regression estimated and compared 5-yr and 10-yr rates of distant metastasis-free survival, cancer-specific survival (CSS), and overall survival (OS).

Results and limitations: The median follow-up was 4.6 yr. Local salvage and systemic salvage were performed more frequently in RP patients (49.0% and 30.1%) when compared with either EBRT patients (0.9% and 19.7%) or EBRT + BT patients (1.2% and 16.1%, $p < 0.0001$). Five-yr and 10-yr distant metastasis-free survival rates were significantly higher with EBRT + BT (94.6% and 89.8%) than with EBRT (78.7% and 66.7%, $p = 0.0005$) or RP (79.1% and 61.5%, $p < 0.0001$). The 5-yr and 10-yr CSS and OS rates were similar across all three cohorts.

Conclusions: Radiotherapy and RP provide equivalent CSS and OS. Extremely dose-escalated radiotherapy with ADT in particular offers improved systemic control when compared with either EBRT or RP. These data suggest that extremely dose-escalated radiotherapy with ADT might be the optimal upfront treatment for patients with biopsy GS 9–10 CaP.

Patient summary: While some prostate cancers are slow-growing requiring many years, sometimes decades, of follow-up in order to compare between radiation and surgery, high-risk and very aggressive cancers follow a much shorter time course allowing such comparisons to be made and updated as treatments, especially radiation, rapidly evolve. We showed that radiation-based treatments and surgery, with contemporary standards, offer equivalent survival for patients with very aggressive cancers (defined as Gleason score 9–10). Extremely-dose escalated radiotherapy with short-course androgen deprivation therapy offered the least risk of developing metastases, and equivalent long term survival.

Keywords

Gleason 9; Gleason 10; Radiotherapy; Radical prostatectomy

1. Introduction

Nearly 15% of the 238 590 men diagnosed with prostate cancer (CaP) in the USA every year have high-risk disease (defined as clinical T-stage ≥ 3, initial prostate-specific antigen [PSA] > 20 ng/ml, or Gleason score [GS] 8–10) [1,2]. The National Comprehensive Cancer Network and European Association of Urology/European Society for Radiotherapy & Oncology/International Society for Geriatric Oncology guidelines for managing high risk CaP suggest that radical prostatectomy (RP) and external beam radiotherapy (EBRT) with androgen deprivation therapy (ADT), with or without a brachytherapy boost (BT), are acceptable options [2,3]. However, recently published series comparing outcomes of RP versus RT have reached conflicting conclusions regarding efficacy [4–7]. Some suggest that RP offers superior local control and allows tailored adjuvant therapy. Others feel these

comparative series are biased because of the use of anachronistic EBRT treatment strategies, an inability to properly adjust for important confounders such as age and disease burden, and an imbalance using salvage therapies [8]. Emerging data indeed suggest that dose-escalation affords increased survival for patients with high-risk CaP [9,10], and several randomized trials have demonstrated the superiority of long-term ADT [11–14].

The aforementioned studies included all high-risk CaP patients, though this group is heterogeneous. Specifically, the GS is the most important prognostic factor [15] and evidence suggests that patients with GS 9–10 disease have inferior outcomes—including more frequent biochemical recurrences (BCRs) and distant metastases (DMs) [16–20]. Indeed, the new International Society of Urological Pathology grading system separates GS 9–10 disease as a distinct entity with poorer outcomes [21,17]. The purpose of this multi-institutional study was to compare the long-term outcomes of patients with biopsy GS (bGS) 9–10 CaP treated with RP, EBRT, or extremely dose-escalated RT (as represented by EBRT + BT) in the modern era. The EBRT + BT cohort was chosen as the paradigm for extremely dose-escalated RT given the availability of long-term outcomes data. We hypothesized that the combination of extremely dose-escalated RT and ADT would lead to superior clinical outcomes in the EBRT + BT cohort.

2. Materials and methods

2.1. Patient population

The study population consisted of 487 consecutively treated men with bGS 9–10 CaP who were treated at the University of California, Los Angeles and its affiliated institutions, the California Endocurie Therapy Center, and Fox Chase Cancer Center between January 2000 and November 2013. Patients were identified using institutional registries. Institutional review board approval was obtained for all institutions. Patients diagnosed before adoption of the 2005 International Society of Urologic Pathology consensus conference guidelines [22] were included if they would have been scored as having bGS 9–10 CaP in modern times. All ADT was pharmacologic, primarily with combined androgen blockade followed by leuprolide monotherapy. One-hundred-and-seventy patients had a RP, 230 had definitive EBRT ± ADT, and 87 had EBRT + BT ± ADT. Of the EBRT + BT patients, 84 had high dose rate BT (HDR-BT) and three had low dose rate BT (LDR-BT).

