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Safer and More Convenient Modern Curative Radiotherapy for Patients With Early Prostate Cancer

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Abstract. *Background/Aim: New fractionation schedules with modern tools are a very rapidly developing area in curative radiotherapy (RT) for early prostate cancer (PC). To apply these techniques in everyday clinical practice, we planned this phase II trial with different fractionation schedules and followed up patients using careful health-related quality of life (QoL) questionnaires for three years. Patients and Methods: Seventy-three PC patients with one or two intermediate PC risk factors according to the National Comprehensive Cancer Network criteria were recruited. Forty-two patients were treated with 78/2 Gy (conventional fractionation, CF) or 60/3 Gy (moderately hypofractionation RT, MHF), and 31 patients were treated with 36.25/7.25 Gy (stereotactic body RT, SBRT). Their PSA levels were measured, and QoL data were assessed for genitourinary (GU), gastrointestinal (GI), and sexual well-being between the baseline and three years after treatment. A Rectafix™ (RF) fixation device was used in 30 patients in the CF/MHF group. Results: Three years after radiotherapy (RT), there were no differences between the groups regarding GU, GI, sexual well-being, PSA response, or clinical outcomes. On QoL questionnaires, men in the SBRT group were more satisfied with their QoL at the end of RT. Urinary symptoms (p=0.004) and urinary incontinence were more common in the CF/MHF group (p=0.016) three months after RT. The use of RF reduced GI toxicity, especially urgency (p=0.002), at three years after RT. Conclusion: Modern, short, five-fraction stereotactic radiotherapy as a local curative treatment for PC is well tolerated and safe. Our novel results showing a decrease in GI toxicity using Rectafix™ fixation should be confirmed in future randomized trials.*

Prostate cancer has the highest incidence of all cancers in Finland. In 2021, approximately 5,200 new prostate cancers were diagnosed (1). Globally, prostate cancer was the second most common cancer diagnosis in men in 2020 (2). The treatment selection for prostate cancer depends on the patient's cancer risk stratification, which includes Gleason score (ISUP grade), T stage, and prostate specific antigen (PSA) levels (3). According to the European Association of Urology prostate cancer guidelines, management approaches for patients with early prostate cancer include radical prostatectomy, external beam radiation therapy, active surveillance, and brachytherapy (3). Early prostate cancer outcomes are excellent with all treatment options (4-6). In addition to PSA levels, treatment responses after RT could be easily followed with MRI (7). Quality of life (QoL) issues are discussed, and comorbidities are evaluated when the optimal treatment for prostate-confined cancer is selected.

The aim of this study was to evaluate an optimal fractionation schedule for modern image-guided external beam radiation therapy in Finnish men with early prostate cancer considering treatment results and patient-reported quality-of-life outcomes (8). The benefits of the rectum immobilization device were also evaluated as a part of this study. Three-year health-related QoL results have been previously published (9). We now report genitourinary, gastrointestinal, and sexual function patient-reported QoL results after a three-year follow-up.

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Key Words: Prostate cancer, radiotherapy, quality of life, late side effects, hypofractionated radiotherapy, stereotactic body radiotherapy, rectal retractor, rectal displacement device.

Table I. *Patient demographics at baseline and the three-year follow-up.*

	Radiation therapy group		
Baseline	CF/MHF (n=42)	SBRT (n=31)	Overall (n=73)
Age years, Mean (range)	69 (59-78)	70 (63-78)	69 (59-78)
Gleason score, n (%)			
3+3	15 (36)	6 (19)	21 (29)
3+4	26 (62)	23 (74)	49 (67)
4+3	1 (2)	2 (7)	3 (4)
T Stage, n (%)			
T1c	5 (12)	6 (19)	11 (15)
T2a	9 (21)	9 (29)	18 (25)
T2b	6 (14)	3 (10)	9 (12)
T2c	22 (52)	13 (42)	35 (48)
Prostate volume, cm^3, at baseline, Median (range)	42 (20-111)	35 (23-80)	40 (20-111)
PSA at baseline, ng/ml, Median (range)	9.0 (3.4-18.4)	9.4 (3.2-19.1)	9.2 (3.2-19.1)
α blockers use at baseline, n (%)	7 (17)	13 (42)	20 (27)
At three-year follow-up	CF/MHF (n=37)	SBRT (n=29)	Overall (n=66)
Reason of lost to follow-up, n			
PSA-relapse	3	0	3
Other malignancy	2	1	3
Other disease	0	1	1
PSA at three-year follow-up, ng/ml, Median (range)	0.4 (0.1-3.0)	0.4 (<0.02-1.8)	0.4 (<0.02-3.0)
α blockers use at three-year follow-up, n (%)	4 (11)	11 (38)	15 (23)

CF/MHF: Conventional fractionation or moderate hypofractionation; SBRT: stereotactic body radiotherapy; PSA: prostate specific antigen.

Patients and Methods

Patients and radiotherapy planning. This was a prospective single-centre study comparing conventionally fractionated radiotherapy (78/2 Gy) and moderately hypofractionated radiotherapy (60/3 Gy) to stereotactic body radiotherapy (36.25/7.25 Gy). Men with biopsy-proven localized T1c-T2cN0M0 prostate carcinoma with one or two intermediate risk factors according to the National Comprehensive Cancer Network criteria were eligible for this study (10). Intermediate risk factors were T2b-T2c disease, Gleason score 7 or prostate-specific antigen (PSA) level of 10-20 ng/ml. Androgen deprivation therapy or the need for transurethral resection of the prostate were exclusion criteria (more details of the inclusion and exclusion criteria have been published previously) (8). Overall, 73 patients (approximately 90-95% of eligible patients) were recruited between May 2014 and December 2017 from Tampere University Hospital. The first 42 consecutive patients were treated with conventionally fractioned radiotherapy or moderately hypofractionated radiotherapy (CF/MHF), and 31 patients were then treated with stereotactic body radiotherapy (SBRT). The Tampere University Hospital Ethics Committee approved the study (R14009), and patients gave their written informed consent. The clinical trial identifier is NCT02319239 at www.ClinicalTrials.gov.

