Evaluating a novel technology in radiotherapy using digital patient-reported outcomes

The PRO-MR-RT study

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PhD Thesis

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November 2022

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Preface

This thesis contains two published papers, one submitted and one under preparation:

Paper I: Møller PK, Pappot H., Bernchou U., Dieperink KB.
Development of patient-reported outcomes item set to evaluate acute treatment toxicity to pelvic online magnetic resonance-guided radiotherapy. *J Patient Rep Outcomes*. 2021. 5, 47.

Paper II: Møller PK, Pappot H, Bernchou U, Schytte T, Mortensen ZV, Brúnni MFÁ, Dieperink KB.
Feasibility, usability and acceptance of weekly electronic patient-reported outcomes among patients receiving pelvic CT- or online MR-guided radiotherapy – A prospective pilot study. *Technical Innovations & Patient Support in Radiation Oncology*. 2022; 21:8-15.

Manuscript III: Møller PK, Pappot H, Schytte T, Bernchou U, Dieperink KB.
Prospective evaluation of online adaptive MR-guided radiotherapy with digital patient-reported acute symptom trajectories for prostate cancer patients. *Submitted to Practical Radiation Oncology, 24-11-2022*

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“For it is an advantage to advance to that which is more knowable,” Aristotle once said, and I believe that is the privilege of entering the world of research. Luckily, there is much more out there to explore since “The more you know, the more you know, you do not know”.

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radiotherapy section in Odense. I never would have or could have done this without your support. This project is your work! I sincerely want to thank you for going along with the idea, trying it out and providing feedback and hugs. You improve the patients' treatments every day with professionalism and respect for the individual patient. Also, a very special thanks to Anne, Janne and Hanne for all your support and for creating a culture we all want to be a part of. Thank you to the department management Stefan Jeppesen and Trine Zachariassen, for supporting me in my PhD and future pathway.

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I look forward to all the exciting opportunities and adventures of the future.

Pia Krause Møller, November 2022

Contents

Abbreviations

ADT	Androgen Deprivation Therapy
AE	Adverse event
AI	Artificial intelligence
CBCT	Cone Beam Computed Tomography
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
3D-CRT	Three-dimensional Conformal Radiation Therapy
EBRT	External beam radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
GI	Gastrointestinal
GU	Genitourinary
HRQoL	Health-related quality of life
IGRT	Image-Guided Radiation Therapy
IMRT	Intensity Modulated Radiation Therapy
MID	Minimal important difference
MR	Magnetic resonance
MRgRT	MR-guided radiotherapy
MRI	Magnetic resonance imaging
MR-linac	Magnetic resonance linear accelerator
OAR	Organs-At-Risk
OUH	Odense University Hospital
PCa	Prostate cancer
PFF	Patient Feedback Form
PRO	Patient-reported outcomes
PROM	Patient-reported outcome measure
PRO-CTCAE	Patient-Reported Outcomes version of the CTCAE
PS	Performance status
PSA	Prostate specific antigen
QoL	Quality of life
RCT	Randomised controlled trial
RT	Radiotherapy
T	Tesla
SBRT	Stereotactic Body Radiotherapy
VMAT	Volumetric Modulated Arc Therapy

English summary

Background

In 2018, patients with cancer could be treated with online adaptive magnetic resonance-guided radiotherapy. The magnetic resonance linear accelerator (MR-linac) is an innovative technology that combines high-quality MR-images with a linear accelerator for cancer treatment and online plan adaption. The MR-linac visualises the tumour and surrounding organs during treatment, making it possible to adapt the radiotherapy plan to the anatomy of the day. Consequently, safety margins around the tumour can be reduced and doses escalated. Especially tumours in the pelvic area are better visualised on high-quality MRI, thus treated at the MR-linac.

Since the toxicity profiles of the patients may change, it is important to evaluate the adverse events (AEs) of this new technology timely and accurately. Weekly toxicity assessment with patient-reported outcomes (PROs) could be valuable, as PROs in prior studies have captured symptoms earlier and with higher severity than clinician toxicity reports. A weekly frequency would request a short, specific questionnaire capturing the most common acute AEs and an integration of PROs into a Danish radiotherapy setting.

This thesis is based on four papers aiming:

- To identify, select and validate a set of symptomatic AEs and corresponding PRO items covering the most common acute AEs among patients receiving pelvic radiotherapy (PAPER I).
- To explore the feasibility, usability, and patient acceptance of weekly electronic PRO assessments during and four weeks following radiotherapy and for six months of follow-up (PAPER II).
- To investigate the acute AE trajectories, time to maximum worsening of symptoms, and the persistence of symptoms among patients with prostate cancer (PCa) treated at the MR-linac (MANUSCRIPT III).
- To explore the clinical impact of PRO integration with real-time symptom monitoring in radiotherapy and patient follow-up selection based on their reported health. Furthermore, to investigate if clinician compliance in acting on PROs is associated with patient response rates and patients experiencing their PROs being used for their care (MANUSCRIPT IV).

Results

- In a literature review and chart audit with MR linac patients, 18 acute symptomatic AEs were identified, and the corresponding PRO items were selected in two validated item libraries. In a pilot study, the content of the pelvic PRO item set was validated (n=40), and 17 acute AEs had a prevalence >20%, thus useful for capturing acute AEs in pelvic radiotherapy.
- It was feasible to recruit (87%) and adhere patients with cervical or prostate cancer to weekly PROs during radiotherapy. The length and weekly frequency of the pelvic PRO item set were acceptable, and 85% responded to more than 80% of the weekly PROs, thus a lower adherence above age 70 (p=0.041). The response rate declined during follow-up, with a retention rate of 47.5% in week 24. The application was usable for digital PRO completion; however, the patients requested real-time clinician feedback.
- For patients with intermediate-risk PCa (n=25) or low-volume metastatic PCa (n=25) treated at the MR-linac, the weekly PROs comprised detailed toxicity profiles. Overall, 20% reported a two-level increase in urinary frequency over two consecutive weeks. Symptoms peaked outside the time points used in prior studies (60 Gy, week 3, 36 Gy, follow-up week 1-2). Urinary symptoms (16%) persisted for more than 12 weeks for patients treated with 20 fractions, while the persistence of bowel symptoms (12%) was more profound in the short courses with six fractions.
- The integration of active real-time monitoring of PROs in radiotherapy for PCa (n=156) improved the patient experience of quality of care (87%), communication (91%) and feeling of being involved (93%). The clinician handled all PROs for most patients (93%), and the patients found PROs were used for their care (95%). Follow-up on acute AEs was deselected by 23%. A higher percentage of these patients (68%) reported deteriorated self-rated health two months following as opposed to those choosing follow-up (40%).

Conclusion

A short PRO item set was developed and validated for pelvic cancer patients and integrated into a clinical radiotherapy setting. A pilot study confirmed the feasibility, usability and acceptance of weekly PRO completion. For patients with PCa treated at the MR-Linac, the weekly PROs comprised acute AE trajectories with real-time improved or deteriorated symptoms. Active digital monitoring of PROs was integrated for all patients with PCa, resulting in high clinician and patient compliance. Patients experienced their PROs were used and improved their care and one-forth deselected follow-up.

Danish summary (dansk resumé)

Baggrund

I 2018 fik patienter med kræft mulighed for at blive behandlet med online adaptiv magnetisk resonans-guidet strålebehandling. En magnetisk resonans lineær accelerater (MR-linac) er en innovativ teknologi, hvor MR-billeder af høj kvalitet kan visualisere tumoren og de omgivende organer under strålebehandling af kræft. Dette gør det muligt at tilpasse strålerne i forhold til dagens anatomi og betyder at sikkerhedsmargener omkring tumoren kan reduceres, og højere doser gives. Særligt tumorer i bækkenet kan bedre ses på MR-billeder af høj kvalitet og behandles derfor på MR-linac.

MR-linac kan få patienternes bivirkningsprofiler til at ændre sig, og derfor er det vigtigt at evaluere bivirkninger rettidigt og præcist. Ugentlig vurdering af bivirkninger rapporteret af patienten i form af patient-rapporterede oplysninger (PRO) har i tidligere studier detekteret symptomer tidligere og med en højere sværhedsgrad end klinikernes bivirkningsregistreringer. Hvis ugentlige PRO skal integreres i strålebehandlingsforløb for patienter med bækkentumorer, vil det være nødvendigt med et kort PRO skema, der dækker relevante, hyppige akutte bivirkninger.

Denne afhandling er baseret på 4 artikler med formålet at:

- Identificere, udvælge og validere symptomer til patientrapportering sammensat i et spørgeskema, der dækker de mest hyppige akutte bivirkninger til strålebehandling mod kræft i bækkenområdet (ARTIKEL I).
- Undersøge gennemførlighed, anvendelighed og patienternes accept af ugentlig elektronisk PRO under og 4 uger efter strålebehandling med et halvt års kontrolforløb (ARTIKEL II).
- Undersøge akutte bivirkningsprofiler over tid, tid til største symptombyrde og varigheden af de akutte bivirkninger hos patienter med prostatakræft behandlet på MR-linac (ARTIKEL III).
- Udforske den kliniske effekt af at integrere PRO med aktiv monitorering og patientfeedback i et strålebehandlingsforløb og patienternes valg af opfølgning ud fra de symptomer, de rapporterer. Vi vil også undersøge, om klinikerens compliance i forhold til håndtering af PRO besvarelserne er associeret med patienternes responsrater og at patienterne oplever, deres svar bliver brugt i deres behandling (ARTIKEL IV).

Resultater

- I en litteraturgennemgang og journalaudit på MR-linac patienter blev 18 akutte bivirkninger identificeret og tilhørende PRO spørgsmål udvalgt fra to validerede PRO biblioteker. PRO skemaet blev valideret i pilotstudiet (n=40), hvor 17 symptomer blev rapporteret af >20% af patienterne som akutte bivirkninger til strålebehandling mod bækkenet.
- Det var muligt at rekruttere (87%) og fastholde patienter med prostata- og livmoderhalskræft i at besvare ugentlige PRO under deres strålebehandling. Skemaets længde og ugentlig frekvens af PRO besvarelser var tilpas, og 85% svarede på > 80% af de ugentlige PRO, dog signifikant færre over 70 år (p=0.041). Denne responsrate faldt i kontrolforløbet, så 47,5% besvarede den sidste uge 24. Applikationen var anvendelig til digital PRO besvarelse, men patienten ønskede feedback på deres svar fra klinikerne.
- For patienter med lokaliseret (n=25) og metastatisk (n=25) prostatakræft behandlet på MR-linac blev de ugentlige PRO besvarelser anvendt til tidstro bivirkningsprofiler. I alt rapporterede 20% en 2-grads øgning i vandladningsfrekvens gennem 2 uger. Symptomerne var værst på tidspunkter, hvor PRO ikke blev målt tidligere (60Gy; Uge 3, 36 Gy: 1-2 uger efter behandling). Efter 12 uger, havde patienter der fik 20 behandlinger (16%) fortsat urinvejssymptomer, mens tarmsymptomer varede ved efter de korte forløb (12%).
- Aktivt monitorering og anvendelse af PRO hos alle patienter med prostatakræft (n=156) i strålebehandling forbedrede patientens oplevede kvalitet af behandlingen (87%), følelse af at blive inddraget (93%) og kommunikation med kliniker (91%). For størstedelen af patienterne (93%) handlede klinikerne på alle deres PRO, og patienterne oplevede deres svar blev anvendt i deres behandling (96%). Opfølgning på akutte bivirkninger blev fravalgt af 23%. Flere af disse patienter (68%) rapporterede forværret selvvurderet helbred to måneder efter i forhold til de, der havde opfølgning (40%)(p=0.044).

Konklusion

Et målrettet PRO spørgeskema blev udviklet og valideret til patienter med kræft i bækkenet og integreret i klinisk strålebehandling. Pilotstudiet bekræftede gennemførlighed, anvendelighed og accept af ugentlig PRO. Hos patienter med prostatakræft behandlet på MR-Linac kortlagde de ugentlige PRO akutte bivirkningsprofiler med tidstro forbedringer og forværringer over tid. Digitale PRO med aktiv symptommonitorering blev integreret hos alle patienter med prostatakræft med høj kliniker og patient compliance. Patienterne oplevede deres PRO blev anvendt og forbedrede deres behandling. En fjerdedel af patienterne fravalgte opfølgning.

Background

Development in Radiotherapy

In the future of radiotherapy, a personalized treatment approach adapts the individual treatment plan according to geometry, tumour biology and patient tolerability. Accurate clinical response measures from frequent patient reports are linked, and algorithms are used to conduct individual risk analyses and manage heterogeneous toxicity profiles. That is a scenario taking advantage of the technological and biological advantages while simultaneously recognising the value of patient involvement and empowerment [1].

Technological advances have significantly transformed radiotherapy within the last decades. Overall, radiotherapy is used to treat more than 50% of all cancer patients, with the majority being patients with breast, lung or prostate cancer [2]. Radiation treatment is based on the results of many prospective clinical trials that were performed during the last century establishing effect and toxicity.

To improve cancer-related outcomes, emergent multimodal treatments have become available. Novel combinations of radiotherapy with surgery, chemotherapy, immunotherapy, radiosensitisers, androgen deprivation therapy, or other drugs have improved treatment efficacy for various cancer diagnoses [3].

Several treatment modalities are available within radiotherapy practice, primarily external beam radiotherapy (EBRT) with photons or protons and internal brachytherapy, where a radiation source is positioned inside the body to boost the dose to the tumour [4]. Tumour localisation and anatomy of the irradiated area determine the most optimal treatment option where tumour damage is maximised and the irradiated volume of healthy tissue is minimised [4].

With the introduction of Computed Tomography (CT) and computers, the EBRT modalities have evolved from three-dimensional Conformal Radiation Therapy (3D-CRT) to techniques like Intensity Modulated Radiation Therapy (IMRT), Volumetric Modulated Arc Therapy (VMAT) and Stereotactic Body Radiotherapy (SBRT). All to modulate the radiation beam to give higher doses to the tumour and lower the doses to the surrounding healthy tissue.

In general, the same treatment plan is used for daily delivery during a treatment course lasting 6-8 weeks. To compensate for uncertainties related to differences

in patient positioning and anatomical changes during the treatment course geometrical safety margins are used to ensure target coverage at the expense of higher doses to the surrounding tissue [5]. The introduction of (daily) Image-Guided Radiation Therapy (IGRT), using Cone Beam CT (CBCT) imaging at the treatment machine to verify the patient position, reduced the positional uncertainties of the dose delivery. That has made it possible to reduce geometrical safety margins, lowering the volume of organs at risk receiving high doses.

The introduction of IGRT also opened up for revision of established fractionation schemes with long treatment courses of daily 1.8-2 Gy fractions to hypo fractionation (>2 Gy), where high doses are delivered to smaller volumes in fewer fractions [6]. With IGRT, daily changes in some patients' anatomy became visible, leading to a wish for daily online plan adaption.

The MR-linac

Until recently, magnetic resonance imaging (MRI) has only been used in the planning phase of radiotherapy to diagnose and define the target volume [7].

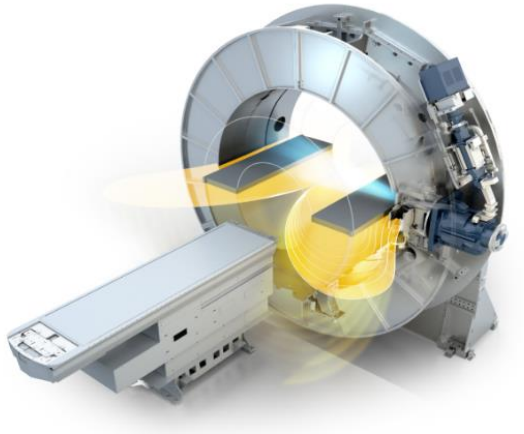


Fig. 1. The 1.5 T Unity MR-linac

Therefore, it was a turning point in 2018 when the high-field Unity MRI-guided linear accelerator (MR-linac) was approved for patient treatment after almost 20 years of development (Fig. 1) [8].

The idea of having online, real-time MRI visualisation of the tumour and surrounding tissue to deliver radiotherapy more precisely was born in 1999 by Bas W Raaymakers and Jan J W Lagendijk in Utrecht, the Netherlands. The improved soft tissue contrast in some anatomical regions with MRI compared to CT would allow for further reduction of safety margins (Fig. 2).

This combined with daily online plan adaption would improve the precision even further [9]. The use of MRI introduced the possibility of biological imaging. Thus, with MRI-guided radiotherapy (MRgRT), it would be not only possible to do geometrical plan adaption but also biological adaption based on the response of the tumour and normal tissue for the individual patient [10].

The Unity system, a 1.5 Tesla (T) MR-linac, was developed to have a diagnostic quality real-time MRI of the patient combined with a 7 MV linear accelerator for radiation therapy. After several years of development, the feasibility was tested on a few patients in Utrecht in 2017 [8, 9, 11, 12].

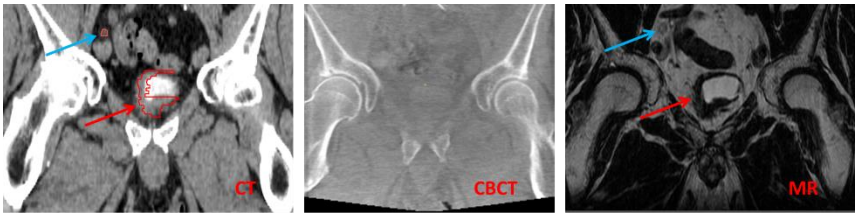


Fig. 2. Visualisation of bladder tumour and lymph node on CT-reference plan, CBCT and MRI

Finally, the Unity MR-linac received the CE mark in June 2018, and the technology was the first high-field MR-linac worldwide ready to treat cancer patients. Meanwhile, another MR-linac based on a low-field 0,35 T magnet was ready for patient treatment [13].

Odense University Hospital (OUH) was the fifth centre worldwide to treat patients on the MR-linac in October 2018 [14]. The first phase of the clinical implementation was challenging, as this was a new way of delivering radiotherapy, a new workflow, other safety guidelines (MR safety) and a new radiotherapy planning system.

The daily MR-guided online workflow includes patient positioning, MR scan for planning, daily plan adaption, MR-scan for validating the target position and cine imaging to monitor the tumour motion during the first part of treatment delivery (Fig. 3). In addition, a research MR-scan is performed during each treatment fraction to access biological changes in the tissue [14].

The treatment time is longer (30-45 minutes) than for conventional treatment (10 minutes) due to the plan adaptation process, and it is well-known that the noise during MRI can cause distress and anxiety-related reactions from the patient [15, 16].

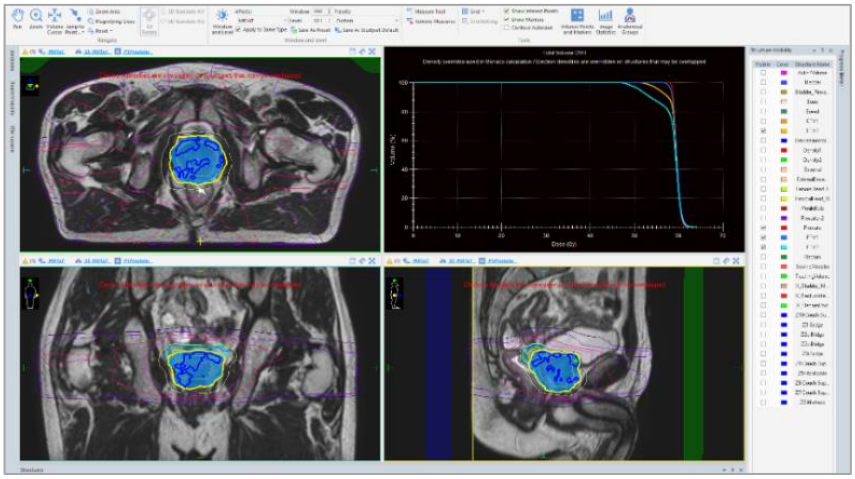


Fig. 3. PCa reference plan in Monaco planning system at the MR-linac

No questionnaire was available capturing the experience of daily MRI combined with radiotherapy at the MR-linac; thus, a questionnaire was developed and validated in a collaboration between different sites in the MR-linac Consortium (Fig. 4) [17].

Patient experience questionnaire: MR Linac (Unity) radiotherapy

Radiotherapy with MR Linac (Unity) using Magnetic Resonance Imaging (MRI) is a new technology.
We'd like to know your opinion about receiving therapy on Unity. This can help us improve the experience for you and other patients.
We'd appreciate it if you'd complete this questionnaire when your therapy is completed and hand it in before you leave.
Please circle the response that best fits your experience.

	0 Not at all	1 Slightly agree	2 Somewhat agree	3 Strongly agree
I needed more detailed information before treatment	Not at all	Slightly agree	Somewhat agree	Strongly agree
I found the treatment position comfortable	Not at all	Slightly agree	Somewhat agree	Strongly agree
I found the treatment bed comfortable	Not at all	Slightly agree	Somewhat agree	Strongly agree
I found it easy to lie still and remain in the treatment position	Not at all	Slightly agree	Somewhat agree	Strongly agree
I wanted to get out of the machine during treatment	Not at all	Slightly agree	Somewhat agree	Strongly agree
I felt relaxed during treatment	Not at all	Slightly agree	Somewhat agree	Strongly agree

Fig. 4. Questions from the MR-linac Patient Experience Questionnaire

Evaluating a novel technology

In 2018, the early steps of the clinical evaluation of the 1.5 T MR-linac as a new technology commenced. The objectives of the clinical evaluations were to determine undesirable side effects and assess if they are a risk against the performance of the new technology. This early-stage clinical evaluation includes non-randomised study approaches to help generate direct evidence about the benefits and short- and long-term patient-relevant outcomes [18].

An international MR-linac research consortium was formed in 2012 for institutes having an MR-linac. The consortium aimed to establish an interdisciplinary collaboration on the design and implementation of clinical studies and a data registry [19]. In addition, a framework for a systematic clinical evaluation of technological innovations in radiotherapy was developed in 2017 to evaluate the 1.5 T MR-linac [20]. The framework was based on the surgical IDEAL framework (Idea, Development, Exploration, Assessment and Long-term evaluation) and adapted to evaluating radiotherapy (R) innovations, therefore R-IDEAL. In radiotherapy, interventions are complex as new technologies are used for different tumour sites with various aims of changes in volume, margins and doses. The R-IDEAL systematic evaluation comprised stages 0 to 4 from predicate studies to long-term evaluation (Table 1) [20].

Table 1. Stages in the R-IDEAL framework

Stage		Outcomes
Stage 0	Predicate studies	MR-sequences, inter-rater reproducibility, treatment strategies, patient selection
Stage 1	Idea	Proof of concept
Stage 2a	Development	Technical improvements, feasibility, and safety
Stage 2b	Exploration	Early effectiveness; toxicity, tumour response, local recurrence
Stage 3	Assessment	Effectiveness compared to standard treatment; disease-free survival, recurrence, toxicity, patient-reported outcomes (CTC-PRO), cost-effectiveness
Stage 4	Long-term evaluation	Long-term toxicity, long-term disease-free survival, rare side effects, patient-reported outcomes

In stage 2, the technical feasibility and safety were to be explored in small prospective cohorts. At the MR-linac at OUH, feasibility studies were conducted to explore technical and clinical feasibility. These prospective studies were the early evidence of clinical effectiveness [14, 21-24]. We progressed with a phase 2 study aiming at exploring SBRT for infra-diaphragmatic soft tissue metastases (the SOFT-study), investigating toxicity, tumour response and local recurrence [25]. The data from this study is currently being analysed.

In stage 3, the formal MRgRT and standard treatment comparison is investigated. For an accurate assessment of treatment-induced toxicity, it is recommended in this stage to include the Patient Reported Outcomes Version of the Common Terminology Criteria for adverse events (PRO-CTCAE) to capture adverse event (AE) outcomes directly from the patient [20].

A prospective international registry, the MOMENTUM study, was established to capture pseudonymised technical and clinical data from patients treated on the 1.5 T MR-linac [26]. The MOMENTUM study was part of the international MR-linac Consortium, and patients needed to provide informed consent. A core set of clinical data is collected for the MOMENTUM registry for the individual patients within specific tumour site groups. In addition, clinician-reported toxicity with the standard Common Terminology Criteria for Adverse Events (CTCAE) and patient-reported outcomes (PROs) are collected.

The PROs collected for the registry is the generic health-related quality of life (QoL) questionnaire EQ-5D-5L from Euroqol [27]. Furthermore, the cancer-specific core QoL questionnaire EORTC QLQ-C30 from the European Organisation for Research and Treatment of Cancer (EORTC) combined with disease-specific modules [28].

Many clinical data have been generated in the early phases of the MR-linac evaluation. However, to improve the treatments, these data must be correlated to and interpreted by accurate and timely obtained toxicity assessments [29].

Prostate cancer

Epidemiology

Prostate cancer (PCa) is the most common cancer among men. The incidence in Denmark is around 4500 men per year (2016-2020), comprising 21.5% of all male cancer incidences [30, 31]. A recent projection of cancer incidence in 2034 estimates an increase in PCa incidence of more than 30% [32].

The clinical detection of PCa is typically after age 50, and the incidence increases with age. Therefore, the risk of being diagnosed with PCa before age 75 is 9.9% [30]. The first sign of having PCa has, in the past century, evolved from having urinary obstruction and pain from bone metastases to having an asymptomatic disease with a microscopic focus or few urinary symptoms [33]. The prognosis is good, with a 5-year survival rate of 90% [30, 31]. Therefore, around 45.000 men lived with prostate cancer in Denmark by the end of 2019.

Staging

Prostatic adenocarcinoma is staged according to the TNM staging system [34]. The tumour stage is based on a rectal exploration, sometimes combined with a transrectal ultrasound scan (TRUS) or an MR scan. MR-positive lesions or clinically suspected malignancy leads to a biopsy. If the patient is a possible candidate for curative intended treatment, the MR scan is conducted to guide the biopsy [35].

The node (N) stage is investigated in intermediate and high-risk PCa patients. If a prostatectomy is performed, a lymphadenectomy is used for staging. However, if radiotherapy is the primary treatment, the patient has a CT scan. Staging of metastasis (M) is explored if the PSA level is >20 µg/L, the Gleason score is $\geq$4+3, or the tumour stage is $\geq$ cT2c.

The treatment options are determined according to PCa in low-, intermediate- or high-risk groups. These groups distinguish between intraprostatic (cT1-T2) or extraprostatic (cT3-T4) tumour growth, PSA level and Gleason score [35] (Fig. 5).

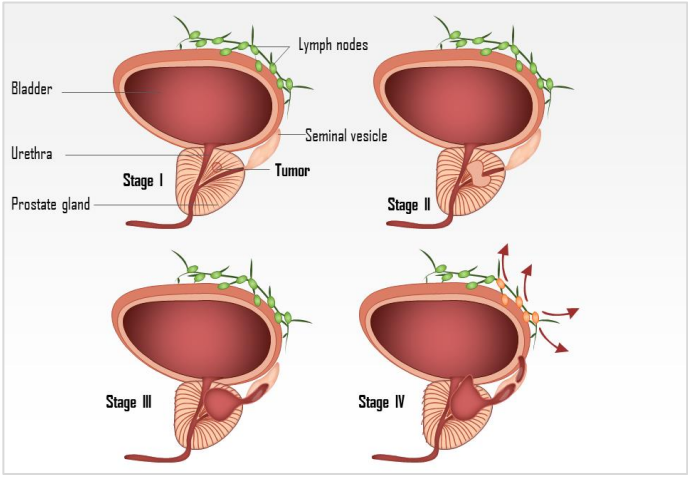


Fig. 5. Stages of prostate cancer

Patients with metastatic PCa have previously been classified as either high or low-burden metastatic PCa according to the extent of their metastases [36, 37]. In these studies, high volume is defined as polymetastatic disease and low volume as oligometastatic disease.

Histopathology

One of the most important prognostic indicators for prostate cancer is the histology grading of adenocarcinoma. Almost 75% of adenocarcinomas are located in the peripheral area of the prostate. Other nonepithelial neoplasms in the prostate are rare. The common growth pattern of adenocarcinoma is reflected in the Gleason grading system, with a grading of the most common and the second most common pattern. A capsule surrounds the prostate gland and normally a layer of basal cells [38].

Treatment

The treatment for different stages of prostate cancer is defined in the national clinical guidelines [35] based on the guidelines from the European Association of Urology [39].

Three primary treatment options are available if the patient is diagnosed with localised PCa. First, around one-fourth of all diagnosed patients have their prostate and seminal vesicles removed with robotic surgery (prostatectomy) [40]. The second option is active surveillance or watchful waiting; the third is external beam radiotherapy (EBRT) +/- androgen deprivation therapy (ADT).

If the patients have a biochemical recurrence of PCa (increased serum PSA) after having a prostatectomy, salvage EBRT may be an option, or lifelong treatment with ADT is the alternative.

For patients with low-volume metastatic PCa, the ESMO guidelines in 2020 recommended EBRT on the prostate. These recommendations were based on two large RCTs finding improved overall survival for patients with newly diagnosed low-volume disease [41]. The local treatment guideline for patients with PCa treated with >30 Gy is listed in Table 2.

Table 2. Local treatment guidelines for PCa based on international guidelines

Risk group	Radiotherapy	ADT
Low risk PCa T1-2aNxM0, PSA<10, GS≤ 6	60 Gy/ 20 Fx	No ADT
Intermediate risk PCa T2bN0M0 or PSA 10-20 or GS=7	60 Gy/ 20 Fx If Brigant < 90 points	
	78-56 Gy/ 39 Fx If Brigant > 90 points	Short ADT course (6 mos) - 3 mos neoajd.
High risk PCa T≥2cN0M0 or PSA > 20 or GS= 8-10	78-56 Gy/ 39 Fx	Long ADT course (3 years) - 3 mos neoajd.
TxN1M0 (max 2 lymph nodes < 2 cm at staging)	78-56 Gy/ 39 Fx	Long ADT course (3 years) – 3 mos neoajd.
Low-volume metastatic PCa Oligometastatic disease	36 Gy/6 Fx	ADT (lifelong)

PSA= Prostate-specific antigen. GS=Gleason score. LN= lymph node. ADT=Androgen Deprivation Therapy

MR-linac - a possible game changer for prostate cancer

Some of the first patients treated on the MR-linac with curative intent were patients with localised PCa. In 2018, a paper questioned whether MR-linac is a 'game changer' for PCa treatment [42]. In the past decades, advancements in radiation treatment for PCa with implanted fiducial markers combined with daily tracking of treatment position with cone-beam computed tomography (CT) have improved tumour control and reduced late toxicity rates [43].

However, the prostate is better visualised on high-quality MRI (Fig.2). An opportunity is provided for reduced target volumes and improved sparring of healthy tissue when combined with daily plan adaption. This will expand the radiotherapeutic options further; thus, the MR-linac is a promising technology to improve the safety of dose-escalation and hypofractionation, taking both the inter- and intrafractional motion and the organ deformation into account [44].

For patients with PCa, it is challenging to keep a constant interfraction bladder volume [45]. The daily plan adaption on the MR-linac shapes the treatment plan to the anatomy of the day of the patient when in their treatment position, making it possible to account for different bladder and bowel fillings [46]. A study of patients with PCa treated at the MR-linac found that it is challenging for patients to have a full bladder throughout the treatment, affecting their treatment experience [47]. However, despite varying adherence to a drinking protocol and varying bladder volumes, the mandatory dose constraints in the study could be achieved [47].

The clinical evidence of the superiority of the MR-linac is still limited, and further research must explore how to select the patients that will benefit the most from this new technology [29].

Moderate- and ultra-hypofractionated treatment

When the MR-linac was ready for patient treatment, moderate hypofractionation became the new standard of treatment for intermediate-risk PCa. This new standard was based on several studies finding non-inferiority in the cumulative incidence of biochemical recurrence of moderate hypofractionation (~3 Gy/Fx) versus standard fractionation (~2 Gy/Fx) [48-51]. There was, however, a short-lasting increase in acute bowel toxicity in the hypofractionated group in all three studies. The increase lasted until 18 weeks following treatment when urinary and bowel adverse events (AEs) were similar.

However, in recent years, ultra-hypofractionated radiotherapy (<10 Fx) for localised PCa has been investigated in several clinical trials on standard CT-guided linacs [52]. A meta-analysis of these trials found a higher prevalence of late severe urinary toxicity with increasing doses [52]. The hypo-FLAME trial treated patients with 35 Gy/5 Fx with an integrated boost and found no $\geq$ acute grade 3 AEs [53]. Finally, the 5-year results of the Scandinavian HYPO-RT-PC trial treating patients with 42.7Gy/ 7 Fx comprised more profound early AEs with ultra-hypofractionation than with conventional fractionation; however, late AEs were similar [54]. In contrast to what is possible with the MR-linac, these studies were conducted on standard linacs with higher safety margins; thus, a larger volume of organs at risk (OAR) received a high dose.

A cohort study looking at data from 10 prospective single-arm studies for prostate SBRT found that the most robust factors associated with late AEs is fractionation and acute toxic AEs [55]. Therefore, it is evident that future studies with hypofractionation include a comprehensive toxicity assessment with accurate measures of acute toxicity. Furthermore, an important consideration before hypofractionation is standard of care is establishing the value of changed treatment regimens for the patient with PROs to explore the patient preference if there is no difference in local control [56].

Adverse events in pelvic radiotherapy

Radiotherapy can cause various early and late AEs in different organs within the irradiated regions [57]. It is not necessarily in the high-dose regions that the AEs occur. The AEs can be prevented with a decreased dose or minimised volume of irradiated healthy tissue. The therapeutic index is the relationship between the

total radiotherapy dose, the late normal-tissue response, and the tumour response. If irreversible late effects can be avoided, then dose escalation of the radiotherapy dose may be possible [57].

Acute toxicity occurs within three months after treatment. In pelvic radiotherapy, the OAR is most notably the bladder and bowel. The acute-responding tissues like the dermis and the mucous membrane of the intestines can cause early AEs like dermatitis and post-radiotherapy inflammation of the mucosal epithelium [57]. The gastrointestinal (GI) AEs caused by inflammation of the intestines may be abdominal pain, bloating and urgency, and inflammation of the rectal lining tissue (proctitis). Radiation proctitis presents with diarrhoea, tenesmus or blood in the stool [58]. Acute genitourinary (GU) AEs are associated with radiation of the bladder and urethra. As the urethra runs through the prostate, it usually receives the same dose as the prostate. The volume irradiated is essential for acute urinary AEs, and the urethral dose has been correlated with both acute and late urinary AEs [59]. Some of the most common urinary irritative/obstructive symptoms are increased urinary frequency, dysuria, nocturia and urinary retention [58]. The incidence of acute urinary symptoms is somewhat similar for men and women treated with primary pelvic radiotherapy [58].

Late radiation AEs may become symptomatic months to several years after radiotherapy and are not a result of inflammation but a result of minor vessel damage, ischemia, fibrosis or necrosis [60]. Therefore, different treatment approaches may be needed for late AEs, and the accurate diagnosis and treatment of these late effects can be challenging [60].

Radiation proctitis, faecal incontinence and increased bowel movement frequency are some of the late GI toxicities caused by pelvic irradiation [58]. Late GU toxicities include urethral stricture, haemorrhagic cystitis and long-term bladder dysfunction with urge and increased frequency [58].

Pelvic radiation may also cause sexual toxicities. Women treated for gynecologic malignancies are at risk of painful acute vaginal mucosal injury and late vaginal stenosis, premature ovarian failure or rectovaginal fistulas. For men treated for genitourinary malignancies, erectile dysfunction and testicular infertility are more common [58].

Other general adverse events measured in cancer patients undergoing pelvic radiation treatment are fatigue, insomnia, depression and decreased appetite [61].

Symptom assessment

The radiotherapy setting

In the radiotherapy section at OUH, around 250 patients are treated daily on seven conventional linacs and one MR-linac. Around 55 radiation therapists deliver the treatments, and the majority (~45) has a nursing background. The radiation therapists working at the MR-linac are trained in MRI, MR safety, Monaco planning system and the onsite clinical workflow.

In Denmark, radiation therapists with different educational backgrounds deliver radiotherapy. For decades, nurses or radiographers have been trained as radiation therapists at the one-year National Education in Radiotherapy [62]. Years ago, education in radiography initiated a clinical specialisation in radiotherapy.

At all the linear accelerators, the radiation therapists handle the most supportive care observations, documentation and interventions. For example, they observe and manage side effects, administer supportive care medication, manage skin care, nutritional guidance, tube feeding and correspondence with primary care. They also assist in physician consultations and register CTCAE on trial patients. Within the past years, some physician consultations have been converted into consultations led by radiation therapists, including follow-up for PCa.

The current practice of symptom assessment

For cancer patients attending cancer clinical trials, it is standard that clinicians ask them about their symptoms and score them using the CTCAE. Incorrect reporting of CTCAEs in clinical trials was found in many publications, only reporting the pooled, selected or worst AEs [63]. In addition, the multimodal treatment regimens and advancing radiotherapy modalities challenge toxicity assessment in clinical radiotherapy [64].

At the consultations in the radiotherapy department at OUH, the current practice of symptom reporting in routine care is various narrative documentation made in the electronic patient record. At the linear accelerators, usual care comprises daily observations and unsystematic dialogues with the patient about new or worsened symptoms, thus unsystematic reporting in the patient record.

Patient-reported outcomes (PROs)

Within the health care system, patients have been increasingly involved as active participants in their own care and in medical decisions [65]. Several studies have

established that there is a difference in the symptoms and symptom severity reported by clinicians versus patients in PROs, as clinicians have been found to downgrade or miss symptoms [64, 66-70]. Therefore, PROs are increasingly used to capture how patients experience their symptoms and care. The U.S. Food & Drug Administration has defined PROs as *'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'* [71].

PROs have also given the patient a voice in cancer clinical trials [72]. PROs are valuable direct indicators of changes in symptom severity and persistence when evaluating AEs in clinical trials [73]. Remarkably, a systematic review of clinician and patient symptom reporting in radical prostate radiotherapy found that acute PROs were underrepresented in clinical trials [74]. In addition, some underserved patients are not included in clinical trials [75].

At an individual level, PROs within radiotherapy are an evidence-based approach to obtaining critical information from the patient. In clinical practice, PROs can improve patient-clinician communication, facilitate shared decision-making, and provide timely, supportive care based on individual needs [75, 76].

Since PROs are outcomes directly from the patients, patient involvement in developing the PRO measures (PROMs) should be evident. However, the level of patient involvement varies considerably in studies developing PROMs, even though patient involvement might influence their willingness to adhere to PRO completion [77, 78].

Several guidelines have been developed to assist clinicians in incorporating PROs in randomised clinical trials (RCTs) (Table 3). However, further recommendations are needed for PRO assessment in non-RCTs with a specific focus on single-arm studies. Ongoing work in the multidisciplinary SISAQOL-IMI Consortium looks at valid PRO objectives and estimands for these studies. The group is also working on recommendations for the terminology and definition of clinically meaningful change and reaching a consensus on analyses and interpretation of PROs [79].