2.2. Classification of failures and deaths

Patients undergoing RP were classified as experiencing BCRs either when their postoperative PSA became ≥0.2 ng/ml or at initiation of salvage RT (SRT) or salvage ADT. Patients receiving RT were classified as experiencing a BCR either when their PSA was ≥nadir + 2 ng/ml [23] or at initiation of local salvage or salvage ADT. Patients were classified as having DMs when they had imaging evidence of lesions that were clinically or pathologically diagnosed as metastatic. Typically, imaging to detect DMs was performed at the time of BCR or for subsequent PSA increases after an initial BCR. Prostate-cancer specific mortality (PCSM) was defined based on either clinical documentation or inclusion of CaP as a primary cause of death on a death certificate. One-hundred-and-two out of

107 patients who were deceased at last follow-up (95.3%) had either form of PCSM determination available.

2.3. Statistical analysis

A two-tailed Student t *test* was used to evaluate differences in age and ADT duration between the cohorts, and the Wilcoxon rank-sum test was used to evaluate differences in initial PSA. Two-tailed chi-square tests (or Fisher's exact test) were used to evaluate differences in categorical variables. Outcomes of interest included BCR-free survival (BCRFS), DM-free survival (DMFS), cancer-specific survival (CSS), and overall survival (OS), which were defined by intervals from the end of treatment to BCR, DM, PCSM, and death, respectively. Follow-up was defined from the end of local treatment (ie, date of surgery or date of completion of RT) rather than from diagnosis in order to avoid introduction of bias stemming from the different lengths of treatments between cohorts. Kaplan-Meier survival analysis was used to evaluate outcomes at 5 yr and 10 yr of follow-up. Patients were censored at the time of the defined outcome or at last follow-up. The log-rank test was used to compare survival curves at 5 yr and 10 yr. Multivariate Cox regression was used to estimate the hazard ratios of these outcomes between treatment cohorts, adjusted for patient age, bGS, clinical T-stage, initial PSA, year of treatment, local salvage (with time to salvage as a covariate), and systemic salvage (with time to salvage as a covariate). All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Patient and primary treatment characteristics

Patient and treatment characteristics are presented in Tables 1 and 2, respectively. The median follow-up of the overall cohort was 4.6 yr (interquartile range [IQR], 2.87–7.36 yr). Median follow-up lengths were 4.2 (IQR, 2.78–6.25) yr, 6.5 (IQR, 3.16–9.19) yr, and 4.9 (IQR, 4.26–8.90) yr for EBRT, EBRT + BT, and RP patients. There were no significant differences between follow-up durations. Patients in the EBRT and EBRT + BT cohorts had higher age, initial PSAs, and clinical stages than patients in the RP cohort ($p < 0.05$). Two hundred and sixteen (93.9%) EBRT and 75 (86.2%) EBRT + BT patients had upfront ADT. The duration of ADT was significantly longer in the EBRT cohort (median of 24 mo vs 8 mo, $p < 0.05$). Pelvic nodal irradiation was performed in similar percentages of EBRT and EBRT + BT patients (76.1% and 78.2%, respectively, $p > 0.5$). In order to compare different dose/fractionation regimens, doses were converted into equivalent doses in 2-Gy fractions (EQD_2s), assuming an alpha/beta ratio of 1.5 [24]. The median EQD_2 for EBRT patients was 76.4 Gy (65–80 Gy), compared with 88.7 Gy (81.9–98.9 Gy) for EBRT + BT patients ($p < 0.0001$). HDR-BT boosts were 24 Gy in six fractions by ^{192}Ir, while LDR-BT boosts were 108 Gy by ^{125}I.

Fifty-eight patients undergoing RP (34.1%) had robotic-assisted RPs. One hundred and forty one RP patients had available first postoperative PSAs, among which 33 (23.4%) had PSAs ≥0.2 ng/ml. Of these, 29 (87.9%) ultimately received SRT. Considerable pathologic upstaging was found ($p < 0.0001$). Thirty-six (21.2%) patients had pathologic GS 7–8 CaP.

Notably, 21 (58%) of these patients still had a component of Grade 5 CaP either as the primary or secondary grade [6], or as the tertiary grade [15].

3.2. Adjuvant and salvage treatments

Twenty-one RP patients (12.4%) had adjuvant radiation therapy (ART). Of RP patients with BCRs but no DMs at time of BCR, 85.3% received SRT. Nine RP patients (5.3%) had adjuvant ADT alone, of which seven had node-positive (pN+) disease. Of the 28 patients with pN+ disease (16.5%), seven (25%) had adjuvant ADT and three (10.7%) had postoperative RT with ADT. Two (0.9%) and one (1.2%) EBRT and EBRT + BT patients received local salvage therapy (cryoablation in all cases), while 73 (49.0%) RP patients not receiving ART received SRT to a median EQD_2 of 68 Gy ($p < 0.0001$).

Forty-five (19.7%), 14 (16.1%), and 52 (30.1%) EBRT, EBRT + BT, and RP patients received salvage ADT, respectively ($p < 0.001$). Among RP patients, median time to SRT was 1.0 yr (0.2–14.4 yr). Time to salvage ADT was 2.9 (0.4–6.6) yr, 3.2 (0.6–8.2) yr, and 2.4 (0.1–14.6) yr after EBRT, EBRT + BT, and RP.