Before radiotherapy, three fiducial markers were inserted into the prostate for the image-guided radiotherapy. Radiotherapy planning computed tomography (CT) and magnetic resonance imaging (MRI) scans were performed, and the MRI scan was fused to the CT scan by fiducial matching to improve the anatomical definition of the prostate. Both groups performed scans with a full bladder. The CF/MHF group had an empty rectum, but the SBRT group used a fleet enema to empty the rectum. A rectal immobilization device (Rectafix™, Scanflex Medical, Täby, Sweden) was used as part of the treatment in 30 men in the CF/MHF group. The patient group who had Rectafix™ as part of their treatment was referred to as the RF group. Further information about this study's radiotherapy planning and execution and arrangements for rectal immobilization can be found in our previous article (8).

Quality of life measurements. Of the patient-reported outcome questionnaires, the International Prostate Symptom Score (IPSS) and the International Index of Erectile Function (IIEF-5) were completed at baseline, at the end of radiotherapy, and 3, 12, 24, and 36 months after treatment (11, 12). The 16-question modified version of the Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic (SOMA) questionnaire was not completed at the end of radiotherapy; otherwise, the same time schedules were used (13). Toxicity mentioned by physicians in patient records was later converted by the first author to the Radiation Therapy Oncology Group scale (14).

Statistical analysis. Statistical analyses were performed with IBM SPSS Statistics version 29.0 for Windows (SPSS Inc., Chicago, IL, USA). The statistical significance of the difference in median scores between radiotherapy groups was tested using the Mann–Whitney two-independent-samples test. Treatment changes within the RT groups before RT and at the appointed follow-up timepoint were analyzed using the Wilcoxon signed-rank test. Fisher's exact test was used to compare treatment group frequencies. In the analyses of questionnaires, the missing values were replaced with the mean

Table II. *Summary of International Prostate Symptom Score (IPSS) results at baseline and follow-up timepoints in the conventionally fractioned radiotherapy or moderately hypofractionated radiotherapy group (CF/MHF) and the stereotactic body radiotherapy group (SBRT).*

	Comparison of frequencies between groups in different follow-up timepoints			Change in the IPSS score medians and quality of life question answer medians between baseline and different follow-up timepoints							
	Radiation therapy group			Radiation therapy group							
	CF/MHF (n=42)	SBRT (n=31)	*p*-Value	CF/MHF (n=42) Median score (IQR)	*p*-Value	QoL median (IQR)	*p*-Value	SBRT (n=31) Median score (IQR)	*p*-Value	QoL median (IQR)	*p*-Value
Baseline, n (%)			0.867	6.0 (3.0-10.0)		2.0 (1.0-2.0)		7.0 (3.3-10.8)		2.0 (1.0-2.5)	
Grade 1	26 (62)	16 (57)									
Grade 2	14 (33)	11 (39)									
Grade 3	2 (5)	1 (4)									
Missing data	0	3									
End of RT, n (%)			**0.025**	14.5 (10.6-22.6)*	**<0.001**	2.5 (2.0-4.0)**	<0.001	10.0 (4.8-14.8)*	**0.003**	2.0 (1.0-3.0)**	0.916
Grade 1	5 (12)	9 (38)									
Grade 2	23 (55)	12 (50)									
Grade 3	14 (33)	3 (12)									
Missing data	0	7									
3 months, n (%)			0.667	6.5 (3.0-10.0)	0.905	1.5 (1.0-2.0)	0.504	6.5 (2.8-10.3)	0.260	1.0 (1.0-2.5)	0.109
Grade 1	26 (62)	18 (60)									
Grade 2	15 (36)	12 (40)									
Grade 3	1 (2)	0 (0)									
Missing data	0	1									
12 months, n (%)			0.409	6.0 (3.0-9.8)	0.661	1.0 (1.0-2.0)	0.626	5.0 (2.0-7.8)	**0.037**	1.0 (0.0-2.0)	**0.014**
Grade 1	26 (65)	21 (75)									
Grade 2	12 (30)	7 (25)									
Grade 3	2 (5)	0 (0)									
Missing data	2	3									
24 months, n (%)			0.722	5.0 (2.0-11.3)	0.567	1.5 (0.0-2.0)	0.216	5.0 (2.5-8.0)	0.114	1.0 (0.0-2.0)	**0.012**
Grade 1	24 (63)	21 (72)									
Grade 2	12 (32)	7 (24)									
Grade 3	2 (5)	1 (3)									
Missing data	4	2									
36 months, n (%)			1.000	5.0 (3.0-8.5)	0.357	1.0 (0.0-2.0)	0.069	5.0 (2.0-9.0)	0.184	1.0 (0.0-2.0)	0.061
Grade 1	27 (73)	19 (70)									
Grade 2	10 (27)	8 (30)									
Grade 3	0 (0)	0 (0)									
Missing data	5	4									