Table 3. Guidelines for incorporating PROs in RCTs and clinical practice

AIM	INSTRUMENT/GUIDELINE	DEVELOPED FOR
Development and validation	COSMIN [80]	Taxonomy, checklists, guidelines
Writing PRO protocols	SPIRIT-PRO (Calvert, 2018)	PROs in RCTs as primary or key secondary outcome
Selecting PRO	ISOQOL recommendation (Reeve, 2013) [81] + COSMIN [80]	Minimum measurement standards for design and selection of PROs
Analysing PRO	SISAQOL recommendation (Coen, 2020) [82]	PROs in RCTs
Reporting PRO	CONSORT-PRO extension (Calvert, 2013) [83]	PROs in RCTs as primary or secondary outcome
Graphically displaying PRO	Recommendations for graphically displaying PRO data (Snyder, 2019) [84]	In comparative research studies and to inform patient
PRO in clinical practice	ESMO Clinical Practice Guidelines (Di Maio, 2022) [76]	Evidence supporting PROs in clinical practice

PRO measures

Within cancer research, PROs cover symptomatic AEs, physical, emotional, social and mental functioning and quality of life (QoL). The outcomes are measured in absolute terms or changes from a previous assessment [85].

QoL is today an integral part of many clinical trials. The most common generic instrument for measuring QoL is the 5-level EQ-5D-5L from Euroqol [86]. The instrument comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has a 5-level score from no problems to extreme problems. In addition, it comprises an EQ-VAS score of the patient's self-rated health from 0 being 'the worst health you can imagine' to 100 being 'the best health you can imagine'.

One of the most commonly used cancer-specific QoL measures is the QLQ-C30 questionnaire from EORTC [87]. This core questionnaire comprises 30 items [28]. Besides the six single-item scales, the remaining 24 scores are aggregated into nine multi-item sales; five functional scales, three symptom scales and one global health status scale. All the scores are recalculated to a score ranging from 0-100 according to a scoring manual [88]. After being used for many years in cancer research, the content validity of the EORTC QLQ-C30 has recently been investigated across countries, cancer sites and stages. It is recommended to combine

the questionnaire with more disease-specific modules or items from the Item Library [89].

Item libraries

According to the research objectives, different generic and disease-specific questionnaires often must be combined to cover the intended outcomes [90]. However, when several questionnaires are combined, the questionnaire may be too extensive and contain questions that the patients find irrelevant. An alternative to the standard static questionnaires is a more flexible approach to creating a customised item set with items from validated item libraries [91].

The standard way of using questionnaires for patients was broadened when the National Cancer Institute's PRO-CTCAE was developed. The PRO-CTCAE library represents 78 symptomatic AEs with 1-3 attributes (frequency, severity and inference in daily activity) [92]. The 78 AEs in the PRO-CTCAE item library were identified as amenable for patient reporting out of the 790 AEs contained in the CTCAE. The item library has been validated for patients in both chemotherapy and radiotherapy and was translated and validated in a Danish setting by Baeksted et al. [93]. Seven days is the preferred recall period for the PRO-CTCAE items [94]. PRO-CTCAE items have been used in several studies investigating AEs to various oncologic treatments [95-99].

A prior study aimed at constructing anatomic site-specific item sets for radiotherapy using PRO-CTCAE items [61]. The symptoms were collected with interviews at a single time point with a risk of recall bias. Some of the most common symptoms in prostate radiotherapy, like urinary retention and nocturia, were not included in the male pelvis item set. This was because these AEs were not available in the PRO-CTCAE item library.

EORTC has developed many standard questionnaires for measuring patient-reported outcomes in cancer populations. Recently, EORTC has constructed its own item library with 950 unique items from various questionnaires to provide a more flexible instrument complementing the EORTC core module (QLQ-C30) and the supplementary questionnaire modules [100, 101]. The specific EORTC questionnaires have the benefit of being thoroughly validated and translated into multiple languages. Therefore, they are widely used in international trials and important for pooled meta-analyses which are more difficult for item sets [87, 101].

As many questionnaires have been developed for clinical research, they are not necessarily suitable for clinical practice. Item libraries are beneficial for item reduction when a short specific questionnaire is needed for frequent assessments. The advantage of item libraries is both having a flexible and dynamic assessment

tool and validated items to select and adapt for the intended outcomes, the specific population, intervention and setting [92, 100].

To ensure the PRO instruments measure what is intended, the patient perspectives of the target population must be included in the development of the item set [102]. Modifications can be made to the content of the PRO, the wording or the mode of administration based on content validation with patient interviews [102].

MR-linac and PROs

In the third stage of the R-IDEAL framework for MR-linac evaluation, PRO-CTCAE was recommended as a supplement to capture patient toxicity [20]. No guidance was provided about the selection of PRO-CTCAEs, the design, or the frequency of assessments. In the Momentum study, CTCAEs are reported regularly during follow-up. However, the AEs during and in the three months following treatment are not captured for most patients. The QoL reports completed for the Momentum registry at baseline and 3, 6, 12 and 24 months after treatment are not actively used nor patient feedback provided [26].

To our knowledge, six studies have collected PROs as a safety outcome evaluating MR-linac treatment for patients with PCa (Table 4).

Table 4. Studies with PROs for patients with PCa treated with online MRgRT on prostate only

Author, year	n	Population	SBRT	Timepoints	Instrument
Bruynzeel (2019) [103] UMC Amsterdam	101	T1-3bN0M0	36.25 Gy/5 Fx	Baseline End of RT FU wk 6+12	QLQ-C30 PR25 IPSS
Alongi (2020) [104] Verona	25	T1-2NOMO	35 Gy/5 Fx	Baseline End of RT	QLQ-C30 PR-25 EPIC-26, IPSS, ICIQ-SF, IIEF-5,
Mazzola (2020) [105] Verona	40	≥ 65 years prostate or abd/pelvic oligomet	35 Gy/5 Fx	Baseline End of RT	QLQ-C30 G8 + CCI
Poon (2021) [106] Hongkong	51	Localized PCa	36.25 or 40 Gy/5 Fx	Baseline FU wk 4, 16 + every 3 mos	EPIC
Teunissen (2022) [107] Utrecht	293	Utrecht Prostate Cohort T1-4	36.25 Gy/5 Fx 62 Gy/20 Fx	Baseline FU wk 4, 12, 24, 36, 52	QLQ-C30 EPIC-26 EQ-5D-5L, IIEF-5, IPSS, HADS , WAI
Leeman (2022) [108] California	22	Localized + 9 low-volume-met	36,25 Gy/5 Fx	Baseline End of RT FU wk 12	EPIC-26 PROMIS

In these studies, a passive PRO collection was made at baseline and acute toxicity was measured at the end of treatment and the earliest four weeks after radiotherapy. No studies investigated the AE trajectories during and in the weeks following online MRgRT and explored the use of frequent PROs to evaluate a new treatment technology within radiotherapy.

Real-time symptom monitoring

The studies in table 4 and many earlier studies in radiotherapy included a collection of paper QoL questionnaires without real-time monitoring of symptoms by clinicians [109]. The PROs were used as a supplement to support the interpretation of the clinical and clinician-reported data from the trial [72].

An increased interest in remote PRO monitoring appeared in 2017 when Basch et al. demonstrated an increased survival after their RCT, where they randomised patients with advanced cancer in routine chemotherapy to usual care or a web-based PRO intervention [110, 111]. Severe or worsening symptoms alerted a clinical nurse who monitored and initiated clinical interventions. Their primary endpoint was a change in health-related quality of life at six months. In addition, they found that the intervention arm tolerated the continuation of chemotherapy longer than the control group and had a five months longer median overall survival. The benefits were greater in the computer-inexperienced group [110, 111]. Other studies investigating PROs as an intervention provided additional evidence of a benefit for patients receiving a PRO intervention [112-114]

A Cochrane review, however, assessed the effect of PROMs feedback to patients or clinicians on patient outcomes or processes of care [115]. The review stated that the evidence of the effect of PROMs at this point is uncertain or only comprises a little or no difference in physical, social and mental functioning, as well as pain and fatigue. However, feedback on PROMS probably increases patient-physician communication, disease control, diagnosis and notation and slightly improves the quality of life [115].

In 2019, the evidence of integrating weekly electronic PROs (ePRO in the clinical workflow of radiotherapy was limited. Three feasibility studies differed in patient population and collection methods, and the patients in the studies were young compared to many cancer populations with a median age of 59 (56-66) [99, 116, 117].

However, in recent years, several studies have explored the feasibility of ePROs in the radiotherapy workflow, finding a high patient acceptance [98, 99, 116-124]. A prior study found it feasible for PROs to identify the need for follow-up after radiotherapy [125]. Even though it is feasible and acceptable, it is challenging to

integrate an actively use PROs in the radiotherapy workflow [109, 118]. The evidence of remote symptom monitoring within radiotherapy with real-time patient feedback is limited (Table 5).

In most of these studies, self-care advice or notifications with reassurance is provided to the patients if symptoms are mild or moderate. Others send notifications to patients to contact the department when symptoms are severe, and they will be contacted by a clinician (Table 5).

One study had recommendations for clinical action on the PROs for in-patients [126], but otherwise, it was nurses, an RTT coordinator or physicians acting on symptoms based on experience. Within radiotherapy, PROs often aim for early detection and clinical management of treatment toxicities to reduce the symptom burden [76]. However, patient responses do not always align with patient health in the clinical context; thus, a dialogue must support the interpretation of the PROs [127]. Only a few studies have used PROs systematically in dialogue. One of the major challenges in the implementation process is engaging clinicians in actively using the patient's responses (Table 5) [126].

Implementing PROs – a complex intervention

Integrating digital PROs into clinical practice in radiotherapy to evaluate the clinical effectiveness of a new treatment is complex. Working with digital patient-reported outcomes as a technology implies that concerns as patients' intended health outcomes and the burden and ease of device usage must be addressed. A clinical utility study could document the impact of integrating patient-reported outcomes [18]. However, for this intervention to succeed, we must adapt the PRO integration to our specific aim and context.

The International Society for Quality of Life Research (ISOQOL) made a user guide with key elements of implementing PROs in clinical practice [128-130]. The guide addresses nine elements to consider before integrating PROs into clinical practice (Fig. 6).

Fig. 6. The nine elements of implementing PROs in clinical practice

Table 5. Studies with remote symptom monitoring with patient feedback in the radiotherapy setting

Authors	n	Location of cancer	Age, median	PRO intervention	Instrument	Systematically used in consultation	Self-care advice provided	Clinician alerts	Alerts triggered by
Maguire (2015) [119] Feasibility study	16	Lung	64 (mean)	DAILY PROMs at home on mobile-phone	Constructed PROs STAI-Y, FACT-L, SUPPH-29, ESAS	☐	☒	☒	Integrated risk model -call within 8 hours or as soon as possible
Sundberg (2017) [131] Non-randomised comparative study	130	Prostate	70	DAILY PROMs	Constructed PROs (15) Health literacy QLQ-C30+PR25	☐	☒	☒	Risk-assessment model Nurse call - during the day or < 1 hour
Hauth (2019) [117] Feasibility study	21	Pelvic, thoracic, head and neck or upper GI	59	WEEKLY (or more often) only patients with e-mail	PRO-CTCAE	☐	☐	☒	Approached by physician if: - Grade IV toxicity - 2-point increase from grade I to grade III
Takala (2021) [121] Registry trial	253	Breast	58	Baseline, end RT + 1 and 3 months FU (Noona)	9 ITEMS: PS, CTCAE, ESAS (anxiety), Pain (VAS scale)	☐	☐	☐	Automated reply when coordinator RTT closed the PROM. If necessary- consulted a physician
Lapen (2021) [98] Pilot implementation study	489	Breast	55	WEEKLY at home or in waiting room	PRO-CTCAE (9) + GAD-2 Anxiety tool	☐	☒	☒	Mild/moderate: -- message "it is normal". Severe/very severe: - Alert to care team – contact
Holch (2022) [123] Pilot RCT	167	Prostate, Gynaecological or anal/rectal cancer	70 54 (mean 61.7)	WEEKLY from home on website	Constructed PROM, FACT-G, QLQ-C30 +PR25,EQ-5D, PAM-13, self-efficacy scale	☒ Staff adviced to discuss the PROs in the weekly consults	☒	☒	Severe symptoms - Alert to clinical team email Unable to monitor clinicians' use of reports
Nordhausen (2022) [126] Implementation study	1355	In-patient radiation oncology	64.9 (mean)	DAILY device next to bed. Guidelines for PRO-based clinical action	EORTC items (11) +3-8 tumour-specific QSC-R10, QLQ-C30	☐	☒	☐	Daily symptom monitoring + at discharge
Ma (2022) [122] Feasibility study	19	ChemoRT: Gastrointestinal, lung, head and neck	59	TWICE PER WEEK during RT, once/week during FU at home No guidance on actions	PRO-CTCAE PROMIS	☒ Symptom report delivered to physician at consultation once weekly	☐	☒	Symptom worsened by ≥2 points OR reached a score of ≥ 3. Nurse take action or notify physician

It is a complex intervention to integrating digital PRO monitoring with consideration to all of these nine elements into the clinical workflow of radiotherapy. A complex intervention is characterised by the Medical Research Council (MRC) as having several interacting components [132]. Other characteristics of the complex intervention are the number and variability of outcomes, the difficulty of behaviours of those receiving the intervention, and the skills and expertise required for those delivering the intervention. A framework has been developed and recently updated on how to develop and evaluate complex interventions impacting patient health [133] (Fig. 7).

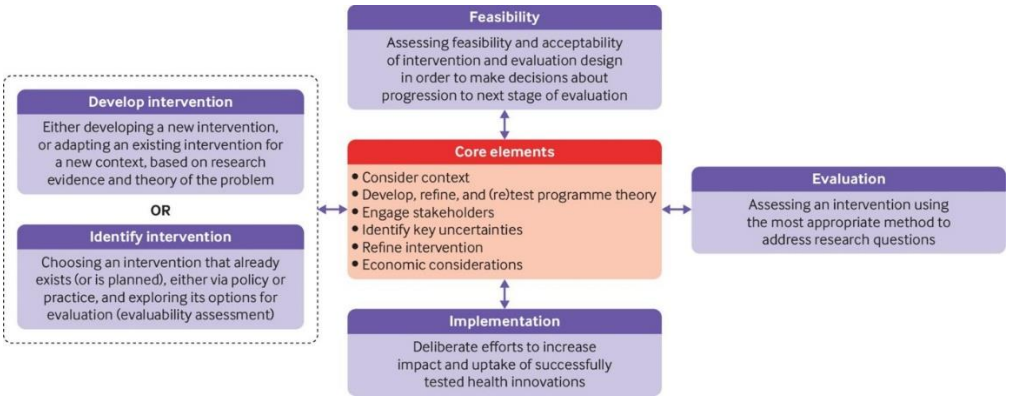


Fig. 7. Framework for developing and evaluating complex interventions
with permission from Kathryn Skivington, BMJ 2021;374:bmj.n2061)

The four phases of the complex intervention are; *Develop or Identify intervention*, *Feasibility*, *Implementation* and *Evaluation*. The *Core elements* are factors to be considered in all four phases, for example, context, stakeholder engagement and economics (Fig. 7).

In developing or identifying an intervention, the new or existing intervention must be adapted to the new setting or population. In this process, there is an awareness of the contextual factors and mechanisms of change when the intervention is designed and planned [133]. The nine elements of implementing PROs must be considered in this phase (Fig. 6).

The feasibility phase involves testing the intervention to examine the pre-defined criteria of recruitment, data collection, retention and outcome. The intervention must be feasible and possible to conduct using a reasonable amount of resources.

At an early stage in the intervention and throughout all phases, the implementation must be considered to increase the chance of adapting the intervention to a real-world setting. A way of doing this could be focusing on minimal resource disruption in the given context and delivering the intervention as close to real-world implementation as possible.

Finally, the evaluation phase is where the impact of the intervention in the specific context is identified. Again, several factors are to be considered, like how the intervention contributes to system change, interacts with the context and supports real-world decisions.

Aims and hypotheses

Hypotheses

- It is possible to construct a short item set for patients with pelvic cancer by identifying the most common acute symptomatic adverse events for patients receiving pelvic radiotherapy with curative intent.
- Electronic weekly reporting of symptoms is feasible and acceptable for patients with pelvic cancer treated with a curative intent with radiotherapy.
- Systematically selected patient-reported outcomes completed weekly contribute to the toxicity assessment for patients treated with online adaptive MR-guided radiotherapy.
- Patient-reported outcomes involve the patient in the symptom assessment, and remote monitoring improves the patient experienced communication and quality of care.

Aim

The aim was to systematically develop, integrate and evaluate a PRO measure in radiotherapy and prospectively investigate the longitudinal trajectory of acute PROs and the clinical impact for patients with prostate cancer receiving online adaptive MR-guided radiotherapy.

Aim study I: Item selection of symptomatic AEs

To identify acute symptomatic AEs for patients receiving primary pelvic radiotherapy and select equivalent items in validated item libraries. Furthermore, to evaluate the content validity of the item set in the course of radiotherapy, including patients treated at the MR-linac.

Aim study II: Feasibility, usability and acceptance

To explore the feasibility, usability and patient acceptance of weekly electronic patient reporting (ePRO) during pelvic radiotherapy.

Aim study III: Acute adverse event trajectories

To investigate the longitudinal acute patient-reported symptomatic AE trajectories based on weekly PROs for patients with prostate cancer treated with online adaptive MR-guided radiotherapy.

Aim study IV: Impact of digital symptom monitoring

To explore the clinical impact of weekly digital monitoring of PROs in radiotherapy for men with prostate cancer.

Overview of studies

Methods

Study Design

As the overall aim was to measure acute AEs for patients treated at the MR-linac there were some requirements for the choice of PRO measure (PROM). It should contain the most relevant acute symptoms and be short and precise to reduce the patient burden and sustain adherence to weekly self-reports. Therefore, the most common acute symptomatic AEs in pelvic radiotherapy needed to be identified to develop a comprehensive instrument for patient self-reporting.

Study I consisted of two phases: initial item selection and testing the content validity of the selected items in a pilot study with a parallel mixed-methods approach [134]. The pilot study was also the basis for study II, testing feasibility, usability and patient acceptance of weekly PRO reporting (Fig. 8).

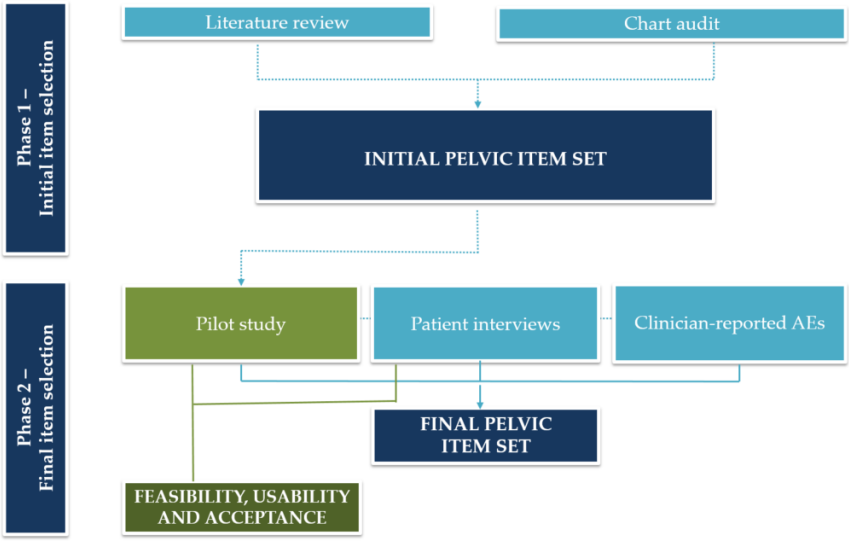


Fig. 8. The mixed methods design of study I and II

The item selection

The initial item selection in phase consisted of a literature review of acute AEs to pelvic EBRT, and a chart audit of the acute AEs reported for patients receiving radical online MRgRT for pelvic cancer.

Literature review and chart audit

The literature search was conducted in June 2019 in Cochrane, PubMed and Embase (Ovid). Endnote and Covidence were used to sort references and exclude doublets. The search was guided by PRISMA guidelines [135].

The literature search strategy was restricted to clinical studies reporting symptomatic acute AEs (<= six months after radiotherapy) to external primary radiotherapy for patients treated for prostate, urinary bladder, cervix or rectum cancer. Research from the past five years (2014-2019) was primarily included since radiotherapy treatment constantly evolves. The literature was excluded if case studies, teaching courses, conference papers or protocols. One reviewer (PKM) screened the references in a three-stage process, reducing the search output by evaluating first titles, abstracts and then full-text papers.

In a chart audit, clinicians reported CTCAEs and symptoms in the electronic health record were extracted on patients with PCa treated radically with online MRgRT from October 2018 - May 2019.

Initial item selection

The acute AEs obtained from the literature review or the chart audit was included in the initial item set if reported 1) for all four pelvic diagnoses or 2) for at least two diagnoses and in the chart audit or the two online MRgRT trials. In addition, corresponding items to the initially selected AEs were selected from two validated item libraries; The PRO-CTCAE [92] and the EORTC item library [100].

The pilot study

The initial set of PRO items was to be applied in a prospective observational pilot study enrolling patients referred for radical EBRT for pelvic cancer at the Department of Oncology at OUH. The patients were eligible for inclusion if they were $\geq$ age 18 years, able to complete PROs and treated for rectal, cervical, urinary bladder or prostate cancer in the study period October 2019 – June 2020. Informed consent was obtained based on written and oral information.

Data collection

The patients completed weekly electronic symptom reports during 4-8 weeks of treatment and four weeks following. After completing radiotherapy, follow-up reports were collected at 8, 12 and 24 weeks. The item selection was completed in October 2020. Health-related quality of life was measured at baseline and week 12 with the EQ-5D-5L and EORTC QLQ-C30 (Fig.9).

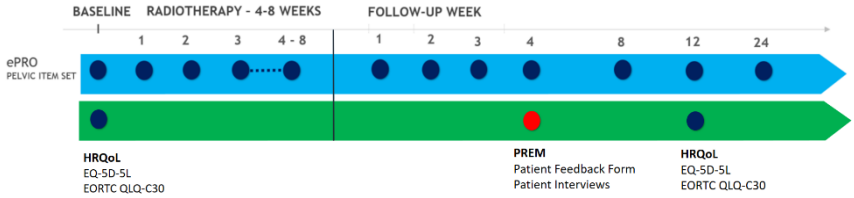


Fig. 9. Study design of the PRO-MR-RT pilot study

At the 4-week follow-up, the patients were asked to complete the Patient Feedback Form. The form was used in 2005 [136], adapted by Snyder et al. in 2014 [137] and translated and culturally adapted to a Danish cancer population [138] (Fig.9). This feedback form measures patient satisfaction with an ePRO intervention. To evaluate the content of the PRO and design alone, the clinicians were not allowed to enter or monitor the PRO system nor give feedback on the PROs. The patients were informed about this before the study entry. We aimed for an intervention feasible without a high workload and extensive resources used in the clinic.

To evaluate the content validity of the questionnaire, usability, and acceptance, we conducted individual semi-structured patient interviews based on a convenience sampling method [139]. Patients were also asked about the PRO symptom coverage, the usability of the questionnaire, the ePRO application, and the communication with clinicians.

The ePRO application

The patient pathway app and website of the Region of Southern Denmark, *My Hospital*, was used for ePRO collection [140] (Fig.10). The app enables patient-entered data to be safely transferred to the electronic health record. The patient enters the app with their eID for public self-service, NemID. Once they are logged

in, they have access to their personal information on treatment and disease, caregiver information and their schedule with hospital appointments.

The patients completed PROs at home on their own devices. Reminders were sent via the application. The previous PROs completed were visible to the patient; however, no graphical overview of the responses, alerts or self-management advice was provided. A paper questionnaire was an alternative if they did not have a device or sufficient technical abilities.

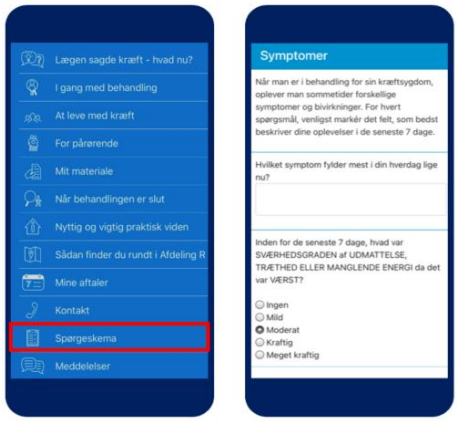


Fig. 10. The Patient Pathway app, *My Hospital*

Data analyses

The prevalence of symptomatic AEs was analysed descriptively. The symptomatic AEs were included in the final item set if ≥20% of patients reported them in the questionnaire, in the interview, or the patient record inspired by Sandler et al. [61].

Feasibility was explored by looking at the consent rate, attrition rate, adherence (participants replying to ≥ 80% of the weekly PRO questionnaires), weekly and follow-up adherence, and retention at follow-up week 24. The semi-structured patient interviews were analysed with a systematic text condensation in four steps [141]. As the themes were selected in advance, a deductive approach was applied; however, new themes could be derived from data inconsistent with the predefined themes [142].

Results study I & II: Item selection & pilot study

Summary of main results study I

The initial screening of 6.182 articles resulted in 46 being selected for the final review, and two recent MR-linac trials were added [103, 143]. Patient charts from 18 patients with PCa treated at the MR-linac were reviewed. The initial item selection resulted in 18 symptomatic AEs identified [144]. The 18 AEs were selected from the PRO-CTCAE item library (9 AEs) and the EORTC item library (9 AEs) (Fig.11). Five free text reporting options were added to report other symptoms during treatment or follow-up. This option was available at all times.

No	Symptom	Items	Response options
1	Decreased appetite	Severity	0-4
		Interference*	0-4
2	Nausea	Frequency	0-4
		Severity	0-4
3	Constipation	Severity	0-4
4	Diarrhea	Frequency	0-4
5	Abdominal pain	Frequency	0-4
		Severity	0-4
		Interference	0-4
6	Radiation skin reaction	Severity	0-4
7	Fatigue	Severity	0-4
		Interference	0-4
8	Painful urination	Severity	0-4
9	Urinary frequency	Frequency	0-4
		Interference	0-4
10	Pain/discomfort around anal opening (rectal pain/discomfort)	Severity	1-4
11	Frequent urination at night (nocturia)	Severity	1-4
12	Unintentional release (leakage) of urine (urinary incontinence)	Severity	1-4
13	Difficulty emptying bladder (retention)	Severity	1-4
14	Urinary urge	Severity	1-4
15	Bloated feeling in abdomen	Severity	1-4
16	Difficulty controlling bowels	Severity	1-4
17	Blood in stools	Severity	1-4
18	Vomiting	Severity	1-4

*Interference with daily acticities

Fig. 11. Items from the PTO-CTCAE and EORTC libraries selected for content validation

In the pilot study, 41 of the 47 patients informed accepted enrollment. As only one patient had bladder cancer, this patient was excluded from the analyses leaving 40 patients included. The study sample comprised 32 PCa and eight cervical cancer patients. Patients declining were older (-73 vs 68 years).

In the content validation, any grade of 17 AEs were reported by more than 20% of all patients post-baseline, with nocturia and urinary frequency being the most common. Vomiting was only reported by 13% and thus excluded.

For 19% of the patients with PCa, clinicians reported proctitis in the patient chart. To cover proctitis, blood-in-stool, rectal pain, and diarrhoea were in the item set; Therefore, in a clinician consensus meeting, we added the item “feeling of not completely emptying bowels” for PCa patients. We concluded that the 17 acute pelvic AEs were relevant and covered the most common symptoms in pelvic radiotherapy, with one AE added for proctitis for PCa.

Summary of main results study II

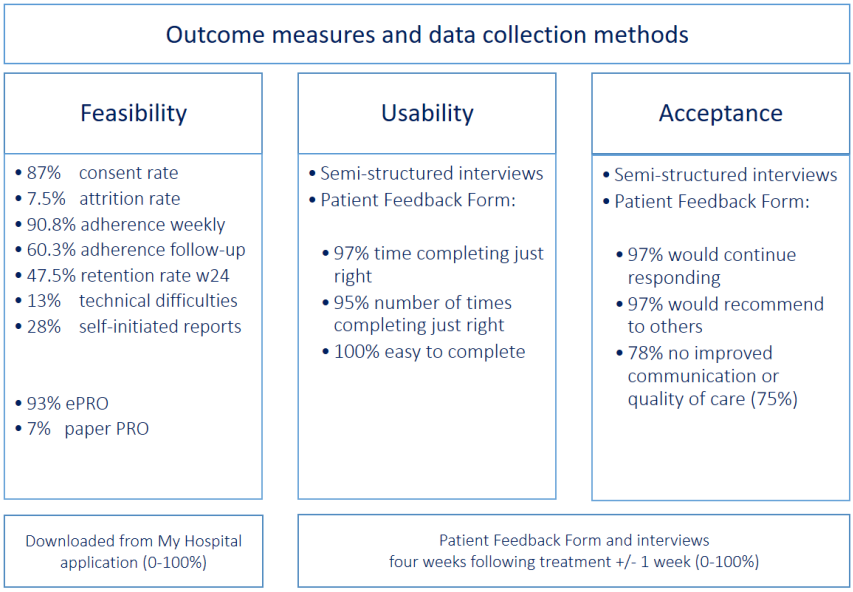
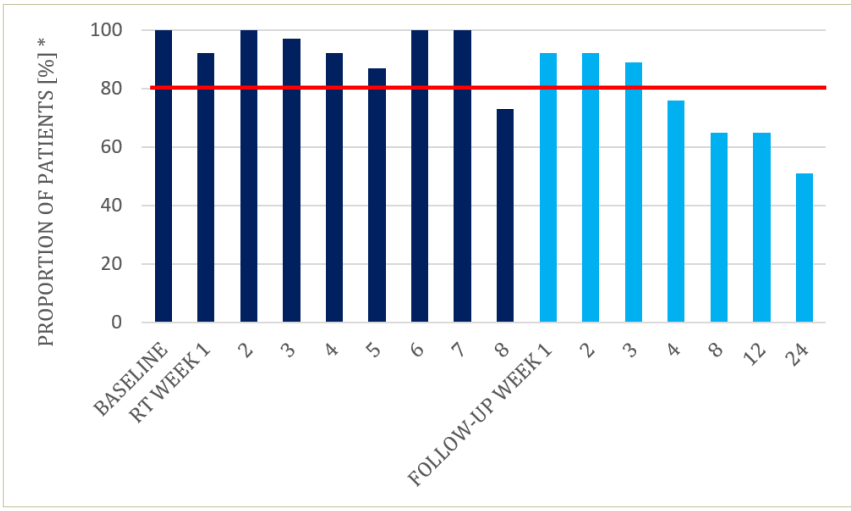


Fig. 12. Feasibility, usability and acceptance outcomes in the PRO-MR-RT pilot study (n=40)

The consent rate was high, and most patients accepted ePRO. The patients found the frequency and time spent on PRO completion just right. Most importantly, adherence to weekly ePRO completion was high, as 85% of patients responded to more than 80% of the weekly questionnaires (Fig.13). We found a

significant difference in age as patients < age 70 had a significantly better adherence (90%) than patients ≥ age 70 (79%) (p=0.041). Although the weekly response rate was high, it declined during follow-up, with a retention rate of 47,5% in week 24 (Fig. 12,13).



*Proportion of participants still alive and enrolled in the trial

Fig. 13. Adherence to PRO completion in the PRO-MR-RT pilot study (n=40)

As the clinicians were not allowed to enter and use the PRO data in their daily symptom management, the patients did not experience that the ePRO completions improved their communication with the clinicians nor their quality of care (Fig. 12). This was elaborated further in the patient interviews (n=14).

The patient interviews revealed technical difficulties for some, but only when entering the app. An essential factor for adherence to reporting ePROs was having it scheduled on a fixed weekday. The caregivers were mainly involved in helping with the reporting in the beginning, but PRO completion made them discuss the symptoms at home. They did not need feedback from the application, as they preferred discussing their health with the clinicians. They were satisfied with the communication during treatment but requested feedback on their PRO responses from the clinicians. This citation from a patient with PCa supports this: "*Well, I think I took it for granted that if I replied that I had major problems with my stomach or something, well then someone would grab me and say "hey, we just have to look at that*". *I took it for granted. Of course, there needs to be some feedback. Otherwise, it does not matter."* (Male, 63 years)

Study III & IV: Acute AEs & Clinical impact

Methods

Study Design

Studies III and IV are samples from a prospective single-arm observational study. From November 2020 - May 2022, observations were made in a real-world setting where patients with PCa were allocated for different RT schedules.

Study III includes the sample of patients treated at the MR-linac focusing on acute toxicity. Study IV includes all patients with PCa to explore the clinical impact of the ePRO intervention.

Patients, setting and ethical considerations

From November 2020 – May 2022, all patients with PCa referred for radiotherapy at Odense University Hospital were eligible for enrollment. The patients were allocated for treatment at the MR-linac (1.5 T Elekta Unity) or at a standard linac (Elekta Versa HD) with different treatment schedules according to the local treatment guidelines. The duration of radiotherapy varied from two to eight weeks.

Patients were eligible for inclusion if age $\geq$ 18 years, had PCa and were referred for radical radiotherapy of the prostate, salvage radiotherapy of the prostate bed or radiotherapy for low-volume metastatic PCa (total dose > 30 Gy). Furthermore, the patients should be cognitively able to provide informed consent and read, understand and complete PRO questionnaires in Danish. If patients were not eligible or declined participation, they were listed on a screening list with the reason for declining, age, cohabitation status, WHO performance status, treatment dose and fractionation.

Oral and written informed consent was obtained from all study participants. The Danish Data Protection Agency approved the study, and no approval was necessary from the Danish Health Research Ethics.

Data collection

The design of the pilot study was applied with weekly PRO completions of the validated pelvic item set during and up to four weeks following radiotherapy and

at follow-up weeks eight, 12 and 24 (Fig. 16). At baseline and 12 weeks following radiotherapy, health-related QoL was measured with EQ-5D-5L and EORTC QLQ-C30 (Fig.14).

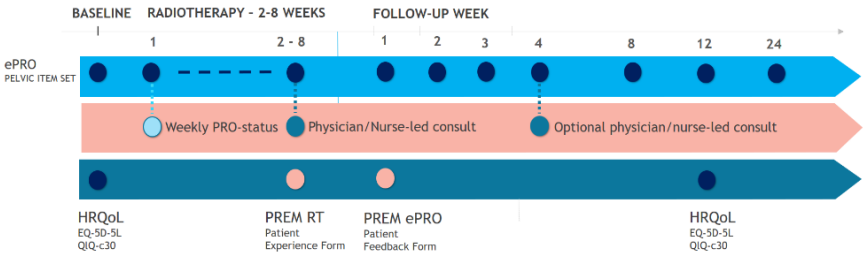


Fig. 14. The data collection in the longitudinal study III and IV

The last treatment week provided a questionnaire exploring patient experience of receiving treatment at the MR-linac [17]. Finally, the Patient Feedback Form used in the pilot study was sent one week following treatment. The Patient Experience Form and the QLQ-C30 will be used for future analyses in a larger sample. Like in the pilot study, reminders to complete PROs were sent to the patient via *My Hospital* during treatment. We sent reminders to the digital public mailbox during follow-up to improve response rates.

Usual care

Daily observations and an unsystematic dialogue between the patient and a radiation therapist about new or worsened symptoms were the usual care before the intervention. Symptom management was initiated based on this dialogue. At the end of the radiotherapy course and four weeks following, the patients with PCa had a physician consultation to manage their acute AEs. At the end of the pilot study, the physician consultations were changed into nurse-led consultations for most patients with PCa. The radiation therapists in the department are referred to as clinicians.

The ePRO intervention

When a physician informed the patient about radiotherapy, the application *My Hospital* was introduced to the patient. When they attended the CT/MR simulation, they were informed about the ePRO intervention by the primary investigator (PKM). How to use *My Hospital* for ePROs was demonstrated on a smartphone,

and written guidance was handed out illustrating how to enter the application and find the questionnaires.

The patient was informed to complete PROs on a fixed weekday. A graphic display of the PROs was immediately available in the electronic patient record for the clinicians to review. The following day, the clinicians used the PROs in a *PRO-status* dialogue with the patient. The symptoms discussed and the supportive care interventions initiated were documented in the electronic patient record as a PRO-status. The nurse-led consultations for patients with PCa also monitored and used the PROs (Fig.15).

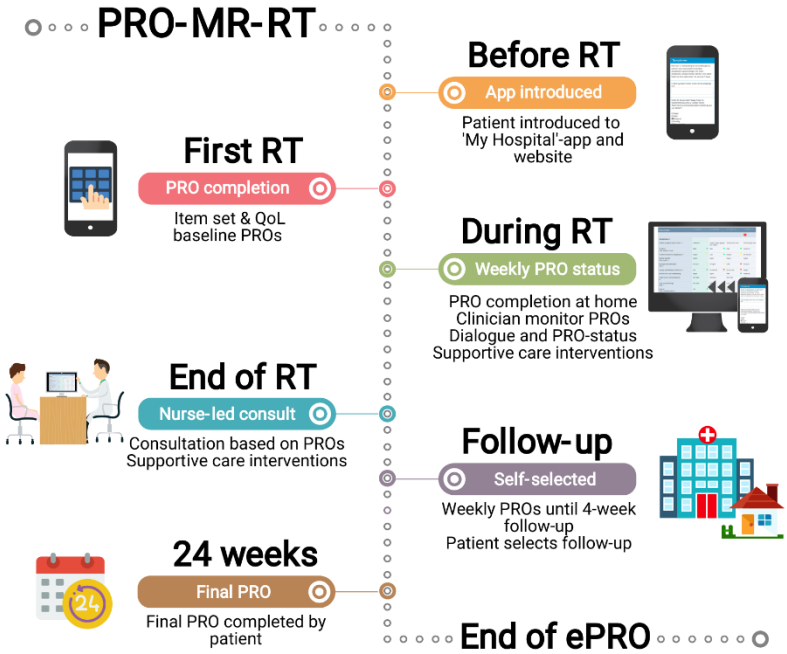


Fig. 15. ePRO workflow with real-time feedback in the course of radiotherapy

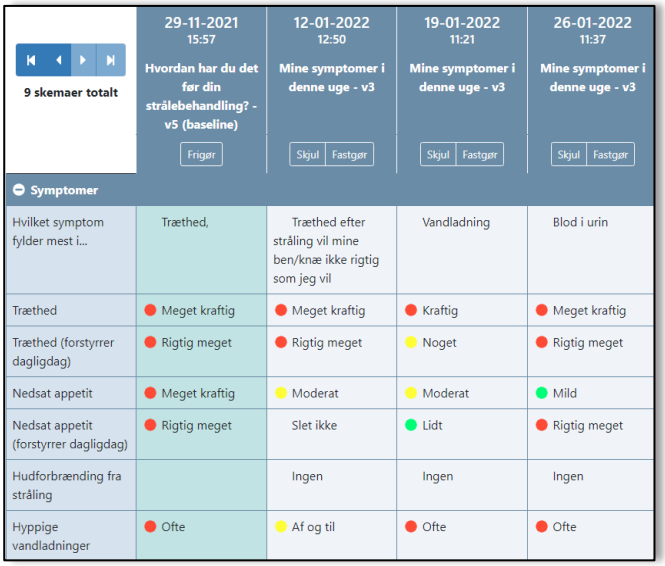
After reporting their symptoms weekly until the 4-week follow-up, the patients were asked about their need for follow-up, except for patients attending clinical trials being prebooked for an in-person consultation.

