1.1. GenesisCare Prostate Radiotherapy Protocol

Version 3.1

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Person responsible: Clinical Leaders Forum

Approval

Approval Committee	Approval Date	Printed Name	Signature	Effective Date
Safety and Quality	April 2018	Emma Spellman		April 2018

Amendment Record

Version	Date	Actioned By	Description
3.0	May 2017	Louise Pardon	Document reviewed, updated and transferred to new document template
3.1	April 2018	Penny Kechagioglou	Clinical Updates

2. Purpose

This document defines GCUK recommended radiotherapy protocol for the treatment of the prostate gland (+-) seminal vesicles, pelvic lymph nodes and prostate bed.

3. Definitions

- Low/Intermediate risk – T1c T2a-c T3, PSA<15, Gleason ≤7.
- CHHiP Low risk of seminal vesicle involvement T1b/c or T2a/b and with PSA + ((Gleason score -6) x10) <15.
- CHHiP Intermediate/high risk of seminal vesicle involvement.

  Clinical stages T1b/c or T2a/b, and with PSA + ((Gleason score -6) x10) >15
- T2c or T3a. Intermediate Risk, small volume (non CHHiP eligible).
- High Risk T3A, MRI T3b; PSA>20; Gleason 8-10 (any one).
- Prostate Bed Low Risk: Pre-op ROACH formula <15% [PSA + 10(Gleason score –6)].
- High Risk: Pre-op ROACH formula >15% - [PSA + 10(Gleason score – 6)].
- High lymph node risk- positive nodes on histology at prostatectomy Pre-op ROACH LN formula >15% [2/3PSA + 10(Gleason score –6)].
- Palliative prostate radiotherapy

4. Policy - Treatment Considerations

3.1 MR Linac SBRT

Stereotactic MR-guided Adaptive Radiation Therapy for Localized Prostate Cancer (SMART) (Physics and Imaging in Radiation Oncology 9 (2019) 76-79

3.2 CHHiP

A Scripted CHHiP protocol has been produced by GCUK available at the clinician's request which will automate the production of PTVs, planning structures and optimiser objectives. Refer to RT-PRO-233.

3.3 HDR/LDR

A 15Gy single # HDR prostate boost may be delivered in high risk cases (Not currently offered at GCUK) following 46Gy in 23 fractions to the whole pelvis or

3.2.1 A low dose brachytherapy boost delivering 110Gy to the prostate (not currently offered at GCUK) may be delivered in high risk cases (ASCENDE-RT trial ,Journal of Clinical Oncology 2015 33:7_suppl, 3-3), following 46Gy in 23 fractions to the whole pelvis or 36Gy/12# or 37.5/15# to the prostate if nodes –ve.

3.4 Locally advanced PC

Treatment of the prostate/seminal vesicles with or without pelvic lymph nodes as determined by local clinician decision.

3.5 Palliative Prostate Radiotherapy is indicated when radical treatment is inappropriate;
Elderly frail with local symptoms or hormone resistant disease.
Metastatic with local symptoms.

5. Patient Selection

4.1 Consent
As per GenesisCare Policy- RT-POL-003.

4.2 Inclusion Criteria
MDT confirmed diagnosis.

For MR Linac see appendix 1 for details

4.3 Exclusion Criteria
4.4 Re-irradiation should only be undertaken with caution and after appropriate consideration of the previous dose delivered, time since irradiation**Scheduling of Patients**
A 7-day planning pathway is available at GCUK pending clinician availability

Radical cases may start any weekday excluding Friday. Palliative cases can start any day. Refer to RT-SOP-005 for further details.

Refer to RT-POL-136 Clinical Advisory Team (CAT) referral criteria.

6. Patient Positioning and Localisation

Immobilisation Device	Set-Up	Suggested Practice	Localisation	Tattoo/reference mark Location	Bladder/rectal status
Head on scoop & rectangle; arms on chest; Combi-fix	Supine, head to gantry; Hands on chest	Mandatory AP/ Lat Mosaiq set-up photograph (Tattoo location visible. All CT wire removed); Clothing & jewellery removed as necessary	Prostate/Bladder only: L4/5 vertebrae to 3cm inf to ischial tuberosities Primary+Nodes: L1/2 vertebrae to 3cm inf to ischial tuberosities	Anteriorly on m/l at approx. 5cm Sup to BOP (male) or at planner discretion depending on patient size Lt & Rt Lat rotation tattoo's at approx. HATT 10-12cm	Bladder comfortably full Rectum, Empty

7. Pre-treatment Imaging

6.1 A planning MR scan is recommended in addition to the planning CT scan with fusion of the images. Contrast is required when pelvic nodal irradiation is wanted and or at the doctors request.