Differences in grades between radiation therapy groups were tested using the Fisher's exact test (frequencies) and the Mann–Whitney two independent samples test (medians): **p*=0.012; ***p*=0.004. Changes between timepoints were analyzed using the Wilcoxon signed rank test. Bolded values are significant at $p<0.05$. IPSS score: Grade 1, mild symptoms (1-7); Grade 2, moderate symptoms (8-19); Grade 3, severe symptoms (20-35). Quality of life due to urinary symptoms: 0, delighted; 1, pleased; 2, mostly satisfied: 3, mixed; 4, mostly dissatisfied; 5, unhappy; 6, terrible. IPSS: International Prostate Symptom Score; CF/MHF: conventional fractionation or moderate hypofractionation; SBRT: stereotactic body radiotherapy; IQR: interquartile range.

value of other answers of this patient in the questionnaire when 20% or less of the answers were missing. There were only few replaced values of all returned answers throughout this study. On the IPSS questionnaire, the ratio of replaced answers to the total number of possible answers was 14/1,687 in the CF/MHF group and 4/1,162 in the SBRT group, the ratios on the IIEF were 5/1,175 and 5/800, and on the LENT-SOMA 19/3,136 and 6/2,256, respectively. All tests used a 2-sided $p<0.05$ for statistical significance.

Results

In our study population (Table I), the mean age was 69 years (range=59-78 years). The majority of the patients had a Gleason score of 3+4, and the median PSA was 9.2 ng/ml (range=3.2-19.1 ng/ml). In three years of follow-up, a total of seven study patients had trial discontinuations. Three men

Table III. *Medians (and interquartile ranges) of Late Effects Normal Tissue Task Force-Subjective, Objective, Management, Analytic (LENT-SOMA) responses presented separately for the conventionally fractioned radiotherapy or moderately hypofractionated radiotherapy group (CF/MHF) and stereotactic body radiotherapy group (SBRT). Change between baseline and all follow-up timepoints presented separately for both the CF/MHF and SBRT groups.*

	Baseline	3 mo	*p*-Value	12 mo	*p*-Value	24 mo	*p*-Value	36 mo	*p*-Value
Genitourinary									
1. Painful urination									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.313	0.0 (0.0-0.0)	0.750	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.750
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.375	0.0 (0.0-0.0)	0.125	0.0 (0.0-0.0)	0.375	0.0 (0.0-0.0)	0.125
2. Frequency (between x h)									
CF/MHF	4.0 (3.0-5.0)	3.5 (3.0-4.8)	**0.226**	**3.5 (2.5-4.0)**	**0.030**	4.0 (3.0-5.0)	0.599	4.0 (3.0-5.0)	0.325
SBRT	3.0 (2.0-4.1)	3.3 (2.5-4.0)	**0.875**	**3.3 (2.6-4.4)**	**0.010**	3.0 (2.8-4.3)	0.596	4.0 (3.0-5.0)	0.068
3. Blood in urine									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.500	0.0 (0.0-0.0)	1.000
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000
4. Incontinence									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-1.0)**	0.406	0.0 (0.0-1.0)	0.258	0.0 (0.0-1.0)	0.188	0.0 (0.0-0.0)	1.000
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)**	0.500	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.500
5. Usage of pads									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.500
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000
6. Decreased stream of urine									
CF/MHF	2.0 (1.0-2.0)	**1.0 (0.0-2.0)**	**0.014**	**1.0 (0.0-2.0)**	**0.022**	**1.0 (0.0-1.8)**	**<0.001**	**1.0 (0.0-2.0)**	**0.011**
SBRT	2.0 (1.0-2.0)	1.0 (0.0-2.0)	0.051	**1.0 (0.0-2.0)**	**0.008**	1.0 (0.0-2.0)	0.260	1.0 (0.0-2.0)	0.154
GU Domain[a]									
CF/MHF	2.0 (1.0-3.0)	1.0 (0.0-3.0)	0.588	2.0 (0.0-3.0)	0.579	1.0 (1.0-3.0)	0.242	1.0 (0.0-3.0)	0.087
SBRT	2.0 (1.0-3.3)	**1.0 (0.0-2.0)**	**0.012**	**1.0 (0.0-2.0)**	**0.009**	1.0 (0.0-2.5)	0.292	1.0 (0.0-2.0)	0.139
Gastrointestinal									
7. Urgency of bowel movement									
CF/MHF	0.0 (0.0-1.0)*	0.0 (0.0-1.0)	0.913	0.0 (0.0-2.0)	0.152	1.0 (0.0-1.3)	0.147	0.5 (0.0-1.0)	0.121
SBRT	0.0 (0.0-0.0)*	0.0 (0.0-0.5)	0.594	0.0 (0.0-1.0)	0.227	0.0 (0.0-1.0)	0.129	0.0 (0.0-1.0)	0.076
8. Mucus on feces									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.281	0.0 (0.0-0.0)	0.781	0.0 (0.0-0.0)	0.250	0.0 (0.0-0.0)	0.359
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.8)	0.359	0.0 (0.0-0.0)	1.000	0.0 (0.0-1.0)	0.531	0.0 (0.0-1.0)	0.449
9. Quality of feces									
CF/MHF	1.0 (1.0-1.5)	1.0 (1.0-1.0)	0.541	1.0 (1.0-1.0)	0.570	1.0 (1.0-2.0)	0.727	1.0 (1.0-1.0)	0.125
SBRT	1.0 (1.0-1.0)	1.0 (1.0-2.0)	0.406	1.0 (1.0-2.0)	0.883	1.0 (1.0-3.0)	0.172	1.0 (1.0-3.0)	0.172
10. Frequency (times/day)									
CF/MHF	1.0 (1.0-2.0)	1.0 (1.0-2.0)	0.166	1.5 (1.0-2.0)	0.051	1.5 (1.0-2.0)	0.245	1.5 (1.0-2.0)	0.872
SBRT	1.3 (1.0-2.0)	1.0 (1.0-2.0)	1.000	1.5 (1.0-2.0)	0.789	1.3 (1.0-1.5)	0.255	1.0 (1.0-2.0)	0.805
11. Incontinence									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.453	0.0 (0.0-0.0)	0.180	0.0 (0.0-0.0)	0.359
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.125	0.0 (0.0-0.0)	0.125
12. Usage of pads									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.500	0.0 (0.0-0.0)	1.000
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000
13. Pain on passing a motion									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.375	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000
14. Blood in feces or from anus									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.219	0.0 (0.0-0.0)	0.453	0.0 (0.0-0.0)	0.531	0.0 (0.0-0.0)	1.000
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	1.000	0.0 (0.0-0.0)	0.625
15. Anus irritation									
CF/MHF	0.0 (0.0-0.0)	0.0 (0.0-1.0)	0.734	0.0 (0.0-0.0)	0.663	0.0 (0.0-1.0)	0.750	0.0 (0.0-1.0)	0.846
SBRT	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.109	0.0 (0.0-0.0)	1.000	0.0 (0.0-1.0)	1.000	0.0 (0.0-0.0)	1.000
GI Domain[a]									
CF/MHF	2.0 (1.0-4.0)	2.0 (1.0-4.0)	0.967	2.0 (1.0-5.0)	0.825	3.0 (1.0-5.0)	0.253	3.0 (1.0-4.0)	0.506
SBRT	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.856	2.0 (1.0-3.8)	0.928	2.0 (1.0-5.0)	0.101	2.0 (1.0-5.0)	0.080