The patient was asked to select one of the following response options based on their current health status; "I have a scheduled telephone consultation and want to keep this", "I do not need my telephone consultation, and I will contact the Department if needed", or "I have a scheduled appointment in the Department".

Training of clinicians

In two sessions, clinicians were trained in the PRO item set, the PRO workflow, *My Hospital* patient interface and *My Hospital* clinician interface. The primary investigator (PKM) was available for coaching during the study period. The PRO-status was prebooked as a task in the patient's schedule the day after ePRO completion. The task needed to be completed by the clinician on the daily list. When the clinicians entered the new PRO completion, they were asked to click the 'handle' icon. That made it visible to their colleagues that the PRO had been reviewed and handled.

The clinicians were informed to use the PROs as a dialogue tool, with attention to new or increased symptoms. There were, however, no guidelines or restrictions on interpreting the PROs. The clinicians could compare the responses over time. A blank, green, yellow or red dot indicated the symptom's frequency/severity or interference (Fig. 16). The green fixed column in the left side of the table was the baseline response being visible at all times together with the latest three completed ePROs.



9 skemaer totalt	29-11-2021 15:57 Hvordan har du det før din strålebehandling? - v5 (baseline) Frigør	12-01-2022 12:50 Mine symptomer i denne uge - v3 Skjul Fastgør	19-01-2022 11:21 Mine symptomer i denne uge - v3 Skjul Fastgør	26-01-2022 11:37 Mine symptomer i denne uge - v3 Skjul Fastgør
Symptomer				
Hvilket symptom fylder mest i...	Træthed,	Træthed efter stråling vil mine ben/knæ ikke rigtig som jeg vil	Vandladning	Blod i urin
Træthed	Meget kraftig	Meget kraftig	Kraftig	Meget kraftig
Træthed (forstyrrer dagligdag)	Rigtig meget	Rigtig meget	Noget	Rigtig meget
Nedsat appetit	Meget kraftig	Moderat	Moderat	Mild
Nedsat appetit (forstyrrer dagligdag)	Rigtig meget	Slet ikke	Lidt	Rigtig meget
Hudforbrænding fra stråling		Ingen	Ingen	Ingen
Hyppige vandladninger	Ofte	Af og til	Ofte	Ofte

Fig. 16. *My Hospital* clinician interface of PROs compared over time

Outcome measures study III and IV

In study III, we decided on a clinically relevant within-patient worsening of urinary frequency based on the results from our pilot study following the SISAQOL recommendations [82]. The clinically relevant change is measured as having a minimum two-level increase from baseline over two consecutive time points inspired by prior study alerts [117, 122]. In the pilot study, 15% of patients with PCa treated at the MR-linac reported this increase.

As secondary outcomes, within-group longitudinal mean changes in acute patient-reported AEs, the median time to the first occurrence of within-patient maximum worsening of AEs and the persistence of deteriorated symptoms were explored (Fig.17). All symptom reports were extracted from *My Hospital* software.

Study IV extracted data from the Patient Feedback Form and QoL questionnaires from *My Hospital* software. Furthermore, we extracted data on the number of PROs handled by clinicians (clinician compliance), the response rates and the selection of follow-up (Fig. 17).

Study III	Patients with PCa treated at the MR-linac
Acute AE trajectories from weekly PROs	*Primary:* • Clinically relevant increase in urinary frequency (≥ 2 level increase for ≥ 2 weeks)
	Secondary: • Acute AE trajectories • Time to first maximum worsening of AEs • Persistence of AEs
Study IV	All patients with PCa treated with radiotherapy
Clinical impact real-time symptom monitoring	*Primary:* • Impact of ePRO with realtime symptom monitoring on patient quality of care, discussion and communication with clinicians and patient involvement
	Secondary: • Association between clinician compliance and patients experiencing the PROs used for their care • Association between clinician compliance and patient response rate • Stratified follow-up – patients' self-selected follow-up • Changes in quality of life from baseline to follow-up week 12

Fig. 17. Outcome measures of the PRO-MR-RT study

In the baseline questionnaire, patients were asked about the technical device used for PRO completion and how frequently they used it for anything other than telephone calls and text messages.

Statistical considerations study III and IV

Descriptive comparisons of baseline characteristics were performed using parametric statistics if the variable were normally distributed; one-way Anova, student's t-test, chi-square and Fisher's exact test. Non-parametric statistics (Wilcoxon rank sum test or Wilcoxon signed-rank test) were used if the variable did not follow a normal distribution. The same analyses were applied to test statistically significant differences between participants and non-participants.

In study III, the proportion of PCa patients having increased urinary frequency was estimated with descriptive statistics stratified in radiotherapy prescription. Time to maximum worsening of the AE was computed as the first within-patient maximum grade reported. Linear mixed models for repeated measures were used for within-group mean changes in AEs over time with 95% confidence intervals. Since the patients in the 36 Gy group were treated with 2 or 3 fractions per week, an 'end of treatment' time variable accounted for different durations. The mean persistence of symptoms was estimated as symptoms still deteriorated compared to the baseline level of the individual patient.

In study IV, responses from the Patient Feedback Form were dichotomised into *agree* (strongly agree/agree) or *disagree* (disagree/strongly disagree). A Fisher's exact test was used to explore if clinician compliance (100% or >100% handled) was associated with the patient experience of PROs being used. Univariate logistic regression was performed to investigate clinician compliance and patient compliance (individual response rate).

Fisher's exact test and univariate logistic regression analyses were used to explore associations between the questions from the Patient Feedback Form and different covariates; age, WHO performance status, cohabitation status, educational status, radiotherapy prescription, concomitant systemic treatment, technical abilities and baseline EQ-5D score and EQ VAS score. The Wilcoxon signed-rank test and Kruskal-Wallis tests were applied to compare mean differences in health-related quality of life with the EQ-5D index score and EQ VAS score. Changes in EQ VAS health state (improved, worsened or no change) [145] were compared in the follow-up selection groups with chi-square tests.

A p-value of ≤ 0.05 was considered statistically significant. Analyses were conducted using STATA/IC 15.

Results study III & IV: Acute AEs and clinical impact

Summary of main results study III

Sixty-three patients at the MR-linac were eligible and informed in the study period, but three declined (consent rate 95%). Thus 60 patients were enrolled, one dropped out, and nine were excluded from the analyses because of treatment-related differences.

Of the 50 patients included in the analyses, patients with localised intermediate-risk PCa (n=25) were allocated to online MRgRT with a curative intent using moderate hypofractionation of 60 Gy over 20 Fx (5 Fx/week), and patients with newly diagnosed low-volume metastatic disease were treated with 36 Gy/6 Fx (2-3 Fx/week). The median age of the participants was 71 years, and patients declining had a median age of 81. Four patients (8%) equally distributed in the two groups completed PROs on paper.

During treatment, the adherence to weekly self-reporting was 96-100%. The mean response rate during follow-up in the 60 Gy group was 87% vs 90% in patients treated with 36 Gy (week 12: 96% vs 84%).

Genitourinary patient-reported AEs

A clinically relevant two-level increase in urinary frequency over two consecutive time points was reported by 28% (n=7) of patients receiving moderate hypofractionation (60 Gy/20 Fx) and 12% (n=3) of patients receiving 36 Gy. There were some baseline score imbalances. In the 60 Gy group, 16% vs 24% in the 36 Gy group had frequent or almost constant frequent urination at baseline; thus, a two-level increase was not possible for these patients (Table 6).

For the 60 Gy group, the median time to the first maximum worsening of urinary AEs was two weeks post-baseline. The maximum mean change from baseline in urinary AEs was reported after three weeks of RT. After follow-up week four, no significant mean changes appeared in any AEs for the 60 Gy group.

In the 36 Gy group, the onset of and median time to the first maximum worsening of most GU symptoms was one week after the start of online MRgRT (Fig. 18). Opposed to the 60 Gy group, urinary urge did not significantly change over time, but 80% reported having any grade of urge at baseline (Table 6). Unlike the patients treated with 60 Gy, this group peaked in urinary retention and increased urination at night two weeks after MRgRT completion (Fig. 18).

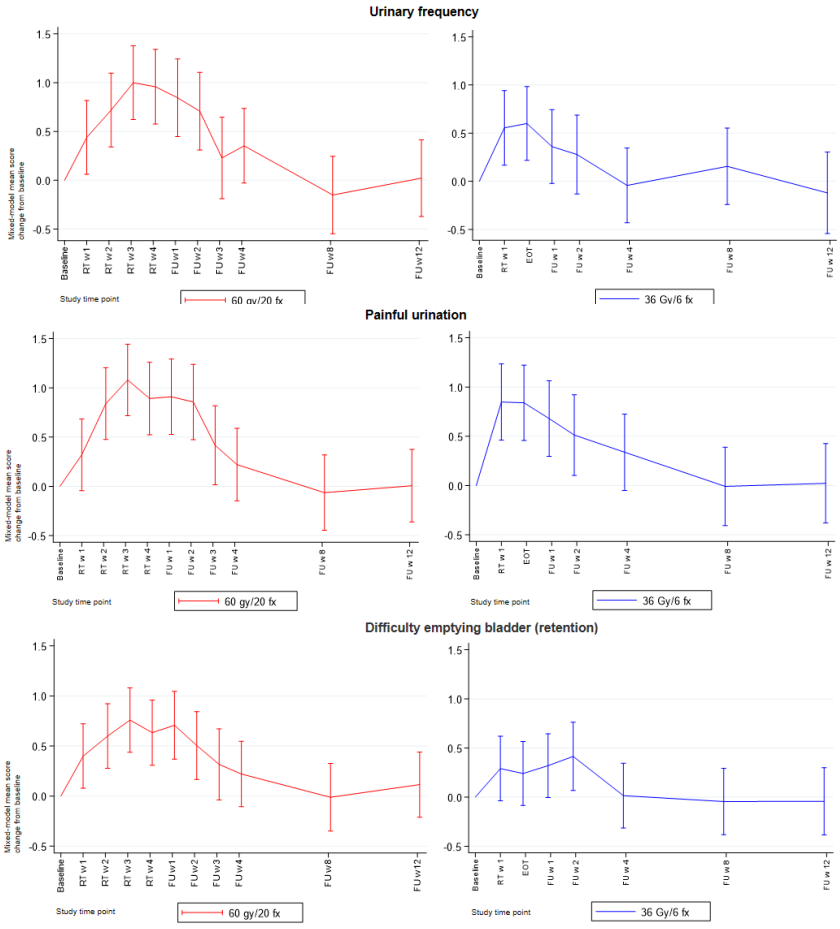


Fig. 18. Mean change over time in selected urinary AEs with 60 Gy/20 Fx (n=25) and 36 Gy/ 6 Fx (n=25)

Gastrointestinal patient-reported AEs

For patients receiving 60 Gy, gastrointestinal (GI) symptoms in terms of diarrhoea and difficulty controlling bowels peaked in their third week of MRgRT (Fig. 19). The peak in constipation and rectal pain occurred in the last week of radiotherapy. One week later, blood in stool peaked in the first week of follow-up (Fig. 19).

In the 36 Gy group, the bowel AEs peaked during follow-up week one (diarrhea) and week two (pain around the anal opening) (Fig. 19). No significant mean changes in AEs were observed in the 36 Gy group after the second week of follow-up.

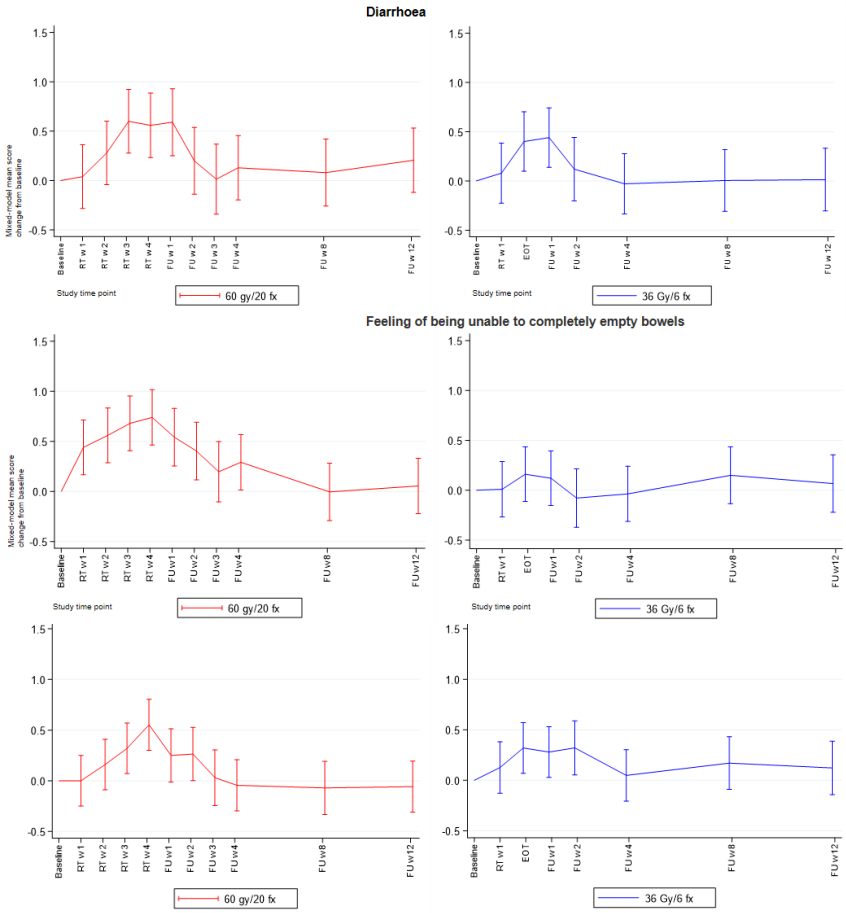


Fig. 19. Mean change over time in selected bowel AEs when receiving 60 Gy (n=25) or 36 Gy (n=25)

Symptom persistence

Patients treated with online MRgRT with moderate hypofractionation (60 Gy/20 Fx) reported more persistent urinary AEs especially urinary frequency (16%) beyond the 12-week follow-up than the ultrahypofractionated patients (0%) (Fig. 20). Conversely, bowel AEs persisted in patients treated with 36 Gy/6 Fx where 12%

(n=3) still reported increased pain around the anal opening compared to baseline after the 12-week follow-up (0%, 60 Gy) (Fig. 22).

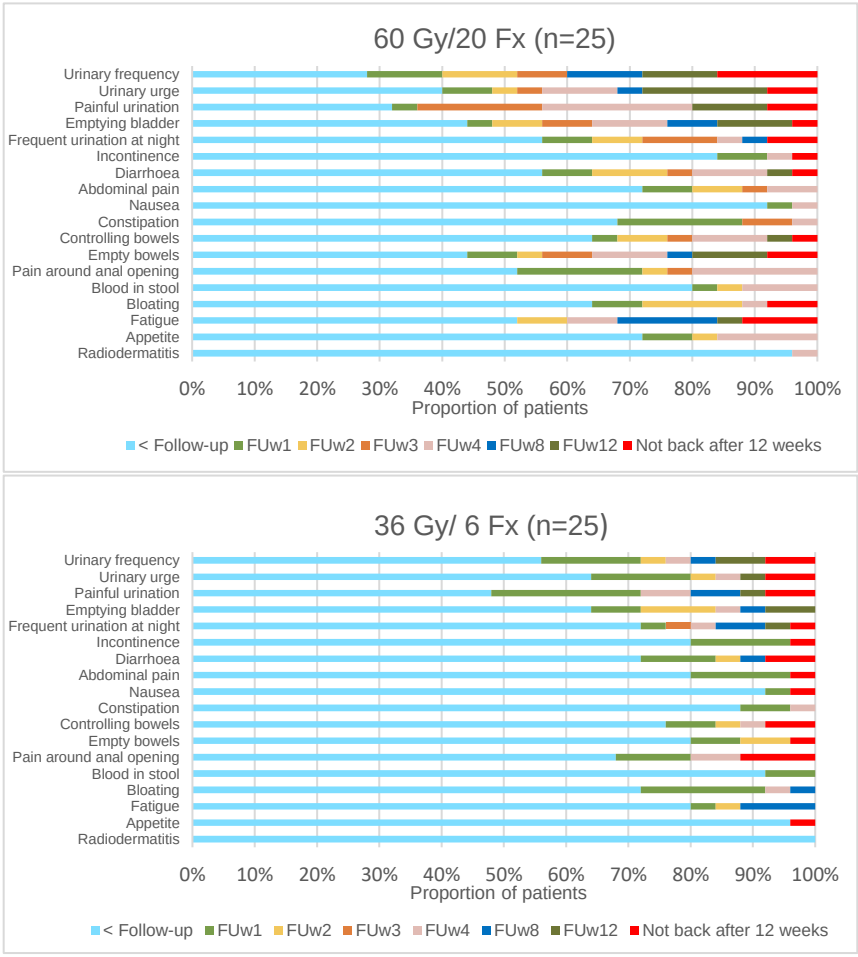


Fig. 20. Time to symptomatic AE score back at baseline level (n=50)

Additional results study III

Preliminary analyses have been conducted of the final follow-up PROs at week 24 after online MRgRT. Urinary frequency persists, with a higher proportion having a moderate or severe grade in both treatment groups (Table 6). Radiodermatitis was reported by 24% of patients treated with 6 Fx. Thus, further analyses must explore if this AE is associated with increased pain around the anal opening and difficulty controlling the bowels. Finally, more patients in both groups reported moderate/severe fatigue in week 24 compared to baseline (Table 6).

Table 6. Patients reporting any grade or moderate/severe symptomatic AEs at baseline (n=50) and 24-week follow-up (n=44)

	Localised Pca 60 Gy/20 Fx, n, %								Low-volume metastatic Pca 36 Gy/ 6 Fx, n, %							
	Any grade				Moderate/severe grade*				Any grade				Moderate/severe grade*			
	Baseline		FU week 24		Baseline		FU week 24		Baseline		FU week 24		Baseline		FU week 24	
	n=25		n=23		n=25		n=23		n=25		n=21		n=25		n=21	
Urinary frequency	20	80%	19	83%	4	16%	8	35%	21	84%	19	90%	6	24%	12	57%
Urge	16	64%	17	74%	7	28%	3	13%	20	80%	14	67%	5	20%	3	14%
Painful urination	3	12%	2	9%	3	12%	0	0	8	32%	4	19%	3	12%	1	5%
Emptying bladder (retention)	10	40%	11	48%	3	12%	2	9%	14	56%	9	43%	1	4%	2	10%
Frequent urination at night	22	88%	20	91%	8	32%	8	36%	23	92%	19	91%	9	36%	2	10%
Incontinence	2	8%	3	13%	0	0%	0	0	4	16%	3	14%	0	0%	0	0
Diarrhoea	7	28%	7	30%	0	0%	0	0	6	24%	5	24%	1	4%	1	5%
Abdominal pain	9	36%	6	26%	2	8%	3	13%	8	32%	8	38%	0	0%	3	14%
Nausea	1	4%	2	9%	1	4%	0	0	5	20%	3	14%	0	0%	0	0
Constipation	5	20%	4	17%	1	4%	1	4%	6	24%	4	19%	0	0%	1	5%
Difficulty controlling bowels	1	4%	3	13%	0	0%	1	4%	2	8%	5	24%	0	0%	0	0
Feeling of not emptying bowels	6	24%	10	43%	2	8%	1	4%	8	32%	7	33%	1	4%	1	4%
Pain around anal opening	5	20%	4	17%	1	4%	1	4%	3	12%	4	19%	0	0%	1	5%
Blood in stool	0	0%	1	4%	0	0%	0	0	0	0%	0	0%	0	0%	0	0
Bloating	7	28%	6	26%	2	8%	2	8%	7	28%	10	48%	1	4%	2	10%
Fatigue	11	44%	15	65%	1	4%	5	22%	19	76%	16	76%	1	4%	9	43%
Decreased appetite	2	8%	4	17%	0	0%	2	9%	4	16%	3	14%	0	0%	1	5%
Radiodermatitis	0	0%	0	0	0	0%	0	0	0	0%	5	24%	0	0%	3	14%

*Moderate/severe: PRO-CTCAE score 2-4, EORTC score 3-4

PROs capturing unanticipated symptoms

Several patients (32%) used the write-in option to report other symptoms during treatment or follow-up. Severe or very severe symptoms were reported, with a peak in treatment week two by 14% of all patients. Some symptoms are not radiotherapy-related but are probably caused by the concomitant hormonal treatment (hot flushes, sexual problems and weight gain). Others must be investigated further.

Summary of main results study IV

The 50 patients from study III were part of the sample analysed in study IV with 156 participants (Fig. 21).

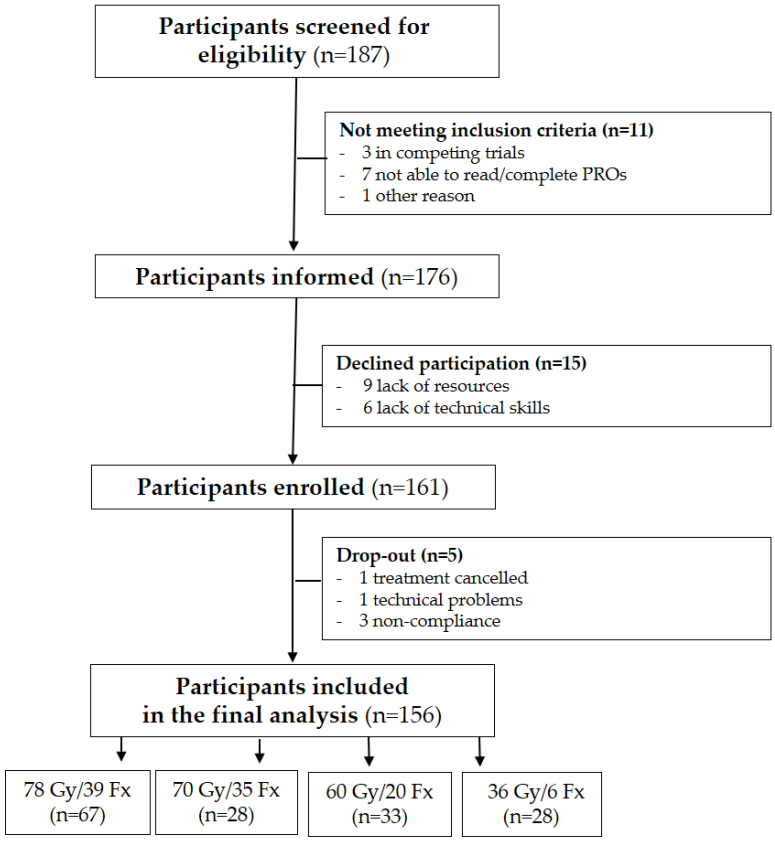


Fig. 21. Flowchart of the Danish PRO-MR-RT study (n=156)

The patients were treated according to different radiotherapy schedules based on their PCa disease stage (Fig. 21). The attrition rate was 5%. The overall median age of the participants was 69. Most had high-risk PCa and were treated with 78 Gy (43%), cohabiting (80%), treated with concomitant androgen deprivation therapy (ADT) (87%) and in WHO performance status 0 (84%) (Table 7).

Most participants accepted electronic reporting of PROs (95%) (Table 7). Participants completing paper PROs were younger (66.3 vs 68.9), their self-rated EQ VAS score was better (90 vs 81), and their highest attained education was primary school or vocational training. A few patients had technical difficulties entering the application and sending the ePROs.

Table 7. Characteristics of study participants with prostate cancer in the PRO-MR-RT study (n=156)

	Total	78 Gy/39 Fx High risk	70 Gy/35 Fx Salvage	60 Gy/20 Fx Intermed. risk	36 Gy/6 Fx Low-vol.met.	*p-value*
	N=156	N=67	N=28	N=33	N=28	
Age, *mean (SD)*	69 (6)	69 (6)	66 (7)	69 (5)	70 (6)	*0.047*
Cohabitation status						
Cohabiting	80% (125)	79% (53)	100% (28)	73% (24)	71% (20)	
Living alone	20% (31)	21% (14)	0% (0)	27% (9)	29% (8)	*0.024*
WHO/ECOG Performance status						
PS 0	84% (131)	79% (53)	93% (26)	82% (27)	89% (25)	
PS 1	13% (21)	19% (13)	4% (1)	15% (5)	7% (2)	
PS 2	3% (4)	1% (1)	4% (1)	3% (1)	4% (1)	*0.302*
Educational status						
Basic school	4% (7)	3% (2)	4% (1)	6% (2)	7% (2)	
Vocational training	38% (60)	40% (27)	29% (8)	48% (16)	32% (9)	
Short-cycle higher education	8% (13)	4% (3)	14% (4)	9% (3)	11% (3)	
Medium-cycle higher education	21% (33)	12% (8)	25% (7)	33% (11)	25% (7)	
Long-cycle higher education	6% (9)	7% (5)	7% (2)	0% (0)	7% (2)	*0.430*
Missing	22% (34)	33% (22)	21% (6)	3% (1)	18% (5)	
Currently working, yes	31% (45)	28% (16)	50% (14)	24% (8)	26% (7)	*0.110*
Concomittant ADT						
Yes	87% (136)	100% (67)	96% (27)	48% (16)	93% (26)	*<0.001*
Accept electronic reporting (ePRO)						
Yes	95% (148)	97% (65)	100% (28)	88% (29)	93% (26)	*0.130*
Use of technology, *frequency*						
Several times a day	56% (88)	50% (32)	82% (23)	55% (17)	64% (16)	
Daily	24% (37)	30% (19)	18% (5)	26% (8)	20% (5)	
Weekly	5% (8)	11% (7)	0	3% (1)	0	
Monthly	3% (5)	4,5% (3)	0	6% (2)	0	
Never	12% (18)	4,5% (3)	0	10% (3)	16% (4)	*0.057*

Patient satisfaction with the PROM and the ePRO intervention was high (Fig. 22). Surprisingly, the only difference we found was between participants completing

electronic PROs and those completing paper PROs. Fewer patients completing paper PROs felt their information was used by the clinician (67% vs 97%) (p=0.018). Similarly, fewer patients reported that paper PROs made them feel more involved in their care (67%) compared to patients completing ePROs (95%) (p=0.050). However, the clinicians handled all questionnaires of the eight patients completing paper PROs (100%).

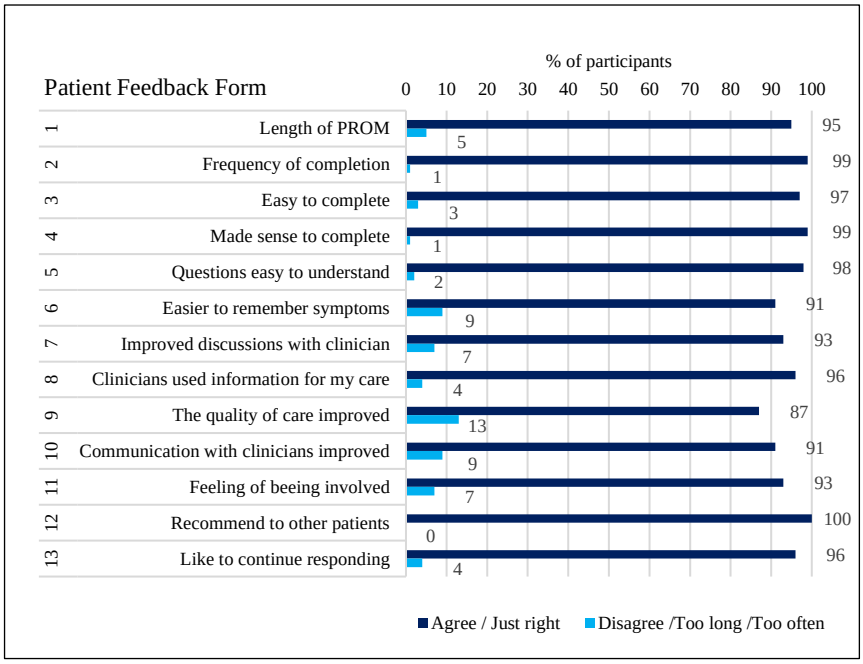


Fig. 22. Patient satisfaction with the ePRO intervention (n=153)

In general, most patients (96%) agreed that the staff used the information from the PROs for their care (Fig. 23). This patient-experienced use of data was not associated with the rate of PROs handled by the clinicians since most patients (93%) had all their questionnaires handled by the clinicians. The remaining patients (7%) all reported that they felt their PROs were used for their care (p=0.487).

Stratified selection of follow-up

Some patients were treated in MR-linac treatment protocols and thus scheduled for physician follow-up. However, out of 107 patients having the choice of follow-

up, 23% deselected the follow-up consultation (Table 8). This choice of follow-up was not associated with age (p=0.232), WHO performance status (p=0.530), co-habitation status (0.868), educational status (p=0.931), radiotherapy schedule (p=0.352), concomitant systemic treatment (p=0.660), technical abilities (p=0.056) or baseline EQ-5D index score (0.255) and EQ VAS-score (n=0.986).

There were no associations between the follow-up selection and admission or other supportive care interventions (Table 8). However, surprisingly, a significantly higher proportion of patients deselecting the 4-week follow-up reported a worsened self-rated EQ VAS score at the 12-week follow-up (68%) as opposed to those selecting follow-up (40%) (p=0.044).

Table 8. Follow-up selection and supportive care interventions (n=156)

% (n)	Prebooked consultation in the department *	Select follow-up consultation	Deselect follow-up consultation	*p-value*
Follow-up selection	31% (49)	53% (82)	16% (25)	
Number of medication prescribed (n=98)				*0.254*
0	26% (12)	41% (32)	40% (10)	
1	26% (12)	27% (21)	36% (9)	
2	30% (14)	22% (17)	12% (3)	
> 2	19% (9)	11% (9)	12% (3)	
Mean diff EQ index score (SD)	-0.017 (0.11)	-0.023 (0.12)	0.022 (0.12)	*0.060*
Mean diff EQ VAS score (SD)	-6.79 (14.05)	-2.49 (13.80)	-3.08 (18.78)	*0.868*
Deteriorated VAS score week 12	49% (24)	40% (33)	68% (17)	*0.044*
Contacted the department outside scheduled appointments	29%	36%	16%	*0.045*
Mean number extra contacts (n=47)	0.57	0.41	0.28	*0.380*
Referred for rehabilitation	23% (11)	17% (14)	16% (4)	*0.575*
Admission (after median 25 days)	2% (1)	6% (5)	8% (2)	*0.524*
KAD during RT or follow-up	8% (4)	9% (7)	0	*0.140*

* 56% in MR-Linac trials. 6 (4%) changed to physician consult due to symptom severity

Changes in health-related QoL

The mean difference between the 12-week EQ-5D index score and EQ VAS score and the baseline scores were not significantly associated with age groups, WHO performance status, cohabitation status or radiotherapy schedule (Table 9). Only patients having concomitant ADT significantly declined more in EQ VAS score compared to patients not having ADT (p=0.05). Most scores decreased at the 12-week follow-up except for WHO performance status 1-2 and cohabitation status, potentially due to baseline imbalances (Table 9). Patients < or $\underline{\geq}$ 70 years

significantly differed in their self-rated health as older patients ≥ age 70 scored better health than the younger patients (median VAS 82 vs 75, p=0.008). A similar difference occurred at follow-up week 12 (EQ VAS 78 vs 72, p=0.034).

Table 9. Mean differences in EQ-5D-5L scores between baseline and follow-up week 12 (n=156)

Higher scores = better health state reported					
	Mean diff EQ index score	*p-value*	Baseline mean EQ-VAS score	Mean diff EQ-VAS score	*p-value*
Overall	-0.017		78.5	-3.93	
Age <70 years	-0.026		74.7	-3.97	
Age ≥70 years	-0.009	*0.637*	82.2	-3.90	*0.934*
WHO PS 0	-0.020		80.5	-4.51	
WHO PS 1-2	0.002	*0.923*	68.4	-0.91	*0.738*
Married	-0.022		78.9	-4.61	
Living alone	0.007	*0.270*	76.4	-0.75	*0.151*
RT 78 Gy	-0.026		75.8	-4.16	
RT 70 Gy	-0.020		79.7	-3.27	
RT 60 Gy	0.011		82.2	-2.97	
RT 36 Gy	-0.024	*0.395*	79.2	-4.36	*0.899*
+ ADT	-0.014		77.8	-4.43	
- ADT	-0.037	*0.612*	83.2	-0.41	*0.050*

Additional results study IV

When comparing the characteristics of non-participants with participants, they were significantly older (p=0.010), and most were treated for high-risk PCa or low-metastatic PCa (p=0.011) (Table 10). Furthermore, more non-participants were performance status 1-2 (50%) as opposed to participants (25%) (p<0.001).

Table 10. Difference between participants (n=156) and non-participants (n=26) in the PRO-MR-RT study

	Participants (n=156)	Non-participants (n=26)	p-value
Age, *mean (SD)*	69 (6)	72 (6)	0.010
Cohabiting	80% (125)	69% (18)	
Living alone	20% (31)	31% (8)	0.209
WHO, performance status			
0	84% (131)	50% (13)	
1	13% (21)	38% (10)	
2	3% (4)	12% (3)	<0.001
Radiotherapy prescription (dose/fx)			
36 Gy/6 Fx	18% (28)	19% (5)	
60 Gy/20 Fx	21% (33)	4% (1)	
70 Gy/ 35 Fx	18% (28)	4% (1)	
78 Gy/39 Fx	43% (67)	73% (19)	0.011

Finally, lets compare the Patient Feedback Form responses from the participants (n=153) with responses from patients with PCa in the PRO-MR-RT pilot study (n=29). Then, questions 6-11 on clinical impact significantly differ (PFF6 p=0.007, PFF7-11 p<0.001).

In the pilot study, PROs were not used by the clinicians, nor did the patient get any feedback on their reports. When adding real-time symptom monitoring with feedback in the PRO-MR-RT study, we found a significantly higher satisfaction with ePROs being used for care, improving discussion, communication and quality of care and giving the patient a feeling of being involved (Fig. 23).

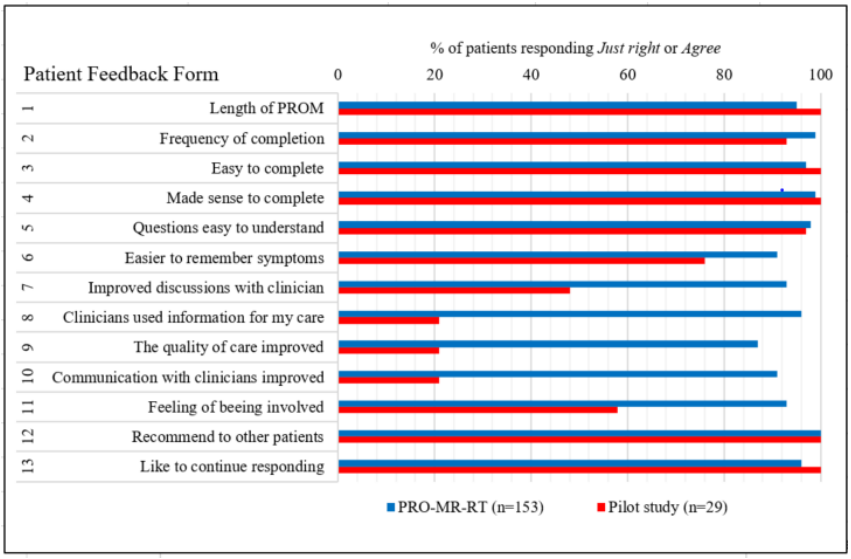


Fig. 23. Comparison of PFF responses for patients with PCa in the pilot study and PRO-MR-RT

Summary of main findings

The main results from the four studies will be discussed according to the radiotherapy setting, patient involvement, methodology, the PROs, clinical implications and the ability of PROs to evaluate new technologies in radiotherapy.

DESIGN	MATERIAL AND METHODS	HIGHLIGHTED FINDINGS
STUDY I - ITEM SELECTION		
Mixed Methods	Literature review: 48 publications Medical record audit: 18 PCa patients Content validation in a pilot study	Pelvic item set with 18 acute symptomatic AEs for the PCa population receiving primary pelvic radiotherapy
STUDY II – FEASIBILITY, USABILITY AND PATIENT ACCEPTANCE		
Prospective, single-arm	Pilot study: 32 PCa, 8 cervical cancer patients Treated at CT- or MR-linac Odense University Hospital Weekly PRO pelvic item set Quality of life (QLQ-C30) Health-related QOL (EQ-5D-5L) Patient Feedback Form (n=38) Patient interviews (n=14)	Feasible and usable weekly PRO reporting in the patient application. High adherence to weekly reporting but decline during follow-up. To improve acceptance, clinician feedback to patients on PROs must be provided.
STUDY III – ACUTE TOXICITY		
Prospective, single-arm	50 patients with PCa: 25 Localised PCa 25 low-volume metastatic PCa Treated at the 1.5 T MR-linac Odense University Hospital Weekly PRO pelvic item set	One-fifth had clinically relevant deterioration in urinary frequency. AE trajectories of the two cohorts varied with peaks in symptoms outside time points in previous PRO studies for MR-linac patients. More GU persistence in 60 Gy cohort as opposed to GI persisting in the 36 Gy cohort.
STUDY IV – CLINICAL IMPACT		
Prospective, single-arm (patients from study III included)	156 PCa patients Treated at CT- or MR-linac Odense University Hospital Quality of life (QLQ-C30) Health-related QOL (EQ-5D-5L) Patient Feedback Form Patient Experience Questionnaire Clinician and patient compliance Selection/deselection follow-up	No association between clinician and patient compliance. Clinicians acted on PROs, and patients found PROs used for care (96%). Weekly ePRO with real-time clinician feedback improved communication (91%), patient involvement (93%) and quality of care (87%). Self-rated health declined more in patients deselecting follow-up.

Adapting PROs to the radiotherapy setting

Planning and designing the complex intervention made us consider the clinical context to which the intervention had to be adapted. We were aware of the changes it would cause in the radiotherapy workflow and workload, as well as in the patient pathway. The tailored PRO intervention would modify the radiotherapy department's organisation and culture. The radiation therapists needed to adapt to a new system and way of involving the patient in a shared symptom assessment.

In the planning phase, we considered a national multicenter study. However, there were fundamental barriers like electronic health records, patient reporting software, and organisational workflows. In a multicenter study by Velikova et al. on PROs in radiotherapy, practice variations in workflows at the two centres made it necessary to tailor the website with patient advice to each centre [114]. Also, the technical integration of PROs in the radiotherapy workflow is challenging at a single centre, where implementation requires continuous process evaluation and optimisation, and adequate resources must be allocated to succeed [126].

Differences in organisational and cultural factors could also be barriers to multicentre implementation. The engagement of the radiation therapists at our centre was a major strength of the current intervention. They were the clinical team monitoring and acting on all PRO responses from the patients, which is why clinician engagement was not a barrier in this study, as in many previous studies [146]. Some of the patient barriers in our study were a few patients having trouble with entering the application and sending the ePROs in the application. A shift in the Danish digital identity used for login caused general problems entering the app. Some patients forgot to respond but were reminded by the clinician the following day. The future implementation process must address what motivates clinicians to use PROs in their routine practice to continue making data 'actionable' [126].

