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Petri Reinikainen , Miikka Lehtonen , Ilari Lehtinen ,  
Tiina Luukkaala , Harri Sintonen ,  
Pirkko-Liisa Kellokumpu-Lehtinen

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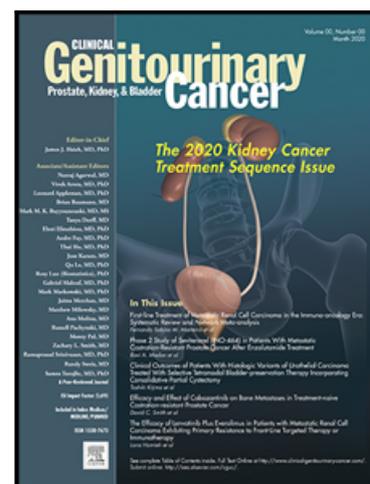
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## **Bullet points**

- ◁ The overall health-related quality of life (HRQoL) of the patients with an early prostate cancer treated with modern image guided RT techniques and without hormonal treatment is equal at three years after treatment to the age-standardized general male population measured with the 15D instrument.
- ◁ More support to the patients with an early prostate cancer should be given in mental health issues at the beginning of treatment and in the sexual issues after the treatment.
- ◁ The HRQoL of the patients with an early prostate cancer treated with three different radiotherapy fractionation was measured with the 15D instrument and The Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and compared. Continuation to treat with stereotactic body radiotherapy seems rational regarding to the HRQoL results.

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

Petri Reinikainen<sup>1</sup>, Miikka Lehtonen<sup>2</sup>, Ilari Lehtinen<sup>3</sup>, Tiina Luukkaala<sup>4</sup>, Harri Sintonen<sup>5</sup> and Pirkko-Liisa Kellokumpu-Lehtinen<sup>1</sup>

<sup>1</sup> Faculty of Medicine and Health Technology and Tampere University and TAUH Cancer Center, Tampere University Hospital, Tampere, Finland

<sup>2</sup> Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland;

<sup>3</sup> Faculty of Information Technology and Communication Sciences, Tampere, Finland;

<sup>4</sup> Research, Development and Innovation Center, Tampere University Hospital, Tampere, Finland and Health Sciences, Faculty of Social Sciences, Tampere University

<sup>5</sup> Department of Public Health, University of Helsinki, Helsinki, Finland

## **Corresponding author**

Dr. Petri Reinikainen

Tampere University Hospital, Elämänaukio 2, PL 2000, 33521 Tampere - Finland

petri.reinikainen@tuni.fi

## **Declaration of interest**

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

## **Microabstract**

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.

## **Abstract**

### *Background*

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 three 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 three months after treatment ( $P = .019$ ), which did not persist at three years. The sexual activity dimension had declined by the end of treatment, and this decline persisted three years later ( $P = .033$ ). Excretion functions were worse compared to those in peers at the end of treatment ( $P < .001$ ) but no longer at three months and later after RT. Regarding the FACT-P, HRQoL remained good at three years after RT in all the treatment groups and there were no significant differences between the different RT groups at this time point.

### *Discussion*

This study demonstrated that patients treated with RT for early PC had similar HRQoL compared to the age-standardized general male population at three years after treatment.

**Keywords:** Prostate Cancer; Radiotherapy; Hypofractionated radiotherapy; Quality of Life; 15D instrument; the FACT-P questionnaire

## Introduction

External beam therapy (EBRT) along with radical prostatectomy (RP), is the gold standard for the treatment of local prostate cancer (PC).<sup>1</sup> 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.<sup>2,3</sup> 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.<sup>4,6</sup> Androgen-deprivation therapy (ADT) seems to have a detrimental effect on HRQoL, which implies that the results of studies consisting of men receiving hormonal treatment cannot be generalized to men not receiving ADT.<sup>7</sup>

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 ten years and in terms of sexual function during the whole 15 year follow-up.<sup>8,9</sup> In another population-based study by Schaake et al., men treated with EBRT had worse QoL measured in role functioning, emotional functioning, social functioning, dyspnoea and insomnia compared to the general population at 3 years after EBRT.<sup>10</sup> This study included both men with and without hormonal treatment (proportions of 69% and 31%, respectively).<sup>10</sup>

