Original Study

Health-related Quality of Life of Patients Treated With Different Fractionation Schedules for Early Prostate Cancer Compared to the Age-standardized General Male Population

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Abstract

This prospective study investigated the health-related quality of life (HRQoL) of the patients with an early prostate cancer (PC) treated with radiotherapy (RT) without hormonal treatment compared to that in the age-standardized general male population. Patients have equal overall HRQoL measured with the 15D instrument compared to the general male population. Patients had more depression at the beginning of RT, and their sexual activity remained at a lower level after RT.

Background: The effects of radiotherapy (RT) patients' health-related quality of life (HRQoL) are usually compared to those of other treatment modalities instead of HRQoL of the general population in oncological studies. We examined HRQoL of patients with an early prostate cancer (PC) not receiving hormonal treatment up to 3 years after RT using the 15D instrument and the FACT-P questionnaire. **Methods:** The 15D results were compared to those in the age-standardized general male population (N = 952) using an independent-sample *t* test. The study population (N = 73) received RT either with 78/2 Gy, 60/3 Gy or 36.25/7.25 Gy fractionation. **Results:** No significant differences in the mean total HRQoL scores were found between the RT groups and the general male population at any time point. Patients with PC had more depression ($P = .015$) and distress ($P = .029$) than the general male population before the treatment and depression up to 3 months after treatment ($P = .019$), which did not persist at 3 years. The sexual activity dimension had declined by the end of treatment, and this decline persisted 3 years later ($P = .033$). Excretion functions were worse compared to those in peers at the end of treatment ($P < .001$) but no longer at 3 months and later after RT. Regarding the FACT-P, HRQoL remained good at 3 years after RT in all the treatment groups and there were no significant differences between the different RT groups at this time point. **Conclusion:** This study demonstrated that patients treated with RT for early PC had similar HRQoL compared to the age-standardized general male population at 3 years after treatment.

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Introduction

External beam therapy (EBRT) along with radical prostatectomy (RP), is the gold standard for the treatment of local prostate cancer (PC).[1] Over the past decades, the reporting of health-related quality of life (HRQoL) results and other patient-related outcome measures have become a norm in modern oncological research, including in EBRT for PC.[2,3] Although PC had global the fourth highest incidence of all cancers in 2020, and the highest incidence of all cancers in Finland in 2019, the independent effects of external beam therapy on HRQoL have been relatively poorly studied in the absence of other treatments.[4-6] Androgen-deprivation therapy (ADT) seems to have a detrimental effect on HRQoL, which implies

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that the results of studies consisting of men receiving hormonal treatment cannot be generalized to men not receiving ADT.[7]

The primary objective of this trial was to investigate, how radiation therapy for the prostate affects HRQoL in the absence of treatment-related confounding factors. We could not find any previous studies that would have been comparing differences in HRQoL between men treated with EBRT for PC and the age-standardized general population and excluded men receiving ADT. In the New South Wales Prostate Cancer Care and Outcomes Study (PCOS) men receiving either EBRT or brachytherapy had a predetermined clinically significant difference in quality of life (QoL) in terms of bowel function up to 10 years and in terms of sexual function during the whole 15 year follow-up.[8,9] In another population-based study by Schaake et al., men treated with EBRT had worse QoL measured in role functioning, emotional functioning, social functioning, dyspnea and insomnia compared to the general population at 3 years after EBRT.[10] This study included both men with and without hormonal treatment (proportions of 69% and 31%, respectively).[10]

After the development of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT), both an increase in the fraction dose and a decrease in the target volume without additional toxicity have become possible, thus reducing side-effects and hospital visits, costs and patient inconvenience.[11-13] Hypofractionated radiotherapy is currently the preferred form of radiotherapy for local PC recommended by National Cancer Comprehensive Network (NCCN) guidelines.[1,14] Current research, as well as our trial, focuses on ultrahypofractionated radiotherapy, which employs stereotactic body radiation therapy (SBRT), aiming to further increase the fraction dose, reduce toxicity and limit the treatment schedule even to 5 to7 visits.[13]

