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Prostate cancer brachytherapy

High dose-rate brachytherapy boost for intermediate risk prostate cancer: Long-term outcomes of two different treatment schedules and early biochemical predictors of success

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ABSTRACT

Background and purpose: To report long-term cancer control rates following high dose-rate (HDR) brachytherapy boost for intermediate risk prostate cancer and explore early biochemical predictors of success.

Material and methods: Results of two sequential phase II trials are updated and compared: (1) Single 15 Gy HDR-boost followed by external beam radiotherapy (EBRT) 37.5 Gy/15fractions, (2) Two HDR fractions of 10 Gy followed by EBRT 45 Gy/25fractions. Patients were followed prospectively for clinical and biochemical outcomes. Nadir PSA (nPSA) and PSA at 3-years were analyzed as continuous variables, and ROC analysis was used to identify the optimal cutoff values. Kaplan–Meier bDFS curves were generated and the log-rank test used to compare different groups

Results: 183 patients were accrued; 123 to the single fraction trial and 60 to the standard fractionation trial, with a median follow-up of 74 months and 99 months, respectively. The 5-year biochemical relapse-free survival was 97.4% and 92.7%, respectively ($p = 0.995$). Median nPSA was 0.08 ng/ml. Failure to achieve a nPSA <0.4 ng/ml was associated with a significantly higher rate of biochemical relapse (5-year bDFS: 100% vs. 72%; $p < 0.0001$).

Conclusion: HDR boost with single fraction 15 Gy provides durable long-term biochemical disease-free survival. PSA nadir <0.4 ng/ml is associated with very low risk of biochemical failure.

High dose-rate brachytherapy (HDR-BT) is widely accepted as a method of local dose escalation in combination with external beam radiotherapy (EBRT) to treat patients with intermediate and high-risk disease [1,2]. Data suggest a higher control rate with a combined approach as compared to EBRT alone [3–6]. Favorable outcomes with disease-free survival above 80% for intermediate and high-risk prostate cancer patients are reported in the literature [7,8]. However the optimal dose and fractionation of HDR in this setting is still unknown. A wide range of dose and fractionation has been used. No particular schedule could be recommended by the ABS Consensus Guidelines because of the heterogeneity of prescription doses described in the literature [2]. To date, there is no randomized trial comparing different fractionation schemes.

We previously reported results of a novel protocol using an HDR boost dose of 15 Gy as a single fraction combined with hypofractionated EBRT to a dose of 37.5 Gy in 15 fractions [9,10]. With medium-term follow-up, cancer control rates were no different from our previous standard protocol using two HDR fractions and conventionally fractionated EBRT. Since then, single 15 Gy as a boost is gaining increasing acceptance and is used as a standard option in ongoing clinical trials of the Radiation Therapy Oncology Group [11]. Given the widespread adoption of this fractionation scheme, it is important to update longer-term disease control rates.

Following EBRT, biochemical failure is defined as a rise in serum prostate specific antigen (PSA) level of 2 ng/mL or more above the nadir [12]. This can take some time to manifest, and there is value in identifying earlier predictors of long-term cancer control based on early PSA kinetics, PSA at particular time-points following treatment, or nadir PSA levels. To date, several reports have attempted to link the rate and magnitude of PSA decline following definitive radiation treatment with clinical outcomes in cohorts of prostate adenocarcinoma patients [13–19], however to our knowledge, no analysis of early biochemical predictors of clinical outcomes after a combination of HDR boost and EBRT has been published.

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The aim of this study is to report long-term cancer control rates following our single fraction protocol and explore early biochemical predictors of success in this cohort of patients treated with a definitive HDR boost. We therefore address the clinical usefulness of two closely linked parameters relating to PSA decline; nadir PSA (nPSA) and PSA at 3 years time point (PSA_{3y}).

Methods and materials

Patient selection and treatment overview

Patients participated in two prospective phase II clinical trials of HDR boost conducted sequentially and approved by our local Research Ethics board; the first consisted of two separate HDR fractions of 10 Gy delivered 1 week apart and followed by EBRT to a total dose of 45 Gy in 25 fractions delivered over 5 weeks (Standard Fractionation) and the second of a single HDR fraction of 15 Gy followed by 37.5 Gy EBRT in 15 fractions delivered over 3 weeks (HDR Single). The patient selection, study design and details of treatment planning and delivery have been documented previously [9,10].

In short, eligibility and exclusion criteria were identical for both clinical trials. Eligible patients had intermediate risk prostate cancer, as defined by the National Comprehensive Cancer Network (NCCN), with no evidence of nodal or distant metastases. Patients were excluded if they had been on androgen deprivation therapy, had a previous transurethral resection of the prostate, or if the prostate volume was >60 cm^3 on transrectal ultrasound.

