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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
ART	**Adaptive Radiotherapy**
CT	**Computed Tomography**
CTV	**Clinical Target Volume**
DSMB	**Data Safety Monitoring Board**
DVH	**Dose Volume Histogram**
EBRT	**External Beam Radiation Therapy**
GCP	**Good Clinical Practice**
Gy	**Gray**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
OAR	**Organ at risk**
PET	**Positron Emission Tomography**
PSMA	**Prostate-Specific Membrane Antigen**
PTV	**Planning Target Volume**
(S)AE	**(Serious) Adverse Event**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SV	**Seminal Vesicles**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale:

One of the key treatment modalities for prostate cancer is external beam radiation therapy. Considering the relatively low alpha/beta ratio of prostate cancer, increasing the dose per fraction could yield higher tumour control rates with acceptable toxicity in a reduced number of treatment fractions (hypofractionation). Ultrahypofractionation (fraction dose > 5 Gy) has shown promising results for low- and intermediate risk prostate cancer.

Ultrahypofractionation for high-risk prostate cancer however is challenging as the seminal vesicles (SV) are included in the target volume, which is not the case for intermediate and low-risk prostate cancer patient. These SV belong to the male reproduction system and their exact shape and size can differ substantially. The SV are attached bilaterally to the prostate and, similarly to the prostate, their motion is caused by changes in bladder and rectal filling status. However, although the cause of motion is similar for both the prostate and the SV, multiple studies report that the inter- and intra-fraction motion of the SV remain significant and largely uncorrelated to the prostate motion.

Considering the SV must be included in the target volume, the significant SV motion has to be accounted for during treatment. A solution is to use safety margins to extend the clinical target volume (CTV) to the planning target volume (PTV). Due to their substantial inter- and intra-fraction motion, the SV require a relatively large PTV-margin of 8 mm, which causes the bladder and rectum to receive more dose per fraction, which in combination with a higher fraction dose could result in unacceptable genitourinary and gastrointestinal toxicity rates.

This means that to safely introduce ultra-hypofractionation for high-risk prostate cancer patients, strategies to minimize PTV-margins around the SV are required. To account for the inter-fraction motion of the SV, adaptive radiotherapy (ART) in the form of online re-planning could be the solution. Online re-planning is a workflow in which a new treatment plan is generated for each fraction, optimized on the anatomy of the day. ART accounting for the intra-fraction motion of the prostate has been studied well, for example by tracking the intra-prostatic markers with the CyberKnife system. Using the in-room Computed Tomography (CT) scan of our institution’s CyberKnife, it is feasible to combine online re-planning with intra-fraction fiducial tracking.

A few papers have recently been published regarding the feasibility of ultra-hypofractionation when including the SV in the target volume, using different methods than we are proposing here. And while they showed feasibility in principle, the overall conclusions were that further research is needed.

To summarize, this study aims to make a first step towards ultra-hypofractionation for high-risk prostate cancer by proving the technical feasibility of margin reduction of the SV by combining the intra-fraction fiducial tracking with an online re-planning workflow for each fraction to account for the inter-fraction SV motion.

Objective: to take a first step towards ultrahypofractionation for high-risk prostate cancer by showing the technical feasibility of PTV-margin reduction around the SV using adaptive radiotherapy.

Primary: To assess the feasibility of reducing the PTV-margins around the SV using online adaptive re-planning.

Secondary:

- To assess treatment tolerance using a standardized questionnaire.
- To assess possibilities for further treatment optimisation, regarding organs at risk dose, for patients without clinical or radiological SV involvement

Study design: Non-randomized single arm prospective phase II Study.

Study population: Patients (n=61) with histologically proven prostate cancer with radiologically proven limited metastatic disease, referred to the Erasmus MC, after multidisciplinary consensus, for local radiotherapy treatment, similar to the STAMPEDE trial.

Intervention (if applicable): Patients will be treated according to current clinical practice and following the procedures and protocols derived from the STAMPEDE trial. Six weekly fractions of 6 Gy will be given and before and after each fraction a CT-scan will be made.

