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Acute Side-effects of Different Radiotherapy Treatment Schedules in Early Prostate Cancer

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Abstract. *Background: Optimal radiation therapy (RT) fractionation in early prostate cancer in elderly patients is controversial. We compared acute toxicities of fractionation schedules: 78/2 Gy, 60/3 Gy and 36.25/7.25 Gy, in this single-centre study. We also evaluated the effect of the rectal immobilization system Rectafix on quality of life (QoL). Patients and Methods: Seventy-three patients with one or two intermediate prostate cancer risk factors according to National Comprehensive Cancer Network criteria were recruited. Twenty-one patients were treated with 78/2 Gy and 60/3 Gy, and 31 patients with 36.25/7.25 Gy. Their QoL data were assessed with regard to genitourinary, gastrointestinal and sexual wellbeing at the beginning and end of RT and at 3 months after treatment. Rectafix was used in the 78/2 Gy and 60/3 Gy groups. Results: There were no statistically significant QoL differences in between the treatment groups 3 months after RT. The 78/2 Gy group had significantly increased bowel movements between baseline and 3 months after RT (p=0.036). At 3 months after RT, this group also had significantly more erectile dysfunction than the 60/3 Gy group (p=0.025). At the end of RT, the 78/2 Gy group had more symptoms than the 36.25/7.25 Gy group. Rectafix did not reduce acute toxicities in the 78/2 Gy or 60/3 Gy groups. Conclusion: Treatment with the 78/2 Gy schedule is no longer to be recommended due to its increased acute toxicity compared to treatments of 60/3 Gy and 36.25/7.25 Gy. The shortest schedule of 36.25 Gy in five fractions seems to be a convenient treatment option with tolerable acute toxicity.*

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Prostate cancer (PC) is the most common cancer in Finland and the whole Western world. In Finland 2019, 5,245 new cases were diagnosed. External-beam radiotherapy (RT) is an important treatment option for prostate cancer. Other options include radical prostatectomy, brachytherapy, active surveillance, and watchful waiting (1). The prognosis of prostate cancer is excellent; the 10-year prostate cancer-specific survival after curative treatment is 95-98% in those with early prostate cancer and 86-91% in high-risk disease (2). Based on dose-escalation studies, the standard radiation dose has been established at between 74 and 78 Gy, with a resulting treatment delivery time of 7 to 8 weeks with 2-Gy fractions (3, 4). Several studies have indicated that in the linear-quadratic model of radiation dose-response, prostate cancer exhibits a low α/β-value (5). Based on this assumption, fewer and larger fractions in RT would increase therapeutic efficacy with reduced treatment-related toxicity to normal tissues, which is related to a higher α/β-value. Patient convenience and optimized use of resources have also increased the rationale for shorter RT courses. Large studies have demonstrated that 3-Gy fractions delivered in 4 weeks have an equal efficacy and toxicity profile to 2-Gy fractions over 8 weeks (6, 7). Based on these results, the treatment schedule of 60 Gy in 20 fractions has been widely adapted. If it is assumed that the α/β-value of prostate cancer is very low, indicating that the cancer cells have high sensitivity to the dose per fraction, it is possible to deliver fewer focused high-dose fractions safely with good local control of disease without increasing damage to normal tissue. The longest efficacy and safety follow-up for this kind of stereotactic body radiation therapy (SBRT) treatment of the prostate is 10 years with a dose of 5×7.25 Gy, wherein the biochemical recurrence-free survival was 93%, and severe toxicity was limited. All patients had early low-risk prostate cancer (8).

In addition, differences in bladder and rectal filling can cause interfractional motion of the prostate during RT (9). This intrafractional motion is caused by gas movements in the rectum, muscle relaxation and patient position adjustments (10). All these factors can have an effect on the outcome of RT for prostate cancer. Intrafractional motion can be detected with electromagnetic tracking devices, such as RayPilot (Micropos Medical, Gothenburg, Sweden) or Calypso (Varian Medical Systems, Palo Alto, CA, USA). Rectal retractors and endorectal balloons can be used to reduce prostate intrafractional motion and to achieve rectal dose sparing. The 3D symmetrical internal margins around the prostate in treatment plans can be reduced by up to 33-40%, and the mean fractional high dose to the rectum is measured as being 39% lower with the use of an endorectal balloon (11, 12). The immobilization device Rectafix (Scanflex Medical, Täby, Sweden) was also developed to reduce the irradiated rectal volume and thus reduce RT-related side-effects (13).

Compliance with prostate cancer RT might be an issue for patients due to the long distances patients need to travel to their therapy centre in countries such as Finland. Moreover, the mean age for prostate cancer diagnosis in Finland, is approximately 70 years. Thus, the aim of this study was to evaluate acute toxicity and patient-reported quality of life outcomes when using three RT schemes (39×2 Gy, 20×3 Gy, 5×7.25 Gy) and new localization and immobilization devices in the treatment of early local prostate cancer in order to develop better tolerated and more convenient treatment options for this elderly patient population.

Patients and Methods

Patients. This was a prospective, single-centre study comparing the conventionally fractionated schedule of 78 Gy in 39 fractions (78/2 Gy) with two hypofractionated schedules of 60 Gy in 20 fractions (60/3 Gy) and 36.25 Gy in five fractions (36.25/7.25 Gy). Men between 30 and 85 years with a biopsy-proven localized T1c-T2cN0M0 prostate carcinoma with one or two intermediate risk factors according to National Comprehensive Cancer Network criteria were eligible (14). Intermediate risk factors were T2b-T2c, Gleason score 7 or prostate-specific antigen (PSA) level of 10-20 ng/ml. Prostate cancer-specific exclusion criteria were the need for androgen deprivation therapy or transurethral resection of the prostate. Other exclusion criteria included hip prosthesis, previous pelvic RT and another active malignancy in the previous 5 years. Overall, 73 patients were recruited between May 2014 and December 2017. The first 42 patients were treated within 78/2 Gy or 60/3 Gy according to the clinician's decision, and 31 patients were then treated with 36.25/7.25 Gy. The Tampere University Hospital Ethics Committee approved the study (R14009), and patients gave their written informed consent. The clinical trial identifier was NCT02319239 at www.ClinicalTrials.gov.

Procedures. Three fiducial markers were placed in the prostate and planning computed tomography (CT) and magnetic resonance imaging (MRI) were performed. For the 78/2 Gy and 60/3 Gy groups, treatment was given in one daily fraction from Monday to Friday. The 36.25/7.25 Gy treatment group received treatment every other day for 10 days. Radiotherapy to all treatment groups was given with volumetric-modulated arch therapy using two full arcs and 6 MV flattened beams. The clinical target volume included the prostate and the base of seminal vesicles. The planning target volume was extended from the clinical target volume by 5 mm. For the 78/2 Gy and 60/3 Gy groups, the risk of seminal vesicle invasion was assessed with the Memorial Sloan Kettering Cancer Centre nomogram (15). When the invasion risk was greater than 15%, RT was given to the seminal vesicles with a 7 mm extension. The RT doses given to them were 56/2 Gy and 46/2.3 Gy accordingly. Seminal vesicles were not included in the 36.25/7.25 Gy group. Dose constraints were defined for dose coverage and for normal tissues, including the rectum, bladder, and femoral heads (16-19). In the 36.25/7.25 Gy group, Fleet Enemas were used prior to planning CT, MRI and each treatment delivery. For the 78/2 Gy and 60/3 Gy groups, treatment localization was performed with orthogonal kilovolt imaging based on three fiducial markers. Cone-beam CT scans were used to evaluate the rectum and bladder before the delivery of each fraction in the 36.25/7.25 Gy group.

Quality of life investigations were performed with patient-reported outcome questionnaires at baseline, at the end of RT and 3 months after the treatment. Bowel, bladder, and sexual function assessments included International Prostate Symptom Score (IPSS), the International Index of Erectile Function (IIEF-5), and 16 questions on a modified version of the LENT-SOMA questionnaire (20-22). The seven IPSS questions led to point totals ranging from 0-35: 0-7 mild, 8-19 intermediate and 20-35 severe symptoms. The IIEF-5 score ranged from 5 (severe dysfunction) to 25 (no dysfunction). When the patient answered the IIEF-5 questionnaire but scored below 5 points, his answers were included. LENT-SOMA genitourinary (GU) and gastrointestinal (GI) domain scores were formulated as a sum of domain-specific questions. The GU domain score ranged from 0 to 20, and the GI domain score ranged from 1 to 28. Physicians completed Common Terminology Criteria for Adverse Effects (CTCAE) version 4 questionnaires at baseline and at the end of RT to evaluate acute toxicity (23). The 36.25/7.25 Gy group also had patient-reported outcome questionnaires and physicians' evaluations of toxicity at 1 month after the end of RT. Based on patient records and CTCAE v4 findings, toxicity was later converted to the Radiation Therapy Oncology Group scale for comparison with other studies (24).