Patient involvement with PROs

The patients are the key stakeholders in this intervention. On an organisational level, patients and caregivers in the department's User Council were involved with reading and commenting on the patient information and guidance to digital PRO completion. However, a further corporation of patient public involvement (PPI) involving the patients as co-investigators would potentially have strengthened the study's validity. The patients could have been involved in weighing the importance of PRO results to improve the interpretation of PROs [78].

On an individual level, patients were involved as research partners in evaluating the content validity of the pelvic item set [78]. They were asked about the coverage and relevance of the selected PRO items. If the patients could not relate to the selected symptoms in the item set, we would have risked a reduced adherence to PRO completion.

When PROs are used to obtain critical information from the patients involved, there are concerns about whether underserved groups are excluded due to different barriers to PRO completion [75]. Only 9% of patients informed face-to-face declined participation in the ePRO intervention. Only eight patients dropped out before the study ended, suggesting that digital PRO completion is feasible for toxicity assessment for patients with PCa in radiotherapy. The patients not eligible or declining were older and had a poorer performance status. We offered paper-based completion as an alternative to uncover this need. This option required substantial resources for data entry into the ePRO system before being reviewed by the clinicians. Despite this effort, participants completing paper PROs did not feel involved, although their data was used to an equally high degree as participants completing ePROs.

Seven patients were not eligible as they could not read or complete PROs in Danish. Unfortunately, the application had no option of reading the questions aloud, nor did we allocate clinicians to complete surveys with the non-compliant patients. A prior study found adherence was worse among patients treated with radiotherapy for other cancer diagnoses than prostate cancer [114]. If weekly PROs are to be implemented in routine care, we need to consider how to involve a broader diversity of patients within the target groups. One way of doing this could be a more user-centred design where different groups of patients are involved in developing the PRO measures and PRO system.

In the future implementation process, we will consider patients' different literacy levels and different modes of delivery, like in-person completion of PROs or assistance in the department. An alternative to ePRO completion could be a proxy or completion, where someone else could report PROs on the patient's behalf [75]. Conversely, we risk inequitable supportive care interventions and data for evaluating radiotherapy regimens being biased.

Methodological considerations

The model of complex interventions framed this thesis to adapt digital PROs into a new setting; radiotherapy in Denmark [133]. Not to measure the effect of PROs but to use PROs as an outcome to evaluate patient AEs at the MR-linac. We were aware that integrating PROs in clinical radiotherapy practice might impact a range

of domains in the context and the patient pathway, and we sought to identify those. This model was very suitable for this complex health research intervention as all the phases were relevant and approached. Especially the dynamic relationship between the context and the intervention emphasises the complexity of the intervention.

Study design

One of the phases in the complex intervention was to test the feasibility and patient acceptance [133]. Our pilot study was designed for and succeeded in reducing our uncertainties about recruitment, attrition, data collection and patient acceptance. It also made us aware of adherence challenges during follow-up and the patients' requests for feedback on their PROs. Instead of passive collection of PRO data, active use of the PROs with real-time monitoring of symptoms would potentially make the patient feel more involved in their care [76]. The mixed-methods design of the pilot study was necessary to provide us with a broader range of information as the qualitative data from patients and caregivers elaborated the quantitative findings from the Patient Feedback Form. It was a major strength that we had specific measures for evaluability assessment in the Patient Feedback Form. We used the results to refine the design of the following prospective study.

Our studies were planned before we started patient treatment at the MR-linac and conducted in the early phases of the MR-linac evaluation. At that time, safety data was needed, but randomisation was not feasible. The non-randomised study design may raise concerns about data integrity and methodology. However, according to ESMO clinical practice guidelines, important evidence supporting the efficacy of PRO integration comes from non-randomised real-world data [76]. The disadvantage of the non-comparative observational study is the risk of confounding by selection bias. Non-participation bias could appear if patients with the worst symptom burden declined participation. The non-participants in our studies who were not eligible or declined differed from the participants. Overall, the consent rate was high in the pilot and longitudinal study, with 13% and 9% declining participation, respectively. The patients declining were, however, older, had a worse performance status, and more were treated for high-risk PCa. That is important in future study designs to avoid excluding underserved groups [75]. Unfortunately, we lack data on the AEs that these patients experienced.

Limiting bias and confounding

To limit the potential bias or confounding with this non-randomised study approach, we restricted the inclusion criteria for the analysis of the MR-linac patients. Restrictions were made on the level of metastatic disease and the treatment volume before the analyses to exclude subgroups that might influence the variability of the outcomes. As a result, we obtained a more homogeneous study sample. Furthermore, we stratified the analyses by the main confounder, radiotherapy dose and fractionation, and estimated adverse events per stratum [18].

However, there is still a risk of confounding by indication as the prospective real-world data from patients allocated to this new, promising treatment at the MR-linac might differ from those not referred for this treatment. That was not the case in this study period, as there were clear guidelines allocating patients according to disease stage. However, future RCTs are needed within other cancer sites [29]. Despite the risk of bias, our studies had the strengths of being prospective studies in a real-world clinical setting without restrictions on age, performance status or comorbidity. In addition, the patient populations may reflect the clinical practice better than patients enrolled in clinical trials [18].

The patient-reported outcome measures

This study demonstrated that frequent PRO completions are feasible and acceptable when a limited number of symptomatic AEs are selected, and patients have been involved in validating the content. We intended to develop a pelvic item set covering the AEs that were common for all patients having pelvic radiotherapy. Unfortunately, only the four pelvic diagnoses treated in the department were included in the literature review and considered eligible for inclusion in the pilot study. Consequently, one could argue that the item set is mainly a prostate cancer item set. Further work is necessary to validate the content and the need for diagnose-specific additions for patients with bladder, cervical, corpus, vulva, anal and rectal cancer.

Content validation

We used a clinimetric approach to construct and validate the content, aiming to identify items for inclusion that clinicians and patients regarded as important. The items needed to be clinically sensible for change and meaningful for the patients with a predictive ability for later outcomes [85, 90].

When we validated the content of the item set in the pilot study, 14 patients reviewed the item set. They were asked if the item set covered their most relevant

symptoms in the specific radiotherapy context. As the item set was meant to capture only acute AEs, the content validation was executed four weeks following radiotherapy, ensuring the patients could still recall the acute symptoms they had experienced. Further testing of validity was the prevalence of acute symptoms reported weekly by the patients supplemented with symptoms reported by clinicians. These prospective data validated that the instrument measured what it was intended to measure [85].

In the study, we investigated multiple measurements per patient and changes over time. The benefit of selecting items from the PRO-CTCAE and EORTC item libraries is that the items are tested for validity, reliability and responsiveness [100, 147]. We chose to use both PRO-CTCAE and EORTC items to increase the instrument's validity regarding item coverage and relevance. Since PRO-CTCAE is the patient version of the CTCAE, it is a safety measure validated for detecting treatment-related adverse events, thus, not intended for baseline symptom assessments [92]. The EORTC items are tolerability measures and, therefore, a more robust measure of baseline symptomatology. In future research, we will consider this as prospective research has found baseline PRO scores to be a strong predictor for urinary symptoms in multivariable models correlating Pros to clinical and dosimetric factors [148].

The benefit of combining items from two different item libraries is covering all relevant symptoms for patients with PCa, resulting in a targeted instrument to evaluate changes over time at the MR-linac. However, the disadvantage is the decreased generalizability of the specific PRO measure [90].

Therefore, we combined the tool with a generic and a disease-specific measure to improve generalisability. The EORTC QLQ-C30 questionnaire was selected to measure QoL and has high sensitivity but lower generalisability as it is a cancer-specific measure. The EQ-5D-5L was included as a generic, simple instrument measuring the impact of the treatment on the emotional, physical and social function of the patient. The EQ-5D has a high generalisability applicable across various diseases and conditions but is not very sensitive to individual patient changes [85].

Response shift

Often PROs are criticised for being subjective; however, also clinicians are subjective in their reporting of CTCAE, which contains both observable and more subjective AEs. Therefore, inter-observer variability in CTCAE grading occurs [149]. All PRO items measuring symptom severity are sensitive to patients changing their perceptions of QoL or symptoms or coping and adapting over time.

These mechanisms may cause response shifts, meaning that the patient perspective may be recalibrated over time [85]. For our results, this means that it is possible that the patients have the same grade of painful urination 12 weeks following treatment as they did in the last week of treatment, but they have come to cope with it, and their subjective perception of pain has changed [85]. Depending on the magnitude of the response shift, there is a risk of patients underreporting over time compared to clinician grading of symptoms [150]. Response shifts in a non-randomised study like ours may change the estimates of the effect size of changes over time [85]. Since patients' responses and the contextual patient information do not always align, the PRO changes over time must be interpretated via dialogue [127].

Another consideration is the possible floor and ceiling effect of the questionnaires. Holch et al. investigated different instruments' score distributions to explore the potential floor and ceiling effects (defined as >15% of patients reporting the highest or lowest score). They found a ceiling effect for the EQ-5D utility score; however, the EORTC QLQ-C30 overall QoL/Health score and the EQ VAS score were considered suitable outcome measures for future research [123].

Finally, guidelines are unavailable on interpreting the between-group differences and within-group changes in scores over time for the specific PRO-CTCAE and EORTC items. Further work must be done to clarify these items' Minimal Important Differences (MIDs). Work packages within the SISAQOL-IMI aim at defining MIDs for different PRO instruments [79]. Meanwhile, it is challenging to determine when the differences are important and clinically relevant. For the QLQ-C30, a within-group and between-group range for improvements and deteriorations have been defined for trials with primary PCa treatment [151]. These MIDs cover the different scales of the QLQ-C30 but only fatigue, pain and diarrhoea as symptom scales. Ongoing work seeks to confirm the findings and establish a MID catalogue.

PROs evaluating a new technology

The PRO intervention in this study may inform future clinical trials. It is, therefore, essential to evaluate whether the integration of weekly PROs is adequate to support the evaluation of new technologies like the MR-linac [133].

One of the main reasons why there are discrepancies between reports by clinicians and patients may be that we, as clinicians, fail to obtain symptom reports systematically [76]. As a result, increasingly more reliable and valid PRO instruments have been developed. In addition, guidelines for analysing, interpreting and reporting the PROs have made PROs a high-quality standard assessment

tool [72, 85]. The patient-reported outcomes support the evaluation of new technologies in radiotherapy on more than one level.

First, a comprehensive assessment of PROs starts with selecting relevant symptom measures and an appropriate frequency of assessment. Timely detection of deterioration and improvements of symptoms using frequent assessments can identify variations in the individual and group-level toxicity profiles [152].

Second, toxicity profiles based on patient reports represent the patient voice in future clinical trials and many subjective measures like pain and nausea are assessed more accurately by the patient [72]. For example, a prior study used patient-reported pain relief as the primary outcome, comparing two different radiotherapy fractionation strategies for bone metastases [153].

Thirdly, with increased personalised radiotherapy, hypofractionation and dose escalation, it is crucial that frequent remote PRO monitoring continues during follow-up. With alerts, severe treatment-related AEs can be detected, and the PROs can be used to tailor the frequency of in-person visits [154]. Active use of the PROs with real-time feedback instead of passive data collection adds value and makes sense to adhere to continuous PRO completion [76].

Forth, non-inferiority trials may be used for evaluating the MR-linac. Even though no differences in the cancer-specific outcomes were found, the PRO profiles are valuable in interpreting how the treatments have affected patient symptoms and QoL. These data can inform future patients when shared decisions must be made about the choice of treatment [72].

In future studies evaluating the MR-linac, patient reports assessing complete AE trajectories are crucial to interpret the clinical data and making data actionable to support real-world decisions [29, 72].

Clinical implications of the studies

These studies have established that it is feasible and acceptable for an elderly patient group treated with radiotherapy and concomitant hormonal therapy to adhere to weekly electronic reporting of their symptoms in routine care. Furthermore, the patients found that their weekly responses were used, improved communication and discussions with the clinicians, and improved their quality of care and feeling involved. The low attrition rate in the six months following treatment emphasises that this model may be favourable for future toxicity assessment and follow-up after radiotherapy.

The current follow-up regimens involve in-person consultations to assess the overall health state, side-effects from treatment and detect recurrence. This study stratified patient follow-up by letting the patients select their preferred follow-up

based on their current health state. This was only manageable as this follow-up aimed at monitoring and supporting them with their acute side effects caused by radiotherapy. Also, it was possible to change the follow-up to a physician consult if necessary due to severe side effects.

One-fourth of the patients having follow-up options deselected the follow-up. The follow-up was prescheduled as a telephone consultation and not a physical attendance in the department. If the follow-up was deselected, this consultation was cancelled. However, since the patients did not need to drive to the hospital for the consultation, that may have minimized their need to cancel it. A remote follow-up does not apply to all radiotherapy follow-up practices since the need for a physical patient examination differs.

Longitudinal capture of patient-reported outcomes might help evaluate long-term treatment outcomes and stratify the patients to varying consultations and supportive care interventions based on individual needs[154]. In addition, the cumulative number of timely follow-up consultations needed for future cancer patients is rapidly increasing, which calls for remote solutions considering PROs as a significant resource [155].

One important factor to remember is that the impressive patient adherence in our study was most likely a consequence of the clinician's engagement in acting on almost all reports in real time. Enhanced awareness and early responsiveness to patient symptoms was a motivational factor for the clinicians; however, we must evaluate the intervention with the radiation therapists before further implementation. Unfortunately, due to the time limit, this has not been done. The intervention has been extended further, which makes it possible to perform later evaluations.

A long-term implementation for different patient groups may demand more flexibility in the intervention [133]. The possibilities of utilising PRO data for different purposes are numerous; however, we must carefully consider the purpose of the PRO measurements, the capacity designated for patient feedback and how to involve the patients in making PRO completions meaningful for their treatment.

Strengths and limitations

The overall strength of the studies is the systematic approach to the complex intervention of integrating PROs with real-time feedback in radiotherapy. The non-randomised design and not involving the patients as co-investigators is the overall limitation of the studies. However, the prospective designs, the high consent and adherence rates were major strengths in improving the completeness and generalisability of data (Table 9).

Table 9. Strenghts and limitations of the PRO-MR-RT studies

	STRENGTHS	LIMITATIONS
OVERALL	Systematic approach	Not involving patients as co-investigators Non-randomised studies
STUDY I Item selection	Systematic approach	Not all pelvic diagnoses included
STUDY II Pilot	Prospective study Mixed methods approach High consent rate High adherence rate of weekly PROs High patient satisfaction with the pelvic item set and frequency of assessments	Single-center study Only two pelvic diagnoses; few patients with cervical cancer Decreasing adherence to PRO completion during follow-up No feedback for patients
STUDY III Acute toxicity	Prospective study Real-world data Use of systematically developed PRO pelvic item set High consent rate High adherence rate Real-time ePRO monitoring and feedback Frequent acute AE assessments	Single-center study Non-comparative study Real-world data Small sample size
STUDY IV Clinical impact	Prospective study Real-world data Use of systematically developed PRO pelvic item set High consent rate High adherence rate High retention rate PROs used real-time in dialogue for timely supportive care High clinician engagement High patient satisfaction Stratified analyses	Single-center study Non-comparative design Real-world data Heterogeneous sample No guidelines or restrictions on PRO interpretation and handling No evaluation of clinician experience with ePROs

Summarising conclusion and perspectives

Conclusion

A short pelvic item set for frequent assessments of acute toxicity in radiotherapy was developed and primarily validated for patients with PCa. In a pilot study, the integration of weekly ePROs in radiotherapy for patients with PCa was feasible, usable and acceptable in six months.

In a prospective, longitudinal study, the acute AE trajectories were explored for patients with intermediate-risk or low-volume metastatic PCa treated at the MR-linac. The frequent PROs timely assessed improvements and deteriorations over time in patient-perceived symptoms and comprised two different toxicity profiles according to the treatment schedules. Many symptomatic AEs peaked outside the time points used in previous studies. Therefore, multiple PRO assessments may lead to different conclusions on the frequency and severity of acute AEs.

The real-world data on all patients with PCa presented a high consent rate to weekly ePRO and high patient adherence. The clinicians monitored and handled almost all PRO responses, and the patient felt their PROs were used for their care. The patients also found weekly digital monitoring of PROs to improve the communication and discussions with clinicians, the feeling of being involved and the quality of care. Almost one-fourth of patients deselected follow-up. Patients choosing to cancel follow-up reported a more deteriorated self-rated health two months following.

Perspectives

At the beginning of this thesis, the future of radiotherapy was described as patient-tailored care based on individual toxicity profiles as a result of personalized treatment approaches [1]. New possibilities with artificial intelligence for automatic delineation on the scans and more rapid planning and tumour tracking opportunities will enhance the opportunity of reduced treatment margins, and new hypofractionated treatment regimens will be possible. With these new treatments, early responsiveness to patient symptoms and enhanced clinician awareness is

crucial to preventing serious complications. In addition, frequent patient self-reports will direct the individual patient care and support decisions about treatment changes.

New emerging treatment technologies, like the MR-linac, need a tool to allocate patients who will most likely benefit from it. Therefore, PROs will be included in model-based approaches with dosimetric and clinical data estimating the risk of normal tissue complication. If baseline PROs are a predictive factor, the knowledge from these models can be used upfront to detect the patients who will benefit from treatment without an extensive symptom burden. Further treatment and patient-specific research will provide us with knowledge on which patient-reported dosimetric predictive factors we must collect at baseline to support the clinical treatment choice. Furthermore, PROs will be used to adjust dose constraints as patients reporting persistent symptoms can be explored further [156].

We are looking at a future with significant healthcare transitions with an increasing amount of elderly cancer patients; thus, increased screening and stratification must ensure continuous, high-quality care. In addition, new ways of health care delivery and remote follow-up will be requested.

Patient care pathway apps with evidence-based algorithms will be used for allocating, screening and selecting the proper care at the right time in the care trajectories of the individual patient. Extraction of PRO data, data mining and artificial intelligence (AI) gives us opportunities for immediate patient feedback and risk analyses to guide precision radiotherapy but also to identify follow-up needs and allocate for an adequate level of follow-up.

However, we must not forget the patient in all these technological advances and algorithms. Even though we involve the patient in providing direct outcome data, our choice of treatment and care may not always be the patient's choice. Sometimes the evidence of treatment outcomes points to non-inferiority. With shared decision-making, the patient must be included in the treatment choice. For these decisions, PROs from previous patients must inform and guide the patient on treatment impact on quality of life, functioning and risk of long-term AEs.

Furthermore, the more subjective PROs will be increasingly correlated to objective measures coming from wearables; blood pressure, pulse and EKG can be extracted from patients' smartwatches at home. These objective measures could be sent to the patient record and combined with the PROs alerting clinicians if action is needed.

As clinicians, we must use the best of these technological advances but never let PROs and other data from patients stand alone without including the patient in the interpretation of their data.

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Papers and appendices

APPENDIX A

Paper I: Møller PK, Pappot H., Bernchou U., Dieperink KB. Development of patient-reported outcomes item set to evaluate acute treatment toxicity to pelvic online magnetic resonance-guided radiotherapy. 2021. J Patient Rep Outcomes 5, 47

APPENDIX B

Paper II: Møller PK, Pappot H, Bernchou U, Schytte T, Mortensen ZV, Brúnni MFÁ, Dieperink KB. Feasibility, usability and acceptance of weekly electronic Patient-Reported Outcomes among patients receiving pelvic CT- or online MR-guided radiotherapy - a prospective pilot study. Technical Innovations & Patient Support in Radiation Oncology. 2022. Volume 21, P 8-15

APPENDIX C

Manuscript III: Møller PK, Pappot H, Schytte T, Bernchou U, Dieperink KB. Prospective evaluation of online adaptive MR-guided radiotherapy with digital patient-reported acute symptom trajectories for prostate cancer patients. Submitted to Practical Radiation Oncology, 24-11-2022.

APPENDIX D

Manuscript IV: Møller PK, Pappot H, Schytte T, Bernchou U, Dieperink KB. Clinical impact of weekly symptom monitoring for patients with prostate cancer using digital patient-reported outcomes in radiation oncology routine care. Under preparation.

APPENDIX E

The PRO pelvic item set
The Patient Feedback Form
The EQ-5D-5L

APPENDIX A

Manuscript I: Møller PK, Pappot H., Bernchou U., Dieperink KB. Development of patient-reported outcomes item set to evaluate acute treatment toxicity to pelvic online magnetic resonance-guided radiotherapy. 2021. J Patient Rep Outcomes 5, 47

Journal of Patient-Reported Outcomes

RESEARCH Open Access

Development of patient-reported outcomes item set to evaluate acute treatment toxicity to pelvic online magnetic resonance-guided radiotherapy

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Abstract

Background: A new technology in cancer treatment, the MR-linac, provides online magnetic resonance-guided radiotherapy (MRgRT) that combines real-time visualization of the tumor and surrounding tissue with radiation therapy to deliver treatment more accurately. Online MRgRT makes it possible to minimize treatment volume, potentially reducing acute treatment toxicity. Patient-reported outcomes (PRO) add the patient perspective to evaluating treatment toxicity related to new technology. The objective of this mixed-methods study was to develop and explore the content validity of a set of PRO items to evaluate acute pelvic toxicity to radiotherapy including online MRgRT.

Methods: A literature review and chart audit were conducted to identify symptomatic adverse events (AEs) to be selected from the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) library and European Organisation for Research and Treatment of Cancer (EORTC) item library. To validate the content, the item set was applied in a prospective pilot cohort of patients referred for primary pelvic RT with curative intent. Patients reported symptoms weekly during RT (4–8 weeks) and the subsequent 4 weeks. Follow-up reports were collected at 8, 12, and 24 weeks after RT. To ensure symptom coverage clinician-reported toxicity and individual patient interviews were conducted. The symptomatic AEs were included in the final item set if ≥20% of patients reported them.

Results: Eighteen acute symptomatic AEs were selected for the initial item set. Forty patients (32 prostate cancer, 8 cervical cancer) were included in the pilot study. Patients with prostate cancer and those with cervical cancer both reported all 18 acute AEs. However, vomiting was not reported by > 20% of patients thus excluded from the item set. Adding a few diagnosis-specific AEs to the final item set was required for both prostate and cervical cancer patients.

Conclusions: A PRO item set for patients with pelvic cancer treated with radiotherapy with a curative intent was developed and content validity explored. In the pilot study, the item set captured the most common acute symptomatic AEs for patients with prostate and cervical cancer related to pelvic RT including online MRgRT. Further validation of the content in broader disease sites would be needed in future studies.

Keywords: Patient-reported outcomes, PRO, Item selection, Cancer, Pelvic, Online MRgRT, Radiotherapy, MR-linac, Acute toxicity

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Background

Radiotherapy has advanced considerably during the past decades, improving survival and quality of life for cancer patients. Online magnetic resonance-guided radiotherapy (MRgRT), a recent innovation in radiation oncology, provides real-time visualization of the tumor and surrounding tissue during radiotherapy. It can increase disease control and survival with equivalent or decreased toxicity rates [1–3]. In 2018, the 1.5 T MR-linac (Unity, Elekta AB, Stockholm, Sweden) providing online MRgRT was ready for clinical use [4].

Until recently, external-beam radiotherapy for patients with pelvic cancer was guided by computed tomography (CT-guided) [3]. Online MRgRT is advantageous for these patients because the superior soft tissue differentiation of magnetic resonance imaging [5] in the pelvic area can reduce radiation exposure in healthy tissue [3, 6]. Treatment toxicity experienced by patients with pelvic cancer depends on the dose received and volume of irradiated healthy tissue [7–10].

Toxicity monitoring in cancer clinical trials is standardized prospective clinician reporting of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), grading adverse events (AEs) on a scale from 0 to 5 [11]. CTCAE grading, as well as patient-reported outcomes [12], is part of the proposed standard assessment methodology for clinical evaluation of radiotherapy innovations like online MRgRT [13]. However, several studies have identified discrepancies between clinician and patient reporting in general oncology treatment. Clinicians appear to underreport the rate and severity of treatment toxicity, compared to patient-reported severity [14–18]. Patient self-reports are an important supplement to evaluating online MRgRT treatment tolerability, as in other oncological settings where they have been used as direct indicators of worsening, persistence or improvement of symptoms and general well-being [19–21]. Patient self-reports add a patient perspective to dose selection and may reduce the risk of undisclosed treatment toxicities.

Only four studies conducted in two sites have investigated patient-reported toxicity during and after online pelvic MRgRT [22–25]. All four studies used standardized validated questionnaires to measure acute PRO at predetermined time points: baseline, end of treatment and follow-up at week 6. Thus, assessment over time was based on few time points with a substantial gap from the end of treatment to 6 weeks after treatment completion, creating a risk of undetected increases in acute treatment toxicity. The authors recommended that future trials include earlier data collection points to map the trajectory of acute treatment toxicity [22]. They also called for a consensus on questionnaires used to capture radiotherapy treatment toxicity for prostate cancer patients because some relevant symptomatic AEs are missing in the standardized PRO questionnaires [23].

To capture the patient perspectives related to online MRgRT, it is important to ensure the right questions are asked. Questions reflecting relevant expected symptoms that are meaningful to the patients [26, 27]. A systematic selection of symptomatic AEs tailors the PRO questionnaire to the right purpose, population and treatment [28]. Selecting items addressing the identified symptomatic AEs is a way of choosing a minimum requirement of outcomes for a specific diagnosis and treatment [29]. Several core outcome set have been developed for pelvic cancer patients; however, the targeted treatment was not always specified nor were instruments for measuring core outcomes often addressed [29]. A previous study developed separate item sets for male and female pelvic radiotherapy patients targeted CT-guided radiotherapy based on interviews with a heterogeneous patient population including patients receiving palliative treatment [30]. Since online MRgRT allows us to enable dose escalation and reduce the treatment volume the incidence and severity of symptoms during the treatment trajectory may differ from standard treatment regimens [31–33]. As a consequence, a short, comprehensive item set is needed to capture weekly changes in the most common symptomatic AEs for patients throughout the treatment course. Symptoms that are not necessarily reported by clinicians, thus being valuable evidence in the evaluation of patient tolerance to online MRgRT. To our knowledge, no PRO item set is available to support the purpose of weekly monitoring of acute symptomatic AES to pelvic radiotherapy with a curative intent including online MRgRT. The objectives of this study were to: 1) identify symptomatic AEs for self-reporting for patients receiving primary pelvic radiotherapy with a curative intent and select equivalent items in validated item libraries and 2) evaluate the content validity of the prospective pilot study to ensure the item set covers the most common symptomatic AEs to pelvic radiotherapy including online MRgRT.

Methods

Study design

A mixed-methods approach included two phases: 1) initial item selection of relevant acute symptomatic AEs for primary pelvic radiotherapy and 2) a prospective pilot study applying the items selected in the first phase (Fig. 1). Methods used in the item selection process were inspired by systematic item selection as previously used [27, 30, 34–36]. A parallel mixed-methods approach was used to validate the content of the pelvic item set in phase 2 [37]. Data collection and analysis of qualitative and quantitative data occurred simultaneously, with findings synthesized in the final item selection.

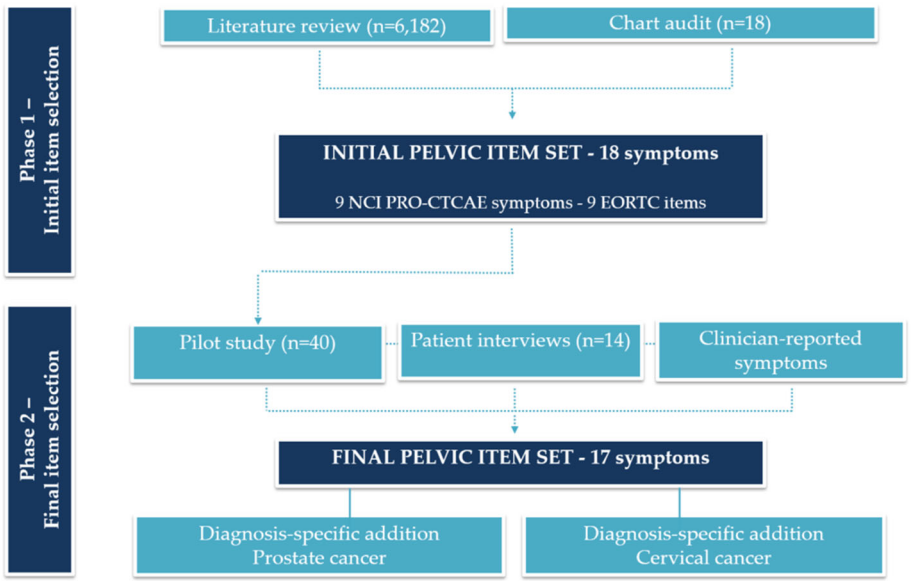

Fig. 1 The item selection process

Phase 1: initial item selection

The initial item selection in phase 1 inspired by Tolstrup et al. [35] consisted of a literature review of acute toxicity to pelvic radiotherapy (rectal, cervical, urinary bladder and prostate cancer) and a chart audit of acute toxicity in patients treated with online MRgRT in the 1.5 T MR-linac at Odense University Hospital from the first patient in October 2018 until May 2019. The objective of the review and chart audit was to identify and map the most common acute symptomatic AEs among patients receiving primary pelvic radiotherapy from the start of radiotherapy until 6 months after completion.

A comprehensive literature search was carried out in June 2019 in the Cochrane, PubMed and Embase (Ovid) (Embase Classic+Embase 1947 to 2019 May 13), using Covidence to manage and sort references [38]. The search was guided by PRISMA guidelines [39] and an expert on literature searches reviewed the search terms. The literature search strategy is available in Additional file 1.

The purpose of the chart audit was to investigate acute symptoms reported by physicians, nurses and radiotherapists to supplement the literature review and assess the consistency of clinical reports with symptoms identified in review. Clinicians documented AEs in a pre-specified CTCAE form at fixed time points, and patient EHRs were searched to find additional symptoms reported at other times.

Acute symptomatic AEs found in the literature review and chart audit were included in the initial item set if they were reported: 1) in the literature for all four pelvic cancer diagnoses or 2) in the MRgRT EHR audit or the two clinical trials with online MRgRT and in the literature review for at least two diagnoses. After identifying initial prevalent symptomatic AEs, corresponding items were selected from validated item libraries. The Patient-Reported Outcomes version of Common Terminology Criteria of Adverse Events (PRO-CTCAE) developed by the National Cancer Institute (NCI) [40] and the European Organisation for Research and Treatment of Cancer (EORTC) item library provides a flexible collection of items [41]. The PRO-CTCAE item library comprises 124 items representing 78 symptomatic toxicities [40]. Some symptoms are not included in the PRO-CTCAE library, thus items were drawn from the EORTC item library to capture all relevant symptoms [41]. These two item libraries were used as they contain multiple items for patient self-reports of symptomatic AEs translated into Danish and tested for construct validity and reliability [41, 42]. When symptoms are available in both item libraries the wording of the item may influence the item selected.

Phase 2: pilot study

The initial set of PRO items representing symptomatic AEs were applied in a prospective pilot study with patients treated at the Department of Oncology at Odense University Hospital in Denmark. The pilot study aimed to evaluate whether the pelvic item set addressed all relevant symptomatic AEs to pelvic radiotherapy including online MRgRT.

Eligibility

All patients aged ≥18 years referred to the department for primary pelvic CT-guided RT or online MRgRT with

a curative intent (rectal, cervical, urinary bladder or prostate cancer) in October 2019–June 2020 were eligible for inclusion. Patients were excluded if they were unable to give informed consent or to read, understand and respond to PRO questionnaires in Danish in electronic or paper formats. Sample size for the pilot study was set at 40 patients, based on sample sizes from previous pilot studies testing the integration of a PRO instrument into clinical cancer therapy [34, 43].

Data collection period

Patients reported symptoms weekly during their four- to eight-week courses of radiotherapy and the subsequent 4 weeks. Seven days is the preferred recall period for the PRO-CTCAE items [44]. Follow-up reports were collected at 8, 12 and 24 weeks after completing radiotherapy. Data were collected from October 2019 to October 2020, at which time the study group completed the final item selection process. The patients were informed that their responses were not available for the clinicians in the pilot study.

Variables

Demographic data on age and Eastern Cooperative Oncology Group/World Health Organization Performance Status (ECOG/WHO PS) [45] were obtained from the EHR, along with data on diagnoses, concomitant treatments, prostate risk group for patients with prostate cancer and the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging system for patients with cervical cancer. In addition, data were collected on radiotherapy: dose absorbed in gray (Gy), number of radiotherapy fractions and whether online MRgRT was used.

Questionnaires and semi-structured interviews

The initial item set was supplemented by five questions for patient free text reporting of other symptoms experienced during treatment. The questions for free-text reporting of symptoms were available for patient-initiated reporting at any time.

The questionnaire was administered electronically through *My Hospital* or paper-based as an alternative. *My Hospital* is an app for patients at hospitals in the Region of Southern Denmark that enables patient-entered data to be shared with hospital clinicians through the EHR [46]. The app was used for data collection to support patient adherence to the reporting schedule because it was already in use in the oncology department to provide an overview of appointments and information about treatment. Patients received verbal and written instructions for reporting PRO in *My Hospital*. A paper-format questionnaire was offered to those not having a device or technical skills to report electronically.

The main investigator (PKM) obtained clinician-reported toxicity reported in the EHR by physicians and radiotherapists during radiotherapy and the subsequent 4 weeks. Individual interviews with patients were conducted using a convenience sampling method 1 month after treatment completion. The patients were interviewed in the chronological order they attended their 4-week follow-up continuing recruitment until no new information or themes emerged from the data and data saturation was reached [47]. A semi-structured interview guide was used to investigate whether the questions were clear and easy to respond to and whether all relevant symptoms they experienced were addressed by the questionnaire. To validate the content of the item set, patients were asked about any symptomatic AEs they experienced but not report in the electronic questionnaire. The symptomatic AEs were included in the final item set if ≥20% of patients reported them inspired by Sandler et al. [30].

Statistical analyses

Sociodemographic and clinical characteristics of all patients were analyzed descriptively, as were the prevalence of items reported post-baseline and the proportion of other symptoms reported in scheduled and patient-initiated reports. All patients with pelvic cancer were included in the analysis. Study analyses were performed using STATA IC 15. Interview data were analyzed with systematic text condensation [48].

Results

Phase 1

In the initial item selection, 6182 articles were screened and 46 reports representing all four pelvic cancers were included in the final review (Fig. 2).

In addition, EHRs were reviewed for 18 patients with prostate cancer treated with online MRgRT (Fig. 1). No patients with other pelvic cancers were treated with online MRgRT. Two clinical trials published after the literature search on acute toxicity to online MRgRT in the pelvic region were added [22, 49] (Fig. 2). Thirty five acute symptomatic AEs that appeared in included literature, EHRs and trials were listed by the related CTCAE v. 5.0 term [50] (Additional file 2).

Ten symptomatic AEs reported by patients with each of the four types of pelvic cancer were selected as core symptoms for the item set. In addition, eight symptomatic AEs were reported by patients with at least two of the included cancer types and by patients receiving online MRgRT and/or in the two clinical MRgRT trials. Nine of the 10 core symptomatic AEs were available in the PRO-CTCAE item library; Fatigue, anorexia, radiation dermatitis, abdominal pain, constipation, diarrhea, nausea, urinary frequency and dysuria. Rectal pain was

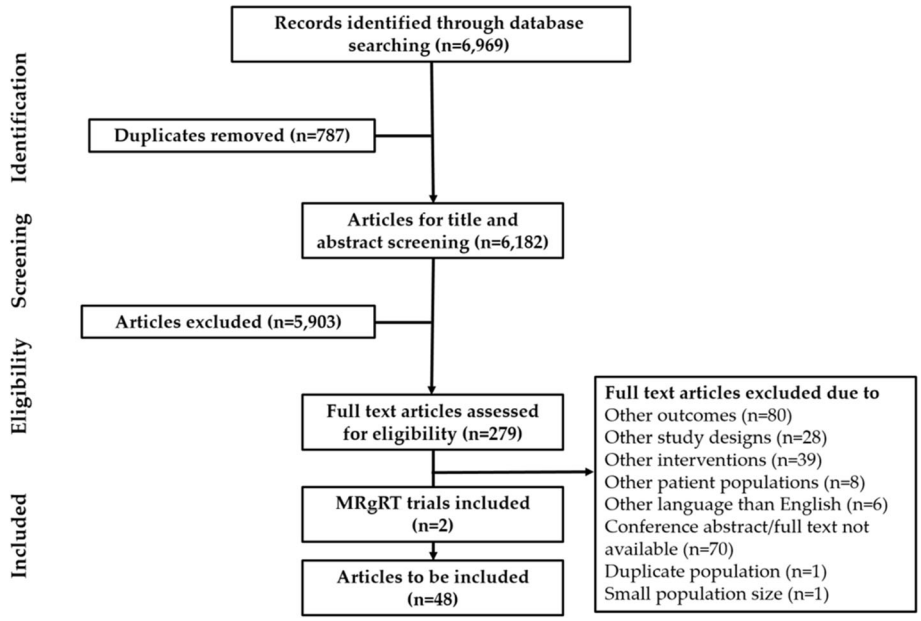

Fig. 2 PRISMA diagram for literature review of acute toxicity to primary pelvic radiotherapy

not in the PRO-CTCAE item library as well as three of the eight additional pelvic symptomatic AEs (urinary retention, nocturia, and rectal hemorrhage). A decision was made to select all supplemental items from the EORTC item library as these items covered the content of the identified symptoms better using a more plain language; Rectal pain, urinary retention, urinary incontinence, urinary urge, nocturia, vomiting, fecal incontinence, rectal hemorrhage and bloating. For some of the symptoms between one to three items were developed in the PRO-CTCAE library reflecting frequency, severity and interference. Consequently, the initial item set comprised 24 items from the PRO-CTCAE and EORTC item libraries addressing 18 symptomatic AEs.

Phase 2

A total of 53 patients were eligible for inclusion in the pilot study after three patients were dismissed based on clinician assessment. Six patients were excluded due to starting RT during the lockdown of clinical trials because of COVID-19. Forty-seven patients were informed about the study. Six patients declined participation because they felt they lacked the resources to join a research study, and 41 patients agreed to participate. No patients with rectal cancer were referred to primary radiotherapy during the study period. One patient with bladder cancer was eligible and enrolled in the pilot study but excluded from the analysis due to this unique status. Forty patients were enrolled and included in the analysis: 32 with prostate cancer and eight with cervical cancer (Fig. 1). Thirty seven patients (93%) reported electronically. Median age was a little lower and with a wider range among the patients with cervical cancer compared to prostate cancer (Table 1). Compared to patients with prostate cancer, a smaller proportion of patients with cervical cancer scored zero ("fully active") on ECOG/WHO performance status. Four patients with cervical cancer (50%) were also treated with weekly concomitant chemotherapy (Cisplatin) and 26 patients with prostate cancer (81%) were simultaneously treated with androgen deprivation therapy (ADT) (Table 1). In addition, 75% of the women ($n = 6$) had brachytherapy in their final week of external radiotherapy and again 1 or 2 weeks after radiotherapy completion (PDR-BT, 2 × 17.5 Gy/20 pulses). Of patients with prostate cancer, 13 (41%) were treated with online MRgRT. This treatment option was not yet available for patients with cervical cancer (Table 1).

Compliance was high as 85% of the patients responded to > 80% of the weekly questionnaires. Reasons for non-compliance were the patients forgetting or not having the resources in that particular week due to fatigue or having many appointments in the clinic.