The secondary objectives were to compare HRQoL between groups undergoing either conventional, hypofractionated or ultrahypofractionated, (Stereotactic Body RT, SBRT) treatment schedules. HRQoL in men treated with ultrahypofractionated schedules has been previously studied only in 2 randomized controlled trials (RCTs), neither of which permitted androgen-deprivation.[15,16] Both trials had both low- and intermediate-risk patients, the HYPO-RT-PC trial used the ASTRO classification and the PACE-B trial used the NCCN classification.[15,16] In the HYPO-RT-PC trial, HRQoL was weaker compared in global health, role functioning, emotional functioning, pain, and diarrhea at the end of radiation of therapy than after conventional therapy, but no difference was observed at follow-ups.[15] The PACE-B trial did not find differences in HRQoL between the ultra-hypofractionation and control group during the 3-month follow-up at any point (the control group consisted of men receiving either conventional or hypofractionated therapy).[16] Moderate hypofractionation has been studied in at least 3 RCTs, which reported acceptable toxicity profile and no differences in HRQoL between hypofractionated therapy and conventional therapy.[17-19]

At present, the treatment results of modern RT for early prostate cancer are excellent in Finland.[20] Therefore, studying the patients' mental and overall health after PC diagnosis is important, as the vast majority of patients are expected to recover (the metastasis-free 5-year survival almost 95 %) and compare HRQoL between the patients with PC treated using 3 RT fractionating schemes and the age-standardized general male population to explore the need for individual psychosocial support for patients with radically treated PC.

Materials and Methods

Patients and Radiation Therapy Planning

Men up to 85 years of age with a biopsy-confirmed localized T1c-T2cN0M0 prostate cancer with 1 or 2 intermediate risk factors (IFRs) according to NCCN criteria were eligible for this study.[21] IFRs were T2b-T2c disease, Gleason score of 7 or a prostate-specific antigen (PSA) level of 10 to 20 ng/mL. Androgen deprivation therapy (ADT) or need of transurethral resection of the prostate (TURP) were exclusion criteria. Between May 2014 and December 2017, a total of 73 patients (approximately 90%-95% of eligible patients) were recruited from Tampere University Hospital. The first 42 patients were treated with a fraction dose of 2 Grays (Gy), 5 fractions per week to a total dose of 78 Grays (78/2 Gy) or 60/3 Gy according to the clinician's decision, and the next 31 patients were then treated with a higher fraction dose: 7.25 Gy and only 5 times = 36.25/7.25 Gy. The Tampere University Hospital Ethics Committee approved the study (R14009), and patients provided written informed consent. The clinical trial identifier was NCT02319239 at www.ClinicalTrials.gov.

Prior to RT, all patients had 3 gold fiducial markers implanted into the prostate gland under transrectal ultrasound guidance. After implantation, planning computed tomography (CT) and magnetic resonance imaging (MRI) were performed (with empty bladder and rectum). The prostate and the base of the seminal vesicles were delineated as the prostate clinical target volume (CTV). A symmetric 5-mm margin was used to achieve prostate planning target volume (PTV). If the seminal invasion (SV) risk was greater than 15%, SV sites were contoured and given 7-mm expansion as SV-PTV in the RT 78/2 Gy and 60/3 Gy groups, and the RT doses to the SV-PTV were 56/2 Gy and 46/2.3 Gy, respectively.[22] In the 36.25/7.25 Gy group SV sites were not included. The bladder, rectum, and femoral heads were defined as organs at risk. Treatment localization was performed by orthogonal kilo voltage (kv) imaging. In the 36.25/7.25 Gy group cone beam CT (CBCT) was used to evaluate the bladder and rectum before every treatment session. In the 78/2 Gy and 60/3 Gy groups radiotherapy was administered daily from Monday to Friday, and the 36.25/7.25 Gy group received treatment every other day for ten days. Volumetric modulated arch therapy (VMAT) with 2 full arcs and 6-MV flattened beams was used for treatment in all groups.

Health-related Quality of Life Instruments

In this study, we used 2 internationally validated patient-reported outcome questionnaires in Finnish to evaluate the HRQoL of patients with PC treated with RT: the 15D instrument and the Functional Assessment of Cancer Therapy-Prostate (FACT-P). These questionnaires were completed before RT (baseline), at the end of treatment, and 3 months, 1 year, 2 years and 3 years after the RT. Altogether, 787 questionnaires were collected during the study, yielding a response rate of 92%.

