Phase I Trial of Stereotactic Body Radiotherapy Neoadjuvant to Radical Prostatectomy for Patients with High-Risk Non-Metastatic Prostate Cancer: Feasibility, Safety, and Translational Assessment of the Immune Environment of the Irradiated Prostates

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Background. The primary objective was to test the hypothesis that Stereotactic Body Radiotherapy (SBRT) directed to the prostate two weeks neoadjuvant to radical prostatectomy is feasible and safe. Secondary objectives included physician reported and patient reported toxicity, and assessments of the intraprostatic immune environment after SBRT.

Methods. Patients with non-metastatic unfavorable intermediate and high-risk, prostate cancer underwent SBRT, 24 Gy in 3 fractions (EQD2 of 60 Gy for an alpha/beta ratio of 2) directed to the prostate and seminal vesicles delivered over five days, two weeks neoadjuvant to radical prostatectomy in a prospective Phase I clinical trial. Feasibility was defined as the percent of patients successfully undergoing radical prostatectomy as scheduled without acute surgical complications. Physician reported toxicity was assessed by CTCAEv4 criteria and patient reported toxicity by EPIC-26 and I-PSS questionnaires. Neoadjuvant androgen deprivation therapy was allowed. Patients who were pN1 additionally were recommended androgen deprivation concurrent with IMRT directed to the pelvic nodes subsequent to surgery. Immune infiltrates in prostates after SBRT were compared to T stage and Gleason Score matched controls without prior RT using multicolor flow cytometry.

Results. 12 patients enrolled and 11 successfully completed SBRT and radical prostatectomy without any acute surgical complications. One patient had advanced disease on PSMA after enrollment but before treatment and dropped out. Median follow-up was >12 months. Three patients had Grade 2 incontinence and two had Grade 3 incontinence and underwent successful placement of artificial sphincters (AUS) with return of continence. At 12 months post-surgery, (N=8), two have a functioning AUS and one has Grade 2 incontinence. There was one resolved Grade 2 GI toxicity in a patient after IMRT delivered to pelvic nodes (pN1). Patient reported outcomes showed declines in domains for urinary incontinence and sexual function, but bowel and urinary irritative/obstructive domains were largely stable. Post SBRT prostates had a notable lymphoid-to-myeloid shift, particularly towards non-classical macrophages, monocytic myeloid derived suppressor cells, and intermediate macrophages.

Conclusions. Radical prostatectomy is uncomplicated by neoadjuvant SBRT at the dose tested. SBRT neoadjuvant to radical prostatectomy is feasible with acceptable acute side effects, although urinary incontinence is higher than that observed for surgery alone. Longer follow-up is necessary to evaluate late toxicity and biochemical control. Some caution is warranted given recent a publication of long-term results of another pre-operative RT trial (Glicksman et al. Int J Radiat Oncol Biol Phys. 2019;104(1):61-66). Three other trials of SBRT neoadjuvant to radical prostatectomy at other institutions are ongoing. The intraprostatic immune environment two weeks after SBRT is myeloid shifted and likely immunosuppressive, although functional assessments were not done. Targeting suppressive myeloid cells may be necessary in combination with SBRT to induce tumor immunity in prostate cancer.

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