Histology was assessed with transrectal ultrasound-guided biopsies and reported with the Gleason system (25). Local staging (TNM) was performed with digital rectal examination and pelvic MRI (26, 27). Other investigations included PSA and standard haematology. Whole-body CT and bone scans were not included because the risk of metastasis was considered low based on the referred guidelines (14, 28). PSA was measured at the end of and 3 months after RT. The 36.72/7.25 Gy group underwent PSA measurement 1 month after treatment.

Rectal immobilization device and intrafractional movement tracking. Part of the study was to evaluate immobilization of the rectum and prostate with rectal rod Rectafix and its effect on rectum dose sparing and intrafractional movement of the prostate. Rectal immobilization was achieved by posterior rectal depression performed with a cylindrical rod (length 110 mm, diameter 20 mm) inserted into the patient's rectum. The rod was fixed to its support column when optimal displacement was achieved. A rectal rod was used in the treatment of 16 patients in the 78/2 Gy group for the first 15 fractions and 14 patients in the 60/3 Gy group for the first

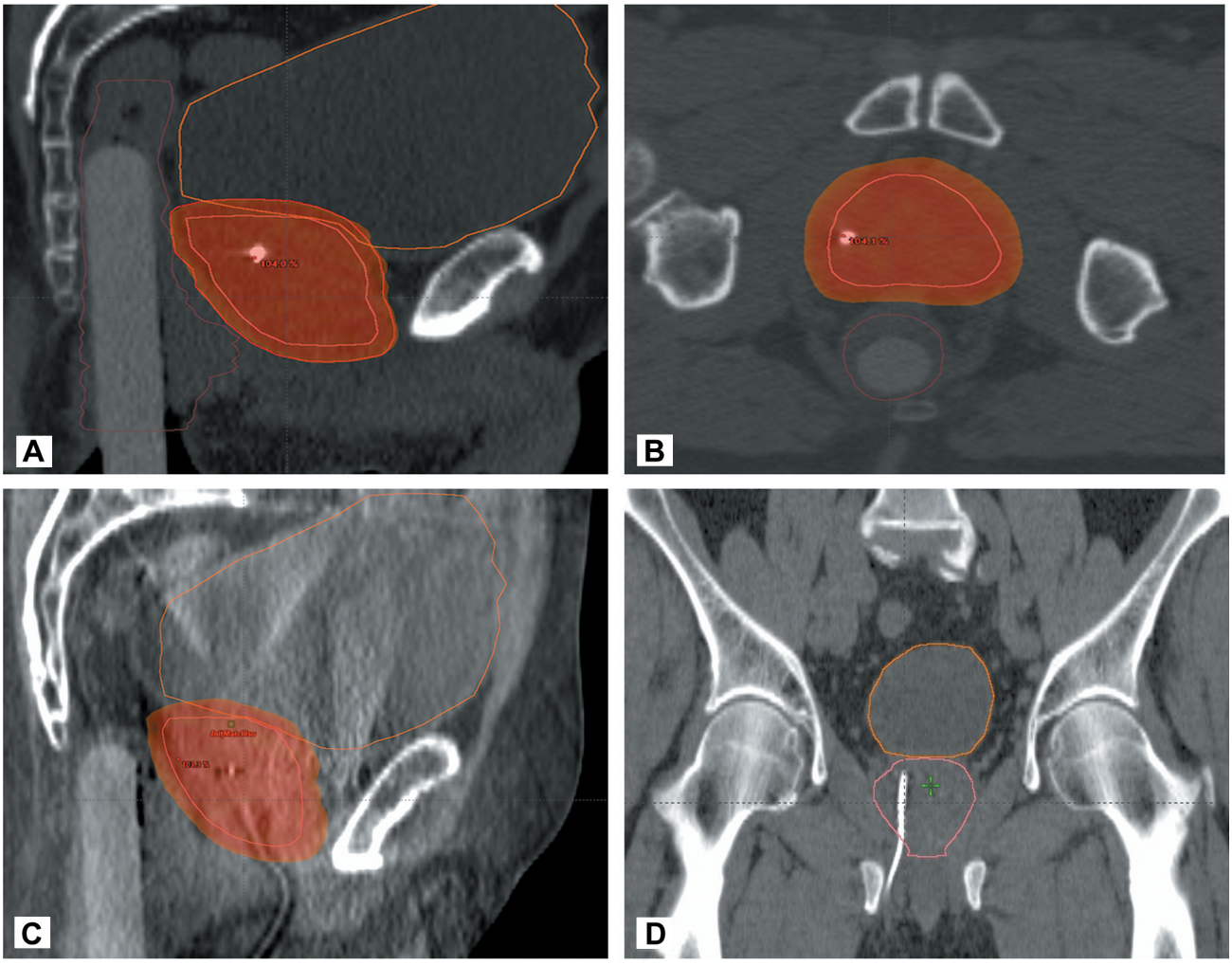

Figure 1. *Planning computed tomography for Rectafix placement in the sagittal (A) and axial (B) planes and in the sagittal plane in cone-beam computed tomography before treatment delivery (C). Coronal plane of planning computed tomography for RayPilot location in the prostate (D). For this patient, RayPilot was implanted in the right globe of the prostate and can be seen in (C) and (D). The red-shaded area in A-C represents 95% of the radiation dose prescribed to the prostate.*

10 fractions. Treatment localization was performed with orthogonal kilovolt imaging of three fiducial markers of the prostate. Cone-beam CT imaging was used at each fraction when the rectal immobilization device was in use and in every other non-rectal rod fraction to evaluate the filling status of the rectum and bladder. Intrafractional movement was tracked using the RayPilot (Micropos Medical, Gothenburg, Sweden) tracking system. A wired transmitter was implanted transperineally to the prostate using ultrasound guidance for 15 patients in the 78/2 Gy group and 13 patients in the 60/3 Gy group. Implantation was performed in a separate session from the insertion of fiducial markers because the transmitter would have caused artefacts in planning MRI due to its ferromagnetic core. After the last fraction, the transmitter was removed. The same patients had Rectafix and RayPilot as part of their treatment, and we referred to them as the RF group (Figure 1).

RectaI immobilization and intrafractional movement tracking were not used in the SBRT treatment arm due to the interim analysis results based on treatment arms 78/2 Gy and 60/3 Gy. Intrafractional movement was increased with the use of a rectal rod compared to fractions with a normal setup (29). In the RayPilot system, instability issues occurred, and it was not better than kilovolt imaging with fiducial markers in the intrafractional localization of the prostate (30).

Statistical analysis. Fisher's exact test was used to compare treatment groups. Missing values were not included in categorical analyses. Changes in continuous variables between time points were studied using the Wilcoxon signed-rank test. In the analyses of questionnaires, the missing values were replaced with the mean value of other answers of patients when 20% or less of the answers were missing. There were only a few replaced values in every treatment group. The Mann-Whitney two-independent samples test was used to compare two treatment groups independently. Changes inside the treatment group between different time points were

Table I. *Baseline patient demographics in different radiation therapy groups and in patients treated with Rectafix (RF) within the treatment groups.*

