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Letter to the Editor

In Regard to Shee et al

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To the Editor:

Based on Enzalutamide having a higher affinity to the androgen receptor than bicalutamide, there are a lot of ongoing studies that combine enzalutamide to treat patients who are undergoing radiation therapy (RT) for prostate cancer. We were intrigued by the article by Shee et al,[1] which demonstrated the safety and efficacy of Enzalutamide in combination with standard androgen deprivation therapy and RT. However, some questions were raised after reading the manuscript.

In the phase II STREAM trial,[2] high-risk patients with prostate specific antigen (PSA) recurrent prostate cancer were given Enzalutamide, androgen deprivation therapy, and underwent salvage RT. Although patients excluded that have pelvic radiation in the STREAM trial comparing Shee et al's study, prostatectomy history may make up the difference far better for evaluating the adverse effects. Using these 3 therapies was reported as safe and improved prostate cancer remission rates at 2 and 3 years. Additionally, in the multicenter, randomized, double-blind phase 3 trial PROSPER,[3] Enzalutamide showed a clinical benefit by delaying pain progression, worsening symptoms, and decreased functional status compared with placebo high-risk, nonmetastatic, castration-resistant prostate cancer. PROSPER study was conducted with 1,401 patients, and all patients were also required to maintain androgen deprivation therapy during the study. Although Shee et al added Enzalutamide to the treatment upfront as a difference, we are hesitating that the current study would contribute more to the literature with such a smaller number of patients needed to provide the power of the trial.

Shee et al demonstrated that the combined nonsteroidal Androgen receptor (AR) antagonist enzalutamide and leuprolide in patients undergoing definitive radiation therapy was well tolerated and effective. Kaplan et al published a comprehensive analysis of adverse events of a phase II trial of Enzalutamide with radiation for intermediate-risk prostate cancer which gynecomastia and hypertension were the most reported side effects.[4] In addition to the adverse events pointed out in Shee et al's analysis, gynecomastia and hypertension evaluation would give additional information regarding the quality of life for these patients.

We have another question regarding the application of fiducial marker: Is it necessary when considering that daily cone beam computed tomography (CBCT) is performed for the external radiation and brachytherapy is used for the prostate boost? With the widespread use of CBCT, prostate visualization without the use of fiducial markers is now possible. In a retrospective analysis of 252 scans from 16 prostate cancer patients, Yıldırım et al[5] reported that mean displacement was similar in the x, y, and z directions, using CBCT alone and CBCT with fiducial matching. In another analysis, the imaging results of 36 prostate cancer patients with daily localization using implanted fiducials supported this finding and demonstrated similar shifts.[6]

Furthermore, the sample size was determined initially based on power calculations for the primary objectives of complete Prostate specific antigen (PSA) response and toxicity, for which an enrollment goal of 53 patients was

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required. Unfortunately, the study had included only 16 patients, and 5 of them had already left the trial initially. Moreover, 4 patients terminated using enzalutamide earlier than planned. As a result, only 9 patients were evaluated for further analysis. A similar phase II study aimed to assess the feasibility and safety of the combination of enzalutamide and leuprolide in patients undergoing definitive radiation therapy for high-risk prostate cancer or pelvic involvement (NCT02508636).[7] The mentioned trial also included 11 patients and was terminated owing to low accrual. In this context, acquiring the predefined quantity of the patients for a trial has a very critical role in assessing the safety and efficiency of treatment. Also, more information from these studies is valuable, considering the difficulty in recruiting such a subgroup of patients.

We believe that the study will become more understandable by outlining our concerns and additional randomized trials with more patients and a more extended follow-up period will shed light to the efficacy and toxicity profiles in high-risk prostate cancer.

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