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The 15D is a generic instrument with 15 dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity) and developed in Finland and used in different type of diseases, interventions, and compare costs using Quality Adjusted Life Years (QALYs) and is comparable to EQ-5D.[23-27] Each dimension has 5 different answers ranging from no problems to extreme problems.[28] The 15D score ranges from 0 to 1, where 1 indicates full health. The minimum clinically important change in the 15D score is interpreted as follows: |0.015-0.035| for slightly better/worse and over |0.035| for much better/worse. A 15D score change of $\geq$ 0.015 is considered clinically meaningful, with the patient feeling the difference in his or her wellbeing.[29] An age-standardized sample of the Finnish male population (N = 952) was used as a comparison group for patients treated with RT, which was obtained from the National Health 2011 Survey.[30] The National Health 2011 Survey was a combination of health interview and health examination aimed to obtain information on public health problems in working-aged and the aged population. It captured 7964 persons aged 30 and over living in the mainland Finland.

The FACT-P is a validated 39-item questionnaire that was developed to measure HRQoL in men with prostate cancer and consists of 5 subscales: 7 items for physical wellbeing (PWB), 7 items for social and family wellbeing (SWB), 6 items for emotional wellbeing (EWB), 7 items for functional wellbeing (FWB) and 12 items for the prostate cancer subscale (PCS).[31] Items are scored from 0 to 4 and it can be worded in a positive or negative direction. The FACT-P total score ranges from 0 to 156. Higher values of total or any subscales indicate better HRQoL. The FACT-G (general) measures general HRQoL in patients with cancer and consist of 27 items (PWB, SWB, EWB and FWB). The FACT-P Trial Outcome Index (TOI) is based on physical, functional and prostate cancer -specific subscales of the FACT-P (PWB, FWB and PCS).

One method to evaluate meaningful changes in the FACT-P total score or in its subscales at different timepoints, is to compare scores to the published minimal important difference (MID) scores. Most of the publications in this area correspond to men with metastatic prostate cancer. Meaningful changes vary from 6 to 10 points for the total FACT-P score, from 5 to 7 points for the FACT-P TOI score, from 2 to 3 points for the FACT-P PCS score and 5 to 8 points for the FACT-G score, respectively.[32,33]

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics version 25.0 for Windows (SPSS Inc. Chicago, IL). The statistical significance of the difference between mean 15D scores between the general male population and patients treated with RT was tested using independent-sample *t* tests. The same test was used for differences between 15D scores and FACT-P scores in the RT treatment groups. Treatment changes within the RT groups before the RT and at the appointed follow-up timepoint were analyzed using paired-sample *t* tests. If the 15D or FACT-P variables were not normally distributed, a corresponding nonparametric test was performed. The Mann-Whitney 2 independent samples test was used to compare 2 RT groups, and changes within the RT group between different time points were analyzed using the Wilcoxon signed-rank test. All tests used a 2-sided $P < .05$ for statistical significance.

Results

The mean and median age of the patients treated with RT was 69 years (range 59-78 years). Most of the patients had a Gleason 3 + 4 disease, and the mean PSA was 9.5 ng/mL. After 3 years of follow-up, 66 patients were included in the study. Of the 7 discontinuations, 3 were in 78/2 Gy group, and 2 in 60/3 Gy and 36.25/7.25 Gy groups. Four men developed another aggressive malignant disease that was not related to RT, and 1 man in 78/2 Gy group and 2 men in 60/3 Gy group had a biochemical relapse according to the Phoenix definition.[34] All 3 relapses had a Gleason 3+4 disease at baseline. The clinical demographics of the patients treated with RT are presented in Table 1.

Results from the 15D Instrument

Changes in the 15D score and scores for different dimensions in patients treated with RT are demonstrated in Figure 1. No statistically significant differences in the mean 15D score were found between patients treated with RT and the general male population at the beginning of treatment or at the 3-year follow-up (Table 2). The acute toxicity of RT treatments did not correspond to the 15D score at the end of RT, or at any timepoint compared to observations in the general male population. The 15D scores of the patients treated with RT ranged from 0.735 to 1.000 (mean 0.913) at the baseline. Six patients were in full health (15D score 1.000). At the end of the treatment 2 patients were in full health and 15D scores ranged from 0.675 to 1.000 (mean 0.898). Three years after RT, 4 patients had a 15D score of 1 and, 15D scores ranged from 0.504 to 1.000 (mean 0.890). The 15D score difference decrease between baseline and the 3-year follow-up was statistically significant ($P = .001$).