The target volume will be defined according to our standard current practice, i.e. the whole prostate and the basis of or the whole SV. For these patients a treatment plan will be generated using the pre-fraction CT-scan and online re-planning to account for differences in daily anatomy, hence justifying treatment with reduced SV PTV-margins. By means of a post-fraction CT-scan dose volume histograms (DVH) parameters will be extracted to estimate the achieved intra-fraction coverage of the SV.

In patients without SV involvement on imaging and no clinical need for including the SV, the SV will be excluded from the target volume. This group of patients will receive an un-adapted treatment plan based on the original planning CT. A pre- and post-treatment CT scan will be made, to simulate offline SV target coverage and gather data for potential Organ at risk (OAR) sparing.

Main study parameters/endpoints: *Main endpoint*: Percentage of patients for which in 0 or 1 fraction out 6 fractions the SV were underdosed. Underdosage being defined as 95% of the volume of SV receiving < 95% of prescribed dose. In the case of unavoidable underdosage of the target on the reference plan, coverage below the achieved coverage in the reference plan will be seen as an underdosed fraction. The margin reduction of the SV is considered feasible

when ≥90% of patients received successful treatments. *Secondary endpoints*: Quantify and assess toxicity using questionnaires. Quantify and assess target coverage and OAR dose when only the prostate is targeted.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The additional burden for the patients consists of a longer treatment fraction duration and filling out questionnaires at regular intervals. The additional risks associated with partaking in this study are, firstly, the added radiation dose associated with the extra CT-scans at the start and end of each fraction (175mGy). Secondly, the possible underdosage of the target volume in the SV. However, considering the SV were not included in the target volume for the STAMPEDE trial, the effect of this underdosage on the efficacy of the treatment is expected to be minimal. The benefits are (1) a significant reduction from 20 to 6 treatment fractions, and thus fewer hospital appointments for a palliative group of patients. (2) A smaller margin for prostate and SV, which we expect to correspond to less toxicity.

1. INTRODUCTION AND RATIONALE

Prostate cancer is shown to be the second most diagnosed cancer and sixth highest cause of cancer-related death in men worldwide in 2018 [1]. One of the key treatment modalities for prostate cancer is external beam radiation therapy (EBRT) [2]. Considering the relatively low alpha/beta ratio of prostate cancer [3, 4], increasing the dose per fraction, could yield higher tumour control rates with acceptable toxicity in a reduced number of treatment fractions (hypofractionation) [5]. Multiple randomized trials on low- and favourable intermediate risk prostate cancer reported a non-inferiority of moderate hypofractionation [6, 7] and ultra-hypofractionation [8] compared to conventional fractionation schemes. For unfavourable intermediate and high-risk Prostate cancer patients, large randomized trials using moderate hypofractionation have shown non-superiority [9, 10].

A next logical step would be to introduce ultra-hypofractionation (fraction dose > 5 Gy) for high-risk prostate cancer patients to possibly improve outcomes and/or reduce the number of hospital visits. This ultra-hypofractionation for these patients however is challenging as the seminal vesicles (SV) are included in the target volume [11] as opposed to the previously mentioned favourable and low-risk Prostate cancer patients where the SV are not included in the target volume.

Regarding the SV, they belong to the male reproduction system and are about 3-5 cm long and 1 cm in diameter [12], however their exact shape and size can differ substantially. The SV are attached bilaterally to the prostate on the cranioposterior side and they lie superior to the rectum, inferior to the fundus of the bladder and posterior to the prostate [12]. The motion of the SV, similarly to the prostate, is caused by changes in bladder and rectal filling status. However, although the cause of motion is similar for both the prostate and the SV, multiple studies report that the inter- and intra-fraction motion of the SV remain significant and largely uncorrelated to the prostate motion [13-23].

Considering the SV must be included in the target volume, the significant SV motion has to be accounted for during treatment. A widely used solution to account for these motions and, lesser so, for other treatment uncertainties, is to use safety margins to extend the clinical target volume (CTV) to the planning target volume (PTV) and thereby insuring that the planned dose is actually delivered to the target [24]. Due to their substantial inter- and intra-fraction motion, the SV require a relatively large PTV-margin of 8 mm [25-28], which causes the bladder and rectum to be, partially, inside the PTV. Which means that the higher the margin, the more dose the rectum and bladder will receive [29], which in combination with a higher fraction dose could result in unacceptable genitourinary and gastrointestinal toxicity rates.