Table III. *Continued*

Table III. *Continued*

	Baseline	3 mo	*p*-Value	12 mo	*p*-Value	24 mo	*p*-Value	36 mo	*p*-Value
Sexual									
16. Interest in intercourse									
CF/MHF	2.0 (1.0-2.0)	**2.0 (1.0-3.0)**	**0.002**	**2.0 (1.0-4.0)**	**0.011**	**2.0 (1.0-4.0)**	**<0.001**	**2.0 (1.0-4.0)**	**<0.001**
SBRT	2.0 (1.0-2.3)	2.0 (1.0-3.0)	0.070	**2.0 (2.0-3.0)**	**0.039**	**2.5 (2.0-3.0)**	**0.014**	**3.0 (2.0-4.0)**	**0.044**

Changes between timepoints were analyzed using the Wilcoxon signed rank test. Differences between radiation therapy groups were tested using the Mann–Whitney two independent samples test. **p*=0.032, ***p*=0.016. Bolded values are significant at $p<0.05$. [a]Domain score is a sum of answers: GU (genitourinary) domain = questions 1, 3-6; GI (gastrointestinal) domain =questions 7-9, 11-15. LENT-SOMA question (1, 3-9, 11-16) choices generally: 0, no problems; 1, seldom problems; 2, occasionally problems; 3, frequent problems; 4, continuous problems CF/MHF: Conventional fractionation or moderate hypofractionation; mo: months; SBRT: stereotactic body radiotherapy; GU: genitourinary; GI: gastrointestinal.

in the CF/MHF group had a biochemical relapse, and all these PSA relapses had Gleason 3+4 disease.

Regarding PSA response, there were no statistically significant differences between groups. The three-year PSA medians were 0.40 ng/ml (range=0.10-3.00 ng/ml) and 0.40 ng/ml (range=0.02-1.80 ng/ml) in the CF/MHF and SBRT groups, respectively. One patient in the SBRT group had a benign PSA bounce at 12 months from 7.4 to 19.3 ng/ml.

Urinary symptoms. Table II presents urinary symptom findings based on the IPSS. At baseline, there were no significant differences between the groups. At the end of RT, men in the SBRT group were more satisfied with their urinary function than men in the CF/MHF group based on the IPSS median score ($p=0.012$), frequencies of symptom grades ($p=0.025$), and IPSS question about QoL due to urinary symptoms ($p=0.004$). After the RT, urinary symptoms were alleviated to a baseline level, and no differences between groups were observed between the three-month and three-year follow-ups. QoL due to urinary symptoms was also ameliorated in both groups over time. In the SBRT group, this change was observed at one year after treatment ($p=0.014$).

At the baseline LENT-SOMA questions, there were no significant differences between groups on urinary symptoms (Table III). Urinary frequency increased in the SBRT group, and when compared to the baseline, the change was significant at one year ($p=0.010$). In the CF/MHF group, the stream of urine increased over time, and the change compared to baseline was significant at the three-year follow-up ($p=0.011$) towards better urinary flow. Three months after RT, the patients in the CF/MHF group had more urinary incontinence than those in the SBRT group ($p=0.016$). The LENT-SOMA genitourinary domain score summarizes the urinary question answers, and in the SBRT group, the genitourinary domain score change was towards better QoL at three months and one year after RT compared to baseline ($p=0.012$, $p=0.009$, respectively), and remained stable between one and three years. At the three-year follow-up, there were no differences between groups on any LENT-SOMA questions of urinary symptoms.

At the level of Radiation Therapy Oncology Group (RTOG) scale grade 2 or worse, GU toxicity was observed in 8% and 7% of patients in the CF/MHF and SBRT groups, respectively (Table IV).

In the SBRT group, the use of tamsulosin hydrochloride was 42% before radiotherapy. In the CF/MHF group, 17% of men used this medication regularly at that point. Three years after RT, the use of tamsulosin hydrochloride was at the same level: 38% in the SBRT group and 11% in the CF/MHF group still needed this medication (Table I).