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.<sup>11,13</sup> Hypofractionated radiotherapy is currently the preferred form of radiotherapy for local PC recommended by National Cancer Comprehensive Network (NCCN) guidelines.<sup>1,14</sup> Current research, as well as our trial, focuses on ultrahypofractionated radiotherapy, which employs stereotactic body radiation therapy (SBRT), aiming to further increase the fraction

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 two randomized controlled trials (RCTs), neither of which permitted androgen-

deprivation.<sup>15,16</sup> 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.<sup>15,16</sup> In the HYPO-RT-PC trial, HRQoL was weaker compared in global health, role functioning, emotional functioning, pain, and diarrhoea at the end of radiation of therapy than after conventional therapy, but no difference was observed at follow-ups.<sup>15</sup> The PACE-B trial did not find differences in HRQoL between the ultrahypofractionation and control group during the three-month follow-up at any point (the control group consisted of men receiving either conventional or hypofractionated therapy).<sup>16</sup> Moderate hypofractionation has been studied in at least three RCTs, which reported acceptable toxicity profile and no differences in HRQoL between hypofractionated therapy and conventional therapy.<sup>17,19</sup>

At present, the treatment results of modern RT for early prostate cancer are excellent in Finland.<sup>20</sup> V j g t g h q t g . " u v w f { k p i " v j g " r c v k g p v u o " o g p v c n " c p f " q x g t c m n " j g c n v j " c h v g t " R E " f k c i p q u k u " k u " 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 three 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 one or two intermediate risk factors (IFRs) according to NCCN criteria were eligible for this study.<sup>21</sup> IFRs were T2b-T2c disease, Gleason score of 7 or a prostate-specific antigen (PSA) level of 10-20 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), five fractions per y g g m " v q " c " v q v c n " f q u g " q h " 9 : " I t c { u " \* 9 : 1 4 " I { + " q t " 8 2 1 5 " I { " c e e q t f k p i " v q " v j g " e n k p k e k c p o u " f g e k u k q p . " c p f " v j g " next 31 patients were then treated with a higher fraction dose: 7.25 Gy and only five 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](http://www.ClinicalTrials.gov).

Prior to RT, all patients had three 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.<sup>22</sup> 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 arc therapy (VMAT) with two 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 two 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 three months, one year, two years and three years after the RT. Altogether, 787 questionnaires were collected during the study, yielding a response rate of 92%.

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.<sup>23,26,27</sup> Each dimension has five different answers ranging from no problems to extreme problems.<sup>28</sup> 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 |0.0257-0.035| considered clinically meaningful, with the patient feeling the difference in his or her wellbeing.<sup>29</sup> 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.<sup>30</sup> 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 five subscales: seven items for physical wellbeing (PWB), seven items for social and family wellbeing (SWB), six items for emotional wellbeing (EWB), seven items for functional wellbeing (FWB) and 12 items for the prostate cancer subscale (PCS).<sup>31</sup> Items are scored from zero to four 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 six to ten points for the total FACT-P score, from five to seven points for the FACT-P TOI score, from two to three points for the FACT-P PCS score and five to eight points for the FACT-G score, respectively.<sup>32,33</sup>

### *Statistical analysis*

Statistical analyses were performed with IBM SPSS Statistics version 25.0 for Windows (SPSS Inc. Chicago, Illinois). 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 analysed 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 two independent samples test was used to compare two RT groups, and changes within the RT group between different time points were analysed 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 three years of follow-up, 66 patients were included in the study. Of the seven discontinuations, three were in 78/2 Gy group, and two 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 one man in 78/2 Gy group and two men in 60/3 Gy group had a biochemical relapse according to the Phoenix definition.<sup>34</sup> All three 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 three-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 two patients were in full health and 15D scores ranged from 0.675 to 1.000 (mean 0.898). Three years after RT, four 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 three-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 three 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 three 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 nonsignificantly lower at the baseline. Immediately and three 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 three years after RT ( $P = .027$ ). Patients also had better cognitive function scores at all timepoints.





































**Figure S1.** The mean 15D scores and mean dimension values at different timepoints in RT groups.