3.3. BCR and DM

Overall outcome frequencies are shown in Supplementary Table 1. Kaplan-Meier curves for DMFS are shown in Fig. 1, and results of multivariate Cox regression are shown in Table 3 and Supplementary Table 2. Similar information for BCRFS is provided in Table 3, Supplementary Table 5, and Supplementary Figure 4. Five-yr and 10-yr DMFS rates were 78.7% and 66.7% for EBRT, 94.6% and 89.8% with EBRT + BT, and 79.1% and 61.5% for RP. On adjusted multivariate Cox regression analysis, EBRT + BT offered significantly higher systemic control compared with either EBRT ($p = 0.0008$) or RP ($p = 0.0003$); EBRT and RP were no different from each other. Increasing radiation dose was associated with improved BCRFS and DMFS, while ADT duration was not (Table 4). Neither SRT nor ART were associated with improved DMFS. Competing risk analyses and cumulative incidence plots for DM and BCR development are found in Supplementary Tables 4 and 5, and Supplementary Figures 2 and 3.

We also defined subsets of patients that received *standard of care* treatments: patients receiving doses isoeffective to or higher than 75.6 Gy in 1.8-Gy fractions (the high-dose arm in a randomized trial showing a systemic control benefit to dose-escalation) [10] and ≥24 mo of ADT in the EBRT cohort, patients receiving ≥6 mo of ADT in the EBRT + ADT cohort, and including only patients with appropriate multimodal management in the RP cohort (eg, excluding patients who experienced isolated BCRs but never received SRT). When analyses were performed in this subset, results were essentially unchanged (Supplementary Table 6).

3.4. CSS and OS

Kaplan-Meier curves for CSS and OS are shown in Fig. 2, and results of multivariate Cox regression are shown in Table 3 and Supplementary Table 2. Five-yr and 10-yr CSS rates were 91.6% and 80.5% for EBRT, 95.6% and 88.1% for EBRT + BT, and 91.7% and 78.5% for RP. Five-yr and 10-yr OS rates were 79.9% and 65.3% for EBRT, 84.7% and 59.2% for EBRT + BT, and 90.3% and 72.1% for RP. On multivariate analysis, no

significant differences in CSS or OS were identified ($p > 0.1$). A competing risk analysis of PCSM is provided in Supplementary Table 3 and Supplementary Figure 1. Multivariate Cox regression analyses, based on the *standard of care* subset defined above, were essentially unchanged and are provided in Supplementary Table 6. Increasing radiation dose was associated with increased CSS. Neither ADT duration, SRT, nor ART were associated with increased CSS or OS (Table 4).

4. Discussion

This is the largest comparative study of outcomes exclusively for patients with bGS 9–10 CaP. After adjusting for age, clinical stage, bGS, initial PSA, year of treatment, and use of salvage therapies, 5-yr and 10-yr CSS and OS rates were similar across all three cohorts. We also found that 5-yr and 10-yr DMFS rates are significantly improved with EBRT + BT when compared with either EBRT or RP. Thus, our data suggest that EBRT-based treatments and RP are at least equivalent for the treatment of bGS 9–10 CaP, with extremely dose-escalated RT potentially offering the best systemic control.

The equivalence of CSS and OS following EBRT-based treatments and RP in our series differs from the majority of prior comparative studies [4–7]. Importantly, the majority of EBRT patients in prior studies received neither long-course ADT nor high-dose RT. In contrast, the majority of RT patients treated in our series were treated in accordance with contemporary standards. Nearly 94% of EBRT patients had upfront ADT with a median duration of 24 mo and 97% of EBRT patients received doses isoeffective to, or higher than, 75.6 Gy in 1.8-Gy fractions (the high-dose arm in a randomized trial demonstrating a systemic control benefit to dose-escalation) [10]. On subset analyses, the total radiation dose was associated with improved long-term outcomes—an effect likely driven by the EBRT + BT cohort. An inability to identify an effect for ADT duration might be related to the homogeneity of ADT duration within the EBRT and EBRT + BT cohorts, and given the small numbers of patients who received no ADT or short-term ADT, our study may not have been powered to detect an effect from ADT duration. Thus, our data suggest that comparisons between RP and substandard EBRT techniques should be regarded with caution.

Several other details warrant consideration. Firstly, post-RP BCRs are diagnosed at a lower PSA threshold than post-RT BCRs, introducing bias when comparing frequency. Thus, we focused on long-term clinical outcomes defined identically between groups. Secondly, it is possible that the upfront usage of ADT in the EBRT + BT cohort, which was not used in the RP cohort, could explain the differences in DMFS. However, upfront use of ADT is not the standard of care for patients undergoing RP. Indeed, while multiple studies have shown that upfront ADT with RT improves OS, upfront ADT with RP has never demonstrated clinical benefit except in the case of patients with pN+ [25,26]. Eighteen of the 28 pN+ patients received adjuvant ADT due to frequent refusal, accounting for ~10.5% of the RP cohort. A higher percentage of EBRT + BT patients did not receive ADT (13.8%), which is also substandard care. Even when pN+ patients are excluded, DMFS remains improved in the EBRT + BT cohort. Further, emerging data suggests that neoadjuvant ADT acts as a radiosensitizer, while adjuvant ADT blocks RT-induced androgen receptor signaling [27,28].

