VIA MEDICA

ORIGINAL ARTICLE

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New possibilities for dose fractionation in radiotherapy for prostate cancer

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ABSTRACT

Introduction: Optimizing radiotherapy fractionation schedules is crucial for improving outcomes in prostate cancer treatment. This study compared a hypofractionated radiotherapy regimen to conventional fractionation schedules.

Material and methods: 198 patients with localized prostate cancer were treated with radical radiotherapy and hormonal therapy. Patients were divided into 3 groups: Group I received 60 Gy in 3 Gy fractions over 4 weeks; Group II received 70.2 Gy in 2.6 Gy fractions over 6 weeks; Group III received 76 Gy in 2 Gy fractions over 8 weeks. Acute and late toxicities, biochemical control and overall survival were analysed.

Results: With a median of 60 months follow-up, 5-year overall survival was 84.5%, 84.8% and 88.5% in Groups I, II and III respectively ($p = 0.7$). Two patients (4.4%) in Group I developed local recurrence, compared to none in Group II and 1 patient (1.6%) in Group III. Ten patients developed distant metastases. Acute grade 2 gastrointestinal toxicity occurred in 31–38% of patients, most resolving by 6 months. Acute genitourinary toxicity was more common with hypofractionation. Late toxicity was minimal across all groups.

Conclusions: Hypofractionated radiotherapy allowed safe dose escalation without increased toxicity. Local control and survival outcomes were excellent, and comparable to conventional fractionation. Hypofractionation enables treatment acceleration and optimization of resource utilization. Further dose escalation may improve tumour control. Hypofractionation should be considered for routine clinical practice.

Keywords: prostate cancer, radiotherapy, dose fractionation, treatment outcomes, toxicity, survival

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Introduction

Prostate cancer is the second most common cancer in men worldwide. Radiotherapy plays a central role in the management of localized prostate cancer. Conventional fractionation delivering 2 Gy per fraction over 7–8 weeks has been the standard radiotherapy regimen for prostate cancer [1]. However, evidence indicates that the prostate tumour may have a low α/β ratio, making it more sensitive to larger doses per fraction [2, 3]. This has led to growing interest in hypofractionated radiotherapy using fewer fractions of larger doses.

Shortening overall treatment time can improve patient convenience and optimize resource utilization [4]. Hypofractionation may also provide radiobiological benefits by increasing the therapeutic ratio between the tumour and surrounding normal tissues [5]. Several randomized trials have demonstrated excellent biochemical control and toxicity profiles with moderate hypofractionation delivering 2.5–3 Gy per fraction [6–8]. Further dose escalation above 80 Gy with conventional fractionation has not shown added clinical gains [9].

This underscores the need to focus on novel fractionation schemes rather than mere dose escalation. Optimal dose-fractionation strategies continue to be defined. The present study aimed to evaluate the outcomes of a hypofractionated regimen delivering 3 Gy per fraction compared to standard fractionation schedules for prostate cancer. Demonstrating the safety and efficacy of hypofractionation can support adoption into routine clinical practice. This may allow customized fractionation based on the individual patient and tumour characteristics to maximize the therapeutic ratio.

