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Original article

Stereotactic ablative radiotherapy in the treatment of low and intermediate risk prostate cancer: Is there an optimal dose?

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ABSTRACT

Purpose: To investigate if stereotactic ablative radiotherapy (SABR) dose is associated with PSA at 3 years (PSA_{3y}) in the treatment of localized prostate cancer and to explore predictors of late genitourinary (GU) toxicity.

Materials and methods: Three prospective trials of SABR were undertaken at our institution: 1) 35 Gy/5 fractions/29 days; 2) 40 Gy/5 fractions/29 days; 3) 40 Gy/5 fractions/11 or 29 days. PSA_{3y} was analyzed as a continuous variable. Toxicity was defined as the worst new toxicity and assessed using the radiation therapy oncology group (RTOG) late morbidity scheme. Univariate and multivariable regression analyses were conducted to assess the association between dose and PSA_{3y}, and to explore predictors of late grade 2+ GU toxicity.

Results: Median PSA3y was 0.64 (intraquartile range (IQR): 0.41–1.12) and 0.27 (IQR: 0.12–0.55) ng/mL for patients treated with 35 and 40 Gy respectively. A dose of 40 Gy was an independent predictor of lower PSA_{3y} on multivariable analysis ($p < 0.001$). Dose of 40 Gy (odds ratio (OR): 16.69, 95%CI: 5.78, 48.20, $p < 0.001$) and higher International Prostate Symptom Score (OR: 1.01, 95%CI: 1.04, 1.16, $p = 0.001$) predicted for late grade 2+ GU toxicity on multivariable logistic regression.

Conclusions: This analysis suggests that higher SABR dose is associated with lower PSA_{3y}. Strategies to allow safe SABR dose escalation should be further investigated.

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There is now mounting evidence of improved biochemical disease free survival (bDFS) with higher biological doses of radiation across all risk groups of prostate cancer patients [1,2]. Stereotactic ablative radiotherapy (SABR) is a new high-precision radiation technique that allows for biological dose escalation. Favorable outcomes with bDFS above 90% for low- and intermediate-risk prostate cancer patients are reported with short- and medium-term follow-up [3–5]. The American Society of Therapeutic Radiology and Oncology (ASTRO) has recently recognized SABR as "an appropriate alternative" for men with favorable-risk prostate cancer [6]. However, SABR doses ranging from 35 to 50 Gy in 5 fractions have been used, and the follow-up is still too short to detect a difference in bDFS [4,7,8].

To date, there are no published randomized data comparing different SABR schemes and the optimal dose is still unknown. While higher dose seems to be associated with long-term toxicity [8,9], several reports have linked the rate and magnitude of prostate-specific antigen (PSA) decline following definitive radiation treatment of prostate cancer patients with clinical outcomes [10–11]. PSA at 3 years (PSA_{3y}) was previously shown to be an early predictor of biochemical failure after radical radiotherapy with high dose-rate brachytherapy (HDR-BT) combined with external beam radiotherapy (EBRT) [12].

This study aims to compare two dose levels of SABR (40 Gy vs. 35 Gy). The primary hypothesis is that SABR total dose is associated with PSA_{3y} in the treatment of low and intermediate-risk prostate cancer. The secondary hypothesis is that at least one baseline patient/tumor factor predicts for grade 2+ genitourinary (GU) toxicity following prostate SABR. Late GI toxicity incidence, prevalence and predictors post-SABR was published previously [13].

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Methods and materials

Population and treatment overview

From October 2006 to January 2014, 265 patients with low- and intermediate-risk prostate cancer (as defined by the American Joint Committee on Cancer (AJCC)) [14] were treated with SABR, on 3 sequential prospective phase II trials conducted at our institution and approved by our local Research Ethics Board: 1) 35 Gy/5 fractions delivered over 29 days; 2) 40 Gy/5 fractions delivered over 29 days; 3) 40 Gy/5 fractions delivered over 11 or 29 days. These doses were prescribed to the clinical target volume (CTV), in all trials, the prostate alone. The planning target volume (PTV) received 95% of the CTV dose in each protocol (ie., 33.25 Gy or 38 Gy, respectively)

The patient selection, study designs and details of treatment planning and delivery have been documented previously [3,8,15]. In short, the first trial accrued low-risk prostate cancer patients ($\leq$T2a, Gleason 6 and PSA $\leq$10 ng/mL) whereas the 2 subsequent trials included low-and intermediate-risk prostate cancer patients ($\leq$T2b, Gleason $\leq$7 or PSA $\leq$20 ng/mL). Neoadjuvant androgen deprivation therapy (NADT) was allowed for cytoreduction (up to 6 months), however baseline PSA had to be obtained prior to NADT in all trials.

Similar simulation protocols were followed in all trials. Treatment was delivered with 6MV linear accelerators (Siemens Primus, Concord, CA; Elekta Synergy, Stockholm, Sweden) in all studies, using daily image guidance with gold seed fiducials. A 4 mm CTV to PTV margin was used in the first trial. This margin was then increased to 5 mm on the subsequent trials based on the intrafraction motion from the 1st trial [16].

