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Original research article

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

Table 2 – Acute GU and GI toxicity of radiation therapy according to modified RTOG criteria.[20]

The severity of acute reaction	Acute GU	Acute GI
Grade 0	2 (13%)	11 (74%)
Grade 1	2 (13%)	2 (13%)
Grade 2	9 (61%)	2 (13%)
Grade 3	2 (13%)	0

digitally reconstructed reference radiographs and correction of the table position was made, when needed.

Patients were treated on linear accelerators equipped with multi-leaf collimators. Treatment was delivered with 20 MV X-rays.

The rectum was contoured as a single solid organ from the bottom of the ischium to the sigmoid flexure, the bladder was also contoured as a solid organ.

Acute toxicity of radiation therapy was assessed once a week during treatment, one month after completing RT, every three months for two years, every six months in the third year of follow-up and annually later on. For the evaluation of acute and late toxicity, we adopted the modified RTOG and LENT scales[19,20] (Appendix 1 and 2). The modified LENT scale includes ways of handling and treating the late complications which makes it easier to be used in a clinic. The differences between the original RTOG classification[21] and the modified scale for acute radiation toxicity according to the paper by Storey[20] are less pronounced (Appendix 1). It divides rectal bleeding into grade 2 (if "mild") and grade 3 (if "requiring one transfusion"). For acute GU, it adds the need for temporary catheterization and puts "infrequent" gross hematuria as grade 2. It lets the need for transfusion (only if one) to be placed as grade 3 urinary acute symptoms.

The quality of life was assessed using EORTC QLQ-C30-PR25 questionnaires. The permission for use of EORTC questionnaires was obtained before the trial.

The questionnaires were filled by our group of patients weekly, starting from the week preceding the beginning of their treatment. It was continued during follow-up, at each visit.

Serum PSA measurements were performed at each follow-up visit.

3.4. *Statistical tests*

To check if a variable fulfills the criteria of normal distribution test W Shapiro–Wilk and K–S were used, non-parametric statistical tests such as ANOVA, Kruskal–Wallis for multiple and *U* Mann–Whitney test for two samples.

4. Results

Median follow-up was 29 months (range: 18.5–37). The most frequent were urinary (GU) acute side effects, with 74% of them with grade 2 or higher toxicity. At the same time gastrointestinal (GI) acute symptoms were mild, with no grade 2 reactions and only 13% of grade 1 acute reaction (Table 2).

In general, one month after the end of radiation therapy all the symptoms of acute GI disappeared, and a major

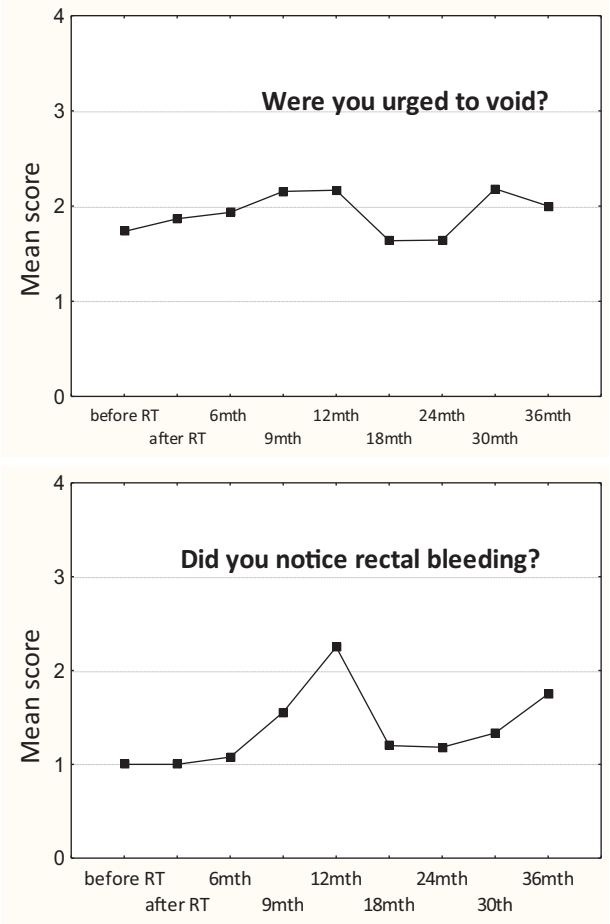

Fig. 1 – The mean score for two questions from EORTC QLQ – PR25 questionnaire, range: 1–4, where 1 means never, 2-sometimes, 3-often, 4-very often.

improvement was observed among the patients suffering from urinary reactions. Only two patients with residual grade 1 and one with grade 2 symptoms were seen.