7. Definition of Target and OAR

7.1 Target Volumes

7.1.1 GTV:

The GTV is the prostate only in the CHHiP protocol.

7.1.2 CTVmrl

The Clinical target Volume for the MR Linac (CTVmrl) are further defined in appendix 1 but reproduced here for easy reference:

Volume and dose prescription are implemented according to the ICRU 83 regulations [Repot 83, 2010]. Target definition is dependent on the risk assessment, in particular to the risk of seminal vesicle invasion. 'Low risk' patients are defined as patients with cT1c-T2a prostate cancer, a Gleason score <7 and a PSA <10 µg/L. 'High risk' patients have cT3-4 prostate cancer, or a Gleason score >7 or a PSA >20 µg/L, and 'intermediate risk' patients are patients not included in the other two groups [EAU guidelines 2013, Heidenreich].

Clinical target volume (CTV) definitions:
The urethral planning organ at risk volume (PRV): urethra plus 3mm; the area of integrated radiation sparing.

For 'low risk' patients: CTV = prostate minus the urethral PRV (see below)
For 'intermediate and high risk' patients: CTV = prostate plus the base of the seminal vesicles (=2cm) plus any visible tumour extension seen on MRI minus the urethral PRV (see below)

7.1.3 CTVp:

Clinical Target Volume (CTVp) defined as prostate gland (+/-) the seminal vesicles.

7.1.4 CTVn:

The CTVn includes the Pelvic nodes below the bifurcation of the common iliac vessels to include the internal lilacs, obturator, presacral and external iliac nodes.

7.1.5 CTVn+:

The CTVn+ includes the clinical or radiological involved lymph nodes to be boosted.

7.1.6 CTV Prostate Bed (Low risk):

The CTV Prostate Bed (Low risk) is defined as***;***

- **Superior border**: Base of seminal vesicle or if removed at estimated position from pre-op scans if available.
- **Inferior border**: 5mm above penile bulb.
- **Anterior border**: Caudal (<2cm above anastomosis) – Posterior border of pubic symphysis. Cranial (>2cm above anastomosis) – Posterior 1/3rd of bladder wall.
- **Below anastomosis**: Posterior third of bladder wall.
- **Posterior border:** Anterior rectal wall.
- **Lateral border**: Medial border obturator internus and levator ani muscles.

7.1.7 CTV Prostate bed (High Risk)

The CTV Prostate bed (High Risk) is defined as per low risk extending superiorly to include tips of seminal vesicles or if absent, estimated position of seminal vesicles from pre-op imaging if available.

7.1.8 CTV Prostate (Palliative):
In palliative cases the CTV is defined as the prostate and any extraprostatic extension.

7.1.9 CTV1 – CHHiP (Low risk):
The CTV1 is prostate and base of seminal vesicles (proximal 2cm) with 5mm margin.

7.1.10 CTV1 – CHHiP (Intermediate/high risk):
CTV1 is the prostate and seminal vesicles with 5mm margin for Group 2.

7.1.11 CTV2 – CHHiP:
CTV2 is the prostate only + 5mm.

7.1.12 CTV3 – CHHiP:
CTV3 is the prostate only.

7.1.13 ITV:
The ITV is not applicable.

7.1.14 PTV Prostate:
The PTV is defined as the CTVp + 7mm uniformly.

Also acceptable: PTV66: CTV66 (Prostate/SV + 10mm)

PTV74: CTV74 (Prostate only + 5mm)

7.1.15 PTVmrl

The PTV for the MR linac (PTVmrl) are further defined in appendix 1 but reproduced here for easy reference:

The combination of MR-guided soft-tissue setup and online MR-imaging during treatment in combination with “gated” treatment (i.e. beam-on only when the target is in the predetermined position) enables the application of small uncertainty margins.

PTV = CTV + 3 mm (in all external directions, i.e. excluding the urethral PRV).

7.1.16 PTV Prostate Bed:
The PTV Prostate bed is defined as the CTV Prostate bed + 10mm uniformly.

(0.7–1.0cm posterior margin depending on rectal area which should be defined on each CT planning slice -LCA guidance).