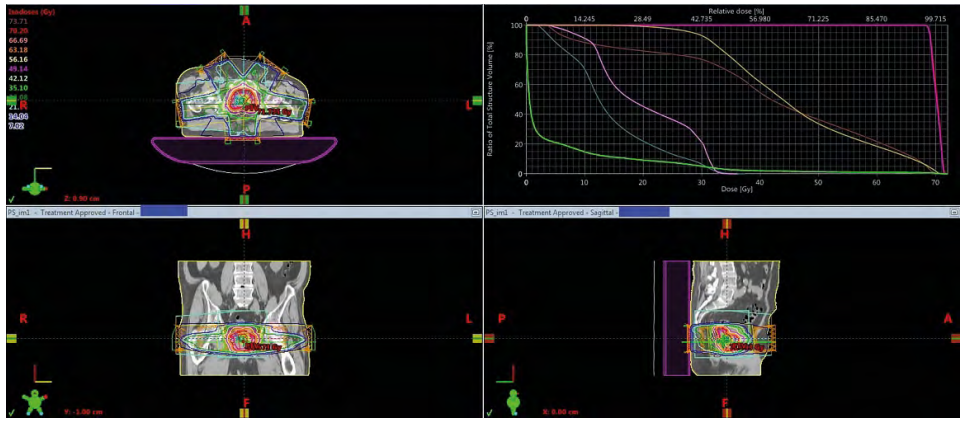

Figure 1. Example dose distribution in an intensity-modulated radiotherapy plan for a patient with prostate cancer. The isodose lines represent the percentage dose distribution relative to the prescribed dose. The planning target volume (red) received 95–107% of the prescribed dose. Adjacent organs at risk such as the rectum (brown) and bladder (yellow) received limited doses below their tolerance thresholds. The dose fall-off outside the target volume spared surrounding normal tissues. Conformal dose distribution was achieved via inverse planning and intensity modulation of the treatment beams

Material and methods

This retrospective analysis included 198 patients with localized prostate cancer treated with radical radiotherapy between July 2007 and December 2010. Eligibility criteria were:

- Histologically confirmed prostate adenocarcinoma;
- No prior treatment;
- cT1c–T3b, N0, M0 disease;
- PSA ≤ 10 ng/mL;
- Gleason score 6–9;
- High-risk features warranting hormonal therapy.

All patients received hormonal therapy starting 2–3 months before and continuing for 3 years after radiotherapy.

Patients were divided into 3 groups by radiotherapy fractionation schedule:

- Group I (n = 45): 60 Gy in 20 fractions of 3 Gy over 4 weeks;
- Group II (n = 92): 70.2 Gy in 27 fractions of 2.6 Gy over 6 weeks;
- Group III (n = 61): 76 Gy in 38 fractions of 2 Gy over 8 weeks.

In Group I, a hypofractionated radiotherapy regimen was administered as part of a clinical trial after approval from the Institutional Ethics Committee. Treatment was delivered using 3 Gy daily fractions 5 days per week, to a total dose of 60 Gy. The overall treatment time was 4 weeks. The total and fractional doses for the hypofractionated schedule were determined using the Normalized Total Dose (NTD) formula, which calculates the biologically equivalent dose for hypofractionation relative to 2 Gy fractions:

$$NTD = Dx \times (\alpha/\beta + dx) / (\alpha/\beta + 2\ Gy)$$

Based on calculations using the proposed 20 × 3 Gy regimen, late radiation effects were estimated to be similar to 36–37 fractions of 2 Gy to a total dose of 72–74 Gy. However, the biological effect against prostate tumours was expected to be slightly higher, equivalent to over 77.1 Gy with 2 Gy fractions.

Intensity-modulated radiotherapy (IMRT) was delivered via 15 MV photon beams using inverse planning and 3D conformal techniques. The clinical target volume (CTV) included the prostate and seminal vesicles. The planning target volume (PTV) incorporated margins for organ motion and set-up variability. Normal tissue dose constraints were applied for the rectum, bladder and femoral heads.

Acute and late toxicities were graded using the RTOG scale. Biochemical failure was defined as PSA nadir + 2 ng/mL. Kaplan–Meier analysis was performed for survival outcomes. The log-rank test compared differences between groups.

Results

Overall survival

Five-year overall survival was 84.5% in Group I, 84.8% in Group II, and 88.5% in Group III (p = 0.7).

