

MRI-guided Focal Boost in Prostate Cancer Radiation Therapy

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1.0 Trial Summary

PROTOCOL TITLE	MRI-guided Focal Boost in Prostate Cancer Radiation Therapy
RATIONALE	<p>The biological rationale for focal boosting stems from the concept that dominant intraprostatic lesions (DILs) represent the main driver of local failure and metastatic progression. Conventional radiotherapy delivers a homogeneous dose to the entire prostate. Therefore, this can lead to relative under-treatment of aggressive tumor subvolumes due to constraints imposed by adjacent organs at risk. MRI-guided focal boost radiotherapy allows selective dose escalation to dominant tumor foci identified on mpMRI while maintaining standard dose to the remaining prostate. By targeting the region with the highest tumor burden, this strategy may improve local tumor control without increasing treatment-related toxicity. One multicenter randomized controlled trial has demonstrated improved freedom from biochemical failure (FFBF) with this approach. Another prospective Phase II trial has demonstrated the safety and efficacy of an ultra hypofractionated approach with focal boosting. This can therefore now be considered a standard of care.</p> <p>We are implementing this technique as a service standard in our department. However, there is a need to rigorously commission this complex treatment technique and prospectively monitor the acute toxicities, quality of life, and FFBF outcomes in this cohort. There is also a need to systematically compare these outcomes to a matching cohort of patients treated with moderate and ultra hypofractionated treatment.</p>
AIMS	To evaluate the toxicities, disease control and patient reported outcomes of MRI guided focal boost.
STUDY OBJECTIVES	<p>To determine</p> <ol style="list-style-type: none"> 1. FFBF of MRI-based focal boost in high-risk and node-positive prostate cancer 2. Acute and late genito-urinary and gastrointestinal toxicities 3. Acute and long-term patient-reported outcomes 4. Interobserver variability of focal boost segmentation 5. Concordance of PSMA-PET based boost with MRI based boost <p>To make a planned comparison FFBF, toxicity and patient reported outcomes of MRI-based focal boost with a historical cohort of moderate and ultra-hypofractionated radiotherapy.</p>
STUDY DESIGN	Single arm, Prospective Observational Study
TRIAL POPULATION	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Age: above 18 years. 2. Participants must be histologically proven adenocarcinoma prostate

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	<p>3. High-risk localized prostate cancer as per NCCN risk criteria (cT3/T4 or Gleason 8-10 or PSA > 20 ng/ml) or Prostate cancer with metastases confined to pelvic lymph nodes (cN1) on mpMRI and PSMA PET-CT scan</p> <p>4. No contraindications for long-term hormone therapy/ orchidectomy</p> <p>5. Karnofsky Performance Score >70 (Appendix 1)</p> <p>Exclusion criteria:</p> <p>1. Patients in whom a pelvic MRI is contraindicated.</p> <p>2. Prior history of radiotherapy to the pelvis or prostatectomy.</p> <p>3. Severe urinary symptoms or a high IPSS score > 15 which in the opinion of the physician, precludes RT</p> <p>4. Patients with known obstructive symptoms with stricture.</p> <p>5. Any contraindication to radiotherapy, such as severe inflammatory bowel disease.</p> <p>6. Unable to report for regular follow up</p>
TREATMENT REGIMENS	<p>Moderate hypofractionated RT, Will receive a total dose of 62 Gy in 20# to the entire prostate and seminal vesicles over 4 weeks, with treatment being delivered daily. Elective nodal regions will receive a dose of 44 Gy in 20# to the pelvic nodes. A focal boost of up to 77Gy in 20 fractions as a simultaneous integrated boost (SIB) will be delivered. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 54-60 Gy/20Fr# as SIB.</p> <p>Extreme hypofractionation with SBRT, Will receive a total dose of 36.25Gy in 5# to the entire prostate and seminal vesicles over 5 weeks, with treatment being delivered once a week. Elective nodal regions will receive a dose of 25 Gy in 5# to the pelvic nodes. A focal boost of up to 42 Gy in 5 fractions as a simultaneous integrated boost (SIB) will be delivered. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 32-35Gy/5Fr# as SIB.</p>
RECRUITMENT TARGET	A Bayesian analysis will be performed. The minimum required sample size under the primary scenario is 95 evaluable patients, corresponding to 105 recruited after 10% attrition. The study will target recruitment of N = 122 patients over three years, with a ceiling of N = 130.
PRIMARY ENDPOINT	To assess the 5 year Freedom from Biochemical Failure (FFBF)
KEY SECONDARY ENDPOINTS	<ol style="list-style-type: none"> 1. To evaluate acute and late toxicity with both treatments. 2. To find Prostate cancer specific survival and overall survival of patients receiving focal boost to the DIL 3. To assess quality of life 4. To compare outcomes, toxicities and patient-reported outcomes of this cohort with a historical prospective randomized cohort of patients treated with moderate and ultra-hypofractionated radiotherapy without focal boost in the PRIME trial 5. To determine inter-observer variability in delineation of boost volume in urethra
TERTIARY ENDPOINT	<ol style="list-style-type: none"> 1. To determine the accuracy of an autosegmentation model for MRI based intraprostatic lesion segmentation.
FOLLOW UP	<ul style="list-style-type: none"> • All patients will follow up 3-6 weeks from end of radiotherapy, followed by 3-6 monthly for the first two years depending on the clinical need and 6

	<p>monthly thereafter. At baseline and every follow-up data will be collected and recorded in CRF</p> <ul style="list-style-type: none">● Physician assessment of toxicity with RTOG toxicity criteria and CTCAE ver 6.0 criteria for proctitis, rectal pain, rectal bleeding and urinary complaints at baseline and follow up.● Physician assessment during and end of RT with scoring of toxicity and IPSS scoring● Physician assessment with clinical examination and serum PSA.● QOL will be assessed at baseline and 6 monthly using the QLQC30 and PR25 EORTC Questionnaire.
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2.0 Introduction

Prostate cancer is one of the most common malignancies among men worldwide and is a major cause of cancer-related morbidity and mortality. Radiotherapy is one of the definitive treatment modalities. In this regard, dose escalation has been shown to improve biochemical response and tumour control. Uniform dose escalation remains a challenge due to the surrounding organs at risk (eg. rectum, bladder) and may lead to gastrointestinal and genitourinary toxicity.¹

Imaging techniques like mpMRI (multiparametric MRI) enables identification of areas of highest tumour burden within the organ - dominant intraprostatic lesions (DILs). These dominant lesions are responsible for a significant proportion of local recurrence following radiotherapy.^{2,3} It is now possible to selectively deliver an escalated dose of radiotherapy to the DILs while maintaining standard dosage to the rest of the organ. These techniques have shown increased survival with minimal additional toxicities and have been validated by long term follow-up.^{4,5,6}

With increasing adoption of hypofractionated radiotherapy schedules in prostate cancer, investigators have explored the integration of focal boosting with stereotactic radiotherapy approaches. Early clinical outcomes show promising results, supporting the feasibility of combining focal boosting with ultra-hypofractionated radiotherapy regimens.⁷ These results have been further strengthened in newer studies with the adoption of standardised imaging frameworks to increase precision in radiotherapy administration.^{8,9,10}

Despite these promising results, the implementation of MRI-guided focal boosting varies across institutions due to differences in imaging protocols, target delineation practices, and treatment planning techniques. Furthermore, most of the available evidence originates from large multicenter trials conducted in highly specialized centers with advanced imaging infrastructure. There is therefore a need for additional clinical data evaluating the feasibility, dosimetric characteristics, and clinical outcomes of MRI-guided focal boosting in diverse clinical settings.

3.0 Rationale

The biological rationale for focal boosting stems from the concept that dominant intraprostatic lesions (DILs) represent the main driver of local failure and metastatic progression. Conventional radiotherapy delivers a homogeneous dose to the entire prostate. Therefore, this can lead to relative under-treatment of aggressive tumor subvolumes due to constraints imposed by adjacent organs at risk. MRI-guided focal boost radiotherapy allows selective dose escalation to dominant tumor foci identified on mpMRI while maintaining standard dose to the remaining prostate. By targeting the region with the highest tumor burden, this strategy may improve local tumor control without increasing treatment-related toxicity. One multicenter randomized controlled trial has demonstrated improved biochemical disease-free survival (bDFS) with this approach. Another prospective Phase II trial has demonstrated the safety and efficacy of an ultra hypofractionated approach with focal boosting. This can therefore now be considered a standard of care.

We are implementing this technique as a service standard in our department. However, there is a need to rigorously commission this complex treatment technique and prospectively monitor the acute toxicities, quality of life, and freedom from biochemical failure (FFBF) outcomes in this cohort. There is also a need to systematically compare these outcomes to a matching cohort of patients treated with moderate and ultra hypofractionated treatment.

4.0 Literature Review

4.1 Radiotherapy dose and fractionation

Radiotherapy is a definitive treatment modality for prostate cancer. Historically, conventional fractionation (64–70 Gy in 1.8–2 Gy fractions) produced moderate biochemical disease-free survival (BDFS), particularly in intermediate- and high-risk disease. Trials such as MD Anderson, Dutch multicenter, and MRC RT01 which looked at dose escalation, established improved biochemical control with doses up to 74–78 Gy, but with increased rectal toxicity^{1,11, 12, 13}. In this era, BDFS was >90% for low-risk, 70–80% for intermediate-risk, and 50–60% for high-risk disease, highlighting the need for improved treatment strategies.

The recognition of a low α/β ratio for prostate cancer (~1.5 Gy) led to the adoption of hypofractionation¹⁴. Moderate hypofractionation is now standard, supported by phase III trials. The CHHiP trial demonstrated non-inferiority of 60 Gy in 20 fractions compared to 74 Gy in 37 fractions, with ~90% 5-year BDFS¹⁵. The PROFIT trial similarly confirmed equivalent biochemical control with shorter treatment duration¹⁶. Indian data from Tata Medical Center (Mallick and Arunsingh et al.) support these findings, reporting ~80% 5-year biochemical control in high-risk patients treated with 60 Gy in 20 fractions with acceptable toxicity^{17, 18, 19, 20}. Acute toxicity rates were low, with minimal grade ≥ 3 events. Overall, BDFS with moderate hypofractionation is ~90–95% in low-risk and 85–90% in intermediate-risk disease.