	Radiation therapy group							
	78/2 Gy			60/3 Gy			36.25/7.25 Gy	Overall
	All (n=21)	RF (n=16)	Non-RF (n=57)	All (n=21)	RF (n=14)	Non-RF (n=7)	All (n=31)	(n=73)
Age, years								
Median (range)	68 (59-78)	68 (59-78)	67 (63-73)	69 (60-78)	69 (60-78)	73 (63-74)	70 (63-78)	69 (59-78)
Gleason score, n (%)								
3+3	7 (33)	5	2	8 (38)	5	3	6 (19)	21 (29)
3+4	13 (62)	10	3	13 (62)	9	4	23 (74)	49 (67)
4+3	1 (5)	1	0	0 (0)	0	0	2 (7)	3 (4)
T-Stage, n (%)								
T1c	2 (10)	1	1	3 (14)	2	1	6 (19)	11 (15)
T2a	5 (24)	4	1	4 (19)	2	2	9 (29)	18 (25)
T2b	3 (14)	2	1	3 (14)	2	1	3 (10)	9 (12)
T2c	11 (52)	9	2	11 (52)	8	3	13 (42)	35 (48)
PSA baseline, ng/ml	10.3	9.3	12.7	7.4	7.6	6.8	9.4	9.2
Median (range)	(4.0-15.2)	(4.0-15.2)	(10.3-15.2)	(3.4-18.4)	(3.4-18.4)	(5.1-13.2)	(3.2-19.1)	(3.2-19.1)
Prostate volume, cm^3	50.5	47.0	52.0	37.0	37.0	38.5	35.0	40.0
Median (range)	(24.0-111.0)	(24.0-92.0)	(45.0-111.0)	(23.0-80.0)	(23.0-80.0)	(30.0-47.6)	(20.0-79.0)	(20.0-111.0
BMI kg/m^2	26.2	25.4	27.2	26.2	28.6	25.4	26.0	26.1
Median (range)	(21.4-40.4)	(21.9-29.3)	(21.4-40.4)	(22.4-34.8)	(22.4-34.8)	(25.0-26.2)	(21.8-40.6)	(21.4-40.6)
≥30 kg/m^2, n (%)	6 (29)	6	0	5 (24)	5	0	8 (26)	19 (26)
Comorbidities, n (%)								
Diabetes type II	4 (19)	3	1	6 (29)	6	0	7 (23)	17 (23)
Hypertension	11 (52)	8	3	10 (48)	6	4	23 (74)	44 (60)
ASO	4 (19)	3	1	3 (14)	2	1	4 (13)	11 (15)
AF	3 (14)	3	0	3 (14)	3	0	2 (7)	8 (11)
PH	6 (29)	4	2	2 (10)	2	0	13 (42)	21 (29)

AF: Atrial fibrillation; ASO: atherosclerosis; BMI: body mass index; PH: prostate hyperplasia; PSA: prostate-specific antigen. All patients in the 36.25/7.25 Gy group were treated without RF.

analysed using Wilcoxon signed-rank test. IBM SPSS Statistics version 25.0 for Windows (IBM, Armonk, NY, USA) was used for statistical analyses. All tests used a two-sided value of $p<0.05$ for statistical significance.

Results

The median age of the patients was 69 years (range=59-78 years) (Table I). The most common Gleason score was 3+4, with 67% of patients. The median baseline PSA was 9.2 ng/ml (range=3.2-19.1 ng/ml) for the whole study group. The median prostate volume was 40.0 cm3 (range=20.0-111.0 cm3). Comorbidities were common, and 26% of patients were obese.

GU symptoms. At baseline, there were no significant differences in GU symptoms between groups. On the IPSS score, severe symptoms were present in only one patient per treatment group (Table II). At the end of RT, severe symptoms increased in all groups, and statistically significant differences between groups were observed in the IPSS symptom score ($p=0.011$). In the 78/2 Gy and 60/3 Gy treatment groups, seven (33%) patients had severe symptoms at the end of RT. Severe symptoms were present in three (12%) patients in the 36.25/7.25 Gy at the end of RT and in one patient (4%) 1 month after RT. The median IPSS at baseline was 6.0 [interquartile range (IQR)=3.0-11.5)] and 7.0 (IQR=3.25-11.75) in the 78/2 Gy and 36.25/7.25 Gy groups, respectively. At the end of RT, GU symptoms were worse, with median scores of 17.0 (IQR=11.0-24.0) and 10.0 (IQR=4.75-14.75), respectively. In the 60/3 Gy group, the change in score was from 6.0 (IQR=3.5-10) to 13.0 (IQR=7.5-21.5). At the end of RT in the 78/2 Gy and 36.25/7.25 Gy groups, the difference in IPSS was statistically significant ($p=0.005$).

At the end of RT, urinary-related toxicity by CTCAE v4 was reported, as shown in Table III. In general, toxicities were mild (grade 1 to 2), haematuria was uncommon, and there was one physical activity-induced grade 2 haematuria in the 36.25/7.25 Gy group at 1 month after treatment. However, this patient used warfarin medication. One grade 3 urinary infection that needed hospitalization occurred in the 60/3 Gy group; this patient belonged in the RF group.

With our patients, Radiation Therapy Oncology Group grade 2 or worse acute GU toxicities were found in 48%, 38% and

Table II. *Frequencies of International Prostate Symptom Score (IPSS) grades at baseline, at the end of radiation therapy and after three months of follow-up for the different radiation therapy groups and in patients treated with Rectafix (RF) within the treatment groups.*

	Radiation therapy group, n (%)										
	78/2 Gy (n=21)			60/3 Gy (n=21)			36.25/7.25 Gy (n=31)		*p*-Value between groups	RF (n=30)	Non-RF (n=43)	*p*-Value between RF groups
	All	RF	Non-RF	All	RF	Non-RF	All					
Baseline, n (%)									0.978[a]			0.915[a]
Grade 1	13 (62)	10	3	13 (62)	9	4	16 (57)			19 (63)	23 (54)	
Grade 2	7 (33)	5	2	7 (33)	5	2	11 (39)			10 (33)	15 (35)	
Grade 3	1 (5)	1	0	1 (5)	0	1	1 (4)			1 (3)	2 (5)	
Missing data	0			0			3			0	3	
End of RT, n (%)								1 Month	**0.011[a]**			0.119[a]
Grade 1	0 (0)	0	0	5 (24)	3	2	9 (38)	8 (35)		3 (10)	11 (26)	
Grade 2	14 (67)	12	2	9 (43)	7	2	12 (50)	14 (61)		19 (63)	16 (37)	
Grade 3	7 (33)	4	3	7 (33)	4	3	3 (12)	1 (4)		8 (27)	9 (21)	
Missing data	0			0			7	8		0	7	
3 Months after RT, n (%)									0.574[a]			0.219[a]
Grade 1	14 (67)	12	2	12 (57)	8	4	18 (60)			20 (67)	24 (56)	
Grade 2	6 (29)	3	3	9 (43)	6	3	12 (40)			9 (30)	18 (42)	
Grade 3	1 (5)	1	0	0 (0)	0	0	0 (0)			1 (3)	0	
Missing data	0			0			1			0	1	
p-Value for change												
Baseline to end of RT	**<0.001[b]**			**<0.001[b]**			**0.003[b]**			**<0.001[b]**	**<0.001[b]**	
Baseline to 3 months	0.987[b]			0.792[b]			0.266[b]			0.637[b]	0.517[b]	

The 36.25/7.25 Gy radiation therapy group had IPSS questionnaire at the end of radiation therapy and 1 month after radiation therapy. All patients in the 36.25/7.25 Gy group were treated without RF. [a]Fisher's exact test. [b]Wilcoxon signed-rank test. Statistically significant *p*-values are shown in bold.

19% in the 78/2 Gy, 60/3 Gy and 36.25/7.25 Gy groups, respectively. One month after RT, GU toxicity increased in the 36.25/7.25 Gy group, and one patient had grade 3 toxicity. Three months after treatment, only one to two patients in each group had grade 2 or more toxicities (Table IV).

Three months after RT, there were no differences between groups or within groups in IPSS compared to baseline (Table II), or LENT-SOMA GU domain score (Table V). One patient in the 78/2 Gy group still had severe symptoms as measured by IPSS. The medians of total IPSS were 6.0 (IQR=3.0-9.5), 7.0 (IQR=3.0-10.5) and 6.5 (IQR=2.75-10.0) for the 78/2 Gy, 60/3 Gy and 36.25/7.25 Gy groups, respectively. The LENT-SOMA symptom about a reduced stream of urine was significantly improved towards better urinary flow in the 60/3 Gy and 36.25/7.25 Gy groups (p=0.036 and p=0.040, respectively) when compared to baseline values (Table V).

Rectafix did not have any effect on urinary symptoms at the end of RT or at the three-month follow-up. In Table VI, all Rectafix results are summarized, and the non-RF group results without SBRT are also presented.

GI symptoms. At baseline, the 78/2 Gy group already had more bowel symptoms than the other groups. The median LENT-SOMA GI domain was 3.0 (IQR=1.25-4) for the 78/2 Gy group and 1.0 for the 60/3 Gy group (IQR=1.0-3.0) and 2.0 (IQR=1.0-3.0) for the 36.25/7.25 Gy. The difference between the 78/2 Gy and 36.25/7.25 Gy groups was statistically significant (p=0.034).

During RT, five (24%) patients in the 78/2 Gy group, three (14%) in the 60/3 Gy group and three (10%) in the 36.25/7.25 Gy had rectal haemorrhage grade 1 assessed with the CTCAE v4 (Table IV). All eight patients with rectal haemorrhage in the 78/2 Gy and 60/3 Gy groups were treated using Rectafix. Rectal discomfort (proctitis grade 1) was common during RT in all groups.

