Title

Prostate-only Versus Whole-pelvis Radiation with or Without a Brachytherapy Boost for Gleason Grade Group 5 Prostate Cancer: A Retrospective Analysis

Permalink

https://escholarship.org/uc/item/6xp7p160

Journal

European Urology, 77(1)

ISSN

0302-2838

Authors

Sandler, Kiri A
Cook, Ryan R
Ciezki, Jay P
et al.

Publication Date

2020

DOI

10.1016/j.eururo.2019.03.022

Peer reviewed

Prostate-only Versus Whole-pelvis Radiation with or Without a Brachytherapy Boost for Gleason Grade Group 5 Prostate Cancer: A Retrospective Analysis

Kiri A. Sandler[a], **Ryan R. Cook**[b], **Jay P. Ciezki**[c], **Ashley E. Ross**[d], **Mark M. Pomerantz**[e], **Paul L. Nguyen**[f], **Talha Shaikh**[g], **Phuoc T. Tran**[h], **Richard G. Stock**[i], **Gregory S. Merrick**[j], **David Jeffrey Demanes**[a], **Daniel E. Spratt**[k], **Eyad I. Abu-Isa**[k], **Trude B. Wedde**[l], **Wolfgang Lilleby**[l], **Daniel J. Krauss**[m], **Grace K. Shaw**[e], **Ridwan Alam**[d], **Chandana A. Reddy**[d], **Daniel Y. Song**[h], **Eric A. Klein**[c], **Andrew J. Stephenson**[c], **Jeffrey J. Tosoian**[d], **John V. Hegde**[a], **Sun Mi Yoo**[a], **Ryan Fiano**[j], **Anthony V. D'Amico**[e], **Nicholas G. Nickols**[a,n], **William J. Aronson**[n,o], **Ahmad Sadeghi**[n], **Stephen C. Greco**[h], **Curtiland Deville Jr.**[h], **Todd McNutt**[h], **Theodore L. DeWeese**[h], **Robert E. Reiter**[o], **Jonathan W. Said**[p], **Michael L. Steinberg**[a], **Eric M. Horwitz**[g], **Patrick A. Kupelian**[a], **Christopher R. King**[a], **Amar U. Kishan**[a,*]

[a]Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA, USA;

[b]Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA;

[c]Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH, USA;

[d]Department of Urology, The James Buchanan Brady Urological Institute, The Johns Hopkins University School of Medicine, Baltimore, MD, USA;

[e]Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;

[f]Department of Radiation Oncology, Brigham and Women's Hospital/Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA;

[g]Department of Radiation Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA;

[h]Department of Radiation Oncology and Molecular Radiation Sciences, The Johns Hopkins University School of Medicine, Baltimore, MD, USA;

[i]Department of Radiation Oncology, The Icahn School of Medicine at Mount Sinai, New York City, NY, USA;

[j]Schiffler Cancer Center, Wheeling Hospital, Wheeling Jesuit University, Wheeling, WV, USA;

[k]Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA;

[l]Department of Oncology, Oslo University Hospital, The Norwegian Radium Hospital, Oslo, Norway;

[m]Oakland University William Beaumont School of Medicine, Royal Oak, MI, USA;

[n]Department of Radiation Oncology, Veteran Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA;

[o]Department of Urology, University of California, Los Angeles, Los Angeles, CA, USA;

[p]Department of Pathology, University of California, Los Angeles, Los Angeles, CA, USA

Abstract

Background: The role of elective whole-pelvis radiotherapy (WPRT) remains controversial. Few studies have investigated it in Gleason grade group (GG) 5 prostate cancer (PCa), known to have a high risk of nodal metastases.

Objective: To assess the impact of WPRT on patients with GG 5 PCa treated with external-beam radiotherapy (EBRT) or EBRT with a brachytherapy boost (EBRT + BT).

Design, setting, and participants: We identified 1170 patients with biopsy-proven GG 5 PCa from 11 centers in the United States and one in Norway treated between 2000 and 2013 (734 with EBRT and 436 with EBRT + BT).

Outcome measurements and statistical analysis: Biochemical recurrence-free survival (bRFS), distant metastasis-free survival (DMFS), and prostate cancer-specific survival (PCSS) were compared using Cox proportional hazards models with propensity score adjustment.

Results and limitations: A total of 299 EBRT patients (41%) and 320 EBRT + BT patients (73%) received WPRT. The adjusted 5-yr bRFS rates with WPRT in the EBRT and EBRT + BT groups were 66% and 88%, respectively. Without WPRT, these rates for the EBRT and EBRT + BT groups were 58% and 78%, respectively. The median follow-up was 5.6 yr. WPRT was associated with improved bRFS among patients treated with EBRT + BT (hazard ratio [HR] 0.5, 95% confidence interval [CI] 0.2–0.9, $p = 0.02$), but no evidence for improvement was found in those treated with EBRT (HR 0.8, 95% CI 0.6–1.2, $p = 0.4$). WPRT was not significantly associated with improved DMFS or PCSS in the EBRT group (HR 1.1, 95% CI 0.7–1.7, $p = 0.8$

for DMFS and HR 0.7, 95% CI 0.4–1.1, $p = 0.1$ for PCSS), or in the EBRT + BT group (HR 0.6, 95% CI 0.3–1.4, $p = 0.2$ for DMFS and HR 0.5 95% CI 0.2–1.2, $p = 0.1$ for PCSS).

Conclusions: WPRT was not associated with improved PCSS or DMFS in patients with GG 5 PCa who received either EBRT or EBRT + BT. However, WPRT was associated with a significant improvement in bRFS among patients receiving EBRT + BT. Strategies to optimize WPRT, potentially with the use of advanced imaging techniques to identify occult nodal disease, are warranted.

Patient summary: When men with a high Gleason grade prostate cancer receive radiation with external radiation and brachytherapy, the addition of radiation to the pelvis results in a longer duration of prostate-specific antigen control. However, we did not find a difference in their survival from prostate cancer or in their survival without metastatic disease. We also did not find a benefit for radiation to the pelvis in men who received radiation without brachytherapy.