Gastrointestinal symptoms. The LENT-SOMA question about urgency of bowel movement differed between the groups at baseline ($p=0.032$) (Table III), but later, there were no other significant differences between the CF/MHF and SBRT groups in LENT-SOMA questions of gastrointestinal symptoms at any timepoints. There were no significant changes in responses to LENT-SOMA questions about gastrointestinal symptoms between baseline and the three-year follow-up in either group.

On the RTOG scale, only one grade 2 or worse toxicity was recorded, and only grade 1 toxicity was seen in 14% and 3% of patients in the CF/MHF and SBRT groups, respectively (Table IV).

Sexual functions. The two RT groups did not exhibit significant sexual functioning differences at any time point in the International Index of Erectile Function (IIEF-5) questionnaires when frequencies of symptom grades or score medians were compared (Table V). When compared to baseline, the erectile dysfunction worsened in the CF/MHF group ($p<0.001$) at the end of RT but not in the SBRT group. The change in the IIEF-5 median score was significant in the CF/MHF group between baseline and all follow-up timepoints. In the SBRT group, the IIEF-5 median score

Table IV. *Radiation therapy group toxicity evaluated using the Radiation Therapy Oncology Group scale.*

		Radiation therapy group and timepoint, n (%)									
		CF/MHF (n=42)					SBRT (n=31)				
		eRT	3 mo	12 mo	24 mo	36 mo	eRT	3 mo	12 mo	24 mo	36 mo
GU	None	3 (7)	25 (60)	32 (76)	29 (74)	30 (81)	7 (23)	20 (65)	18 (60)	21 (70)	19 (66)
	Grade 1	21 (51)	13 (31)	8 (19)	8 (21)	4 (11)	18 (58)	10 (32)	12 (40)	9 (30)	8 (28)
	Grade 2	18 (43)	4 (10)	2 (5)	2 (5)	3 (8)	6 (19)	1 (3)	0	0	2 (7)
	Grade 3	0	0	0	0	0	0	0	0	0	0
	Missing data	0	0	0	3	5	0	0	1	1	2
GI	None	14 (33)	28 (67)	33 (79)	31 (80)	31 (84)	17 (55)	26 (84)	26 (87)	28 (93)	28 (97)
	Grade 1	22 (52)	12 (29)	7 (17)	8 (21)	5 (14)	11 (36)	5 (16)	4 (13)	2 (7)	1 (3)
	Grade 2	5 (12)	2 (5)	2 (5)	0	1 (3)	3 (10)	0	0	0	0
	Grade 3	1 (2)	0	0	0	0	0	0	0	0	0
	Missing data	0	0	0	3	5	0	0	1	1	2

No Grade 4 or 5 toxicities were reported. Values indicate number of patients with percentages. CF/MHF: Conventional fractionation or moderate hypofractionation; mo: months; SBRT: stereotactic body radiotherapy; GU: genitourinary; GI: gastrointestinal.

change between baseline and one-year follow-up was significant toward worsened erectile function and remained at that level thereafter (Table V).

In the LENT-SOMA question regarding interest in intercourse, the change was significant in both groups between baseline and the three-year follow-up (Table III). The loss of interest was seen in all follow-up points after RT in the CF/MHF group and after one-year follow-up in the SBRT group.

Using Rectafix fixation and QoL. Table VI summarizes the QoL results from the Rectafix™ population of patients. The use of Rectafix™ did not have any effect on urinary symptoms or the development of erectile dysfunction or loss of interest in intercourse, and the findings followed the RT group results. At the three-year timepoint, the RF group IIEF-5 median score concerning erectile functioning was better, and there was a significant difference compared to the IIEF-5 median score of men treated with a similar RT fractionation (non-RF CF/MHF group) (p=0.048).

Between baseline and the three-year follow-up, there was a change towards more gastrointestinal symptoms in the non-RF group measured by the LENT-SOMA gastrointestinal domain score (p=0.022). In the RF group, the LENT-SOMA gastrointestinal domain score median did not change. There was a significant difference between the RF group and the non-RF CF/MHF group in the LENT-SOMA gastrointestinal domain scores (p=0.023) at the three-year timepoint in which the RF group had fever symptoms. In a LENT-SOMA question about urgency of bowel movement, the RF group exhibited fewer problems than both non-RF groups (non-RF and non-RF CF/MHF) at three years after radiotherapy when compared to the baseline (p=0.002 and p=0.016, respectively). The answer concerning median urgency of bowel movement in the RF group was unchanged between these two timepoints. At baseline, the bowel urgency question median score was similar between the RF group and the non-RF group and the non-RF CF/MHF group (baseline comparisons p=0.100 and p=0.939, respectively).

Discussion

Our study shows that curative radiotherapy for early prostate cancer delivered with modern RT equipment and a short fractionation schedule is safe and convenient for patients. This is especially important and cost-effective in Finland, where distances to RT units could be hundreds of kilometers. The novel results showed that using the Rectafix™ device to reduce the radiation dose to the rectum and thus avoid gastrointestinal late side effects, functions well, and as far as we know, the late health-reported QoL (HRQoL) results using this device are reported here for the first time in the worldwide science literature.