Grade 2 or worse acute Radiation Therapy Oncology Group GI toxicities were recorded in 15%, 14% and 10% of patients in the 78/2 Gy, 60/3 Gy and 36.25/7.25 Gy groups, respectively. Three months after treatment, grade 2 or worse toxicity was rare. Only two patients in the 60/3 Gy group had grade 2 toxicity (Table III).

With the LENT-SOMA GI domain score, there were no differences between groups at 3 months after treatment. Significant changes in the LENT-SOMA GI domain score were not reported in the RT groups when compared between baseline and 3 months after RT. On a question regarding bowel frequency, the median increased in the 78/2 Gy group from 1.0 (IQR=1.0-2.0) time per day to 1.8 (IQR=1.0-2.8) times per day (p=0.036).

Table III. *Toxicity evaluated with Common Terminology Criteria for Adverse Effects (CTCAE) at baseline and at the end of radiotherapy (RT) in different radiation therapy groups and in patients treated with Rectafix (RF) within the treatment groups. CTCAE evaluation was performed in the 36.25/7.25 Gy group at 1 month after RT.*

	Radiation therapy groups and toxicity grade, n (%)														
	78/2 Gy (n=21)			60/3 Gy (n=21)			36.25/7.25 Gy (n=31)			RF (n=30)			Non-RF (n=43)		
	Grade			Grade			Grade			Grade			Grade		
	0	1	2	0	1	2	0	1	2	0	1	2	0	1	2
Urinary frequency[a]															
Baseline	10 (48)	4 (19)	7 (33)	14 (67)	6 (29)	1 (5)	10 (32)	9 (29)	12 (39)	19 (63)	6 (20)	5 (17)	15 (35)	13 (30)	15 (35)
End of RT	4 (19)	17 (81)	0	2 (10)	5 (24)	14 (67)	0	1 (3)	30 (97)	1 (3)	8 (27)	21 (70)	1 (2)	2 (5)	40 (93)
1 Month							27 (87)	3 (10)	1 (3)						
Urinary incontinence															
Baseline	19 (91)	2 (10)	0	19 (91)	1 (5)	1 (5)	25 (81)	6 (19)	0	28 (93)	2 (7)	0	35 (81)	7 (16)	1 (2)
End of RT	13 (62)	6 (29)	2 (10)	17 (81)	3 (14)	1 (5)	24 (77)	7 (23)	0	25 (83)	4 (13)	1 (3)	29 (67)	12 (28)	2 (5)
1 Month							27 (87)	3 (10)	1 (3)						
Dysuria (painful urination)															
Baseline	21 (100)	0	0	21 (100)	0	0	29 (94)	2 (7)	0	30 (100)	0	0	28 (93)	2 (7)	0
End of RT	12 (57)	8 (38)	1 (5)	8 (38)	9 (43)	4 (19)	14 (45)	15 (48)	2 (7)	17 (57)	9 (30)	4 (13)	17 (40)	23 (54)	3 (7)
1 Month							18 (58)	11 (36)	2 (7)						
Bladder spasms															
Baseline	18 (86)	3 (14)	0	18 (86)	2 (10)	1 (5)	26 (84)	5 (16)	0	28 (93)	2 (7)	0	34 (79)	8 (19)	1 (2)
End of RT	11 (52)	10 (48)	0	15 (71)	6 (29)	0	24 (77)	7 (27)	0	21 (70)	9 (30)	0	29 (67)	14 (33)	0
1 Month							29 (94)	2 (7)	0						
Urinary retention															
Baseline	15 (71)	6 (29)	0	16 (76)	5 (24)	0	21 (68)	10 (32)	0	22 (73)	8 (27)	0	30 (70)	13 (30)	0
End of RT	14 (67)	7 (33)	0	11 (52)	10 (48)	0	12 (39)	19 (61)	0	21 (70)	9 (30)	0	16 (37)	27 (63)	0
1 Month							18 (58)	12 (39)	1 (3)						
Haematuria															
Baseline	21 (100)	0	0	21 (100)	0	0	31 (100)	0	0	30 (100)	0	0	43 (100)	0	0
End of RT	21 (100)	0	0	21 (100)	0	0	31 (100)	0	0	30 (100)	0	0	43 (100)	0	0
1 Month							30 (97)	0	1 (3)						
Urinary infection															
Baseline	21 (100)	0	0	21 (100)	0	0	31 (100)	0	0	30 (100)	0	0	43 (100)	0	0
End of RT	19 (91)	0	2 (10)	20 (95)	0	0	31 (100)	0	0	27 (90)	0	2 (7)	43 (100)	0	0
1 Month							31 (100)	0	0						
Prostatic pain (due to RT)															
Baseline	21 (100)	0	0	21 (100)	0	0	31 (100)	0	0	30 (100)	0	0	43 (100)	0	0
End of RT	18 (86)	3 (14)	0	19 (91)	2 (10)	0	25 (81)	6 (19)	0	28 (93)	2 (7)	0	34 (79)	9 (21)	0
1 Month							29 (94)	2 (7)	0						
Proctitis (during RT)															
Baseline	20 (95)	1 (5)	0	21 (100)	0	0	31 (100)	0	0	30 (100)	0	0	42 (98)	1 (2)	0
End of RT	10 (48)	10 (48)	1 (5)	6 (29)	15 (71)	0	14 (45)	16 (52)	1 (3)	13 (43)	16 (53)	1 (3)	17 (40)	25 (58)	1 (2)
1 Month							24 (77)	7 (23)	0						
Rectal/anal pain															
Baseline	21 (100)	0	0	20 (95)	1 (5)	0	31 (100)	0	0	30 (100)	0	0	41 (95)	2 (5)	0
End of RT	18 (86)	3 (14)	0	17 (81)	3 (14)	1 (5)	28 (90)	3 (10)	0	27 (90)	3 (10)	0	27 (90)	6 (14)	1 (2)
1 Month							31 (100)	0	0						
Rectal haemorrhage/ haematochezia															
Baseline	20 (95)	1 (5)	0	21 (100)	0	0	31 (100)	0	0	29 (97)	1 (3)	0	43 (100)	0	0
End of RT	16 (76)	5 (24)	0	18 (86)	3 (14)	0	28 (90)	3 (10)	0	23 (77)	7 (23)	0	39 (91)	4 (9)	0
1 Month							30 (97)	1 (3)	0						

No grade 4 or 5 toxicities were reported. One grade 3 finding was reported: urinary infection at the end of RT in the RF group (60/3 Gy). The RF group consisted of 16 patients from the 78/2 Gy group and 14 patients from the 60/3 Gy group. All patients in the 36.25/7.25 Gy group were treated without RF. Use of tamsulosine hydrochloride was part of the treatment protocol in the 36.25/7.25 Gy group and it was in use at the end of RT. Use of tamsulosine hydrochloride medication was marked to grade 2 to urinary frequency due to CTCAE.

Table IV. *Acute toxicity in the radiation therapy (RT) groups evaluated with Radiation Therapy Oncology Group scale.*

		Radiation therapy group and timepoint, n (%)						
		78/2 Gy (n=21)		60/3 Gy (n=21)		36.25/7.25 Gy (n=31)		
		End of RT[a]	3 Months[c]	End of RT[a]	3 Months[c]	End of RT[a]	1 Month[b]	3 Months[c]
GU	None	1 (5)	11 (52)	2 (10)	14 (67)	7 (23)	10 (71)	20 (65)
	Grade 1	10 (48)	8 (38)	11 (52)	5 (24)	18 (58)	11 (36)	10 (32)
	Grade 2	10 (48)	2 (10)	8 (38)	2 (10)	6 (19)	9 (29)	1 (3)
	Grade 3	0	0	0	0	0	1 (3)	0
GI	None	8 (38)	15 (71)	6 (29)	13 (62)	17 (55)	22 (71)	26 (84)
	Grade 1	10 (48)	6 (29)	12 (57)	6 (29)	11 (36)	8 (26)	5 (16)
	Grade 2	2 (10)	0	3 (14)	2 (10)	3 (10)	1 (3)	0
	Grade 3	1 (5)	0	0	0	0	0	0

No Grade 4 or 5 toxicities were reported. [a]Worst grade during RT; [b]worst grade during 1 month after RT (only in the 36.25/7.25 Gy group); [c]worst grade during 3 months after RT in the 78/2 Gy and 60/3 Gy groups and during 1 to 3 months in the 36.25/7.25 Gy group.