1. Introduction

The question of whether to electively irradiate pelvic lymph nodes when delivering definitive external-beam radiotherapy (EBRT) to men with prostate cancer (PCa) is one of the most extensively debated topics in radiation oncology [1]. A number of retrospective studies suggesting a benefit for elective nodal irradiation led to the development of Radiation Therapy Oncology Group (RTOG) 9413, a 2×2 randomized controlled trial comparing whole-pelvis radiation therapy (WPRT) with prostate-only radiation as well as neoadjuvant/concurrent androgen deprivation therapy (ADT) with adjuvant ADT [2,3]. The initial report of this trial demonstrated a significant improvement in biochemical recurrence-free survival (bRFS) when combining WPRT with neoadjuvant/concurrent ADT, a benefit that has recently been shown to persist and translate into a progression-free survival benefit on long-term follow-up [4]. However, many experts remain skeptical [5], and a separate randomized controlled trial, the Groupe d'études des tumeurs urogénitales (GETUG)-1 study, reported no benefit of WPRT [6]. Testament to the controversy, a third randomized trial, RTOG 0924, is actively investigating the benefit of WPRT in a higher-risk subset of PCa, though it is not estimated to be completed until 2031.

It is possible that the benefit of WPRT was diluted in RTOG 9413 and GETUG-1 by the inclusion of patients with a very low risk of lymph node involvement [5]. Alternatively, the benefit of WPRT may be modest for patients with the highest risk of nodal involvement, as these patients are also at high risk of harboring micrometastases outside of the pelvic nodes [7]. Indeed, RTOG 0924 was designed based on a post hoc analysis of RTOG 9413, indicating that an intermediate-risk group may derive the most benefit from WPRT. Patients with Gleason grade group (GG) 5 (formerly, Gleason score [GS] 9–10) PCa are at high risk of both nodal metastases and extrapelvic micrometastases [8,9]. Recently, intensified local treatment (treatment with EBRT with a brachytherapy boost [EBRT + BT]) was shown to be

associated with significantly improved clinical outcomes in this patient population when compared with dose-escalated EBRT alone in this patient population, but it is unknown how WPRT impacts these outcomes [10]. In a companion cohort of patients undergoing radical prostatectomy (RP), the frequency of positive pelvic lymph nodes was 17%; as patients undergoing either form of radiotherapy had higher clinical T stage and initial prostate-specific antigen (PSA) values, the frequency of nodal involvement in those cohorts is likely to be at least as high if not higher. The objective of this study is to interrogate the benefit of WPRT among patients undergoing definitive radiation—either EBRT or EBRT + BT—in this modern, multi-institutional cohort of patients with GG 5 PCa with an a priori high risk of nodal metastases.

2. Methods and materials

2.1. Patient population

Institutional databases from 12 tertiary referral centers were queried for patients with biopsy-proven GG 5 PCa treated between 2000 and 2013, as described previously [10]. Institutional review board approval was obtained by all institutions, with management by the coordinating center (University of California, Los Angeles, Los Angeles, CA, USA). All 1170 patients who were treated with either EBRT or EBRT + BT were included. All ADTs were pharmacologic, primarily androgen blockade followed by leuprolide monotherapy. Radiation plans were not available for review; however, the majority of institutions ($n = 11$) defined their institutional policy during that time frame as treating with an upper border at L5–S1. One institution defined its policy as treating the obturator nodes alone.

2.2. Classification of events

Follow-up was calculated from the end of radiation therapy. Biochemical failure was defined by either a PSA nadir + 2 ng/ml [11] or at the initiation of local salvage or salvage ADT. Distant metastases (DMs) were identified either pathologically or radiographically. Prostate cancer-specific survival (PCSS) was defined by the presence of PCa as the primary cause of death on a patient's death certificate or clear documentation of PCa-specific mortality in the medical record.

2.3. Statistical analysis

Prior to analysis, univariate statistics (medians and percentages) were used to describe sample characteristics. Cox proportional hazards regression models were utilized to compare distant metastasis-free survival (DMFS), PCSS, and bRFS rates between patients treated with EBRT ± BT ± WPRT. Analyses first tested for multiplicative interaction between WPRT and BT. If the interaction term was nonsignificant, the effect of WPRT was estimated, controlling for receipt of BT. However, based on the premise that improved nodal control would only be relevant in the setting of primary disease control [4], and that EBRT + BT would offer improved primary disease control compared with EBRT alone, we also chose to report subgroup-specific estimates. Cox models included site as a random effect to account for the multi-institutional design. Adequacy of the proportional hazards assumption was evaluated by examining plots and tests of scaled Schoenfeld residuals [12]. Cox models included propensity scores (PSs) as covariates to control for confounding by age, ln(iPSA),

clinical T stage, and the individual GS (i.e., 9 vs 10). ADT duration was also included in Cox models as a separate, time-varying covariate. PSs were estimated using logistic regression with multiple imputation used to estimate missing covariate values [13]. To assess balance achieved by the PS, the standardized mean difference in covariate values was compared across treatment groups in an inverse probability of treatment-weighted (IPTW) sample [14]. PS models were fit iteratively by adding or deleting nonlinear terms and two-way interactions and checking standardized mean differences until optimal balance was achieved [15]. Finally, covariate-adjusted survival curves and estimates were generated using IPTW, as described by Cole and Hernan [16]. Confidence intervals (CIs) for IPTW-adjusted survival estimates were obtained by bootstrapping. All analyses were completing using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria) [17].