An interim analysis after one year revealed a higher rate of late rectal injury than expected, resulting in an early closure of the trial after recruitment of 15 patients. Such decision was also based on the observed severity of late GI toxicity as scored using modified LENT criteria (Table 3). We noted that the symptoms of rectal bleeding subsided at a longer follow-up, although at 24–36 months after radiotherapy there were still more frequent than expected (Fig. 1 and Table 3).

In the following months, the decrease of its intensity was observed (Table 3). At the third year of follow-up, nocturia, incontinence requiring the use of pads were still observed with 22% and 14% patients suffering from late GU toxicity grade 1 and 2, respectively. Twenty-one percent of patients complained of slight rectal bleeding at the thirtieth month of follow-up. Fig. 1 illustrates the mean score from EORTC QLQ PR 25 questionnaires in the following weeks of treatment and follow-up. One year after radiotherapy, one patient was diagnosed with sigmoid colon cancer, which eventually was fatal.

Table 3 – Late GU and GI toxicity of radiation therapy according to modified LENT criteria.[19,20]

The severity of late reaction	9 mth	12 mth	15 mth	24 mth	30 mth
Late GU toxicity					
No at risk	15	15	14	14	14
0	60%	66%	57%	79%	57%
1	20%	13%	22%	14%	22%
2	13%	20%	14%	7%	14%
No data	7%		7%		7%
Late GI toxicity					
No at risk	15	15	14	14	14
0	73%	73%	72%	79%	72%
1	7%		14%	21%	21%
2	13%	27%	7%	0	0
No data	7%		7%		7%

We searched for possible connection between the side effects and co-morbidities. We gathered data about history of hemorrhoids, diabetes, hypertension and α1-inhibitors, anticoagulants, but no clear correlations were found. Higher average volume of the bladder that received 56 Gy (V70 Gy – equivalent dose at 2 Gy per fraction, or EQD2) was recorded in patients with peak grade 1 or 2 acute toxicity, compared to grade 0 (23% vs. 4%, $p = 0.027$ *U*-Mann–Whitney test).

The review of contouring the organs at risk revealed the wide range of bladder volumes. Although all the patients were given the same instructions on drinking fluids and not to void for half an hour before the irradiation, we found great differences among the volumes of their bladders at the CT: starting from 108 to 623 cm^3 (mean value 312 cm^3). A similar heterogeneity was found in rectal volumes contoured from sigmoid colon to the anal verge: 44–193 cm^3 (mean value 89 cm^3).

The PSA concentration decreased with exception of one patient (Fig. 2).

We observe a gradual constant decrease with mean value after 30 months: 0.63 (range: 0.05–2.6) ng/ml, 0.47 ng/ml (range: 0.06–1.54 ng/ml) after 36 months. There is only one patient with PSA bounce to the value of 5.19 ng/ml, which occurred 18 months after RT, with 1.54 ng/ml six months before the bounce. The additional diagnostic exams were performed including bone scintigraphy and spectroscopy MRI. His last blood test for PSA was 0.64 ng/ml at 30 months after he completed RT. There has been no biochemical recurrence diagnosed so far.

5. Discussion

5.1. *Toxicity of treatment*

Several treatment modalities are currently being used in therapy for low-risk prostate cancer. Active surveillance, radical prostatectomy, fractionated radiotherapy are among the options. Fractionated radiotherapy can be used as a sole treatment or in combination with brachytherapy. HDR or LDR brachytherapy alone is a valid option. The morbidity of these methods has a major impact on the selection of treatment. The assessment and comparison of adverse effects in these methods is difficult, particularly outside the prospective clinical trials. Diverse scoring systems are used that often disable