Some study limitations need to be pointed out. Our study was not designed to be statistically powerful enough to detect differences in HRQoL between SBRT and the two more conventional RT groups; conventionally fractionated (CF) and moderately hypofractionated (MHF) RT. That is why these two groups were combined. However, statistical significance cannot be ruled out in domains and timepoints, and only a trend towards differences could be observed. The patients were not randomized into fractionation schedule groups because we used a technical developmental approach in this pilot trial. Consecutive patients referred by urologists

Table V. *Summary of International Index of Erectile Function (IIEF-5) results at baseline and follow-up timepoints within the conventionally fractioned radiotherapy or moderately hypofractionated radiotherapy group (CF/MHF) and the stereotactic body radiotherapy group (SBRT).*

	Comparison of frequencies between groups in different follow-up timepoints			IEFF-5 median scores (Interquartile ranges) in different follow-up timepoints and their comparison to baseline score			
	Radiation therapy group			Radiation therapy group			
	CF/MHF (n=42)	SBRT (n=31)		CF/MHF (n=42)		SBRT (n=31)	
			p-Value	median score (IQR)	*p*-Value	Median score (IQR)	*p*-Value
Baseline, n (%)			0.289	17.0 (12.5-20.3)		16.0 (4.0-20.5)	
Grade 1	9 (21)	5 (17)					
Grade 2	23 (55)	12 (41)					
Grade 3	10 (24)	12 (41)					
Missing data	0	2					
End of RT, n (%)			0.816	9.0 (2.5-20.5)	**<0.001**	9.5 (2.0-20.0)	0.501
Grade 1	8 (20)	4 (15)					
Grade 2	10 (24)	8 (31)					
Grade 3	23 (56)	14 (54)					
Missing data	1	5					
3 months, n (%)			0.878	13.0 (3.3-20.8)	**<0.001**	11.0 (2.0-19.0)	0.326
Grade 1	9 (21)	5 (18)					
Grade 2	13 (33)	9 (32)					
Grade 3	18 (45)	14 (50)					
Missing data	2	3					
12 months, n (%)			0.466	9.0 (1.3-19.8)	**<0.001**	9.5 (2.0-17.5)	**0.011**
Grade 1	5 (13)	1 (4)					
Grade 2	14 (35)	9 (35)					
Grade 3	21 (53)	16 (62)					
Missing data	2	5					
24 months, n (%)			0.084	7.0 (1.0-20.0)	**<0.001**	8.5 (1.0-15.3)	**0.002**
Grade 1	7 (19)	1 (4)					
Grade 2	5 (14)	8 (31)					
Grade 3	25 (67)	17 (65)					
Missing data	5	5					
36 months, n (%)			0.261	6.0 (1.0-23.0)	**<0.001**	8.0 (2.5-19.0)	**0.035**
Grade 1	9 (26)	5 (20)					
Grade 2	4 (11)	7 (28)					
Grade 3	22 (63)	13 (52)					
Missing data	7	6					

Differences in grades between radiation therapy groups were tested using the Fisher's exact test (frequencies). Changes between timepoints were analyzed using the Wilcoxon signed rank test. Bolded values indicate statistical significance at $p<0.05$. IIEF-5 score: Grade 1, no ED (22-25); Grade 2, mild and mild to moderate ED (12-21); Grade 3, moderate to severe ED (5-11). When the patient scored below 5 points, his answers were included. IIEF: International Index of Erectile Function; CF/MHF: conventional fractionation or moderate hypofractionation; SBRT: stereotactic body radiotherapy; IQR: interquartile range.

to the RT unit were allocated by the same RT clinician in the referral order into the three trial groups. Furthermore, a rectal immobilization device (Rectafix™) was used only in moderately or conventionally hypofractionated RT patients (73.1%). Thus, it is not plausible that such a device could negatively impact QoL in a broader view. The strength of this study was the careful follow-up of all patients using a wide spectrum of HRQoL instruments.

We observed very low incidences of late GU and GI toxicities comparable to a few published long-term studies. At two and three years after RT, our incidence of GU RTOG grade 2 or worse toxicity was 5% and 8% in the CF/MHF group, and 0% and 7% in the SBRT group, respectively. In comparison, PACE-B reported two years of GU RTOG grade 2 or worse toxicity of 2% in the control group (CRT) and 3% in the SBRT group and 3.2% and 5.5% after five years, respectively (15, 16). The HYPO-RT trial reported five-year results of GU RTOG grade 2 or worse toxicity, and it was 5% with both groups (17). GI RTOG grade 2 or worse toxicity was 0% and 3% in the CF/MHF group after 2 and 3

years and 0% and 0% in the SBRT group, respectively. After two years, the PACE-B toxicity rates were 3% in the CRT group, and 2% in the SBRT group, and after five years of follow-up, there was one patient in each group (15, 16).

Patient-reported genitourinary outcomes after three years of RT were not better in the CF/MHF group than those in the SBRT group. In both groups, men were pleased with their QoL after treatment. Our findings are in line with the PACE-B genitourinary outcomes, where the IPSS questionnaire was also used to assess QoL and patient-reported outcomes with similar findings (15). Regarding patient-reported gastrointestinal outcomes, the PACE-B reported a low degree of bowel incontinence after two years of RT in both treatment groups, as measured by the Vaizey Faecal Incontinence Score (18). We assessed bowel symptoms with the LENT-SOMA questionnaire and had comparable findings in both study groups regarding gastrointestinal incontinence after two and three years of treatment. Rectafix™ seemed to have a protective effect regarding these symptoms when compared to men treated without this device. The published HYPO-RT study reported patient outcomes after six years of follow-up, and overall discomfort in genitourinary and gastrointestinal symptoms deteriorated significantly in both the ultrahypofractionated and conventionally fractionated groups (19). We evaluated patient-reported overall genitourinary and gastrointestinal burden with the LENT-SOMA domain score and observed that there was no deterioration in urinary symptoms after three years in either of our treatment groups. Regarding the gastrointestinal bother, there was a trend towards more symptoms in the CF/MHF group, but that was not statistically significant.