At the baseline, patients treated with RT had lower mean scores for depression and distress ($P = .015$ and $P = .029$, respectively) than the general male population. At the end of RT, these mental problems continued, and 3 months after the treatment, the mean dimension score for depression was still significantly lower ($P = .019$). However, in the end of the follow-up at 3 years, the mental health of the patients treated with RT was similar to the general population ($P > .05$ for both distress and depression). The sexual activity of patients treated with RT was also non significantly lower at the baseline. Immediately and 3 years after the treatment sexual activity was significantly lower than that in the general male population. When bowel and bladder symptoms (Excretion) were compared, patients treated with RT had better mean scores at baseline and significantly worse scores at the end of RT ($P < .001$), but subsequently, no differences compared to the general male population were identified. Patients seemed to score better than the general male population for physical discomfort and symptoms at 3 years after RT ($P = .027$). Patients also had better cognitive function scores at all timepoints.

When observing the changes within the RT groups (supplementary Table S1), the HRQoL measured by the 15D score worsened significantly in the 78/2 Gy and 60/3 Gy groups, but not in the SBRT 36.25/7.25 Gy group between baseline and 3 years after treatment ($P = .034$, $P = .044$ and $P = .153$, respectively). Bowel and

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Table 1 Patients Clinical Demographs

	Radiation Therapy Group			
	All N = 73	39 × 2 Gy N = 21	20 × 3 Gy N = 21	5 × 7.25 Gy N = 31
Age, years				
Mean (range)	69 (59-78)	68 (59-78)	70 (60-78)	70 (63-78)
BMI				
Mean (range)	28.1 (21.4-40.6)	28.4 (21.4-40.4)	27.8 (22.4-34.8)	28.1 (21.8-40.6)
BMI ≥ 30, N (%)	19 (26)	6 (29)	5 (24)	8 (26)
Comorbidities, N (%)				
Diabetes type II	17 (23)	4 (19)	6 (29)	7 (23)
Hypertension	44 (60)	11 (52)	10 (48)	23 (74)
ASO	11 (15)	4 (19)	3 (14)	4 (13)
AF	8 (11)	3 (14)	3 (14)	2 (7)
Gleason score, N (%)				
3 + 3	21 (29)	7 (33)	8 (38)	6 (19)
3 + 4	49 (67)	13 (62)	13 (62)	23 (74)
4 + 3	3 (4)	1 (5)	0 (0)	2 (7)
T stage, N (%)				
T1c	11 (15)	2 (10)	3 (14)	6 (19)
T2a	18 (25)	5 (24)	4 (19)	9 (29)
T2b	9 (12)	3 (14)	3 (14)	3 (10)
T2c	35 (48)	11 (52)	11 (52)	13 (42)
PSA baseline, ng/mL				
Mean (range)	9.5 (3.2-19.1)	10.5 (4.0-15.2)	8.7 (3.4-18.4)	9.5 (3.2-19.1)
Questionnaires returned, N (%)				
Baseline	70 (96)	21 (100)	21 (100)	28 (90)
End of RT	67 (92)	21 (100)	21 (100)	25 (81)
3 months	70 (96)	21 (100)	21 (100)	28 (90)
12 months	68 (93)	19 (90)	21 (100)	28 (90)
24 months	64 (88)	17 (81)	20 (95)	27 (87)
36 months	63 (86)	18 (86)	18 (86)	27 (87)

Abbreviations: Gy = Gray; BMI = Body mass index; ASO = Atherosclerosis; AF = atrial fibrillation; PSA = Prostate specific antigen; N = number of patients

bladder problems (Excretion) were present in all RT groups at the end of treatment. According to the mean dimension scores at 3 years after the RT, the scores in the 78/2 Gy and 60/3 Gy groups were worse than the baseline scores. Sexual activity worsened in all RT groups from baseline to the 3-year of follow-up. The men in the 60/3 Gy group felt less energetic (Vitality) and more depressed (Depression) 3 years after RT, but they had less physical discomfort and fewer symptoms. The men in the 36.25/7.25 Gy group had more discomfort and symptoms during the follow-up. Three years after RT the men in the 78/2 Gy group had more symptoms related to ageing than the men in the other groups. The dimensions related to vision, hearing, breathing and sleeping became worse between the baseline and the 3-year follow-up.