For both clinical trials, HDR brachytherapy, as previously described, was administered prior to EBRT [10]. Transperineal catheters were inserted under transrectal ultrasound (TRUS) guidance and fixed to a template, which was sutured to the perineum. After a first CT scan, any catheter displacement was corrected and a final CT scan obtained. Images were transferred to the Nucletron PLATO planning system version 14.3.2 (Nucletron B.V., Veenendall, The Netherlands). The clinical target volume (CTV) was the prostate. No further margin was added for Planning Target Volume (PTV); rectum, bladder and urethra were contoured. Dwell time optimization was performed using Inverse Planning with Simulated Annealing (IPSA) [20]. Dose was prescribed as a minimal peripheral dose to the CTV. The goal was to deliver the prescription dose to >95% of the prostate volume (V100). An attempt was made to keep the volumes treated to 150% (V150) and 200% (V200) of the prescription dose below 40% and 14%, respectively, while keeping the maximal urethral dose at <118% and both the maximal rectal and bladder doses at <80% of the prescription dose. For both protocols, EBRT began 2 weeks later, and was delivered using a 4-field conformal technique, to the prostate and proximal 2 cm of seminal vesicles. The PTV was a uniform 1 cm beyond the CTV and received at least 95% of the prescription dose. Rectum and bladder were contoured and dose volume histograms obtained but with no predetermined dose constraints. No patient received androgen deprivation therapy.

Follow-up

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 for the following 4 years, and annually thereafter. Prostate biopsy was performed at 24 months. Toxicity was evaluated using the Common Terminology Criteria for Adverse Events v3.0, health related quality of life (QOL) measured using the Expanded Prostate Index Composite (EPIC) [21] at baseline and annually thereafter, and urinary symptoms documented using the International Prostate Symptom Score (IPSS) at baseline and annually thereafter. Biochemical, toxicity, QOL and pathologic outcomes of both trials were previously reported and compared with a medium-term follow-up [10]. An update of biochemical outcomes for both trials will be presented in this report. An analysis of long term toxicity and QOL will be reported separately.

Statistical analysis

Time zero (T_0) was defined as the date of first treatment. Follow-up was calculated between last PSA date and T_0. Disease-free survival was measured from T_0 to the date of clinical or biochemical recurrence. The latter was defined using the RTOG-ASTRO Phoenix definition "nadir + 2" [12]. Nadir PSA (nPSA) was defined as the lowest PSA value following treatment but prior to any salvage intervention. PSA_{3y} was the PSA value documented closest (±6 months) to the 3-year time point. Subjects who had no PSA value at 3-year ± 6 months were excluded from the PSA_{3y} analyses. nPSA and PSA_{3y} were primarily analyzed as continuous variables. Receiver operator curve (ROC) analysis was also used to determine the accuracy of nPSA and PSA_{3y} in predicting biochemical failure for all patients. The area under the curve (AUC), sensitivity, specificity, overall accuracy, positive predictive value (PPV), and negative predictive value (NPV) were estimated for different nPSA and PSA_{3y} cutoff values, respectively. Arbitrary Cutoff values of 0.1, 0.2, 0.3, 0.4 and 0.5 were considered for nPSA and 0.3, 0.4, 0.5, 0.6 and 0.7 for PSA_{3y}. Kaplan–Meier (KM) bDFS curves were generated and the log-rank test used to compare the different groups. The association of different clinical prognostic factors with bDFS was assessed by univariate Cox-proportional hazard model. Hazard ratio (HR) and its 95% confidence interval (CI) were also calculated. To search for significant predictive factors of nPSA and PSA_{3y} continuous outcomes, univariate and multivariate linear regression analyses were conducted on the covariates of age, Gleason score (6 vs.7), PSA at baseline, and HDR treatment (single vs. two fractions). R^2 for each covariate in the univariate analysis and the cumulative R^2 in the multivariate model were calculated, respectively. Because of the skewed distribution of nPSA, PSA_{3y}, and PSA at baseline, the natural log transformation was applied. All analyses were conducted by Statistical Analysis Software (SAS version 9.3). P-value <0.05 was considered statistically significant.

Results

Overall 183 patients were accrued; 123 to the single fraction trial and 60 patients to the standard fractionation trial. As previously described, median age was 67 years; 59% had stage T1c, 41% Stage T2; 89% Gleason 7 and 11% Gleason 6; and median baseline PSA was 6.8 ng/mL (1.2–17.9 ng/mL). Median follow-up for the entire group was 74 months (interquartile range [IQR], 61.9–88.3); 73 months (IQR, 62.9–84.6) and 99 months (IQR, 58.3–110.2) respectively for the single and standard fractionation cohorts. Median nadir PSA was 0.08 ng/mL (range 0.01–3.63), 0.08 for single fraction and 0.05 for standard fraction. Median PSA at 3 years was 0.22 ng/mL (range <0.02–10.86), 0.24 for single fraction and 0.18 for standard fraction.

Disease control

At the time of the current analysis, 12 (6.6%) patients had a biochemical failure; 4 from the standard fractionation group and 8 from the single fractionation group. The median time to biochemical failure was 3.7 years (range 1.0–6.9 years). In the single fraction trial, 5- and 7-year bDFS were 97.4% (CI, 94.5–100%) and 89.1% (CI, 81.6–97.3%) as compared to 92.7% (CI, 86.0–99.9%) and 92.7% (CI, 86.0–99.9%) in the standard fractionation trial. Kaplan–Meier bDFS curves for both clinical trials are demonstrated in Fig. 1. No