Ultra-hypofractionation (SBRT) further exploits radiobiology by delivering high doses per fraction. The PACE-B trial demonstrated comparable early disease control between SBRT (36.25–40 Gy in 5 fractions) and conventional schedules²¹, while HYPO-RT-PC confirmed non-inferiority in failure-free survival²². Emerging data from the SHORTER trial and SHARP consortium support safety and efficacy of SBRT. Indian contributions include the PRIME trial, evaluating extreme hypofractionation in high-risk and node-positive disease²³. SBRT achieves BDFS >95% in low-risk and ~90% in intermediate-risk cohorts.

Despite advances in whole-gland radiotherapy, failures predominantly occur at the dominant intraprostatic lesion (DIL)²⁴. This led to focal boosting strategies. The FLAME trial demonstrated improved 5-year BDFS (92% vs 85%) with MRI-guided focal boost up to 95 Gy without increased ≥Grade 2 toxicity²⁵. The Hypo-FLAME study further showed feasibility of combining SBRT with focal boosting. These findings represent a shift toward precision dose escalation targeting biologically aggressive tumor subvolumes.

Brachytherapy has historically achieved the highest intraprostatic doses, as demonstrated in ASCENDE-RT, which showed superior biochemical control with brachytherapy boost compared to EBRT alone^{25, 26}. However, this came at the cost of increased genitourinary toxicity. MRI-guided focal boosting replicates these dose-escalation benefits non-invasively, achieving dose intensification comparable to brachytherapy.

Toxicity outcomes remain favorable with modern techniques. FLAME reported no significant increase in grade ≥2 gastrointestinal or genitourinary toxicity, and Indian series similarly demonstrate acceptable toxicity profiles. Dose constraints to rectum and bladder remain critical. Importantly, patterns of failure consistently demonstrate intraprostatic recurrence, supporting focal dose escalation strategies.

In conclusion, prostate radiotherapy has evolved from conventional fractionation to hypofractionation and MRI-guided focal boosting. Evidence from global trials and Indian studies supports improved biochemical control with acceptable toxicity. The FLAME trial represents a paradigm shift toward biologically guided precision radiotherapy. More studies evaluating dose escalation to DILs can augment and refine treatment modalities to optimize recovery while minimizing toxicities.

Study Title	Aim	Study Design	No. of Patients	Median Follow-up	Dose	Dose/Fraction	Results
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CHHiP	Hypo vs conventional	Phase III RCT	3216	5 yrs	60 Gy	3 Gy	5-yr BDFS ~90%; non-inferior; no increase in late \geq G2 GI/GU toxicity; slightly reduced acute toxicity
PROFIT	Hypo vs conventional	Phase III RCT	1206	6 yrs	60 Gy	3 Gy	5-yr BDFS ~85–90%; non-inferior; similar late GI/GU toxicity; shorter treatment duration advantageous
PACE-B	SBRT vs conventional	Phase III	874	~5 yrs	36–40 Gy	~7–8 Gy	Comparable biochemical control; increased acute G2 GU toxicity (~27% vs ~18%); similar late toxicity
HYPO-RT-PC	Ultra-hypo RT	Phase III	1200	5 yrs	42.7 Gy	6.1 Gy	5-yr failure-free survival non-inferior (~84%); slightly higher acute GU/GI toxicity; no difference in late toxicity
FLAME	Focal boost	Phase III	571	5 yrs	95 Gy boost	Variable	5-yr BDFS 92% vs 85%; significant improvement in local control; no increase in \geq G2 GI/GU toxicity; minimal QoL impact

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Hypo-FLA ME	SBRT + boost	Phase II	~100	~3 yrs	~50 Gy	10 Gy	Excellent early biochemical control (>90%); low rates of \geq G2 GI toxicity; acceptable GU toxicity; feasible dose escalation
ASCENDE-RT	Brachy boost	Phase III	398	6.5 yrs	>100 Gy EQD2	-	9-yr BDFS ~83% vs 62%; superior local control; significantly higher late G3 GU toxicity (~18%)
Mallick et al.	Hypo RT (India)	Prospective	~100	~5 yrs	60 Gy	3 Gy	5-yr biochemical control ~80% (high-risk); good local control; acceptable late toxicity; feasible in resource-limited settings
Arunsingh et al.	Toxicity (India)	Prospective	~80	~2–3 yrs	60 Gy	3 Gy	Acute G2 GU ~6–7%; minimal \geq G3 toxicity; low GI toxicity; confirms safety of moderate hypofractionation
PRIME Trial	Extreme hypo RT	Ongoing Phase II/III	—	—	SBRT	\geq 5 Gy	Ongoing; aims to establish non-inferiority; expected improved compliance and reduced treatment time

4.2 Interobserver variation (IOV) in prostate cancer target delineation

Traditional CT based contouring in prostate cancer has been shown to have a relatively high IOV due to a lack of clear boundaries in the soft-tissues of the prostate and the surrounding pelvic floor muscles, rectum and bladder. Organs at risk e.g. the penile bulb also has a high reported IOV on CT based contouring. MRI based planning has been shown to yield lower IOV due to superior soft-tissue contrast, especially for the seminal vesicles, and organs at risk.

There is very limited prior study of IOV in the delineation of DILs in prostate cancer. Hearn et al²⁷ evaluated DIL delineation by four observers (two radiation oncologists, two radiologists) using biparametric MRI (T2W + DWI), 68Ga-PSMA-PET/CT, and co-registered bpMRI/PSMA-PET in 16 patients. Interobserver agreement was significantly higher for PSMA-PET GTV (DSC 0.822, MDA 1.12 mm) compared with MRI GTV alone (DSC 0.705, MDA 2.44 mm), with the co-registered modality intermediate (DSC 0.787). Intermodality agreement between PSMA-PET and MRI contours was poor (DSC 0.440, MDA 4.64 mm), highlighting that the two modalities capture fundamentally different aspects of disease extent. Semi-automated thresholding methods performed poorly for MRI (DSC 0.370) but better for PSMA-PET (DSC 0.571), suggesting PSMA-PET is more amenable to quantitative segmentation approaches.

Salgues et al took a novel approach by investigating predictive factors for IOV in DIL segmentation²⁸. In 68 patients, three independent readers delineated the index lesion on T2W and ADC sequences. The median DSC was 0.69 (95% CI 0.65–0.71), with only 42.6% achieving a DSC >0.7 — a rate reflecting the inherent difficulty of precise lesion boundary identification on MRI. Multivariate logistic regression identified the PI-QUAL score (Prostate Imaging Quality) as the sole significant predictor of achieving a DSC >0.7 ($p=0.008$), with higher image quality translating directly into better observer agreement. This finding has direct practical implications: patients with low PI-QUAL score MRIs may require multi-reader or radiologist-radiotherapist consensus approaches, or repeat imaging, before proceeding to focal treatment planning.

The impact of IOV in the context of focal boosting has not been reported.

5.0 Hypothesis

MRI guided focal boosting of radiotherapy to prostate cancer dominant intraprostatic lesion leads to improved freedom from biochemical failure with an acceptable toxicity profile.

6.0 Aims

To evaluate the toxicities, disease control and patient reported outcomes of MRI guided focal boost.

7.0 Objectives

To determine

1. FFBF of MRI-based focal boost in high-risk and node-positive prostate cancer
2. Acute and late genito-urinary and gastrointestinal toxicities
3. Longitudinal patient-reported outcomes
4. Interobserver variability of focal boost segmentation volumes
5. The optimal PSMA-PET SUV threshold with the best match with MRI based boost volume

To make a planned comparison FFBF, toxicity and patient reported outcomes of MRI-based focal boost with an identical historical cohort of patients treated to moderate and ultra-hypofractionated radiotherapy in a randomized controlled trial at Tata Medical Center

8.0 Endpoints

8.1 Primary endpoint:

To assess the 5 year Freedom from Biochemical Failure (FFBF)

8.2 Secondary endpoints:

1. To evaluate acute and late toxicity with both treatments.
2. To find Prostate cancer specific survival and overall survival of patients receiving focal boost to the DIL
3. To assess quality of life
4. To compare outcomes, toxicities and patient-reported outcomes of this cohort with a historical prospective randomized cohort of patients treated with moderate and ultra-hypofractionated radiotherapy without focal boost in the PRIME trial
5. To determine inter-observer variability in delineation of boost volume in urethra

8.3 Tertiary endpoint

1. To determine the accuracy of an autosegmentation model for MRI based intraprostatic lesion segmentation.

9.0 Methodology

9.1 Study Design

This will be a single-arm, prospective observational study

9.2 Patient Selection

9.2.1 Inclusion criteria:

1. Age: above 18 years.
2. Participants must be histologically proven adenocarcinoma prostate
3. High-risk localized prostate cancer as per NCCN risk criteria (cT3/T4 or Gleason 8-10 or PSA > 20 ng/ml) or Prostate cancer with metastases confined to pelvic lymph nodes (cN1) on mpMRI and PSMA PET-CT scan
4. No contraindications for long-term hormone therapy/ orchidectomy
5. Karnofsky Performance Score >70 (Appendix 1)

9.2.2 Exclusion criteria:

1. Patients in whom a pelvic MRI is contraindicated.
2. Prior history of radiotherapy to the pelvis or prostatectomy.
3. Severe urinary symptoms or a high IPSS score > 15 which in the opinion of the physician, precludes RT (Appendix 2)
4. Patients with known obstructive symptoms with stricture.
5. Any contraindication to radiotherapy, such as severe inflammatory bowel disease.
6. Unable to report for regular follow up

9.3 Pre-treatment evaluation:

All patients with biopsy proven Adenocarcinoma of the prostate (TRUS guided) after screening will undergo the following investigations prior to enrolment

- Complete history and physical examination
- Serum PSA < 3 weeks of enrolment
- Staging investigation including mpMRI pelvis/ PSMA PET CT to rule out distant metastasis.
- IPSS scoring
- Documentation of pre-treatment urinary and rectal symptoms and quality of life.

