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Review

Improving outcomes in high-risk prostate cancer with radiotherapy

*William R. Polkinghorn, Michael J. Zelefsky**

Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, United States

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ABSTRACT

There have been significant improvements in the radiotherapeutic management of patients with high risk prostate cancer. Randomized trials have clearly demonstrated improved outcomes with the combination of radiotherapy in conjunction with androgen deprivation. While these trials have utilized low doses of radiotherapy in the range of 70 Gy, recent studies have suggested that significant benefits of combined androgen deprivation therapy with dose escalated radiotherapy are also observed. The use of high radiation dose levels in the setting of high risk prostate cancer is important, and strategies which combine external beam radiotherapy with a brachytherapy boost may provide an opportunity for even greater intensification of the radiation dose to the prostate target. Systemic therapies, second generation anti-androgen therapy and novel targeted agents integrated with radiotherapy will open up new vistas and challenges for further improved outcomes in patients with high-risk disease.

1. Background

External beam radiation therapy (EBRT) is considered a standard treatment intervention for patients with high-risk prostate cancer. However, EBRT alone is generally inadequate to achieve durable disease control for high-risk patients, and long-term outcomes with radiation therapy used as monotherapy for this cohort are far from optimal. From the radiotherapy-only arms of various randomized trials where low doses of EBRT in the ranges of 65–70 Gy were administered, the 10-year prostate-specific antigen (PSA) failure rates were greater than 75%.[1–4] Randomized trials[1–4] for high-risk prostate cancer have evaluated the combination of EBRT plus androgen-deprivation therapy (ADT) and have consistently demonstrated improved outcomes with combined-modality therapy for this high-risk population (Table 1). The greatest benefit may be seen among those patients with high-grade cancers. This notion is further supported by a meta-analysis of five Radiation Therapy Oncology Group (RTOG) trials incorporating 2743 patients[5] where it was demonstrated that patients with Gleason 8–10 or T3 disease experience superior survival outcomes when treated with ADT in conjunction with EBRT compared with EBRT alone.

Clinical evidence suggests that not only is the use of ADT in conjunction with EBRT an important element in the management of high-risk prostate cancer, but in addition the use of longer-durations of ADT may be associated with

* *Corresponding author*. Tel.: +1 212 639 6802; fax: +1 212 639 8876.
E-mail address: zelefskm@mskcc.org (M.J. Zelefsky).

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Table 1 – Outcomes for combined androgen-deprivation therapy and radiotherapy in high-risk disease.

Study	PSA failure	Distant metastasis	Prostate cancer death	Overall survival
Pilepich et al.[4]	65% at 10 years	35% at 10 years	23% at 10 years	43% at 10 years
Horwitz et al.[3]	52% at 10 years	23% at 10 years	11% at 10 years	52% at 10 years
Pilepich et al.[2]	31% at 10 years (PSA < 1.5 ng/mL)	24% at 10 years	16% at 10 years	49% at 10 years
Bolla et al.[1]	24% at 5 years	10% at 5 years	6% at 5 years	78% at 5 years

PSA = prostate-specific antigen.

improvement in survival outcomes. RTOG 92-02 included over 1500 patients and compared 28 months of ADT (consisting of 2 months neo-adjuvant ADT, 2 months concurrent ADT with EBRT, and 24 months adjuvant ADT) with 4 months of ADT (consisting of 2 months neo-adjuvant ADT and 2 months concurrent ADT with EBRT without adjuvant ADT). In a subset analysis, a 10% survival advantage was noted among the Gleason 8–10 cohort who received the long-term ADT regimen compared with the short-course treatment.[3] European Organisation for Research and Treatment of Cancer (EORTC) 22961 randomized high-risk patients to 6 months ADT (neo-adjuvant and concurrent ERBT) or 3 years of ADT (additional 30 months adjuvant ADT). Nine hundred seventy patients were randomized to this trial, and with a median follow-up of 6.4 years a 4% survival advantage was observed for the group treated with long-term ADT, with significant improvement in other parameters including progression-free survival outcomes and biochemical relapse–free survival outcomes.[1]