At the end of RT, the 36.25/7.25 Gy group had a better HRQoL than the 78/2 Gy group when comparing 15D total scores ($P = .023$) (Figure S1). The men in the 36.25/7.25 Gy group had fewer problems with excretory functions ($P = .014$) and were more satisfied with their sexual activity ($P = .013$) at the end of RT than men in the 78/2 Gy group. The difference in the dimension of sexual activity was at 3 months after RT in favor of the 36.25/7.25 Gy group ($P = .034$). One year after treatment, the men in the 36.25/7.25 Gy group reported better HRQoL with respect to the 15D total score than the men in the 78/2 Gy group ($P = .015$). The men in the 36.25/7.25 Gy group were more content with usual activities (UACT) than the men in the 78/2 Gy group ($P = .006$). Between the 60/3 Gy and 36.25/7.25 Gy groups, the men treated with SBRT had less distress at 3 years after RT ($P = .045$), and between the 78/2 Gy and 60/3 Gy groups, men treated with hypofractionated RT had less discomfort and symptoms ($P = .028$) at 1 year after RT.

Results from the FACT-P Questionnaires

The baseline FACT-P total score of the whole study population was 128.5 (SD 16.9). The treatments had a transient negative effect on HRQoL (Table 3.). At the end of the RT, the FACT-P total score declined significantly (124.7, SD 18.1, $P = .013$). However, after 3 years of follow-up the FACT-P total score returned to baseline level (128,5, SD 18.8, $P = .364$). At the end of RT, significant negative changes in physical activity (PWB, $P = .002$), the prostate-cancer-specific subscale (PCS, $P = .002$), and the trial outcome index (TOI) ($P = .002$) were observed. Negative changes in physical activ-

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Figure 1 The mean 15D dimension scores of RT patients and the age-standardized general male population at different timepoints. Population 1 is the control population for the treatment group at baseline until 3 months and population 2 is the control population for the treatment group at 36 months. Statistically significant changes in RT patients' dimension scores between the baseline and follow-up timepoints are marked with asterisks (*).

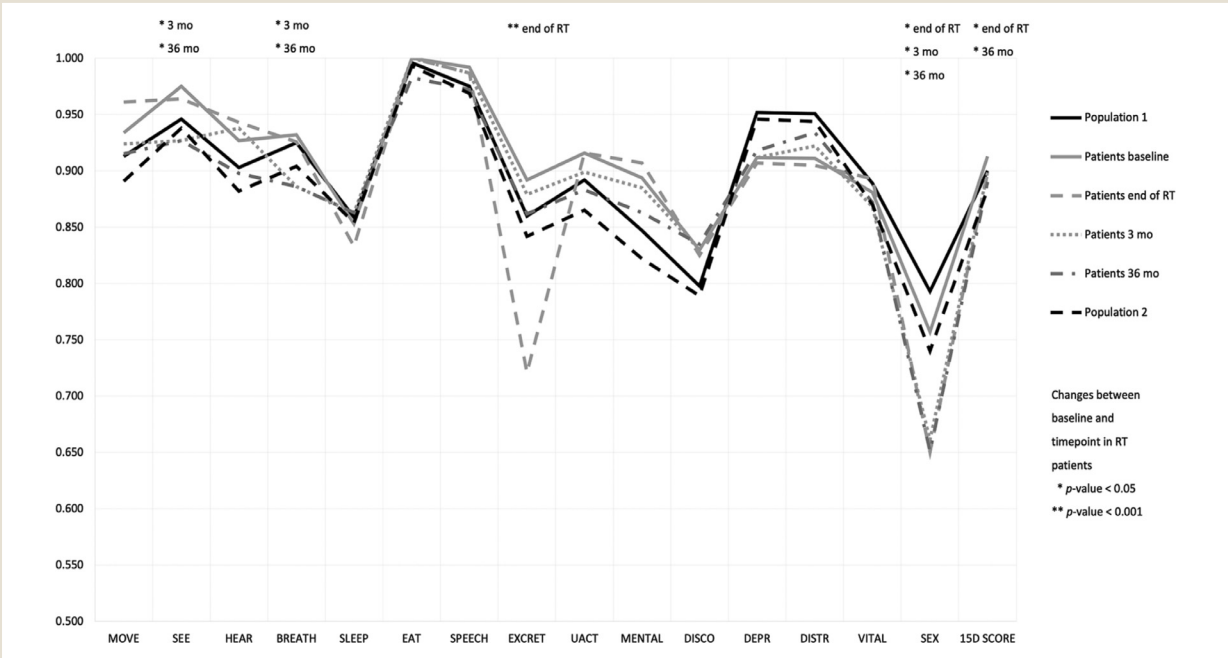

Table 2 The Mean 15D Scores and Dimension Values of RT Patients at Different Timepoints Compared to The Age-Standardized General Male Population