9.4 Registration

Patients will be identified and checked for eligibility from outpatient clinics. Suitable patients will be considered for the study by a member of the investigating team after thoroughly explaining the study process and enough time for thinking over if they need.

Patients with high-risk prostate carcinoma on presentation will be screened for eligibility criteria. They must meet all of the inclusion criteria and have none of the exclusion criteria to be eligible for the trial. Written informed consent will be obtained from all these patients at the time of registration for collection of patient reported outcomes over a 5 year period.

Subjects must be registered before starting study treatment. Once the registration process is complete, the subject will be assigned a study number.

9.5 Radiotherapy Patient Preparation

- **Bladder:** Patients will be asked to have a comfortably full urinary bladder both during simulation and treatment. A consistent bladder filling procedure should be used for an individual patient for simulation and for each treatment. Bladder filling may be achieved by asking patients to drink 500 ml of water 30 minutes prior to treatment and to refrain from urinating between this time and treatment.
- **Bowel:** Patients will be advised to consume a low-residue diet to reduce flatulence and take measures to avoid constipation, including the use of stool softeners and laxatives.

9.6 Patient positioning

Patient positioning: Supine with the arms folded over the chest. Standard foam head support. Knee rest as required. No other specific immobilisation will be used.

9.7 Simulation

Computed Tomography (CT)

The steps of patient preparation outlined above will be followed. Patients will be simulated in the supine position with their hands over their chest. A knee rest will be used for immobilisation and reproducibility. Three markers will be placed over the skin at laser intersections; one at the symphysis pubis and two laterally. CT scans will be taken with contrast from xiphisternum to at least 5 cm below the ischial tuberosities with a slice thickness of 2.0-2.5mm. Laser marks will be permanently tattooed for setup. A screening scan will be done to assess rectal distension, and if the rectal diameter is greater than 4 cm, then the planning scan will be kept on hold until appropriate measures are taken to help reduce the distension.

Magnetic Resonance Imaging (MRI)

Multiparametric magnetic resonance imaging (mpMRI) plays a critical role in the identification and delineation of dominant intraprostatic lesions (DILs) in prostate cancer. It provides superior soft tissue contrast and improved visualization of tumor foci within the prostate gland.

- **Timing of MRI** - MRI will be performed before initiation of radiotherapy planning and preferably androgen deprivation therapy, if feasible, to avoid treatment-related changes in tumor visibility.
- The required sequences are T2W (one additional axial sequence with no tilt), Diffusion +/- DCE each of slice thickness matching the planning CT scan.

9.8 Contouring

- Whole organ Target Volumes: CTV prostate (and SV): For patients without clinical or radiological involvement of SV, CTV will consist of the whole of the prostate gland, including any ECE, and the base of the seminal vesicles, defined as the proximal 1 cm of the seminal vesicles will be included in the CTV. For patients with radiological involvement of the SV, the entire SV will be included.
- Focal boost volumes: Visible tumor lesions on mpMRI will be contoured as a focal boost volume in collaboration with either an experienced uro-radiologist or after peer review with an expert radiation oncologist.
- CTV nodes: Patients with node-positive disease will receive radiotherapy to pelvic nodes. Contouring will begin from the bifurcation of the abdominal aorta. Contour will be drawn around the major vessels with margins of about 7 mm and then modified depending on the anatomical boundaries like bone, muscles, and peritoneum. The external iliac vessel contouring will be stopped at the top level of the femoral head. The delineation of the upper external iliac region will also include the lateral and medial presacral nodal areas from S1-3, with a thickness of 8-10mm. The internal iliac lymph node contouring (including the obturator node) will stop at the beginning of the obturator foramen. The prophylactic lymph nodal delineations follow the pattern shown at the RTOG. The whole nodal CTV (bilateral) will be drawn as a single structure, and a 1 cm thick presacral space will be included by joining bilateral nodal CTV up to the caudal border of S3, posterior border being the anterior sacrum, and anterior border approximately 10 mm anterior to the anterior sacral bone, carving out bowel, bladder, and bone.
- PTV nodes: A margin of 5 mm will be grown isotropically over CTV nodes.
- PTV Prostate (and SV): A margin of 5mm will be grown in all directions over the CTV prostate.
- Organs at risk:
 - The prostatic urethra will be contoured with the help of the fused planning MRI scan. A planning organ at risk volume (PRV) margin of 2 mm will be added to this structure.
 - The whole rectum will be drawn as a solid structure starting from recto sigmoid flexure up to the bottom of ischial tuberosity. The rectal wall will not be drawn separately. A planning organ at risk volume (PRV) margin of 2 mm will be added to this structure.
 - The entire bladder will be drawn as a solid structure from the dome to the base including the wall. The Bowel bag will be represented by a single solid structure encompassing the peritoneal cavity and any loops of bowel in the pelvis. The upper extent will be kept constant at 5 cm superior to the uppermost extent of the PTV to have comparability of the dose volume data. Penile bulb will be contoured on the CT image below the pelvic diaphragm with reference to the MRI of the pelvis. Both femoral heads will be drawn within the acetabulum without including the neck of the femur.

9.9 Treatment planning

This protocol requires the use of Volumetric arc based IMRT or helical tomotherapy. The recommended photon energies for this protocol are 6-15 MV with or without a flattening filter. All patients will undergo daily image guided radiotherapy.

Planning will be done as a single phase simultaneous integrated boost (SIB) technique.

The goal will be to deliver an isotoxic focal boost dose of up to 77Gy in 20 fractions (with a dose of 62 Gy to the entire prostate) in the moderate hypofractionated regimen and up to 42 Gy in 5 fractions (with a dose of 36.25 Gy to the entire prostate) in the ultrahypofractionated regimen. The essential

and optimal dose ranges to the boost volume are based on the BED of the doses prescribed in the FLAME trial.

The dose volume constraints and the biologically equivalent doses (BED) of each dose fractionation schedule is given in **Table 1 (Appendix 3)**

9.10 Hormonal therapy

Patients with high-risk localized prostate cancer (N0) will receive 2 years of androgen deprivation therapy with GnRH analogues or antagonists.

Patients with node-positive(N1) will receive a combination of GnRH agonist/antagonist and an approved Androgen Receptor pathway Inhibitor for 2 years.

9.11 Pilot plan implementation

A pilot study will be conducted for commissioning the planning protocol before study initiation. This pilot will comprise a cohort of 10 patients who will be initially evaluated for image fusion, target delineation independently by 2 observers. Other pilot analyses will include planning feasibility of achieving target doses and dose constraints, and radiotherapy quality assurance maintenance.

10.0 Assessments

10.1 Clinical Assessments

1. Objective criteria for toxicity evaluation.

The RTOG acute and late toxicity criteria will be used to document acute and late toxicities (Appendix 4-5)

National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 6.0 will also be used for documentation of proctitis, rectal pain, rectal bleeding, rectal ulcer; and urinary tract toxicities such as frequency, urgency, retention, pain, obstruction for both acute and late toxicity assessments. (Appendix 6)

RTOG and CTCAE based reporting of toxicities and IPSS scoring will be carried out at baseline, 3-6 weeks post RT and at 6 monthly thereafter, as a part of routine clinical assessment

QOL will be assessed at baseline, end of treatment and 3-6 monthly thereafter using the QLQC30 and PR25 EORTC Questionnaire with validated translations in Hindi and Bengali (Appendix 7-8). Electronic methods may be used for capture of PR data.

2. Disease evaluation: Clinical evaluation of the disease will be done at each follow up visit with a serum PSA and clinical examination.

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- All patients will follow up 6 weeks from the end of radiotherapy. Thereafter follow up visits would be scheduled three to six monthly for the first two years depending on the clinical need and 6 monthly thereafter as per standard practice. Clinical data will be recorded prospectively in the Case Record Form.

Assessment	Recruitment	Start of RT	end-of-RT	6 weeks post RT	3 months post RT	3 monthly upto 24 months from RT	6 monthly from 24 month from RT - indefinitely
Baseline	X						
Radiotherapy Treatment details		X					
Toxicity assessments (CTCAE and RTOG)		X	X	X	X	X	X
Patient reported outcomes (EORTC QLQ C30 and PR25)		X	X	X	X	X	X
Survival and disease control assessments					X	X	X
Interobserver variability for contouring		X					

10.2 Interobserver variability

Thirty consecutive patients meeting the study eligibility criteria, and with satisfactory MRI-CT co-registration (target registration error < 2 mm) will be included in this substudy. A nested sub-cohort of at least 20 patients who additionally undergo 68Ga-PSMA PET-CT at Tata Medical Center will form the concordance analysis group. The study does not alter the clinical treatment pathway.

Imaging and Contouring Protocol: All patients undergo standard contrast-enhanced CT simulation co-registered with T2-weighted (T2W) and diffusion-weighted (DWI/ADC) MRI sequences on the institutional treatment planning system (TPS). Three observers — two expert radiation oncologists (RO1, RO2) and one expert urologist (UR1) — independently delineate the dominant intraprostatic lesion gross tumour volume (GTV_boost) on the co-registered T2W/DWI-fused MRI dataset, blinded to each other's contours. The GTV_boost is the entire volume of tumor foci visible on T2W and/or DWI,

constrained within the T2W-defined prostate capsule, with no margin expansion. For the PSMA PET-CT concordance sub-study, a nuclear medicine physician independently generates 3 threshold-based GTV_PET volumes per patient, at 40%, 50% and 60% of intraprostatic SUVmax, co-registered to the planning CT prior to comparison.