3. Results

3.1. Patient and treatment characteristics

Disease and treatment characteristics are presented in Table 1. The median follow-up length was 5.1 yr for EBRT patients (interquartile range 2.9–7.7 yr) and 6.3 yr for EBRT + BT patients (interquartile range 3.9–9.4 yr). Overall, 53% (619/1170) of patients received WPRT: 41% (299/734) in the EBRT group and 73% (320/436) in the EBRT + BT group. ADT receipt was similar in the EBRT group and in the EBRT + BT group (89.5% vs 92.4%), but the duration was significantly longer (median 22 mo vs 12 mo, $p < 0.001$). Local and systemic salvage rates were low for both EBRT and EBRT + BT groups (2.5% vs 0.1% for local salvage and 12.1% vs 5.5% for systemic salvage). The median dose, equivalent in 2-Gy fractions, was 74.3 in the EBRT group (range 65–81.4) and 91.5 in the EBRT + BT group (range 75.8–131.4).

3.2. Biochemical recurrence-free survival

Covariate-adjusted Kaplan-Meier curves for bRFS are presented in Fig. 1. Overall, 383 patients (33%) experienced a biochemical failure. The adjusted 5-yr bRFS rates with WPRT in the EBRT and EBRT + BT groups were 66% (95% CI 59–72%) and 88% (95% CI 80–90%), respectively. Without WPRT, the rates for EBRT and EBRT + BT were 58% (95% CI 53–63%) and 78% (95% CI 69–86%), respectively. Hazard ratios (HRs) are presented in Tables 2 and 3. The bRFS rate trended toward improvement overall, when controlling for receipt of BT (HR 0.71, 95% CI 0.5–1.03). There was no statistically significant evidence for an interaction between WPRT and BT ($p = 0.12$). When divided by subgroup, WPRT was associated with significantly improved bRFS in patients who received EBRT + BT in a PS-adjusted model (HR 0.5, 95% CI 0.2–0.9, $p = 0.02$). The adjusted model did not identify a significant benefit of WPRT in the EBRT group (HR 0.8, 95% CI 0.6–1.2, $p = 0.4$).

3.3. Distant metastasis-free survival

Covariate-adjusted Kaplan-Meier curves for DMFS are presented in Fig. 2. A total of 264 (23%) experienced DMs. The adjusted 5-yr DMFS rates with WPRT in the EBRT and EBRT + BT groups were 77% (95% CI 70–82%) and 93% (95% CI 89–96%), respectively. Without WPRT, the rates were 74% (95% CI 69–79%) and 90% (95% CI 85–96%), respectively. Overall, when controlling for receipt of BT, WPRT was not associated with

improved DMFS (HR 0.9, 95% CI 0.6–1.4; *p* value for interaction 0.23; Table 2). Similarly, when stratified by subgroup, WPRT was not associated with improved DMFS in either the EBRT or the EBRT + BT group, with PS-adjusted models yielding HRs of 1.1 (95% CI 0.7– 1.7, *p* = 0.8) and 0.6 (95% CI 0.3–1.4, *p* = 0.2), respectively (Table 3).

3.4. Prostate cancer-specific survival

The covariate-adjusted Kaplan-Meier curves for PCSS are presented in Fig. 3. In the entire cohort, 163 patients (14%) died from PCa. The adjusted 5-yr PCSS rates with WPRT for the EBRT and EBRT + BT groups were 92% (95% CI 88–95%) and 98% (95% CI 93–99%), respectively. Without WPRT, the rates were 87% (95% CI 82–90%) and 94% (95% CI 89– 99%), respectively. Overall, when controlling for BT receipt, PCSS trended toward improvement with WPRT (HR 0.7, 95% CI 0.4–1.03; *p* value for interaction 0.58; Table 2). However, when stratified by subgroup, WPRT was not associated with improved PCSS in either group (Table 3). HRs for the EBRT and EBRT + BT groups were 0.7 (95% CI 0.4– 1.1, *p* = 0.1) and 0.5 (95% CI 0.2–1.2, *p* = 0.1), respectively.

3.5. Effect of ecological bias

As some institutions only provided patients receiving WPRT and others provided no patients receiving WPRT, a sensitivity analysis was performed to assess for ecological bias. Five institutions contributing data from a single treatment type were removed from the analysis. In this sensitivity analysis, WPRT maintained a similar HR for bRFS. The other outcomes continued to fail to show a benefit (Supplementary Tables 1–3).

4. Discussion

In this study of 1170 patients with biopsy-proven GG 5 PCa treated with either EBRT or EBRT + BT, WPRT was found to be associated with improved bRFS in the EBRT + BT subgroup, although when all patients were analyzed together, WPRT was not found to be associated with improved bRFS. No associations between WPRT and any clinical outcomes were identified in either cohort.

Contrary to an increased push toward extended lymphadenectomy within the urologic community [18,19], enthusiasm for WPRT has dwindled over the years among radiation oncologists [20]. In this series of patients with aggressive GG 5 disease, only 53% received WPRT, despite the known high incidence of pathologic node positivity in patients with GG 5 disease who undergo surgery (17% in a companion cohort) [10]. Given the more advanced nature of the disease in both the EBRT and the EBRT + BT cohorts, the occult lymph node positivity rate in the radiotherapy cohorts examined here would be expected to be even higher than 17%. Yet, despite this high a priori risk of nodal disease, WPRT was associated with improved bRFS only in the EBRT + BT cohort, and was not associated with improved clinical outcomes in either cohort.

The findings in the EBRT cohort are similar to those reported in the aforementioned trials for patients with less aggressive disease [3,6,21]. The proportion of patients with GG 5 PCa in these trials is not reported, but presumed to be low given the rarity of the disease. However, there has been retrospective investigation into the benefit of WPRT in high-risk

disease, summarized in Table 4 [22–25]. In general, even among high-risk patients, the benefit of WPRT is masked in the larger cohort and becomes apparent only when the results are isolated to only those patients with the highest risk of nodal disease. It is important to note, however, that the proportion of patients with GG 5 disease in these studies is unknown. The largest proportion of patients with GS 8–10 was in Aizer et al. [23] at 46%, but it is fair to assume that it was largelycomposed of patients with GS 8. Our study is unique in that it explores exclusively those patients with GG 5 disease, a separate histologic entity that likely behaves differently than other high-risk PCa.

