A Reminder App to Optimize Bladder Filling during a Course of Radiotherapy for Prostate Cancer: Protocol of the Prospective REFILL-PAC Trial

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Abstract

Background: Many patients with non-metastatic prostate cancer receive radiotherapy, which may be associated with acute cystitis, particularly if the volume of the urinary bladder is small. Three studies showed bladder volumes <200 ml or <180 ml to be associated with increased urinary toxicity. Therefore, it appears important to achieve bladder volumes >200 ml at as many radiation fractions as possible. Several studies investigated drinking protocols, where patients were asked to drink a certain amount of water prior to radiotherapy sessions. This may require considerable discipline from the mainly elderly patients. Adherence to a drinking protocol may be facilitated by a mobile application (app) that reminds the patients prior to each radiation session to drink water. Our present study investigates the effect of such an app on the filling status of the bladder in prostate cancer patients receiving external beam radiotherapy alone (EBRT).

Objective: The main goal of this study is to evaluate the impact of an app, which reminds patients irradiated for prostate cancer to drink 300 ml of water prior to each radiotherapy session, on the number of fractions with bladder volumes <200 ml during the radiotherapy course.

Methods: This phase 2 study is ongoing and requires recruitment of 28 patients treated with EBRT alone for non-metastatic prostate cancer. Radiotherapy will be administered using normo-fractionation with 70-80 Gy in 35-40 fractions of 2.0 Gy, preferably with volumetric-modulated arc therapy (VMAT). Treatment volumes include the prostate with or without the seminal vesicles. A newly developed app will remind the patients to drink 300 ml of water 45 minutes prior to each fraction of radiotherapy. At the end of the radiotherapy course, patients will be asked to complete a questionnaire regarding their satisfaction with the app. In case of a dissatisfaction rate >40%, the app will be considered not useful. Patients will also be asked about the impact of the app on the general use of health technology. In addition, the phase 2 cohort will be matched and compared to a historical control group not supported by an app. The control group is considered appropriate for the comparison, since all patients were treated very recently (in 2022 or 2023) with EBRT alone.

Results: This trial is the first study that evaluates the impact of a reminder app on the number of radiotherapy fractions with bladder volumes <200 ml in patients irradiated for localized prostate cancer.

Conclusions: This study will help identify the potential benefit of a reminder app on the bladder filling status of prostate cancer patients during a course of radiotherapy. Clinical Trial: Clinicaltrials.gov NCT06653751;

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Abstract

Background: Many patients with non-metastatic prostate cancer receive radiotherapy, which may be associated with acute cystitis, particularly if the volume of the urinary bladder is small. Three studies showed bladder volumes <200 ml or <180 ml to be associated with increased urinary toxicity. Therefore, it appears important to achieve bladder volumes >200 ml at as many radiation fractions as possible. Several studies investigated drinking protocols, where patients were asked to drink a certain amount of water prior to radiotherapy sessions. This may require considerable discipline from the mainly elderly patients. Adherence to a drinking protocol may be facilitated by a mobile application (app) that reminds the patients prior to each radiation session to drink water. Our present study investigates the effect of such an app on the filling status of the bladder in prostate cancer patients receiving external beam radiotherapy alone (EBRT).

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Trial registration: Clinicaltrials.gov NCT06653751; https://clinicaltrials.gov/show/NCT06653751

Keywords: Prostate cancer, external beam radiation therapy, radiation toxicity, mobile application.