Thus, the effects of ADT in the EBRT + BT patients may not readily be extrapolated to patients undergoing RP.

Our results cannot be ascribed to inferior outcomes in the RP cohort. The largest prior surgical series included 259 patients with bGS 9–10 disease [20]. Our surgical cohort had more patients with positive margins (40.6% vs 36.4%) and seminal vesicle invasion without pN+ (36.5% vs 22.4%), but a similar percentage with pN+ disease (16.5% vs 17.4%). Our 5-yr and 10-yr CSS rates of 91.7% and 78.5% compare favorably with that study's reported rates of 92% and 60.7%, respectively. Additionally, a recent multi-institutional series including 1051 RP reported 5-yr and 8-yr BCRFS rates of 25% and ~15%, comparable to our 5-yr and 10-yr rates of 26.4% and 16.2% [17]. Our results also compare favorably with previously reported outcomes of patients with bGS 9–10 treated with either RP or EBRT [16,19]. Tsao et al. [16] recently reported 5-yr BCRFS and DMFS rates of approximately 40% and 60%, respectively, in a cohort of 363 patients treated with RP or EBRT for bGS 9–10 CaP, compared with rates of 81.9% and 58.6%, respectively, in the entire population for the current study.

Our finding that EBRT + BT provides improved systemic control over both EBRT and RP in this setting is novel, and suggests that optimal local control (offered by extreme dose-escalation) and an upfront method of systemic control (offered by a frequent use of ADT in this cohort) may represent the best upfront treatment strategy for these patients who are at high risk of harboring micrometastatic disease at presentation. A link between local control and systemic control has been previously suggested [9,10,29–32], and the results of a randomized trial have suggested a DMFS benefit to dose-escalated RT [10]. We chose EBRT + BT as a model for extremely dose-escalated RT given the availability of long-term clinical outcomes. Preliminary results of the ASCENDE-RT trial, where randomized patients with intermediate- or high-risk CaP were given EBRT alone or EBRT with an LDR-BT boost to demonstrate a progression-free survival benefit [32]. Because the median duration of ADT was actually lower in the EBRT + BT cohort, the improved systemic control between the EBRT and BT cohorts is likely attributable to dose-escalation. While the benefits of ADT may not be immediately extrapolated from a RT setting to a RP setting, as discussed above, the difference in systemic control between EBRT + BT and RP may conceivably be related to a systemic effect of even short duration ADT on micrometastatic disease in the majority of patients in the EBRT + BT cohort. In that case, upfront use of hormonal- or chemotherapy-based systemic agents with RP may provide better outcomes. Nonetheless, it must be emphasized that despite a systemic control benefit, no differences were found in CSS or OS. This may be due to limited power with a relatively smaller EBRT + BT cohort, the utilization of effective systemic salvage modalities at the time of metastatic disease, and/or a longer natural history for death after metastatic disease than originally assumed.

This work has several limitations. Primarily, because this was a retrospective analysis, the treatments within cohorts are not homogeneous; for example, ADT duration, EBRT dose, postoperative EBRT strategies were heterogeneous, and follow-up protocols were not standardized. Further, to maximize power, we pooled data from several institutions, likely compounding this issue. Therefore, our results are primarily hypothesis-generating and will need prospective evaluation. However, our overall outcomes are consistent with previously

reported series as noted above, suggesting an element of generalizability to our results. Not all patients received *standard of care* treatment. Specifically, the National Comprehensive Cancer Network and European Association of Urology/European Society for Radiotherapy & Oncology/International Society for Geriatric Oncology guidelines suggest a *multimodal* approach (including either ART or SRT) for patients with high-risk CaP—a suggestion supported by a recent large surgical series in patients with high-risk CaP [3,33]. While only 12.4% of patients received ART, 80% of the remaining RP patients with BCR but no DM at the time ultimately received SRT, and therefore a majority of surgical patients did receive appropriate multimodal therapy [2,3]. When analysis was restricted to only these surgical patients, and comparisons were made to EBRT patients with high-dose RT and long duration ADT and EBRT + BT patients with >6 mo of ADT, our results were essentially unchanged, suggesting our results are not only generalizable to de facto clinical practice (which may or may not be standard of care), but to standard of care practice as well. Additionally, proportionately greater numbers of RP patients received standard of care per this definition than EBRT or EBRT + BT patients (84.1% vs 48.3% and 60.9%, respectively). However, earlier initiation of SRT has been shown to improve outcomes, particularly for patients with high GS disease, and thus it is possible that earlier SRT might have improved outcomes [34]. The numbers of patients analyzable for clinical outcomes at 10 yr of follow-up were fairly limited across cohorts, and thus our Cox analyses using data from 10 yr of follow-up, as well as exact estimates by Kaplan-Meier analysis at 10 yr, must be interpreted judiciously. We did not account or adjust for comorbidities, which have previously been shown to be unbalanced between EBRT and RP cohorts [8]; a uniform comorbidity index was not available for most patients, and we did not feel it was appropriate to perform a comorbidity-adjusted analysis on a limited subset. However, our competing risk analysis for PCSM did not yield different findings from our main analyses. Because not all biopsies were performed uniformly and were done over a broad time period, we did not include percentage of core involvement with bGS 9–10 CaP as a variable of interest. At least one prior study has suggested that *burden* of bGS 9–10 might be associated with outcomes [20]. It is possible that an imbalance of percentage involvement between the arms might explain the results, though again, outcomes for each cohort were consistent with prior results. A central pathology review was not possible.