One prospective study did identify bRFS and PCSS benefits with the addition of WPRT to EBRT when treating high-risk disease [26]. While this study had more patients with GG 5 disease, we did not identify any association with improvement following WPRT in the EBRT cohort. This may in part be due to improved outcomes both with and without WPRT in general, decreasing the event rate and thus the power to identify significant differences. The benefit of WPRT in patients being treated with EBRT + BT has not been studied prospectively. One retrospective series compared outcomes following EBRT + BT with either WPRT or a smaller "mini-pelvis" field that treated only below the sacroiliac joints [27]. The authors found no differences in bRFS or PCSS between the two field sizes. The discrepancy between a lack of benefit of WPRT versus "mini-field," and the presence of a bRFS benefit from WPRT versus no elective nodal radiotherapy as reported in this study, may relate to the nodes at risk. The "mini-field" in the Bittner et al. [27] study covered the obturator nodes, which is known to be a major site of occult positive nodes, whereas the prostate-only fields in this study did not offer any nodal coverage. Thus, it is possible that the benefit of nodal radiotherapy is strongest in covering the first echelon obturator nodes.

In this study, bRFS benefit from WPRT was only seen in the subgroup of patients who received EBRT + BT upon subgroup-specific analysis. One possible explanation—and indeed the rationale for exploring subgroup-specific analysis in the absence of a significant interaction term between receipt of BT and benefit of WPRT—is that sterilizing nodal disease only impacts outcomes if the primary disease remains controlled without seeding metastases. Indeed, in the recent publication of the long-term results of RTOG 9413 [4], the authors posit that the benefit of WPRT in the setting of inadequate dose to the prostate may be masked by a second wave of progression due to local failure. The primary tumor doses in the GETUG-01 and RTOG 9413 studies were only 66–70 Gy and 70.2 Gy, respectively [29–31]. The median dose in the current EBRT group was 74 Gy in 2-Gy fractions, which is standard dose-escalated treatment, and still a benefit was not seen. However, it is possible that extreme dose escalation is needed for a benefit of WPRT to emerge. Indeed, the association with overall improved clinical outcomes despite shorter duration of ADT with EBRT + BT versus EBRT alone suggests the importance of local control, although post-treatment biopsies to prove this are absent [10,32]. Thus, WPRT may benefit a subset of patients who have microscopic nodal disease, so long as optimal local control to the prostate is achieved. By contrast, it is also possible that the bRFS difference is at least partially explained by the difference in ADT utilization, although we attempted to reduce this effect by including it in our model as a time-varying covariate. One may argue that the overall duration of ADT is relatively short in this study overall, at 12 mo in the EBRT + BT group and 22 mo in the EBRT group. However, this duration is acceptable according to National

Comprehensive Cancer Network (NCCN) guidelines [33], and both arms of the Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT)* trial received 12 mo of ADT [34]. Regardless of the explanation, it remains to be seen whether this bRFS benefit will translate into a benefit in DMFS or PCSS. While no statistically significant difference was seen in these outcomes in our study, the number of events is relatively small thus far.

On a related note, WPRT at traditional doses (45–50.4 Gy) may selectively benefit patients with truly microscopic nodal disease, but those with larger, but still radiographically occult, tumor deposits in the pelvic nodes are likely receiving inadequate dose. Recent studies suggest that improved visualization with modalities such as ^{68}Ga-prostate-specific membrane antigen-11 positron-emission tomography/computed tomography could aid in detection of pelvic nodal metastases, potentially offering targets to boost during radiotherapy [28].

The strengths of this study lie in its large number of patients and its multi-institutional design. Although a randomized, prospective trial would be ideal, the scarcity of GG 5 PCa makes this impractical, and large observational studies remain the main source of data for rare cancers. There are limitations, including those biases inherent to any retrospective study. Despite the large number of patients, the study may be underpowered to assess whether a true benefit exists. In an attempt to control for bias, we utilized PS including age, T stage, GS, and initial PSA, and accounted for ADT duration using a time-varying covariate. However, other potentially biasing variables such as comorbidity were unavailable. It is likely that patients in the EBRT group had more comorbidity than those in the EBRT + BT group, as BT patients by definition must be candidates for an invasive procedure, but we cannot know this for certain. However, a recent study suggests that comorbidity indices may not be impactful when assessing oncologic outcomes in patients with PCa [35]. In addition, although follow-up was calculated from the end of radiation therapy, there are variable practice patterns with respect to the timing of neoadjuvant ADT and we cannot fully assess subtle differences between the effect of neoadjuvant and concurrent or adjuvant ADT. Furthermore, not all contributing centers provided data for both treatment types; some institutions treat exclusively with WPRT and others never treat with WPRT, which may introduce bias. However, we did perform a sensitivity analysis to assess for ecological bias, and our results did not change significantly. Another limitation is the lack of information about field size in our study, as the superior border of the pelvic field has been suggested as a determinant of the success of WPRT [5]. While we did obtain the institutional policy for pelvis treatment during the time frame of our study, we were not able to review radiation plans for each patient. It is important to note that RTOG 0924 uses a pelvic field that includes the common iliac nodes, to a level corresponding to the top of L4–L5. In addition, we unfortunately do not have toxicity data. The recent publication of RTOG 9413 explores toxicity in detail and found that grade ≥3 gastrointestinal and genitourinary events were more frequent in patients who received WPRT. However, it is worth noting that the rates were still low (< 8%), and the study took place prior to the widespread adoption of intensity-modulated radiation therapy. Unfortunately, there was also no central pathologic or radiologic review in this study. Lastly, a median follow-up of 5.6 yr is relatively short, but given the aggressive nature of GG 5 disease, many events do occur within that time frame.