Component A (Interobserver Variability) The primary endpoint is the proportion of patients in whom at least two of the three pairwise observer comparisons achieve a Dice Similarity Coefficient (DSC) ≥ 0.70 for the GTV_boost, reported with an exact 95% Wilson score binomial confidence interval. Secondary continuous metrics — DSC, surface-DSC, Jaccard Index, Mean Distance to Agreement (MDA), Hausdorff Distance (HD), GTV_boost volume, and STAPLE-referenced performance per observer are summarised as median (IQR) and visualised with box and violin plots. The intraclass correlation coefficient (ICC, two-way mixed-effects, absolute agreement) is computed across all three observers for volume. Pairwise metric comparisons across observer pairs use the Wilcoxon signed-rank test with correction for multiple testing. Exploratory logistic regression will examine predictors of DSC ≥ 0.70 , with PI-RADS score, PI-QUAL score, lesion zone (peripheral vs. transition), maximum lesion diameter, and ADC value as candidate covariates. A sample size of 30 patients provides a 95% CI width of approximately ± 18 percentage points around an anticipated proportion of $\sim 60\%$, consistent with feasibility-level methodological sub-studies in this setting.

Component B (PSMA PET-CT Concordance): For each of the three GTV_PET threshold methods, concordance with the STAPLE consensus MRI GTV_boost is characterised by DSC, MDA, HD, and volume. A Friedman test across the three thresholds, with Dunn's post-hoc correction, determines whether concordance metrics differ significantly by thresholding strategy, and the method achieving the highest median DSC is designated the exploratory optimal threshold. Bland-Altman analysis quantifies systematic volume differences between each PET threshold and the STAPLE MRI volume. Spatial sensitivity (proportion of STAPLE GTV_boost captured by GTV_PET) and positive predictive value (proportion of GTV_PET overlapping the STAPLE volume) are computed per threshold. The union (GTV_union = GTV_PET \cup STAPLE) and intersection (GTV_intersection = GTV_PET \cap STAPLE) volumes are described qualitatively for their potential dosimetric implications in focal boost planning.

All geometric metrics are computed using the in-house software using standard formulae (<https://github.com/CHAVI-India/COMET>)²⁹.

10.3 Autosegmentation

As an exploratory objective, consensus GTV_boost contours accumulated from a minimum of 50 patients drawn from the primary study cohort and supplemented by sequential enrolment beyond the primary 30-patient IOV window will be used as ground-truth training labels for a deep learning-based auto-segmentation model developed within the DRAW (Deep learning Radiotherapy Auto-contouring Workflow) segmentation system at Tata Medical Center.

The model will be trained on co-registered T2W/DWI planning MRI inputs, with a parallel training arm incorporating PSMA PET-CT-derived threshold volumes (optimal threshold identified in Component B) as an additional input channel for the subset of patients with available PSMA PET-CT.

The primary architecture will be nnU-Net, the current standard for autosegmentation. It has demonstrated strong performance for prostate structures on MRI in recent literature by Schubert et al who trained a 3D nnU-Net on 40 patients achieving a surface DSC of 0.82 across prostate and erectile

structures³⁰, while Konrad et al.³¹ demonstrated that an in-house nnU-Net reduced online adaptive MR-Linac delineation time by 46% with no significant quality compromise

More recent architectures (e.g., transformer-based or hybrid CNN-transformer models) will be evaluated if they demonstrably outperform nnU-Net on internal cross-validation.

Model performance will be assessed with the primary metric being DSC against a held-out set of consensus GTV_boost, supplemented by MDA, HD, and clinician-rated acceptability scores. The primary purpose is to establish the feasibility and initial performance of an institutionally trained, locally deployable auto-segmentation tool for DIL contouring within the DRAW framework, with findings intended to inform the design of a subsequent prospective validation study.

11.0 Safety considerations

11.1 Adverse Event reporting

MRI-guided focal boost is one of the standards of care following the results of the Phase III randomized FLAME trial. Therefore, adverse events will be documented, but no formal reporting of serious adverse events is mandated in this observational study.

11.2 Safety monitoring

An ongoing review of acute toxicities will be performed for safety monitoring of this protocol using a Bayesian approach. The study uses a Beta-Binomial conjugate model with sceptical priors anchored to a historical cohort of over 500 patients treated without focal boosting in the PRIME trial, in whom acute Grade ≥ 2 GU and GI toxicity rates were 25% and 15% respectively, and Grade 3 toxicity was $< 2\%$ for both endpoints.²³ Formal interim analyses are performed after every cohort of 15 patients, beginning at $n=15$ for descriptive reporting and from $n=30$ onward for all decision rules, giving seven analyses in total. At each interim, twelve posterior probabilities are computed and reported across four endpoint strata: Grade ≥ 2 GU, Grade ≥ 2 GI, Grade 3 GU, and Grade 3 GI.

The trial operates a four-criterion stopping framework and a parallel four-trigger safety review framework, all evaluated from $n=30$. Enrolment is immediately halted if any one of the following co-primary stopping criteria is met based on posterior probability $\geq 95\%$ that:

- Grade ≥ 2 GU toxicity exceeds 40% (Criterion A),
- Grade ≥ 2 GI toxicity exceeds 30% (Criterion B),
- Grade 3 GU toxicity exceeds 10% (Criterion C),
- Grade 3 GI toxicity exceeds 10% (Criterion D).

A Trial Management Committee review is mandated if the posterior probability reaches $\geq 95\%$ that Grade ≥ 2 GU exceeds 35% or GI exceeds 25% corresponding to an absolute excess of more than 10 percentage points above historical rates — or that Grade 3 toxicity in either site exceeds 5%.

If none of the stopping criteria are met across all seven interims, the safety monitoring will complete at 105 patients and the final analysis will characterise the full posterior distributions for all endpoints under both primary sceptical priors and pre-specified sensitivity priors.

12.0 Data and statistical considerations

12.1 Data collection methods

This study will utilize the institutional secure web installation of REDCap (Research Electronic Data Capture), an application developed by Vanderbilt University to capture and store data. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and export data to statistical software for further data analysis. All data will be secured with a regular back-up and stored in a storage server.

A separate secure server based application developed at Tata Medical Center may be used for collecting electronic PRO measures (<https://saathi.chavi.ai>)

12.2 Definition of outcome measures

Freedom from biochemical/clinical failure [FFBF]: Freedom from biochemical failure will be defined as duration from date of recruitment to PSA>2ng/ml over the nadir PSA (Phoenix definition of biochemical failure), or documented prostate cancer progression, related treatment or prostate cancer related death.

Metastasis-free Survival (MFS) is defined as the time from recruitment to time to distant metastasis of prostate cancer or death from any cause.

Overall survival (OS) is defined as the time from randomization to the time of death from any cause

Prostate cancer-specific survival (PCSS) will be calculated from the date of randomization to the date of the death due to prostate cancer.

Quality of life (QoL) is defined as patient-reported outcomes captured using the EORTC QLQ c30 and PR25 questionnaire

12.3 Statistical considerations

12.3.1 Study Sample Size

This is a prospective observational study with the primary aim of evaluating a new standard of care, and not a formal evaluation of an experimental approach. The sample size considerations are based on having enough numbers to be able to achieve the following tasks:

1. Determine a reasonably precise estimate of 5-year FFBF, acute toxicity, and patient reported outcomes in a typical cohort of patients with high-risk and node positive prostate cancer treated in India.
2. Compare the outcomes of this cohort to a historical cohort of 140 patients treated at Tata Medical Center without a focal boost but in a prospective randomized trial with identical eligibility criteria.

3. Perform an interobserver variation assessment for MRI based focal boost volume delineation and train an autosegmentation model.

Sample size calculations have been primarily based on the second objective, based primarily on a time-to-event endpoint of FFBF.

A Bayesian two-prior framework is used to determine sample size and conduct the primary analysis, following the method of Horiguchi et al³² for single-arm trials with time-to-event endpoints. This approach was selected over the conventional frequentist one-sample log-rank test for three reasons specific to this study: a) the internal 140-patient historical cohort provides genuine prior information about the baseline hazard rate that should not simply be discarded after setting a threshold; b) the projected 83% five-year FFBF is derived from an immature cohort and carries uncertainty that the Bayesian prior directly encodes; and c) the magnitude of the treatment effect is uncertain, with the external RCT suggesting +8 percentage points in a similar but not identical population.

The framework separates the analysis prior, a Gamma(10, 12.78) distribution on the hazard ratio, centred at the midpoint between null and alternative and incorporating prior knowledge from a design prior, a truncated normal distribution ($\sigma = 0.109$) representing uncertainty in the anticipated treatment effect over a plausible range of 88–92% five-year FFBF. Bayesian power is computed by averaging over the design prior rather than conditioning on a single assumed effect size, avoiding the local optimality problem of classical methods.

The primary endpoint is five-year FFBF analysed as a time-to-event outcome under a proportional hazards model. The historical control survival function $S_0(t)$ is modelled as exponential with five-year FFBF of 83% ($\lambda_0 = 0.0373/\text{year}$) based on the assumptions of the PRIME trial. The conservative target FFBF is 90% at 5 years.

The sample size calculation is provided as a part of the statistical analysis plan in Appendix 9.

The minimum required sample size under the primary scenario (informative analysis prior, $\sigma = 0.109$ design prior, 80% Bayesian power) is 95 evaluable patients, corresponding to 105 recruited after 10% attrition. The study will target recruitment of N = 122 patients (to accommodate a wider design prior of 85-95%) over three years, with a ceiling of N = 130.

12.3.2 Statistical Analysis

Categorical data will be expressed as percentages and compared between the treatment groups using the chi-square test (or the Fisher's exact test). Continuous Quantitative data will be expressed as means/medians and standard deviations (or medians and interquartile ranges) and compared between the treatment groups using the Student's t-test (or the Wilcoxon test).

Longitudinal patient-reported outcome data will be analyzed using linear mixed models. Linear mixed models are appropriate for this analysis as the data is longitudinal, correlated and likely to contain missing observations. This is also recommended by the recent SISAQOL guidelines³³ on the analysis of longitudinal patient reported outcomes.