This means that to safely introduce ultra-hypofractionation for high-risk prostate cancer patients, strategies to minimize PTV-margins around the SV are required, as a reduction in PTV-margin should lower the probability of developing genitourinary or gastrointestinal side-effects [30]. As mentioned, these margins mainly correct for the inter- and intra-fraction motion of the SV and prostate [24]. When trying to account for these motions, adaptive radiotherapy (ART) could be the solution. ART has been described as being a closed-loop treatment process in which systematically monitoring treatment variations and incorporating the findings leads to re-optimization of the treatment plan during treatment and thereby improving the treatment [31].

When looking at the inter-fraction motion of the SV specifically, ART could provide a solution. ART for prostate has been extensively studied and reported [32-38]. Fuelled by the developments around MR linear accelerators (Linacs), recent publications on ART for prostate cancer focused on online re-planning [39, 40]. Online re-planning is a workflow in which a new treatment plan is generated for each fraction, optimized on the anatomy of the day [40]. However, ART for SV is a relatively new topic.

ART accounting for the intra-fraction motion of the prostate has been studied as well [39, 41-43], for example by tracking the intra-prostatic markers with the CyberKnife system. This has been studied previously for localized prostate cancers with excellent results [42]. This led to the current clinical application of the CyberKnife system in our institution, which is to treat low-risk prostate cancer patients (without SV in target volume), using 3 mm PTV-margins around the prostate. These relatively small margins are made possible by the intra-fraction tracking of the intra-prostatic markers.

Using the in-room CT-scan of our institution's CyberKnife, it is feasible to combine online re-planning with intra-fraction fiducial tracking. This has been shown in dummy runs by our department for pancreatic cancer and abdominal lymph node metastasis already.

A few papers have recently been published regarding the feasibility of ultra-hypofractionation when including the SV in the target volume, using different methods than we are proposing here. Using an MR-Linac, 5 fractions of 7 Gy has shown excellent tolerability in the 21 patients with SV in the target volume. The data on technical feasibility of the adaptive radiotherapy approach used were promising as well, however they conclude that more data is warranted [44]. Similarly, using an IMRT-approach ultra-hypofractionation (5 x 7 Gy) was shown to be well tolerated in patients with node-positive Prostate cancer and SV involvement. Relatively small margins were used (5mm) in this study and they also concluded that prospective validation of these retrospective results are necessary [45].

To summarize, this study aims to make a first step towards ultra-hypofractionation for high-risk prostate cancer by proving the technical feasibility of margin reduction of the SV by combining the intra-fraction fiducial tracking with an online re-planning workflow for each fraction to account for the inter-fraction SV motion.

2. OBJECTIVES

Primary Objective:

- To assess the feasibility of reducing the PTV-margins around the SV without compromising coverage using an online re-planning approach

Secondary Objective(s):

- To measure Genitourinary and Gastrointestinal toxicity rates
- To assess possibilities for further treatment optimisation, regarding organs at risk dose, for patients without clinical or radiological SV involvement

3. STUDY DESIGN

This is a single-centre prospective interventional cohort study evaluating the feasibility of margin reduction for the SV in patients with limited metastatic prostate cancer.

Eligible for this study, will be the patients with limited metastasised prostate cancer, who are deemed eligible for local radiotherapy treatment by a multidisciplinary team of specialists. This group of patients are currently treated with a combination of systemic and local treatments, based on the results of the STAMPEDE trial [46]. The STAMPEDE trial has shown that the addition of EBRT on the primary tumour of the prostate to lifelong systemic androgen deprivation therapy leads to improved survival for the subgroup of patients with limited metastatic burden [46]. By a possible reduction in PTV-margins, a reduction in genitourinary and gastrointestinal toxicity rates could be achieved [47]. Furthermore, underdosing the SV likely has little impact on the efficacy of the treatment, as the SV are, in contrast to local clinical practice, not included in the target volume in the STAMPEDE trial [46].