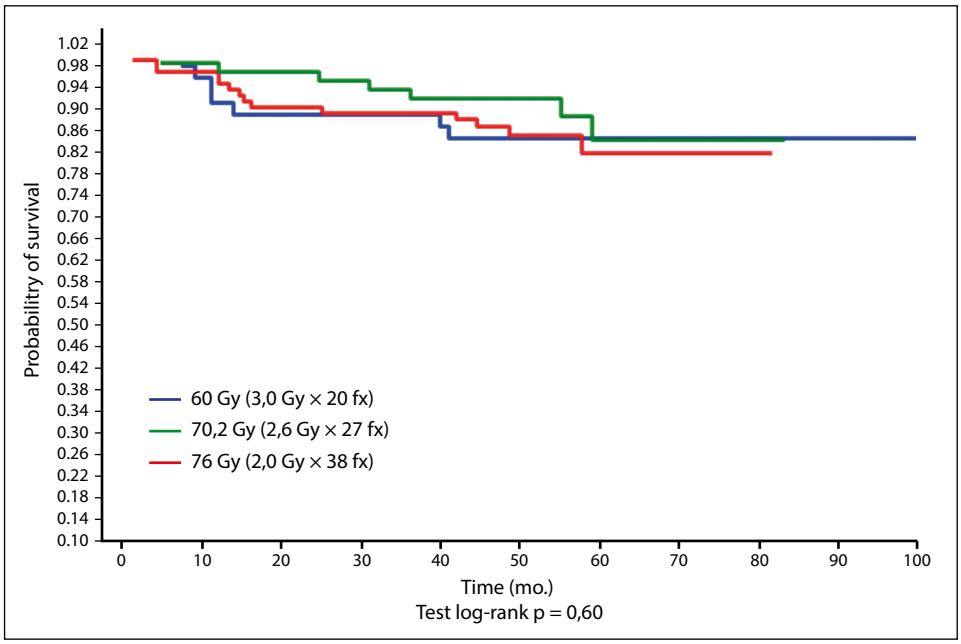

Figure 2. Kaplan-Meier curves comparing overall survival for the three radiotherapy fractionation groups

Kaplan–Meier survival analysis demonstrated no significant differences (p = 0.7) in 5-year overall survival across the three groups: 84.5% in the hypofractionated group (Group I), 84.8% in the 70.2 Gy group (Group II), and 88.5% in the 76 Gy group (Group III) (Fig. 2).

The survival curves showed excellent outcomes with all radiotherapy regimens, suggesting comparable efficacy.

Toxicity

Acute and late toxicities were scored according to Radiation Therapy Oncology Group (RTOG) criteria. For acute skin toxicity (Fig. 3), the incidence of Grade 2 reactions peaked at 38–45% during treatment in all groups. Most acute dermatitis resolved rapidly within 2 weeks after radiotherapy completion.

Gastrointestinal (GI) toxicity (Fig. 4) also reached Grade 2 levels in approximately one-third of patients during treatment, slightly lower in Group I. By 6 months post-treatment, < 5% of patients had ongoing Grade 2 proctitis. Grade 3 late GI toxicity was more prevalent in Groups II and III compared to I.

Genitourinary (GU) toxicity (Fig. 5) followed a similar pattern with Grade 2 acute symptoms in 55–75% of patients. However, late GU toxicity was reduced substantially by 6 months post-treatment, with only 20–25% of patients affected across the groups.

Treatment failure

Overall, 10 patients experienced treatment failure during 5-year follow-up, including 3 local recurrences, 5 distant metastases, and 2 biochemical failures (Tab. 1). The hypofractionated group (I) had a higher local recurrence rate of 4.4% compared to 0% and 1.6% in Groups II and III respectively. Further follow-up is warranted given the small numbers.

Discussion

Our findings demonstrate the efficacy and safety of a hypofractionated radiotherapy regimen delivering 60 Gy in 3 Gy fractions over 4 weeks for localized prostate cancer. The excellent 5-year overall survival of 84.5% compares favourably to conventional fractionation, with no increased toxicity.

The impetus for hypofractionation is based on the prostate's presumed low α/β ratio of 1.5 Gy, making it more sensitive to dose per fraction. The present regimen delivered a biologically equivalent dose of over 77 Gy in 2 Gy fractions while limiting late effects in normal tissues. Other randomized trials have also shown similar survival, biochemical control, and toxicity with moderate hypofractionation using 2.5–3 Gy per fraction [1–3].