Time-to-event outcomes will be estimated using the Kaplan-Meier method with 95% confidence Intervals. The comparison will be adjusted on stratification factors using the Cox model. The median follow-up will be estimated using the reverse Kaplan-Meier method.

The primary Bayesian analysis for FFBF computes the posterior probability $P(\theta < 1 \mid \text{data})$ using the Gamma conjugate update, reports the posterior mean and 95% highest density interval for both the hazard ratio and the five-year FFBF probability, and delivers a binary decision against the pre-specified threshold of 0.95, provided the minimum five observed events requirement is met.

A Kaplan-Meier estimate with 95% confidence interval for observed five-year FFBF will be reported alongside the Bayesian posterior.

Pre-specified sensitivity analyses address variation in analysis prior strength from non-informative through strongly informative, widening of the design prior to reflect greater treatment effect uncertainty, variation of the historical baseline assumption by ± 3 percentage points, worst-case attrition treating dropouts as failures, a proportional hazards assumption check with Weibull fallback if violated, competing risks analysis if non-prostate mortality is substantial, and a frequentist one-sample log-rank test for contextual comparison. Any deviation from the pre-specified plan will be documented prospectively with justification before the deviation is executed.

The plan for analysis of acute physician reported toxicities is outlined in the section on safety monitoring (Section 11.2)

All analyses will be performed in R (version $\geq 4.3.0$). A detailed version of the Statistical analysis plan is presented in Appendix 9.

13.0 Other considerations

13.1 Translational Research

Data regarding imaging, segmentation, and patient-reported outcomes will be recorded in the CHAVI database, an open oncology imaging and data archive initiated by Tata Medical Center.

13.2 Research ethics approval

This protocol and the template informed consent forms contained in Appendix will be reviewed and approved by the institutional IRB with respect to scientific content and compliance with applicable research and human subjects' regulations. The protocol, site-specific informed consent forms (local language and English versions), participant education and recruitment materials, and other requested documents—and any subsequent modifications — also will be reviewed and approved by the IRB. Subsequent to initial review and approval, the IRB will review the protocol at least annually. The Investigator will make safety and progress reports to the IRB at intervals mandated by the IRB policies, and within three months of study termination or completion.

13.3 Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Any and all such amendments will be communicated to the institutional IRB for review and approval. Administrative changes of the protocol are minor corrections and/or

clarifications that have no effect on the way the study is to be conducted. These may be communicated to the IRB at the investigators' discretion.

13.4 Consent

Patients will be given the patient information sheet by the trial investigators / nurses. The purpose and reasons behind the study will be communicated to the patient. All patients will be provided with a copy of the written informed consent as well as the patient information sheet. Consent will be on as per institutional IRB guidelines.

13.5 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID [identification] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

13.6 Access to data

Role-based, password-protected data access will be provided on REDCap to members of the study team.

13.7 Trial Quality Assurance

All patients will be planned strictly according to the institutional protocol for MRI-guided focal boost including image fusion, target delineation, treatment planning, patient-specific QA and daily image-guidance.

14.0 Substudy for DNB thesis

As a part of the DNB thesis for Dr Gopinath, the following limited assessments will be performed

14.1 Aim

To evaluate the rate of Grade 2+ acute toxicities following MRI-guided focal boost radiotherapy, along with assessment of early patient-reported outcomes.

14.2 Objectives

Primary Objective:

- To document the rate of Grade 2+ acute toxicities of MRI guided focal boost and determine an initial posterior probability of higher acute toxicities compared to the PRIME trial

Secondary objectives

- To obtain early patient-reported quality of life outcomes for MRI guided focal boost
- To determine interobserver variability in the boost volume segmentation between experts
- To determine the dosimetric compliance to target coverage and organs-at-risk doses

14.3 Sample size

The first 30 patients enrolled in this study will be evaluated in the thesis. This sample will allow the following:

- a) The completion of the interobserver variability study for MRI assisted boost volume segmentation
- b) An assessment of the plan dosimetry to determine if organs-at-risk doses can be kept within constraints.
- c) An initial bayesian estimate of posterior probability of higher acute toxicities
- d) An initial assessment of early quality of life data from this new treatment which has not been reported earlier.

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Appendix 1 : Karnofsky Performance Scale

- 100- Normal, no complaints, no evidence of disease
 90 - Able to carry on normal activity: minor symptoms of disease
 80 - Normal activity with effort: some symptoms of disease
 70 - Cares for self: unable to carry on normal activity or active work
 60 - Requires occasional assistance but is able to care for needs
 50 - Requires considerable assistance and frequent medical care
 40 - Disabled: requires special care and assistance
 30 - Severely disabled: hospitalization is indicated, death not imminent
 20 - Very sick, hospitalization necessary: active treatment necessary
 10 - Moribund, fatal processes progressing rapidly

Appendix 2 : IPSS score**International Prostate Symptom Score (I-PSS)**

Patient Name: _____ Date of birth: _____ Date completed _____

In the past month:	Not at all	Less than 1 in 5 times	Less than half the time	About half the time	More than half the time	Almost always	Your score
1. Incomplete Emptying How often have you had the sensation of not emptying your bladder?	0	1	2	3	4	5	
2. Frequency How often have you had to urinate less than every two hours?	0	1	2	3	4	5	
3. Intermittency How often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
4. Urgency How often have you found it	0	1	2	3	4	5	

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difficult to postpone urination?							
5. Weak Stream How often have you had a weak urinary stream	0	1	2	3	4	5	
6. Straining How often have you had to strain to start urination?	0	1	2	3	4	5	
	None	1 Time	2 Times	3 Times	4 Times	5 Times	
7. Nocturia How many times did you typically get up at night to urinate?	0	1	2	3	4	5	
Total I-PSS Score							

Score: 1-7: *Mild* 8-19: *Moderate* 20-35: *Severe*

Quality of Life Due to Urinary Symptoms	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?	0	1	2	3	4	5	6

About the I-PSS

The International Prostate Symptom Score (I-PSS) is based on the answers to seven questions concerning urinary symptoms and one question concerning quality of life. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic).

The questions refer to the following urinary symptoms:

Questions	Symptom
1	Incomplete emptying
2	Frequency
3	Intermittency
4	Urgency
5	Weak Stream
6	Straining
7	Nocturia

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Question eight refers to the patient's perceived quality of life.

The first seven questions of the I-PSS are identical to the questions appearing on the American Urological Association (AUA) Symptom Index which currently categorizes symptoms as follows:

Mild (symptom score less than or equal to 7)

Moderate (symptom score range 8-19)

Severe (symptom score range 20-35)

The International Scientific Committee (SCI), under the patronage of the World Health Organization (WHO) and the International Union Against Cancer (UICC), recommends the use of only a single question to assess the quality of life. The answers to this question range from "delighted" to "terrible" or 0 to 6. Although this single question may or may not capture the global impact of benign prostatic hyperplasia (BPH) Symptoms or quality of life, it may serve as a valuable starting point for a doctor-patient conversation.

The SCI has agreed to use the symptom index for BPH, which has been developed by the AUA Measurement Committee, as the official worldwide symptoms assessment tool for patients suffering from prostatism.

Appendix 3 : Table 1 - Dose constraints for both dose-fractionation schedules

Ultrahypofraction (5 fractions)					Moderate hypofractionation (20 fractions)				
Structure	Dose/ volume	Constraint	Dose (Gy)	BED	Structure	Dose/ volume	Constraint	Dose (Gy)	BED
GTV_boost	V42Gy (optimal)	>99%	42.0	277.2	GTV_boost	V77Gy (optimal)	>99%	77.0	274.6
	V38Gy (essential)	>99%	38.0	230.5		V70Gy (essential)	>99%	70.0	233.3
	V45Gy	<0.1cc	45.0	315.0		V82Gy	<0.1cc	82.0	306.1
PTVp_36.25/5	V36.25Gy	≥95%			PTVp_62/20	V62Gy	≥95%		
PTVn_25/5	V25Gy	≥95%			PTVn_44/20	V44Gy	≥95%		
CTVp_36.25/5	V36.25Gy	>99%			CTVp_62/20	V62Gy	>99%		
CTVn_25/5	V25Gy	≥99%			CTVn_44/20	V44Gy	≥99%		
Anorectum_PRV	V42Gy	<0.035 cc	42.0	159.6	Anorectum_PRV	V72Gy	<0.035 cc	72.4	159.8
Anorectum	V40Gy	<0.035 cc	40.0	146.7	Anorectum	V68Gy	<0.035 cc	68.5	146.7
	V37Gy	< 0.5cc	37.0	128.3		V62.7Gy	<0.5cc	62.7	128.2
	V36.25Gy	<2%	36.3	123.9		V61Gy	<2%	61.2	123.6
	V35Gy	<3% (<1 cc)	35.0	116.7		V59Gy	<3% (<1 cc)	59.0	117.0