Our follow-up time was only three years, but in other RT studies, we have learned that genitourinary and gastrointestinal patient-reported outcomes (PROs) usually remain stable after two years of follow-up. In earlier reports, patients treated with 35-36.25/7-7.25 Gy had urinary and bowel symptoms after RT, but these symptoms alleviated to baseline by two years after treatment and remained stable thereafter (20). Patient-reported outcomes from the CHHiP trial were similar with a 60/3 Gy treatment schedule (21). Bowel and urinary symptoms remained stable and at low levels between the two- and five-year follow-ups.

When evaluating the toxicity of prostate radiotherapy trials, it is good to remember that toxicity assessments are usually made by physicians (22) In modern studies, there has been increasing interest in evaluating patient-reported quality-of-life outcomes as a part of trial outcomes because it has been recognized that physicians underreport side effects in this type of prospective trial. The other reason might be that the patients are too ashamed to tell their symptoms directly to physicians (23-26). Recent studies compared toxicity assessed by physicians to patient-reported outcomes concerning prostate RT. In these studies, there was a low agreement between symptoms experienced by patients and those observed and recorded by physicians. Usually, the physician underreported the severity of the symptoms (27, 28). When evaluating gastrointestinal toxicity in our study, there was also underreporting of bowel problems by physicians. With the RTOG instrument, physicians' grade 2 or worse for gastrointestinal toxicity was low. Only one exception was observed (3%) in the CF/MHF group after three years of treatment. Minor grade 1 bowel problems were reported in 14% and 3% of patients in the CF/MHF and SBRT groups, respectively. Patient-reported outcomes were measured by the LENT-SOMA GI domain score, which was used to assess overall bowel problems. The median score was three (meaning frequent problems) in the CF/MHF group and two (occasionally problems) in the SBRT group. One possible reason for this might be that physicians asked specifically about radiotherapy side effects, and patients reported the entirety of their symptoms in terms of QoL. From the patients' point of view, ageing might also cause increasing symptoms and have an effect on this reporting bias.

Prostate cancer has a high sensitivity to RT fractionation (29, 30). A low radiobiological α/β ratio is suggested to increase treatment efficacy with improved patient comfort and reduce health-care costs when the α/β ratio for late normal tissue toxicity is presumed to be higher than the α/β ratio for prostate cancer (31, 32). Novel data suggest that the α/β ratio for gastrointestinal side effects is indeed higher (3.0 Gy), but the α/β ratio for genitourinary side effects is lower (0.6-2.0 Gy) or at the same level as the presumed prostate cancer α/β ratio (1.1-1.7 Gy) (29, 33, 34). According to this finding, genitourinary toxicity is increased when larger fraction sizes are used, but rectal toxicity is decreased. In our study, all RTOG grades of genitourinary side effects were 19% and 35% after three years of treatment in the CF/MHF and SBRT groups, respectively. In the three-year follow-up, all RTOG grade gastrointestinal side effects were 17% and 3% in the CF/MHF and SBRT groups, respectively. When evaluating late genitourinary toxicity, age is a confounding factor. Many prostate cancer patients are elderly with a change to develop lower urinary tract symptoms not induced solely by RT during the follow-up period. In the future, a possible way to reduce SBRT-induced genitourinary toxicity is to recognize anatomical structures behind this type of toxicity. There is a hypothesis that limiting the dose to the urethra might reduce genitourinary toxicity (35). Another critical structure under investigation is the bladder trigone (36).

One aim of this study was to reduce RT-induced long-term side effects with the rectal retractor Rectafix™ . Some previous studies have demonstrated that rectal retractors can reduce the dose-volume parameters of the rectum during prostate RT by reducing prostate motion and physically separating the rectal wall from the prostate (37-39). Men treated with Rectafix™ reported fewer bowel symptoms. Overall bowel bother was measured by the LENT-SOMA GI domain score, and in the Rectafix™ group, bowel bother remained at the baseline level;

Table VI. *Summary of patient-reported quality of life results in the Rectafix group and control groups at baseline, end of treatment, and three years of follow-up.*