Introduction

Prostate cancer is one of the most common solid malignancies worldwide [1]. Most patients with non-metastatic disease receive either prostatectomy or radiotherapy. Radiotherapy is often performed with normo-fractionated (5 × 2.0 Gy per week) external beam radiotherapy (EBRT) alone or EBRT plus a high-dose rate (HDR) brachytherapy boost [2]. In case of normo-fractionated EBRT alone, the recommended total dose is 74-80 Gy corresponding to 37-40 fractions of 2.0 Gy [2]. Radiotherapy of prostate cancer may be associated with significant acute urinary toxicity such as cystitis, particularly if the volume of the urinary bladder is small. Three studies showed that bladder volumes <200 ml or <180 ml, respectively, were associated with increased acute or late urinary toxicity [3-5]. In another study, a planned bladder volume >200 ml was associated with reduced intra-fraction motion of the prostate [6]. Therefore, it appears important to achieve bladder volumes >200 ml at as many radiation fractions as possible. In a very recent study of our group that investigated the bladder volumes at each of the first 35 radiation fractions in 72 patients receiving EBRT alone, the mean and median numbers of radiation fractions with bladder volumes <200 ml were 17.8 and 16.5, respectively, being significantly higher in patients with pre-radiotherapy bladder volumes <200 ml [7]. Several studies investigated the role of drinking protocols [5, 6, 8-17]. Patients were asked to drink a certain amount of water prior to the planning computed tomography (CT-simulation) and the radiotherapy sessions. However, intake of water at a predefined time can be stressful for the mainly elderly or very elderly patients. These considerations led to the idea of developing a mobile application (app) that reminds the patients prior to each radiation session to drink a certain amount of water. This prospective study investigates the impact of such an app on the number of radiation fractions with bladder volumes <200 ml.

Methods

Objectives and endpoints

The main goal of this prospective study is to evaluate the impact of a reminder app on the number of fractions with bladder volumes <200 ml during the course of radiotherapy in patients irradiated for prostate cancer. The app reminds the patients to drink 300 ml of water 45 minutes prior to each radiotherapy session.

The primary endpoint is the number of radiation fractions with bladder volumes <200 ml

after 35 fractions of radiotherapy. In addition, the following endpoints will be evaluated: Number of radiation fractions with bladder volumes <200 ml at the end of radiotherapy, patient satisfaction with the reminder app, and the impact of the reminder app on the use of health technology.

Trial design and duration

This is a single-arm prospective study, which will investigate the effect of a reminder app on the number of radiation fractions with bladder volumes <200 ml during a course of radiotherapy for definitive treatment of prostate cancer in comparison to a historical control group [7]. The control group is considered appropriate for the comparison to the cohort of the present study, since these patients were treated very recently (in 2022 or 2023) with external beam radiotherapy alone in three of the five centres participating in the present study and received a Cone Beam Computed Tomography (CBCT) prior to each radiation fraction, which allowed assessment of the bladder volume as precisely as in the present study. To ensure comparability of total number of fractions administered in the prospective study with those in the historical control group, the primary endpoint is restricted to the first 35 fractions administered. The recruitment of all 28 patients is planned to be completed within 20 months. The follow-up period will end directly after the radiotherapy course, which is scheduled to take 7 to 8 weeks. This equals a total running time for the study of 22 months. In accordance with the previous study assessing the number of radiation fractions with bladder volumes <200 ml during a course of radiotherapy for definitive treatment of prostate cancer, the following characteristics will be recorded to allow adequate comparison with the historical control group: Initial (pre-radiotherapy) bladder volume, body-mass index (BMI), age, prostate volume prior to radiotherapy, Karnofsky performance score, risk group of prostate cancer, and antihormonal therapy [7].

Patient selection

This trial will be performed in prostate cancer patients receiving definitive normo-fractionated radiotherapy. Patients must be adequately informed about their diagnosis and about the nature, significance and scope of the trial. Patients may only be included after completing pre-therapy clarification, on fulfilment of all inclusion criteria, and on non-fulfilment of all exclusion criteria (see Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria	1. Histologically proven prostate cancer 1. Indication for definitive normo-fractionated radiotherapy 2. Possession of and ability to use a smartphone 3. Bladder volume at CT-simulation <200 ml 4. Male gender 5. Age ≥18 years 6. Written informed consent 7. Capacity of the patient to contract
Exclusion criteria	2. Radiotherapy of pelvic lymph nodes 3. Expected non-compliance

Treatment

Radiotherapy

In all patients, radiotherapy will be administered using normo-fractionation with 70-80 Gy in 35-40 fractions of 2.0 Gy given on 5 days per week (overall treatment time = 7-8 weeks), preferably with volumetric-modulated arc therapy (VMAT) [2]. Treatment volumes include the prostate with or without the seminal vesicles.