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	V33.5Gy	<8%	33.5	108.3		V56Gy	<8%	56.0	108.3
	V32Gy	<10% (<9.7cc)	32.0	100.3		V53Gy	<10% (<9.7cc)	53.0	99.8
	V28Gy	<20% (<15.9cc)	28.0	80.3		V47Gy	<20% (<15.9cc)	47.0	83.8
	V25Gy	< 30%	25.0	66.7		V40 Gy	< 30%	40.0	66.7
	V21Gy	< 40%	21.0	50.4		V32 Gy	< 40%	32.0	49.1
	V16Gy	< 50%	16.0	33.1		V24 Gy	< 50%	24.0	33.6
	V10Gy	< 65%	10.0	16.7		V15 Gy	< 65%	15.0	18.8
						V10 Gy	< 90%	10.0	11.7
Bladder	V42.0Gy	<1 cc	42.0	159.6	Bladder	V72Gy	<1cc	72.0	158.4
	V37.0Gy	<5cc	37.0	128.3		V63Gy	<0.5cc	63.0	129.2
	V36.25Gy	< 2%	36.3	123.9		V62Gy	<2%	61.2	123.6
	V35Gy	< 3%	35.0	116.7		V59 Gy	<3%	59.0	117.0
	V33.5Gy	< 8% (<23.6cc)	33.5	108.3		V56 Gy	<8% (<23.6cc)	56.0	108.3
	V32Gy	< 10% (<38.1cc)	32.0	100.3		V53 Gy	< 10% (<38.1cc)	53.0	99.8
	V28Gy	< 20%	28.0	80.3		V47 Gy	< 20%	47.0	83.8
	V25Gy	< 30%	25.0	66.7		V40 Gy	< 30%	40.0	66.7
	V21Gy	< 40%	21.0	50.4		V32 Gy	< 40%	32.0	49.1
	V16Gy	< 50%	16.0	33.1		V24 Gy	< 50%	24.0	33.6
	V10Gy	< 65%	10.0	16.7		V15 Gy	< 65%	15.0	18.8
						V10 Gy	< 90%	10.0	11.7
Urethra	V40Gy	<0.035cc	40.0	146.7	Urethra	V68Gy	<0.035cc	68.0	145.1
Urethra_PRV	V42Gy	<0.035cc	42.0	159.6	Urethra_PRV	V72Gy	<0.035cc	72.0	158.4
Bag_Bowel	V25Gy	< 90cc	25.0	66.7	Bag_Bowel	V45Gy	<90cc	45.0	78.8
	V27.5Gy	< 2cc	27.5	77.9					
Femur_Head	V15Gy	≤ 5%	15.0	30.0	Femur_Head	V23Gy	<5%	23.0	31.8
PenileBulb	V28Gy	≤ 50%	28.0	80.3	PenileBulb	V47Gy	< 50%	47.0	83.8

Appendix 4 : RTOG Acute Toxicity

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/ 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 distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion
GU	No change	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis

Appendix 5 : RTOG Late Toxicity

Organ	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Small/ Large intestine	No change	Mild diarrhoea; mild cramping; bowel movement 5 times daily; slight rectal discharge or bleeding	Moderate diarrhoea and colic; bowel movement > 5 times daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis / perforation fistula
Bladder	No change	Slight epithelial atrophy; minor telangiectasia (microscopic hematuria)	Moderate frequency; generalized telangiectasia; intermittent macroscopic hematuria	Severe frequency & dysuria; severe telangiectasia (often with petechiae); frequent hematuria; reduction in	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis

				bladder capacity (<150 cc)	
--	--	--	--	-------------------------------	--

Appendix 6 : Common Terminology Criteria for Adverse Events (CTCAE) version 6.0

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Proctitis	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); fecal urgency or stool incontinence; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Rectal Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self-care ADL	-	-
Rectal Hemorrhage (Bleeding)	Mild; no intervention required	Moderate; minimal intervention (e.g., medication)	Transfusion, endoscopic or radiologic intervention indicated	Life-threatening; urgent intervention	Death
Rectal Ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g., altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Urinary Frequency	Present	Medical management indicated; limiting instrumental ADL	-	-	-

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Urinary Urgency	Present	Medical management indicated; limiting instrumental ADL	-	-	-
Urinary Retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Urinary Pain (Dysuria)	Present	-	-	-	-
Urinary Tract Obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Altered organ function (e.g., hydronephrosis or renal dysfunction); invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Appendix 7 : QLQC30 questionnaire

ENGLISH

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31

--	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

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HINDI

**EORTC QLQ-C30 (version 3) (वर्जन ३.०)**

हम आपके और आपके स्वास्थ्य के बारे में कुछ बातें जानना चाहते हैं . कृपया आप सब प्रश्नों का उत्तर स्वयं उस अंक पर गोला बनाकर दें जो आपको सबसे सही लगता है . कोई भी उत्तर सही या गलत नहीं है . आपके द्वारा दी गयी जानकारी गुप्त रखी जाएगी .

केस फाईल क्रमांक : अनुक्रमांक :

आपके नाम के अक्षर :

आपकी जन्मतिथि (दिन, मास, वर्ष) :

आज की तिथि (दिन, मास, वर्ष) :

क्रमांक		विलकुल नहीं	थोड़ा सा	थोड़ा अधिक	बहुत अधिक
1.	क्या आपको मेहनत के काम करने में कठिनाई होती है? जैसे कि बाज़ार की भारी थैली या सुटकेस उठाना?	1	2	3	4
2.	क्या आपको दूर तक टहलने में कोई कष्ट होता है?	1	2	3	4
3.	क्या आपको घर के आसपास थोड़ा टहलने में कोई तकलीफ होती है?	1	2	3	4
4.	क्या आपको दिन में कुर्सी में बैठने की या बिस्तर पर लेटे रहने की जरूरत महसूस होती है?	1	2	3	4
5.	क्या आपको खाने, कपड़े पहनने, नहाने या शौचालय जाने में मदद की जरूरत पड़ती है?	1	2	3	4
	पिछले एक सप्ताह के दौरान	विलकुल नहीं	थोड़ा सा	थोड़ा अधिक	बहुत अधिक
6.	क्या आपको अपना काम करने में या दूसरे दैनिक कार्यों में रुकावट महसूस हुई?	1	2	3	4
7.	क्या आपको अपने शौक पूरे करने में या दूसरे फुर्सत के कार्यों में रुकावट महसूस हुई?	1	2	3	4
8.	क्या आपको साँस लेने में तकलीफ हुई?	1	2	3	4
9.	क्या आपको दर्द था?	1	2	3	4
10.	क्या आपको आराम की जरूरत थी?	1	2	3	4
11.	क्या आपको सोने में कठिनाई हुई?	1	2	3	4
12.	क्या आपको कमजोरी महसूस हुई?	1	2	3	4
13.	क्या आपकी भूख कम हो गयी थी?	1	2	3	4
	अगले पन्ने पर				

	पिछले एक सप्ताह के दौरान	विलकुल नहीं	थोड़ा सा	थोड़ा अधिक	बहुत अधिक
14.	क्या आपको मचली महसूस होती थी?	1	2	3	4
15.	क्या आपको उल्टी हुई?	1	2	3	4
16.	क्या आपको कब्जियत रही थी?	1	2	3	4
17.	क्या आपको जुलाब होते थे?	1	2	3	4
18.	क्या आपको थकान महसूस होती थी?	1	2	3	4
19.	क्या दर्द के कारण आपके दैनिक कार्यों में रुकावट आयी?	1	2	3	4
20.	क्या आपको ध्यान लगाकर कोई काम करने में परेशानी हुई थी, जैसे की अखवार पढ़ना या टीवी देखना?	1	2	3	4
21.	क्या आप तनाव महसूस करते थे?	1	2	3	4
22.	क्या आपको चिंता रहती थी?	1	2	3	4
23.	क्या आपको चिड़चिड़ापन महसूस होता था?	1	2	3	4
24.	क्या आप उदास रहे?	1	2	3	4
25.	क्या आपको चीजे याद रखने में कठिनाई हुई?	1	2	3	4
26.	क्या आपको शारीरिक अवस्था या दवा इलाज के कारण आपके पारिवारिक जीवन में बाधा आई है?	1	2	3	4
27.	क्या आपकी शारीरिक अवस्था या दवा इलाज के कारण आपके सामाजिक क्रियाकलाप में बाधा आई है?	1	2	3	4
28.	क्या आपकी शारीरिक अवस्था या दवा इलाज के कारण आपको आर्थिक परेशानी हुई है?	1	2	3	4

इन प्रश्नों का उत्तर 1 से 7 तक के अंकों में से उस पर गोला बनाकर दें, जो आप पर सबसे ज्यादा लागू होता हो।

29. पिछले सप्ताह के अपने पूर्ण स्वास्थ्य का मूल्यांकन आप कैसे करेंगे?

1	2	3	4	5	6	7
वहत खराब						वहत अच्छा

30. पिछले सप्ताह के अपने कुल जीवन स्तर का मूल्यांकन आप कैसे करेंगे?

1	2	3	4	5	6	7
बहुत खराब						बहुत अच्छा

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BENGALI



EORTC QLQ - C30 (version 3)

আমরা আপনার এবং আপনার স্বাস্থ্য সম্পর্কে খবর রাখতে চাই। সমস্ত প্রশ্নগুলির আপনি নিজে উত্তর দিন এবং যে নম্বরগুলি সবচেয়ে বেশী প্রযোজ্য তাতে বোল দাগ দিন।
এখানে ঠিক বা ভুল বলে কোন উত্তর হবে না। আপনার দেওয়া সমস্ত খবরগুলি গোপন রাখা হবে।

আপনার নামের প্রথম অক্ষরটি লিখুন

(প্রসেস কুমার দাশগুপ্ত - আপনি লিখবেন পি কে ডি)

আপনার জন্ম তারিখ (দিন, মাস, বছর)

আজকের তারিখ

	একবারেই না	অল্পবিধুর	অনেকটাই	অত্যন্ত বেশী ভাবে
1 কোল জরুরী কাজে, যেমন জরুরী ব্যক্তিরের খপি বা দুটাকম বহন করতে আপনার কি কোন কষ্ট হয়?	1	2	3	4
2 লম্বা পথ হটিতে গেলে কি আপনার কষ্ট হয়?	1	2	3	4
3 বাড়ীর বাইরে একটু হটাচলা করতে গেলে কি আপনার কষ্ট হয়?	1	2	3	4
4 নিজের বেশার কি আপনাকে বিছাদা বা চেয়ারে শুষে বা বসে থাকতে হয়?	1	2	3	4
5 দৈনন্দিন কাজ যেমন খাওয়া, জামাকাপড় পরা, হাঙ্গ করা অথবা বাথরুম যাওয়ার জন্য আপনার কি সাহায্যের প্রয়োজন হয়?	1	2	3	4
গত এক সপ্তাহের মধ্যে				
6 চাকুরী ক্ষেত্রে অথবা দৈনন্দিন জীবনযাত্রার কাজে আপনার কি কোন শারীরিক সীমাবদ্ধতা এসেছিল?	1	2	3	4
7 অবসর সময়ে আপনার ব্যক্তিগত সমের কাজগুলো, যেমন বাগানের পরিচর্যা করা ইত্যাদি করার সময়ে শারীরিক ভাবে কোন বাধা এসেছিল কি?	1	2	3	4
8 আপনার কি হাঁট পরেছিল?	1	2	3	4
9 কোন বাধা হয়েছিল?				
10 আপনার কি বিশ্রাম নিতে হয়েছিল?	1	2	3	4
11 ঘুমের কোন অসুবিধা হয়েছিল কি?	1	2	3	4
12 দুর্বল লাগেছিল?	1	2	3	4