Sexual wellbeing. Groups differed at baseline on the IIEF-5 score (p=0.025) related to sexual wellbeing (Table VII). Only one patient (5%) in the 60/3 Gy group had moderate to severe erectile dysfunction (grade 3). However, in the 78/2 Gy and 36.25/7.25 Gy groups, this was a common finding, with 9 (43%) and 12 (41%) patients, respectively. At the end of RT, there were no significant differences between the groups in IIEF-5 scores. When compared to baseline, erectile function worsened in the 78/2 Gy and 60/3 Gy groups but not in the 36.25/7.25 Gy group (p=0.009, p=0.023 and p=0.501, respectively). The same tendency was also observed at 3 months after the treatment (p=0.015, p=0.018 and p=0.326, respectively). In IIEF-5, the median change in the groups between baseline and 3 months were: 78/2 Gy group, from 14.0 (IQR=8.5-19.0) to 6.0 (IQR=2.3-19.5); group 60/3 Gy, from 19.0 (IQR=15.5-22.5) to 16.5 (IQR=10.8-22.0); and group 36.25/7.25 Gy, from 16.0 (IQR=4.0-20.5) to 11.0 (IQR=2.0-19.0), all towards worse sexual function. For the 60/3 Gy group, this score was statistically better than that for the 78/2 Gy group at the 3-month timepoint (p=0.025), and the median change was smallest for the 60/3 Gy group between baseline and 3 months.

The LENT-SOMA questionnaire had one question about interest in intercourse; when comparing baseline to 3 months after RT, the 60/3 Gy group of patients reported more loss of interest (p=0.027) than the 78/2 Gy (p=0.068) and 36.25/7.25 Gy groups (p=0.555) (Table V).

Rectafix did not have any effect on the IIEF-5 score at any timepoint. In the LENT-SOMA question, the RF group had more loss of interest in intercourse at 3 months after RT (p=0.016).

Discussion

General aspects. Our results show that all the RT treatment schedules studied were well tolerated. No severe acute toxicity was reported at 3 months after RT in any treatment group. However, in the standard treatment group (78/2 Gy), acute GI toxicities and erectile dysfunctions were more common. We used modern treatment techniques, including immobilization devices and Rectafix, which did not worsen GU symptoms or sexual functioning (Table VI). To the best of our knowledge, this is a novel finding during era of hypofractionated RT for prostate cancer.

A randomized trial comparing conventionally fractionated to moderately hypofractionated RT showed increased acute toxicity from hypofractionation (31). Dearnaley *et al*. reported more grade 2 or worse GU toxicity and GI toxicity with hypofractionation at the end of RT compared to conventionally fractionated RT (32). Catton *et al*. randomized patients to similar treatment arms as we used in this study (78/2 Gy or 60/3 Gy), and they reposted more grade 2 or worse GU and GI acute toxicities with 60/3 Gy during the first 14 weeks after the start of RT (7). A Scandinavian noninferiority phase III trial (HYPO-RT-PC) randomized patients to conventionally fractionated treatment (78/2 Gy) or to ultra-hypofractionated treatment (42.7/6.1 Gy), and the study showed increased acute toxicity in the ultra-hypofractionated arm (33). On the other hand, an international randomized phase III noninferiority trial, PACE-B, compared conventionally fractionated 78/2 Gy or moderately hypofractionated 62/3.1 Gy RT to 36.25/7.25 Gy SBRT. In contrast to the three aforementioned trials, PACE-B reported that acute GI and GU toxicities did not increase with SBRT treatment (34). Valeriani *et al*. evaluated outcomes in patients treated with 60/3 Gy with and without image-guidance. During the treatment, grade 1-2 GU toxicity occurred in 45.1%, grade 3 GU toxicity in 1.1% and grade 1-2 GI toxicity in 29.1% of patients. In their study, acute GI toxicity was lower in patients treated with image-guided RT with 5 mm isometric margin as in our study. Grade 2 or worse GU or GI toxicity were rare at 2 months after RT (35). The

Table V. *Median scores for LENT-SOMA questions at baseline (BL) and at 3 months of follow-up in different radiation therapy groups and in patients treated with Rectafix (RF) within the groups. Changes between timepoints were analysed using the Wilcoxon signed-rank test.*

	Radiation therapy group														
	78/2 Gy (n=21)			60/3 Gy (n=21)			36.25/7.25 Gy (n=31)			RF (n=30)			Non-RF (n=43)		
	BL	3 Months	*p*-Value	BL	3 Months	*p*-Value	BL	3 Months	*p*-Value	BL	3 Months	*p*-Value	BL	3 Months	*p*-Value
Genitourinary															
1. Painful urination	0	0	0.531	0	0	0.750	0	0	0.750	0	0	0.750	0	0	0.807
2. Frequency (between x h)	4.0	3.0	0.813	4.0	3.8	0.077	3.0	3.3	0.404	4.0	4.0	0.507	3.5	3.0	0.370
3. Blood in urine	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99
4. Incontinence	0	0	>0.99	0	0	0.531	0	0	0.500	0	0	0.500	0	0	0.938
5. Usage of pads	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99
6. Decreased stream of urine	2	1	0.232	2	1	**0.036**	2	1	**0.040**	2	1	**0.019**	2	1	**0.045**
Domain score (Q 1, 3-6)[a]	2	1	0.698	2	2	0.412	2	1	0.156	2	1	0.346	2	1	0.061
Gastrointestinal															
7. Urgency of bowel movement	0	0	0.809	0	0	>0.99	0	0	0.594	0	0	0.914	0	0	0.628
8. Mucus on faeces	0	0	0.063	0	0	>0.99	0	0	0.359	0	0	0.563	0	0	0.148
9. Quality of faeces	1	1	0.250	1	1	>0.99	1	1	0.813	1	1	0.531	1	1	0.492
10. Frequency (times/day)	1.0	1.8	**0.036**	1.0	1.0	0.656	1.3	1.0	>0.99	1.0	1.0	0.675	1.0	1.0	0.076
11. Incontinence	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99
12. Usage of pads	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99	0	0	>0.99
13. Pain on passing a motion	0	0	0.625	0	0	0.500	0	0	>0.99	0	0	>0.99	0	0	>0.99
14. Blood in faeces or in anus	0	0	>0.99	0	0	0.250	0	0	>0.99	0	0	0.219	0	0	>0.99
15. Anal irritation	0	0	0.555	0	0	>0.99	0	0	0.109	0	0	>0.99	0	0	0.143
Domain score (Q 7-9, 11-15)[a]	3	2.5	0.988	1	2	>0.99	2	2	0.435	2	2	0.864	2	2	0.692
Sexual															
16. Interest in intercourse[b]	2	3	0.068	2	2	**0.027**	2	2	0.555	2	2	**0.016**	2	2	**0.016**

All patients in the 36.25/7.25 Gy group were treated without RF. [a]Domain score is the sum of scores for answers. [b]Excluded for not answering/missing data: At baseline: 0, 1 and 6 patients, and at 3 months 1, 2 and 7 patients of the 78/2 Gy, 60/3 Gy and 36.25/7.25 Gy groups, respectively. Statistically significant *p*-values are shown in bold.

trial toxicities are compared in Table VIII. Our findings were in line with PACE-B results. In our patients, grade >2 acute GU and GI toxicity was lowest in the ultra-hypofractionated 36.25/7.25 Gy group at the end of RT. One month after RT, acute GU toxicity increased in the 36.25/7.25 Gy group to the same level as in the other groups at the end of RT. This phenomenon, called delayed toxicity, is typical of SBRT. Three months after RT, grade 2 or worse toxicities were rare. Thus, our findings are comparable to modern published studies and demonstrate low acute toxicity of ultra-hypofractionated treatment. The modern immobilization device, Rectafix, was used in our groups treated with 78/2 Gy and 60/3 Gy, and it might have had an effect on acute GI toxicities in those groups. All of these treatment schedules demonstrated good outcomes for disease control and long-term toxicity.

GU symptoms. At the end of RT, the 'ultra-fractionated' 36.25/7.25 Gy group had the best patient reported quality of life. Mild symptoms reflected in IPSS score were present at baseline in 38% and at 1 month in 35% of patients. None of the patients of the 78/2 Gy groups and 24% of the 60/3 Gy group reported mild symptoms. The use of Rectafix did not have any adverse effects on GU symptoms at the end of RT. To our knowledge, there are no previously published quality of life reports regarding Rectafix and GU toxicity. The most intensive radiation-related urinary symptoms were reported in the stereotactic group; one patient had marked maximum 10 of the Visual Analog Score for pain due to urinary symptoms, and another had haematuria. These findings are in line with earlier reported publications of acute toxicity during SBRT treatment (36). Patients in the conventionally fractionated group seemed to have the lowest quality of life when taking into account urinary symptoms. Possible reasons for this might be treatment fatigue due to the long, 8-week treatment period or relatively large prostates in this treatment group. Our reported acute GU toxicity profiles for RT groups are similar to reported studies comparing hypofractionated RT and conventional fractionation.