The standard of care for limited metastasised prostate cancer in the Erasmus MC is a combination of systemic and local treatment, in line with the results of the STAMPEDE trial [46]. The systemic treatment consists of lifelong androgen deprivation therapy (ADT). The sole focus of this research is however the local treatment: EBRT. The current clinical workflow is as follows. The CTV consists of the prostate and the entire SV, when the SV show tumour ingrowth on imaging or physical examination. Before the treatment all patients receive 4 fiducial markers, placed in the prostate, and 4 days later a planning CT-scan in treatment position, without contrast, is made. After delineation by a radiation oncologist, a treatment plan is generated in the Monaco treatment planning system. The treatment is delivered on an Elekta Linac in 20 daily fractions of 3 Gy using a fixed PTV-margin around the prostate (5mm) and the SV (8mm). Before each fraction patients are asked to adhere to “full” bladder instructions. Lastly, before each fraction a Cone-Beam CT is made for position verification.

In this study the standard of care regarding the systematic treatment will be upheld. The local treatment, will be delivered on the CyberKnife Linac using a fractionation scheme of 6 weekly fractions of 6 Gy each (according to the fractionation scheme that has been used in the STAMPEDE trial) [46]. At the start of treatment two groups are defined: with (part of the) SV and without the SV in the target volume. For both groups the treatment preparation will be in line with the current clinical practice, including the fiducial placement and the full bladder instructions before the planning CT-scan and before each treatment. A treatment plan based on the planning CT will be generated using margins of 3 mm around the prostate and 5 mm around the (basis of the) SV, in the case of SV being part of the target volume. These PTV-margins are derived from the standard of care protocols in our institution regarding CyberKnife treatment, based on the work of Van de Water et al. [48], and ultrahypofractionated treatment with curative intent, based on the work of De Muinck Keizer et al. [49]. Before each fraction the patient will be aligned to the correct treatment position and receive a non-contrast CT-scan using the in-room CT of the CyberKnife.

At this point the treatment for both groups will start to differ. For the patient group with (part of the) SV in the target volume plan adaptation will be applied (see figure 1). Using artificial intelligence software the contours of the reference plan will be propagated onto the fraction scan after which these contours will be adapted manually where needed by or under

supervision of a radiation oncologist. Based on the CT scan and contours a new treatment plan will be generated and approved by the radiation oncologist. Subsequently, quality assurance of the new plan will be carried out before the start of treatment.

The group without any part of the SV in the target volume receives the un-adapted treatment plan (see figure 2). After treatment we will simulate an adaptive treatment plan offline with the SV in the target to assess intra-fraction target coverage.

Both groups receive a final CT-scan without contrast directly after treatment in treatment position.

During the course of and after the treatment the patient will be asked to fill out a questionnaires regarding the toxicity experienced.