	Baseline		End of RT		3 Months After RT		3 Years After RT	
	Mean	Δ	Mean	Δ	Mean	Δ	Mean	Δ
15D score	0.913	0.013	0.898	-0.012	0.899	-0.011	0.890	0.006
Mobility	0.934	0.023	0.961	0.048[b]	0.924	0.011	0.915	-0.019
Vision	0.975	0.029[a]	0.964	0.018	0.927	-0.019	0.927	-0.011
Hearing	0.927	0.024	0.943	0.040[a]	0.938	0.035	0.898	0.016
Breathing	0.932	0.007	0.926	0.001	0.886	-0.039	0.886	-0.018
Sleeping	0.853	-0.006	0.833	-0.026	0.863	0.004	0.863	0.009
Eating	1.000	0.004	1.000	0.004	1.000	0.004	0.983	-0.010
Speech	0.992	0.017	0.987	0.012	0.987	0.012	0.972	0.003
Excretion	0.892	0.032	0.721	-0.139[b]	0.879	0.019	0.862	0.020
Usual activities	0.916	0.024	0.916	0.024	0.899	0.007	0.883	0.018
Mental function	0.894	0.047[a]	0.907	0.053[a]	0.885	0.038	0.863	0.041
Discomfort and symptoms	0.830	0.032	0.825	0.027	0.830	0.032	0.835	0.046[a]
Depression	0.912	-0.040[a]	0.907	-0.045[a]	0.912	-0.040[a]	0.918	-0.028
Distress	0.911	-0.040[a]	0.905	-0.046[a]	0.922	-0.029	0.934	-0.010
Vitality	0.881	-0.008	0.893	0.004	0.868	-0.021	0.872	0.002
Sexual activity	0.757	-0.036	0.650	-0.143[b]	0.661	-0.132[b]	0.651	-0.089[a]

Δ, difference compared to the age-standardized male population (positive values for better score to RT patients in comparison to general population).
Differences between RT population and age-standardized male population were analyzed using independent-sample *t* test
[a] $P < .05$
[b] $P < .001$.

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Table 3 The Mean FACT-P Scores and Standard Deviations (SD) of RT Patients (N = 73)

	Baseline (N = 70)	End of RT (N = 67)	3 Months (N = 70)	12 Months (N = 68)	24 Months (N = 64)	36 Months (N = 63)
FACT-P total	128.5 (16.9)	124.7 (18.1)[a]	126.9 (18.9)	126.6 (16.9)	127.6 (17.0)	128.5 (18.8)
FACT-G total	90.8 (12.3)	89.3 (13.5)	89.9 (14.5)	89.0 (12.3)	89.8 (12.0)	90.7 (13.7)
Physical (PWB)	25.7 (2.7)	24.4 (3.4)[a]	25.1 (3.2)	25.2 (3.2)	25.1 (3.1)	24.9 (3.4)[a]
Social (SWB)	22.0 (4.9)	21.9 (5.1)	21.8 (5.9)	21.2 (5.6)	21.7 (4.5)	22.0 (5.0)
Emotional (EWB)	20.4 (3.0)	20.7 (3.0)	20.8 (2.7)	20.8 (3.0)	20.4 (2.9)	20.9 (3.0)
Functional (FWB)	22.4 (4.9)	22.1 (5.3)	22.2 (5.8)	21.9 (5.3)	22.3 (4.3)	22.7 (4.6)
Prostate cancer specific (PCS)	37.7 (6.0)	35.2 (6.4)[a]	37.2 (5.7)	37.4 (5.8)	37.7 (5.9)	37.9 (6.1)
Trial Outcome Index (TOI)	85.9 (11.2)	81.7 (12.9)[a]	84.4 (12.5)	84.5 (12.0)	85.2 (12.1)	85.5 (12.9)

The FACT-P, FACT-G and subscales score (range): FACT-P (0-156); FACT-G (0-108); PWB, SWB, FWB (0-28); EWB (0-24); PCS (0-46); TOI (0-104).
Changes between baseline and timepoints were analyzed using paired-sample *t* test
[a] $P < .05$; $P < .001$.

ity in the whole study population were still observed after 3 years of follow-up ($P = .019$).