Radiotherapy of prostate cancer may be associated with acute side effects including dermatitis, cystitis, proctitis, diarrhea, and fatigue. In case of a grade 3 toxicity according to CTCAE 5.0, radiotherapy may be delayed for a maximum of 7 days without consequences [18]. If it is delayed for more than 7 days, participation in the study will be terminated, and the coordinating investigator of the trial must be informed.

Concomitant Systemic Treatment

Patients may receive concurrent systemic agents as part of their anticancer treatment, regardless of the participation in this trial [2]. These agents will be indicated and prescribed by treating medical oncologists or urologists outside this trial. Regarding dose, type and duration of systemic treatment, contraindications, side effects, and pharmacological characteristics and details, please see the corresponding product information.

Examinations

The following parameters will be recorded prior to the start of radiotherapy: Medical history including micturition disorders, medication including anticancer treatment, physical examination, age, body height and weight, Karnofsky performance score, pre-radiotherapy bladder volume, pre-radiotherapy prostate volume, tumour stage, histology, Gleason score, prostate specific antigen, risk group, planned radiation dose and dose per fraction, number of fractions, radiation boost, treatment volume, radiation technique, experience with smart phones, need for support regarding the use of the reminder app. Throughout the course of the trial, the bladder volume will be assessed by staff members prior to the radiotherapy course (based on CT-simulation) and prior to each radiation fraction using a Cone-Beam Computed Tomography. Adverse events will be assessed on an ongoing basis according to CTCAE v5.0 [18]. At the end of the radiotherapy course, the patients will be asked to complete a questionnaire regarding their satisfaction with the reminder app and the impact of its use on the patient's attitude towards health technology.

Safety management

An adverse event is any event experienced by a patient or subject of a clinical trial, which does not necessarily have a causal relationship to treatment. An adverse event (AE) can therefore be any adverse or inadvertent occurrence (including notable laboratory findings), symptom or illness that occurs in the treatment period, no matter whether there is a causal relationship or not. Existing illnesses that deteriorate during the trial should be reported as adverse events. They may lead to serious adverse events if they fulfil the criteria below. Events covered by the documentation for concomitant diseases and radiation-related acute toxicities Grade ≤2 do not have to be additionally documented as adverse events. Serious adverse events are those which fulfil one of the following criteria at any dose level: Lethal, life-threatening, requiring hospitalization or extent of a hospital stay, permanent or significant disability, birth defects or malformations, any medically significant event or any event necessitating surgery to prevent one of the abovementioned concomitant

illnesses. Hospitalization should be defined as such that it was necessary in order to treat the adverse event. Hospital stays as part of the treatment outlined in the protocol or as a result of a planned, elective operation are not classified as serious adverse events. Likewise, an elective hospitalization to facilitate the trial process does not count as a serious adverse event.

Sample size calculation

The primary goal of this study is to assess the impact of an app that reminds patients irradiated for prostate cancer to drink water prior to each radiotherapy session on the number of fractions with bladder volumes <200 ml during the radiotherapy course and to demonstrate that this number is lower than without using an app (historical control group). To allow for a skewed distribution of the primary endpoint, the Wilcoxon-Mann-Whitney test will be applied for confirmatory statistical analysis. Sample size calculation is based on the article of Noether [19]. In the external historical control group consisting of 35 patients, the mean number of radiation fractions with bladder volumes <200 ml was 26.7 (SD 8.5), and the median number was 30 fractions (IQR 22-34). A decrease of this mean value by roughly 30% (to 18.7 fractions) is considered clinically relevant. For illustrative purposes, translating this decrease into a non-parametric effect size framework (assuming for simplicity normal distribution) leads to a probability of roughly 0.25 that the number of fractions <200 ml with the reminder app is larger than without the app. Based on this effect size, a sample size of 25 patients in the prospective trial is required for the comparison with the historical control group to ensure 90% power to reach statistical significance with a two-sided Wilcoxon Mann-Whitney-U-test and a 5% significance level. Assuming that roughly 10% of the enrolled patients will not be eligible for the primary analysis, since they received less than 35 fractions, a total number of 28 patients should be enrolled.

