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Original Article

Prospective Phase II Trial of Once-weekly Hypofractionated Radiation Therapy for Low-risk Adenocarcinoma of the Prostate: Late Toxicities and Outcomes

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Abstract

Aims: To report the long-term toxicities and sexual quality of life of a once-weekly hypofractionated radiation therapy schedule for low-risk prostate cancer.
Materials and methods: A multi-institutional phase II trial was conducted, using a three-dimensional conformal radiation therapy (3D-CRT) approach for low-risk prostate cancer (T1a-T2a, Gleason $\leq$ 6 and prostate-specific antigen $\leq$ 10 ng/ml). Forty-five Gray (Gy) were delivered in nine fractions of 5 Gy given on a weekly basis. Acute and late genitourinary and gastrointestinal toxicities were graded according to the Radiation Therapy Oncology Group toxicity scale. Sexual function and sexual bother were assessed with the Expanded Prostate Cancer Index Composite (EPIC) questionnaire.
Results: Between March 2006 and August 2008, 80 patients were treated, with a median age of 69 years (interquartile range 64–72). The median follow-up was 83 months (interquartile range 73–85 months). At 7 years, overall survival was 88%. No patients died of prostate cancer. Cumulative grade $\geq$2 genitourinary and gastrointestinal late toxicity was reported for 31.3% and 30% of our patients, respectively. Cumulative grade $\geq$3 genitourinary and gastrointestinal late toxicity was seen in 3.8% and 12.5% of cases, respectively. Late genitourinary grade 2 toxicity was correlated with the occurrence of acute genitourinary grade 2 toxicity ($P = 0.006$). The occurrence of late gastrointestinal toxicity was not correlated with acute gastrointestinal toxicity. Pre-treatment EPIC sexual function was low (37.5%) and the mean EPIC sexual function score at 7 years after treatment was 14%. On the other hand, pre-treatment EPIC sexual bother reached 80.5%, meaning little bother, and remained stable during follow-up.
Conclusions: Once-weekly 3D-CRT leads to excellent biochemical disease-free survival and acceptable toxicities. Pre-treatment EPIC sexual function dropped by 42% at 5 years of follow-up. This functional deficit did not bother patients, possibly due to the already low sexual function at baseline.

Key words: Hypofractionation; prostate cancer; radiation therapy; sexual function

Introduction

Recently, hypofractionated radiation therapy has been gaining popularity as a treatment for prostate cancer. This may be in part due to a growing body of evidence suggesting that prostate cancer might have a very low α/β ratio, potentially as low as 1.5 Gy (0.9–2.2 Gy) [1]. Surrounding organs at risk, such as the rectum or bladder, are deemed to have higher α/β ratios, in the range of 3–7 Gy [2,3]. One implication of a lower α/β ratio for prostate cancer cells compared with normal tissue is that it may be possible to increase the therapeutic ratio by using hypofractionation schedules, theoretically resulting in better tumour control and a lower toxicity rate [4].

Most published studies addressing hypofractionation for prostate cancer used either moderate hypofractionation schedules (2.4–4.0 Gy/fraction for 15–30 fractions) or extreme hypofractionation (6.5–10 Gy/fraction in four to seven fractions) with stereotactic body radiation therapy

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(SBRT) [5]. Our study explores an alternative fractionation with a higher dose per fraction (5 Gy/fraction) without acceleration intent in the setting of an image-guided, three-dimensional conformal radiation therapy (3D-CRT).

Previously, acute and mid-term toxicities were reported at a median follow-up of 33 months [6]. This study provides an update on these results with a median follow-up of close o 7 years, focusing on late toxicities and sexual function outcome.

Materials and Methods

This study was a phase II prospective trial of non-accelerated, hypofractionated, image-guided 3D-CRT. Favourable-risk prostate cancer patients were eligible, according to the American Joint Committee on Cancer (AJCC) [7]. The study was approved by the institutional research ethics boards of both participating institutions.

In total, 81 patients were accrued in both institutions from March 2006 to August 2008.