Finally, while our median follow-up of 4.6 yr was enough to capture a fair number of systemic failure events, this follow-up period may still be too short to capture mortality outcomes. Additionally, some may contend that the long duration of ADT, particularly in the EBRT cohort, may simply be delaying, rather than truly preventing, the emergence of metastatic disease. This is certainly possible, but the median follow-up of the EBRT + BT cohort, which had a median ADT duration of only 8 mo, was 6.5 yr, versus 4.9 yr for the RP cohort. Further, as discussed above, ADT has never demonstrated a benefit when combined with RP; a contention that ADT only delays metastases does not address the superior outcomes of EBRT + ADT over EBRT alone and the lack of superior outcomes of RP + ADT over RP alone, and delaying metastatic disease is in and of itself an important endpoint.

5. Conclusions

In conclusion, our data suggest that the RP and EBRT-based treatments provide equivalent CSS and OS for patients with bGS 9–10 CaP, with extremely dose-escalated RT (as exemplified here by EBRT + BT) providing the best systemic control. It is important to note that 55% of patients who underwent upfront RP ultimately received ART or SRT. This should be emphasized when specialists partake in shared-decision making with these patients. These data are hypothesis-generating in suggesting that optimal outcomes in patients with GS 9–10 CaP require a combination of local control (offered by extremely-dose escalated RT) and systemic therapy (offered by upfront ADT). Alternative strategies, perhaps including some form of systemic therapy with RP, may offer comparable outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Financial disclosures:

Amar U. Kishan certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

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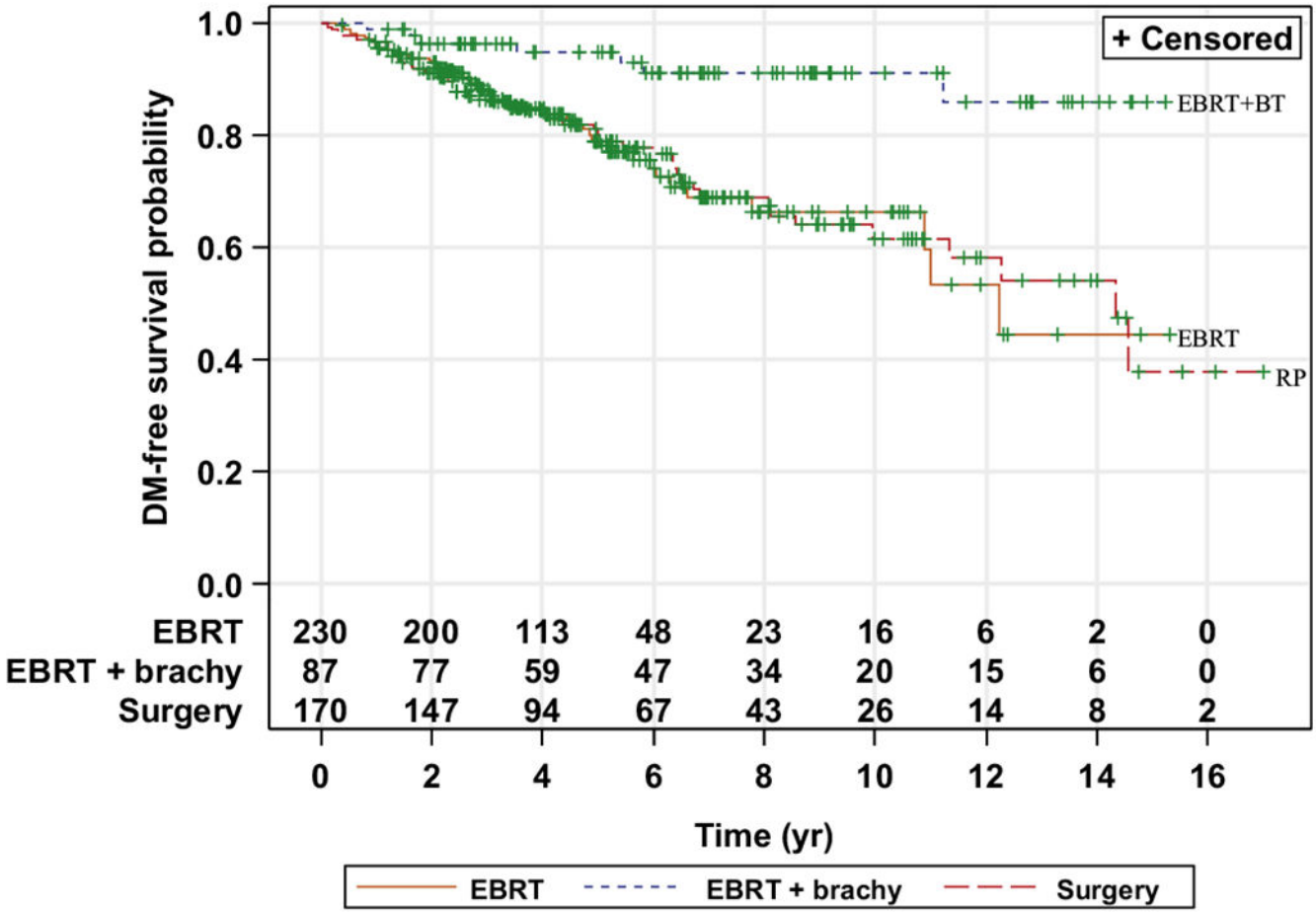