GI symptoms. To our knowledge, there are no previous studies reporting quality of life with the Rectafix bowel immobilization

Table VI. *Summary of patient reported quality-of-life scores (median) for the Rectafix (RF) and control groups at baseline (BL), end of treatment and 3 months of follow-up. The non-RF group included five patients of the 78/2 Gy group, seven patients of the 60/3 Gy group and all 31 patients in the 36.25/7.25 Gy group. The non-RF CFR group included patients of the 78/2 Gy and 60/3 Gy groups. The RF group included 16 patients of the 78/2 Gy group and 14 patients of the 60/3 Gy group.*

	Radiation therapy group														
	Non-RF (n=43)					RF (n=30)					Non-RF Cfr (n=12)				
	BL	End	*p*-Value	3 Months	*p*-Value	BL	End	*p*-Value	3 Months	*p*-Value	BL	End	*p*-Value	3 Months	*p*-Value
IPSS	7.0	11.5	**<0.001**	7.0	0.517	6.0	14.5	**<0.001**	6.0	0.637	6.5	16.0	**<0.001**	7.5	0.713
IEFF-5	17.0	9.0	**0.040**	11.0	**0.008**	17.5	11.0	**0.008**	14.5	**0.028**	17.0	7.5	**0.021**	9.5	**0.011**
LENT-SOMA GU domain score[a]	2			1	0.061	2			1	0.346	2			2.5	0.734
LENT-SOMA GI domain score[b]	2			2	0.692	2			2	0.864	2			2	0.703
1. Painful urination	0			0	0.807	0			0	0.750	0			0	0.375
2. Frequency (between x h)	3.5			3.0	0.370	4.0*			4.0	0.507	3.0			3.0	0.105
3. Blood in urine	0			0	>0.99	0			0	>0.99	0			0	>0.99
4. Incontinence	0			0	0.938	0			0	0.500	0			0	0.750
5. Usage of pads	0			0	>0.99	0			0	>0.99	0			0	>0.99
6. Decreased stream of urine	2			1	**0.045**	2			1	**0.019**	2			1.5	0.531
7. Urgency of bowel movement	2			0	0.628	0			0	0.914	0			0.5	>0.99
8. Mucus on faeces	0			0	0.148	0			0	0.563	0			0	0.500
9. Quality of faeces	0			1	0.492	1			1	0.531	1			1	>0.99
10. Frequency (times/day)	1.0			1.0	0.076	1.0			1.0	0.675	1.0			1.3	**0.031**
11. Incontinence	0			0	>0.99	0			0	>0.99	0			0	>0.99
12. Usage of pads	0			0	>0.99	0			0	>0.99	0			0	>0.99
13. Pain on passing a motion	0			0	>0.99	0			0	>0.99	0			0	>0.99
14. Blood in faeces or in anus	0			0	>0.99	0			0	0.219	0			0	>0.99
15. Anal irritation	0			0	0.143	0			0	>0.99	0			0	>0.99
16. Interest in intercourse[c]	2			2	**0.016**	2			2	**0.016**	2			2.5	0.188

Cfr: Conventional fractionation; GI: gastrointestinal; GU: genitourinary; IIEF-5: International Index of Erectile Function; IPSS: International Prostate Symptom Score. [a]Included questions 1 and 3-6. [b]Included questions 7-9 and 11-15. [c]Excluded for not answering/missing data: At baseline: 0, 1 and 6 patients, and at 3 months 1, 2 and 7 patients of the 78/2 Gy, 60/3 Gy and 36.25/7.25 Gy groups, respectively. Changes between timepoints were analysed using the Wilcoxon signed-rank test; Differences between radiation therapy groups were tested using the Mann–Whitney two independent samples test. Statistically significant *p*-values are shown in bold. *Significantly different at 0.048 from non-RF group at baseline.

system. The PROMETHEUS study aimed for a non-surgical SBRT prostate boost with using rectal displacement devices, such as Rectafix. They assessed toxicity with CTCAE v4 and reported discomfort with Rectafix, which was moderate in 35% and severe in 14% of men (37). Patient reported quality of life data have not yet been published.

In this study, patients treated with Rectafix had more frequent rectal haemorrhages, which worsened their quality of life at the end of RT. Rectafix was used as a part of 78/2 Gy treatment in 15 fractions and 60/3 Gy in 10 fractions. It was originally designed to be used as a part of SBRT treatment. In our study, it increased intrafractional movement, which is why patients belonging to the 36.25/7.25 Gy group were treated without it. In addition, 3 months after treatment, the use of Rectafix did not have a protective effect on our patients' bowel symptoms.

At the end of RT, 60/3 Gy had a worsened quality of life due to GI symptoms. Physicians reported more proctitis and prostatic pain in this group (36.25/7.25 Gy) than in the other groups but that difference was not seen in the quality of life results. CHHiP (6) and PROFIT (7) studies reported significantly higher proportions of acute GI toxicity with hypofractionation when compared to conventional fractionation ($p<0.001$ and $p=0.003$, respectively), which were expected findings when treating with hypofractionation. The HYPO-RT-PC study had similar findings, with more patients and doctors reporting acute toxicity in the SBRT group (33). In our study, no differences were found in this respect between the groups three months after RT (Table VIII).

Sexual wellbeing. The overall prevalence of erectile dysfunction (grade 2-3) was reported at 80% of patients before treatments and 79% at the 3-month follow-up. This rate was almost the same as that in a population-based sample of 50- to 75-year-old Finnish men, where the overall prevalence of erectile dysfunction was 76.5% (38). Severe erectile dysfunction was found in 21% of our men at the beginning and in 41% at 3 months after treatment. Severe problems with sex life occurred

Table VII. *Frequencies of International Index of Erectile Function (IIEF-5) symptom grades at baseline, at the end of radiation therapy (RT) and after three months of follow-up between the radiation therapy groups and in patients treated with Rectafix (RF) within the groups.*

	Radiation therapy group										
	78/2 Gy (n=21)			60/3 Gy (n=21)			36.25/7.25 Gy (n=31)		*p*-Value[a] Between groups	RF (n=30)	Non-RF (n=43)	*p*-Value[a] RF *vs.* non-RF
	All	RF	Non-RF	All	RF	Non-RF	All					
Baseline, n (%)									**0.025**			0.734
None	3 (14)	3	0	6 (29)	4	2	5 (17)			7 (23)	7 (16)	
Mild and mild to moderate	9 (43)	6	3	14 (67)	9	5	12 (41)			15 (50)	20 (47)	
Moderate to severe	9 (43)	7	2	1 (5)	1	0	12 (41)			8 (27)	14 (33)	
Missing data	0			0			2			0	2	
End of RT, n (%)							End of RT	1 Month	0.439			0.530
None	2 (10)	2	0	6 (29)	5	1	4 (15)	2 (9)		7 (23)	5 (12)	
Mild and mild to moderate	4 (20)	4	0	6 (29)	3	3	8 (31)	8 (35)		7 (23)	11 (27)	
Moderate to severe	14 (70)	9	5	9 (43)	6	3	14 (54)	13 (57)		15 (50)	22 (51)	
Missing data	1	1		0			5	8		1	5	
3 Months, n (%)									0.150			0.425
None	3 (15)	3	0	6 (30)	5	1	5 (18)			8 (27)	6 (14)	
Mild and mild to moderate	4 (20)	4	0	9 (45)	4	5	9 (32)			8 (27)	14 (33)	
Moderate to severe	13 (65)	8	5	5 (25)	4	1	14 (50)			12 (40)	20 (47)	
Missing data	1	1		1	1		3			2	3	
p-Value for change[b]												
Baseline to END of RT	**0.009**			**0.023**			0.501			**0.008**	**0.040**	
Baseline to 3 months	**0.015**			**0.018**			0.326			**0.028**	**0.008**	

The 36.25/7.25 Gy group completed the IIEF-5 questionnaire at the end of RT and 1 month after RT. All patients in the 36.25/7.25 Gy group were treated without RF. Symptom scores for erectile dysfunction: Grade 1, none; Grade 2, mild and mild to moderate; Grade 3, moderate to severe. [a]Fisher's exact test. [b]Wilcoxon signed-rank test. Statistically significant *p*-values are shown in bold.