5. Conclusions

The role of WPRT remains a contentious topic in PCa radiation oncology. In this study, we analyzed the benefit of WPRT in patients with GG 5 disease, a group at a much higher a priori risk of having occult nodal metastases, based on prostatectomy series and emerging data with advanced imaging agents. Overall, WPRT was not associated with a benefit in bRFS. However, on subgroup-specific analysis, WPRT was associated with a significant benefit in patients receiving EBRT + BT, but not EBRT alone. These data suggest that in the highest-risk patients, if local control is achieved in the prostate, WPRT may be valuable in sterilizing regional microscopic disease. The lack of an association with clinical outcome benefits could be attributed to lack of power and may become apparent with time. Further studies designed to optimize WPRT, including with the use of more potent radiosensitizing ADT agents and/or optimization with advanced imaging, are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

[1]. Nguyen PL, D'Amico AV. Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer despite two negative randomized trials. J Clin Oncol 2008;26:2055–6, [author reply 2056–7]. [PubMed: 18421061]

[2]. Roach M 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. J Clin Oncol 2003;21:1904–11. [PubMed: 12743142]

[3]. Lawton CA, DeSilvio M, Roach M 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94–13, with emphasis on unexpected hormone/radiation interactions. Int J Radiat Oncol Biol Phys 2007;69:646–55. [PubMed: 17531401]

[4]. Roach M, Moughan J, Lawton CAF, et al. Sequence of hormonal therapy and radiotherapy field size in unfavourable, localised prostate cancer (NRG/RTOG 9413): long-term results of a randomised, phase 3 trial. Lancet Oncol 2018;19:1504–15. [PubMed: 30316827]

[5]. Morikawa LK, Roach M 3rd. Pelvic nodal radiotherapy in patients with unfavorable intermediate and high-risk prostate cancer: evidence, rationale, and future directions. Int J Radiat Oncol Biol Phys 2011;80:6–16. [PubMed: 21481721]

[6]. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Update of the long-term survival results of the GETUG-01 randomized study. Int J Radiat Oncol Biol Phys 2016;96:759–69. [PubMed: 27788949]

[7]. Seaward SA, Weinberg V, Lewis P, Leigh B, Phillips TL, Roach M 3rd. Identification of a high-risk clinically localized prostate cancer subgroup receiving maximum benefit from whole-pelvic irradiation. Cancer J Sci Am 1998;4:370–7. [PubMed: 9853136]

[8]. Koloff ZB, Hamstra DA, Wei JT, et al. Impact of tertiary Gleason pattern 5 on prostate cancer aggressiveness: lessons from a contemporary single institution radical prostatectomy series. Asian J Urol 2015;2:53–8. [PubMed: 29264120]

[9]. Jackson W, Hamstra DA, Johnson S, et al. Gleason pattern 5 is the strongest pathologic predictor of recurrence, metastasis, and prostate cancer-specific death in patients receiving salvage radiation therapy following radical prostatectomy. Cancer 2013;119:3287–94. [PubMed: 23821578]

[10]. Kishan AU, Cook RR, Ciezki JP, et al. Radical prostatectomy, external beam radiotherapy, or external beam radiotherapy with brachytherapy boost and disease progression and mortality in

patients with Gleason score 9–10 prostate cancer. JAMA 2018;319:896–905. [PubMed: 29509865]

[11]. Roach M 3rd, Hanks G, Thames H Jr, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. Int J Radiat Oncol Biol Phys 2006;65:965–74. [PubMed: 16798415]

[12]. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. Biometrika 1994;81:515–26.

[13]. Van Buuren S, Brand JPL, Groothuis-Oudshoorn CGM, Rubin DB. Fully conditional specification in multivariate imputation. J Stat Comput Simul 2006;76:1049–64.

[14]. Morgan SL, Todd JJ. A diagnostic routine for the detection of consequential heterogeneity of causal effects. Sociol Methodol 2008;38:231–81.

[15]. Rosenbaum PR, Rubin DB. Reducing bias in observational studies using subclassification on the propensity score. J Am Stat Assoc 1984;79:516–24.

[16]. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. Comput Methods Programs Biomed 2004;75:45–9. [PubMed: 15158046]

[17]. RC Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2016.

[18]. Maderthaner L, Furrer MA, Studer UE, Burkhard FC, Thalmann GN, Nguyen DP. More extended lymph node dissection template at radical prostatectomy detects metastases in the common iliac region and in the fossa of Marcille. BJU Int 2018;121:725–31. [PubMed: 28834085]

[19]. Briganti A, Blute ML, Eastham JH, et al. Pelvic lymph node dissection in prostate cancer. Eur Urol 2009;55:1251–65. [PubMed: 19297079]

[20]. Zelefsky MJ, Moughan J, Owen J, Zietman AL, Roach M 3rd, Hanks GE. Changing trends in national practice for external beam radiotherapy for clinically localized prostate cancer: 1999 Patterns of Care survey for prostate cancer. Int J Radiat Oncol Biol Phys 2004;59:1053–61. [PubMed: 15234039]

[21]. Asbell SO, Krall JM, Pilepich MV, et al. Elective pelvic irradiation in stage A2, B carcinoma of the prostate: analysis of RTOG 77–06. Int J Radiat Oncol Biol Phys 1988;15:1307–16. [PubMed: 3058656]

[22]. Seaward SA, Weinberg V, Lewis P, Leigh B, Phillips TL, Roach M 3rd. Improved freedom from PSA failure with whole pelvic irradiation for high-risk prostate cancer. Int J Radiat Oncol Biol Phys 1998;42:1055–62. [PubMed: 9869229]

[23]. Aizer AA, Yu JB, McKeon AM, Decker RH, Colberg JW, Peschel RE. Whole pelvic radiotherapy versus prostate only radiotherapy in the management of locally advanced or aggressive prostate adenocarcinoma. Int J Radiat Oncol Biol Phys 2009;75:1344–9. [PubMed: 19464821]