7.1.17 PTVs1-3 (CHHiP):
PTVs 1-3 Add 5mm to the relevant CTV except for adding a 0mm margin posteriorly or posterior-inferiorly (towards the rectum) for PTV2+3 (with SpaceOAR, a 5mm can be maintained posteriorly and posterior-inferiorly).

Also acceptable: PTV48 (1cm around prostate/SV) and PTV60 (5mm around prostate).

7.1.18 Recommended modifications to margins
Lymph node volumes should follow vessels as defined by contrast CT using asymmetric manual expansions to nodes along tissue planes as defined in table below from Taylor et al Clinical Oncology 2007; 19: 542-550.

Lymph node group	Recommended margins
Common Iliac	7mm margin around vessels; extend posterior and lateral borders to psoas and vertebral body
External Iliac	7-mm margin around vessels; extend anterior border by additional 10-mm anterolaterally along iliopsoas muscle to include lateral external iliac nodes
Obturator	Join external and internal iliac regions with 18-mm-wide strip along pelvic sidewall
Internal Iliac	7-mm margin around vessels; extend lateral borders to pelvic sidewall
Presacral	10-mm strip over anterior sacrum
Also include any visible nodes	

Contouring Atlases available below:

https://www.rtog.org/LinkClick.aspx?fileticket=glmTGKHTmr0%3d&tabid=234 **(LNs)**

https://www.rtog.org/LinkClick.aspx?fileticket=glmTGKHTmr0%3d&tabid=234 **(Postop +ve apex margin)**

https://www.rtog.org/LinkClick.aspx?fileticket=_znZLMP1yco%3d&tabid=232 **(Postop +ve SV)**

7.2 Organs at Risk (OAR)

Organs at risk are to be outlined as per GCUK anatomy atlas RT-MAN-188.

7.2.1 OAR 1- Rectum

The rectum should be outlined from the anus (Usually at the level of the ischial tuberosities or 1cm below the lower margin of the PTV (whichever is more inferior) to the recto-sigmoid junction. The recto-sigmoid junction can usually be identified on the CT slice where the bowel turns anteriorly and laterally. This will give a length of 10-12cm in most cases. Any additional bowel in the volume should be outlined separately.

7.2.2 OAR 2 – Bladder

The whole bladder should be outlined from base to dome.

7.2.3 OAR 3 – Femoral Heads

The femoral heads should be outlined as per RT-MAN-188 Excluding the femoral neck.

7.2.4 OAR 4 – Bowel

The bowel is to be outlined when there is nodal involvement 2cm superior the PTV.

7.2.5 OAR 5 – Penile Bulb

The penile bulb should be contoured using the fused diagnostic MRI to aid recognition.

7.2.6 OAR for the MR Linac are further defined in appendix 1 but reproduced here for reference:

OAR should be contoured following the male pelvis normal tissue RTOG consensus contouring guidelines: [https://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx]

Urethra :	delineate the prostatic urethra using MRI
Bladder:	delineate the outer contour of the bladder on MRI
Rectum and anus: until 4 cm above the PTV	delineate the full circumference of the rectum and anus
Penile bulb:	delineate the full penile bulb
Femoral heads:	delineate both femoral heads

- *NB: the tumour and organs at risk outlines may be outlined by competent members of the planning team for all non-clinical trial patients. Assessment and approval of this competency is delegated to the physics department.*

7.3 Treatment Planning - Prostate Dose Prescription

7.3.1 MR Linac: As per inclusion criteria. PTV dose prescription: 36.25 Gy in 5 fractions

7.3.2 Low/Intermediate risk: T1c T2a-c T3, PSA<15, Gleason ≤7. (Level 1 Evidence): **PTVp -60Gy/ 20#** over 4 weeks (CHHiP eligible)

7.3.3 Intermediate risk: small volume (non CHHiP eligible). (Level 1 Evidence): **PTVp 78Gy/ 39#** over 7.5 weeks. Also acceptable: 74Gy/37# over 7.5 weeks and 76Gy/38# over 7.5 weeks.