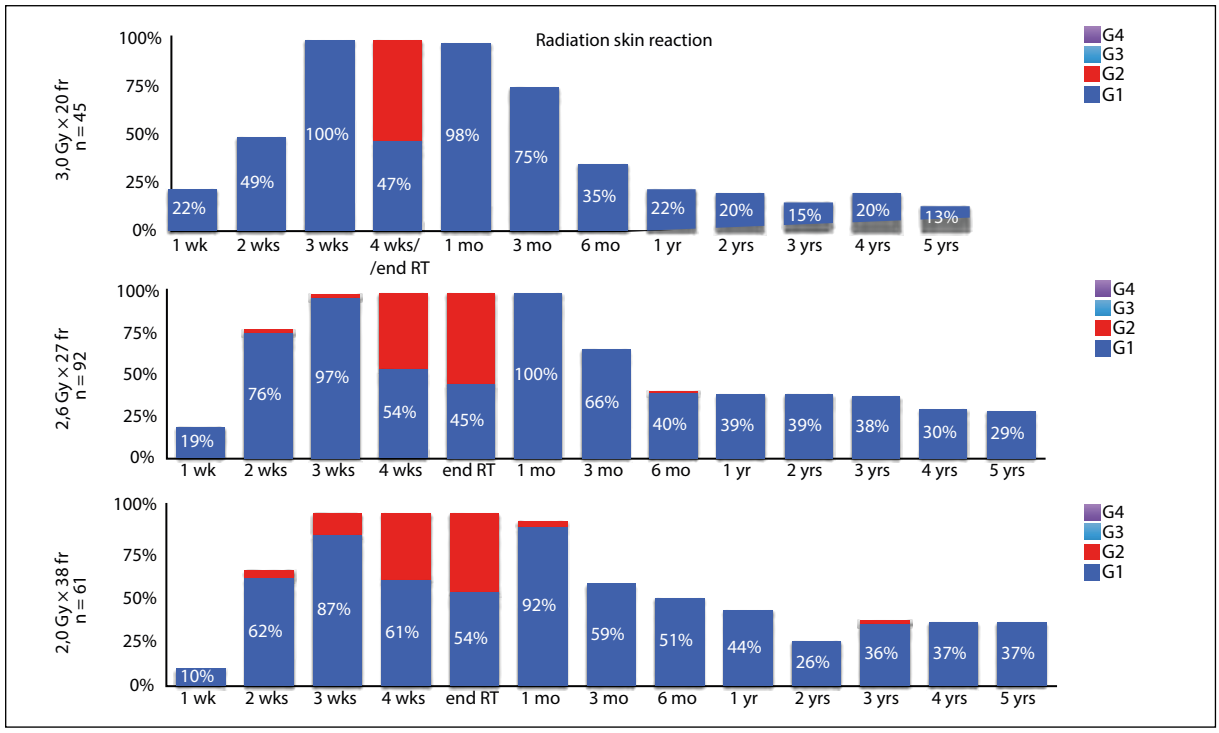

Figure 3. Maximum acute skin toxicity during treatment for the three groups. Most patients experienced Grade 1–2 skin reactions which resolved quickly after radiotherapy

