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Early closure of phase II prospective study on acute and late tolerance of hypofractionated radiotherapy in low-risk prostate cancer patients

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ABSTRACT

Aim: To assess acute and late toxicity of hypofractionated radiotherapy, its efficacy and impact on quality of life in patients with low-risk prostate cancer.

Materials and methods: Since August 2006 to October 2007, 15 prostate cancer patients with favorable clinical features, aged 54–74 years (mean 67 years) entered the study. Tumor stage in the majority (73%) of patients was T2a, the mean pretreatment PSA value was 7.2 ng/ml (range 5–10.9 ng/ml). The study group was treated 3 times a week with 4 Gy per fraction to the total dose of 60 Gy within 5 weeks. 3D conformal treatment planning was used with no fiducial markers. Acute and late toxicity was evaluated using modified EORTC/RTOG/LENT scoring systems. Patients regularly filled the EORTC QLQ-PR25 questionnaires.

Results: All patients completed radiotherapy according to the plan. During radiotherapy, 26% of patients had grade 1–2 rectal symptoms. The incidence of acute urinary toxicity score was 26%, 60%, and 14% for grade 0–1, 2 and 3, respectively. One year after RT, the incidence of grade 2 GI toxicity was 27%, which was the reason for an early closure of the accrual. Grade 2 late urinary toxicity was noted in 20% of patients. The mean PSA level was 0.61 ng/ml after 24 months and 0.47 ng/ml after 36 months (range: 0.06–1.54 ng/ml).

Conclusions: Low number of patients does not allow to determine the influence of hypofractionation on unsatisfactory tolerance of this regimen. Suboptimal (from the present day's perspective) target localization (no fiducial markers) could potentially explain higher than expected late GI reactions in our series.

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Table 1 – Clinical characteristics of patients.

Age (year)	
<70 years	7 (47%)
≥70 years	8 (53%)
T stage	
T1c	1 (7%)
T2a	12 (80%)
T2b	2 (13%)
PSA	
<7 ng/ml	7 (47%)
≥7 ng/ml	8 (53%)
Gleason score	
2–4	6 (40%)
5–6	9 (60%)

1. Background

Following the publication of Brenner and Hall[1] that postulated high sensitivity of prostate cancer to fraction size (alpha/beta value of 1.5 Gy {0.8–2.2}), there was an increase of clinical interest in the use of high fraction doses (hypofractionation) in curative radiotherapy for prostate cancer.[2] The results of several prospective studies were published, including randomized trials that compared standard fractionation and hypofractionation.[3–6] There were also several attempts to re-evaluate α/β value for prostate cancer, leading to somewhat conflicting results,[7–12] with most estimates supporting its low value.[7,9–11] The presumed benefit from hypofractionation in prostate cancer that originated from radiobiological considerations, created the basis for the present study.

2. Aim

The aim of this study was to assess acute and late toxicity of hypofractionated radiotherapy, its efficacy and impact on quality of life.

We focused on patients with low-risk prostate cancer, hormonally naive, to have unbiased observation of PSA dynamic during follow-up.

3. Materials and methods

3.1. *Clinical characteristics of the patients*

Between August 2006 and October 2007, a prospective pilot study on hypofractionated radiotherapy in prostate cancer patients was conducted in Maria Skłodowska-Curie Memorial Cancer Center and Institute, Gliwice Branch. The primary endpoint was tolerance of treatment, as assessed by recording acute and late genitourinary and gastrointestinal normal tissue reactions, with biochemical free survival (BFS) being the secondary endpoint. The Phoenix definition was used as the criterion of biochemical failure (BF).[13] We planned to enroll twenty low-risk prostate cancer patients.

Fifteen patients with newly diagnosed prostatic adenocarcinoma were finally enrolled, Gleason score 6 or less, with PSA mean concentration equal or less than 10 ng/ml (mean 7.2 ng/ml), at early stage of disease according to 6th edition (2002) of AJCC staging guidelines (Table 1). The routine diagnostic procedures included TRUS and MRI spectroscopy of prostate gland.

Patients who fulfilled the trial criteria signed the informed consent. The institutional bioethical committee approved the trial design.

3.2. *Radiobiological considerations*

The total dose routinely used for treatment of low-risk prostate cancer patients in our hospital is 76 Gy in 2 Gy per fraction. Based on the assumption that α/β for late effects in organs at risk (OAR) is 6 Gy,[14,15] it corresponds to the total dose of 60.8 Gy/g in 4 Gy per fraction, which was calculated following the formula proposed by Withers et al.[16]:

$$D(4) = D(2) \times [\{\alpha/\beta + d(2)\}:\{\alpha/\beta + d(4)\}]$$
$$D(4) = 76\ \text{Gy}\ [\{6+2\}:\{6+4\}]$$
$$D(4) = 60.8\ \text{Gy}$$

$D(4)$ – total dose for 4 Gy per fraction, α/β – sensitivity of OAR to fraction dose (assumed 6 Gy).

According to the assumed parameters, the total dose of 60 Gy given in 4 Gy fractions corresponds to 75 Gy for late effects in OAR ($\alpha/\beta = 6$ Gy) and to 94.3 Gy for the tumor ($\alpha/\beta = 1.5$ Gy).

Based on reports[17,18] that 75 Gy (given in 2 Gy per fraction) is the tolerance dose to small volumes of rectum, it was assumed that increasing the dose per fraction from 2 to 4 Gy should be safe for OAR with the total dose of 60 Gy.

The dose volume constraints for 5%, 30% and 40% volume of the rectum were: 60 Gy, 56 Gy and 52 Gy, respectively (for fraction doses of 4 Gy). Those constraints correspond to $V75 \leq 5\%$, $V70 \leq 30\%$, $V65 \leq 40\%$ for conventional fractionation with a fraction size of 2 Gy. The dose volume constraint for the bladder was such that no more than 30% could receive 56 Gy in 4 Gy per fraction.

3.3. *Treatment*

Patients were treated in a supine position, stabilized with a vacuum mattress and thermoplastic mask with fixed a head, hips and feet. They were instructed to drink 0.5 l of fluids one hour before CT scanning. There were no specific instructions about the filling of the rectum, however, patients were informed how to avoid constipation. Laxatives or alpha antagonists were not used prophylactically. Non-contrast CT was collected every 3 mm. Clinical target volume was described as the whole prostate, the irradiated volume consisted of CTV with 1 cm margin from the rectal wall and 1.5–2 cm margin in all other directions, which was typical at that time for a standard fractionation regimen.

The dose was prescribed to the isocenter, we used the recommendation from the ICRU Report 62. Only two patients were treated with IMRT, all the others with conventional 3D conformal radiotherapy, with 3–7 fields.

Treatment verification consisted of a classical simulation of fields and isocenter positions. Patients were initially set up according to isocenter positions and in-room lasers. Before each fraction, kV image of bone structures of the pelvis was obtained. The images were then compared with