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Original article

Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): A phase 2 randomized trial

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ABSTRACT

Background and purpose: Prostate stereotactic body radiotherapy (SBRT) regimens differ in time, dose, and fractionation. We completed a multicentre, randomized phase II study to investigate the impact of overall treatment time on quality of life (QOL).

Material and methods: Men with low and intermediate-risk prostate cancer were randomly assigned to 40 Gy in 5 fractions delivered once per week (QW) vs. every other day (EOD). QOL was assessed using the Expanded Prostate Cancer Index Composite. The primary endpoint was the proportion with a minimum clinically important change (MCIC) in bowel QOL during the acute (≤12 week) period, and analysis was by intention-to-treat. ClinicalTrials.gov NCT01423474.

Results: 152 men from 3 centres were randomized with median follow-up of 47 months. Patients treated QW had superior acute bowel QOL with 47/69 (68%) reporting a MCIC compared to 63/70 (90%) treated EOD ($p = 0.002$). Fewer patients treated QW reported moderate–severe problems with bowel QOL during the acute period compared with EOD (14/70 [20%] vs. 40/70 [57%], $p < 0.001$). Acute urinary QOL was also better in the QW arm, with 52/67 (78%) vs 65/69 (94%) experiencing a MCIC ($p = 0.006$). There were no significant differences in late urinary or bowel QOL at 2 years or last follow-up.

Conclusion: Prostate SBRT delivered QW improved acute bowel and urinary QOL compared to EOD. Patients should be counselled regarding the potential for reduced short-term toxicity and improved QOL with QW prostate SBRT.

Introduction

Studies support an increased fraction sensitivity of prostate cancer, with an estimated alpha–beta ratio in the range of 0.9–2.2 [1]. This motivated a number of randomized trials which have shown that moderately hypofractionated versus conventionally fractionated radiotherapy is non-inferior for biochemical disease-free survival and results in similar toxicity [2–4].

More recently, promising results from trials using larger doses per fraction (7–10 Gy delivered in 5 fractions) have been reported with the use of stereotactic body radiotherapy (SBRT) [5–9]. However, the overall treatment time (OTT) has been variable with fractions delivered in consecutive days, every other day (EOD), twice per week, and once per week (QW) [5–9]. Nonetheless, these single arm studies have shown good biochemical disease-free survival rates with moderate rates of toxicity.

The impact of OTT has been shown to be important in prostate cancer radiotherapy from both a disease control perspective as well as toxicity. In a multi-institutional study involving 4839 patients treated with conventionally fractionated radiotherapy, Thames et al. found a statistically significant improvement in biochemical disease free survival when patients receiving 70–72 Gy completed treatment in less than 52 days [10]. However, the impact of even shorter treatment times through hypofractionated regimens has not been studied.

With respect to toxicity, small differences in treatment times can have a significant impact. In an unplanned analysis by King et al. of 41 patients who received 36.25 Gy in 5 fractions, there was less rectal toxicity in patients treated EOD ($n = 20$) compared to consecutive daily treatment ($n = 21$) [11].

Thus, as studies increase the dose per fraction, the optimal OTT is critical to avoid excess morbidity. No studies have specifically

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addressed this issue. We report on the Prostate Accurately Targeted Radiotherapy Investigation of Overall Treatment Time (PATRIOT), a randomized, phase 2 study to investigate the impact of OTT on toxicity and QOL using prostate SBRT.

Materials and methods

PATRIOT is a multicentre, randomized, phase 2 trial comparing 40 Gy in 5 fractions delivered QW versus EOD. Men aged >18 years with T1-T2b (TNM 2002), Gleason score ≤7 centrally reviewed prostate adenocarcinoma, and PSA ≤20 ng/mL were eligible. Exclusion criteria included androgen deprivation therapy for more than 6 months, prior pelvic radiotherapy, prostate size >90 cc, anticoagulation or bleeding diathesis, immunosuppressive medications, or inflammatory bowel disease. Initially patients with an International Prostate Symptom Score (IPSS) >19 were excluded but this criterion was removed after preliminary analysis showed no significant association with acute toxicity.

The study was approved by the institutional research ethics board of each centre. All patients provided written informed consent. This study is registered at ClinicalTrials.gov (NCT01423474) and was overseen by an independent Data Safety & Monitoring Committee.

Patients were randomly allocated (1:1) to receive 40 Gy in 5 fractions SBRT delivered QW or EOD, via a web-based application housed at the Sunnybrook Health Sciences Centre. Randomization was stratified by treatment centre. Patients and physicians were not masked to treatment allocation.

Treatment

Patients received 40 Gy delivered in 5 fractions. Individuals randomized to treatment QW had a minimum 5 days and maximum 9 days between fractions with an OTT between 27 and 30 days. Patients randomized to treatment EOD had a minimum of 1.5 days and maximum of 4 days between fractions with an OTT between 9 and 12 days.