7.3.4 High Risk disease: T3A, MRI T3b; PSA>20; Gleason 8-10 (any one)
Two schedules are in use depending upon, whether the entire treatment is to be with external beam or an HDR boost will be used

7.3.4.1 External Beam Only (78Gy/ 39# or 76Gy/38# or 74Gy/37#)

- PTVn: 60-62Gy in 37-39#
- PTVp: 78Gy in 39# or 76Gy/38# or 74Gy/37#
- PTVn+: 65-70Gy in 37-39# over 7.5 weeks
- In case of excess bowel, reduce LN to 55Gy and nodal boost to 60Gy (LCA guidance).

7.3.4.2 External Beam IMRT+HDR Brachytherapy Boost (Level 1 Evidence)

- PTVp & n combined: 46Gy in 23# over 4.5 weeks
- PTVn+: 58Gy in 23# (if radiologically involved nodes)
- HDR Boost: 15Gy single dose to HDR PTV
- For node –ve disease, also acceptable is 37.5Gy/15# EBRT followed by 15Gy HDR boost.

7.1.1.1 External Beam IMRT+ LDR Brachytherapy Boost

- PTVp & n combined: 46Gy in 23# over 4.5 weeks
- PTVn+: 58Gy in 23# (if radiologically involved nodes)
- LDR Boost: 110Gy
- For node –ve disease, also acceptable is 37.5Gy/15# or 36Gy/12# EBRT followed by 110Gy LDR boost.

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7.3.4 Prostate bed radiotherapy

Three schedules are in use for adjuvant and salvage radiotherapy depending upon the risk of pelvic lymph node involvement.

7.3.4.1 Prostate Bed Dose Prescription (Level 1 Evidence)

- 52.5Gy 20# Low/High Risk opting not to treat nodes over 4 weeks
- 66Gy/33# over 6.5 weeks.

7.3.4.2 High lymph node risk- positive nodes on histology at prostatectomy

- 66Gy in 33# PTVp over 6.5 weeks
- 52-55Gy in 33# PTVn (RADICALS)
- 58-70Gy in 33# PTVn+ (MVH protocol, AUA 2013, EUA 2016)

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7.3.3.5 Palliative Radiotherapy

Aim for local disease control where either there is evidence of metastatic disease or a patient is judged not fit for radical treatment

- IMRT – **36Gy in 6#. Treated 1 fraction per week over 6 weeks**
- AP PA Fields/3D CRT – **21Gy in 3#** MPD/Target mean dose alternate days over 1 week.
- AP PA Fields/3D CRT - **10Gy in 1#** MPD/Target mean dose.

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7.4 Delivery Technique

The standard technique will typically employ VMAT.

7.5 Dose Targets and Constraints

7.5.1 Minimum Target Coverage

As per RT36; V95>99% is optimal and V95%>98% is acceptable if required to meet OAR constraints.

7.5.2 Max dose

The maximum 2cc dose to the PTV should be ≤107

7.5.3 OAR Dose Constraints:

7.5.3.1 Prostate

Organ at Risk	Dose (Gy)	78Gy/39# Mandatory/optimal Volume (%)		60Gy 20# Volume (%)
Rectum	30	-	80	
	40	-	65	
	42			60
	50	60	50	50

	54			30
	58			15
	60	50	35	
	65	30	-	
	70	25	15	
	75	5	3	
Bladder	42			55
	50	50	-	40
	60	25	-	
	62			5
	74	15	5	
	50	50	5	
	50	17cc		
Penile Bulb	50	-	50	
	60	-	10	

7.5.3.2 Prostate Bed/Prostate with HDR Boost

Organ at Risk	Dose (Gy)	52Gy 20# Volume (%)	66Gy 33# Volume (%)	Prostate with HDR Boost 46Gy 23# Volume (%)
Rectum	24	80		
	30		80	
	31.1			80
	32	70		
	37.3			60
	40	60	70	
	40.4			40
	43.5			25
	46.6			2
	48	50		

	50		60	
	52.5	30		
	60		50	
	66		30	
Bladder	31.1			90
	37.3			70
	40	80		
	43.5			40
	48	50		
	50		80	
	60		50	

7.5.3.3. CHHiP trial Constraints

Organ at Risk	Dose for 2Gy/# Prescribed Dose	Dose for 3Gy/# Prescribed Dose	% of prescription dose	Max Vol (% or cc)
Rectum	30	24.6	41	80%
	40	32.4	54	70%
	50	40.8	68	60%
	60	48.6	81	50%
	65	52.8	88	30%
	70	57	95	15%
	74	60	100	3%
Bladder	50	40.8	68	50%
	60	48.6	81	25%
	74	60	100	5%
Femoral Heads	50	40.8	68	50%
Bowel	50	40.8	68	17cc
Urethral Bulb	50	40.8	68	50%