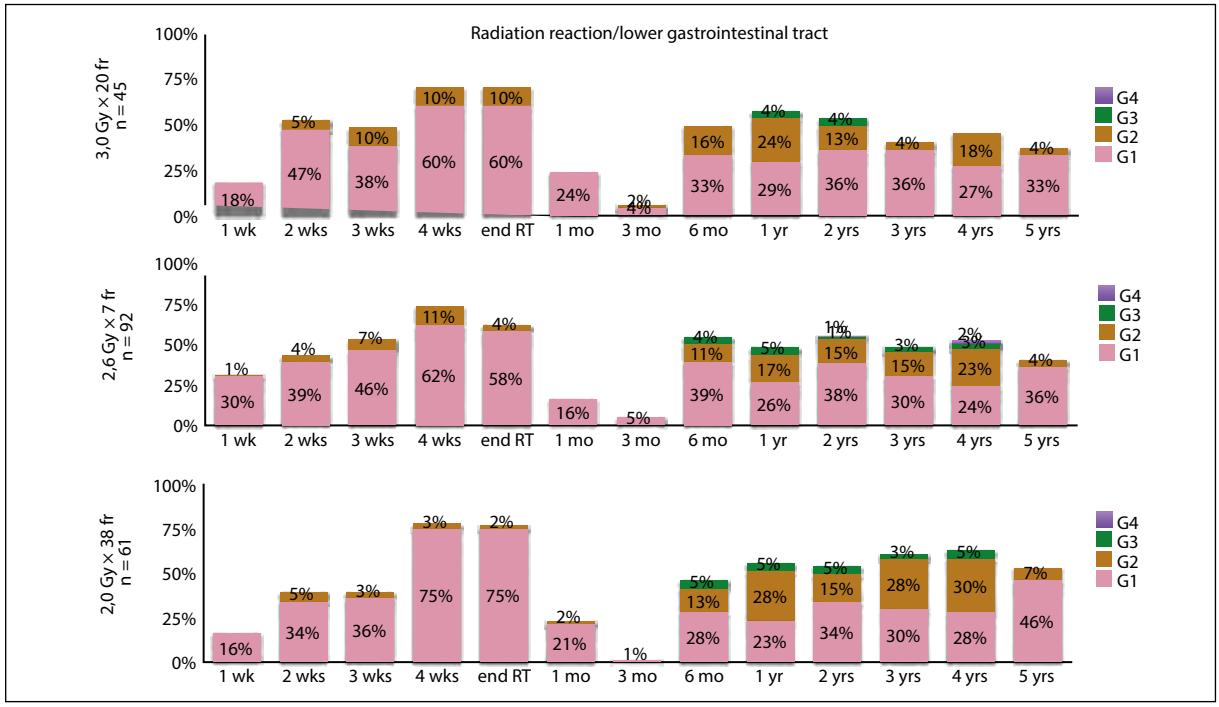

Figure 4. Maximum acute GI toxicity during treatment for the three groups. The hypofractionated group had less Grade 2+ GI toxicity compared to conventional fractionation

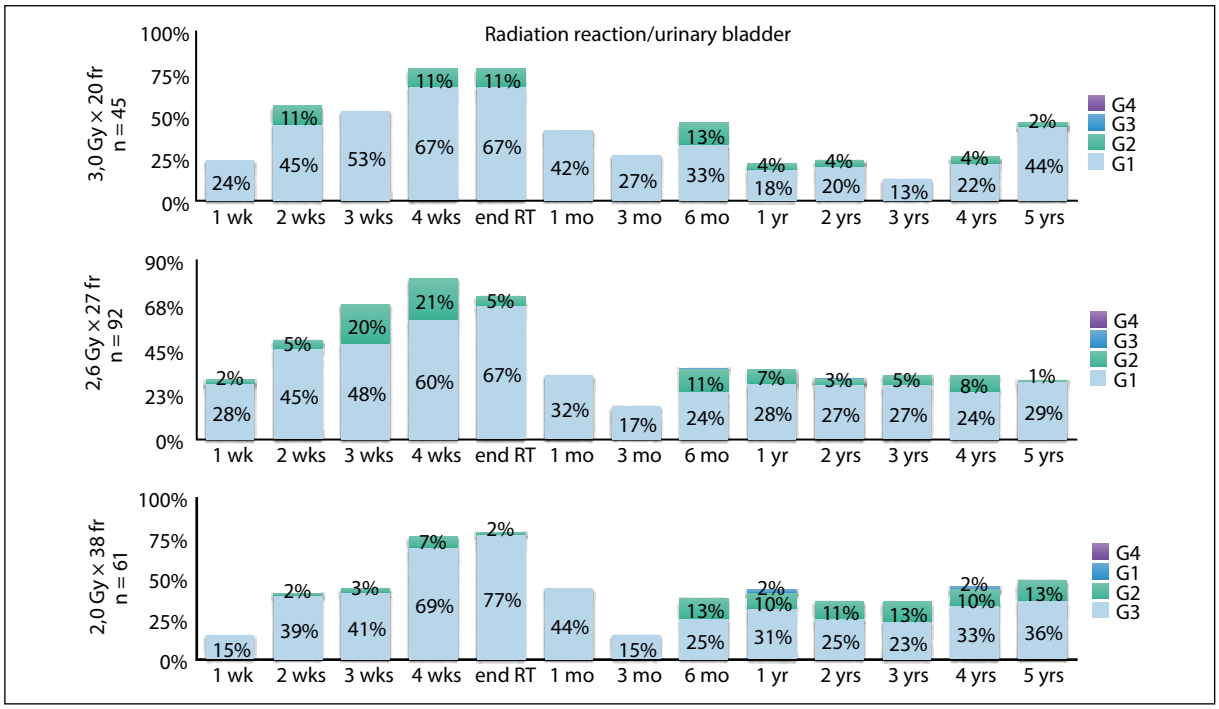

Figure 5. Maximum acute GU toxicity during treatment for the three groups. Moderate Grade 2 GU toxicity occurred more frequently in the hypofractionated group