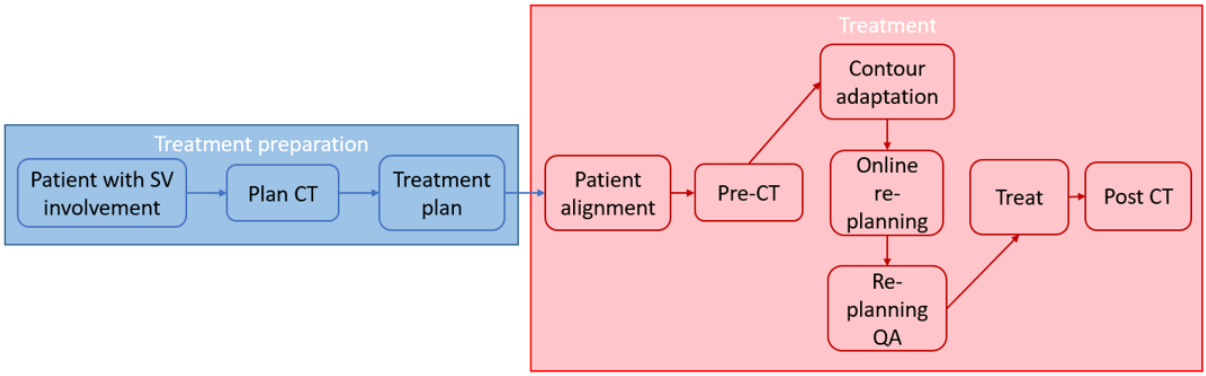

Figure 1: Flowchart for patients with (the base of the) SV in the target volume. Blue steps are done once at the start of treatment, red steps are repeated every fraction. SV = seminal vesicle; CT = Computed Tomography; Plan CT = planning CT-scan; Pre-CT = pre-fraction CT-scan; post CT = Post-fraction CT-scan; QA = quality assurance.

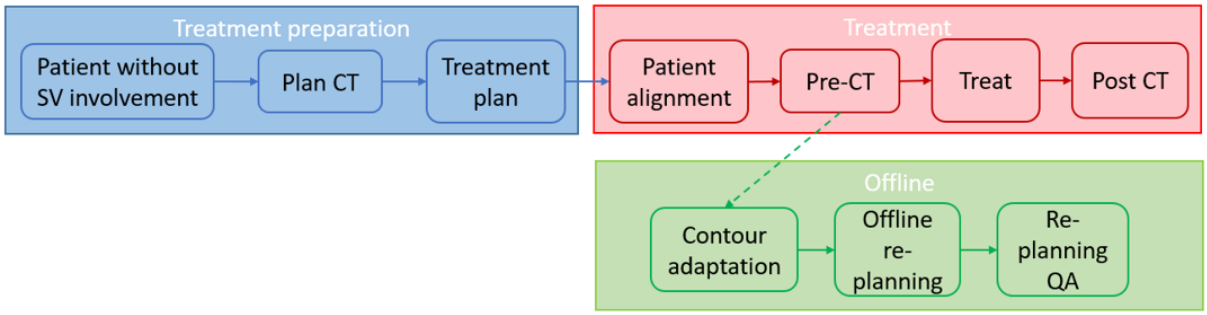

Figure 2: Flowchart for patients without SV in the target volume. Blue steps are done once at the start of treatment, red steps are repeated every fraction, green steps are simulated/offline. CT = Computed Tomography; Plan CT = planning CT-scan; Pre-CT = pre-fraction CT-scan; Post CT = Post-fraction CT-scan; QA = quality

4. STUDY POPULATION

4.1 Population (base)

This study will focus on male patients with recently diagnosed limited metastatic prostate cancer, eligible for local treatment at Erasmus MC. The number of patients per year fitting this criteria is approximately 100. Estimated inclusion rate is around 50 patients per year.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Histologically proven prostate cancer
- Limited metastatic disease as confirmed on Bone scintigraphy or on soft-tissue imaging: CT-scan or by means of a prostate-specific membrane antigen (PSMA) positron emission tomography (PET)-CT scan
- Deemed a candidate for local radiotherapy by a multidisciplinary team of medical specialists.
- Willing to and capable of personally filling out online questionnaire
- Signed written informed consent

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Previous pelvic radiotherapy or surgery for prostate cancer (excluding surgery to improve urinary function in benign prostate hyperplasia, i.e. trans-urethral resection of the prostate or prostatectomy according to Millin or Hryntschak).
- According to current clinical protocols, at discretion of the treating physician, patients can be excluded in case of, for example, an IPSS score of more than 20 or a prostate volume of more than 90ml, expecting an unacceptable rise in toxicity

4.4 Sample size calculation

A patient's treatment will be considered a success if at least 5 out of the 6 planned (online or offline) fractions have sufficient coverage of the SV as defined in section 8.1.1 below. The sample size was calculated for an A'Hern one-stage phase-2 design. The null hypothesis will be that the success probability is 90% (any lower probability would not warrant further investigation of the new margin recipe). If the true probability of success is 98%, then an exact binomial test with a one-sided alpha of 0.05 will have 80% power if the sample size is 61 or more patients. If the sample size is 61 patients (counting only evaluable patients), then the test will reject the null hypothesis if at least 59 successes are observed among the 61 patients. Evaluable in this instance is defined as underwent all 6 fractions with CT-scans before and after.

