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Treatment outcomes with hypofractionated high-dose radiation therapy for prostate cancer

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ABSTRACT

Aim: To report the treatment results of a retrospective cohort of prostate cancer patients treated with Hypo-RT with a high equivalent biological effective dose (BED).

Background: Hypofractionated radiotherapy (Hypo-RT) has gained popularity and interest in the treatment of prostate cancer. However, there are few experiences with adequate follow-up reporting treatment results using high equivalent dose with Hypo-RT.

Materials and methods: We assigned 149 men with low-, intermediate- and high-risk prostate cancer to receive Hypo-RT with a total dose of 69 Gy/23 fractions. Late gastrointestinal (GI) and genitourinary (GU) toxicity were prospectively evaluated according to modified RTOG criteria. Biochemical no evidence of disease (bNED) was defined as the nadir prostate-specific antigen level plus 2 ng/mL.

Results: The median follow-up was 53 months. For the entire cohort, the 5-year bNED rate was 94.6%, and for low-, intermediate- and high-risk patients the 5-year bNED was 100%, 96.4%, and 86% ($p = 0.007$), respectively. The 5-year overall survival rate was 92%. Only 1 patient died from the disease at 48 months after treatment, giving a 5-year cancer-specific survival of 98%. The worst grade ≥2 rate GI and GU toxicity was 13.4% and 14%, respectively. No grade >3 toxicity was observed. The presence of grade ≥2 GI and GU toxicity at the last follow-up was only 1.3% and 3%, respectively.

Conclusions: Hypo-RT (69 Gy/23 fractions) with a high equivalent BED produces excellent rates of biochemical control for low, intermediate and high-risk prostate cancer. The long term GU and GI toxicity rates were considered low and acceptable.

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1. Background

In the last decades, randomized clinical trials and meta-analyse have showed that higher radiotherapy doses (>74 Gy) produce better biochemical control than conventional doses (<74 Gy).[1–3] Evidence from experimental and clinical studies suggest that prostate cancer has a lower α/β ratio than the surrounding organs.[4,5] This relationship between the α/β has raised the idea that a hypofractionated schedule might be more advantageous in terms of patient convenience, cost, and resource utilization than conventional schedules.[6] The clinical results of randomized clinical trials have also supported the practice of hypofractionated schedule in patients with localized prostate cancer.[7–10] These studies show that the hypofractionated schedule with high biological effective dose produces similar biochemical control and toxicity rates to conventional fractionation. However, there are a few clinical reports with adequate follow-up describing the clinical results with the use of hypofractionated high-dose radiotherapy (HypoHD-RT). In 2009, we decided to introduce this hypofractionated schedule in our clinical practice. The decision was made based on the clinical results of dose escalation trials and due to the concept of the low α/β ratio of prostate cancer. In 2013, we compared this hypofractionated schedule with the conventional one (78 Gy in 39 fractions) in terms of acute toxicity.[16]

2. Aim

In this report, we analyzed the treatment outcomes in terms of late gastro-intestinal (GI) and genitourinary (GU) toxicity, and biochemical control of a cohort of 149 men with prostate cancer who receive HypoHD-RT.

3. Materials and methods

The present study is a retrospective cohort with data prospectively collected in a single institution. The study enrolled 149 prostate cancers with localized disease. The study began in November 2009 and closed in January 2011. The ethic committee of our institution has approved the present work.

4. Evaluation

All patients, before the treatment, were evaluated by a full history and physical examination. Patients were classified into low, intermediate and high-risk group according to their Gleason score, T stage and initial PSA (iPSA). Low-risk group included patients with Gleason score <7/stage T1–T2a, and iPSA <10 ng/mL. Intermediate risk included Gleason score <7, or Stage T1–T2b, or iPSA level of 10–20 ng/mL; and high-risk patients with Gleason score >7, or Stage >T2b, or iPSA >20 ng/mL. All patients classified as high risk were submitted to the bone scans. Patients with metastases, prior history of prostatectomy, pelvic radiotherapy treatment, or chemotherapy treatment were excluded of this study.

5. Treatment

The 3D-CRT plan consisted of six fields to deliver a total dose of 69 Gy/23 fractions of a single daily dose of 3 Gy. The prescribed dose should cover 95% of PTV.

By the linear-quadratic formula, considering an α/β ratio of 1.5 Gy for prostate cancer, 69 Gy/23 fractions are equivalent to 88.7 Gy in fractions of 2 Gy. All patients were simulated on CT simulator. Patients were advised that extreme bladder or rectal filling could not be present at the time of the planning CT. An enema before the planning CT scan to empty the rectum and 2 glasses of water were recommended. A triangle sponge under the knees was used for all patients on the treatment planning CT. The following structures were contoured as organs at risk; femoral heads, rectum, bladder, and penile bulb. The contours of structures followed the recommendations of RTOG.[11] The rectum was contoured from the anal verge to the rectosigmoid transition. The low-risk group had only the prostate gland countered as clinical target volume (CTV). Intermediate and high-risk group had the prostate gland plus the seminal vesicles base (1 cm) contoured as CTV. The planning target volume (PTV) was created with 1 cm margin on the CTV, except for the rectal wall (7 mm). A single-radiation oncologist did all contours, and other two checked it. The study used the following rectal dose volume histogram (DVH); V50 < 50%, V60 < 35%, V65 < 25%, V70 < 20%, and V75 < 15%. To adapt the DVH for a hypofractionated schedule, the equivalent DVH to the dose of 3 Gy by fraction (assuming $\alpha/\beta = 3$ Gy) was calculated. Consequently, the rectal DVH constraints for hypofractionated were V42 Gy $\leq$ 50%, V51 Gy $\leq$ 35%, V58 Gy $\leq$ 25% and V62 Gy $\leq$ 15%. The following adapted bladder DVH constraints were used; V54 Gy $\leq$ 50%, V58 Gy $\leq$ 35%, V62 Gy $\leq$ 25% and V65 Gy $\leq$ 15%. All the treatment planning was performed by the Eclipse version 7.0 (Varian Medical Systems, Inc, Palo Alto, USA). All fields were treated daily in a megavoltage linear accelerator – 6 MV with 120-multileaf collimators. The digital portal images with X-ray using bone landmarks were obtained before the treatment for all patients. Patients with no set-up error on the first digital portal image were checked weekly. Patients with set-up errors on the digital portal images were checked with repeat imaging (three sequential images). Patients without set-up errors on the repeat imaging were checked by orthogonal images weekly. Only set-up errors greater than 2 mm were corrected.

Patients classified as intermediate, and high-risk group underwent an androgen blockage. The androgen blockage was done with acetate of goserelin of 3.6 mg. A total of 6 and 24 months of androgen blockage (neoadjuvant, concomitant and adjuvant) were administered for patients classified as intermediate and high-risk group, respectively.

6. End points

The primary endpoint of this trial was biochemical control defined as nadir+2 ng/mL, according to PHOENIX criteria.[12] Late toxicity was considered as any treatment reaction developed after 3 months of treatment. The radiation oncologists collected toxicity data prospectively. The RTOG system