	60	48.6	81	10%

7.5.3.4 MR Linac Dose constraints OAR

Rectum and anal canal:

- $D_{105\%}$ (38.1 Gy) ≤ 0.1 cc
- $D_{100\%}$ (36.25 Gy) ≤ 1cc
- $D_{95\%}$ (34.4 Gy) ≤ 5cc
- $D_{90\%}$ (32.6 Gy) ≤ 10 cc

Bladder: (because of daily adaption, bladder is chosen instead of bladder wall)

- $D_{102\%}$ (37.0 Gy) ≤ 0.1 cc
- $D_{100\%}$ (36.25 Gy) ≤ 1 cc
- $D_{90\%}$ (32.62 Gy) ≤ 15 cc

Femoral heads:

- $D_{2\%}$ ≤50% of the prescribed PTV dose (18.1 Gy)

Penile bulb

- D_{mean} ≤75% of the prescribed PTV dose (27.2 Gy)

7.5 Plan Approval

7.6.1 Plan approval should be by a Clinical Oncologist, or where agreed and documented by the oncologist by competent members of physics staff may perform the plan approval for all radical prostate plans as long as:

a) The consultant has electronically approved the prescription.
b) The consultant has signed The GTV and CTV, OARs are approved by either the consultant or a competent member of physics staff
c) All PTV and OAR constraints are met and distribution is within current ICRU guidelines
d) Assessment and approval of this competency is delegated to the physics department.

7.6.2 For the MR Linac, daily adaptive plans are approved by the attending clinician.

8. Pre-treatment Quality Assurance

8.1 All complex IMRT/VMAT plans undergo a fluence delivery check on the linac (e.g. using MapCheck2 or ArcCheck). For guidance on this process see RT189 and MapCheck/ArcCheck manuals. This check is usually carried out prior to commencing treatment, and always before a fifth of the treatment has occurred (e.g. before fraction 5 on a 25# treatment).

8.2 For the MR Linac, daily adaptive plan quality assurance is carried out with the patient on the couch prior to treatment.

9. Pre-treatment Verification

9.1 Treatment verification is to be undertaken day 1 prior to treatment.

9.2 MR Linac treatment verification is undertaken daily.

10. Treatment IGRT

10.1 Image Guidance is to be performed using daily CBCT.
10.2 On the MR Linac, daily adaptive treatment requires daily MR planning and target tracking with live MR images.

11. Image Assessment

11.1 As per RT-POL-028; Clip-box to include the surrounding bony anatomy not including the femur.

11.2 Perform Bony match then match to prostate.

11.3 Review rotations + translations are in tolerance.

11.4 Ensure the CTV remains within the 95% Isodose.

11.5 Review bladder/rectal filling/gas.

11.6 Assess position of seminal vesicles if part of CTV.

11.7 Review skin contour; if >1cm difference in tissue discuss with planning.

11.8 Try to ensure the patient's legs (femoral head/neck) are in a similar position to planning CT; this can alter consistently on treatment if the patient was tense and "clenching" at CT.

12. Treatment Delivery

12.1 As per Radiotherapy treatment Policy **RT-POL-014**

12.2 **RT-POL-008v12**

Weekly radiographer-led on-treatment reviews are documented on MOSAIC.

12.3 **RT-POL-010**

Radiographer-led end of treatment reviews documented on MOSAIC.

13. Stereotactic Radiotherapy

13.1 Stereotactic radiotherapy on a standard linear accelerator (non-MR Linac) is a potential treatment option for patients who fulfil the PACE trial entry criteria (outlined below) who are accepting of the lack of randomised outcome data.

