Two Years of Anti-Androgen Treatment Increases Other-Cause Mortality in Men Receiving Early Salvage Radiotherapy: A Secondary Analysis of the NRG Oncology/RTOG 9601 Randomized Phase III Trial

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Abstract

Purpose/Objective: Salvage radiation therapy (SRT) is recommended for men with biochemically recurrent prostate cancer post-radical prostatectomy. RTOG 9601 was a randomized phase 3 clinical trial that demonstrated an overall survival (OS) benefit from the addition of long-term anti-androgen therapy to SRT. However, hormone therapy has well documented side effects and has been shown to increase cardiac event rates, and there remains no evidence of an OS benefit from hormone therapy for men treated with early SRT. Herein, we aim to determine if pre-SRT PSA can serve as both a prognostic and predictive biomarker of benefit from hormone therapy.

Materials/Methods: A secondary analysis of the NRG Oncology/RTOG 9601 double-blind, placebo-controlled randomized trial was conducted (NCT00002874). Patients were treated between 1998-2003 at over 100 centers across North America. Men with adverse pathology (positive surgical margin or pathologic T3 disease) and a PSA of 0.2-4.0 ng/mL were enrolled. Patients were stratified by entry PSA (0.2-1.5 vs >1.5-4.0 ng/mL). Men were randomized to either SRT plus a nonsteroidal anti-androgen (bicalutamide 150mg/day) or placebo for two years. The primary endpoint was OS. Secondary endpoints relevant to the present analysis include distant metastasis (DM) and other-cause mortality (OCM).

Subgroup analyses were performed using the pre-specified PSA stratification variable (1.5 ng/mL) including tests for interaction. Competing risk analyses were performed for DM and OCM.

Results: Of 760 patients, 85% (n=642/760) were in the pre-SRT PSA of ≤1.5 ng/mL stratum. There was no significant OS benefit with bicalutamide in men with PSA ≤1.5 ng/mL (HR 0.87 [95%CI 0.66-1.16]), whereas in men with PSA >1.5 ng/mL (n=118) OS was significantly improved (HR 0.45 [0.25-0.81]). Interaction test of PSA and hormone therapy benefit for OS was significant (p=0.02). Within the PSA ≤1.5 ng/mL subgroup, men with pre-SRT PSA ≤0.6 ng/mL (n=389) had increased OCM (sHR:1.94, [1.17-3.20]) from bicalutamide which was greatest in men with PSA 0.2-0.3 (n=148; sHR:4.14 [1.57-10.89]). There was also increased grade 3-5 cardiac events in those treated on the bicalutamide arm (p=0.04). The present subgroup analysis met 8 of 10 criteria for the reliability and credibility of this subgroup analysis.

Conclusions and Relevance: Pre-SRT PSA is both a prognostic and true predictive biomarker for benefit of hormone therapy with SRT. Long-term anti-androgen therapy did not improve OS in patients receiving early SRT, and may increase OCM. Ongoing trials are enrolling to identify which patients receiving early SRT will benefit from hormone therapy (NRG GU006, NCT03371719).