No significant changes in the FACT-P total scores were identified in any of the RT groups between baseline and the 3-year of follow-up (Table S2). The highest scores were in the 36.25/7.25 Gy group. The 60/3 Gy group was the only group in which the FACT-P total score decreased between baseline and 3 years after RT. At the end of RT, the mean TOI worsened in the 60/3 Gy group by 6 points ($P = .011$). Between baseline and the end of RT, the mean score in PCS of the 60/3 Gy group decreased by 3.9 points ($P = .006$), and at 3 months after RT, these patients still had more symptoms than at baseline ($P = .014$). None of the RT groups had significant changes in the PCS scores between baseline and the 3-year of follow-up.

Discussion

This study had several strengths. According to our review, this is the first prospective trial comparing short-term (< 5 year) results in patients of exclusively after EBRT for early prostate cancer treated with modern RT techniques to results in an age-standardized general male population. The PCOS study reported results for a combined group of EBRT and brachytherapy group, which does not accurately depict the effects of EBRT since the QoL effects differ, particularly considering urinary functions.[8,35] To our knowledge, this study is also the first to compare short-term results in men exclusively without ADT, therefore accurately depicting the HRQoL effects of EBRT without confounding factors. However, this factor can also be considered a limitation, because most men treated with EBRT will receive adjuvant or neoadjuvant ADT (approximately 80% in Finland).[10,20] HRQoL effects of EBRT for prostate cancer seem tolerable, and acceptable, and minor compared with those of adjuvant EBRT treatment of breast cancer, for instance.[36]

Overall, our results are in line with those in the PCOS study and Schaake et al., considering general HRQoL and sexual functions.[8,10] Compared to the PCOS study results, no decrease in excretory functions was observed at 3 months or later after EBRT.[8] However, the 15D instrument does not separate urinary and fecal excretory functions, which could also be viewed as a limitation. Compared to our study, in the PCOS study, the mental well-being scores were lower in the patient population than in the reference population at 1, 2 and 3 years after EBRT, but the result did not exceed the clinically significant difference.[8] Our study did not use an identical time frame, and the results are therefore not directly comparable, but our results support the results of the PCOS study considering 3-year HRQoL.[8] In our study, depression was more common in the patient population than in the general population for at least 3 months, and distress was more common until the end of treatment. Our results suggest that mental health interventions may be beneficial. However, according to the previous research, nontargeted approaches are unlikely to improve mental health-related QoL.[37] A recent review by Mundle et al., suggested screening of mental problems in men treated for PC and targeted treatment, although more study is needed on what exact form or method should be used for screening.[38] Sexual rehabilitation programs seem to reduce sexual bother and improve adherence to the standard pharmaceutical treatments for erectile dysfunction, but whether they actually improve HRQoL or its sexual domain, requires more study and one of the

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key issues is to include an uro-oncological nurse to PC team and she/he should have enough time to discuss with the patient and his spouse about the multidimensional issues related to PC and its treatments.[39] Electronic patient reported outcomes (PROs) is a modern way to follow-up patients HRQoL life and increase it as we have first done with patients with breast cancer.[40] The same system was initiated in 2019 for patients with prostate cancer treated with RT.

Compared to those in Schaake et al., our patients did not have weaker sleep- or breathing-related HRQoL at 3 years.[10] As Schaake et al., showed that increased reported dyspnea was related to the prevalence of chronic obstructive pulmonary disease (COPD) and asthma in this cohort, indicating that the difference was likely caused by differences in the characteristics of the study populations.[10] However, the difference in sleep-related quality of life cannot be explained and remains a topic for further study.[10]