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গত এক সপ্তাহের মধ্যে	একবারেই না	অন্যকিছুর	অনেকটাই	অত্যন্ত বেশী ভাবে
13 খিদে কমে গেছে?	1	2	3	4
14 গা গুলিয়েছিল?	1	2	3	4
15 ঘনি হয়েছিল?	1	2	3	4
16 কোষ্ঠকাঠিন্য ছিল?	1	2	3	4
17 পেট খারাপ অথবা গ্যাসের ব্যথা হতো?	1	2	3	4
18 ক্লান্তি বোধ করতেন?	1	2	3	4
19 ব্যর্থতা জেনে কি আপনার দৈনন্দিন কাজে কোন বাধা হয়েছিল?	1	2	3	4
20 বই পড়া, টিভি দেখা অথবা খবরের কাগজ পড়ার সময় কি মনোযোগে ব্যাঘাত ঘটত?	1	2	3	4
21 কোন মাসিক উদ্বেগের পোশ করতেন?	1	2	3	4
22 দুশ্চিন্তায় ভুগতেন?	1	2	3	4
23 মেজাজ কি খিটখিটে হয়ে যেত?	1	2	3	4
24 মাসিক অবসাদগ্রস্ত হতেন কি?	1	2	3	4
25 কোন কিছু স্বপ্ন করতেন কি অসুবিধা হত?	1	2	3	4
26 আপনার শারীরিক অবস্থা অথবা চিকিৎসা পদ্ধতি আপনার পারিবারিক জীবন ব্যাঘাত ঘটাত কি?	1	2	3	4
27 আপনার শারীরিক অবস্থা অথবা চিকিৎসা পদ্ধতি আপনার অন্য সামাজিক কাজে কি বাধাত সৃষ্টি করত?	1	2	3	4
28 আপনার শারীরিক অবস্থা অথবা চিকিৎসা পদ্ধতির জন্য আপনার কি কোন অর্থিক সমস্যায় পড়তে হয়েছিল?	1	2	3	4

নিম্নলিখিত প্রশ্নগুলির উত্তরের জন্য 1 থেকে 7 নম্বর পর্যন্ত সংখ্যার মধ্যে যেটি আপনার ক্ষেত্রে সব থেকে বেশী প্রযোজ্য ভাবে ওপর গেল দশ দিন

29 গত এক সপ্তাহে আপনার স্বাস্থ্য সামান্যতবে যে রকম ছিল তা বোঝাতে কি ভাবে প্রতীকিত করবেন?

1 2 3 4 5 6 7
(ভীষণ খারাপ) (অসামান্য)

30 গত এক সপ্তাহে আপনার দৈনন্দিন জীবন যাত্রার মান কেমন ছিল বোঝাতে কিভাবে দর দেবেন?

1 2 3 4 5 6 7
(ভীষণ খারাপ) (অসামান্য)

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Appendix 8 : PR25 EORTC questionnaire

ENGLISH



EORTC QLQ - PR25

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week	Not at all	A little	Quite a bit	Very much
31. Have you had to urinate frequently during the day ?	1	2	3	4
32. Have you had to urinate frequently at night ?	1	2	3	4
33. When you felt the urge to pass urine, did you have to hurry to get to the toilet?	1	2	3	4
34. Was it difficult for you to get enough sleep, because you needed to get up frequently at night to urinate?	1	2	3	4
35. Have you had difficulty going out of the house because you needed to be close to a toilet?	1	2	3	4
36. Have you had any unintentional release (leakage) of urine?	1	2	3	4
37. Did you have pain when you urinated?	1	2	3	4
38. Answer this question only if you wear an incontinence aid. Has wearing an incontinence aid been a problem for you?	1	2	3	4
39. Have your daily activities been limited by your urinary problems?	1	2	3	4
40. Have your daily activities been limited by your bowel problems?	1	2	3	4
41. Have you had any unintentional release (leakage) of stools?	1	2	3	4
42. Have you had blood in your stools?	1	2	3	4
43. Did you have a bloated feeling in your abdomen?	1	2	3	4
44. Did you have hot flushes?	1	2	3	4
45. Have you had sore or enlarged nipples or breasts?	1	2	3	4
46. Have you had swelling in your legs or ankles?	1	2	3	4

During the last 4 weeks...	Not at all	A little	Quite a bit	Very much
47. Has weight loss been a problem for you?	1	2	3	4
48. Has weight gain been a problem for you?	1	2	3	4
49. Have you felt less masculine as a result of your illness or treatment?	1	2	3	4
50. To what extent were you interested in sex?	1	2	3	4
51. To what extent were you sexually active (with or without intercourse)?	1	2	3	4

PLEASE ANSWER THE NEXT FOUR QUESTIONS ONLY IF YOU HAVE BEEN SEXUALLY ACTIVE OVER THE LAST 4 WEEKS

52. To what extent was sex enjoyable for you?	1	2	3	4
53. Did you have difficulty getting or maintaining an erection?	1	2	3	4
54. Did you have ejaculation problems (eg dry ejaculation)?	1	2	3	4
55. Have you felt uncomfortable about being sexually intimate?	1	2	3	4

HINDI



EORTC QLQ – PR25

रोगी कभी बताते हैं कि उन्हें निम्न लक्षण या कष्ट हैं। पिछले सप्ताह में आपको किस हद तक यह लक्षण या कष्ट थे यह सूचित करें।
कृपया आप सब प्रश्नों का उत्तर सही अक्षरों पर गोला बनाकर दें।

पिछले सप्ताह में

	बिल्कुल नहीं	थोड़ासा	थोड़ा अधिक	बहुत अधिक
31. क्या आपको दिन में बार बार पेशाब होता था?	१	२	३	४
32. क्या आपको रात में बार बार पेशाब होता था?	१	२	३	४
33. क्या पेशाब लगने पर आपको तुरन्त मुबालय जाना पड़ता था?	१	२	३	४
34. क्या आपकी नींद पूरी होने में बाधा हुई थी, क्योंकि आपको पेशाब के लिए रात में बार बार उठना पड़ता था?	१	२	३	४
35. क्या आपको घर के बाहर जाने में बाधा हुई थी, क्योंकि आपको मुबालय के आसपास रहने की जरूरत पड़ती थी?	१	२	३	४
36. क्या अज्ञाने में कभी आपका पेशाब निकल जाता था?	१	२	३	४
37. क्या आपको पेशाब करते समय दर्द होता था?	१	२	३	४
38. इस प्रश्न का उत्तर तभी दें अगर अनियमित पेशाब को रोकने के लिए किसी साधन का उपयोग कर रहे हैं – क्या ऐसे साधन के उपयोग से आपको परेशानी हुई?	१	२	३	४
39. क्या आपकी दिनचर्या आपकी पेशाब की समस्या के कारण सीमित हो गई थी?	१	२	३	४
40. क्या आपकी दिनचर्या आपकी पछाने की समस्या के कारण सीमित हो गई थी?	१	२	३	४
41. क्या अज्ञाने में कभी आपको पछाना हो जाता था?	१	२	३	४
42. क्या आपके पछाने में खून आया था?	१	२	३	४
43. क्या आपको पेट में फूलन महसूस हुई थी?	१	२	३	४
44. क्या आपको बहुत गर्मी लगी और चेहरा लाल हो गया था?	१	२	३	४
45. क्या आपके स्तन या स्तनाग्र का आकार बढ़ा या उनमें दर्द हुआ था?	१	२	३	४
46. क्या आपके पंखों या ऐडियों में सूजन हुई थी?	१	२	३	४

BENGALI

**EORTC QOL-PR25**

রোগীরা কখনও কখনও তাদের নিম্নলিখিত উপসর্গ বা সমস্যার কথা জানিয়ে থাকেন। অনুগ্রহ করে কলুন গত সপ্তাহে আপনি এই উপসর্গ অথবা সমস্যাগুলি ঠিক কতটা অনুভব করেছিলেন। অনুগ্রহ করে আপনার ক্ষেত্রে সবচেয়ে প্রযোজ্য নম্বরটিতে পোল দাগ দিয়ে প্রতিটি প্রশ্নের উত্তর দিন।

