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Image-guided hypofractionated proton beam therapy for low-risk prostate cancer: Analysis of quality of life and toxicity, PCG GU 002

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ABSTRACT

Aim: This interim analysis evaluated changes in quality of life (QOL), American Urological Association Symptom Index (AUA), or adverse events (AEs) among prostate cancer patients treated with hypofractionation.

Background: Results for hypofractionated prostate cancer with photon therapy are encouraging. No prior trial addresses the role of proton therapy in this clinical setting.

Materials and methods: Forty-nine patients with low-risk prostate cancer received 38-Gy relative biologic effectiveness in 5 treatments. They received proton therapy at 2 fields a day, magnetic resonance imaging registration, rectal balloon, and fiducial markers for guidance pre-beam. We evaluated AEs, Expanded Prostate Index Composite (EPIC) domains, and AUA at pretreatment and at 3, 6, 12, 18, and 24 months. An AUA change >5 points and QOL change of half a standard deviation (SD) defined clinical significance.

Results: Median follow-up was 18 months; 17 patients reached follow-up of ≥24 months. For urinary function, statistically and clinically significant change was not seen (maximum change, 3). EPIC urinary QOL scores did not show statistically and clinically significant change at any end point (maximum, 0.45 SD). EPIC bowel QOL scores showed small but statistically and clinically significant change at 6, 12, 18, and 24 months (SD range, 0.52–0.62). EPIC sexual scores showed small but statistically and clinically significant change at 24 months (SD, 0.52). No AE grade ≥3 was seen.

Conclusions: Patients treated with hypofractionated proton therapy tolerated treatment well, with excellent QOL scores, persistently low AUA, and no AE grade ≥3.

Abbreviations: AE, adverse event; AUA, American Urological Association Symptom Index; EPIC, Expanded Prostate Index Composite; OTV, optimization target volume; RBE, relative biologic effectiveness; RT, radiation therapy; SD, standard deviation.

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1. Background

Proton therapy is a radiation modality that uses particles to deliver large doses to the tumor with high accuracy and low doses to surrounding normal tissue. However, with standard doses for image-guided proton radiation therapy (RT) or intensity-modulated RT, daily treatments for 8–9 weeks are typically used. Patients who are ideal candidates for external RT or proton therapy may elect alternative modalities because of the extended treatment time. Therefore, in the present protocol, we proposed to combine a hypofractionated approach that benefits from the low α/β ratio of prostate cancer and the conformality achieved with proton therapy to deliver an abbreviated course of therapy for low-risk prostate cancer.[1–6]

All patients required image guidance with fiducial placement and magnetic resonance imaging registration. The rationale of this image guidance approach for proton therapy has been reviewed previously.[7,8]

2. Aim

To evaluate changes in quality of life (QOL), American Urological Association Symptom Index (AUA), or adverse events (AEs) among prostate cancer patients treated with hypofractionation over time.

3. Materials and methods

3.1. *Design overview*

This report corresponds to first analysis of the hypofractionated arm. The main objective was to evaluate initial rectal and bladder toxicity and quality-of-life metrics at different time intervals. Statistical calculations for toxicity were done using a double-sided $\alpha < .05$ for significance.

3.2. *Patients*

We enrolled 85 patients between 2011 and 2014. Three patients withdrew consent, and the 82 other patients were assessable. Forty-nine were randomly assigned to receive 38-Gy relative biologic effectiveness (RBE). No major violations were seen for any patient. Patients were stratified by pre-enrollment initial prostate-specific antigen level (<4 ng/mL vs ≥4 to <10 ng/mL), positive cores (1–4 vs ≥5), and stage (T1 vs T2). All patients were required to have a Gleason score of 6. A prepopulated, block randomization sheet was used for assignment by the protocol research office.

3.3. *Radiation therapy*

Briefly, planning for proton therapy involved the fusion of 1.5 T magnetic resonance images to computed tomography images. Patients were positioned supine. The clinical target volume contained the prostate only; the planning target volumes were 2 mm posteriorly and 3 mm elsewhere.[9] The constructed optimization target volume (OTV) included an additional 5 mm in the beam direction distally and proximally. Proton-specific expansions accommodated changes in dose deposition and improved treatment delivery robustness. The proton beams were oriented laterally left and right, and expansions were in the lateral direction only and appropriately. The plan was optimized, normalized, and evaluated on the basis of the OTV. Two beams were used every day, and image guidance was done before each beam. Rectal balloon was used every day before treatment.

We believed that it was a safe assumption to define the α/β ratio for normal tissue first on the basis of available literature. On the basis of published data, the dose to achieve rectal isotoxicity between the 2 arms[10–12] was defined. In this manner, 38-Gy RBE in 5 treatments was equivalent to 79.2-Gy RBE in 44 treatments, for a rectal α/β ratio of 3.5 Gy (Tables 1 and 2). The dose to the target was 38-Gy RBE. If prostate α/β ratio is <3.5-Gy RBE, the resulting biologic equivalent dose will be >79.2-Gy RBE in 44 treatments.

3.4. *Toxicity assessment*

Protocol toxicity was measured with the Common Terminology Criteria for Adverse Events version 4.0.

3.5. *Statistical analysis*

The primary end point was the cumulative incidence of an adverse event (AE) grade 3 or higher. Adverse bowel and urinary events were analyzed through incidence and prevalence. Prevalence was calculated at 3, 6, 12, 18, and 24 months after RT. For incidence, we considered AEs of grade 2 or higher occurring for each arm for 3 years. All analyses were carried out in the intention-to-treat population through Fisher exact test and 2-sided .05 significance levels. Patients completed the Expanded Prostate Index Composite (EPIC)[13] and American Urological Association Symptom Index (AUA)[14] before treatment and during routine follow-up visits at 3, 6, 12,

Table 1 – Dose constraints in 38-Gy relative biologic effectiveness.

Structure	Goal	Minor deviation	Major deviation
Rectum	V24 <35%	V24 <40%	V24 ≥40%
	V33.6 <10%	V33.6 <20%	V33.6 ≥20%
Bladder	V39 <8 cc	V39 <12 cc	V39 ≥12 cc
Femoral heads	V23 <1 cc	V23 <2 cc	V23 ≥2 cc
PTV	Min dose	99.5% >36.1 Gy	
OTV	PTV coverage	95% to 38 Gy	

Abbreviations: min, minimum; OTV, optimization target volume; PTV, planning tumor volume.