Considering the FACT-P results, Monga et al. reported a similar decline in PWB and PCS subdomains at the end of radiotherapy.[41] In their study, the differences in FACT-P were not present any longer at 2 months, similar to our 3-month result.[41] This suggests that HRQoL declines are transient. Compared to the HYPO-RT-PC and PACE-B trials, our study included only intermediate-risk patients.[15,16] Compared to the PACE-B study, which also used the NCCN classification, we report HRQoL results up to 3 years vs. the 3 months in the PACE-B study.[16] No results from RCTs that combine ADT and SBRT have yet been published, although studies are ongoing.[18,42]

Limitations

This study has also several limitations. First, the number of patients with PC in our study was quite small compared to those in the HYPO-RT-PC and PACE-B trials for evaluating the secondary objective.[15,16] The sample size was large enough to evaluate patients as 1 group (N = 73) in relation to the general population but unfortunately is too small to account for statistically powerful comparisons between different fractionation groups. Small sample size bears a risk for false negative results. However, as the results of HYPO-RT-PC and PACE-B are in conflict with each other considering the HRQoL at the end of treatment, our trial provides further information on the long-term HRQoL and thus we decided to report also the results for different fractionation groups briefly.[15,16] Our study reports also HRQoL results for 3 years after RT, which neither of the aforementioned trials do not, since PACE-B HRQoL results were reported up to a year and HYPO-RT-PC long-term results 1, 2, 4 and 6 years after RT.[15,16]

The study was not randomized, which predisposes to both unknown and known types of confounders, such as selection bias.[43] Our study was also single-center design, which may limit its generalizability. The study population was superior compared to the age-matched general population in some features (vision and mental/cognitive functions at baseline), likely because we did not account for possible differences in educational levels between populations. There is also some possible bias in relation with time, since the population sample (N = 952) used in comparison was collected in 2011, and the study took place between 2014 and 2017. Also, the first patients were assigned either 78/2 Gy or 60/3 Gy fractionation, but the later participants were systematically assigned to 36.25/7.25 Gy fractionation, which is another source of possible bias. It is known that certain phenomena that occur periodically, such as economic crises or pandemics, may affect physical and mental health and thus also HRQoL.[44–46]

Finally, our results only apply to those men belonging to NCCN intermediate-risk group and treated with EBRT. There are currently many good care options for men belonging to those group, including active surveillance, brachytherapy and RP.[1] According to the current NCCN guideline, observation is preferable to the EBRT, if life expectancy is under 10 years and the disease belongs to the favourable intermediate risk group.[1] Our study did not distinguish between favorable and unfavorable intermediate risk groups.

Conclusion

The HRQoL of our patients treated with RT for PC seems to be at a high level except for sexuality-related issues, and more attention should be devoted to this important aspect of HRQoL and to the development of possible therapeutic interventions/approaches according to patients' personal needs. SBRT was also tolerated as conventional and moderately hypofractionated treatment, and the overall HRQoL of EBRT-treated PC patients in this study compared with the age-standardized general population was good. SBRT seems to be a convenient treatment in daily clinical practice.

Clinical Practice Points

- There are limited studies comparing the effects of curative-intent RT on early PC patients' to HRQoL in the general population. In this study we demonstrated that the overall HRQoL of early PC patients treated with modern image guided RT techniques and without hormonal treatment is equal at 3 years after treatment to the age-standardized general male population measured with the 15D instrument. The patients with prostate cancer had more depression and distress in the time of active treatment to their cancer when compared to the age-standardized male population. Patients' sexual activity declined during RT and remained at the lower level during 3-year follow-up. In the future, more support should be given to the PC patients at the beginning of the treatment to mental issues and also later to address sexual issues.
- The HRQoL of 3 different RT groups; conventional fractionation (78/2 Gy), moderate hypofractionation (60/3 Gy) or stereotactic body radiotherapy (36.25/7.25 Gy), were compared with the 15D instrument and the FACT-P questionnaire. The changes within the RT groups measured by the 15D score worsened significantly in the 78/2 Gy and 60/3 Gy groups, but not in the SBRT 36.25/7.25 Gy group, but there were no significant changes in the FACT-P total scores in any of the RT groups, between baseline and 3 years after treatment. This study confirms the rationale of treating early PC with stereotactic body radiotherapy.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Expert Responsibility area of Tampere University Hospital (protocol code R14009, 2014-02-24).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

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Disclosure

Harri Sintonen is the developer of the 15D and obtains royalties from its electronic versions. The other authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.clgc.2022.07.013.

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