5. TREATMENT OF SUBJECTS

Not applicable

6. INVESTIGATIONAL PRODUCT

Not applicable

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

Feasibility of margin reduction will be measured using the post-fraction CT-scan. The dose of the online re-planned treatment plan or the offline simulated treatment plan will be copied, based on a fiducial match, to the post-fraction CT-scan after which dose volume histograms will be calculated and relevant DVH parameters will be extracted. For every fraction the coverage of the SV will be calculated, as well as the dose on the OARs. A coverage of ≥95% of the SV volume received 95% of the prescribed dose is accepted, any less will be seen as a failure to reduce margins. Patients for whom 95% coverage cannot be achieved in the reference plan, further coverage loss below the coverage achieved on the reference plan will be seen as a failure. Considering all patients receive 6 fractions of 6 Gy, we will consider margin reduction feasible if at most one out of six fractions is considered underdosed on the SV. To conclude we consider margin reduction to be feasible when >90% of patients have received a successful treatment (i.e. coverage of ≥95% for 5 or 6 out of 6 fractions given).

8.1.2 Secondary study parameters/endpoints (if applicable)

To measure the tolerance of the patients for this treatment, multiple questionnaires (see appendix 1: EPIC, EORTC-Q and EQ5D) will be given to the patients before treatment starts as a baseline. The questionnaire regarding the acute toxicity (EORTC-Q) will then be given in the last week of treatment and on month 1 and 3 after the end of treatment. The questionnaires regarding the late toxicity (EPIC and EQ5D) will be given on 6, 12, 24 and 36 months after end of treatment. These questionnaires will be used, along with information in HiX, to assign toxicity scores (according to the RTOG/EORTC system) to each patient during the treatment.

8.1.3 Other study parameters (if applicable)

Relevant patient and tumour characteristics will be collected form HiX. Patient characteristics include age, start of systematic treatment, ECOG performance status, relevant medical history, etc… Tumour characteristics include TNM-stage, imaging data (images and reports), etc…

8.2 Randomisation, blinding and treatment allocation

Not applicable

8.3 Study procedures

Online re-planning: See chapter 3 for the detailed rundown. The treatment plan aims to achieve a target coverage of 95% of the target volume (SV) to receive 95% of the prescribed dose of 36Gy (34.2Gy). The prescribed dose will be given on the 90% isodoseline, thereby accepting a maximum dose of 40Gy. The OAR constraints used during the planning and re-planning process are in adherence to current clinical standards in our institute as well as the constraints used in the PACE-trial, albeit converted to a 6 fraction-schedule using the linear-quadratic model. These converted constraints will undergo extensive validation during upcoming Dummy-runs to check whether it is feasible to obtain clinically acceptable plans, also in the case of quite extreme daily anatomical differences in especially bladder- and/or rectal filling.
CT-scans: Before and after each fraction a CT-scan without contrast will be made using the in-room CT-scan of our institution's CyberKnife Linac system. This differs from the standard of care in which 1 cone beam CT is made before each fraction.
Questionnaires: All questionnaires will be distributed though the Gemstracker application, which is coordinated by the Outcome Unit. The patient will receive emails to notify the patient that he is asked to fill out an online questionnaire on the moments mentioned in 8.1.2.
Toxicity scores: Acute toxicity scores (according the RTOG system) will be assigned, based on the acute questionnaires and information in Hix. For this purpose, an acute toxicity form will be implemented in Castor. Late toxicity scoring according CTCAE will be included in standard clinical care and extracted from the Gemstracker system for the study patients for research purposes. Late toxicity scoring according RTOG/EORTC will be done retrospectively (in Castor), based on the assigned CTCAE scores, questionnaires, and information in Hix.
Informed consent: Patients participating in this study are asked to sign informed consent before being included in the study population. All patients have received detailed information about this study beforehand through a patient information form (PIF) as well as verbal information. The investigators of this study are at all times willing to answer any remaining questions of the patients. The patient can withdraw consent at any time.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual subjects after withdrawal

Any subject that withdraws form the study will be replaced as to make sure the calculated number of evaluable patients is met.