Table VIII. *Comparison of acute toxicities of Radiation Therapy Oncology Group grade 2 or worse at the end of radiation therapy (RT) in selected studies.*

	Treatment schedule					
	Conventional		Hypofractionation		SBRT	
Study	GU	GI	GU	GI	GU	GI
TAYS (this study)	48%	15%	38%	14%	19-29%	10-3%
CHHiP (32)	46%	25%	49%	38%	-	-
PROFIT (7)	31%	11%	31%	17%	-	-
HYPO-RT-PC (33)	23%	9%	-	-	28%	6%
PACE-B (34)	27%	12%	27%	12%	23%	10%

GI: Gastrointestinal; GU: genitourinary; SBRT: stereotactic body radiotherapy. TAYS (data from this study): Conventional 78/2 Gy, n=21; hypofractionation 60/3 Gy, n=21; SBRT 36.25/7.25 Gy, n=31; SBRT toxicity reported at the end of and 1 month after RT. Conventional and hypofractionation groups had Rectafix as a part of the treatment schedule. CHHiP (32): Conventional 74/2 Gy, n=1065; hypofractionation 60/3 Gy, n=1074. PROFIT (7): Conventional 78/2 Gy, n=598; hypofractionation 60/3 Gy, n=608. HYPO-RT-PC (33): Conventional 78/2 Gy, n=602; SBRT 42.7/6.1 Gy, n=598. PACE-B (34): Conventional 78/2 Gy and hypofractionation 62/3.1 Gy, n=432; SBRT 36.25/7.25 Gy, n=415. Toxicities in conventional and hypofractionation was reported as a single group.

in 16% of men at baseline and 27% at 3 months. In the Nordic study HYPO-RT-PC, severe problems with sex life were observed in approximately 15-20% of patients at baseline and 20-25% at 3 months (39), which our findings are similar to.

In general, the hypofractionated groups seemed to perform better than the conventionally fractionated group. The effect of RT on sexual wellbeing was negative overall in all treatment groups, but the men in the 36.25/7.25 Gy group

seemed to have fewer changes than the men in other groups. In studies comparing SBRT to moderate hypofractionation or conventional fractionation, no differences in sexual function between treatments were reported at the three-month follow-up (33, 34). In addition, the use of Rectafix did not have any protective effects against erectile dysfunction.

Strengths and limitations. All our patients were treated with modern, image-guided RT with implanted fiducial markers. All questionnaires were internationally verified and validated in the Finnish language, and they surveyed a wide variety of different RT-related symptoms. In 98% of the treated patients, the same doctor (PR) made the RT contours in the CT-based planning system and verified the plans, and every patient had pretreatment MRIs. In approximately 90% of cases, the same doctor (PR) interviewed and examined the patients, making this study material highly coherent compared to multicentre and multinational trials. The limitation of this study is the small number of patients in different treatment arms and the nonrandomized setting. Additionally, the use of Rectafix was interrupted during the study, making the treatment arms somewhat imbalanced. On the other hand, this is one of the most comprehensive studies of Rectafix use in connection with radical RT for prostate cancer.

Conclusion

In this prospective single-centre study, patients treated with conventionally fractionated RT (78/2 Gy) experienced worse urinary and sexual function and more bowel symptoms than those in the hypofractionated treatment arms (60/3 Gy and 36.75/7.25 Gy). Continuing to treat with 78/2 Gy is no longer rational. In elderly populations, 36.25 Gy in five fractions seems to be a very convenient treatment option, with tolerable acute toxicity, especially for men with longer distances to travel to treatment centres. Treatment with 60/3 Gy is also an acceptable option for men who are worried about the slight risk of intense acute toxicity with SBRT. The use of Rectafix did not reduce acute toxicities in this study.

Conflicts of Interest

None to declare.

Authors' Contributions

Petri Reinikainen: Patient recruitment, treatment and follow-up, Implantations of RayPilot tracking devices, article writing. Mika Kapanen: Conceptualization, funding acquisition, article revision. Tiina Luukkaala: Statistical analyses, article revision. Pirkko-Liisa Kellokumpu-Lehtinen: Conceptualization, funding acquisition, article writing and revision.

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References

1 Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, Davis M, Peters TJ, Turner EL, Martin RM, Oxley J, Robinson M, Staffurth J, Walsh E, Bollina P, Catto J, Doble A, Doherty A, Gillatt D, Kockelbergh R, Kynaston H, Paul A, Powell P, Prescott S, Rosario DJ, Rowe E, Neal DE and ProtecT Study Group: 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. N Engl J Med *375(15)*: 1415-1424, 2016. PMID: 27626136. DOI: 10.1056/NEJMoa1606220

2 Robinson D, Garmo H, Lissbrant IF, Widmark A, Pettersson A, Gunnlaugsson A, Adolfsson J, Bratt O, Nilsson P and Stattin P: Prostate cancer death after radiotherapy or radical prostatectomy: a nationwide population-based observational study. Eur Urol *73(4)*: 502-511, 2018. PMID: 29254629. DOI: 10.1016/j.eururo.2017.11.039

3 Kalbasi A, Li J, Berman A, Swisher-McClure S, Smaldone M, Uzzo RG, Small DS, Mitra N and Bekelman JE: Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. JAMA Oncol *1(7)*: 897-906, 2015. PMID: 26181727. DOI: 10.1001/jamaoncol.2015.2316

4 Kuban DA, Tucker SL, Dong L, Starkschall G, Huang EH, Cheung MR, Lee AK and Pollack A: Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys *70(1)*: 67-74, 2008. PMID: 17765406. DOI: 10.1016/j.ijrobp.2007.06.054

5 Dasu A and Toma-Dasu I: Prostate alpha/beta revisited – an analysis of clinical results from 14 168 patients. Acta Oncol *51(8)*: 963-974, 2012. PMID: 22966812. DOI: 10.3109/0284186X.2012.719635

6 Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfield D, Graham J, Kirkbride P, Logue J, Malik Z, Money-Kyrle J, O'Sullivan JM, Panades M, Parker C, Patterson H, Scrase C, Staffurth J, Stockdale A, Tremlett J, Bidmead M, Mayles H, Naismith O, South C, Gao A, Cruickshank C, Hassan S, Pugh J, Griffin C, Hall E and CHHiP Investigators: Conventional *versus* hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol *17(8)*: 1047-1060, 2016. PMID: 27339115. DOI: 10.1016/S1470-2045(16)30102-4

7 Catton CN, Lukka H, Gu CS, Martin JM, Supiot S, Chung PWM, Bauman GS, Bahary JP, Ahmed S, Cheung P, Tai KH, Wu JS, Parliament MB, Tsakiridis T, Corbett TB, Tang C, Dayes IS, Warde P, Craig TK, Julian JA and Levine MN: Randomized trial of a hypofractionated radiation regimen for the treatment of localized prostate cancer. J Clin Oncol *35(17)*: 1884-1890, 2017. PMID: 28296582. DOI: 10.1200/JCO.2016.71.7397

8 Katz A: Stereotactic body radiotherapy for low-risk prostate cancer: a ten-year analysis. Cureus *9(9)*: e1668, 2017. PMID: 29152425. DOI: 10.7759/cureus.1668

9 Langen KM and Jones DT: Organ motion and its management. Int J Radiat Oncol Biol Phys *50(1)*: 265-278, 2001. PMID: 11316572. DOI: 10.1016/s0360-3016(01)01453-5

10 Tong X, Chen X, Li J, Xu Q, Lin MH, Chen L, Price RA and Ma CM: Intrafractional prostate motion during external beam radiotherapy monitored by a real-time target localization system. J Appl Clin Med Phys *16(2)*: 5013, 2015. PMID: 26103174. DOI: 10.1120/jacmp.v16i2.5013

11 Wang KK, Vapiwala N, Deville C, Plastaras JP, Scheuermann R, Lin H, Bar Ad V, Tochner Z and Both S: A study to quantify the effectiveness of daily endorectal balloon for prostate intrafraction motion management. Int J Radiat Oncol Biol Phys *83(3)*: 1055-1063, 2012. PMID: 22115790. DOI: 10.1016/j.ijrobp.2011.07.038

12 Patel RR, Orton N, Tomé WA, Chappell R and Ritter MA: Rectal dose sparing with a balloon catheter and ultrasound localization in conformal radiation therapy for prostate cancer. Radiother Oncol *67(3)*: 285-294, 2003. PMID: 12865176. DOI: 10.1016/s0167-8140(03)00056-2

