

Low PSA, Low Benefit? - Rethinking Androgen Deprivation With Early Salvage Radiotherapy

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Letter to the Editor

In patients receiving Salvage Radiotherapy (SRT) after radical prostatectomy, without radiographic evidence of recurrence and with Prostate-Specific Antigen (PSA) levels of 0.2–0.5 ng/mL, the role of Androgen Deprivation Therapy (ADT) deserves reconsideration in light of recent individual-patient data. Although Hormonal Therapy (HT) improves disease-control outcomes in selected postoperative settings, its absolute benefit may vary according to PSA level at SRT initiation and individual disease risk. The POSEIDON individual-patient-data meta-analysis included 6,057 patients from six randomized phase III trials, with approximately nine years of median follow-up. Overall, adding HT to postoperative radiotherapy did not significantly improve overall survival (OS; HR 0.87, 95% CI 0.76–1.01; $p = 0.06$). No significant OS benefit was observed among patients treated at PSA ≤ 0.20 ng/mL (HR 1.14; $p = 0.43$) or 0.21–0.50 ng/mL (HR 0.94; $p = 0.70$) [1,2]. These findings do not establish that ADT is ineffective in every low-PSA patient; rather, they highlight the absence of a

demonstrated population-level OS benefit in the setting of contemporary very early SRT.

This distinction is clinically relevant because improvements in biochemical or metastasis-related outcomes do not necessarily translate into longer survival. Moreover, evidence supporting ADT with definitive radiotherapy, including the MARCAP individual-patient-data meta-analysis, cannot automatically be extrapolated to the postoperative setting, where treatment targets predominantly microscopic residual disease [1]. GETUG-AFU 16 demonstrated improved long-term progression-free outcomes with six months of androgen suppression added to SRT [3]. Conversely, NRG/RTOG 9601 established the long-term efficacy of adding antiandrogen therapy to salvage prostate-bed radiotherapy in selected patients, although subsequent analyses highlighted the importance of pre-SRT PSA in interpreting the benefit–risk balance [4]. These trials remain fundamental, but their populations and treatment strategies differ from today's increasingly common practice of initiating SRT below 0.5 ng/mL.

The key question is therefore not whether ADT should accompany every course of SRT, but which patients derive sufficient absolute benefit to justify treatment intensification. For men with pN0, PSMA-PET-negative disease and PSA 0.2–0.5 ng/mL, SRT alone represents a reasonable evidence-based option. ADT should be individualized according to PSA kinetics, Grade Group, surgical margins, pathological stage, genomic risk and comorbidities. At higher PSA levels or in the presence of adverse biological features, the potential benefit of systemic treatment may be greater, although decisions should remain grounded in the available evidence.

Treatment duration also warrants scrutiny. Prolonged ADT increases metabolic, cardiovascular, skeletal, sexual and quality-of-life burdens, making careful patient selection essential. Molecular classifiers may further refine this approach. NRG-GU006 investigated whether adding apalutamide to salvage radiotherapy could improve outcomes and explored the role of molecular stratification in this setting [5]. Ultimately, the era of very early SRT calls for a shift from routine treatment intensification toward biologically informed, risk-adapted therapy. Integrating PSA kinetics, pathological features, molecular biomarkers and patient preferences may help identify those who need ADT and those who can reasonably avoid its toxicity without compromising established oncological outcomes.

Keywords: Salvage radiotherapy; Androgen deprivation therapy; Prostate-specific antigen; Overall survival

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