	Change in group medians between baseline and end of RT, and baseline and 3-year follow-up															Comparison between groups in different timepoints, *p*-value					
	Radiation therapy group															RF *vs.* Non-RF	RF *vs.* Non-RF CF/MHF	RF *vs.* Non-RF	RF *vs.* Non-RF CF/MHF	RF *vs.* Non-RF	RF *vs.* Non-RF CF/MHF
	Non-RF (n=43)					RF (n=30)					Non-RF CF/MHF (n=12)											
	bl	eRT	*p*-Value	3 y	*p*-Value	bl	eRT	*p*-Value	3 y	*p*-Value	bl	eRT	*p*-Value	3 y	*p*-Value	bl	bl	eRT	eRT	3 y	3 y
IPSS	7.0	11.5	**<0.001**	5.0	0.104	6.0	14.5	**<0.001**	4.0	0.507	6.5	16.0	**0.001**	5.0	0.502	0.905	0.863	0.138	0.685	0.590	0.464
IEFF-5	17.0	9.0	**0.040**	6.0	**<0.001**	17.5	11.0	**0.008**	12.0	0.078	17.0	7.5	**0.021**	2.0	**<0.001**	0.616	0.645	0.521	0.422	0.171	**0.048**
LENT-SOMA GU domain score[a]	2.0			2.0	0.118	2.0			1.0	0.097	2.0			2.5	0.594	0.391	0.310			0.281	0.055
LENT-SOMA GI domain score[b]	2.0			3.0	**0.022**	2.0			2.0	0.701	2.5			4.0	0.102	0.507	0.806			0.117	0.023
1. Painful urination	0.0			0.0	0.156	0.0			0.0	0.750	0.0			0.0	1.000	0.294	0.522			0.585	0.098
2. Frequency (between x h)	3.5			4.0	0.313	4.0			4.0	0.563	3.8			4.0	0.441	**0.048**	0.330			0.304	0.226
3. Blood in urine	0.0			0.0	1.000	0.0			0.0	1.000	0.0			0.0	1.000	1.000	1.000			1.000	1.000
4. Incontinence	0.0			0.0	0.391	0.0			0.0	1.000	0.0			0.0	1.000	0.767	0.170			0.212	**0.043**
5. Usage of pads	0.0			0.0	0.500	0.0			0.0	1.000	0.0			0.0	1.000	1.000	1.000			0.701	0.771
6. Decreased stream of urine	2.0			1.0	**0.029**	2.0			1.0	0.068	2.0			1.0	0.109	0.821	0.800			0.651	0.642
7. Urgency of bowel movement	0.0			1.0	**0.002**	0.0			0.0	0.965	0.0			1.0	**0.016**	0.100	0.939			0.143	**0.012**
8. Mucus on feces	0.0			0.0	0.199	0.0			0.0	1.000	0.0			0.0	0.250	0.452	0.582			0.413	0.664
9. Quality of feces	1.0			1.0	0.371	1.0			1.0	0.250	1.0			1.0	1.000	0.088	0.231			0.830	0.395
10. Frequency (times/day)	1.0			1.5	0.133	1.0			1.0	0.297	1.0			1.8	**0.031**	0.441	0.351			0.776	0.322
11. Incontinence	0.0			0.0	0.070	0.0			0.0	0.750	0.0			0.0	0.625	1.000	0.565			0.181	0.149
12. Usage of pads	0.0			0.0	1.000	0.0			0.0	1.000	0.0			0.0	1.000	1.000	1.000			1.000	0.333
13. Pain on passing a motion	0.0			0.0	1.000	0.0			0.0	1.000	0.0			0.0	1.000	0.314	0.545			1.000	1.000
14. Blood in feces or from anus	0.0			0.0	0.188	0.0			0.0	0.625	0.0			0.0	1.000	0.135	0.486			0.554	0.245
15. Anus irritation	0.0			0.0	0.793	0.0			0.0	0.438	0.0			1.0	0.531	0.654	0.544			0.132	**0.005**
16. Interest in intercourse	2.0			2.5	**0.004**	2.0			2.0	**0.008**	2.0			2.0	0.078	0.338	0.213			0.226	0.199

Changes between timepoints were analyzed using the Wilcoxon signed rank test. Differences between radiation therapy groups were tested using the Mann–Whitney two independent samples test. Bolded values indicate statistical significance at $p<0.05$. The Non-RF group included 12 patients from the group CF/MHF and all 31 patients from the group 36.25/7.25 Gy. The Non-RF CF/MHF group included 12 patients only from the group CF/MHF. The RF group included 30 patients from the group CF/MHF. [a]GU Domain score included questions 1, 3-6; [b]GI Domain score included questions 7-9, 11-15. RF: Rectafix; y: years; CF/MHF: conventional fractionation or moderate hypofractionation; IPSS: International Prostate Symptom Score; IIEF-5: International Index of Erectile Function; LENT-SOMA: Late Effects Normal Tissue Task Force (LENT)-Subjective, Objective, Management, Analytic (SOMA); GU: genitourinary; GI: gastrointestinal.

however, in men treated without a rectal retractor, overall bowel bother worsened. In particular, bowel urgency was a more common symptom in men treated without Rectafix™. When compared to men treated without rectal retractors and with similar fractionation schedules, the long-term bowel protective effect of rectal retractors seems to be worthwhile. This non-Rectafix™ group was small (n=12), which diminishes the reliability of this finding. Our results support the hypothesis that rectal retractors reduce radiotherapy-induced long-term gastrointestinal toxicity, but these findings need more confirmation in larger controlled trials.

A worsening of sexual function during the follow-up was observed in both groups. At the end of RT, patients in the SBRT group had fever sexual symptoms, but otherwise, there were no apparent differences between the study groups. These findings are mostly similar to ultrahypofraction studies comparing RT to conventional treatment (15, 19). In our study population, the worsening of sexual function and loss of interest in intercourse came later in the SBRT group than in the CF/MHF group. One reason for this might be the time difference in the treatments' overall duration. In our study population, the subpopulation of men who did not have an erectile dysfunction at the baseline remained the same in all groups at the three-year follow-up. Katz reported that the proportion of men treated with 35-36.25/7-7.25 Gy sustaining sexual potency during follow-up is quite remarkable, but in general, sexual QoL declined by 23% during the year after treatment but remained stable afterwards (20). In addition, the use of Rectafix™ seemed to correlate with better sexual functioning during the follow-up. Previously, the use of a hydrogel spacer was shown to reduce the penile bulb mean dose and preserve erectile function over time better than the patients treated without spacer (40). Our finding needs to be confirmed with a controlled trial.

Conclusion

The results of this study confirm that SBRT is safe in treating early prostate cancer also in daily clinical practice. There were no meaningful quality-of-life differences between study groups in genitourinary, gastrointestinal, or sexual functions at the three-year follow-up. Overall, the genitourinary and gastrointestinal toxicities were low throughout the study. The rectal retractor Rectafix™ had a mitigating effect on patient-reported long-term overall bowel discomfort and sexual functioning. To our knowledge, this is the first report of the long-term protective efficacy of rectal retractors. The findings of this study have to be confirmed in phase 3 clinical trials.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

P.K. designed, directed, and coordinated this study. P.R. performed data collecting and statistical analysis. P.R. wrote the original draft of this article and I.L., T.L., and P.K. participated in the editing of this article. All Authors have read and approved the manuscript.

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