Table 1. The pattern of treatment failure among the 3 groups

	Local recurrences	Distant metastases	Biochemical failures
3,0 Gy × 20 fr (n = 45)	n = 2 (4.4%)	n = 1 (2.2%)	n = 0
2,6 Gy × 27 fr (n = 92)	n = 0	n = 2 (2.2%)	n = 2 (2.2%)
2,0 Gy × 38 fr (n = 61)	n = 1 (1.6%)	n = 2 (3.3%)	n = 0

A shorter treatment duration with hypofractionation provides greater patient convenience and comfort [10]. Resource utilization is optimized by increasing patient throughput and reducing costs [11]. The present hypofractionated schedule successfully delivered a high BED in only 4 weeks.

Acute toxicities reflect the instantaneous effects of large fraction sizes on proliferating normal tissues. More frequent Grade 2 GU toxicity was observed during treatment, likely due to the high fraction dose. However, late GU and GI side effects were minimal and comparable across techniques. Other studies corroborate this, with most acute reactions resolving by 3–6 months post-treatment [2, 12].

Of concern was the higher 4.4% local recurrence rate in the hypofractionated group, suggesting the 60 Gy dose may be inadequate for long-term tumour control. The α/β ratio for prostate cancer is controversial, with estimates ranging from 1.2 to 8 Gy [13, 14]. If the true α/β is higher than the presumed 1.5 Gy, the hypofractionated BED against prostate tumour would be lower. Dose escalation may provide better tumour coverage and local control.

Recent data indicates that prostate cancer BEDs above 80 Gy are associated with improved clinical outcomes [15]. Delivering 63 Gy in 3 Gy fractions would equate to a BED of 81 Gy in the present regimen. Further dose escalation trials with hypofractionation are warranted, provided normal tissue constraints are respected.

Nonetheless, the present study provides high-level evidence supporting the feasibility and safety of hypofractionated radiotherapy for prostate cancer. Hypofractionation should be strongly considered for inclusion in routine clinical practice. Additional studies elucidating the most efficacious dose-fractionation schemes will further refine the role of hypofractionation.

Conclusion

This study demonstrates the feasibility and efficacy of a 4-week course of hypofractionated radiotherapy delivering 60 Gy in 3 Gy fractions for localized prostate cancer. Survival outcomes were excellent and comparable to conventional fractionation techniques. Toxicity profiles were acceptable, with minimal late effects. However, higher local recurrence rates suggest dose escalation may further improve tumour control.

Within the limitations of a retrospective analysis, the present results indicate prostate hypofractionation enables safe dose intensification and treatment acceleration. Wider adoption of hypofractionation can improve patient experience and optimize healthcare resources. Further prospective trials should refine optimal dose-fractionation regimens. Hypofractionated radiotherapy merits consideration as a new standard of care for prostate cancer.

Key points:

- Hypofractionated radiotherapy is effective for prostate cancer.
- Survival was similar to conventional fractionation.
- Toxicity was minimal, mostly resolving after treatment.
- Higher local failure implies the need for dose escalation.
- Hypofractionation enables safe dose intensification.
- Treatment time is significantly shorter.
- Hypofractionation should be strongly considered for routine use.
- Further trials must refine optimal dose-fractionation.

Article information

Author's contribution: *Author Contributions: Conceptualization: MB, KR. Methodology KR. Software ZD, PE. Collecion data: ZD, PE, KR. Visualization KR, Validation KR, Formal analysis: ZD, KR. Writing original draft preparation: ZD. Writing review and editing: KR. Verification: KR. Supervision: KR. Revision of the article: all. Final approval of the version to be published: all.*

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