All 18 acute AEs were reported at some point during the weekly responses by patients with prostate cancer (Table 2) and those with cervical cancer (Table 3). Only one of the 18 symptoms, vomiting, had ≤20% prevalence among patients with prostate cancer (Table 2). No additional symptoms were reported by ≥20% of the patients or by clinicians for ≥20% of patients with either diagnosis. Therefore, only the symptomatic AE of vomiting was removed from the initial pelvic item set.

Table 1 Characteristics of patients with pelvic cancer enrolled in the pilot study ($n = 40$)

Clinical data		All ($n = 40$)	Prostate ($n = 32$)	Cervix ($n = 8$)
Age, *median*	Years (range)	68 (36–76)	69 (54–76)	67 (36–75)
ECOG/WHO PS	0	33 (83%)	27 (84%)	6 (75%)
	1	6 (15%)	4 (13%)	2 (25%)
	2	1 (2%)	1 (3%)	0
Prostate risk group	Low risk		1 (3%)	–
	Intermediate risk		10 (31%)	–
	High Risk		21 (66%)	–
FIGO staging, cervical cancer	I		–	1 (13%)
	II		–	5 (62%)
	III		–	2 (25%)
Radiotherapy dose (Gy) /fractions	78/39	17 (42%)	17 (53%)	0
	62/21	1 (3%)	1 (3%)	0
	60/20	14 (35%)	14 (44%)	0
	55/25	2 (5%)	0	2 (25%)
	50/25	2 (5%)	0	2 (25%)
	46/26	1 (3%)	0	1 (12%)
	45/25	3 (7%)	0	3 (38%)
Online MRgRT	Yes	13 (33%)	13 (41%)	0
Brachytherapy (PDR-BT)	Yes		–	6 (75%)
Concomitant systemic treatment	Yes	30 (75%)	26 (81%)	4 (50%)

Table 2 Proportion of symptoms reported by patients with prostate cancer (n = 32)

Symptoms reported in weekly item set from baseline to follow-up week 4	Reported in pelvic item set, %	Reported in free-text or interview, %	Reported by clinicians in the patient chart, %
Nocturia	100	6	50
Urinary frequency	97		69
Fatigue	94	16	38
Diarrhea	94	3	38
Urinary retention	94	9	44
Urinary urgency	91	3	28
Painful urination	81	6	44
Bloating	78		13
Abdominal pain	75	6	16
Rectal pain	69	3	16
Faecal incontinence	66	3	6
Constipation	56		13
Decreased appetite	47	13	9
Urinary incontinence	47		13
Nausea	31	3	16
Radiation skin reaction	28	3	3
Blood in stools	28		13
Vomiting	13	3	3
Other symptomatic AEs			
Proctitis			19

Table 3 Proportion of symptoms reported by patients with cervical cancer (n = 8)

Symptoms reported in weekly item set from baseline to follow-up week 4	Reported in pelvic item set, %	Reported in free-text or interview, %	Reported by clinicians in the patient chart,%
Nocturia	88		
Urinary frequency	88		13
Fatigue	100	25	88
Diarrhea	100	25	63
Urinary retention	75		
Urinary urgency	88		
Painful urination	88	13	38
Bloating	100	13	
Abdominal pain	100	25	25
Rectal pain	100	13	25
Faecal incontinence	88		
Constipation	88		25
Decreased appetite	88		25
Urinary incontinence	50		
Nausea	100		88
Radiation skin reaction	88	38	0
Blood in stools	25	13	
Vomiting	88		38
Other symptomatic AEs			
Vaginal bleeding		38	13
Haemorrhoids		25	13
Vaginal pain		25	13

Diagnosis-specific additions were needed for both prostate and cervical cancer patients. Clinicians reported inflammation of the rectum (proctitis) for 19% of patients with prostate cancer at the end of treatment or 4 weeks later. Interviews revealed that patient-reported diarrhea arose from proctitis in some cases. Consequently, an item from the EORTC Proctitis module must be added when using the item set for patients with prostate cancer. For patients with cervical cancer, additional items were needed for symptoms of vaginal bleeding, vaginal pain and hemorrhoids and chemotherapy-related symptoms like vomiting if relevant. Abdominal pain was used to capture pain in the pelvic area. In addition, pain in the specific irradiated area was reported in free-text responses by 25% of patients with cervical cancer and 9% of patients with prostate cancer.

The 14 semi-structured interviews (11 patients with prostate cancer and three with cervical cancer) confirmed that the most relevant symptomatic AEs for their respective diagnosis were addressed by the pelvic item set. When directly asked about symptoms other than those included in the questionnaire, only a few additional symptoms were mentioned by < 20% of interview participants: memory loss and confusion, cystitis, weight gain/weight loss and symptoms related to systemic treatment.

Discussion

To the best of our knowledge, this is the first study to define and test a PRO item set to assess weekly symptomatic AEs related to primary pelvic RT including online MRgRT. Literature review and patient charts were consistent in identifying the 18 most common acute symptomatic AEs. To capture all relevant symptomatic AEs, items were selected from two item libraries: PRO-CTCAE and EORTC item library. Previous studies have selected items from a single library [30, 34, 35], adding one or two items from other questionnaires. Our decision was based on the need to include all identified symptoms relevant to evaluating MRgRT treatment using items with a plain wording covering the content of the identified symptoms.

The international MR-linac Consortium has recommended using PRO-CTCAE for future prospective clinical trials to estimate treatment-induced toxicity; however, no specific items were suggested [13]. The pelvic item set follows the recommendation of being intended for the specific population investigated with

the specific purpose of having a tool for prospective evaluation of acute treatment toxicity to online MRgRT [28].

The benefit of using an item set specifically developed for this purpose is that it captures the acute symptomatic AEs to RT with a 7 days recall period. In addition, using a simple item set for weekly PRO covering the most common symptomatic AEs rather than using several standardized questionnaires minimizes patient burden [51]. It ensures symptom coverage and relevance for this specific population in pelvic radiotherapy. Few proposals exist for measuring PRO when recommending symptomatic AEs in core outcome sets [29]. As a result, the pelvic item set reported here, tailored to the properties of online MRgRT, may enhance consistency in the measurement of identified acute symptomatic AEs. Tetar et al. [23] investigated PRO in online MRgRT and similarly pointed out that the standardized questionnaires they used were not developed for external radiotherapy and did not evaluate all relevant symptoms.

A single previous study defined disease site-specific item sets for PRO in pelvic radiotherapy [30]. Sandler et al. defined male and female pelvis item sets based on patient interviews. Among female patients, 10% had cervical cancer and 14% were in palliative treatment; among male patients, 30% had diagnoses other than prostate cancer [30]. We ended up including prostate and cervical cancer patients only, a rather homogenous group that was uniformly treated with curative intent. We experienced that the 17 most common symptomatic adverse events in the item set were similar for patients treated for prostate and cervical cancer. The additional symptomatic adverse events needed were related to the specific irradiated areas. Therefore, we find it relevant to have a generic pelvic item set supplemented by diagnosis-specific additions related to the irradiated area for the specific patient-group investigated rather than having gender-specific item set.

In Sandler et al. [30], item selection was based on interviews and a checklist of 40 items presented to patients during their last week of radiotherapy. Patients were asked to recall all symptoms they had experienced during radiotherapy. In contrast, we based the final item set on prospective weekly reports from baseline to 4 weeks after radiotherapy completion, limiting the risk of recall bias.

Clinicians reported proctitis for 19% of the patients with prostate cancer and interviews supported the need for a broader interpretation of proctitis without multiple proctitis symptoms being included in the item set. A review by Atkinson et al. investigating the association between CTCAE and PRO found poor agreement between well-validated PRO measures and clinician rating (CTCAE) for proctitis among patients with rectal or anal cancer [52]. A few years later, EORTC validated the first radiation proctitis-specific quality-of-life module (QLQ-PRT20) [53]. It comprises 21 items, some of which (i.e., rectal pain, diarrhea and rectal bleeding) were already included in the pelvic item set. To minimize response burden, we added one additional item (feeling unable to completely empty bowels) from this module. It is arguable whether these items accurately identify the prevalence of proctitis. However, if patients' self-reports are used in communicating with clinicians during the course of radiotherapy, these symptomatic AEs may contribute to the assessment of proctitis [54].

Differences between female patients in the Sandler et al. study [30] and ours could potentially account for discrepancies in selected items. However, we agree with Sandler et al. that an additional PRO-CTCAE item covering pain in the irradiated area is relevant for patients undergoing radiotherapy as e.g. abdominal pain is not covering pain in different anatomical irradiated sites in the abdominal or pelvic area. The symptom nocturia was omitted by Sandler et al. [30] even though thirty-nine (98%) patients in our pilot study reported nocturia at some point during radiotherapy. However, this item is not in the PRO-CTCAE item library and would have needed to be selected from another item library or questionnaire, which may have led to its omission in the previous study. Another item omitted from the Sandler et al. female item set was urinary urgency, which was reported by 88% of cervical cancer patients in our pilot study. This illustrates why selecting PRO for a purpose is important [28].

As six women in the current study received brachytherapy parallel to external radiotherapy, this may have affected the severity of symptoms like vaginal pain among these patients in the weeks following radiotherapy completion. Since the purpose of this study was to validate if the item set captures the most common symptoms for patients with pelvic cancer during radiotherapy this does not affect the outcome, however, the need for diagnosis-specific additions for cervical cancer patients also receiving chemotherapy or brachytherapy should be investigated further in future studies.

Sexual health is relevant for patients with prostate cancer and Sandler et al. included three items related to sexual health in their male pelvic item set [30]. However, the site-specific item set was empirically established and validated for assessment of radiation-induced toxicity but not for weekly reporting during radiotherapy. The majority of patients with prostate cancer in the present pilot study had concomitant androgen deprivation therapy (ADT) for at least 6 months and also mentioned symptoms about sexual health in the weekly free-text responses, thus being constant throughout radiotherapy. In the following prospective study two PRO-CTCAE

items covering sexual health will be added to baseline and follow-up PRO measures.

Study strengths included the systematic item selection process based on existing literature and the health records of the first patients receiving pelvic online MRgRT at our institution. Items were selected from item libraries to cover all relevant symptomatic AEs using items assessed for construct validity and reliability. Validating the content of the item set among members of the target population in a prospective pilot study is a major strength and is bolstered by the opportunity for patients and clinicians to add other symptoms. The multiple and regular scheduled assessment time points reflected the intended use of the PRO measures, providing optimal informational value [29].

Several limitations deserve mention. First, a limited number of patient charts were reviewed during initial item selection; however, they accounted for all the pelvic cancer patients being treated with online MRgRT at our institution at the time. To some extent, the use of mixed methods enhances the reliability of our findings. However, interviews were analyzed relatively superficially for the purpose of ensuring AE symptom coverage for the target patient population. An opportunity was missed to synthesize the quantitative findings with more detailed qualitative findings [37]. Further interview data analysis must be conducted to explore patient experience, acceptability and usability of integrating electronic PRO during radiotherapy. Finally, the content of the pelvic item set is validated only for patients with prostate cancer and a small sample of patients with cervical cancer. Only eight cervical cancer patients were enrolled, mainly due to Covid-19 enrollment restrictions and other competing research protocols. Inclusion of broader disease sites (bladder, vulvar, rectal and anal cancer) and higher sample sizes would be needed in future studies.

In future prospective clinical trials of online pelvic MRgRT, replacing standardized questionnaires with a rigorous pelvic PRO item set will support measuring the most relevant acute symptomatic AEs [23]. PRO-CTCAE free-text response options are available to capture unsolicited and unexpected symptoms that may occur due to differences in tumor size, radiotherapy dose or fractionation [40]. Using a systematic approach to item selection helps to ensure that the right questions are asked for the right purpose. Future trials must ensure that patient responses are acknowledged and used for individual symptom management in radiotherapy [55].

Conclusion

A PRO item set for patients with pelvic cancer receiving radiotherapy with a curative intent was developed to capture expected and unanticipated symptoms of acute treatment toxicity related to online MRgRT in future prospective trials. Further validation of the content in broader disease sites would be needed in future studies. Diagnosis-specific items must be added to address all patient-reported symptoms.

Abbreviations

AE: Adverse event; CTCAE: Common Terminology Criteria of Adverse Events; PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PRO: Patient-Reported Outcome; ePRO: Electronic Patient-Reported Outcome; NCI: National Cancer Institute; EORTC: European Organization for Research and Treatment of Cancer; QLQ-C30: EORTC general core module; QoL: Quality of life; MR: Magnetic resonance; RT: Radiotherapy; MRgRT: Magnetic resonance guided radiotherapy; Gy: Gray; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization Performance Status; FIGO: 2018 International Federation of Gynecology and Obstetrics staging

Supplementary Information

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Additional file 1.

Additional file 2.

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Authors' contributions

Planning and designing the study: PKM, KBD, HP, UB, TS. Literature review, chart audit and initial item selection: PKM, KBD, HP. Data collection: PKM. Data analysis: PKM, UB, KBD. Manuscript drafting: PKM, KBD, HP, UB, TS. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The data supporting the findings presented in this article are available from Pia Krause Møller. However, data use was restricted to the current study and data are not publicly available. Literature search strings and chart audit notes are stored at the Department of Oncology at Odense University Hospital in Denmark and available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The Danish National Data Protection Agency approved the conduction of the studies included in this manuscript (file no 18/51369). All participants in the chart review and the prospective pilot study provided written and oral informed consent. In Denmark, no ethical approval is necessary for studies collecting questionnaire and interview data only.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Publisher's Note

APPENDIX B

Manuscript II: Møller PK, Pappot H, Bernchou U, Schytte T, Mortensen ZV, Brúnni MFÁ, Dieperink KB. Feasibility, usability and acceptance of weekly electronic Patient-Reported Outcomes among patients receiving pelvic CT- or online MR-guided radiotherapy - a prospective pilot study. Technical Innovations & Patient Support in Radiation Oncology. 2022. Volume 21, P 8-15

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Feasibility, usability and acceptance of weekly electronic patient-reported outcomes among patients receiving pelvic CT- or online MR-guided radiotherapy – A prospective pilot study

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ABSTRACT

Introduction: The potential of patient symptoms being monitored longitudinally in radiotherapy (RT) is still unexploited. When novel technologies like online adaptive MR-guided radiotherapy (MRgRT) are evaluated, weekly electronic patient-reported outcomes (ePROs) may add knowledge about the symptom trajectory. This study aimed at evaluating feasibility, usability and acceptance of weekly ePRO among patients receiving pelvic radiotherapy.

Materials and Methods: In a mixed-methods convergent design, a prospective pilot study enrolled patients referred to pelvic radiotherapy with curative intent. Patients used their own device at home to self-report PRO weekly during and four weeks following radiotherapy and week 8, 12, and 24 (paper-questionnaire as an alternative). Feasibility was extracted from the ePRO software. The Patient Feedback Form and patient interviews were used to explore usability and patient acceptance. Patients were informed that clinicians had no access to PRO responses.

Results: In total, 40 patients were included; 32 patients with prostate cancer and 8 with cervical cancer (consent rate 87%), median age 68 (36–76). The majority did digital reporting (93%). 85% of patients responded to ≥80% of the weekly questionnaires with 91% average adherence to weekly completion (60% for follow-up), although lower for patients ≥age 70. Time spent on ePRO (97%) and frequency of reporting (92%) was considered appropriate. Interviews (n = 14) revealed the application was usable and the patients requested real-time feedback from the clinicians.

Conclusion: Recruitment for ePRO during radiotherapy was feasible and adherence to weekly self-reporting high. The digital application was usable and weekly frequency and time spent acceptable. Real-time feedback from the clinicians is requested by the patients.

Introduction

Symptoms may go undetected for patients with cancer treated with radiotherapy, as digital monitoring of patient symptoms is not an integral part of radiation oncology. Many patients are affected by this as radiotherapy contributes to the cure or palliative care of >50% of

Abbreviations: AE, Adverse event; CTCAE, Common Terminology Criteria of Adverse Events; PRO-CTCAE, Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events; PRO, Patient-Reported Outcome; ePRO, Electronic Patient-Reported Outcome; NCI, National Cancer Institute; EORTC, European Organization for Research and Treatment of Cancer; QLQ-C30, EORTC general core module; QoL, Quality of life; MR, Magnetic resonance; RT, Radiotherapy; MRgRT, Magnetic resonance guided radiotherapy; Gy, Gray; ECOG, Eastern Cooperative Oncology Group; WHO, World Health Organization Performance Status.

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patients diagnosed with cancer [1,2]. Even though modern radiotherapy techniques and technologies have reduced the severity of treatment-related toxicity, symptomatic adverse events (AEs) still have a substantial impact on the everyday lives of the patients [2]. They receive their treatment in an outpatient setting with limited time for the clinicians to assess the severity of their acute symptoms and initiate supportive care.

Having patients report their symptoms during treatment has made it possible to detect symptoms earlier and intervene earlier during chemotherapy [3]. Patient-Reported outcome (PRO) engages patients in providing measures of their health status directly without clinician interpretation [4]. When clinicians monitor and use PRO responses it may improve patient-clinician dialogue and patient satisfaction and enhance a focused symptom recognition and assessment [5,6]. This, as chemotherapy-related symptoms tend to be under-reported by clinicians compared to patient reporting [7,8].

Improved outcomes have been established when real-time symptom monitoring is used among adult patients with cancer in systemic treatment [5,9-11]. Real-time monitoring of PRO allows for timely patient-centered care [5,12].

Unlike chemotherapy, recording of radiotherapy toxicity is still inconsistent [13,14]. Studies with patients in radiotherapy found, that patients reported symptoms earlier and more frequently than physicians and a higher rate of patient reported clinically meaningful symptoms was found compared to clinician reporting [15,16]. In addition to being used in clinical care, PROs are recommended in comparative effectiveness research [17]. A clinical benefit of novel technical innovations in radiation oncology is expected, however, systematic prospective evaluation of clinical effectiveness is scarce [18]. PRO data completes the picture by enabling the provider with real-world evidence of treatment safety directly from the patients [19].

The magnetic resonance-guided linear accelerator, the MR-linac, is an innovative technology providing online magnetic resonance-guided radiotherapy (online MRgRT) combining real-time soft-tissue imaging with radiotherapy [20,21]. In 2018, the first high field MR-linac was approved for clinical use [22-24]. A systematic evaluation of this new technology was initiated [21]. To systematically include assessment of PRO in a prospective, longitudinal evaluation of online MRgRT it requires that the relevant symptoms for the specific patient population is identified, using valid PROs, and collecting data digitally when possible [6,25].

A key challenge when electronic PROs (ePROs) are incorporated in cancer treatment is that implementation process considerations are often not addressed [6]. Previous studies found that the use of mobile apps for symptom reporting during pelvic radiotherapy has been reported acceptable by patients [26,27]. However, the purpose of incorporating PRO in the specific clinical setting for a specific patient group must be considered carefully. To reduce the risk of PRO not bringing meaningful change to the patient feasibility, usability and patient acceptance of self-reporting must be explored for direct insight into the perceived value for the patients in the specific setting [6,12,28].

A few studies have investigated daily PRO in radiotherapy for intensive symptom management [29,30]. However, a 1-week recall has been found to correspond well to daily reporting reducing the burden for patients in daily contact with the radiotherapy staff [31]. To our knowledge, only a few studies have investigated the feasibility of incorporating weekly ePRO in the course of radiotherapy [26,32,33]. None of these studies had the same patient population with pelvic cancer. In one of the studies, patients without an email address were excluded [26]. Two other studies offered patients an alternative option to web-based reporting at home; an automated telephone system [33] or patients being approached with a computer in the clinic waiting area [32]. The median ages in these three studies were 56, 59 and 66 years, respectively. Oncology trials with PROs as primary or secondary endpoint rarely includes a population with median age $\geq$70 [34]. Therefore, there is a need for investigating an integration of weekly ePRO into the clinical workflow of radiotherapy with a simple setup being feasible for all patients including patients age 70 or above. The current study is part of the PRO-MR-RT study evaluating the trajectory of patient symptoms to online MR-guided radiotherapy (MRgRT). This pilot study aims at investigating feasibility, usability, and patient acceptance of weekly ePRO among patients with pelvic cancer treated with radiotherapy with a curative intent to ensure sustainability in the integration of ePRO in radiation oncology.

Material and methods

Study design and participants

The study was designed as a prospective single-center observational pilot study. A mixed-methods convergent design was applied where the data collection of the survey data and interview data occurred simultaneously in the same period of time (October 2019–November 2020) [35]. All patients referred to pelvic radiotherapy with a curative intent at Department of Oncology in Odense in the study period were eligible for inclusion. The patients were to be aged 18 or above, able to give informed consent and able to read, understand and complete questionnaires in Danish. Patients were excluded if they were taking part in other clinical trials involving substantial completion of questionnaires during their course of radiotherapy. All eligible patients (n = 53) were approached and informed in the department by the primary investigator PKM.

A systematically developed item set with 18 acute symptomatic AEs was used [36]. Data were collected at baseline and weekly during radiotherapy (for 4–8 weeks according to diagnosis and treatment plan) and four weeks following to capture acute toxicity. Follow-up reports were to be collected at week 8, 12 and 24 (Fig. 1). Patient-initiated free-text reporting of symptoms was available at all times. The patients were informed that their responses were not available for the clinicians in the pilot study. A Patient-Reported Experience Measure (PREM) was also included having the patients fill out the Patient Feedback Form on paper four weeks following treatment ($\pm$1 week) supplemented by patient interviews.

Health-related quality of life (HRQoL) was collected according to recommendations for prospective evaluation of online MR-guided radiotherapy [37] using EQ-5D-5L (EuroQol-5 dimensions) [38] and the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer QLQ-C30) [39] (Fig. 1). These data are not presented in this publication.

Online platform for patient reporting

The patients had to use their own device and internet access at home to report. If the patients did not have a device or technological abilities for electronic reporting, they were offered paper questionnaires. The patient app and website *My Hospital* was selected as ePRO application. My Hospital is an app or website for patients at hospitals in the Region of Southern Denmark developed by MedWare. MedWare has no influence on the study or publication of data. The app was already used in the department and the design of the app was therefore pre-defined. The app allows entered patient data to be transferred directly to the clinicians at the hospital in the Electronic Health Record and it contributes with written and visual information about e.g. appointments and treatment. At the time of enrollment, a demonstration and a written guideline on ePRO were provided to the patient. Two push-messages were set up for those using the app to remind the patient to respond the questionnaire. In addition, the patients were offered text messages if they found it hard to remember or used a computer.

Variables

Demographic data on age, marital status, comorbidity and Eastern Cooperative Group/World Health Organization Performance Status

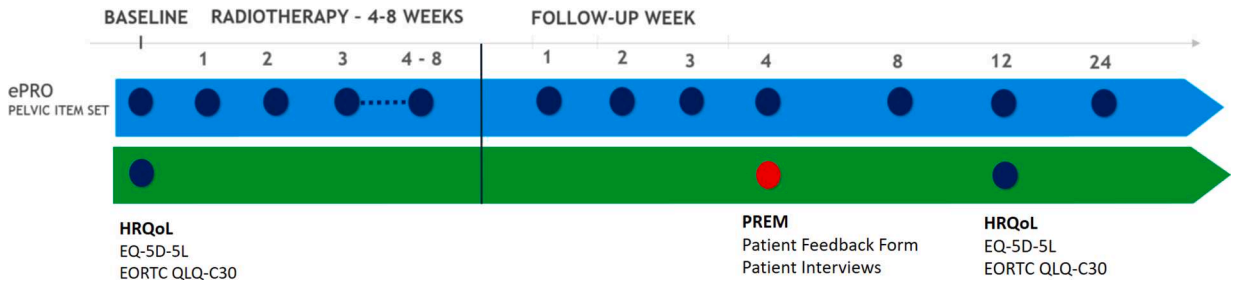


Fig. 1. Data collection in the PRO-MR-RT pilot study.

(ECOG/WHO PS) [40] were extracted from the electronic health record as well as clinical data on primary diagnosis, concomitant treatment and prescribed radiotherapy dose and fractionation. In a baseline questionnaire, patients responded to questions about educational length, employment status and how frequent they used technological devices.

Outcome measures

The feasibility of integrating electronic acute PRO in the pelvic radiotherapy course was measured with data from *My Hospital* software complemented by notes on technical difficulties (Fig. 2) [41].

To investigate usability and patient acceptance of ePRO, the Patient Feedback Form was used. The form was adapted by Snyder et al. [42] from Basch et al. [43] to measure patient satisfaction with online self-reporting of toxicity. The form consists of 13 items and has been translated, culturally adapted and validated for measuring patient satisfaction with ePROs in a Danish cancer population [44]. In addition, usability and acceptance was also investigated with qualitative semi-structured patient interviews (Fig. 2). The quantitative and qualitative data were analyzed separately and the findings were compared and synthesized.

Patient interviews

Patients were informed about the interview at enrollment. A convenience sampling method was applied interviewing patients in the order they attended their 4-week follow-up continuing recruitment until data saturation was reached [45]. When caregivers accompanied the patient they were invited to join the interview.

The main investigator (PKM) carried out interviews and audio recording. For a wider analytical space, the transcription, data coding and analysis of data was carried out by two research assistants (ZVN, MFB) supervised by PKM. The research assistants were not involved in the clinical work of the department and did not have any contact with the participants.

As previous research has pointed out relevant themes for investigating patient acceptance of ePRO, these themes were selected in advance for the interview guide and the framework of the coding (Fig. 2). The strategy used for data analysis of the interviews was a systematic text condensation in four steps [46]. A deductive approach was applied given the themes were identified in advance [47]. Data not possible to characterize under one of the predicted themes was given a new code to be open for additional themes derived from the data.

Statistical analyses

Descriptive statistics were performed to describe the sociodemographic and clinical characteristics. The consent rate was defined as the proportion of informed patients giving consent. The attrition rate was calculated as the proportion of participants withdrawing or dying from the intervention leaving no data on outcomes available. The retention

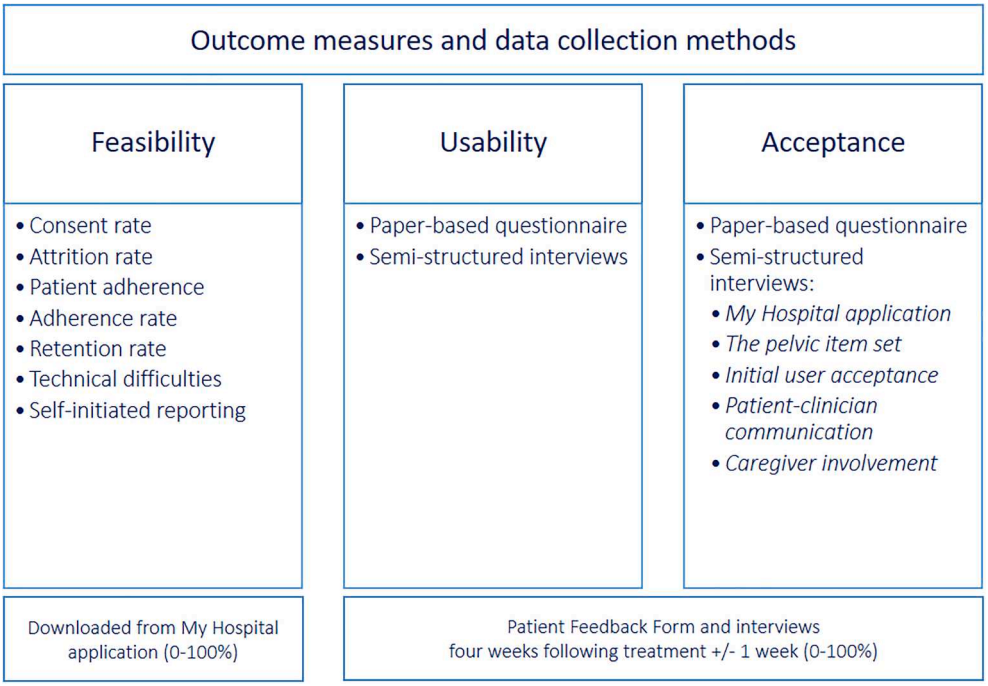


Fig. 2. Outcome measures and data collection methods in PRO-MR-RT pilot study.

rate was the number of individuals who remained in the study and responded to the questionnaire in week 24. Patient adherence was the proportion of patients completing self-reports for each time point adjusted for withdrawals and death and the adherence rate as the proportion of participants replying to ≥80% of the weekly PRO questionnaires [15]. Adherence to weekly completion was analyzed according to gender, age (≥70 years), marital status, WHO PS and educational level using the Fishers Exact test. Frequencies were calculated for the categorical data in the analysis of the Patient Feedback Form. A pilot study sample size of 40 patients was established based on the sample sizes from other pilot studies testing PRO integration in clinical cancer therapy [48,49]. Statistics were performed using STATA IC 15.

Ethical approval

Oral and written informed consent was obtained from all study participants. Approval was obtained from the Danish Data Protection Agency (18/51369). According to Danish Law, no approval was needed from the Health Research Ethics for Southern Denmark (20182000-172).

Results

Between October 2019 and May 2020 41 patients consented to participate; 32 patients with prostate cancer, eight with cervical cancer and one with bladder cancer. Being the only patient with bladder cancer, this patient was excluded from all analyses (Fig. 3). The median age was 68 (range 36–76). Most patients (93%) were comfortable using their own device for electronic reporting, thus three patients reported on paper (Table 1).

Feasibility

The majority of patients informed about the study consented to participate (consent rate 87%). Patients declining were mostly men with high-risk prostate cancer (83%) with a median age of 73. Not being able to report electronically was not the reason for them declining although 83% had no device for reporting. Three patients left the study; two dropped out during treatment and one died after follow-up week 4 (attrition rate 7.5%).

Overall, 448 of the 554 questionnaires distributed at 12–16 time points were completed (completion rate 81%). Reasons for missing responses were not collected systematically. However, patients explained they sometimes forgot, were too tired, or had too many appointments that day. The average patient adherence to weekly completions was 90.8% but the average adherence to follow-up weeks 8, 12 and 24 was 60.3% for patients still alive and enrolled in the study (Fig. 4). The adherence rate of patients responding to ≥ 80% of the weekly PRO item set questionnaires was 85%. Overall 65% of the patients responded to all 12–16 questionnaires according to study protocol. Nine patients received additional text messages to remember responding.

Adherence of responding to ≥80% of the weekly questionnaires appeared significantly poorer in the group ≥70 years compared to patients <70 years (79% vs. 90%, p = 0.041). No statistically significant

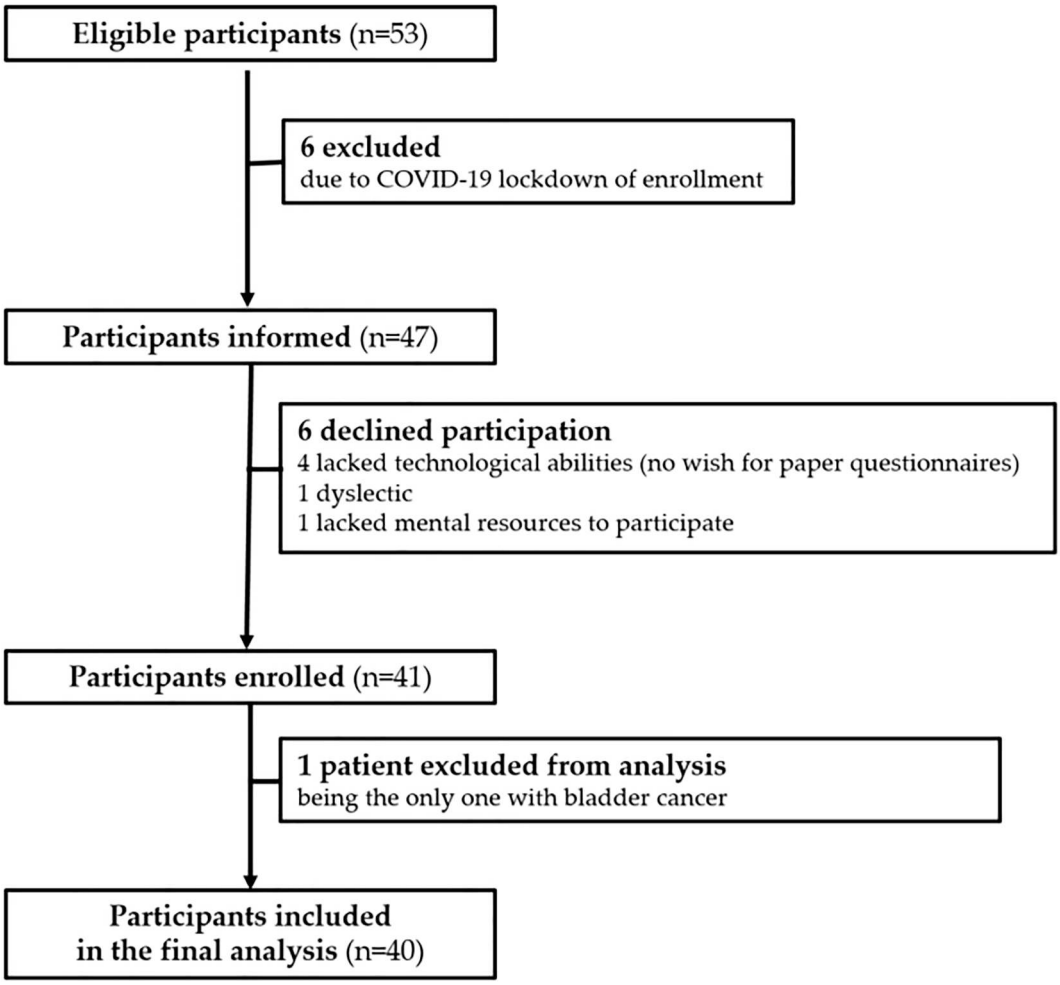


Fig. 3. Flow-chart of the Danish PRO-MR-RT pilot study.

Table 1
Characteristics of the study population in the Danish PRO-MR-RT pilot study (n = 40).

Characteristics	All, n (%)		Prostate cancer, n (%)		Cervical cancer, n (%)	
Gender						
Men	32	(80%)	32	(100%)		
Women	8	(20%)			8	(100%)
Age, median (range)	68	(36–76)	69	(54–76)	67	(36–75)
<70 years	21	(52.5%)	16	(50%)	5	(62.5%)
≥70 years	19	(47.5%)	16	(50%)	3	(37.5%)
Cohabitation status						
Cohabiting	32	(80%)	27	(84%)	5	(62%)
Living alone	8	(20%)	5	(16%)	3	(38%)
Highest attained education						
Basic or high school	6	(15%)	5	(15.6%)	1	(12.5%)
Vocational training	13	(32.5%)	11	(34.4%)	2	(25%)
Short-cycle higher education	4	(10%)	2	(6.3%)	2	(25%)
Medium-cycle higher education	6	(15%)	4	(12.5%)	2	(25%)
Long cycle higher education	5	(12.5%)	5	(15.6%)	0	(0 %)
Not applicable	6	(15%)	5	(15.6%)	1	(12.5%)
Currently working, yes	11	(28%)	8	(25%)	3	(38%)
WHO, performance status						
0	30	(75%)	25	(78.1%)	5	(62.5%)
1	5	(12.5%)	3	(9.4%)	2	(25%)
2	1	(2.5%)	1	(3.1%)	0	(0%)
Not applicable	4	(10%)	3	(9.4%)	1	(12.5%)
Treatment data, RT dose/fx						
78 Gy/39 fx	17	(42.5%)	17	(53%)	0	(0%)
62 Gy/21 fx	1	(2.5%)	1	(3%)	0	(0%)
60 Gy/20 fx	14	(35%)	14	(44%)	0	(0%)
55 Gy/25 fx	2	(5%)	0	(0%)	2	(25%)
50 Gy/25 fx	2	(5%)	0	(0%)	2	(25%)
45 Gy/25 fx	3	(7.5%)	0	(0%)	3	(38%)
46 Gy/26 fx	1	(2.5%)	0	(0%)	1	(12%)
Online MR-guided radiotherapy, yes	13	(33%)	13	(41%)	0	(0%)
Concomitant systemic treatment, yes	28	(74%)	24	(80%)	4	(50%)
Technological abilities						
Web-based reporting, *yes*	37	(93%)	29	(91%)	8	(100%)
Device at home, *yes*	40	(100%)	32	(100%)	8	(100%)
Frequency of device usage prior to RT						
Several times a day	22	(55%)	18	(56%)	4	(50%)
Daily	17	(43%)	13	(41%)	4	(50%)
Weekly or less	1	(2%)	1	(3%)	0	(0%)

differences in weekly completions was found according to gender (p = 0.549), marital status (0.876), WHO performance status (p = 0.717) or educational level (p = 0.683). Approximately half of the patients remaining at the last time point of data collection completed the questionnaire week 24 (retention rate 47.5%).

Technical difficulties

Five patients contacted the investigator for technical support in the pilot study (13%) with problems finding the questionnaire in the app and difficulties responding (technical error on the day).

Self-initiated reporting

Eight patients with prostate cancer (25%) and three with cervical cancer (38%) took advantage of the possibility to report symptoms outside the fixed time points (mean age 63 (range 38–76)). Each patient reported at 1–3 time points and self-reports covered 24 symptoms (1–5 symptoms/day 1–79 days after first treatment). Of these, 15 symptoms (62.5%) were included in the weekly questionnaire. No symptoms were reported by more than one patient and some used it only to write 'no new symptoms'.

Usability and patient acceptance

37 patients (97% of patients still enrolled) completed the Patient Feedback Form. The patients found the frequency (95%) and time spent (97%) was sufficient and the questionnaire easy to understand (95%) and complete (100%). As there was no clinician feedback on the responses, the majority found ePRO did not improve discussion with clinicians (54%) nor was the information used (83%), communication (78%), or care improved (75%). Despite of this, all but one would like to continue responding (Table 2).

Patient interviews

No patients declined to participate in the interview and after 14 patients data saturation was reached as diversity sampling was assessed appropriately. Mean age of informants was 64 years (37–74), three women and 11 men. The caregivers were present in nine of the interviews. They contributed with information about usability and acceptance of weekly reporting and how much the patient needed technical assistance.

For the analysis, a total of 215.53 min of interview was available. The mean duration of the interviews was 15.4 min (range 7–27 min).

Theme 1: *My Hospital* application

Once the participants had entered the ePRO application, they found it easy to use. Only half of the participants experienced receiving push messages reminding them to respond since some reported on a computer. Overall, the fixed weekday made it easy to remember. Some of the patients requested some kind of feedback whether the severity of side effects they reported was normal, how to act on it and what to expect. All but one participant said that they had no need for advice or feedback from the application, as they preferred discussing their health with clinicians in the department.

Theme 2: The pelvic item set

All participants reported the length of the questionnaire being adequate using 3–20 min on self-reporting every week and almost half added other symptoms in the free-text response option. Many described the content being relevant and did not find it burdensome to respond weekly to questions about symptoms they did not experience themselves.