[24]. Mantini G, Tagliaferri L, Mattiucci GC, et al. Effect of whole pelvic radiotherapy for patients with locally advanced prostate cancer treated with radiotherapy and long-term androgen deprivation therapy. Int J Radiat Oncol Biol Phys 2011;81:e721–6. [PubMed: 21277100]

[25]. Pan CC, Kim KY, Taylor JM, McLaughlin PW, Sandler HM. Influence of 3D-CRT pelvic irradiation on outcome in prostate cancer treated with external beam radiotherapy. Int J Radiat Oncol Biol Phys 2002;53:1139–45. [PubMed: 12128113]

[26]. Milecki P, Baczyk M, Skowronek J, Antczak A, Kwias Z, Martenka P. Benefit of whole pelvic radiotherapy combined with neoadjuvant androgen deprivation for the high-risk prostate cancer. J Biomed Biotechnol 2009;2009:625394. [PubMed: 19859572]

[27]. Bittner N, Merrick GS, Wallner KE, Butler WM, Galbreath R, Adamovich E. Whole-pelvis radiotherapy in combination with interstitial brachytherapy: does coverage of the pelvic lymph nodes improve treatment outcome in high-risk prostate cancer? Int J Radiat Oncol Biol Phys 2010;76:1078–84. [PubMed: 19553031]

[28]. Calais J, Kishan AU, Cao M, et al. Potential impact of ^{68}Ga-PSMA-11 PET/CT on the planning of definitive radiation therapy for prostate cancer. J Nucl Med 2018;59:1714–21. [PubMed: 29653978]

[29]. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M.D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:67–74. [PubMed: 17765406]

[30]. Heemsbergen WD, Al-Mamgani A, Slot A, Dielwart MF, Lebesque JV. Long-term results of the Dutch randomized prostate cancer trial: impact of dose-escalation on local, biochemical, clinical failure, and survival. Radiother Oncol 2014;110:104–9. [PubMed: 24246414]

[31]. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American College of Radiology 95–09. J Clin Oncol 2010;28:1106–11. [PubMed: 20124169]

[32]. Fuks Z, Leibel SA, Wallner KE, et al. The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation. Int J Radiat Oncol Biol Phys 1991;21:537–47. [PubMed: 1869452]

[33]. National Comprehensive Cancer Network. NCCN Practice Guidelines in Oncology, v.3.2012 Prostate cancer. National Comprehensive Cancer Network Web site 2012 http://www.nccn.org/professionals/physician_gls/PDF/prostate.pdf

[34]. Morris WJ, Tyldesley S, Pai HH, et al. ASCENDE-RT*: a multicenter, randomized trial of dose-escalated external beam radiation therapy (EBRT-B) versus low-dose-rate brachytherapy (LDR-B) for men with unfavorable-risk localized prostate cancer. J Clin Oncol 2015;33, 3–3.

[35]. Rajan P, Sooriakumaran P, Nyberg T, et al. Effect of comorbidity on prostate cancer-specific mortality: a prospective observational study. J Clin Oncol 2017;35:3566–74. [PubMed: 28930493]
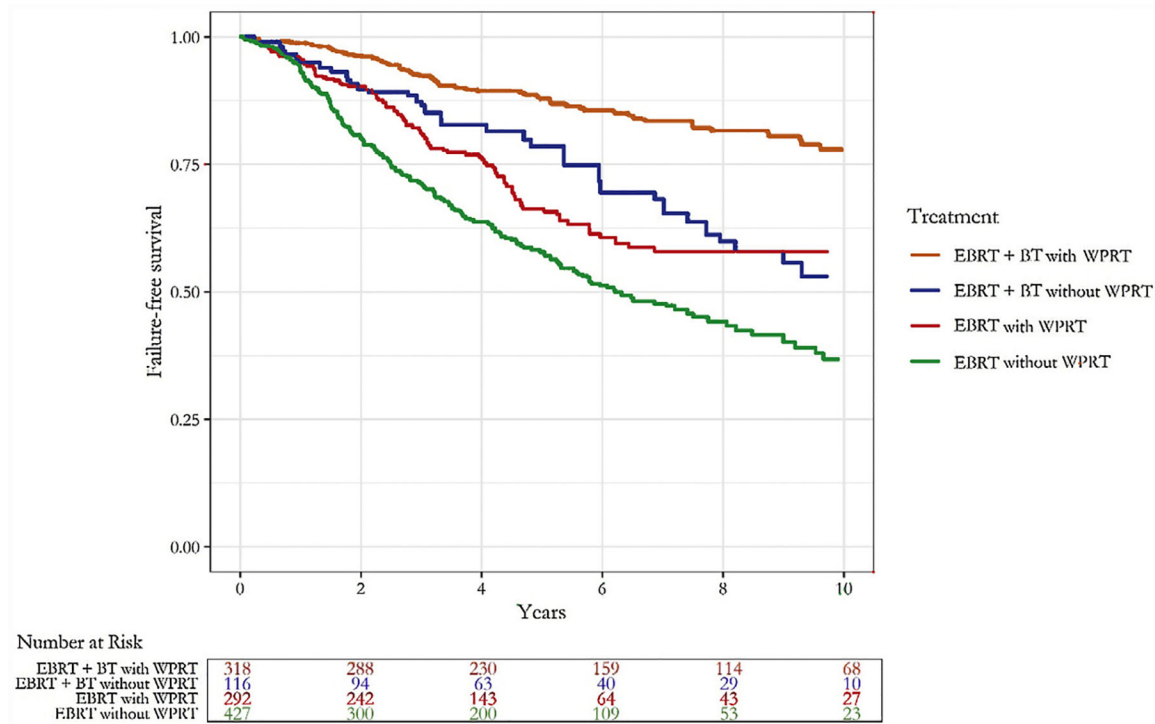
Fig. 1 –.
Adjusted Kaplan-Meier curve and number at risk for biochemical recurrence-free survival by treatment group. BT = brachytherapy; EBRT = external-beam radiation therapy; WPRT = whole-pelvis radiation therapy.
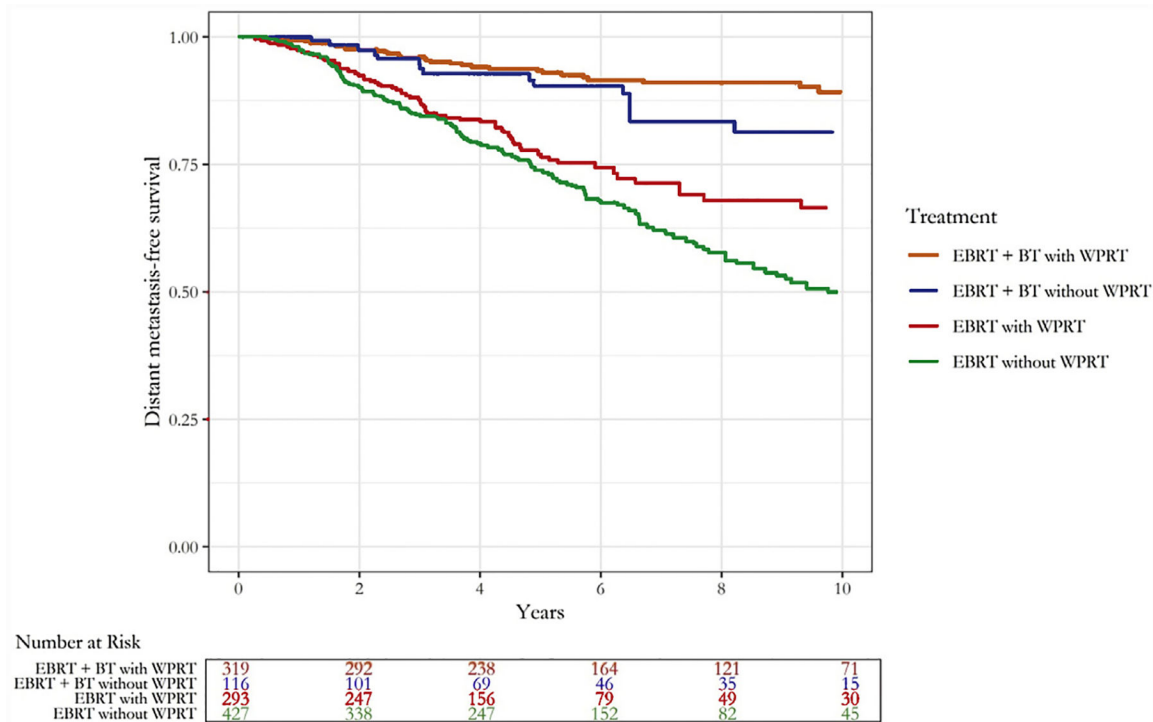
Fig. 2 –.