13.2 **Inclusion criteria:**

- Low to intermediate risk disease
- T1/2 disease
- Gleason 3+4 or 3+3
- PSA<20
- PS 0-2
- Prostate volume ≤90cc
- Inclusion of patients to treatment under PACE trial parameters should be agreed by the MDT

13.3 **Dose Prescription**

36.25Gy in 5 fractions on alternate days over 2 weeks (7.25Gy x 5) prescribed to PTV

- GTV = prostate gland
- CTV= prostate gland (low risk patients)
- Prostate gland and proximal 2 cm seminal vesicles (Intermediate risk patients)
- PTV= CTV+5mm margin all directions except posteriorly 3mm edited off rectum
- Dose constraints as per PACE trial

14. References

Dearnaley D, et al (2016): Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: 5-year outcomes of the randomised, non-inferiority, phase 3 CHHiP trial. Lancet Oncol. 2016

B.R. Prestidge et al (2016): H.M. Sandler

Affiliations - Cedars-Sinai, Los Angeles, CA

Initial Report of NRG Oncology/RTOG 0232: A Phase III Study Comparing Combined External Beam Radiation and Transperineal Interstitial Permanent Brachytherapy with Brachytherapy Alone for Selected Patients with Intermediate Risk Prostatic Carcinoma Identification and

Validation of Intrinsic Subtypes of Prostate Cancer: http://www.redjournal.org/article/S0360-3016(16)30352-2/fulltext

PACE TRIAL: https://www.clinicaltrials.gov/ct2/show/NCT01584258.

Appendix 1

Stereotactic **M**R-guided **A**daptive **R**adiation **T**herapy for **L**ocalized **P**rostate **C**ancer.

Stereotactic radiotherapy is a treatment option for patients who fulfil the entry criteria (outlined below) who are accepting of the lack of randomized outcome data. Long term outcome and toxicity data from non-randomised series does support the safety and efficacy of this therapy.

3.1 Population (base)

Patients with localized prostate cancer with a clinical stage T1-3b, with a maximal volume of 90 cc on transrectal ultrasound (TRUS) and no suspicious lymph nodes observed on either a diagnostic MRI or CT scan and no signs of distant metastases on radiological staging are eligible. All patients will be discussed in a multidisciplinary team meeting (MDT) .

3.2 Inclusion criteria

- Age of 18 years or older
- WHO performance score 0-2
- Biopsy proven adenocarcinoma of the prostate
- Gleason ≥ 6
- Prostate volume ≤ 90 cc on TRUS
- T-stage: cT1c-T3b (on MRI and/or endorectal ultrasound)
- All patients should be able to undergo MRI scans
- No evidence of lymph node or distant metastases on radiological staging
- The multidisciplinary team advised external beam radiotherapy treatment
- IPSS (International Prostate Symptoms Score) ≤19
- Previous TURP is allowed provided there is at least 8 weeks interval with radiotherapy
- The administration of concomitant hormonal therapy is allowed
- Ability to provide written informed consent.

3.3 Exclusion criteria

- Previous irradiation in the pelvic region
- Contra-indications for MRI
    - As no safety data for 0.35 Tesla MRI scanners are available on electronic devices such as pacemakers or implanted defibrillators, deep brain stimulators, cochlear implants, this constitutes an absolute contraindication for this study, even for devices that have been considered safe for MRI scans with higher magnetic field strengths.
    - Patients who have a metallic foreign body in their eye, or who have an aneurysm clip in their brain, cannot have an MRI scan since the magnetic field may dislodge the metal
    - Patients with severe claustrophobia may not be able to tolerate an MRI scan
    - Patients with a hip prosthesis will not be eligible for the MRI scan

4. TREATMENT

4.1 Radiotherapy treatment schedule

The treatment consists of a short course of radiotherapy with 5 fractions of 7.25 Gy per fraction delivered on the prostate with a simultaneous integrated sparing (SIS) of the urethra with a dose of 32.5 Gy in 5 fractions (6.5 Gy per fraction). Treatment is delivered on alternate days within a maximum overall treatment duration of 14 days.

4.2 Treatment preparation

In preparation for treatment delivery, all patients will undergo a planning-MRI scan (MRIdian) and a planning-CT scan. Patients will be simulated and treated in supine position. The CT scan slice thickness will be 2 mm. The superior limit of the CT scan will be at least at L1 and inferior limit will be half-way the femur. The planning-CT will be fused with the planning-MRI scan. If a diagnostic MRI scan is performed, including T1 and T2 sequences these scans can be co-registered to assist in target definition. The fusion will be centred on the area of interest, i.e the prostate. All patients will be treated using online MR-guided gated radiotherapy with adaptation of treatment plans immediately prior to each treatment delivery (SMART). Patients will be instructed to have a full bladder and if possible, an empty bowel prior to the planning CT and MRI scan and prior to each treatment fraction. In order to achieve this with some reproducibility patients are instructed to empty their bladder two hours before treatment, followed by

intake of 500cc of water. In case of constipation, mild laxatives will be prescribed. No rectal balloons or routine pre-treatment enemas will be used.