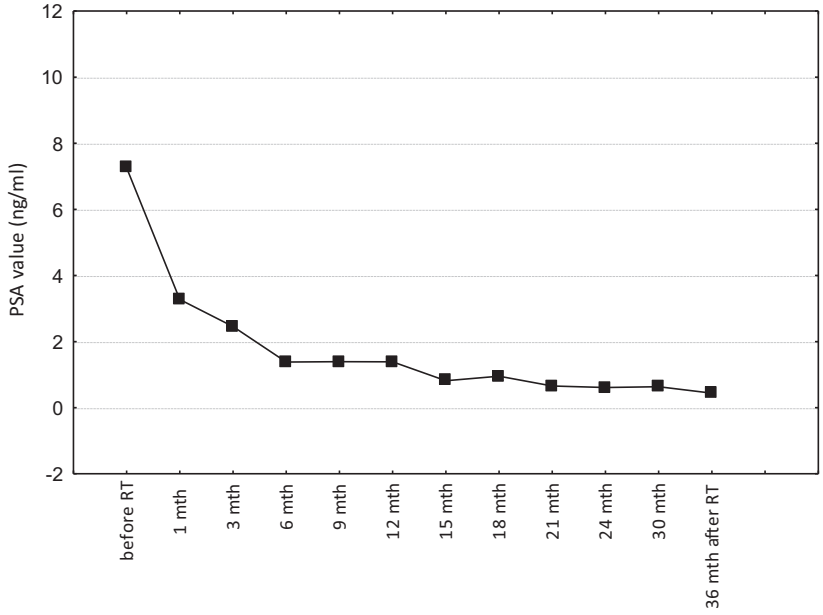

Fig. 2 – The mean value of serum PSA measurements before radiotherapy and at follow-up visits (ng/ml).

direct comparisons of the outcome. The incidence of late GI toxicity observed in this series was higher than expected, particularly at 12 months after treatment. It exceeded the numbers reported by most authors[4,22–26] with the reported rate of grade 2 late reactions below 10%, compared to 27% in the present series. This necessitated an early closure of the study. Some studies that recorded a higher than average rate of late GI reactions used higher than the standard equivalent doses. Akimoto et al.[27] observed relatively high late GI reactions among patients treated to 69 Gy in 3 Gy per fraction that would correspond to 77.6 Gy EQD2 for late reactions (assuming α/β =6 Gy). We note that the EQD2 dose used in this study was comparable to the present one. Statistically significant increase in acute GI and GU toxicity was observed in the group of patients treated with hypofractionated radiotherapy in comparison with a conventional treatment in a randomized trial of Lukka et al.,[4] although it did not result in higher late toxicity rates. Acute GI, but not GU, toxicity scores were higher in the experimental arm in the Australian randomized trial.[5] At two and three years of follow up, total GU symptoms were significantly worse in the hypofractionated RT arm, with no statistically significant difference in GI symptoms at follow up, with the exception of urgency of defecation. The five-year results of a randomized trial previously published by Pollack et al.[3] was presented at the 2011 ASTRO Conference,[28] with a significantly higher grade 2 or higher GU late reactions in the hypofractionation group.

5.2. *Radiobiological considerations*

The higher than expected rate of late GI reactions necessitates caution with respect to the future assumptions of the α/β value of late reactions of the rectum. The outcome of the study may suggest that the assumed α/β value of 6 Gy was too high. A relatively wide of α/β values for late reactions of the rectum is provided in the literature[14,15,29] with 6 Gy being apparently at the upper end of the postulated ranges. The outcome of the study may suggest that more restrictive assumptions (e.g. α/β = 3 Gy) should be used in future attempts to estimate the late effects in the rectum. For the same reason, dose constraints for radiation treatment given in 4 Gy fractions that were used in the present study cannot be further recommended. Also, the proposed treatment schedule (60 Gy in 4 Gy per fraction) may have to be modified if lower α/β values for the rectum are considered. The physical dose of 60 Gy would correspond to 84 Gy in 2 Gy equivalents assuming α/β = 3 Gy for late effects. This may be too intense, particularly considering radiation techniques that were used.

5.3. *Quality assurance and treatment technique*

In this series of patients the interfraction patient set-up was based on kV imaging of bone structures. Such a technique might be considered obsolete according to the present-day standards. Routine use of fiducial markers implanted to the prostate and advanced on-board imaging (e.g. cone-beam CT) may contribute to a better treatment precision.[23,24,30–32]

Considering the outcome in the present series, one may postulate that kV imaging of bone structures may appear insufficient for treatment set-up of prostate cancer patients whenever higher than standard fraction or total doses are used.

Modern technique, e.g. IMRT plans instead of 3DCRT, and daily localization with advanced systems based on fiducial markers used in studies on hypofractionated radiation therapy, seem to be necessary to secure its satisfactory tolerance.

6. 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.

Conflict of interest

None declared.

Financial disclosure

None declared.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.rpor.2014.02.006.

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