Whole Pelvis Versus Prostate-Only Radiotherapy With or Without Short-Course Androgen Deprivation Therapy and Mortality Risk

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Abstract

Whole-pelvis radiotherapy or a short-course (approximately 4 months) of androgen deprivation therapy yield an all-cause mortality benefit among patients with unfavorable-risk prostate cancer. However, the combination of these 2 treatments does not further improve mortality outcomes, suggesting a shared therapeutic mechanism.

Background: The purpose of the study was to determine whether the extent of prostate radiotherapy (ie, whole-pelvic radiotherapy [WPRT] vs. prostate and seminal vesicle radiotherapy [PSVRT]) is associated with all-cause mortality (ACM) in men treated with or without androgen deprivation therapy (ADT). **Patients and Methods:** A multiple-institution cohort of 3709 prostate cancer patients was prospectively assembled from 1991 to 2006. The median age was 72 years and all patients had T1c-T3N0M0 adenocarcinoma of the prostate. Patients were treated with WPRT or PSVRT followed by a brachytherapy boost, with or without neoadjuvant ADT (median duration, 4.2 months). Seventy percent of patients had unfavorable-risk disease (Gleason score ≥ 7; prostate-specific antigen ≥ 10 ng/mL; or stage $\geq$ T2b). Cox regression was applied to determine whether the radiation treatment volume affected the risk of ACM. The interaction between radiation volume and ADT use was assessed. **Results:** After a median follow-up of 3.3 years, 561 deaths were observed. A decreased risk of ACM was noted with the use of WPRT versus PSVRT (adjusted hazard ratio [AHR], 0.58; 95% confidence interval [CI], 0.38-0.89; $P = .01$), or with ADT use (AHR, 0.71; 95% CI, 0.58-0.90; $P = .004$). However, a combination of WPRT and ADT did not further improve ACM compared with either WPRT alone or PSVRT with ADT. Moreover, there was a significant interaction between the radiotherapeutic treatment volume and ADT (AHR, 1.61; 95% CI, 1.004-2.58; $P = .048$). **Conclusion:** Treatment with WPRT or short-course ADT is associated with a decreased risk of ACM, although a combination of the two does not yield greater benefit. This observation suggests a shared mechanism for this risk reduction, which we hypothesize to be via the treatment of micrometastatic disease within the pelvic lymph nodes.

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Introduction

Treatment of regional lymph nodes (LNs) with radiotherapy (RT) yields improved outcomes in a variety of malignancies. Specifically, although local control after LN RT might be expected from a mechanistic standpoint, LN RT has also heralded improved overall survival in certain cancers of the breast, head and neck, gastrointestinal tract, female genitourinary system, skin, and soft tissues, among others.[1-8] Despite this proof-of-principle among several disease sites, it remains unclear whether pelvic LN irradiation stands to improve outcomes for patients with prostate cancer (PC).

The combination of whole-pelvic RT (WPRT) with prostate and seminal vesicle (PSV) RT was studied in conjunction with short-course (4 months) androgen deprivation therapy (ADT) in Radiation Therapy Oncology Group (RTOG) 94-13.[9,10] Initial reports from that study demonstrated a significant improvement in progression-free survival (PFS) favoring WPRT (4-year PFS = 54.2%