"…from what I read about it..which side-effects you could get. Then it fit very well into that " (Male, 66 years)

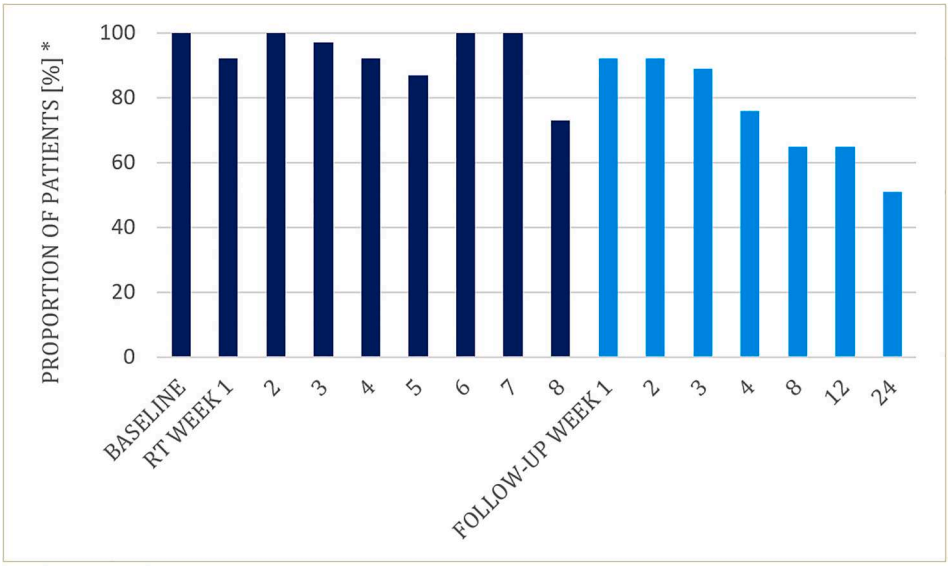
Theme 3: Initial user acceptance

Providing weekly reports on their health did not cause insecurity in the patients. On the contrary, patients described it as a positive experience and for some patients a feeling of being lucky not to have all the symptoms listed in the questionnaire.

Theme 4: Patient-clinician communication

The participants all talked about having good communication with the clinicians about their symptoms. However, the majority requested some kind of feedback on their PRO responses for it to be meaningful.

"Well, I think I took it for granted that if I replied that I had major problems with my stomach or something, well then someone would grab me and say "hey, we just have to look at that". I took it for granted. Of course, there needs to be some feedback. Otherwise, it does not matter." (Male, 63 years)



*Proportion of participants still alive and enrolled in the trial

Fig. 4. Adherence to PRO completion at pre-specified time-points in the PRO-MR-RT pilot study (n = 40).

Table 2
Evaluation of PRO-MR-RT weekly ePRO in a Danish pelvic radiotherapy setting (n = 37).

	Response (%)		
	Too short	**Just right**	**Too long**
1. Time it took to complete		97%	3%
	Not often enough	**Just right**	**Too often**
2. Number of times completing		95%	5%
	Strongly agree or agree	**Disagree or strongly disagree**	
3. Easy to complete	100%		
4. Completing was useful	100%		
5. Easy to understand	95%	5%	
6. Easier to remember symptoms and side effects	78%	22%	
7. Improved discussions with clinician	46%	54%	
8. Clinicians used information for my care**	17%	83%	
9.The quality of care improved because of the questionnaire*	25%	75%	
10. Communication with clinician improved	22%	78%	
11. Made me more in control of care*	64%	36%	
12. Recommend to other patients	97%	3%	
13. Would like to continue responding	97%	3%	

* 1 missing.
** 2 missing.

Theme 5: Caregiver involvement

In the beginning, some of the participants had their caregivers helping them with the technique, however, the majority handled the electronic reporting themselves. Weekly reporting made them discuss their symptoms at home with their caregivers.

Discussion

This pilot study is one of the first studies to investigate weekly PRO reporting from home during radiotherapy in a population with a sizable proportion age 70 or above including patients treated with online MR-guided radiotherapy. The study aimed at and found that it is feasible to integrate weekly ePROs, that the patients find it usable and accept electronic reporting at home. In addition, the study reports that for the patients it matters to have real-time feedback on their weekly responses from the clinicians.

Electronic reporting from home via app or web site was feasible and conducted by all but three patients. We tried to accede patients not using technology by having the possibility of paper questionnaires. Other studies chose to include other solutions for PRO responding or only included those with a smartphone or email [26,30,32]. However, the six patients declining, having a higher median age, lacked the resources to enter a study completing questionnaires at all, thus non-participation was not caused by a lack of technological skills.

Reasons for missing data in this pilot study is essential in the planning of the following prospective longitudinal PRO study. First, this pilot study depended on the patients using *My Hospital* on their own device at home. Adherence to weekly PRO completions in the app was high though no clinician feedback was provided. One reason might be that the app was already well implemented in the radiotherapy department and introduced to all patients. The average adherence to weekly PRO completion was similar to previous findings where the median age was 2–12 years below median age of this study [26,32,33]. This, although almost half of the patients in our study were age 70 or older and appeared to have worse compliance to weekly completion of questionnaires than the patients below 70 did. This is supported by previous findings that younger patients tend to use ePRO data capture more [26,32,33,50].

Decreased response rates during follow-up was expected as compliance previously has been found to be higher during active treatment than after the course of treatment [32,33]. A previous study found the same initial response rate six months post-treatment but collected additional responses that constituted one-third of the total responses via central coordinator backup calls [33]. We chose not to use backup calls for this study as it is time-consuming and we wanted a setup that subsequently would be feasible in clinical practice. Real-time feedback and further retention strategies may, however, enhance adherence in a patient group like this with patients above the age of 70 during treatment and follow-up [51].

Overall, the ePRO application was easy to use for the patients. The

patients agreed on the frequency on fixed weekdays and time spent was appropriate. The need for self-initiated reporting outside the fixed time-points was limited, confused the patients and most symptoms was contained in the weekly item set. Thus, the initial user acceptance was positive and some even found it a help to remember symptoms and side effects like previous findings with ePRO in cancer care did [52].

As expected, the majority did not find their quality of care or communication with clinicians enhanced by questionnaire completion like other studies established [10]. To be meaningful and to have the reassurance of the symptom severity being normal, the patients and caregivers in this study found it essential to have real-time feedback. A minority of oncology practitioners have integrated PRO with clinician feedback even though previous studies found that the communication and quality of care could be improved when the patients felt their information was used by the clinicians [10,52,53]. In some ePRO solutions today, advice is provided to the patient via the app or website [54]. The patients and caregivers in this study, however, agreed that the feedback should be in the dialogue with the clinicians in the radiotherapy department and not via the application. Unlike the chemotherapy setting having longer periods without clinical visits, where it makes sense that alerts are triggered to the care team, the daily contact between patient and clinicians during radiotherapy makes it easy to make ePROs an integral part of care [55]. It is possible and relevant to monitor severe or worsened symptoms the day after ePRO completion and use the disease- and treatment-specific PROs as a communication tool to potentially intervene earlier and improve the physical well-being of the patient [9,53].

This pilot study has some strengths worth mentioning. First, this study used mixed-methods to capture both feasibility, usability and patient acceptance. Furthermore, longitudinal weekly PRO reporting was successfully demonstrated in a clinical radiotherapy setting without the clinicians having extra tasks as the patients completed their PRO responses at home on their own device. In addition, caregiver experiences were included in the interviews. This is essential, as caregiver support is important for patient engagement in digital health interventions [56]. Finally, a sizable percentage of patients above 70 years consented to participate making it possible to explore if adherence was related to age.

One potential limitation of the study is the limited number of patients with cervical cancer included. Further recruitment was not possible in the study period; however, the total intended sample size was still reached. Secondly, the deductive approach used for the analysis of the interview data predetermined the structure of the coding framework with the risk of bias. However, the fact that the transcription and coding were conducted by two research assistants who worked with the data without any prior involvement in the interview minimizes the risk of bias as they could suggest other relevant topics appearing during coding. A third limitation is data on reasons for missing responses not being systematically collected. It would have been interesting to explore the barriers for completion during follow-up. Consequently, it is important to look at potential retention strategies and explore this further in future studies.

In conclusion, this pilot study confirmed that it is feasible to integrate weekly ePRO in the course of radiotherapy, thus the adherence to weekly self-reporting was high in a population with a sizable proportion of patients above the age of 70. The digital application and the questionnaire was usable and the frequency and time spent on weekly reporting acceptable for the patients, however, real-time feedback from the clinicians is requested by patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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APPENDIX C

Manuscript III: Møller PK, Pappot H, Schytte T, Bernchou U, Dieperink KB. Prospective evaluation of online adaptive MR-guided radiotherapy with digital patient-reported acute symptom trajectories for prostate cancer patients. Submitted to Practical Radiation Oncology, 24-11-2022.

Prospective evaluation of online adaptive MR-guided radiotherapy with digital patient-reported acute symptom trajectories for prostate cancer patients

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Abstract

Purpose

Frequent assessments of patient-reported outcomes (PROs) ensure the detection of changes in patient symptoms over time. The current study aimed to investigate the acute adverse event (AE) trajectory of patients treated with online MR-guided radiotherapy (MRgRT) for prostate cancer (PCa).

Materials and methods

Patients with PCa referred for treatment at the 1.5 T Unity MR-linac were informed about the study. They reported weekly longitudinal electronic PROs (ePROs) until four weeks following treatment and follow-up weeks eight and 12. A systematically developed pelvic item set was used for ePRO. The primary endpoint was a clinically relevant increase in urinary frequency. Clinicians had access to real-time monitoring of the patients using ePROs.

Results

Fifty patients were analysed; 25 with localised PCa (60 Gy/20 Fx) and 25 with low-volume metastatic disease (36 Gy/6 Fx). A two-level increase in urinary frequency was reported more frequently for 60 Gy than for 36 Gy (28% vs 12%) after a median of three weeks. The AE trajectories for both cohorts revealed different onset and peak of AEs. Three months after MRgRT, increased urinary frequency persisted for 16% of patients treated with 60 Gy. At this time, the most persistent symptom in the 36 Gy group was pain around the anal opening (12%).

Conclusion

Frequent ePRO toxicity monitoring detects deterioration in AEs in real-time, and enables timely supportive care. This approach contributes to evaluating MRgRT with precise detection of symptom onset, time to maximum worsening and symptom persistence according to dose and duration for PCa patients.

Introduction

Evaluating new treatment technologies in radiation oncology is challenging and calls for accurate patient toxicity monitoring. The magnetic resonance-guided linear accelerator (MR-linac) was recently implemented for patient treatment internationally [1, 2]. The MR-linac offers high soft tissue contrast combined with software for daily plan adaption to the anatomy of the day. This new technology provided opportunities for new treatment sites and possible further dose escalation. The daily online replanning changes the dose distribution for the individual patient and accounts for varying shapes and sizes of the organs at risk. With online MR-guided radiotherapy (MRgRT), it is conceivable that the volumes and margins will be reduced and doses to the target increased. The delivery precision is therefore important, as well as monitoring variations in the toxicity profiles [3, 4].

The gold standard for adverse events (AEs) reporting in clinical cancer trials is the Common Terminology Criteria for Adverse Events (CTCAE V.5.0) [5]. To complement the clinician-reported CTCAEs, patient-reported outcomes (PROs) capture symptomatic AEs without clinician interpretation. Including the patient's voice in clinical trials enriches our understanding of the risks and benefits of the new treatment. PROs can be used to interpret the clinical data obtained in the complex evaluation of a new radiotherapy technology [6-8]. Furthermore, PROs may enhance personalised treatment and cancer care in radiotherapy [9].

To ensure the detection of unanticipated toxicities, patient-reported free-text write-in options must be included in the questionnaires [10, 11]. Multiple PRO completions over time have been suggested as the primary toxicity assessment during follow-up in future randomised clinical trials (RCTs) evaluating online MRgRT [12].

Patients with prostate cancer (PCa) potentially benefit from the improved soft-tissue contrast offered by the MR-linac; thus selected to be treated with online MRgRT [13]. The first studies collected PROs at the end of treatment and four, six or twelve weeks after MRgRT [14-20]. The studies found that genitourinary (GU) and gastrointestinal (GI) toxicity, in general, was low at the selected time points. However, earlier follow-up measures are needed based on the maximum symptom burden assessed at the last treatment fraction [14]. The studies mainly enrolled patients with localised PCa [14, 16, 18, 19]. Since evidence of radiotherapy increasing the overall survival for newly diagnosed low-volume metastatic PCa patients, online MRgRT is a treatment option for this group [21]. A small cohort was included in a prior study with follow-up week 12 post-treatment, but the results were not stratified for this group [20].

Most importantly, frequent assessment of PROs can optimise the accuracy of symptom assessment and detect additional or deteriorated symptoms otherwise undetected with less frequent PROs [22]. In addition, serial longitudinal assessments can detect within-group changes over time and the persistence of symptoms instead of a single focus on the maximum grade of toxicity [7].

To our knowledge, no studies have investigated AE trajectories during and in the weeks following MRgRT reported weekly by patients with localised or low-volume metastatic PCa. The ability of PROs capturing other unanticipated symptoms during online MRgRT is also undiscovered. This study aimed to investigate the longitudinal patient-reported acute AE trajectory for patients treated with online MRgRT for localised or low-volume metastatic PCa. We wanted to explore the prevalence of a clinically relevant increase in urinary frequency, within-group changes in acute symptomatic AEs, time to maximum worsening and symptom persistence.

Materials and Methods

Study design

The PRO-MR-RT study is a prospective observational study with patients treated at Odense University Hospital in Denmark. Longitudinal repeated measures of PROs were collected at baseline, weekly during and up to four weeks following treatment and during follow-up weeks 8, 12 and 24. This paper reports the acute toxicity defined as follow-up until week 12.

Participants and treatment procedures

From November 2020 to May 2022, all patients with PCa referred for treatment at the Elekta Unity 1.5 T MR-linac were eligible for inclusion. The inclusion criteria were age 18 or above, cognitively able to provide informed consent and able to read, understand and complete PROs in Danish.
Patients with localised PCa were allocated to online MRgRT with a curative intent using moderate hypofractionation of 60 Gy over 20 fractions (Fx) (5 Fx/week) based on previous studies [23-25] and treated according to the PRISM trial [26]. Some patients received six months of androgen deprivation therapy (ADT) initiated three months before radiotherapy. Patients with newly diagnosed low-volume metastatic disease were treated using 36 Gy/6 Fx (2-3 Fx/week) based on the study by Parker et al. [27]. The treatment workflow is previously described in detail [28-30]. Treatment guidelines are given in Appendix 1.

Data collection

A systematically developed and content-validated pelvic item set with 18 systematic AEs was used for collecting PROs during treatment [31]. A pilot study established the feasibility, usability and acceptance of weekly electronic PROs (ePROs) in our radiotherapy setting [32]. The AEs were graded on a 4- or 5-point numerical scoring system for EORTC or PRO-CTCAE items. In addition, five other symptoms could be added and graded (0-4) in the PRO-CTCAE free-text write-in feature if the patients felt some AEs were not covered

by the pelvic item set. To focus the conversation further, an optional write-in box asked the patient, 'Which symptom takes up most of your everyday life right now?' In addition, baseline patient and treatment characteristics were extracted from the Electronic Health Records.

Data software

PROs were collected and monitored using the software *My Hospital*. *My Hospital* is a patient pathway application already used for patients in the department. A secure login system individualises the content for the specific patient with information about their disease, treatment and hospital appointments [33]. PROs were available for the clinicians in real-time in the Electronic Health Record. The radiation therapists used the PROs to dialogue with the patient for weekly status on symptom burden. Also, at the follow-up consultation at the end of and four weeks following radiotherapy, PROs were available. If electronic reporting was not possible, the patients had the option of completing PROs on paper. The paper reports were entered into the electronic patient record immediately.

Outcome measurement

Urinary frequency is identified as the most frequently reported genitourinary toxicity post-baseline and up to two years following treatment for PCa [34, 35]. According to the SISAQOL recommendations [10], we decided on a clinically relevant within-patient worsening of urinary frequency based on the results from our pilot study [31]. The clinically relevant change is measured as having a minimum two-level increase from baseline over two consecutive time points. In the pilot study, 15% of patients with PCa treated in the MR-linac reported this increase [31]. As secondary outcomes, we explored the within-group longitudinal mean changes in acute patient-reported AEs, the median time to the first occurrence of within-patient maximum worsening of AEs and the persistence of deteriorated symptoms.

Ethics and Disclosures

From all study participants, oral and written informed consent was obtained. The study was approved by the Danish Data Protection Agency (20/29991). Due to Danish law, approval from the Health Research Ethics for Southern Denmark was not demanded. In addition, all the participants were asked to be enrolled in the MOMENTUM study, a prospective international registry, where clinical and technical data are pseudonymised and stored [36]. The study was registered in ClinicalTrials.gov (NCT05615909).

Statistics

Descriptive statistics were performed on baseline characteristics. All analyses were stratified according to

localised (60 Gy/20 Fx) or low-volume metastatic disease (36 Gy/6 Fx). Descriptive statistics were used to estimate the proportion of PCa patients having increased urinary frequency. Time to maximum worsening of the AE was computed as the first within-patient maximum grade reported.

PRO-CTCAE scores for each attribute (frequency, severity and interference) were computed to a single composite grade for each item [37]. In addition, raw symptom scores were calculated for EORTC items according to the EORTC QLQ-C30 scoring manual [38].

Linear Mixed Models for repeated measures were used for within-group mean changes in AEs over time with 95% confidence intervals. In the 36 Gy group, we accounted for different durations of the MRgRT course with an 'end of treatment' time variable for the last treatment week. PRO responses were absent in follow-up week three for patients treated with 2 Fx/week and this time point was excluded. The mean persistence was defined as symptoms still increased compared to the individual baseline level.

The study is reported according to the STROBE Statement for Observational Studies [39]. Analyses were conducted using STATA/IC 15.

Results

In the study period, 63 patients were eligible and informed about the study (Figure 1). Three patients with a median age of 81 declined. Sixty patients accepted (consent rate 95%), but one dropped out due to technical problems (n=59). In addition, nine patients were excluded from the analyses because of disease or treatment-related differences (Figure 1). Four patients (8%) equally distributed in the two groups completed PROs on paper.

The patients had a median age of 71 years, and the majority of patients (86%) were in good health with WHO Performance Status 0 (Table 1). Of the 50 patients included in the analyses, 25 had localised disease, and 25 had low-volume metastatic disease (Table 1). In the metastatic group, the 36 Gy/6 Fx were given within 11 to 24 days. Patients treated with 3 Fx/week (n=11) were treated over a median of 12 days (11-17), and patients with 2 Fx/week (n=14) over a median of 17 days (14-24).

All patients were included in the Momentum study, where they completed QoL questionnaires [36]. In addition, two patients with localised disease were enrolled in the local PRISM trial (Prostate Radiotherapy Integrated with Simultaneous MRI) [26]. Tamsulosin was used by ten patients (20%) prior to MRgRT to reduce their urinary symptoms.

The patient's adherence to self-reporting of symptoms was, in general, good. During treatment, both groups had a 96-100% response rate. The mean response rate during follow-up was 87% of patients in the 60 Gy group and 90% of patients receiving 36 Gy (week 12: 96% vs 84%).

Of all patients, 20% (n=10) had a two-level increase from baseline urinary frequency in two consecutive weeks. A higher proportion was reported in the 60 Gy group (28%) than in the 36 Gy group (12%) after a median of three or one week, respectively. However, baseline score imbalances may have added to the difference as a two-level increase was not possible for patients reporting urinary frequency frequently or almost constantly at baseline (16% of 60Gy and 24% of 36 Gy group) (Table 2).

For patients in the 60 Gy group, the magnitude of within-group changes in GU symptoms was highest in their third week of MRgRT (Figure 2).

The median time to the first maximum worsening of most AEs was two weeks post-baseline (Figure 3). GI symptoms in terms of diarrhoea and difficulty controlling their bowels peaked in the third week of MRgRT for patients receiving 60 Gy. In the following last week of treatment, proctitis-related symptoms were reported (Figure 2, Table A.2). Blood in the stool was the only symptom peaking after the end of treatment (follow-up week 1) when receiving 60 Gy/20 Fx. (Table A.2). After follow-up week four, there were no significant mean changes in any AEs for the 60 Gy group. However, at follow-up week eight, 20-28% of the patients in this group still reported increased urinary frequency, urinary urge, painful urination and feeling of not emptying bowels (Figure 4, Table A.2).

In the 36 Gy group, the onset of increased irritative GU symptoms was in the first week of online MRgRT (Figure 2). The median time to the first maximum worsening of GU symptoms was primarily one week (Figure 3).

No within-group significant mean change was observed for urinary urge (Table A.2), however, 80% reported having any grade of urge at baseline (Table 2). Unlike the patients treated with 60 Gy, this group peaked in increased urinary retention and urination at night two weeks after MRgRT (Figure 2, Table A.2). Maximum mean change in diarrhoea was reported in follow-up week one, and pain around the anal opening peaked in follow-up week two (Figure 2, Table A.2). No significant mean changes in AEs were observed in the 36 Gy group after the second week of follow-up (Figure 2, Table A.2).

The persistence of AEs 12 weeks following treatment was higher for GU symptoms in the 60 Gy group than in the 36 Gy group, with 16% having worsened urinary frequency. However, for the 36 Gy group, the GI persistence was higher, with 12% still reporting increased pain around the anal opening compared to baseline (Figure 4).

Fatigue was the symptom most patients reported as moderate-severe when adjusting for baseline severity (60 Gy 76%, 36 Gy 52%). The mean fatigue score significantly changed after two weeks in the 60 Gy and persisted until follow-up week 8 (Figure A.3) (Table 2).

Finally, up to 32% of all patients reported other symptoms at all time points, with the highest proportion being severe or very severe additional symptom in treatment week 2 (14% of all patients). The symptoms

reported are listed in table A.4.

Discussion

This was the first study to present the acute patient-reported longitudinal AE trajectories during online MRgRT for PCa patients. We included two populations treated with moderate- or ultra-hypofractionated radiotherapy. One group had localised disease, and the other had low-volume metastatic disease; thus, the treatment dose, duration and disease stage differed, and variations in AE changes were detected.
We chose to explore a clinically meaningful increase in urinary frequency and found that one-fifth of the patients reported this two-grade increase for more than one week compared to pre-treatment. A lower proportion was reported in the ultra-hypofractionated group, however, this group had a higher baseline score.
The detailed findings of AE deterioration and improvement for PCa patients receiving online MRgRT supplements previous studies [14-18]. In these studies of hypofractionated online MRgRT to PCa patients, PROs were collected at few specific time points, and patients mainly treated with a five-fraction schedule. In our study, a six-fraction schedule was used for patients with low-volume metastatic disease. We found, that in the weeks following treatment, where PROs were not collected in previous studies, patients reported maximum severity of several symptoms. This is an example of how longitudinal analyses of frequently assessed AEs may lead to other conclusions. With less frequent assessments there is a risk of underestimating the worsening and severity of symptoms [22]. Remote monitoring of patient symptoms with PROs fills a gap in the comprehensive toxicity assessment especially for patients having short-course treatments [40]. Frequent longitudinal patient symptom reports are valuable and required to optimise future radiotherapy regimens safely and enhance timely supportive care [41-47].
A strength of the study was that we used a short pelvic item set developed explicitly to capture the most clinically relevant AEs for PCa patients treated with online adaptive MRgRT. A short treatment-specific questionnaire is essential for frequent completion to enhance adherence to PRO completion [48]. The weekly frequency is one of this study's most important strengths as well as the high adherence rate. A prior study sucesfully adding electronic patient self-reports with self-management advice to usual care had 69% of PCa patients still responding 12 weeks following the first radiotherapy fraction [49]. At all times, the response rate in our study was above 80%, which may be due to real-time monitoring and immediate clinician feedback on all completed PROs. The multiple responses over time contributes with critical information on the onset, severity, deterioration and persistence of symptoms for patients treated with online MRgRT. In addition, the free-text write-in option was another strength of the study as other severe symptoms were reported. This approach is an opening for us to capture unanticipated or less common AEs

in future studies.

One limitation was that the patient population was rather heterogeneous. This study was conducted in a real-world setting, including all PCa patients treated in the study period. That potentially increases the generalisability of the data and gives us valuable information about patient outcomes and safety outside a clinical trial. We excluded a few patients from the analyses to increase homogeneity, which unfortunately reduced the sample size. However, we succeeded in having two cohorts with within-group similar doses and constraints. Another limitation is that the electronic PROs requested having a device at home with a risk of excluding the elderly or patients with reduced technological abilities. To include underserved patient groups, we offered paper questionnaires [50]. The three patients declining participation had a median age 10 years higher than the study participants and wanted neither the technological nor paper-based solution. In the future, continuous multimodal treatments, new technologies, and dose escalation in radiation oncology will make toxicity monitoring even more challenging and important [51, 52]. In addition, ultra-hypofractionation, daily adaptive radiotherapy and increased use of concomitant treatment might lead to more heterogeneous toxicity profiles [53]. High-quality prospective PRO assessments reflect the actual symptomatology and have the possibility of informing the impact of changes in clinical and dosimetric factors [12, 54]. Some studies already correlated PRO data with clinical and dosimetry data, and there is great potential for further research in this area [55, 56]. In addition, individual PRO data have the potential for clinical decision-making about radiotherapy modality and fractionation in the future of personalised radiotherapy, taking both the tumour and patient into account [8, 9, 12].

Conclusions

A high adherence rate to weekly reporting was achieved as PROs were monitored in real-time. One-fifth of the patients had a clinically relevant increase in urinary frequency. Within-patient maximum worsening of specific AEs varied according to dose and duration of treatment. Twelve weeks following MRgRT, acute urinary symptoms persisted after moderate hypofractionation and acute bowel symptoms in the ultra-hypofractionated group. Other unanticipated symptoms were reported by one-third of the patients. Frequent ePROs should be used to optimise future MRgRT regimes to ensure changes in patient-perceived AEs are detected and monitored and timely supportive care provided.

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Table 1. Baseline characteristics of patients with PCa treated with online adaptive MR-guided radiotherapy (n=50)

Characteristics	All (n=50)		Localised Pca (n=25)		Metastatic Pca (n=25)	
	n	%	n	%	n	%
Age, median (range)	71	(60-81)	71	(61-76)	71	(60-81)
Cohabitation status						
Cohabiting	38	76%	19	76%	19	76%
Living alone	12	24%	6	24%	6	24%
WHO performance status						
0	43	86%	21	84%	22	88%
1	6	12%	4	16%	2	8%
2	1	2%	0	0%	1	4%
Pre-treatment PSA[a], median (IQR) range						
Before radiotherapy	10 (13.9)	0.4-124	7.4 (8.1)	0.4-31	16 (16.6)	1.1-124
Before ADT[b]	45 (59)	5.4-487	15 (10.8)	5.4-54	64 (70)	13-487
Gleason score, total						
6	1	2%	0	0%	1	4%
7	35	70%	25	100%	10	40%
8	3	6%	0	0%	3	12%
9	11	22%	0	0%	11	44%
Tumour stage						
T1	16	32%	15	60%	1	4%
T2	11	22%	8	32%	3	12%
T3	18	36%	0	0%	18	72%
T4	2	4%	0	0%	2	8%
Not applicable	3	6%	2	8%	1	4%
RT prescription (dose/Fx)						
60 Gy/20 Fx	25	50%	25	100%	0	0%
36 Gy/ 6 Fx	25	50%	0	0%	25	100%
Concomitant systemic treatment						
None	18	36%	16	64%	1	4%
≤ 6 months	8	16%	8	32%	0	0%
> 6 months	24	48%	1	4%	24	96%

[a]PSA= prostate-specific antigen. [b]ADT= Androgen deprivation therapy

Table 2. Baseline proportion of patients reporting any grade or moderate/severe symptomatic AE (n=50)

	Localised Pca (n=25) 60 Gy/20 Fx				Low-volume metastatic Pca (n=25) 36 Gy/ 6 Fx			
	Any grade		Moderate/severe*		Any grade		Moderate/severe*	
	n	%	n	%	n	%	n	%
Urinary frequency	20	80%	4	16%	21	84%	6	24%
Urge	16	64%	7	28%	20	80%	5	20%
Painful urination	3	12%	3	12%	8	32%	3	12%
Emptying bladder	10	40%	3	12%	14	56%	1	4%
Frequent urination at night	22	88%	8	32%	23	92%	9	36%
Incontinence	2	8%	0	0%	4	16%	0	0%
Diarrhoea	7	28%	0	0%	6	24%	1	4%
Abdominal pain	9	36%	2	8%	8	32%	0	0%
Nausea	1	4%	1	4%	5	20%	0	0%
Constipation	5	20%	1	4%	6	24%	0	0%
Controlling bowels	1	4%	0	0%	2	8%	0	0%
Empty bowels	6	24%	2	8%	8	32%	1	4%
Pain around anal opening	5	20%	1	4%	3	12%	0	0%
Blood in stool	0	0%	0	0%	0	0%	0	0%
Bloating	7	28%	2	8%	7	28%	1	4%
Fatigue	11	44%	1	4%	19	76%	1	4%
Appetite	2	8%	0	0%	4	16%	0	0%
Radiodermatitis	0	0%	0	0%	0	0%	0	0%
Erection**	16	64%	4	16%	23	90%	18	70%
Libido**	14	56%	2	8%	21	84%	9	36%

*Moderate/severe: PRO-CTCAE score 2-4, EORTC score 3-4
*Libido, Erection: Those not responding did not want to respond or were no sexually active

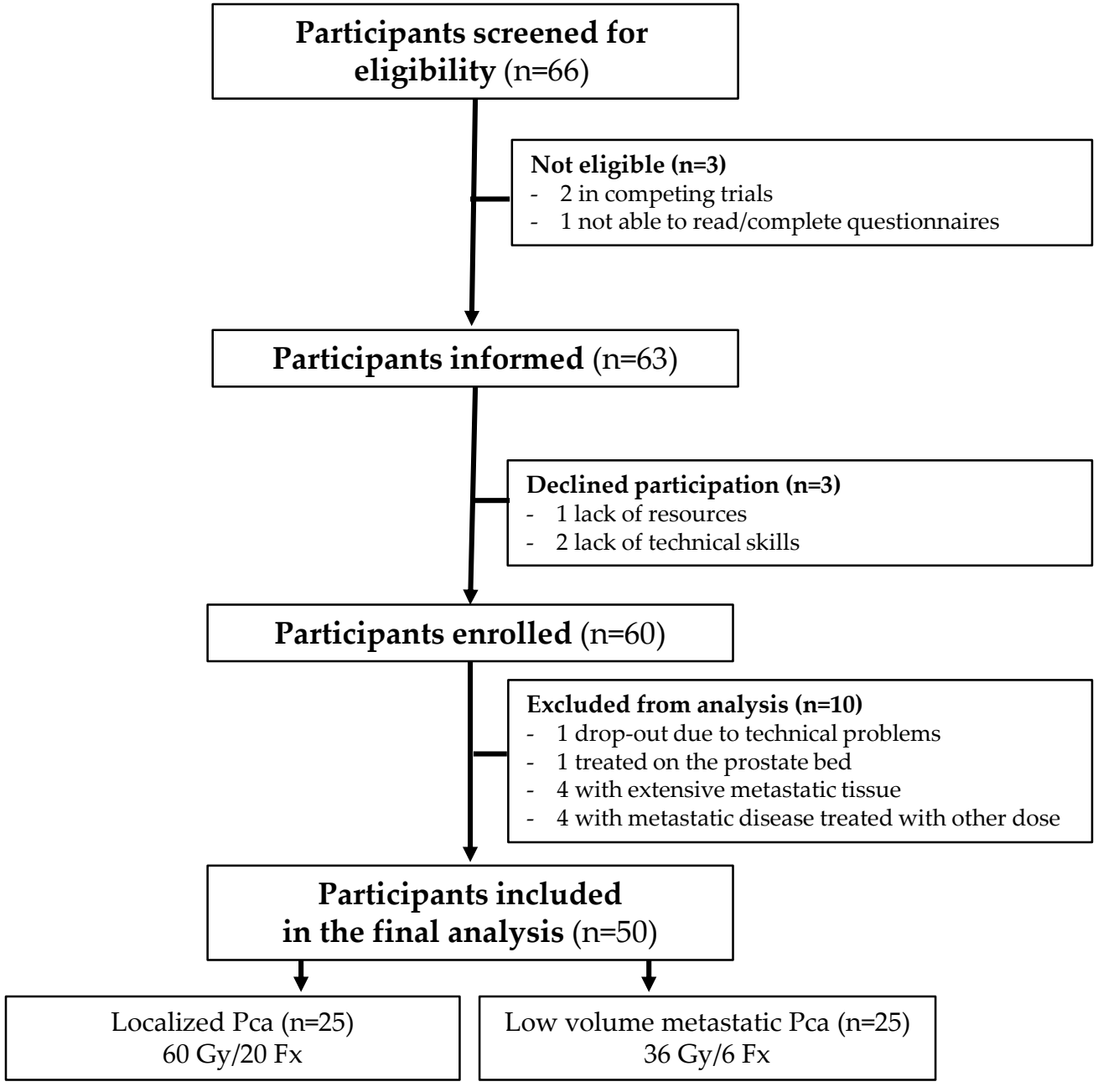


Figure 1. Flowchart

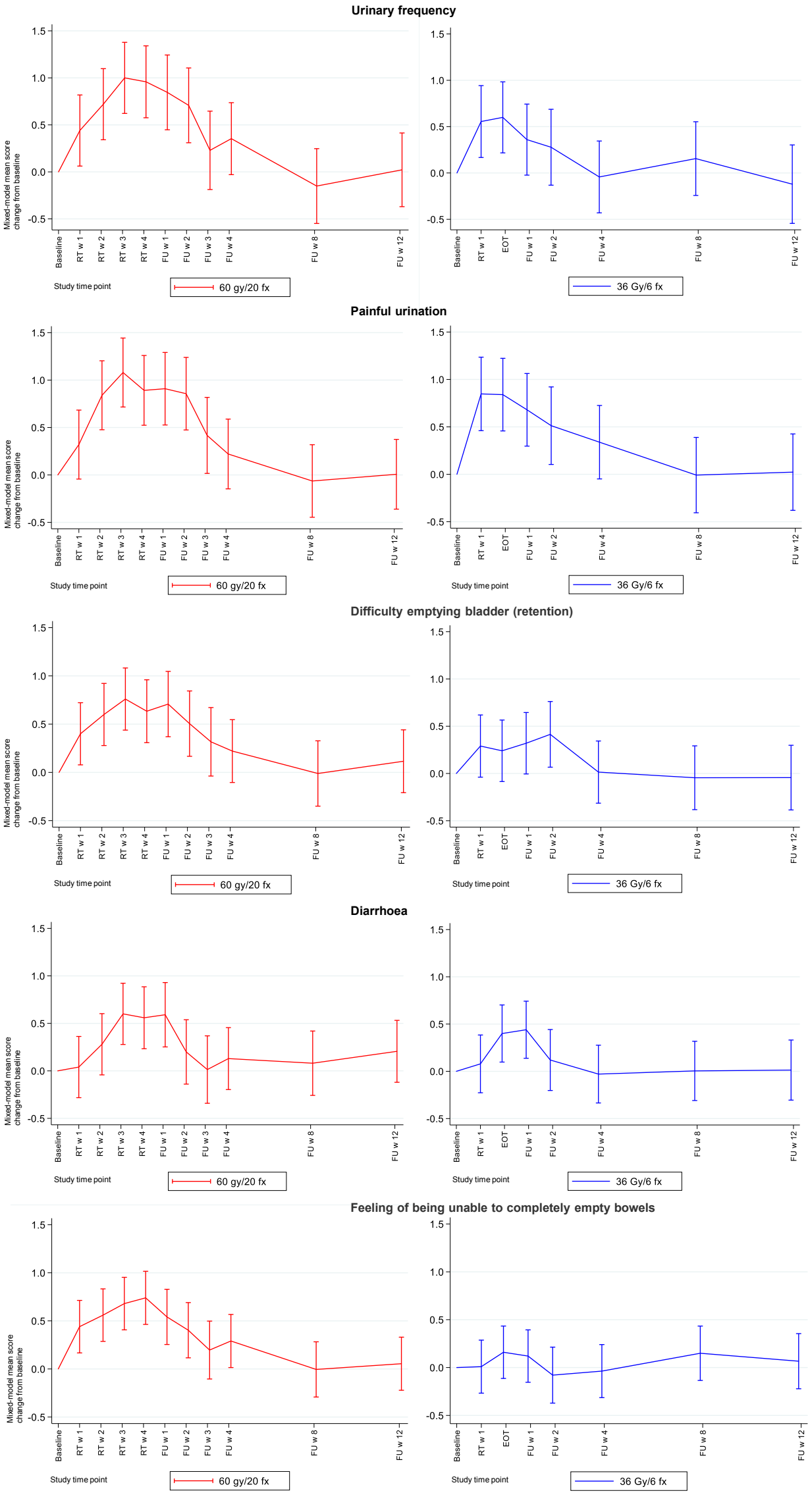


Figure 2. Mean change in symptom score from baseline (95% CI) for patients treated with 60 Gy/20 Fx (n=25) or 36 Gy/6 Fx (n=25)

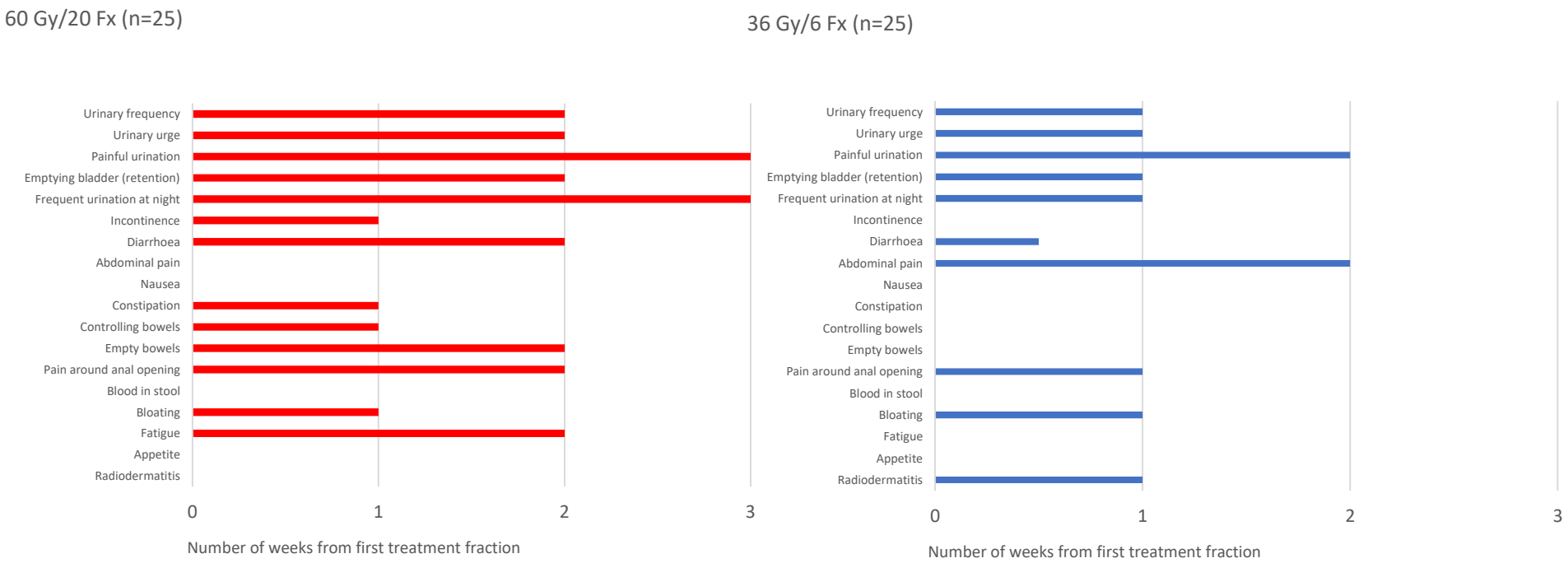


Figure 3. Median time to first within-patient maximum worsening of the symptomatic patient-reported AEs (n=50)

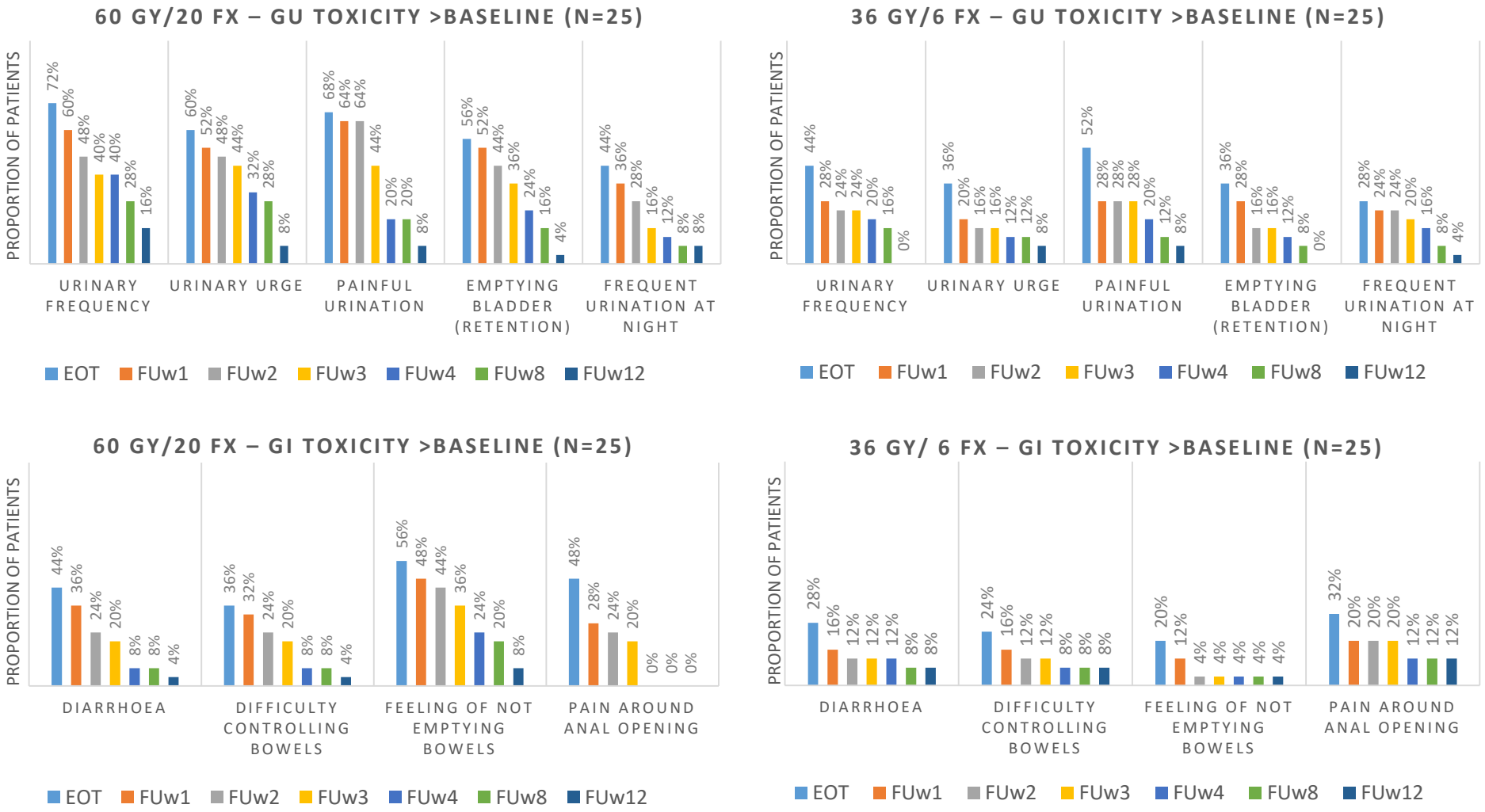


Figure 4. Persistence of symptomatic patient-reported AEs above baseline level (n=50)

Appendix A

The MR-linac workflow

All patients were treated with an adapt-to-shape workflow. During each treatment fraction, a T2w 3D MR scan was acquired, and contours were propagated from the pre-treatment MR to the daily session MR using deformable image registration. Manual corrections of the transferred contours were usually needed before treatment plan adaptation optimisation was initiated. A second MR scan was acquired during plan adaptation for position verification. If the target had moved more than 2 mm, a second plan adaptation process was initiated, and a new position verification scan was acquired.
All patients were instructed to empty their bladder one hour before radiotherapy and drink 3-500 ml of water.