Fig. 1 –.

Kaplan-Meier curves distant metastasis (DM)-free survival. The curves have not been adjusted for age, Gleason score, clinical stage, initial prostate-specific antigen, year of treatment, or utilization of local or systemic salvage therapies (with salvage treated as a time-dependent variable). Following multivariate regression adjusted for these factors, patients treated with external beam radiotherapy + brachytherapy (brachy; EBRT + BT) had significantly higher 5-yr and 10-yr DM-free survival rates than patients treated with either radical prostatectomy (RP) or EBRT ($p < 0.01$ for both).

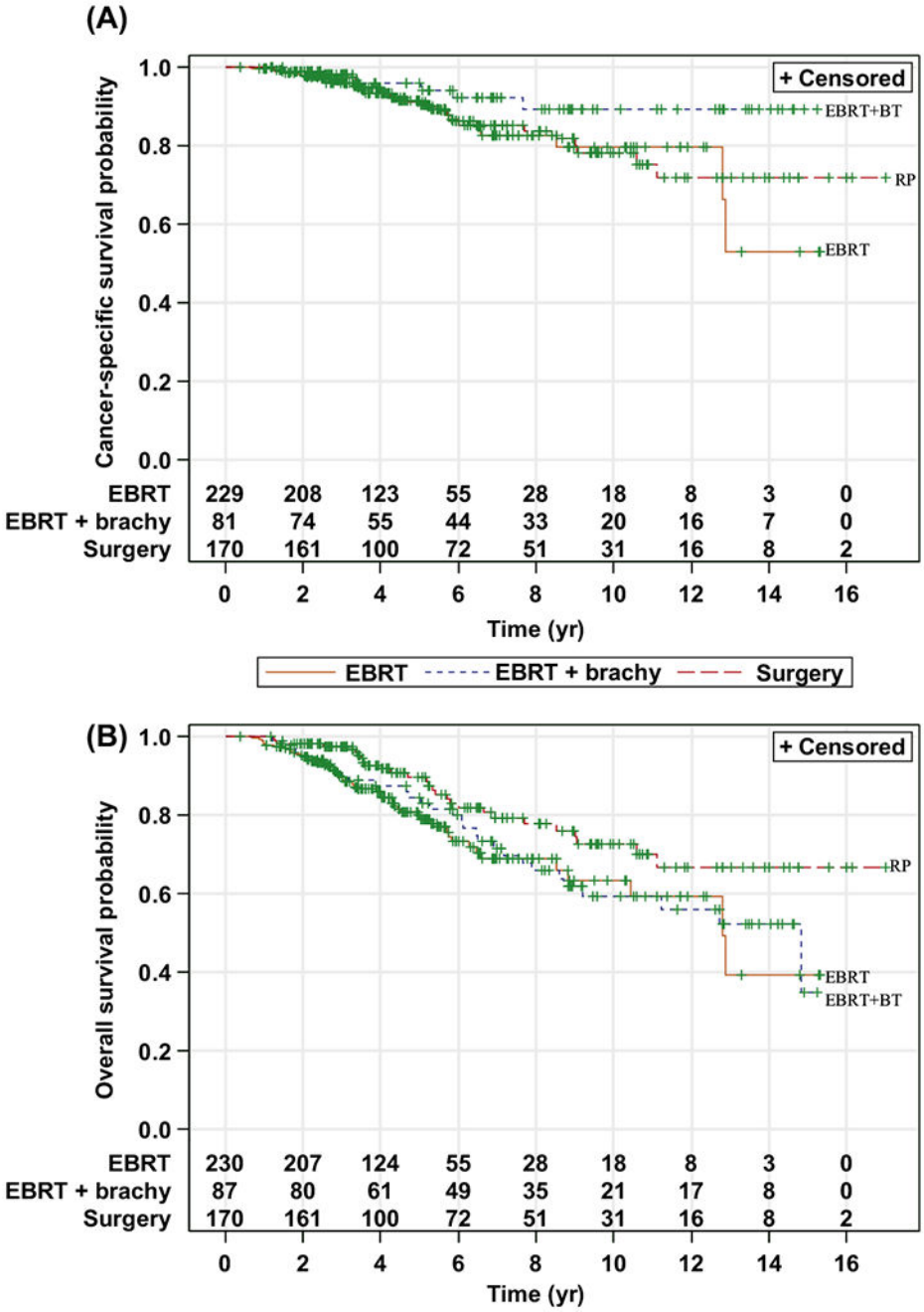

Fig. 2 –.