8.6 Follow-up of subjects withdrawn from treatment

No further follow-up within the scope of this study will be conducted.

8.7 Premature termination of the study

When the treatment of three patients with SV involvement is unsuccessful, the hypothesis cannot be rejected and therefore the study will be put on hold. The data up to that point will be analysed to determine whether an increase of the PTV-margin around the SV, e.g. from 5 mm to 6 mm, would lead to successful treatments. If this does not prove a solution, this study will be terminated prematurely.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the study procedures. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report only SAEs that are related to the study procedures to the sponsor without undue delay after obtaining knowledge of the events.

The sponsor will report the SAEs related to study procedures through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB)

For this study a DSMB will not be installed.

10. STATISTICAL ANALYSIS

10.1 Primary study parameter(s)

The primary endpoint will be, as discussed in Chapter 8.1, the percentage of patients with successful treatments, which will be analysed with an exact one-sided test with significance level alpha of 0.05. If the null hypothesis of 90% can be rejected, the treatment will be considered feasible. This data will be collected using the DVH parameters obtained after copying the adapted treatment plan onto the post-fraction CT-scan and adapting the contours to the anatomy. Patients with missing CT-scans or treatments will not be evaluable and will therefore be removed from the analysis of the primary endpoint and replaced (see Chapter 8).

10.2 Secondary study parameter(s)

The assessment of tolerance will be done using questionnaires and information in HiX to determine toxicity scores (according to RTOG/EORTC) per patient on different time points. The evolution of toxicity scores through time will be visually represented using a graph and depending on the distribution of the data, a student's t-test or a Wilcoxon signed-ranked test will be used to determine statistical significance between time points. Patients with missing data at a time point will be removed from the analysis of that particular time point.

10.3 Other study parameters

Data collection will be done in the electronic patient dossier in HiX. From here all the relevant patient and tumour characteristics are gathered and entered in Castor EDC, in co-operation with the outcome unit. These will be summarized in the form of a table, using means of medians where necessary.

10.4 Interim analysis (if applicable)

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association, 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO) and appropriate other guidelines, regulations and Acts.

11.2 Recruitment and consent

All newly referred prostate cancer patients will be assessed for study eligibility at their first outpatient clinic in Erasmus MC, and eligible patients will be asked to participate by their treating radiation oncologist. Patients will be given one week consideration time. After all questions of the patient are answered satisfactorily by their treating physician, patients will be asked to sign the informed consent form. After obtaining written informed consent, a unique study subject ID number will be assigned by the Datacenter. This unique identifier will be used on the patient questionnaires and in the study database.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

11.4 Benefits and risks assessment, group relatedness

The benefits of participation are twofold. The number of hospital visits decreases significantly from 20 to 6, which should improve patient convenience and hospital logistics. Secondly, the reduction of the PTV-margin from 5 to 3 mm, around the prostate and, for the patient group with (the base of the) SV in the target volume, from 8 to 5 mm around the SV is expected to reduce toxicity rates [47]. Additional burdens for all the patients will be the 6 questionnaires they are asked to fill out. Another burden for the patients, will be the longer on-couch time for each treatment. For the group without SV involvement an on-couch time of 45 min is expected, for the group with involvement the on-couch time is expected to be 60-70 min.

The risks associated with participation are twofold. As mentioned in Chapter 8.3, each patient will receive 1 planning CT-scan, 6 pre- and 6 post-fraction CT-scans (total radiation dose of 311 mGy) instead of 1 planning CT-scan and 20 Cone-beam CT-scans (total radiation dose of 136 mGy). In this study the patients will receive a small amount of extra radiation dose from the imaging required: 175 mGy. See “details on radiation exposure”, enclosed in this submission, for more information on the radiation exposure. Secondly, there is a risk of underdosing the SV for the patients which have SV involvement. However, the effect

underdosing has on the overall efficacy of the treatment is likely negligible, considering the SV were not included in the target volumes in the STAMPEDE trial.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives (if applicable)

Not applicable

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

After checking eligibility criteria and availability of written informed consent, candidate patients may be enrolled in the study after registration at the Datacenter. Each patient will receive a unique study subject ID number from the Datacenter after inclusion in the trial. This unique study subject ID number will be used as identifier for clinical data, lab samples and tissue samples.