Table A.1: CTV to PTV margins, OAR constraints, and target coverage requirements for patients with localised PCa

The primary clinical target volume (CTV) was defined as the prostate and proximal 1 cm of the seminal vesicles.
The secondary CTV comprised the proximal 2 cm of the seminal vesicles exterior to the primary CTV.

PTV margin	Prior to January 2022: PTV1 = CTV1 + 5 mm left, right, superior, inferior, ant, and 3 mm post PTV2 = CTV2 + 0,5 cm isotropic From January 2022: PTV1 = CTV1 + 3 mm left, right, 4 mm superior, inferior, and 5 mm ant and post PTV2 = CTV2 + 3 mm left, right, 4 mm superior, inferior, and 5 mm ant and post			
Target coverage requirements	CTV1(60Gy): V95%=100%, mean dose=99%-101% PTV1(60Gy): V95%>99%, V90%=100%, V107%=0% CTV2(48,6Gy): V95%=100% PTV2(48,6Gy): V95%>99%, V90%=100% External-PTV1 V105%=0%			
OAR dose constraints	Organ at risk	Dose (Gy)	Max Volume (% or cc)	
			Optimal	Mandatory
	Rectum	24.4 32.4 40.5 47.0 48.6 52.7 56.8 60.8 61.8	80% 65% 50% 35% - 3%	- - 60% * 50% 30% 15% 5% 0%
	Bladder	40.5 48.7 52.7 56.76 60.8	50% 25 % 5% 3%	 50% 35% 25%
	Femoral head	40.5		50%
	Bowel	36.5 40.5	78cc 17cc	158cc 110cc

		44.6 48.7 52.7	14cc 0.5cc	28cc 6cc <0.01cc
	Penile Bulb	40.5		50%
	*47 Gy isodose line may not surround the circumference of the rectum in any horizontal slice.			
Prioritise	1) OAR mandatory 2) Coverage of PTV 3) Remaining OAR			

Table A.1: CTV to PTV margins, OAR constraints, and target coverage requirements for patients with low-volume metastatic disease

The CTV for the patients treated with 36 Gy/6 Fx consisted of the prostate and the visible extra-prostatic tumour tissue.

PTV margin	Prior to February 2022: PTV = CTV + 5 mm left, right, 4 mm superior, inferior, and 5 mm ant and post From February 2022: PTV = CTV + 3 mm left, right, 4 mm superior, inferior, and 5 mm ant and post			
Target coverage requirements	CTV(36Gy): V95%=100%, mean dose=99%-108% PTV(36Gy): V95%>98%, V120%<0.01cc			
OAR dose constraints	Organ at risk	Dose (Gy)	Max Volume (% or cc)	
			Optimal	Mandatory
	Rectum	36 34.2 32.4 25 20	0.1cc 3cc 7cc 25cc	0.3cc 6cc 10cc 30cc *
	Bladder	36 35 33	0.3cc 5cc 20cc	0.6cc 7.5cc 25cc
	PRV_Urethra (Urethra+3mm)	36	0.3cc	0.6cc
	Femoral head	20	1%	2%
	Bowel	34.4 32.4 20	0.1cc 1cc 5cc	0.5cc 3cc 15cc
	Penile Bulb	25		50%
	*20 Gy isodose line may not surround the circumference of the rectum in any horizontal slice.			
Prioritise	1. PRV Urethra 2. Rectum 3. CTV coverage 4. Remaining OAR 5. PTV coverage			

Linear mixed models estimates

Table A.2 - Changes in mean symptom scores relative to baseline for patients treated with 60 Gy/ 20 fractions with online adaptive MR-guided radiotherapy (n=25)

			During MRgRT (mean change, CI 95%)							Follow-up week after MRgRT (mean change, CI 95%)											
Symptom	Attributes*	W0	1		2		3		EOT	1		2		3		4		8		12	
PRO-CTCAE items (score 0-4)		Mean (SD)	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%
Decreased appetite	Severity	0.08 (0.28)	0.04	-0.16-0.24	0.16	-0.04-0.36	0.12	-0.08-0.32	**0.29**	0.09-0.49	0.18	-0.03-0.39	0.13	-0.08-0.34	0.10	-0.12-0.32	-0.04	-0.25-0.16	0.03	-0.18-0.24	-0.04	-0.24-0.17
	Composite	No observations																			
Nausea	Frequency	0.12 (0.60)	0.08	-0.10-0.26	-0.00	-0.18-0.18	-0.12	-0.30-0.06	-0.08	-0.26-0.11	-0.08	-0.27-0.11	-0.08	-0.27-0.11	0.09	-0.12-0.29	0.00	-0.18-0.19	-0.02	-0.22-0.17	-0.10	-0.29-0.08
	Composite	No observations																			
Constipation	Severity	0.32 (0.75)	-0.08	-0.39-0.23	0.12	-0.19-0.43	0.12	-0.19-0.43	**0.38**	0.08-0.69	0.06	-0.26-0.38	**0.35**	0.03-0.67	-0.08	-0.42-0.25	-0.04	-0.35-0.27	-0.11	-0.43-0.21	-0.22	-0.53-0.09
	Composite	0.36 (0.91)	-0.12	-0.47-0.23	0.16	-0.19-0.51	0.12	-0.23-0.47	**0.43**	0.07-0.78	0.07	-0.30-0.44	**0.40**	0.3-0.77	-0.08	-0.46-0.31	-0.08	-0.44-0.27	-0.15	-0.52-0.22	-0.25	-0.61-0.10
Diarrhoea	Frequency	0.28 (0.46)	0.04	-0.28-0.36	0.28	-0.04-0.60	**0.60**	0.28-0.92	**0.56**	0.23-0.89	**0.59**	0.25-0.93	0.20	-0.14-0.54	0.01	-0.34-0.37	0.13	-0.20-0.46	0.08	-0.26-0.42	0.21	-0.12-0.53
	Composite	0.56 (0.92)	0.08	-0.42-0.58	0.44	-0.06-0.94	**0.88**	0.38-1.38	**0.83**	0.32-1.33	**0.66**	0.13-1.19	0.32	-0.20-0.84	-0.07	-0.62-0.48	0.14	-0.36-0.64	0.11	-0.41-0.63	0.24	-0.26-0.74
Abdominal pain	Frequency	0.64 (0.99)	0.04	-0.28-0.36	0.00	-0.32-0.32	0.12	-0.20-0.44	0.03	-0.29-0.36	0.08	-0.26-0.41	0.04	-0.30-0.37	-0.14	-0.49-0.21	-0.03	-0.35-0.29	-0.13	-0.46-0.21	-0.27	-0.59-0.05
	Composite	1.10 (0.50)	0.13	-0.30-0.55	0.18	-0.25-0.61	0.22	-0.21-0.64	0.21	-0.22-0.65	0.15	-0.29-0.59	0.30	-0.16-0.75	0.05	-0.45-0.55	0.20	-0.23-0.63	0.12	-0.34-0.58	-0.12	-0.65-0.41
Radiation skin reaction	Severity	Collinearity																			
Fatigue	Severity	0.64 (0.86)	0.32	-0.01-0.65	**0.48**	0.15-0.81	**0.80**	0.47-1.13	**0.59**	0.25-0.92	**0.76**	0.41-1.11	**0.61**	0.26-0.96	**0.54**	0.17-0.91	**0.38**	0.04-0.71	0.04	-0.31-0.39	0.30	-0.04-0.64
	Composite	1.4 (0.70)	0.09	-0.27-0.46	0.09	-0.26-0.44	0.22	-0.14-0.57	0.17	-0.20-0.54	0.19	-0.18-0.55	0.21	-0.16-0.59	0.03	-0.38-0.43	0.01	-0.36-0.38	-0.07	-0.50-0.37	0.11	-0.26-0.49
Painful urination	Severity	0.28 (0.79)	0.32	-0.04-0.68	**0.84**	0.48-1.20	**1.08**	0.72-1.44	**0.89**	0.52-1.26	**0.91**	0.53-1.29	**0.86**	0.47-1.24	**0.42**	0.02-0.82	0.22	-0.15-0.59	-0.06	-0.45-0.32	0.01	-0.36-0.37
	Composite	0.32 (0.95)	0.32	-0.12-0.76	**0.88**	0.44-1.32	**1.20**	0.76-1.64	**0.93**	0.49-1.38	**0.96**	0.49-1.42	**0.86**	0.40-1.32	0.42	-0.07-0.90	0.18	-0.27-0.62	-0.11	-0.58-0.35	-0.02	-0.46-0.43
Urinary frequency	Frequency	1.52 (1.08)	**0.44**	0.06-0.82	**0.72**	0.34-1.10	**1.00**	0.62-1.38	**0.96**	0.58-1.34	**0.85**	0.45-1.24	**0.71**	0.31-1.10	0.23	-0.19-0.65	0.35	-0.03-0.74	-0.15	-0.55-0.25	0.02	-0.37-0.41
	Composite	1.21 (0.54)	0.18	-0.18-0.55	0.30	-0.05-0.66	**0.54**	0.18-89.54	**0.60**	0.24-0.96	0.34	-0.04-0.72	0.26	-0.12-0.63	0.02	-0.38-0.41	0.18	-0.18-0.54	0.01	-0.39-0.41	0.03	-0.34-0.41
EORTC items (score 1-4 and raw score 0-100)																					
Frequent urination at night	Raw score	41.33 (24.11)	2.67	-7.14-12.48	8.00	-1.81-17.81	**12.00**	2.19-21.81	**16.35**	6.42-26.37	**15.32**	5.00-25.64	**16.31**	5.99-26.63	8.31	-2.50-19.12	7.97	-1.96-17.89	-3.60	-13.92-6.71	-3.19	-13.11-6.73
Unintentional release (leakage) of urine	Raw score	2.67 (9.23)	-1.33	-6.72-4.05	0.00	-5.39-5.39	2.67	-2.72-8.05	2.94	-2.51-8.39	2.10	-3.56-7.76	2.73	-2.94-8.39	1.62	-4.31-7.55	2.76	-2.69-8.21	1.92	-3.74-7.58	3.58	-1.87-9.02
Difficulty emptying bladder (retention)	Raw score	20.00 (30.43)	**13.33**	2.60-24.07	**20.00**	9.27-30.73	**25.33**	14.60-36.07	**21.13**	10.27-31.99	**23.59**	12.30-34.88	**16.84**	5.55-28.13	10.56	-1.27-22.39	7.36	-3.50-18.22	-0.38	-11.67-10.90	3.84	-7.01-14.69
Urinary urge	Raw score	33.33 (31.91)	1.33	-9.16-11.83	**12.00**	1.50-22.50	**21.33**	10.84-31.83	**20.73**	10.11-31.35	**19.91**	8.87-30.96	**15.61**	4.56-26.65	11.11	-0.47-22.68	**12.76**	2.14-23.28	4.50	-6.55-15.54	2.35	-8.27-12.96
Pain/discomfort around anal opening	Raw score	8.00 (17.43)	0.00	-8.31-8.31	5.33	-2.98-13.65	**10.67**	2.35-18.98	**18.42**	10.01-26.83	**8.34**	-0.40-17.08	8.80	0.06-17.54	1.00	-8.16-10.16	-1.50	-9.91-6.91	-2.36	-11.11-6.38	-1.94	-10.35-6.46

Bloated feeling in abdomen	Raw score	13.33 (25.46)	0.00	-8.72-8.72	6.67	-3.04-25.38	4.00	-4.71-12.71	4.18	-4.64-12.99	6.71	-2.46-15.87	-1.22	-10.39-7.95	3.70	-5.90-13.31	0.19	-8.62-9.01	2.75	-6.41-11.92	-2.46	-11.26-6.35
Difficulty controlling bowels	Raw score	1.33 (6.67)	2.67	-4.70-10.03	5.33	-2.03-12.70	**16**	8.64-23.36	**13.02**	5.57-20.47	**11.23**	3.49-18.97	4.85	-2.89-12.59	3.70	-4.41-11.81	5.53	-1.92-12.98	2.55	-5.19-10.29	5.09	-2.35-12.54
Blood in stools	Raw score	0.00	**5.33**	0.56-10.11	4.00	-0.77-8.77	**5.33**	0.56-10.10	**6.84**	2.01-11.67	**7.71**	2.69-12.73	2.22	-2.80-7.24	2.56	-2.70-7.82	-0.14	-4.97-4.68	0.98	-4.04-6.00	**5.43**	0.61-10.26
Empty bowels	Raw score	10.67 (20.91)	**14.67**	5.56-23.77	**18.67**	9.56-27.77	**22.67**	13.56-31.77	**24.66**	15.45-33.87	**18.05**	8.48-27.63	**13.44**	3.86-23.01	6.56	-3.48-16.59	**9.69**	0.49-18.90	-0.16	-9.73-9.42	1.82	-7.38-11.03

*composite grade presented (interference left out)

**score 1-4 recalculated to raw score 0-100

Table A.2 - Changes in mean symptom scores relative to baseline for patients treated with 36 Gy/ 6 fractions with online adaptive MR-guided radiotherapy (n=25)

			During MRgRT (mean change, CI 95%)				**Follow-up week after MRgRT** (mean change, CI 95%)									
Symptom	Attributes	**W0**	**1**		**EOT**		**1**		**2**		**4**		**8**		**12**	
PRO-CTCAE items (score 0-4)		Mean (SD)	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%	Δ mean	CI 95%
Decreased appetite	Severity	0.24 (0.60)	0.02	-0.18-0.22	--0.08	-0.28-0.12	0.00	-0.20-0.20	-0.05	-0.26-0.16	-0.12	-0.32-0.08	-0.04	-0.25-0.17	0.13	-0.08-0.34
	Composite	No observations														
Nausea	Frequency	0.20 (0.41)	0.00	-0.19-0.19	0.00	-0.19-0.19	-0.04	-0.23-0.15	0.01	-0.19-0.21	0.00	0.19-0.19	-0.07	-0.26-0.13	0.13	-0.07-0.33
	Composite	No observations														
Constipation	Severity	0.24 (0.44)	-0.10	-0.41-0.20	0.04	-0.26-0.34	0.16	-0.14-0.46	0.27	-0.05-0.59	0.00	-0.30-0.30	0.21	-0.11-0.52	0.00	-0.32-0.32
	Composite	0.24 (0.44)	-0.10	-0.44-0.24	0.04	-0.30-0.38	0.04	-0.30-0.39	0.26	-0.11-0.62	0.00	-0.34-0.34	0.25	-0.10-0.60	0.00	-0.36-0.60
Diarrhoea	Frequency	0.32 (0.69)	0.08	-0.23-0.38	**0.40**	0.10-0.70	**0.44**	0.14-0.74	0.12	-0.20-0.44	-0.03	-0.33-0.28	0.00	-0.31-0.32	0.01	-0.30-0.33
	Composite	0.56 (1.08)	0.18	-0.29-0.65	**0.60**	0.14-1.06	**0.72**	0.26-1.18	0.24	-0.25-0.74	-0.04	-0.51-0.43	0.03	-0.45-0.52	0.06	-0.43-0.55
Abdominal pain	Frequency	0.44 (0.71)	0.04	-0.27-0.36	0.08	-0.23-0.39	-0.12	-0.43-0.19	-0.17	-0.50-0.17	-0.19	-0.50-0.13	0.31	-0.01-0.63	0.18	-0.15-0.51
	Composite	1.13 (0.64)	-0.21	-0.70-0.29	-0.07	-0.56-0.42	-0.14	0.65-0.37	-0.07	0.69-0.55	-0.15	-0.73-0.42	0.29	-0.17-0.76	0.18	-0.34-0.70
Radiation skin reaction	Severity	Collinearity														
	Composite	Collinearity														
Fatigue	Severity	1.12 (0.83)	-0.01	-0.34-0.32	0.04	-0.29-0.37	0.04	-0.29-0.37	-0.04	-0.39-0.31	-0.05	-0.38-0.29	-0.10	-0.44-0.24	0.01	-0.34-0.35
	Composite	1.28 (0.57)	0.24	-0.06-0.54	0.15	-0.12-0.43	0.12	-0.17-0.41	0.08	-0.22-0.38	0.06	-0.23-0.34	-0.04	-0.33-0.24	0.27	-0.04-0.58
Painful urination	Severity	0.48 (0,82)	**0.85**	0.48-1.22	**0.84**	0.48-1.20	**0.68**	0.32-1.04	**0.51**	0.12-0.90	0.34	-0.03-0.71	-0.01	-0.39-0.37	0.02	-0.36-0.41
	Composite	0.52 (0.96)	**0.99**	0.55-1.43	**1.00**	0.57-1.43	**0.63**	0.19-1.07	**0.48**	0.01-0.96	0.42	-0.02-0.86	-0.05	-0.50-0.40	0.03	-0.43-0.49
Urinary frequency	Frequency	1.8 (1.00)	**0.56**	0.17-0.94	**0.60**	0.22-0.98	0.36	-0.02-0.74	0.28	-0.13-0.69	-0.04	-0.43-0.34	0.16	-0.24-0.55	-0.12	-0.54-0.30
	Composite	1.19 (0.51)	**0.37**	0.02-0.72	**0.47**	0.12-0.82	0.32	-0.03-0.66	0.17	-0.20-0.54	0.00	-0.35-0.35	0.03	-0.33-0.38	0.12	-0.27-0.50
EORTC items (raw symptom score 0-100)**																
Frequent urination at night	Raw symptom score	42.67 (20.46)	6.23	-3.42-15.88	4.00	-5.54-13.53	5.33	-4.20-14.87	**10.66**	**0.35-21.01**	1.80	-7.85-11.44	-6.68	-16.58-3.22	-2.56	-12.59-7.48
Unintentional release (leakage) of urine	Raw symptom score	5.33 (12.47)	-1.05	-6.45-4.36	5.33	-0.01-10.68	1.33	-4.01-6.68	-0.36	-6.07-5.35	-0.96	-6.37-4.45	0.67	-6.22-4.88	-0.46	-6.09-5.17

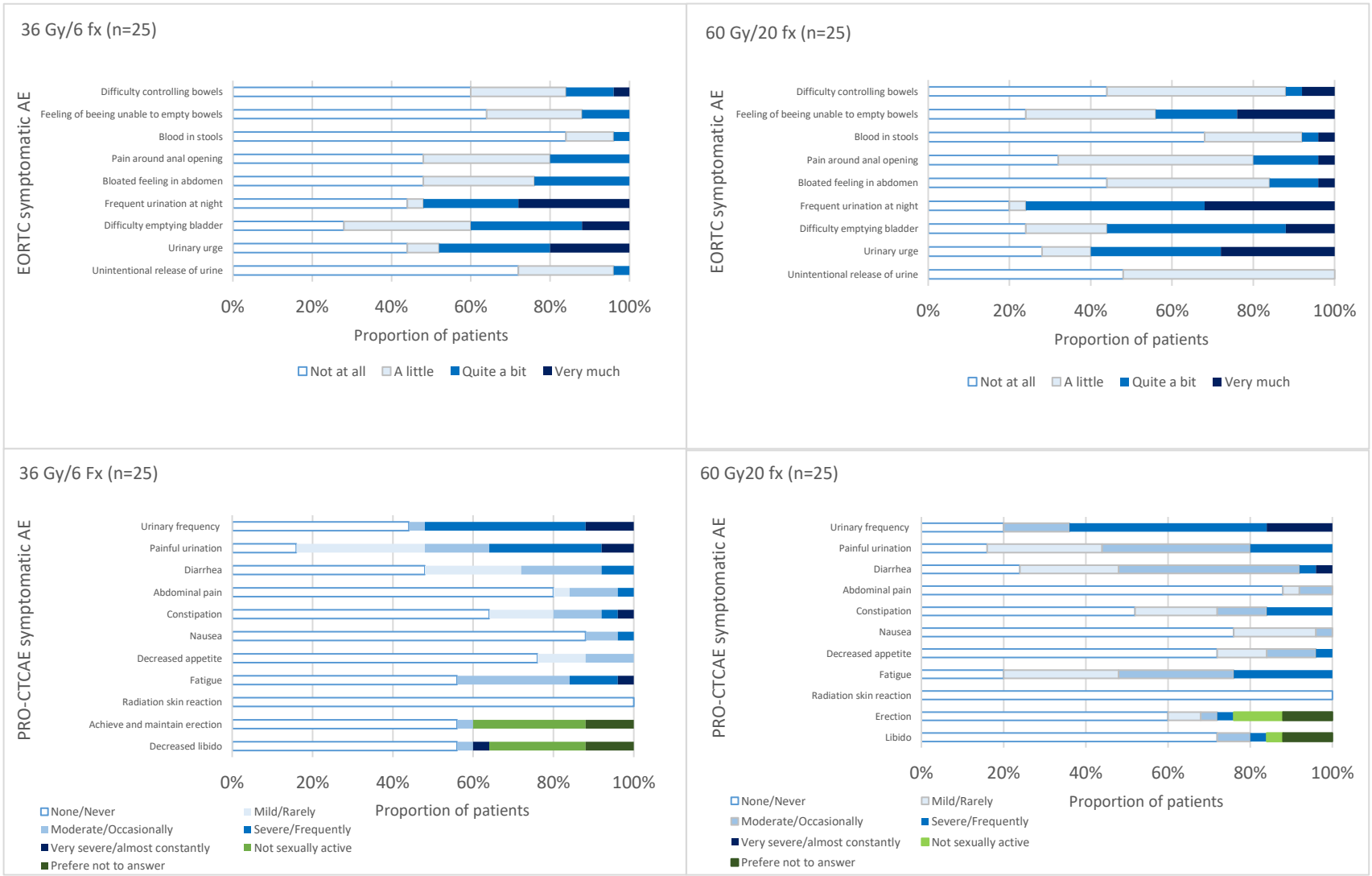
Difficulty emptying bladder (retention)	Raw symptom score	21.33 (23.33)	9.67	-1.21-20.56	8.00	-2.76-18.76	10.67	-0.09-21.43	**13.81**	2.31-25.30	0.49	-10.40-11.37	-1.51	-12.67-9.66	-1.46	-12.78-9.87
Urinary urge	Raw symptom score	36.00 (27.08)	0.12	-10.50-10.74	9.33	-1.16-19.83	4	-6.49-14.49	7.08	-4.13-18.29	1.30	-9.32-11.91	1.52	-9.37-12.42	-2.11	-13.16-8.94
Pain/discomfort around anal opening	Raw symptom score	4.00 (11.06)	4.22	-4.23-12.69	**10.67**	2.30-19.03	**9.33**	0.97-17.70	**10.70**	1.77-19.63	1.61	-6.85-10.07	5.68	-3.00-14.36	4.08	-4.72-12.88
Bloated feeling in abdomen	Raw symptom score	12.00 (23.33)	-2.83	-11.63-5.98	8	-0.70-16.70	8	-0.70-16.70	3.03	-6.26-12.33	0.14	-8.67-8.94	5.08	-3.95-14.11	1.64	-7.53-10.80
Difficulty controlling bowels	Raw symptom score	2.67 (9.23)	6.41	-0.45-13.26	**10.67**	3.89-17.44	6.67	-0.11-13.44	1.20	-6.03-8.43	1.12	-5.74-7.97	0.68	-6.35-7.71	2.79	-4.34-9.91
Blood in stools	Raw symptom score	0.00	-0.04	-4.46-4.39	4.00	-0.37-8.37	1.33	-3.04-5.71	1.48	-3.18-6.15	1.36	-3.06-5.78	-0.12	-4.66-4.41	0.00	-4.60-4.60
Empty bowels	Raw symptom score	12.00 (18.95)	0.34	-8.61-9.30	5.33	-3.52-14.19	4.00	-4.85-12.85	-2.61	-12.07-6.84	-1.24	-10.19-7.72	4.99	-4.20-14.18	2.22	-7.10-11.53

*composite grade presented (interference left out)

**score 1-4 recalculated to raw score 0-100

Maximum baseline-adjusted symptom scores (n=50)

Figure A.3



Maximum adjusted score post-baseline tabulated for each symptomatic AE being the maximum grade ≥ 1-grade above the baseline score.
If the score was equal to or lower than the baseline level, the adjusted maximum score was zero according to Dueck et al 2020.

Other symptoms reported in free-text response option (n=50)

Table A.4

	n pt	%	Symptom severity reported, grade (% of all patients)					Symptoms reported	
			0	1	2	3	4		
			None	Mild	Moderate	Severe	Very Severe	Symptoms grade 3-4	Symptoms grade 0-2
Baseline	2	4%	0%	4%	0%	0%	0%		Hematuria
Wk 1	11	22%	0%	10%	8%	4%	0%	Blood from the anus, sensory disturbance in left thigh	Sore testicles, pain in groin, rumbling stomach, dysuria at night, pain in ear
Wk 2	16	32%	2%	4%	14%	14%	0%	Urinary retention, heartburn, fatigue, bloating, insomnia and fatigue due to discomfort with MR-linac, irritable, cold sweat at night, diarrhoea from antibiotics	Weak urinary flow, increased daily bowel movements, sore testicles, heat flashes, bowel movement when urinating
Wk 3	7	14%	0%	4%	4%	6%	2%	Decreased libido and erection, faecal urge, urinary retention	Nocturia, rectal discomfort, sore testicles, mucus from rectum
Wk 4	5	10%	0%	2%	6%	0%	2%	Discomfort around ribs (anxious about if it is metastasis)	Hot flashes, urination and diarrhea every half hour and blood in stool, decreased void volume
FU wk 1	9	18%	2%	4%	2%	4%	6%	Urination every hour, sore groin and testicles, back pain, painful frequent urination, diarrhea	Irritable bowel with mucus
FU wk 2	5	10%	4%	2%	2%	2%	0%	Urination every hour	Frequent flatulence, pain in left side of back, pelvis pain
FU wk 3	3	6%	2%	0%	4%	0%	0%		Decreasing urinary frequency, fatigue, pelvic/abdominal pain
FU wk 4	5	10%	2%	2%	2%	0%	4%	Discomfort around ribs and back, sexual problems, pain around KAD	Retention at night, pain in left hip
FU wk 8	10	20%	2%	4%	14%	2%	0%	Itching around the anus	Sensory disturbance in feet and toes, dry or no ejaculation, bloating, pain in groin, pain in legs, pelvic pain, sore back, xerostomia
FU wk 12	13	26%	0%	12%	6%	8%	0%	Weak stream, weight gain, itchy skin around anal opening	Muscle and joint pain, foreskin stricture, frequent urination, rumbling stomach

APPENDIX D

Manuscript IV: Møller PK, Pappot H, Schytte T, Bernchou U, Dieperink KB. Clinical impact of weekly symptom monitoring for patients with prostate cancer using digital patient-reported outcomes in radiation oncology routine care. Under preparation.

Clinical impact of weekly symptom monitoring for patients with prostate cancer using digital patient-reported outcomes in radiation oncology routine care

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Abstract

Purpose

Integrating active symptom monitoring of electronic patient-reported outcomes (ePROs) in the clinical workflow and engaging clinicians in acting on the data is challenging. Therefore, this study aimed to adapt digital symptom monitoring into the radiotherapy (RT) workflow. Furthermore, we aimed to investigate if there was an association between patient and clinician compliance and explore the impact of PROs on communication, care, quality of life and self-selected follow-up.

Method

Patients with prostate cancer (PCa) referred for RT were eligible for inclusion. Weekly ePRO was reported in *My Hospital* application during RT, four weeks after, and weeks eight, 12 and 24. During treatment, clinicians used the PROs displayed in the patient record in real-time in a weekly status with the patient. A validated Patient Feedback Form was used to evaluate patient satisfaction with ePROs, and clinician engagement was measured as PROs handled in the patient record. Nurse-led follow-up could be selected or deselected by the patient. Health-related quality of life was measured with the EQ-5D-5L.

Results

A consent rate of 91.5% resulted in 156 PCa patients included in the analyses (161 enrolled, attrition rate 5%). The median age was 69, and 95% accepted electronic completion (ePROs). The mean response rate was 81%, and patients found ePROs improved communication (91%), discussion (93%), quality of care (87%) and the feeling of being involved (93%). Clinicians acted on all PROs during radiotherapy for most patients (93%), and 96% of patients experienced their PROs being used for their care. Follow-up was deselected by 23% of patients. More of these patients reported declining self-rated health in EQ VAS two months later ($p=0.044$). Patients having concomitant hormonal therapy (ADT) also had a higher mean decline in EQ VAS ($p=0.050$).

Conclusion

Weekly ePRO with real-time clinician feedback was found to improve communication, patient involvement and quality of care for most patients. We found no association between clinician and patient compliance as the clinicians acted on most PROs, and almost all patients found their PROs were used in their care. However, more patients deselecting follow-up or having concomitant hormonal therapy reported a deteriorated health state twelve weeks following radiotherapy.

Introduction

An increased digital collection of patient-reported outcomes (ePROs) in radiotherapy routine care creates real-world evidence of toxicity and addresses the patient's needs [17]. However, integrating and taking action on PROs within the clinical workflow is still a challenge that must be directed by looking at the added value of ePROs on patient care [9, 37].

In radiotherapy, an exact measure of the treatment-related morbidity is essential as an escalation of doses to the tumour depends on patient morbidity [14]. PROs are essential for tracking acute toxicity in radiotherapy courses [11, 28]. Having a toxicity assessment directly from the patients with PROs enhances the interpretation of clinical data in routine care and clinical trials [7, 10].

Early studies included PROs in research without real-time monitoring. However, in the past decade, the evidence of symptom monitoring improving the clinical management of symptoms has been growing [17]. Utilising real-time data for timely patient care is a goal to enhance the patient experience and quality of life (QoL). To succeed with the integration of PROs, an infrastructure for PRO reporting and clinical workflow must be designed for this complex intervention [24, 37].

Several studies investigating the feasibility of ePROs in the radiotherapy workflow found a high patient acceptance [5, 6, 18, 25, 26, 30-33, 35, 42]. Patient self-reports filled a gap in the radiation oncology pathway, especially in short-course radiotherapy, where the risk of deteriorated symptoms might be higher [30]. PROs have also proved feasible for highlighting the need for follow-up after radiotherapy treatment [40]. Despite these benefits and patients accepting ePRO completion, it is challenging to find the right way to integrate digital symptom monitoring in the radiotherapy workflow [24, 32]. One major challenge with ePROs is patient compliance, as missing data often is a problem [24]. Another challenge is patients requesting additional functionalities from some digital applications [18]. In addition, frequent PRO assessments demand a short treatment-specific questionnaire to minimise the time to complete and be meaningful and relevant for the patients [32, 34].

These considerations should be addressed in a structured intervention implementation to improve patient adherence [32, 37]. To address the lack of patient compliance, patient motivation must be maintained by making their responses more actionable in the clinical workflow. It should, however, be considered in planning how to do so without significantly increasing the workload [37]. In prior studies within radiotherapy, the clinical action on PROs varies, with some studies providing self-management advice for patients [26, 30, 33], some communicating via the application [42], and others having clinician alerts if symptoms are severe [26, 30, 31, 33]. Other studies only collected the PROs without making them actionable [5, 6, 32].

The questionnaire does not cause the value of PROs but the active management of symptoms based on the PRO responses [2, 4, 15, 26]. This immediate value from PRO completion within radiotherapy demands clinical action plans and infrastructure for patients to recognise the consequence of their self-reports [8].

Patients with prostate cancer (PCa) treated with radiotherapy may benefit from consultations with experienced nurses to support their self-management of urinary symptoms [19]. PROs can be utilised for these consultations to identify patients with moderate or severe symptoms and need of care [20, 21]. In addition, remote symptom monitoring of PROs might support nurse-led follow-up care, where PROs and telephone consultations might be an adequate replacement for in-person consultations [20].
The eRAPID study found an association between online patient adherence and clinician engagement [2]. However, in the eRAPID radiotherapy study, they could not monitor clinician engagement and had no way of reminding the clinicians to use PRO responses because of the complex clinical pathways [26]. Thus, further knowledge of how clinician engagement relates to patient satisfaction and compliance during radiotherapy is needed. Furthermore, it must be explored how weekly clinician feedback affects the patient experience when patients have daily attendance in the department. To our knowledge, no studies have explored the clinical benefits of weekly ePROs with systematic real-time feedback from clinicians in radiotherapy for PCa outpatients. Finally, factors influencing patient self-selected follow-up after radiotherapy combined with ePROsmust be identified. This study aimed to describe the clinical impact of weekly ePRO monitoring on the outpatient radiotherapy setting, looking at satisfaction with ePROs and initiated supportive care interventions for patients with PCa. We aimed to investigate if patient compliance and satisfaction are related to clinician engagement and explore follow-up stratification and potential changes in QoL.

Methods and Materials

Study design

This study is a longitudinal observational single-arm study. Patients with PCa $\geq$ 18 years, referred for radiotherapy with a definitive intent at Odense University Hospital in November 2020 – April 2022, were eligible for enrollment. Furthermore, the patients should be cognitively able to provide informed consent and read, understand and complete PRO surveys in Danish.
Treatment included radical radiotherapy, salvage radiotherapy of the prostate bed or radiotherapy of the prostate for low-volume metastatic PCa (total dose > 30 Gy). The patients were allocated for treatment on the MR-linac (1.5 T Elekta Unity) or standard linear accelerators (Elekta Versa HD) with different treatment schedules according to the local treatment guidelines. Therefore their duration of treatment varied from two to eight weeks. Oral and written informed consent were obtained from the participants. The department's patient and caregiver user council read and provided feedback on the patient information, and feedback was collected in the pilot study [35].
Patients not eligible or declining participation were listed on a screening list describing the reason for the decline, and non-participation was recorded along with age, cohabitation status, WHO performance status and treatment modality.

Patients completed PROs weekly for up to four weeks following radiotherapy and at follow-up weeks eight, 12 and 24 (Figure 1).

Before the intervention, usual care for patients with PCa consisted of daily observation and unsystematic dialogue between the patient and radiation therapist about new or worsened symptoms. Based on this dialogue, symptom management was initiated. At the end of the radiotherapy course and four weeks following, the patients with PCa had a physician consultation to manage their acute toxicity. Shortly before this study was initiated, the physician consultations were changed into nurse-led consultations for most patients. Most radiation therapists in the department are nurses of background and are referred to as clinicians in this paper.