(A) Kaplan-Meier curves for cancer-specific survival. (B) Kaplan-Meier curves for overall survival. The curves have not been adjusted for age, Gleason score, clinical stage, or prostate-specific antigen. Following multivariate regression adjusted for these factors, all patients had statistically similar 5-yr and 10-yr cancer-specific survival and overall survival rates.

brachy = brachytherapy; EBRT = external beam radiotherapy; RP = radical prostatectomy.

Table 1 –

Clinical and pathologic characteristics.

	Treatment cohort			
	EBRT (*n* = 230)	**EBRT + BT (*n* = 87)**	**RP (*n* = 170)**	***p* value**
Age, mean, median (range yr)	69.9 70 (43–98)	69.1 70 (50–82)	61.9 62 (42–77)	>0.5 (EBRT vs EBRT + BT) <0.0001 (RP vs EBRT) <0.0001 (RP vs EBRT + BT)
Initial PSA, mean, median (range ng/ml)	18.7 9.76 (0.54–270)	16.7 11.7 (1.7–95.2)	11.5 7.8 (0.4–124)	>0.1 (EBRT vs EBRT + BT) <0.001 (RP vs EBRT + BT) <0.01 (RP vs EBRT)
Biopsy Gleason Score				
9	208 (90.4)	82 (94.3)	161 (94.7)	>0.1
10	22 (9.6)	5 (5.7)	9 (5.3)	
Clinical stage, *n* (%)				
1c	71 (29.6)	17 (19.5)	95 (55.9)	<0.05 (EBRT vs EBRT + BT)
2a	41 (17.8)	14 (16.1)	27 (15.9)	<0.0001 (RP vs EBRT)
2b	25 (10.7)	20 (23.0)	20 (11.8)	<0.0001 (RP vs EBRT + BT)
2c	17 (7.4)	2 (2.3)	7 (4.1%	
3a	38 (16.5)	13 (14.9)	13 (7.7)	
3b	11 (4.9)	8 (9.2)	2 (1.2)	
4	27 (11.8)	13 (14.9)	6 (3.5)	
Pathological stage, *n* (%)				
2a			13 (7.6)	
2b			3 (1.8)	

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	Treatment cohort			
	EBRT (*n* = 230)	**EBRT + BT (*n* = 87)**	**RP (*n* = 170)**	***p* value**
2c			21 (12.4)	
3a			39 (17.7)	
3b			81 (47.7)	
4			22 (12.9)	
Pathological Gleason Score[a], *n* (%)				
7			20 (11.8)	
8			16 (9.4)	
9			128 (75.2)	
10			6 (3.5)	
Adverse pathologic features, *n* (%)				
Positive margins			69 (40.6)	
pN+			28 (16.5)	
Treatment center, *n* (%)				
UCLA	132 (57.4)	20 (23)	145 (85.3)	
CET		67 (77)		
FCC	98 (42.6)		25 (14.7)	

BT = brachytherapy; CET = California Endocurie Therapy Center; EBRT = external beam radiotherapy; FCC = Fox Chase Cancer Center; pN+ = positive nodes on lymph node dissection; PSA = prostate-specific antigen; RP = radical prostatectomy; UCLA = University of California, Los Angeles.

[a]Two patients had androgen deprivation therapy effect preventing Gleason scoring at radical prostatectomy.

Table 2 –

Treatment details.

	EBRT (*n* = 230)	EBRT + BT (*n* = 87)	RP (*n* =170)
Radiotherapy patients			
Total dose in EQD_2, median (range Gy)	76.4 (65–80)	88.7 (81.9–98.9)	
Upfront ADT usage, *n* (%)	216 (93.9)	75 (86.2)	
Duration of ADT, median (range mo)	24 (2–56)[a]	8 (1–30)	
Pelvic nodal irradiation, *n* (%)	176 (76.1)	68 (78.2)	
RP patients, *n* (%)			
Neoadjuvant systemic therapy			18 (10.6)
Adjuvant RT			21 (12.3)
Adjuvant systemic therapy			12 (7.1)
All patients, *n* (%)			
Local salvage	2 (0.87)	1 (1.2)	73 (49.0)[b]
Systemic salvage	45 (19.6)	14 (16.1)	52 (30.6)

ADT = androgen deprivation therapy; BT = brachytherapy; EBRT = external beam radiotherapy; EQD_2 = equivalent dose in 2-Gy fractions assuming an alpha/beta ratio equal to 1.5; RP = radical prostatectomy; RT = radiotherapy.

[a] Ten EBRT and six EBRT + BT patients had lifelong ADT.

[b] For calculation of local salvage frequency, we excluded patients who received adjuvant RT; however, this figure is only a crude frequency intended to report the percentage of patients undergoing RP that eventually received salvage RT. If restricting analysis to those patients with biochemical recurrence but no evidence of distant metastases, the salvage RT rate is higher (85.3%).