Nevertheless, the optimal duration of ADT when administered with radiation therapy (RT) remains to be defined. In a subset analysis of a Phase III trial from Canada that randomized high-risk patients to 3 versus 8 months of neo-adjuvant ADT, patients were reported to have an improvement in 5-year disease-free survival outcomes from 42% to 71% ($P < 0.01$); however, no advantage was noted for overall survival.[6] To date, while it is common practice for patients with high-risk disease to receive 2–3 years of adjuvant ADT, current trials have never established if ADT courses with durations of only 12 or 18 months may be sufficient, especially in the setting of escalated doses of radiotherapy at 80 Gy or higher. Previously published trials comparing ADT plus EBRT versus EBRT alone utilized low doses of radiotherapy, often in the absence of targeted conformal treatment delivery such as intensity-modulated radiotherapy. Therefore the optimal duration of ADT remains unclear with the use of high-dose conformal EBRT. Only randomized trials evaluating various ADT durations in the setting of high-dose radiotherapy administration will be able to resolve these clinical uncertainties.

2. Is there an established role for ADT in the era of dose-escalated IMRT for high-risk patients?

Prior randomized trials[1–4] in locally advanced prostate cancer demonstrating the benefit of concomitant and adjuvant ADT in conjunction with EBRT have all been in the setting of low-dose radiotherapy. In retrospect, the dose levels of 65–70 Gy (in the absence of conformal radiotherapy techniques) routinely utilized in these studies would be considered inadequate by current standards and associated with an increased likelihood of local tumor failure. Zelefsky et al. have recently shown that even in the setting of dose levels of 81 Gy and higher, the use of ADT for higher-risk patients provides an incremental benefit for improved PSA relapse-free survival outcomes and distant metastases-free survival outcomes. Zelefsky et al. reviewed the outcome of 2551 patients treated with three-dimensional conformal radiotherapy (3D-CRT)/IMRT with dose levels ranging from 64.8 Gy to 86.4 Gy.[7] In this experience the median duration of ADT was 6–8 months. The use of ADT for intermediate- and high-risk patients was associated with significantly improved biochemical tumor control and distant metastases-free survival outcomes. The benefit of ADT was observed even among patients who were treated to dose levels of 81 Gy or higher. These data suggest that ADT (at least 6–8 months and probably longer) is still required in conjunction with high-dose radiotherapy for high-risk patients. We concur and believe that for high-risk prostate cancer patients, longer courses of ADT such as 2–3 years would be more appropriate in the setting of high-dose radiotherapy and represent our current practice.

3. Dose intensification with EBRT and brachytherapy

Another important direction to improve the prostate cancer-specific outcomes of high-risk patients includes the intensification of the radiation dose with the addition of brachytherapy to external RT and ADT. It would appear that the use of traditional escalated radiation dose levels in the range of 78–80 Gy may still be inadequate to eradicate locally advanced prostate cancer. A meta-analysis of the Phase III dose-escalation trials in patients for high-risk prostate cancer that comprised over 2800 patients demonstrated continued improvements in biochemical control outcomes with escalation of doses from 64 Gy to 81 Gy, and there was no apparent suggestion of a plateau being reached.[8] Some reports have in fact noted that dose-escalation even beyond 80 Gy has been associated with similar improvements in tumor control outcomes.[9,10] In one report from the Fox Chase Cancer Center investigators noted that patients who received doses of 80 Gy or more had improved local and distant control compared with those treated with doses less than 80 Gy.[9] Pahlajani et al. noted that for high-risk patients treated with EBRT there appears to be an overall survival advantage with dose escalation up to 84 Gy compared with doses <80 Gy.[10]

Several reports have noted improved outcomes with combined-modality regimens of EBRT and brachytherapy. In one study, 1342 patients with PSA >20 ng/mL, cT3 or higher, or biopsy Gleason 8–10 prostate cancer were retrospectively studied. Patients were treated with brachytherapy alone