Adjusted Kaplan-Meier curve and number at risk for distant metastasis-free survival by treatment group. BT = brachytherapy; EBRT = external-beam radiation therapy; WPRT = whole-pelvis radiation therapy.
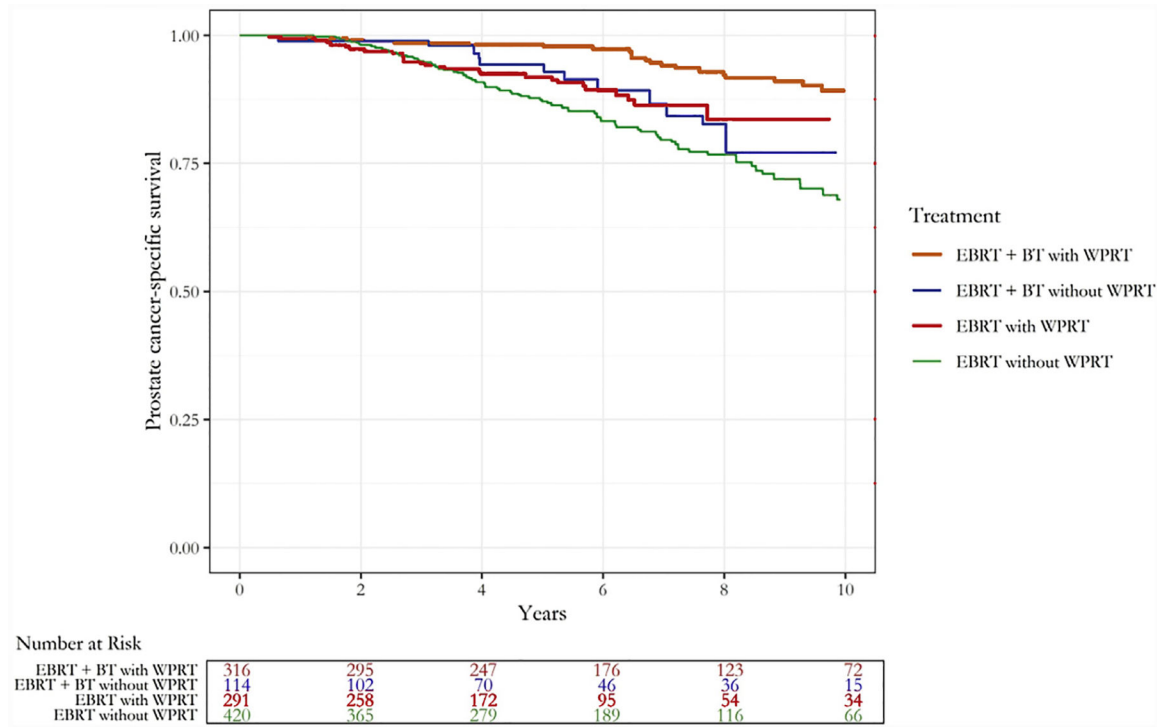
Fig. 3 –.
Adjusted Kaplan-Meier curve and number at risk for prostate cancer-specific survival by treatment group. BT = brachytherapy; EBRT = external-beam radiation therapy; WPRT = whole-pelvis radiation therapy.