In this study clinical data will be collected from the electronic patient dossier HiX to Castor EDC. Computer generated data will be merged with other study data by adding the unique study subject ID number to these datasets, and after validation of the completeness and correctness by the investigator, and secured against accidental loss or changes after merging. All data will be processed according to the General Data Protection Regulation (“Algemene Verordening Gegevensbescherming”) and the General Data Protection Regulation Implementation Act (“Uitvoeringswet Algemene Verordening Gegevensbescherming”).

Essential Documents are those documents that permit evaluation of the conduct of a trial and the quality of the data produced. The essential documents may be subject to, and should be available for, audit and inspection by the regulatory authority. The Sponsor will file all essential documents relevant to the overall conduct of the trial. Essential documents should be filed in such a manner that they are protected from accidental loss and that they can be easily retrieved for review.

Essential documents will be retained for 15 years after the end of the study. Source documents (i.e. medical records) of patients should be retained for at least 15 years after the end of the study.

12.2 Monitoring and Quality Assurance

Based on the guideline by the NFU (Dutch Federation of University Medical Centers) about quality insurance in human research (“Kwaliteitsborging van mensgebonden onderzoek”) we qualify the risk of this study as “low”.

The independent Monitoring Team assigned by the Sponsor will perform on-site monitoring visits to verify that the rights and well-being of patients are protected, the reported trial data are accurate, complete, and verifiable from source documents and the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). Monitoring visits will take place according to the study specific monitoring plan. On-site monitoring includes checking the informed consent procedure, and the verification of completeness of the Trial Master File, conform the study specific monitoring plan. Minor and major findings of the monitor will be discussed with the investigator, and documented in a standard monitoring report that will be provided to the

Sponsor. The Sponsor may decide to increase the monitoring frequency or intensity if the results of monitoring require this to ensure patient safety and/or data quality.

All clinical data that will be collected in the e-CRF will be checked by the principal investigator before they are marked as final.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.
The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Erasmus MC Research Code “guidelines on publishing and authorship” will be applicable. The main results of the trial will be presented in international meetings and medical journals by the principal investigator. Before that moment, the results will be presented to the co-investigators who will have the rights to make their comments. Those who have contributed to the development of the protocol and the conduct of the study can be considered also as co-authors.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

Not applicable.

13.2 Synthesis

Based on the guideline by the NFU (Dutch Federation of University Medical Centres) about quality insurance in human research (“Kwaliteitsborging van mensgebonden onderzoek”) we qualify the risk of this study as ‘low’, meaning it has a small chance of serious damage.

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Appendix A: Acute RTOG scoring

CTCAE version 5.0,
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf

Items	
Gastrointestinal (GI)	*Genitourinary (GU)*
Diarrhea	Cystitis (non-infectious)
Fecal incontinence	Urinary frequency
Proctitis	Urinary incontinence
Gastrointestinal pain	Urinary urgency
Rectal Hemorrhage	Urinary tract obstruction
Rectal Mucositis	Dysuria
	Hematuria

Acute RTOG

Table A1. Acute GI complications according to the RTOG morbidity scale (adaptations with regard to the original RTOG scale in italics)

	Grade 1	Grade 2	Grade 3	Grade 4
GI	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/severe mucous or blood discharge necessitating sanitary pads/ abdominal distension (flat plate radiograph demonstrates distended bowel loops)	Obstruction, fistula, or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
GU	Frequency of urination or nocturia twice pretreatment habit/ dysuria or urgency not requiring medication	Frequency of urination is less frequent than every hour (*day: 12–16 times; nocturia 5–8 times*)/dysuria, urgency, bladder spasm requiring local anaesthetic	Frequency of urination is more frequent than every hour (*day: >16 times; nocturia: >8 times*)/dysuria, bladders spasm, urgency requiring frequent regular narcotic/gross hematuria/ *complaints requiring permanent or suprapubic catheter*	Hematuria requiring transfusion/ obstruction not due to clots/ulceration/necrosis

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