Assuming that a rate of 15% for ≥grade 2 late rectal toxicity was clinically acceptable and a rate of 8.5% expected, we calculated that a sample size of at least 74 patients was required to detect a significant difference in toxicity. Target accrual was set at 78 to account for a 5% loss of patients at follow-up and expanded to 81 patients for fear of further loss to follow-up with time. One patient withdrew his consent and opted for treatment with low dose rate brachytherapy. Eighty patients were available for the final analysis. Follow-up was carried out until 31 January 2015, when analysis took place.

The methods have previously been described in detail, together with early toxicity results [6]. Briefly, eligible men had histologically confirmed prostate adenocarcinoma with favourable-risk features defined as clinical stage T1-T2a, pre-treatment prostate-specific antigen (PSA) $\leq$ 10 ng/ml and Gleason score $\leq$ 6. Other inclusion criteria included good performance status (Karnofsky $\geq$ 70) and an estimated life expectancy exceeding 10 years.

Neoadjuvant, concurrent or adjuvant hormone therapy was not permitted. Through follow-up, erectile dysfunction treatment with phosphodiesterase type 5 inhibitors (PDE5i) was at the attending physician's discretion.

The planning target volume was obtained by expanding the clinical target volume with a 1.0–1.5 cm margin on all sides, except posteriorly where the margin was 0.5–1 cm. Patients had daily image guidance with either fiducial markers (19% of patients, posterior margin for the first seven treatments 7 mm and for last two treatments 5 mm) or with the B-mode acquisition and targeting (BAT) system (81% of patients, posterior margin first 10 mm and for last two treatments 7 mm).

An isocentric technique of five, six, seven or nine fields was used. Intensity-modulated radiation therapy (IMRT) was not permitted. The regimen consisted of 45 Gy in 5 Gy fractions, given once weekly over 9 weeks (57 days). Using the linear quadratic model without time correction, that corresponds to a biologically equivalent dose (BED) of 83.6 Gy in 2 Gy fractions (EQD2), assuming an α/β ratio of 1.5 for the prostate [8]. The BED for late effects on normal tissue is 72 Gy in 2 Gy fractions, assuming an α/β ratio of 3 [9].

Dose constraints to organs at risk were based on the Radiation Therapy Oncology Group (RTOG) 0126 protocol and estimated using the linear quadratic model, assuming an α/β ratio of 3 for late effects on normal tissue. Because tissue with a low α/β ratio such a low risk prostate cancer is theoretically not influenced by treatment time, we chose a once-a-week treatment schedule to decrease acute side-effects that are a risk factor for late side-effects and to offer an attractive treatment schedule. No dose constraints were applied to the penile bulb. A daily localisation procedure was mandatory using either implanted fiducial gold markers or transabdominal ultrasound (BAT system).

End Points

The primary end points of the study protocol were maximal late rectal toxicity (occurring more than 6 months after treatment), assessed using the RTOG scoring tables [10], and feasibility, defined as the proportion of enrolled patients who completed treatment.

Secondary end points included acute rectal and urinary toxicity, biochemical disease-free survival and overall survival, as well as an assessment of sexual quality of life (QoL) using the sexual domain (11 items) section of the Expanded Prostate Cancer Index Composite (EPIC) questionnaire.

Biochemical failure was defined as per the Phoenix criteria, as the post-radiation therapy nadir plus 2 ng/ml [11].

Patient Follow-up

Acute and late genitourinary and gastrointestinal toxicities were scored by the physician at baseline and weekly during radiation therapy, according to the RTOG criteria [10]. This is a 0–5 scale in which lower scores are equated with fewer symptoms.

Follow-up visits were scheduled at 4 weeks after radiation therapy, every 4 months during the first year, every 6 months during the second and third years and yearly thereafter. Each visit consisted of a medical history, a physical examination including a digital rectal examination and serum PSA measurement.

Patients completed the sexual domain section of the EPIC questionnaire before treatment and during routine follow-up visits [12]. We used a self-translated version of the EPIC questionnaire, as most of our patients were French native speakers. We are not aware of any validated French version of the EPIC questionnaire published to date.

The sexual domain section of the EPIC includes two subscales: sexual function and sexual bother. Sexual function evaluates symptom severity (nine items pertaining to libido, orgasm, erectile function, frequency of sexual intercourse and activity), whereas sexual bother evaluates the degree to which symptoms are problematic (four items asking participants to rate the degree to which they consider sexual side-effects to be a problem).

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