My Hospital application

The patient pathway app and website of the Region of Southern Denmark, *My Hospital*, was used for ePRO completion [13]. The application's utility was tested in a pilot study [35]. When the patient logs into *My Hospital*, it contains all patient information about their treatment, disease, caregiver information, and schedule with all hospital appointments (Figure 2). The patients could see their previous PROs completed in the application; however, no graphical overview or self-management advice was provided. The patients completed PROs at home on their own devices. Paper questionnaires were an alternative if they did not have a device or sufficient technical abilities.

Outcome measures

The questionnaire used for weekly PRO provision was specifically developed and validated in a pilot study as a pelvic item set with 18 symptomatic adverse events [34, 35]. Patient satisfaction with online PROs and the impact on communication and quality of care was measured with the Patient Feedback Form used by Basch et al. in 2005 [3] and adapted by Snyder et al. in 2014 [41]. The Feedback Form has been translated and culturally adapted for the Danish population (Figure 1) [44]. The Feedback Form also contained the question whether the patient felt their PROs were used for their care. Patient response rates and proportion of PROs handled by clinicians were extracted from the digital application, *My Hospital* and the electronic patient record. In addition, supportive care interventions, contacts to the department outside the scheduled appointments, admission and referrals were derived from the patient record.

After reporting their symptoms in the 4-week follow-up questionnaire, the patients were asked about their need for follow-up. The patients were asked to select their type of follow-up. Some patients enrolled in a treatment protocol were prebooked for an in-person consultation. The patient could select one of the following response options; "I have a scheduled telephone consultation and want to keep this", "I do not

need my telephone consultation, and I will contact the Department if needed", or "I have a scheduled appointment in the Department".

Health-related QoL was measured at baseline and 12 weeks following treatment using the generic Eoroqol EQ5D5L questionnaire and the cancer-specific European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire. The QLQ-C30 and The Patient Experience Form, exploring the patient experience of having radiotherapy, will not be reported here but will be used in future analyses. In the baseline questionnaire, patients were asked which device they used to complete the PRO and how frequently they used it for anything other than telephone calls and text messages. In addition, baseline characteristics were extracted from the electronic health record. The study is reported according to STROBE guidelines [1].

Patient PRO pathway

The patients were informed about *My Hospital* application after consultation with the physician before the CT simulation. When they attended their CT simulation, the investigator informed them about the study and demonstrated the use of *My Hospital* for PROs. Written guidance was handed out with illustrations showing how to enter the application and how to respond to the PROs. The patient was informed to complete PROs on a fixed weekday, which was an essential factor for adherence in the pilot study. Reminders were sent on the day of completion and one day following. As an attempt to improve retention during follow-up, the public digital mail system was used for reminders. The patients were informed that the clinicians would review and use their weekly PRO responses the day after their completion and use their responses in their dialogue about symptoms.

The clinician PRO pathway

The clinicians were trained at two sessions about the PRO item set, *My Hospital* patient interface and the clinician interface. The PROs were displayed for the clinicians with direct access in the electronic health record. There was a discussion on looking at the results, but no guidelines or restrictions on interpreting the PROs. The clinicians were informed that the PROs should be used as a dialogue tool, with particular attention on new symptoms or increased symptom severity. The 'PRO-status' was booked in the patient's schedule as a task to be completed by the clinicians. In the clinician interface, the PRO responses could be compared over time, with a green (mild), yellow (moderate) or red (severe) dot indicating the symptom's frequency, severity or interference. When the clinicians entered the patient's PRO completion of the week, there was a button where they could 'handle' the PRO. That made it visible to their colleagues whether the PROs had handled. The observations and interventions of the 'PRO-status' were documented in the electronic health record.

Statistical methods

One-way Anova and Fisher's Exact Test were applied for baseline characteristic comparison. All responses from the Patient Feedback Form (PFF) with four categories were dichotomised into agree (strongly

agree/agree) or disagree (disagree/strongly disagree). Fisher's exact test was used for comparison of clinician compliance rate (< 100% or = 100% PROs handled) and the patient experience of PROs being used (PFF8). For comparing clinician compliance with patient response rates univariate logistic regression was used. Univariate logistic regression analyses or Fisher's Exact Tests were used to explore associations between improvement of care or communication (PFF6-13) or selection of follow-up and different covariates; age, WHO performance status, cohabitation status, educational status, radiotherapy prescription, concomitant systemic treatment, technical abilities and baseline EQ-5D score and EQ VAS score. Changes in EQ VAS health state (improved, worsened or no change) [16, 43] were compared in the follow-up selected groups with chi-square tests. Mean differences in the subgroups of changes in health-related quality of life (EQ-5D index score and EQ VAS score) were analysed with the Wilcoxon signed-rank test and Kruskal-Wallis test.
A p-value of ≤ 0.05 was considered statistically significant. Statistical analyses are conducted in STATA IC15.

Results

All 187 patients referred for treatment were screened for eligibility. Eleven patients did not meet the inclusion criteria due to competing trials or inability to read, understand or complete PROs. Out of 176 patients informed, 15 declined participation (9%) due to a lack of resources to participate in a study or a lack of technical skills and not wanting paper questionnaires (Figure 3).
Finally, 161 patients were enrolled (91.5%); five dropped out at baseline and three more patients during follow-up (attrition rate 5%). The 156 patients enrolled were in four different PCa risk groups, some with metastatic disease. Therefore, the total radiotherapy doses differed, and the patients were stratified into four groups according to treatment dose; 78 Gy, 70 Gy, 60 Gy and 36 Gy.
Participants were overall median age 69, most treated for high-risk PCa with 78 Gy, and most patients were married or cohabiting with a good performance status (Table 1). The proportion of participants having concomitant systemic treatment with androgen deprivation therapy (ADT) differed as expected between the four groups. The electronic reporting was accepted by 95% of the patients, with minor differences in the four groups (Table 1).
There was a statistically significant difference in age between the 26 non-participants and participants (72 vs 69, p=0.012). Also WHO performance status significantly differs (p<0.001), with 50% vs 25% in performance status 1-2. Furthermore, the allocated radiotherapy schedule differed, with more non-participants treated for high-risk PCa and fewer in the other three groups (p=0.011).
The characteristics of participants using paper PRO vs ePRO did not significantly differ; however, in the paper PRO group, the mean age was lower (66 vs 69), the median EQ VAS score was higher (90 vs 81), and the highest attained education was basic school or vocational training. Most patients (80%) used electronic devices daily; however, 12% (n = 18) never used them for things other than phone calls or text messages.

Impact of PROs on patient involvement and communication

PRO completion made it easier for most patients to remember symptoms and side effects when they spoke with the clinicians (91%). The weekly dialogue about changes in the PROs resulted in 93% reporting an improved discussion with the clinicians and 91% improved communication. Furthermore, 93% felt the PROs made them feel more involved in their care, and 100% would recommend it to other patients. The proportion of patients reporting improved quality of care was 87% (Figure 4). The improvement of care, communication or involvement was not significantly associated with age, WHO performance status, cohabitation status, educational status, radiotherapy prescription, concomitant systemic treatment, technical abilities or baseline EQ5D-score and EQVAS-score. Patients completing paper PRO responded differently to the question 'Clinicians used information for my care' than patients reporting electronically, with 33% vs 3% not feeling their responses were used (p=0.018). A similar difference was found for the question if PRO completions made them 'feel more involved in their care, with 33% vs 5% for ePRO not feeling more involved (p=0.050). The clinicians acted on all questionnaires for all eight patients completing paper PROs (100%).

Clinician compliance vs patient-experienced use of PROs

The Patient Feedback Form was completed by almost all patients (98%). Almost all patients (96%) agreed that the clinicians used the information from the PROs for their care (Figure 4). We explored whether this was related to how many PROs were acted on by the clinicians. However, most patients (93%) had all their questionnaires (100%) acted on by clinicians. No differences were found since the remaining patients (7%) all agreed that the PROs were used for their care (p=0.487). Patient compliance was high, as the overall mean response rate was 81% (42% - 91%). During follow-up weeks eight, 12 and 24, the retention rate was 92%, 94% and 74%, respectively. The response rate was not significantly associated with the proportion of PROs handled since a response rate of 73%-100% was found for patients having less than 100% reviewed by clinicians (p= 0.921).

Stratified selection of follow-up

In 98% of the nurse-led consultations at the end of treatment, the ePRO responses were used in the consultation. Of the 107 patients choosing a 4-week follow-up, 23% deselected the follow-up (Table 2). Selection or deselecting was not significantly associated with age (p=0.232), WHO performance status (p=0.530), cohabitation status (0.868), educational status (p=0.931), radiotherapy schedule (p=0.352), concomitant systemic treatment (p=0.660), technical abilities (p=0.056) or baseline EQ-5D index score (0.255) and EQ VAS-score (n=0.986). Changes in EQ VAS health state (improved, worsened or no change) revealed a higher proportion of patients deselecting follow-up reporting deteriorated EQ VAS score at the 12-week follow-up (68%) than those attending follow-up (40%) (p=0.044). No significant association was found with patients' response rate (p=0.574) or proportion of PROs handled (p=0.736). We looked at the number of prescribed supportive care medications throughout the treatment; however, this was not

significantly associated with selecting follow-up or not (p=0.254). When we compared it with the number of contacts for the department, this was not significantly associated with selected follow-up either (p=0.380); thus, those selecting follow-up were more likely to contact the department outside scheduled appointments (p=0.045) (Table 2).

Change in QoL

The mean difference between the 12-week EQ-5D index score or EQ VAS score and the baseline scores were not significantly associated with age groups, WHO performance status, cohabitation status and radiotherapy schedule (Table 3). Patients having concomitant ADT significantly declined more in EQ VAS compared to those not having ADT (p=0.050). Most scores decreased at the 12-week follow-up except for those with poor WHO performance status or living alone, potentially due to baseline imbalances.

Comparing the baseline EQ VAS score between patients below or above age 70, the older patients ≥ age 70 scored better self-rated health (median VAS 82) than younger patients (median VAS 75) (p=0.037) and similar at follow-up week 12 with EQ VAS 78 vs 72 (p=0.028) (Table 3).

Discussion

Almost all patients in this study provided feedback on their satisfaction with ePRO. They experienced that the weekly PROs improved the communication and discussions with clinicians about symptoms, the feeling of being involved, and the quality of care. A Cochrane review on the effect of routine provision of PRO feedback in clinical practice stated that the evidence supporting feedback on PROs increasing patient-clinician communication and disease control was low to moderate [22]. The improved communication our patients reported might be due to the PROs being used on the individual level as it engages patients more actively in their treatment [23, 39].

PROs do not always improve patient satisfaction in routine care, potentially due to cancer patients having overall high satisfaction with their care; subsequently, the ceiling effect affects the results [23]. This was not the case in this study since the questionnaire was not constructed for before and after assessments but simply an evaluation of the patient's satisfaction with ePROs. No characteristics were detected for patients who reported that PROs did not improve their care. However, a significant proportion of the eight patients completing paper PROs experienced their PROs not being used, and it did not improve their feeling of being involved (33%). This group did not significantly differ from the ePRO group but had a lower age and educational level. One reason for their lower satisfaction could be that the paper PROs were harder to administer; however, the clinicians handled all questionnaires.

This study investigated the association between clinician engagement and patients' experience of their PRO data being used for their care. We found no significant difference between clinician engagement and the patient's experience of clinician engagement since almost all of the PRO measures were acted on by the clinicians, and almost all patients experienced their PROs being used. Nor was the clinician engagement

correlated to the patient response rate. The response rate was high during follow-up, with 94% in week 12 and 73% in week 24 after the last radiotherapy fraction, even though no feedback was provided. In the prostate group in the eRAPID study, the response rate was 69% and 43% for 12 and 24 weeks after the first radiotherapy fraction [26]. After the pilot study, we changed the reminders during follow-up to the public mail system since patients stopped using the app when their follow-up course in the department ended. That could be a reason for the improved response rates.

In this study, 23 % of the patients having the option to select or deselect follow-up reported that they did not need the follow-up based on their current health status. A study identifying patients with no need for follow-up based on their symptoms alone found that 29% did not need a face-to-face appointment [40]. The patients in that study had different oncologic treatments, and the criteria for needing a follow-up were having any grade $\geq$2 CTCAE toxicity or PS 3-4. In our study, the need for follow-up was based on patient preference alone, not correlated with symptom grading. Surprisingly we found that a higher proportion of patients deselecting the follow-up had a deteriorated EQVAS score two months after the follow-up. Potentially it could mean that patients deselecting follow-up have a higher risk of decreased health state after treatment. Perhaps that could have been managed more proactively had the patient not had the opportunity to deselect the follow-up. A few patients had their consultation changed to a physician consultation due to timely detection of symptoms leading to patients at risk of severe treatment morbidity being identified [27, 39]. We found no correlations between deselecting follow-up and patients being admitted or the amount of medication that had been prescribed. The correlation with the severity of symptoms must be explored further. The eRAPID study explored the ceiling effect of the PROMs they used and found that EQ-VAS performed well and could be recommended for future trials [26]. The baseline EQ-VAS for the patients with PCa in that study was 76.3 and 80.4 in the two groups having radical radiotherapy. They found a median change at 12 weeks of 0.71(n=38) in the group using ePROs and -2.77 (n=39) having standard care. We found a similar overall baseline EQ VAS score of 78.5. However, the mean change in our study was -3.93 at week 12 after the last radiotherapy fraction, not after the first fraction as in eRAPID. Another difference was that only patients with localised PCa receiving a standard treatment of 60 Gy/20 Fx were included in the eRAPID study [26]. Performance status was not reported, nor was the proportion of patients having ADT, presumably higher in our study involving many patients with metastatic disease. Therefore, deterioration in EQ VAS in our study could be explained by the inclusion of patients with metastatic disease and more patients having concomitant ADT. However, none of the changes in EQ-5D index scores exceeds the suggested Minimal Important Difference (MID) for a cancer population of 0.06 or the mean change of 7 for EQ VAS scores [38]. Surprisingly, we found that the elderly patients ($\geq$ age 70) reported better health on the EQ VAS at baseline than the younger patients (< age 70). A reason might be that the patients having a biochemical recurrence of their disease or high-risk disease had a lower or similar mean age as the other groups. These were also the groups with the highest proportion having ADT, which is known to decrease QoL [12].

One of the most notable strengths of the current study was engagement of the clinician. We used the weekly PROs as a tool for dialogue in a formalised conversation on new or changed symptoms between the experienced radiation therapists (RTTs) and the patients. Since patients' responses and the contextual patient information do not always align, the change over time in PROs must be interpreted via dialogue [29]. The RTTs have expertise in evaluating side effects and were trained in PROs and the PRO system. This expertise might have minimised some of the barriers previously found for integrating PROs: lack of knowledge to interpret and act upon PRO data in their clinical practice and lack time [36]. It is also essential to notice that before this study, no weekly symptom report was obtained. In the current study, the RTTs systematically carried out the weekly PRO status within the usual time set aside for the patient.

Furthermore, previous findings recommended focusing on existing technical systems and clinical workflows [37]. We used an application, *My Hospital*, which was already integrated into the electronic health records and adapted the active use of ePROs to the existing workflow as much as possible. Another strength of this study is the large heterogeneous sample of patients with PCa. That might increase the generalisability of the data by comprising real-world evidence of ePRO in a setting where inclusion was not restricted by age, performance status or comorbidity. Furthermore, it represents a radiotherapy setting where patients often receive different radiotherapy schedules with different indications and disease stages. The consent and real-world adherence rates were high, and the attrition rate was low. In addition, this is the first study engaging the RTTs who observe and talk to the patient daily in conducting a weekly symptom status based on PROs. Our pilot study revealed that the patients preferred having advice and feedback from the RTTs rather than from the application since they had a good relationship with them and a daily talk about and management of side effects. That might have added to the high response rates and patient satisfaction.

The limitation of this study was that it was a single-arm, non-randomised study which increases the risk of bias. However, the data were collected on the non-participants comprising an older mean age and a higher performance status than the participants. In addition, we offered paper PROs to patients who did not have the device or ability to do electronic reporting, which is recommended to avoid excluding under-served groups [17]. Additionally, we stratified the analyses by radiotherapy schedule, which is an important confounder as the dose and fractionation also indicate disease stage and the risk of side effects. Conversely, the ESMO clinical practice guidelines stated that substantial evidence supporting the efficacy of PRO integration comes from non-randomised real-world data [17]. Another limitation is that we did not collect formalised feedback from the clinicians. However, we had an ongoing dialogue and alignment of the workflow throughout the study period, and future research has been planned to investigate the clinician experience.

This study adds to the evidence of why and how to integrate patient reporting in the radiotherapy setting. We successfully integrated real-time monitoring of weekly ePROs during treatment with a high engagement from radiation therapists. Most importantly, the PRO responses were interpreted in dialogue and used for timely supportive care. As a result, the patients experienced their PROs being used and their communication

and involvement in their care improved. However, further research has to be done on how to use the PROs for follow-up stratification.

Conclusion

This study found that almost all patients reported that weekly ePRO with real-time clinician feedback improved communication, patient involvement and quality of care. There were no differences in clinician engagement and patient satisfaction as the clinicians acted on most PROs, and almost all patients found their PROs were used for their care. We found no differences in the characteristics of patients selecting or deselecting follow-up. However, more patients deselecting follow-ups reported a deteriorated health state afterwards. Health-related quality of life declined more in patients having concomitant hormonal therapy.

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Tables and figures

Table 1. Characteristics of study participants with prostate cancer in the PRO-MR-RT study (n=156)

	Total	78 Gy/39 Fx High risk	70 Gy/35 Fx Salvage	60 Gy/20 Fx Intermediate risk	36 Gy/6 Fx Low-volume metastatic	p-value
	N=156	N=67	N=28	N=33	N=28	
Age, *mean (SD)*	69 (6)	69 (6)	66 (7)	69 (5)	70 (6)	*0.047*
< age 70	48% (75)	46% (31)	57% (16)	48% (16)	43% (12)	
≥ age 70	52% (81)	54% (36)	43% (12)	52% (17)	57% (16)	
Cohabitation status						*0.024*
Cohabiting	80% (125)	79% (53)	100% (28)	73% (24)	71% (20)	
Living alone	20% (31)	21% (14)	0% (0)	27% (9)	29% (8)	
WHO/ECOG Performance status						*0.302*
PS 0	84% (131)	79% (53)	93% (26)	82% (27)	89% (25)	
PS 1	13% (21)	19% (13)	4% (1)	15% (5)	7% (2)	
PS 2	3% (4)	1% (1)	4% (1)	3% (1)	4% (1)	
Educational status						*0.430*
Basic school	4% (7)	3% (2)	4% (1)	6% (2)	7% (2)	
Vocational training	38% (60)	40% (27)	29% (8)	48% (16)	32% (9)	
Short-cycle higher education	8% (13)	4% (3)	14% (4)	9% (3)	11% (3)	
Medium-cycle higher education	21% (33)	12% (8)	25% (7)	33% (11)	25% (7)	
Long-cycle higher education	6% (9)	7% (5)	7% (2)	0% (0)	7% (2)	
Missing	22% (34)	33% (22)	21% (6)	3% (1)	18% (5)	
Currently working, yes	31% (45)	28% (16)	50% (14)	24% (8)	26% (7)	*0.110*
Concomittant ADT						*<0.001*
Yes	87% (136)	100% (67)	96% (27)	48% (16)	93% (26)	
Does the patient accept electronic reporting (ePRO) ?						*0.130*
Yes	95% (148)	97% (65)	100% (28)	88% (29)	93% (26)	
Use of technology, *frequency*						
Several times a day	56% (88)	50% (32)	82% (23)	55% (17)	64% (16)	
Daily	24% (37)	30% (19)	18% (5)	26% (8)	20% (5)	
Weekly	5% (8)	11% (7)	0	3% (1)	0	
Monthly	3% (5)	4,5% (3)	0	6% (2)	0	
Never	12% (18)	4,5% (3)	0	10% (3)	16% (4)	*0.057*

Table 2. Follow-up selection and supportive care interventions (n=156)

% (n)	Prebooked consultation in the department *	Select follow-up consultation	Deselect follow-up consultation	*p-value*
Follow-up selection	31% (49)	53% (82)	16% (25)	
Number of interventions/medicin (n=98)				*0.254*
0	26% (12)	41% (32)	40% (10)	
1	26% (12)	27% (21)	36% (9)	
2	30% (14)	22% (17)	12% (3)	
> 2	19% (9)	11% (9)	12% (3)	
Mean diff EQ index score (SD)	-0.017 (0.11)	-0.023 (0.12)	0.022 (0.12)	*0.060*
Mean diff EQ VAS score (SD)	-6.79 (14.05)	-2.49 (13.80)	-3.08 (18.78)	*0.868*
Deteriorated VAS score week 12	49% (24)	40% (33)	68% (17)	*0.044*
Contacted the department outside scheduled	29%	36%	16%	*0.045*
Mean number extra contacts (n=47)	0.57	0.41	0.28	*0.380*
Referred for rehabilitation	23% (11)	17% (14)	16% (4)	*0.575*
Admission (median 25 days after first RT)	2% (1)	6% (5)	8% (2)	*0.524*
KAD during RT or follow-up	8% (4)	9% (7)	0	*0.140*

* 56% in MR-Linac trials. 6 (4%) changed to physician consult due to symptom severity

Table 3. Mean differences in EQ-5D-5L scores from baseline to follow-up week 12 (n=156)

	Higher scores = better health state reported				
	Mean diff EQ index score	*p-value*	Baseline mean EQ-VAS*	Mean diff EQ-VAS score	*p-value*
Overall	-0.017		78.5	-3.93	
Age <70 years	-0.026		74.7	-3.97	
Age ≥70 years	-0.009	*0.637*	82.2	-3.90	*0.934*
WHO PS 0	-0.020		80.5	-4.51	
WHO PS 1-2	0.002	*0.923*	68.4	-0.91	*0.738*
Married	-0.022		78.9	-4.61	
Living alone	0.007	*0.270*	76.4	-0.75	*0.151*
RT 78 Gy	-0.026		75.8	-4.16	
RT 70 Gy	-0.020		79.7	-3.27	
RT 60 Gy	0.011		82.2	-2.97	
RT 36 Gy	-0.024	*0.395*	79.2	-4.36	*0.899*
+ ADT	-0.014		77.8	-4.43	
- ADT	-0.037	*0.612*	83.2	-0.41	*0.050*

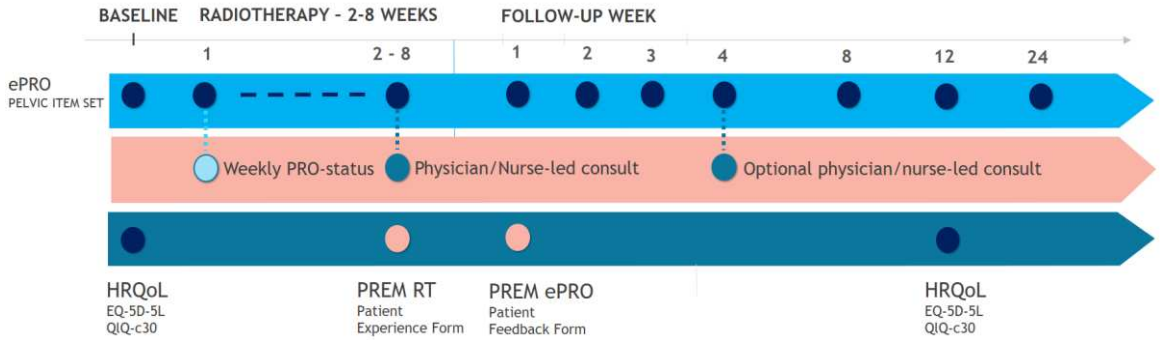

Figure 1. Study design of the PRO-MR-RT study

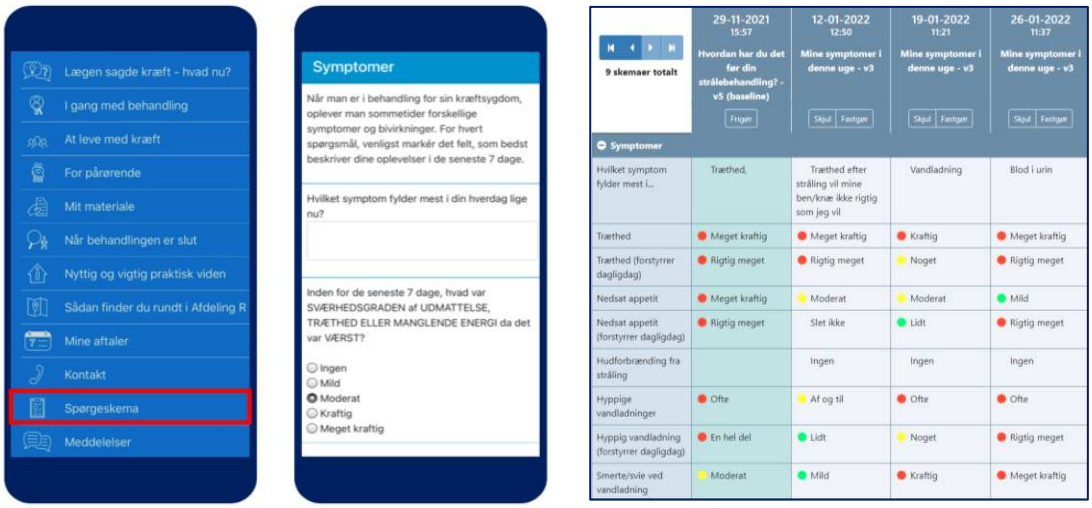

Figure 2. *My Hospital* patient and clinician interface

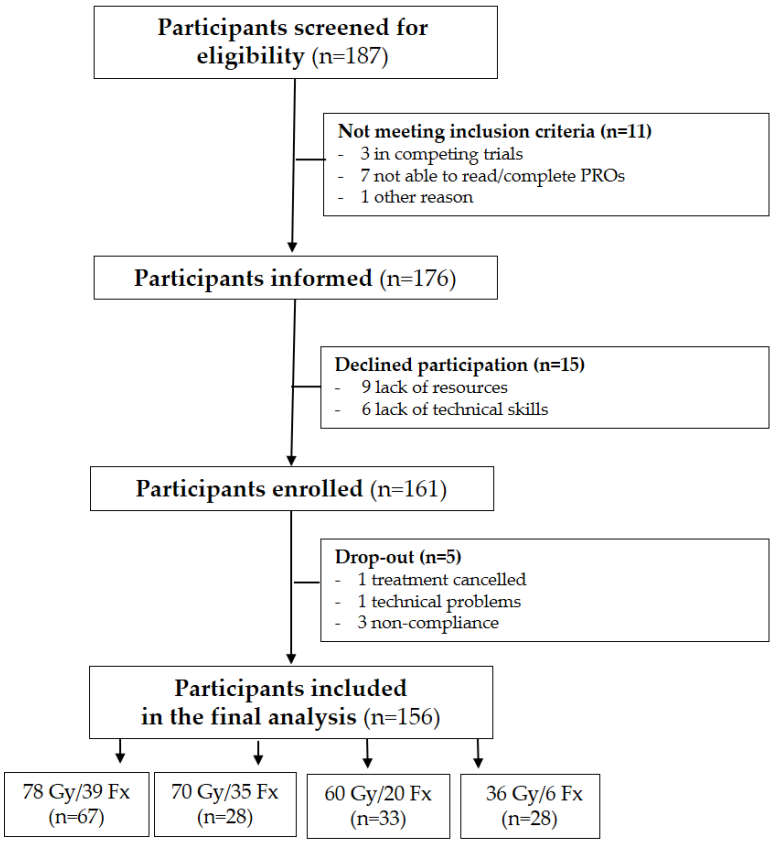

Figure 3. Flowchart of the PRO-MR-RT study (n=156)

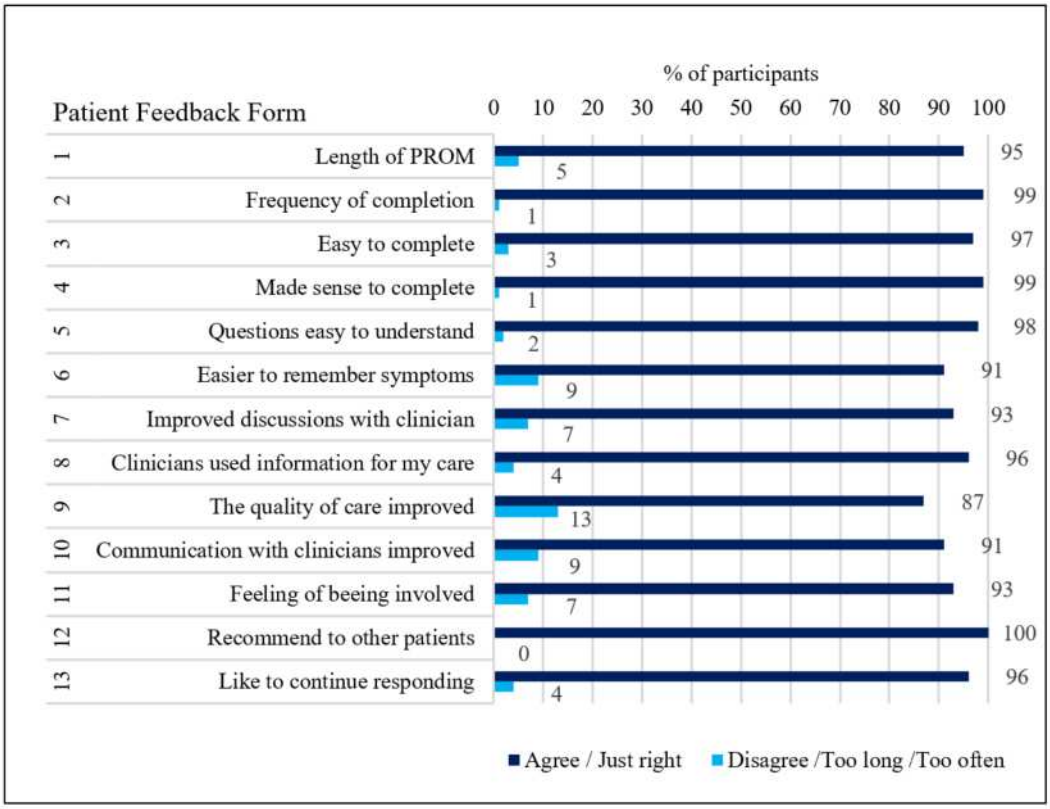

Figure 4. Patient evaluation of ePRO completion and digital symptom monitoring during radiotherapy (n= 153)

APPENDIX E

The PRO pelvic item set
The Patient Feedback Form
The EQ-5D-5L questionnaire

The PRO pelvic item set

PRO-CTCAE symptomatic AE	PRO-CTCAE question	Response option
Decreased appetite	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?	None / Mild / Moderate / Severe / Very Severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?	Not at all / A little bit / Somewhat / Quite a bit / Very Much
Nausea	In the last 7 days, how OFTEN did you have NAUSEA?	Never / Rarely / Occasionally / Frequently / Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?	None / Mild / Moderate / Severe / Very Severe
Constipation	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?	None / Mild / Moderate / Severe / Very Severe
Diarrhea	In the last 7 days, how often did you have LOOSE OR WATERY STOOLS (DIARRHOEA)?	Never / Rarely / Occasionally / Frequently / Almost constantly
Abdominal pain	In the last 7 days, how often did you have PAIN IN THE ABDOMEN (BELLY AREA)?	Never / Rarely / Occasionally / Frequently / Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?	None / Mild / Moderate / Severe / Very Severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?	Not at all / A little bit / Somewhat / Quite a bit / Very Much
Radiation skin reaction	In the last 7 days, what was the SEVERITY of your SKIN BURNS FROM RADIATION at their WORST?	None / Mild / Moderate / Severe / Very Severe
Fatigue	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?	None / Mild / Moderate / Severe / Very Severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?	Not at all / A little bit / Somewhat / Quite a bit / Very Much
Painful urination	In the last 7 days, what was the SEVERITY of YOUR PAIN OR BURNING WITH URINATION at its WORST?	None / Mild / Moderate / Severe / Very Severe
Urinary frequency	In the last 7 days, were there times when you had to URINATE FREQUENTLY?	Never / Rarely / Occasionally / Frequently / Almost constantly
	In the last 7 days, how much did FREQUENT URINATION INTERFERE with your usual or daily activities?	Not at all / A little bit / Somewhat / Quite a bit / Very Much
EORTC symptomatic AE	**EORTC question**	**Response option**
Pain/discomfort around anal opening (rectal pain/discomfort)	During the past week: Have you had pain/discomfort around your anal opening (back passage)?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
Frequent urination at night (nocturia)	During the past week: Have you had to urinate frequently at night?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
Unintentional release (leakage) of	During the past week: Have you had any unintentional release (leakage) of urine?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much

urine (urinary incontinence)		
Difficulty emptying bladder (retention)	During the past week: Have you had difficulty emptying your bladder?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
Urinary urge	During the past week: When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
Bloated feeling in abdomen	During the past week: Have you had a bloated feeling in your abdomen?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
Difficulty controlling bowels	During the past week: Have you had difficulty in controlling your bowels?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
Blood in stools	During the past week: Have you had blood in your stools?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
Vomiting	During the past week: Have you vomited?	1 Not al all / 2 A little / 3 Quite a bit / 4 Very Much
ADDITIONAL ITEMS measured at baseline, 4, 8, 12 and 24 weeks following radiotherapy		
Achieve and maintain erection	In the last 7 days, what was the SEVERITY of your DIFFICULTY GETTING OR KEEPING AN ERECTION at its WORST?	None / Mild / Moderate / Severe / Very Severe / Not secually active / Prefer not to answer
Ejaculation	In the last 7 days, how often did you have EJACULATION PROBLEMS?	Never / Rarely / Occasionally / Frequently / Almost constantly/ Not secually active / Prefer not to answer

PATIENT FEEDBACK FORM **SUBJECT #: _____**

Date: _____

We are interested in your opinion of the questionnaires you have been asked to complete. Please answer all of the questions yourself by circling the number that best applies. There are no "right" or "wrong" answers to the questions. The information that you provide here will remain strictly confidential.

		Too short	Just right	Too long
1.	The amount of time it took me to complete the computerized questionnaire was:	1	2	3

		Not often enough	Just right	Too often
2.	The number of times I was asked to complete the computerized questionnaire was:	1	2	3

		Strongly Agree	Agree	Disagree	Strongly Disagree
3.	The questionnaire was easy to complete.	1	2	3	4
4.	Completing the questionnaire was useful.	1	2	3	4
5.	The questionnaire was easy to understand.	1	2	3	4
6.	Completing the questionnaire made it easier for me to remember my symptoms and side effects when I met with my doctor.	1	2	3	4
7.	Completing the questionnaire improved discussions with my doctor.	1	2	3	4
8.	My doctor used information from the questionnaire for my care.	1	2	3	4
9.	The quality of my care was improved because of the questionnaire.	1	2	3	4
10.	Communication with my doctor was improved because of the questionnaire.	1	2	3	4
11.	Completing the questionnaire made me feel more in control of my own care.	1	2	3	4
12.	I would recommend completing the questionnaire to other patients.	1	2	3	4
13.	I would like to continue responding to the questionnaire in the future.	1	2	3	4

PATIENTTILBAGEMELDING

Patientnr.: _____
Dato: _____

Vi er interesseret i din mening om de elektroniske spørgeskemaer, som du har besvaret. Vi beder dig besvare alle spørgsmålene selv ved at sætte en ring om det tal, som passer bedst. Der er ingen "rigtige" eller "forkerte" svar på spørgsmålene. Dine svar vil blive behandlet fuldt fortroligt.

		For kort	**Passende**	**For lang**
1.	Længden på spørgeskemaet var	1	2	3

		For få	**Passende**	**For mange**
2.	Det antal gange, jeg blev bedt om at besvare spørgeskemaet var	1	2	3

		Meget enig	**Enig**	**Uenig**	**Meget uenig**
3.	Det var nemt at besvare spørgeskemaet	1	2	3	4
4.	Det gav mening at besvare spørgeskemaet	1	2	3	4
5.	Det var nemt at forstå spørgsmålene	1	2	3	4
6.	At besvare spørgeskemaet gjorde det nemmere for mig at huske mine symptomer og bivirkninger, når jeg talte med personalet	1	2	3	4
7.	At besvare spørgeskemaet forbedrede samtalen med personalet	1	2	3	4
8.	Personalet anvendte oplysninger fra spørgeskemaet i forbindelse med min behandling	1	2	3	4
9.	Jeg oplever, at kvaliteten af min behandling blev forbedret, fordi jeg havde besvaret spørgeskemaet	1	2	3	4
10.	Jeg oplever, at kommunikationen med personalet blev forbedret, fordi jeg havde besvaret spørgeskemaet	1	2	3	4
11.	At besvare spørgeskemaet fik mig til at føle, at jeg blev inddraget i min behandling	1	2	3	4
12.	Jeg vil anbefale andre patienter at besvare spørgeskemaet	1	2	3	4
13.	Jeg vil gerne fortsætte med at besvare spørgeskemaet fremover	1	2	3	4

Helbredsspørgeskema

Dansk version for Danmark

(Danish version for Denmark)

Odense Universitetshospital
Onkologisk afdeling R

PRO-MR-RT

Pt. nr. _____
Dato _____
Besøg _____

Under hver overskrift bedes du sætte kryds i DEN kasse, der bedst beskriver dit helbred I DAG.

BEVÆGELIGHED

Jeg har ingen problemer med at gå omkring ❑
Jeg har lidt problemer med at gå omkring ❑
Jeg har moderate problemer med at gå omkring ❑
Jeg har store problemer med at gå omkring ❑
Jeg kan ikke gå omkring ❑

PERSONLIG PLEJE

Jeg har ingen problemer med at vaske mig eller klæde mig på ❑
Jeg har lidt problemer med at vaske mig eller klæde mig på ❑
Jeg har moderate problemer med at vaske mig eller klæde mig på ❑
Jeg har store problemer med at vaske mig eller klæde mig på ❑
Jeg kan ikke vaske mig eller klæde mig på ❑

SÆDVANLIGE AKTIVITETER *(fx. arbejde, studie, husarbejde, familie- eller fritidsaktiviteter)*

Jeg har ingen problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg har lidt problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg har moderate problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg har store problemer med at udføre mine sædvanlige aktiviteter ❑
Jeg kan ikke udføre mine sædvanlige aktiviteter ❑

SMERTER / UBEHAG

Jeg har ingen smerter eller ubehag ❑
Jeg har lidt smerter eller ubehag ❑
Jeg har moderate smerter eller ubehag ❑
Jeg har stærke smerter eller ubehag ❑
Jeg har ekstreme smerter eller ubehag ❑

ANGST / DEPRESSION

Jeg er ikke ængstelig eller deprimeret ❑
Jeg er lidt ængstelig eller deprimeret ❑
Jeg er moderat ængstelig eller deprimeret ❑
Jeg er meget ængstelig eller deprimeret ❑
Jeg er ekstremt ængstelig eller deprimeret ❑

- Vi vil gerne vide, hvor godt eller dårligt dit helbred er I DAG.
- Denne skala er nummereret fra 0 til 100.
- 100 svarer til det bedste helbred, du kan forestille dig.
  0 svarer til det dårligste helbred, du kan forestille dig.
- Sæt et X på det sted på skalaen, der viser, hvordan dit helbred er I DAG.
- Skriv derefter det tal, du har markeret på skalaen, ind i boksen nedenunder.

DIT HELBRED I DAG = ☐