Outcomes and follow-up

Time zero (T_0) was defined as the date of first treatment. All patients had a pre-treatment PSA measurement. The PSA levels were prospectively obtained after treatment every 3 months for the first year, every 6 months up to 5 years, and annually thereafter. The PSA_{3y} was the PSA value documented closest (±6 months) to the 3-year time point. Late GU and gastrointestinal (GI) toxicity ($\geq$6 months) was defined as the worst new toxicity reported for each patient, and assessed using the Radiation Therapy Oncology Group (RTOG) late radiation morbidity scheme at 6 months and every 6 months until 5 years. Predictors of GI toxicity following SABR were previously reported [13]. Health related quality of life (HRQoL) was assessed prospectively using the expanded prostate index composite score (EPIC) in both trials and HRQoL analysis will be reported separately.

Independent factors

Prior to treatment commencement, patient's baseline characteristics were recorded: age in years, Gleason score, tumor stage (T), PSA at time of diagnosis (ng/mL), the use of NADT, prostate volume at diagnosis (cc) and urinary symptoms using the International Prostate Symptom Score (IPSS).

Statistical analysis

Follow-up was calculated between last follow-up date and T_0. Patients who had a follow-up <6 months were excluded from all the analyses. Descriptive analyses were summarized as means with standard deviations (SD) and medians with interquartile ranges (IQR) for normally and non-normally distributed continuous characteristics respectively, frequencies and proportions for categorical characteristics. Baseline characteristics across treatment groups were compared using two-sample *t*-test and Fisher's exact test for categorical characteristics as appropriate.

PSA_{3y} (primary endpoint) was analyzed as a continuous variable. Univariate linear regression analyses were conducted to assess the association of PSA_{3y} with dose and potential confounders: age, Gleason score (6 vs. 7), PSA at baseline, NADT, treatment duration (11 vs. 29 days) and T stage (T1 vs. T2). A multivariable linear regression analysis was then conducted to test whether the dose is an independent predictor of PSA_{3y} while controlling for the clinically relevant confounders determined "a priori". Multicollinearity was assessed using the variance inflation factor (VIF), with values >4 indicating collinearity. In the presence of collinearity, the factor yielding the highest coefficient of determination (R^2) was kept in the model. The adjusted beta coefficients with their 95% CI, the tests statistics and the associated *p*-values were assessed to evaluate the significant association of each predictor with the outcome. The assumptions of linear regression were verified for each linear regression model. A natural log transformation was applied for PSA_{3y} and PSA at baseline because of the skewed distribution of the residuals.

Late GU toxicity grade 2+ (secondary endpoint) was analyzed as a binary outcome (<2 vs. 2+). Univariate logistic regression analyses were conducted to assess bivariate association between late GU toxicity and clinically relevant covariates: dose (40 Gy vs. 35 Gy), age, IPSS, prostate volume, treatment duration and the use of NADT, as those parameters could potentially be associated with GU toxicity. A multivariable logistic regression analysis was then conducted to assess the independent association of each variable with the outcome. A "purposeful selection" of potential confounders was performed [17]. Factors with *p*-values <0.25 obtained from univariate analyses were candidate for the multivariable analysis. The assumptions of logistic regression were checked. The model fit was assessed using the Hosmer–Lemeshow test for fit and c-statistics. In addition, a 50:50 split-sample approach was used to validate the variable selection. The c-statistics between the training and validation sets were compared. SAS University Edition was used for all the analysis. A two-tailed *p*-value of $\leq$0.05 was considered statistically significant for our analysis.

Results

Descriptive analysis

Two hundred and fifty-nine patients had adequate follow-up ($\geq$6 months); 82 in the 35 Gy group and 177 in the 40 Gy group. The median follow-up was 38 months (IQR: 30–53). Patient characteristics in the entire cohort and by dose-level group are outlined in Table 1. Patients treated with 40 Gy had shorter median follow-up (33 vs. 54 months, $p < 0.001$), were older (70 vs. 66 years, $p < 0.001$) with higher PSA at baseline (7.52 vs. 5.31 ng/mL, $p < 0.001$) when compared to those treated with 35 Gy. In addition 30% of patients treated with 40 Gy had T2 disease as opposed to 6% of those treated with 35 Gy ($p < 0.001$) and there was a predominance of Gleason 7 among patients treated with 40 Gy.

PSA at 3 years

Overall a total of 199 patients had available PSA3y. Median PSA_{3y} was 0.36 ng/mL (IQR: 0.18–0.81); 0.64 ng/mL (IQR: 0.41–1.12); and 0.27 ng/mL (IQR: 0.12–0.55), respectively for the overall cohort and those patients treated with 35 Gy and 40 Gy. On univariate analyses, a dose of 40 Gy, older age, the use of NADT, a T2 stage at diagnosis, treatment duration of 11 days and a Gleason score of 7, were associated with lower PSA_{3y} (Appendix A).

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