4.3 Definitions of target volumes and organs at risk

Volume and dose prescription are implemented according to the ICRU 83 regulations [Repot 83, 2010]. Target definition is dependent on the risk assessment, in particular to the risk of seminal vesicle invasion. 'Low risk' patients are defined as patients with cT1c-T2a prostate cancer, a Gleason score <7 and a PSA <10 µg/L. 'High risk' patients have cT3-4 prostate cancer, or a Gleason score >7 or a PSA >20 µg/L, and 'intermediate risk' patients are patients not included in the other two groups [EAU guidelines 2013, Heidenreich].

Clinical target volume (CTV) definitions:

The urethral planning organ at risk volume (PRV): urethra plus 3mm; the area of integrated radiation sparing.

For 'low risk' patients: CTV = prostate minus the urethral PRV (see below)

For 'intermediate and high risk' patients: CTV = prostate plus the base of the seminal vesicles (=2cm) plus any visible tumour extension seen on MRI minus the urethral PRV (see below)

Planning target volume (PTV) margins:

The combination of MR-guided soft-tissue setup and online MR-imaging during treatment in combination with "gated" treatment (i.e. beam-on only when the target is in the predetermined position) enables the application of small uncertainty margins.

PTV = CTV + 3 mm (in all external directions, i.e. excluding the urethral PRV).

Organs at risk (OAR) definitions:

OAR should be contoured following the male pelvis normal tissue RTOG consensus contouring guidelines: [https://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx]

Urethra: delineate the prostatic urethra using MRI

Bladder: delineate the outer contour of the bladder on MRI

Rectum and anus: delineate the full circumference of the rectum and anus until 4 cm above the PTV

Penile bulb: delineate the full penile bulb

Femoral heads: delineate both femoral heads

4.4 Radiation technique

Radiation therapy will be delivered using online MR-guided gated radiotherapy with adaptation of treatment plans immediately prior to each treatment delivery. Treatment technique consists of static field intensity modulated radiotherapy fields from three Cobalt-sources in the MRIdian. Standard plans will consist of 10 beam groups (30 beams) with a maximum of 10 segments from each beam.

4.5 Treatment planning, dose calculation and set-up verification

Radiation dose prescription will be performed according to the following specifications:

PTV dose prescription: 36.25 Gy in 5 fractions (PTV minus urethral PRV)

- $D_{95\%}$ ≥95% of the prescribed dose (95% of the PTV receives at least 95% of the prescribed dose)
- $D_{2\%}$ ≤110% of the prescribed dose (2% of the PTV receives a maximum dose of 110% of the prescribed dose)

Urethral PRV dose prescription (SIS): 32.50 Gy in 5 fractions

- $D_{98\%}$ ≥95% of the prescribed dose (98% of PRV receives at least 95% of PD, i.e. 30.9 Gy)
- Urethral PRV: ≤110% of the prescribed dose (2% of PRV receives a maximum of 107% of PD, i.e. 35.8 Gy)

Dose constraints OAR

Rectum and anal canal:

- $D_{105\%}$ (38.1 Gy) ≤ 0.1 cc
- $D_{100\%}$ (36.25 Gy) ≤ 1cc
- $D_{95\%}$ (34.4 Gy) ≤ 5cc
- $D_{90\%}$ (32.6 Gy) ≤ 10 cc

Bladder: (because of daily adaption, bladder is chosen instead of bladder wall)

- $D_{102\%}$ (37.0 Gy) ≤ 0.1 cc

- $D_{100\%}$ (36.25 Gy) ≤ 1 cc
- $D_{90\%}$ (32.62 Gy) ≤ 15 cc

Femoral heads:

- $D_{2\%}$ ≤50% of the prescribed PTV dose (18.1 Gy)

Penile bulb

- D_{mean} ≤75% of the prescribed PTV dose (27.2 Gy)

BIOLOGICAL EQUIVALENT DOSES

Biological equivalent doses

Total dose (Gy)	Dose/fraction (5fr)	Tissue	α/β (Gy)	EQD-2Gy
36.25	5	tumor	1.5	90
36.25	5	late toxicity	3.0	74
36.25	5	acute toxicity	10.0	50
32.50	5	tumor	1.5	74
32.50	5	urethra	3.0	62