Statistical analyses

General Considerations

All data recorded in the case report forms describing the study population, efficacy, safety, and quality of life will be analyzed descriptively. Categorical data will be presented in contingency tables with frequencies and percentages and 95% confidence intervals. Continuous data will be summarized with at least the following: frequency (n), median, quartiles, mean, standard deviation (standard error), minimum and maximum. Number of subjects with protocol deviations during the study and listings describing the deviations will be provided.

Chi-square tests will be used to compare percentages in a two-by-two contingency table, replaced by Fisher´s exact test if the expected frequency in at least one cell of the associated table is less than five. Stratified two-by-two contingency tables will be analyzed using Cochran-Mantel-Haenszel tests. Logistic regression models serve as multivariable methods for binary endpoint data. Comparison of ordinal variables between treatment arms will be performed using the asymptotic Wilcoxon-Mann-Whitney test, replaced by its exact version in case of ordinal categories with small number of categories and/or sparse data within categories. Any shift in location of quantitative variables between study groups will be performed with the Wilcoxon-Mann-Whitney tests. All patients who have started the radiotherapy and provide data on the primary endpoint will be analyzed (Full Analysis Set). The data analysis will be performed according to the statistical analysis plan (SAP), and which will be finalized prior to database lock and any statistical analysis.

Primary Endpoint

The primary study endpoint is defined as the number of radiation fractions with bladder volumes <200 ml after 35 fractions of radiotherapy. Descriptive measures of location and dispersion will be used to describe the results of the prospective study. The impact of patient characteristics on the primary endpoint will be assessed by means of Wilcoxon-two sample tests. These characteristics include age (<75 vs. ≥75 years), Karnofsky performance score (70-80 vs. 90-100), body-mass index (<30 vs. ≥30=obesity), prostate volume prior to radiotherapy (<60 vs. ≥60 mL), risk group of prostate cancer (low to intermediate vs. high), and antihormonal therapy prior to and/or during the course of radiotherapy (no vs. yes). For confirmatory analysis, the prospective study will be compared with the historical control group by means of a two-sided Wilcoxon-Mann-Whitney two sample test and significance level of 5%. A high degree of comparability of patient population is expected between the prospective trial data and the retrospective patient data set. However, potential heterogeneity of study populations will be identified by comparing the patient characteristics listed above with Wilcoxon-Mann-Whitney tests. Homogeneity is assumed if all resulting p-values are above 20%. Any factor indicating a tendency towards heterogeneity (i.e. $p<0.20$) will be included in a multivariable count data Poisson regression model with the number of radiation fractions with bladder volumes < 200 ml as dependent variable and including the respective factors and the binary factor (prospective study vs historical control) as independent variables. In case of evidence of overdispersion the Poisson model will be replaced by a negative binomial model.

Secondary Endpoints

In addition, secondary endpoints will be subjected to statistical analysis. Since no comparison with historical data is possible, these analyses focus on descriptive statistical analysis only. Results of patient satisfaction will be used to decide whether the app needs modification. In case of a dissatisfaction rate >20%, it needs modifications. In case of a dissatisfaction rate >40%, it will be considered not useful.

Ethical and legal principles

The examinations to be carried out as part of this trial are all considered standard procedures. There are no additional laboratory investigations or X-rays to be done, or any other examinations that could be potentially burdensome for the patient. The trial protocol was approved by responsible the ethics committee, and the trial has been registered at clinicaltrials.gov. Prior to inclusion in the trial, each patient will be fully informed about the content and procedure of the trial. If the potential trial patient has received the necessary information and if the investigator is sure that the patient has understood this information, the patient will be asked to give his consent by signature. The patient will receive a copy of the patient information and the signed informed consent form. The investigator must also inform the patient that he has the right to withdraw consent to participate in the trial at any time and without having to give any reasons. Patients must be informed that the data collected as part of the trial will be documented anonymously and will then be forwarded for scientific evaluation. The trial will be conducted in accordance with the principles laid out in the Declaration of Helsinki. Data will be collected in accordance with the regulations set out in the Data Protection Act. All findings from the clinical trial will be stored on electronic data storage devices and treated with utmost confidentiality. Organization measures have been taken in order to prevent the data from being communicated to unauthorized persons. Patients will only be identified via their individual patient numbers throughout the entire documentation and evaluation phase and their names or any information which would make