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Table 3 –

Kaplan-Meier analysis and multivariate Cox regression of clinical outcomes.

	Kaplan-Meier analysis[a]		Multivariate Cox regression		
Clinical outcome	**5-yr**	**10-yr**	**HR**	**95% CI**	***p* value**
Biochemical recurrence					
EBRT vs RP (%)	28.2% vs 73.6[a]	39.7% vs 83.8[b]	0.21	(0.14, 0.32)	<0.0001
EBRT + BT vs EBRT (%)	17.1% vs 28.2	30.0% vs 39.7	0.76	(0.44, 1.32)	0.33
EBRT + BT vs RP (%)	17.1% vs 73.6[a]	30.0% vs 83.8[b]	0.16	(0.09, 0.28)	<0.0001
Distant metastasis					
EBRT vs RP (%)	21.3 vs 20.9	33.3 vs 38.5	0.78	(0.45, 1.35)	0.37
EBRT + BT vs EBRT (%)	5.4 vs 21.3[a]	10.2 vs 33.3[a]	0.30	(0.12, 0.72)	0.008
EBRT + BT vs RP (%)	5.4 vs 20.9[a]	10.2 vs 38.5[a]	0.23	(0.09, 0.6)	0.003
Prostate cancer specific mortality					
EBRT vs RP (%)	8.4%vs 8.3	19.5 vs 21.5	0.75	(0.34, 1.65)	0.47
EBRT + BT vs EBRT (%)	4.4 vs 8.4	11.9 vs 19.5	0.64	(0.24, 1.71)	0.37
EBRT + BT vs RP (%)	4.4 vs 8.3	11.9 vs 21.5	0.48	(0.16, 1.4)	0.18
Overall survival					
EBRT vs RP (%)	79.9 vs 90.3	65.3 vs 72.1	1.07	(0.58, 1.98)	0.82
EBRT + BT vs EBRT (%)	84.7 vs 79.9	59.2 vs 65.3	0.99	(0.58, 1.69)	0.98
EBRT + BT vs RP (%)	84.7 vs 90.3	59.2 vs 72.1	1.06	(0.53, 2.12)	0.86

CI = confidence interval; BT = brachytherapy; EBRT = external beam radiotherapy; HR = hazard ratio; RP = radical prostatectomy; RT = radiotherapy.

[a]The Kaplan-Meier analysis was not adjusted for age, Gleason score, clinical T stage, or initial prostate-specific antigen, and comparisons between cohorts was performed using the log-rank test. The multivariate Cox regression model derived-hazard ratios are adjusted for age, Gleason score, clinical T-stage, initial prostate-specific antigen, year of treatment, local salvage (with time to salvage as a

covariate), and systemic salvage (with time to salvage as a covariate) and refer to outcomes through 10 yr of follow-up (Cox analysis for outcomes through 5 yr of follow-up can be found in Supplementary Table 2). For example, a hazard ratio <1 for the comparison external beam radiotherapy versus radical prostatectomy suggests that the given outcome (eg, biochemical recurrence) has a lower hazard of occurring with external beam radiotherapy versus with radical prostatectomy.

[b] These comparisons showed statistically significant differences on Kaplan-Meier survival analysis.

Table 4 –

Multivariate Cox regression of clinical outcomes by subgroups.

Clinical outcome	HR	95% CI	*p* value
Biochemical recurrence[a]			
Total RT dose	0.95	(0.91, 0.98)	0.0043
ADT duration	1.00	(0.99, 1.01)	0.48
Distant metastasis			
Total RT dose	0.91	(0.87, 0.96)	0.0001
ADT duration	1.01	(1, 1.02)	0.26
Salvage RT	0.47	(0.19, 1.15)	0.099
Adjuvant RT	0.86	(0.2, 3.72)	0.84
Prostate cancer specific mortality			
Total RT dose	0.93	(0.87, 0.99)	0.020
ADT duration	1.01	(1, 1.02)	0.051
Salvage RT	0.53	(0.19, 1.5)	0.23
Adjuvant RT	0.55	(0.07, 4.23)	0.57
Overall survival			
Total RT dose	0.98	(0.95, 1.01)	0.23
ADT duration	1.00	(0.99, 1.01)	0.53
Salvage RT	0.47	(0.19, 1.15)	0.099
Adjuvant RT	0.86	(0.2, 3.72)	0.84

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; RT = radiotherapy.

[a]The multivariate Cox regression model derived-hazard ratios are adjusted for age, Gleason score, clinical T-stage, and initial prostate-specific antigen, year of treatment, local salvage (with time to salvage as a covariate), and systemic salvage (with time to salvage as a covariate) and refer to outcomes through 10 yr of follow-up. Hazard ratios <1 suggest the outcome (eg, distant metastasis) has a lower hazard of occurring with higher values of continuous variables (total radiotherapy dose or androgen deprivation therapy duration) or “yes” for binary variables (salvage radiotherapy or adjuvant radiotherapy).