13 Isacsson U, Nilsson K, Asplund S, Morhed E, Montelius A and Turesson I: A method to separate the rectum from the prostate during proton beam radiotherapy of prostate cancer patients. Acta Oncol *49(4)*: 500-505, 2010. PMID: 20397777. DOI: 10.3109/02841861003745535

14 Mohler JL, Kantoff PW, Armstrong AJ, Bahnson RR, Cohen M, D'Amico AV, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Kawachi MH, Kuettel M, Lee RJ, Macvicar GR, Malcolm AW, Miller D, Plimack ER, Pow-Sang JM, Richey S, Roach M 3rd, Rohren E, Rosenfeld S, Small EJ, Srinivas S, Stein C, Strope SA, Tward J, Walsh PC, Shead DA, Ho M and National comprehensive cancer network: Prostate cancer, version 1.2014. J Natl Compr Canc Netw *11(12)*: 1471-1479, 2013. PMID: 24335682. DOI: 10.6004/jnccn.2013.0174

15 Prediction Tools/Prostate Cancer Nomograms: Pre- Radical Prostatectomy. Memorial Sloan Kettering Cancer Center. Available at: https://www.mskcc.org/nomograms/prostate/pre_op [Last accessed on March 15, 2022]

16 Viswanathan AN, Yorke ED, Marks LB, Eifel PJ and Shipley WU: Radiation dose-volume effects of the urinary bladder. Int J Radiat Oncol Biol Phys *76(3 Suppl)*: S116-S122, 2010. PMID: 20171505. DOI: 10.1016/j.ijrobp.2009.02.090

17 Michalski JM, Gay H, Jackson A, Tucker SL and Deasy JO: Radiation dose-volume effects in radiation-induced rectal injury. Int J Radiat Oncol Biol Phys *76(3 Suppl)*: S123-S129, 2010. PMID: 20171506. DOI: 10.1016/j.ijrobp.2009.03.078

18 Benedict SH, Yenice KM, Followill D, Galvin JM, Hinson W, Kavanagh B, Keall P, Lovelock M, Meeks S, Papiez L, Purdie T, Sadagopan R, Schell MC, Salter B, Schlesinger DJ, Shiu AS, Solberg T, Song DY, Stieber V, Timmerman R, Tomé WA, Verellen D, Wang L and Yin FF: Stereotactic body radiation therapy: the report of AAPM Task Group 101. Med Phys *37(8)*: 4078-4101, 2010. PMID: 20879569. DOI: 10.1118/1.3438081

19 Grimm J, LaCouture T, Croce R, Yeo I, Zhu Y and Xue J: Dose tolerance limits and dose volume histogram evaluation for stereotactic body radiotherapy. J Appl Clin Med Phys *12(2)*: 3368, 2011. PMID: 21587185. DOI: 10.1120/jacmp.v12i2.3368

20 Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK and Cockett AT: The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol *148(5)*: 1549-57; discussion 1564, 1992. PMID: 1279218. DOI: 10.1016/s0022-5347(17)36966-5

21 Rosen RC, Cappelleri JC, Smith MD, Lipsky J and Peña BM: Development and evaluation of an abridged, 5-item version of the International Index of Erectile Function (IIEF-5) as a diagnostic tool for erectile dysfunction. Int J Impot Res *11(6)*: 319-326, 1999. PMID: 10637462. DOI: 10.1038/sj.ijir.3900472

22 Livsey JE, Routledge J, Burns M, Swindell R, Davidson SE, Cowan RA, Logue JP and Wylie JP: Scoring of treatment-related late effects in prostate cancer. Radiother Oncol *65(2)*: 109-121, 2002. PMID: 12443807. DOI: 10.1016/s0167-8140(02)00286-4

23 Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. National Cancer Institute, National Institutes of Health, US Department of Health and Human Services, Bethesda, MA, USA. NIH publication 09-7473, 2009.

24 Cox JD, Stetz J and Pajak TF: Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). Int J Radiat Oncol Biol Phys *31(5)*: 1341-1346, 1995. PMID: 7713792. DOI: 10.1016/0360-3016(95)00060-C

25 Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL and ISUP Grading Committee: The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. Am J Surg Pathol *29(9)*: 1228-1242, 2005. PMID: 16096414. DOI: 10.1097/01.pas.0000173646.99337.b1

26 Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A and Washington MK: AJCC Cancer Staging Atlas. New York, NY, Springer New York, 2012.

27 Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G, Rouviere O, Logager V, Fütterer JJ and European Society of Urogenital Radiology: ESUR prostate MR guidelines 2012. Eur Radiol *22(4)*: 746-757, 2012. PMID: 22322308. DOI: 10.1007/s00330-011-2377-y

28 Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, Zattoni F and European Association of Urology: EAU guidelines on prostate cancer. Eur Urol *53(1)*: 68-80, 2008. PMID: 17920184. DOI: 10.1016/j.eururo.2007.09.002

29 Vanhanen A and Kapanen M: The effect of rectal retractor on intrafraction motion of the prostate. Biomedical Physics & Engineering Express *2(3)*: 035021, 2020. DOI: 10.1088/2057-1976/2/3/035021

30 Vanhanen A, Syrén H and Kapanen M: Localization accuracy of two electromagnetic tracking systems in prostate cancer radiotherapy: A comparison with fiducial marker based kilovoltage imaging. Phys Med *56*: 10-18, 2018. PMID: 30527084. DOI: 10.1016/j.ejmp.2018.11.007

31 Benjamin LC, Tree AC and Dearnaley DP: The role of hypofractionated radiotherapy in prostate cancer. Curr Oncol Rep *19(4)*: 30, 2017. PMID: 28343352. DOI: 10.1007/s11912-017-0584-7

32 Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, Gao A, Hassan S, Horwich A, Huddart R, Khoo V, Kirkbride P, Mayles H, Mayles P, Naismith O, Parker C, Patterson H, Russell M, Scrase C, South C, Staffurth J and Hall E: Conventional *versus* hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol *13(1)*: 43-54, 2012. PMID: 22169269. DOI: 10.1016/S1470-2045(11)70293-5

33 Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, Kindblom J, Ginman C, Johansson B, Björnlinger K, Seke M, Agrup M, Fransson P, Tavelin B, Norman D, Zackrisson B, Anderson H, Kjellén E, Franzén L and Nilsson P: Ultra-hypofractionated *versus* conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet *394(10196)*: 385-395, 2019. PMID: 31227373. DOI: 10.1016/S0140-6736(19)31131-6

34 Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, Ford D, Tolan S, Jain S, Martin A, Staffurth J, Camilleri P, Kancherla K, Frew J, Chan A, Dayes IS, Henderson D, Brown S, Cruickshank C, Burnett S, Duffton A, Griffin C, Hinder V, Morrison K, Naismith O, Hall E, van As N and PACE Trial Investigators: Intensity-modulated fractionated radiotherapy *versus* stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. Lancet Oncol *20(11)*: 1531-1543, 2019. PMID: 31540791. DOI: 10.1016/S1470-2045(19)30569-8

35 Valeriani M, Bonfili P, Reverberi C, Marinelli L, Ferella L, Minniti G, DE Sanctis V, Osti MF, Bonome P, Tronnolone L, Varrassi E, Gravina GL, Franzese P, Tombolini V and DI Staso M: Moderate hypofractionation in patients with low-risk prostate cancer: long-term outcomes. Anticancer Res *38(3)*: 1671-1676, 2018. PMID: 29491101. DOI: 10.21873/anticanres.12400

36 King CR, Collins S, Fuller D, Wang PC, Kupelian P, Steinberg M and Katz A: Health-related quality of life after stereotactic body radiation therapy for localized prostate cancer: results from a multi-institutional consortium of prospective trials. Int J Radiat Oncol Biol Phys *87(5)*: 939-945, 2013. PMID: 24119836. DOI: 10.1016/j.ijrobp.2013.08.019

37 Pryor D, Sidhom M, Arumugam S, Bucci J, Gallagher S, Smart J, Grand M, Greer P, Keats S, Wilton L and Martin J: Phase 2 multicenter study of gantry-based stereotactic radiotherapy boost for intermediate and high risk prostate cancer (PROMETHEUS). Front Oncol *9*: 217, 2019. PMID: 31001481. DOI: 10.3389/fonc.2019.00217

38 Shiri R, Koskimäki J, Hakama M, Häkkinen J, Tammela TL, Huhtala H and Auvinen A: Prevalence and severity of erectile dysfunction in 50 to 75-year-old Finnish men. J Urol *170(6 Pt 1)*: 2342-2344, 2003. PMID: 14634411. DOI: 10.1097/01.ju.0000090963.88752.84

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