Table 1 –

Patient characteristics stratified by treatment group

	EBRT (n = 734)	EBRT + BT (n = 436)	EBRT with WPRT (n = 299)	EBRT without WPRT (n = 435)	EBRT + BT with WPRT (n = 320)	EBRT + BT without WPRT (n = 116)
Median age (yr)	68	68	70	67	67	71
iPSA	9.9	9.6	10.5	9.5	10.1	8.6
Patients with GS 10 (%)	6.5	8.7	3	3.5	6	2.5
T stage, n (%)						
T1c	210 (29)	147 (34)	85 (28)	125 (29)	132 (41)	15 (13)
T2a	135 (18)	63 (14)	55 (18)	80 (18)	53 (17)	10 (9)
T2b	111 (15)	88 (20)	32 (11)	79 (18)	51 (16)	37 (32)
T2c	50 (7)	44 (10)	29 (10)	21 (5)	23 (7)	21 (18)
T3a	103 (14)	63 (14)	50 (17)	53 (12)	38 (12)	25 (22)
T3b	73 (10)	17 (4)	25 (8)	48 (11)	11 (3)	6 (5)
T4	43 (6)	13 (3)	16 (5)	27 (6)	11 (3)	2 (2)
Follow-up time (yr)	5.1	6.3	4.8	5.4	6.6	5.4
Received WPRT, n (%)	299 (41)	320 (73)				
Received ADT, n (%)	657 (89.5)	401 (92.4)	288 (96)	369 (85)	287 (90)	114 (98)
Median ADT duration (mo)	22	12	24	18	12.5	9
Median dose in EQD2 (IQR)	74.3 (71.2–78)	91.5 (88.7–98.2)	76 (73–78)	71.3 (71.3–78)	93 (88.7–115.7)	88.7 (85.8–94)
Local salvage, n (%)	18 (2.5)	4 (0.1)	3 (1)	15 (3)	1 (<1)	3 (2.6)
Systemic salvage, n (%)	89 (12)	24 (5.5)	48 (16)	41 (9)	17 (5)	7 (6)
BCF, n (%)	296 (40)	87 (20)	92 (31)	204 (47)	52 (16)	35 (30)
DM, n (%)	222 (30)	42 (10)	69 (23)	153 (35)	28 (9)	14 (12)
PCSS, n (%)	129 (18)	34 (8)	31 (10)	98 (23)	21 (7)	13 (11)

ADT = androgen deprivation therapy; BCF = biochemical failure; DM = distant metastasis; EBRT = external-beam radiation therapy; EBRT + BT = external-beam radiation therapy with brachytherapy boost; EQD2 = equivalent dose in 2-Gy fractions; GS = Gleason score; iPSA = initial prostate-specific antigen; IQR = interquartile range; PCSS = prostate cancer-specific survival; WPRT = whole-pelvis radiation therapy.

Table 2 –

Propensity score and time-varying ADT-adjusted effects of WPRT on clinical outcomes, controlling for receipt of brachytherapy

Endpoint	Hazard ratio (95% CI)	*p* value
bRFS	0.7 (0.5–1.03)	0.07
DMFS	0.9 (0.6–1.4)	0.7
PCSS	0.7 (0.4–1.03)	0.06

ADT = androgen deprivation therapy; bRFS = biochemical recurrence-free survival; CI = confidence interval; DMFS = distant metastasis-free survival; PCSS = prostate cancer-specific survival; WPRT = whole-pelvis radiation therapy.

Table 3 –

Propensity score and time-varying ADT-adjusted effects of WPRT on clinical outcomes, stratified by brachytherapy subgroup

Endpoint and subgroup	Hazard ratio (95% CI)	*p* value
EBRT		
bRFS	0.8 (0.6–1.2)	0.4
DMFS	1.1 (0.7–1.7)	0.8
PCSS	0.7 (0.4–1.1)	0.1
EBRT+BT		
bRFS	0.5 (0.2–0.9)	0.02
DMFS	0.6 (0.3–1.4)	0.2
PCSS	0.5 (0.2–1.2)	0.1

ADT = androgen deprivation therapy; bRFS = biochemical recurrence-free survival; CI = confidence interval; DMFS = distant metastasis-free survival; EBRT + BT = external-beam radiation therapy with brachytherapy boost; PCSS = prostate cancer-specific survival; WPRT = whole-pelvis radiation therapy.

Table 4 –

Summary of prior retrospective series comparing WPRT with PORT in patients with high-risk prostate cancer receiving external-beam radiotherapy alone

	% GG 5	Median RT dose (EQD2)	Pelvic field size	ADT use/Duration	bRFS PORT	bRFS WPRT	Significant difference
Seaward et al. (1998) [22]	Unknown (27% GS 8–10)	70–72	L5/S1	20% of patients, most <4 mo	21 mo	34.3 mo	Yes
Aizer et al. (2009) [23]	Unknown (46% GS 8–10)	75.6	L5/S1	92–98%, 12–24 mo	69% at 4 yr	86% at 4 yr	No, but WPRT better on adjusted analysis
Mantini et al. (2011) [24]	Unknown (18% GS 8–10)	70.2–73.8	L5/S1	All patients, median 24 mo	90.5% at 4 yr	90.4% at 4 yr	No, except in the nodal risk >30% group
This study (EBRT only)	100	74.3	Majority L5/S1	90% of patients, median 22 mo	57% at 5 yr	65% at 5 yr	No

ADT = androgen deprivation therapy; bRFS = biochemical recurrence-free survival; EBRT = external-beam radiation therapy; EQD2 = equivalent dose in 2-Gy fractions; GG = Gleason grade; GS = Gleason score; PORT = prostate-only radiation therapy; WPRT = whole-pelvis radiation therapy.