the patient identifiable will not be used. For personal activation of the App for each study participant, Nextlabel OHG will receive the participant's e-mail address. To ensure the protection of the participant's e-mail address, a contract has been concluded between the Sponsor (University Medical Center Schleswig-Holstein, UKSH) and Nextlabel OHG. The contract includes an approved data protection concept. Nextlabel will have access to no patient data that are not pseudonymized. Amendments to the study protocol may only be implemented if again approved by the responsible ethics committee. Only the coordinating principal investigator may carry out such changes. However, all co-investigators should contact the coordinating principal investigator if modifications seem to be necessary. In case of changes to the study protocol, all investigators will be informed after ethics committee approval and the notice has to be confirmed.

Data management and monitoring

Data management

All data relating to patients will be recorded in a pseudonymous way. Each patient will be identifiable only by the unique patient number, date of birth and gender. A patient identification list will only be kept in the relevant trial centers and will not be forwarded to the sponsor. Data collection will be done using the study-specific data documentation forms that must be filled in using a ballpoint pen. Do not use fountain pens or pencils. Corrections must be made as follows: Cross the error out once with a straight line, enter the correct information next to it and note the date and/or reason for correction. Comments must be made if data fields cannot be filled in because of missing information. The forms should be filled in as soon as possible and submitted to the checker for review, signed, dated, and forwarded to the study management.

Storage of trial documents

The originals of all key trial documents, including the documentation sheets, will be kept at the trial headquarters (i.e. the sponsor responsible for the trial) for a minimum of 10 years after the final report.

The principal investigator/head of the trial center will keep all administrative documents (written correspondence with the ethics committee, regulatory authorities, trial management, trial headquarters), the patient identification list, the signed informed consent forms, copies of the documentation sheets and the general trial documentation (protocol, amendments) for the abovementioned period. Original patient data must also be kept for the length of time stipulated for the trial centers, but not for less than 10 years.

Monitoring

Clinical on-site monitoring at the German sites will be conducted according to GCP and written standard operating procedures (SOPs) to ensure the patients' rights and safety as well as the reliability of trial results. For initiation, trial sites will be visited on-site by a clinical research associate. During the trial, sites will be visited at regular intervals depending on the rate of recruiting and data quality. Informed consent and defined key data will be checked of all patients. Medical files will be screened for adverse and serious adverse events. Patients' questionnaires will be checked for existence. According to SOPs, all trial specific monitoring activities will be defined before starting the trial and documented in writing (monitoring manual). The sites in other countries will be monitored according to the corresponding national regulations in their own responsibility. No regular audits are planned. However, to ensure correct execution of the study, audits may be conducted if necessary. As the current study is not linked to the German pharmaceutical or medicinal product act, no inspections of higher federal authorities are scheduled.

Dissemination of Results and Publication Policy

The coordinating principal investigator will work towards comprehensive internal and external dissemination of project results and knowledge. Coordinating principal investigator, biostatistician and staff members of the center where the study is performed will create a report regardless of regular or abnormal study termination.

The scientific results will be published in an international, peer-reviewed journal. In addition, results are planned to be presented at meetings and symposia. Reports and publications related to the study need to be coordinated with the statistician to avoid misinterpretations. Conclusions need to be statistically secured and approved by the statistician. For publications of any kind the study acronym REFILL-PAC will be used.