Three gold-fiducial markers were implanted transperineally into the prostate under trans-rectal ultrasound guidance. CT simulation was performed a minimum of one week afterwards. Patients were simulated and treated supine with an empty rectum and comfortably full bladder. Immobilization such as custom vacuum lock bags or thermoplastic casts were used as per institutional policy. CT images were acquired at a slice thickness of ≤3 mm from the top of the iliac crests to the perineum.

The clinical target volume (CTV) consisted of the prostate gland alone. The seminal vesicles were not included. The planning target volume (PTV) included the CTV plus an additional 0.5 cm margin in all directions. Organs at risk (OAR) were contoured as solid organs and included the bladder, rectum, and femoral heads. The rectum was contoured from the rectosigmoid flexure superiorly to the most inferior plane of the ischial tuberosities. Planning objectives included the volume of CTV receiving 40 Gy (CTV V40 Gy) >99%, PTV V38 Gy >99%, PTV V42 Gy <1 cc, and PTV maximum dose (Dmax) ≤42.8 Gy. Normal tissue constraints were rectum V28 Gy ≤20%, V32 Gy ≤15%, bladder V28 Gy ≤20%, V32 Gy ≤15%, and femoral head V28 ≤5%.

Treatment was delivered with image-guided, intensity-modulated radiotherapy. Daily orthogonal images (kV or MV) or cone beam CT was used to identify the implanted fiducials to calculate patient shifts to ensure proper positioning. Imaging was performed before and after each fraction. SBRT was delivered via linear accelerator with megavoltage photons of energies 6–15 MV. Optimal radiotherapy technique including number of beams and beam angles was at the discretion of each treatment centre, but was the same for both treatment groups.

Patient assessments

QOL was assessed using the Expanded Prostate Cancer Index Composite (EPIC) [12] and Medical Outcomes Study Short-Form 12 (SF-12) v2. EPIC is a validated 50-item patient-reported instrument that measures prostate cancer-specific QOL. It consists of four summary domains (urinary, bowel, sexual, and hormonal) with function and bother subscales for each domain. Scores were transformed to a 0–100 scale, with higher scores indicating better QOL.

Day zero was defined as the start of radiotherapy. QOL was assessed at baseline, weeks 2, 4, 6, 12, then at months 6, 12, and annually thereafter. GU and GI toxicities were measured using the Radiation Therapy Oncology Group (RTOG) acute (≤3 months) and late (>3 months) radiation morbidity schema with Fox Chase modification [13,14]. The RTOG toxicity schema was chosen as it is commonly used and would allow comparison to other prostate radiotherapy trials of moderate hypofractionation and SBRT. Toxicities were assessed at baseline, weeks 2, 4, 6, 12, then at months 6, 12, 18, 24 and annually thereafter. Prostate specific antigen (PSA) and testosterone was assessed at baseline, weeks 6, 12, month 6 and every 6 months thereafter. Follow-up for all endpoints continued for 5 years.

Statistical analysis

The primary endpoint was acute bowel QOL, as measured using the EPIC. Additional endpoints included remaining EPIC quality of life domains and the Medical Outcomes Study Short-Form 12 (SF-12) v2, incidence of acute and late RTOG gastrointestinal (GI) and genitourinary (GU) toxicities, and biochemical failure as per Phoenix definition [15].

Analyses were conducted on an intention-to-treat basis. Patient characteristics were summarized as median with interquartile range (IQR) for continuous variables and proportions for categorical variables. EPIC scores were calculated as mean +/- standard deviation (SD) and graphically presented as mean (with 95% confidence intervals [CI]) over time. A minimum clinically important change (MCIC) was defined as a change in QOL from baseline to follow-up which exceeded half of the SD of that value at baseline [16]. The MCIC does not reflect severe changes in QOL but represents clinically detectable differences. The MCIC threshold scores were 5.53 for urinary and 5.76 for bowel summary scores. Missing data were not imputed. All men with EPIC questionnaires completed at baseline and at least one follow-up time point were included in the analysis.

The "average" EPIC change was calculated by (mean of EPIC scores after month 3 – baseline score) while the "worst" EPIC change was calculated by (lowest of EPIC scores from weeks 2 to 12 – baseline score). These metrics were chosen to identify the average change in late QOL as well as the maximum change in acute QOL, respectively.

Waterfall plots were created using changes in EPIC scores. Fisher's exact test was used to compare the proportion of patients experiencing MCIC and the proportion with moderate/big problems in specific EPIC items. Wilcoxon rank-sum test was used to compare continuous data. A p-value <0.05 was considered statistically significant. All analyses were conducted using Statistical Analysis Software (SAS version 9.4 for Windows).

Based on an in-house study of QW SBRT, we anticipated 17% of patients to experience a MCIC in acute bowel QOL. We assumed that treatment EOD would be unacceptable to patients if there was an absolute increase of 20% with significant changes in bowel

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