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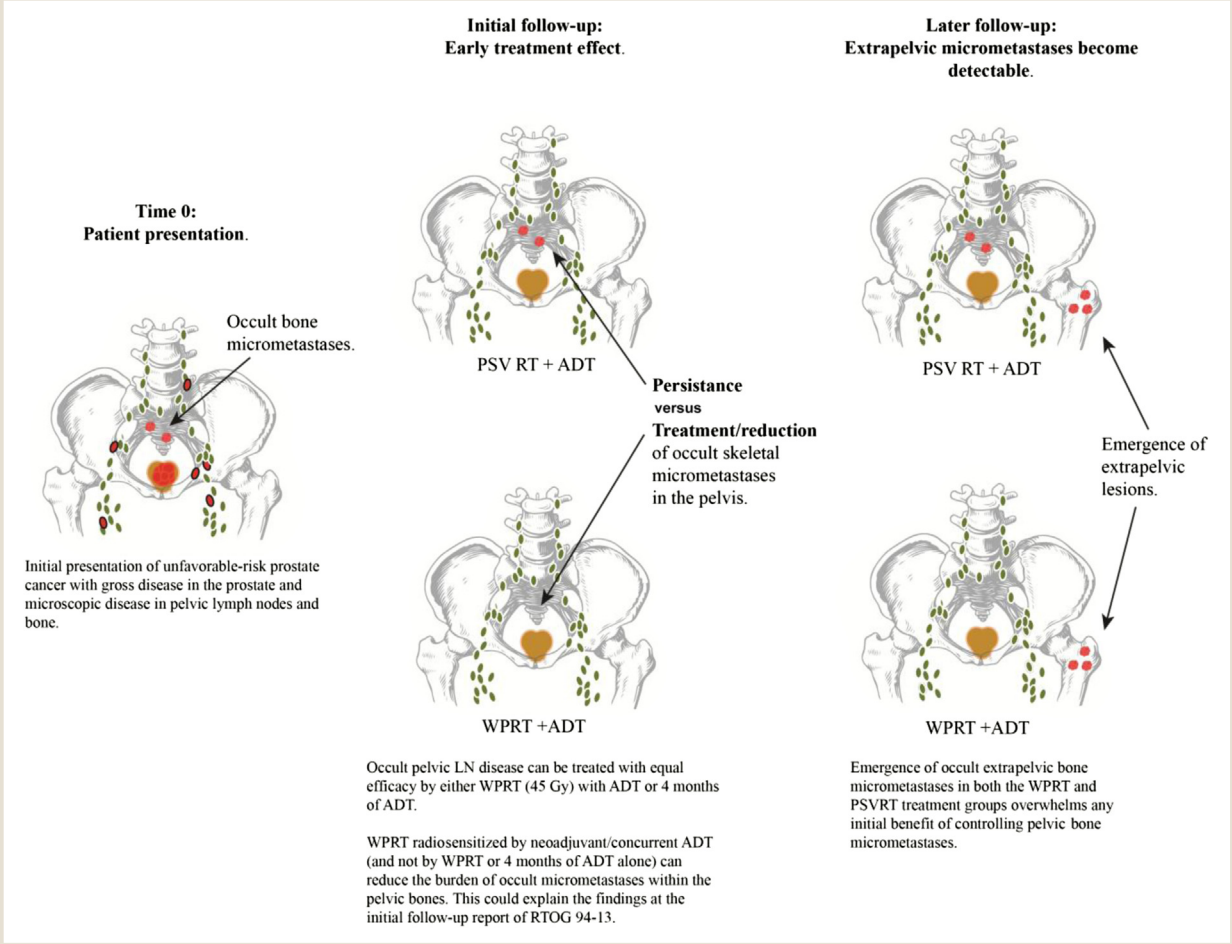
for WPRT vs. 47% for PSV RT; $P = .02$). However, the final analysis showed no significant difference in PFS between WPRT and PSV RT ($P = .99$). As a result of this and the similarly negative trial, Genitourinary Tumor Group-01,[11] pelvic radiation has not been widely adopted in the treatment of PC.

In contrast, the combination of ADT with RT has reproducibly demonstrated a survival benefit in men with intermediate- or high-risk disease.[12-18] To date, it remains unclear whether this benefit is driven by the treatment of micrometastatic disease in the pelvic LNs and/or bones, by hormonal radiosensitization of the primary tumor, or by some combination thereof. In addition, although ADT and WPRT were ultimately not found to be superior to ADT and PSV RT in men with unfavorable-to intermediate- or high-risk PC, such a comparative approach has yet to be studied in the setting of high-dose prostate RT with modern treatment planning and image-guided RT techniques, with an evaluation of all-cause mortality (ACM) as the primary end point.

A hypothesis arising from these observations is that short-course ADT might treat disease in the pelvic LNs in a manner comparable with that of WPRT. In addition, if WPRT in synergy with neoadjuvant/concurrent ADT is effective at reducing the burden of micrometastatic bony disease within the RT treatment portal, one might expect a transient benefit in biochemical PFS compared with WPRT alone or PSV RT with or without a short course of ADT. The benefit, though, would be temporary because as occult micrometastases in bones beyond the pelvis begin to progress (having been treated neither by short-course ADT, WPRT, or the combination), this initial advantage of WPRT and ADT would be lost in terms of biochemical and clinical PFS (Figure 1).

Therefore, the purpose of this study was to determine whether the extent of prostate RT (ie, WPRT vs. PSV RT) is associated with the risk of ACM in men with PC treated with or without short-course ADT. A formal test for interaction between the RT volume and ADT use was performed to assess whether ADT affected

Figure 1 Illustration of a Hypothesis Explaining an Early Progression-Free Survival Benefit to Whole-Pelvic Radiotherapy That Was Not Observed at Longer Follow-Up in RTOG 9413 (Cancer and Involved Lymph Nodes Are Shown in Red; Uninvolved Lymph Nodes in Green; Prostate in Tan)



Abbreviations: ADT = androgen deprivation therapy; LN = lymph node; PSVRT = prostate and seminal vesicle radiotherapy; PSV RT + ADT = prostate and seminal vesicle radiotherapy with androgen deprivation therapy; WPRT = whole-pelvis radiotherapy; WPRT + ADT = whole-pelvis radiotherapy with androgen deprivation therapy.