Results

Radiotherapy of prostate cancer can lead to significant acute urinary toxicity such as cystitis, particularly if the volume of the urinary bladder is <200 ml [3-5]. In a pre-study of the present trial, we investigated the bladder volumes at each of the first 35 radiation fractions in 72 patients receiving 74-80 Gy of EBRT alone [7]. Mean and median number of radiation fractions with bladder volumes <200 ml were 17.8 (SD, standard deviation = 12.0) and 16.5 (IQR, interquartile range = 7.5 – 29.5) fractions, respectively. Whereas the mean and median number of radiation fraction with bladder volumes <200 ml were only 9.4 (SD = 8.3) and 8.0 (IQR = 2-16), respectively, in the subgroup of 37 patients with pre-radiotherapy bladder volume of ≥200 ml, the mean (26.7, SD = 8.5) and median (30, IQR = 22-34) were significantly higher in the subgroup of 35 patients with pre-radiotherapy bladder volumes <200 ml [8]. Therefore, there is a medical need for improvement especially in the latter subgroup. Since drinking a certain amount of water at a specific time can be difficult for the patients, a mobile app is developed that reminds the patients prior to each radiation session to drink a certain amount of water. The present phase 2 trial investigates the number of radiation fractions with bladder volumes <200 ml in a prospective cohort of patients using this reminder app. In addition, the study evaluates whether the use of the app leads to a significant reduction of the proportion of fractions with bladder volumes <200 ml when compared to a historical control group not supported by an app. As of October 2024, the study is ongoing, and recruitment of patients has not started yet.

Discussion

Radiotherapy of prostate cancer may be associated with significant urinary toxicity such as cystitis, particularly if the volume of the urinary bladder is <200 ml at the time of irradiation [3-5]. In the retrospective study of Pisani *et al.* that included 280 patients treated with EBRT for prostate cancer, bladder filling (volumes <200 ml *vs*. ≥200 ml) was an independent predictor of grade ≥2 acute urinary toxicity [3]. In the prospective study of

Pinkawa *et al*., quality-of life was assessed in 80 patients irradiated for prostate cancer at different points in time [4]. At follow up 6-10 weeks following radiotherapy, pain with urination was reported less frequently by patients with an initial bladder volume of ≥180 ml compared to <180 ml. In another study prospective from Germany, 193 patients received training via a biofeedback mechanism to achieve a bladder volume of 200-300 ml at each radiation session [5]. Results included that reproducible bladder volumes >180 ml were associated with a significant decrease in grade ≥2 acute urinary toxicity. Considering the results of these studies, it becomes clear that the patients should drink a sufficient amount of water each day prior to irradiation in order to achieve a bladder volume of <180 ml or, even better, ≥200 ml. To achieve appropriate bladder filling, protocols asking the patients to drink water prior to CT-simulation and/or each radiation fraction have been investigated [5, 6, 8-17]. In the corresponding studies, the amount of water ranged between 200 and 600 ml and the time interval until CT-simulation or the radiation session between 30 and 60 minutes. Sometimes, bladder volumes during the course of radiotherapy varied considerably. Moreover, adherence to the drinking protocols was not optimal. It may be questioned whether an app reminding the patients prior to each radiation session of the required water intake can improve the adherence to the corresponding drinking protocol. The present phase 2 study investigates the impact of a reminder app on the number of radiation fractions with bladder volumes <200 ml. The hypothesis is that the use of such an app will significantly reduce the number of fractions <200 ml. Therefore, the cohort of the phase 2 study will be matched and compared to a historical control group of patients treated with EBRT alone for localised prostate cancer in 2022 or 2023. Although a proper matching will be performed considering seven patient and tumour related characteristics, the risk of a hidden selection bias cannot be entirely excluded due to the retrospective nature of the data obtained from the control group. Moreover, the fact that patients of the phase 2 cohort must possess a smart phone and be able to use the app may lead to a selection bias. These limitations need to be considered at the time when the results of the comparative part of this study will be available and distributed.

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Authors' contributions

All authors are involved in the Interreg project HeAT and participated in the development of the study protocol. D.R. drafted the article, which was reviewed and finally approved by all other authors.

Conflicts of interest

The authors declare that they have no competing interests related to this study.

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Abbreviations

BMI	Body-Mass Index
CBCT	Cone Beam Computed Tomography
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	External Beam Radiotherapy
GCP	Good Clinical Practice
IQR	Interquartile Range
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOP	Standard Operating Procedure
VMAT	Volumetric-Modulated Arc Therapy