গত এক সপ্তাহের মধ্যে:	একেবারেই না	অল্প বিস্তার	অনেকটাই	অত্যন্ত বেশী ভাবে
31. আপনার দিনের বেলায় বার বার প্রস্রাব হয়েছে কি?	1	2	3	4
32. আপনার রাতের বেলায় বার বার প্রস্রাব হয়েছে কি?	1	2	3	4
33. প্রস্রাব পেলে আপনাকে অবিলম্বে শৌচালয়ে যেতে হয়েছে কি?	1	2	3	4
34. রাতের বেলায় বার বার প্রস্রাব করতে ওঠার প্রয়োজনে আপনার ঘুম অপর্যাপ্ত হয়েছে কি?	1	2	3	4
35. শৌচালয়ের কাছাকাছি থাকার প্রয়োজন বোধ করেন বলে আপনার বাড়ির বাহিরে বেরতে অসুবিধে হয়েছে কি?	1	2	3	4
36. আপনার অনিচ্ছাকৃতভাবে প্রস্রাব হয়ে গেছে কি?	1	2	3	4
37. আপনি প্রস্রাব করার সময় ব্যাথা অনুভব করেছেন কি?	1	2	3	4
38. এই প্রশ্নের উত্তর তবেই দেবেন যদি আপনি অনিয়ন্ত্রিত প্রস্রাবের জন্য কোন সাধন পরিধান করে থাকেন – এই সাধন পরিধান করতে আপনার অসুবিধে হয়েছে কি?	1	2	3	4
39. আপনার প্রস্রাবের সমস্যার জন্য আপনি দৈনন্দিন কাজকর্মে সীমাবদ্ধতা অনুভব করেছেন কি?	1	2	3	4
40. আপনার পায়খানার সমস্যার জন্য আপনি দৈনন্দিন কাজকর্মে সীমাবদ্ধতা অনুভব করেছেন কি?	1	2	3	4
41. আপনার কি কখন অনিচ্ছাকৃতভাবে পায়খানা বেরিয়ে (নির্গত হয়ে) গেছে?	1	2	3	4
42. আপনার পায়খানার সঙ্গে রক্ত বেরিয়েছে কি?	1	2	3	4
43. আপনার পেট ফোলা বলে মনে হয়েছিল কি?	1	2	3	4
44. আপনার কি হঠাৎ সারা শরীরে গরম ভাব লেগেছে?	1	2	3	4
45. আপনার শ্বন বা শ্বনাশ্র্যে ব্যাথা হয়েছে বা তা আকারে বড় হয়েছে কি?	1	2	3	4
46. আপনার পা বা গোড়ালি ফুলে গেছে কি?	1	2	3	4

MRI-guided Focal Boost in Prostate Cancer Radiation Therapy

পত চার সপ্তাহে :	একেবারেই না	অল্প বিস্তার	অনেকটাই	অত্যন্ত বেশী ভাবে
47. ওজন কমে যাওয়ায় আপনার সমস্যা হয়েছে কি?	1	2	3	4
48. ওজন বেড়ে যাওয়ায় আপনার সমস্যা হয়েছে কি?	1	2	3	4
49. আপনার রোগ বা চিকিৎসার ফলে আপনি পৌরুষের অভাব অনুভব করেছেন কি?	1	2	3	4
50. আপনি যৌনতা নিয়ে কতটা আগ্রহ বোধ করেছেন?	1	2	3	4
51. আপনি যৌনভাবে কতটা সক্রিয় ছিলেন (শারীরিক মেলামেশা করে বা না করে)?	1	2	3	4
পরবর্তী চারটি প্রশ্নের উত্তর তবেই দেবেন যদি আপনি পত চার সপ্তাহের মধ্যে যৌনভাবে সক্রিয় হয়ে থাকেন -				
52. যৌন সম্পর্ক আপনি কতটা উপভোগ করেছেন?	1	2	3	4
53. আপনার লিঙ্গকে উত্তেজিত করতে বা উত্তেজিত রাখতে অসুবিধে হয়েছে কি?	1	2	3	4
54. আপনার বীর্ষপাত করতে কোন সমস্যা হয়েছে কি (যেমন শুকনো বীর্ষপাত)?	1	2	3	4
55. যৌন-সম্পর্কের ঘনিষ্ঠতার কথা ভাবলে আপনি অস্বস্তি বোধ করেছেন কি?	1	2	3	4

Appendix 9 : Statistical analysis plan

STATISTICAL ANALYSIS PLAN

MRI-Guided Focal Boost Radiotherapy in High-Risk Localised Prostate Cancer

Single-Arm Prospective Study — Bayesian Adaptive Design | Version 1.1

Element	Specification
Study Design	Single-arm prospective Bayesian adaptive — efficacy (time-to-event) + safety (sequential)
Population	High-risk localised prostate cancer receiving MRI-guided focal dose boost radiotherapy
Primary Efficacy Endpoint	5-year freedom from biochemical failure (FFBF) — time-to-event, vs. historical 83%
Primary Safety Endpoint	Acute Grade ≥2 GU toxicity rate (CTCAE v5.0) within treatment + 3 months
Secondary Safety Endpoint	Acute Grade ≥2 GI toxicity rate (CTCAE v5.0) within treatment + 3 months
Historical Controls	Efficacy: 83% 5-yr FFBF (n=140 internal cohort) Safety: GU 25%, GI 15% (n=500)
Sample Size	Efficacy: N=122 target (ceiling 130) Safety monitoring: max N=105 (7 interims of 15)
Efficacy Decision	$P(\theta < 1 \text{data}) \geq 0.95$ AND ≥ 5 observed failure events
Safety Stopping	$\Pr(\theta_{GU} \geq 2 > 0.40 \text{data}) \geq 0.95$ OR $\Pr(\theta_{GI} \geq 2 > 0.30 \text{data}) \geq 0.95$ OR Grade 3 analogues
Statistical Models	Gamma-Exponential conjugate (efficacy) Beta-Binomial conjugate (safety) — no MCMC
Software	R ≥ 4.3.0 (survival, gsDesign, ggplot2)

1. Background and Rationale

Clinical context. MRI-guided focal boost delivers an escalated radiation dose to the dominant intraprostatic lesion (DIL) while treating the whole prostate to standard dose. An external RCT demonstrated +8 percentage points improvement in 5-year FFBF (85%→93%). This single-arm study asks whether this benefit replicates in a slightly higher-risk population with historical 5-year FFBF of 83%, where the technique is not yet universally available, and a well-characterized internal historical cohort (n=140) provides the reference control.

This statistical analysis plan for the time-to-event endpoint adopts the **two-prior framework** of Horiguchi, Yokota & Teramukai (*Pharmaceutical Statistics*, 2026): an **analysis prior** $\pi^A(\theta)$ encodes historical knowledge and drives the posterior; a **design prior** $\pi^D(\theta)$ models uncertainty about the true effect size and drives sample size via Bayesian power. For safety monitoring, a conjugate Beta-Binomial model provides exact closed-form posteriors at each interim without simulation.

2. Efficacy Analysis — Time-to-Event Model

2.1 Hypotheses and decision threshold

A Bayesian two-prior framework is used to determine sample size and conduct the primary analysis, following the method of Horiguchi et al for single-arm trials with time-to-event endpoints. This approach was selected over the conventional frequentist one-sample log-rank test for three reasons specific to this study: a) the internal 140-patient historical cohort treated under the PRIME trial provides genuine prior information about the baseline hazard rate that should not simply be discarded after setting a threshold; b) the projected 83% five-year FFBF is derived from an immature cohort and carries uncertainty that the Bayesian prior directly encodes; and c) the magnitude of the treatment effect is uncertain, with the external RCT suggesting +8 percentage points in a similar but not identical population.

H₀: $\theta \geq 1.0$ (5-year FFBF $\leq 83\%$). **H₁:** $\theta < 1.0$ (5-year FFBF $> 83\%$), where $\theta = \lambda_i/\lambda_0$ is the hazard ratio relative to the historical control. **Conservative target:** FFBF = 90% ($\theta_1 = 0.565$, +7pp). **Optimistic target:** FFBF = 92% ($\theta_1 = 0.447$, +9pp). **Decision criterion:** $P(\theta < 1 \mid \text{data}) \geq 0.95$ at primary analysis, with ≥ 5 observed failure events.

2.2 Proportional hazards model and Horiguchi transformation

Model: $S(t) = [S_0(t)]^\theta$, where $S_0(t)$ is the historical control survival and θ is the HR. No parametric form for S_0 is required; the mature Kaplan-Meier curve from the internal cohort will be used at final analysis. For sample size purposes, S_0 is modelled as exponential: $S_0(t) = \exp(-\lambda_0 t)$ with $\lambda_0 = -\log(0.83)/5 = 0.0373/\text{year}$.
Key transformation: For each patient, define transformed follow-up $W_i = -\log S_0(X_i)$. Under proportional hazards, $T^*_i = -\log S_0(T_i) \sim \text{Exponential}(\theta)$. The sufficient statistics are **d** (events) and **U** = $\sum W_i$ (sum of transformed times). For exponential S_0 : $W_i = \lambda_0 X_i$. *This transformation achieves exponentiality on the transformed scale without requiring it on the original time scale — proportional hazards, not constant hazard, is the operative assumption.* Verified at analysis by log-log KM plot and Schoenfeld residuals.

2.3 Conjugate posterior and analysis priors

Likelihood: $L(\theta) \propto \theta^d \times \exp(-\theta U)$. With Gamma(a, b) analysis prior, the posterior is analytically exact: $\pi(\theta \mid \text{data}) = \text{Gamma}(a+d, b+U)$. Decision probability: $P(\theta < 1 \mid \text{data}) = \text{pgamma}(1, a+d, \text{rate}=b+U)$.
The rate parameter $b = a/\theta^*$ where $\theta^* = (\theta_0 + \theta_1)/2$. This centres the prior midway between null and alternative, at the most neutral defensible location. Three pre-specified analysis priors:

Prior	Gamma(a,b)	ESS	Role
★ Primary (informative)	Gamma(10, 12.78)	10	~9% weight; efficiency gain without dominating data
Weakly informative	Gamma(2, 2.56)	2	~2% weight; near-frequentist behaviour
Non-informative (Jeffreys)	Gamma(0.5, 0)	0.5	Fully data-driven reference

Design prior for sample size: Truncated Normal on $\log(\theta)$ with mean $\log(0.565)$ and $\sigma = 0.109$ (primary) or $\sigma = 0.20$ (conservative), modelling uncertainty about whether the full RCT effect replicates.

2.3 Study design parameters

Parameter	Value
Historical 5-yr FFBF (null, p_0)	0.83 ($S_0(5) = 83\%$)
Null hazard rate λ_0	$-\log(0.83)/5 = 0.0373/\text{yr}$
Conservative target θ_1 (HR)	0.565 (FFBF = 90%)

Parameter	Value
Optimistic target θ_1 (HR)	0.447 (FFBF = 92%)
Null hazard ratio θ_0	1.0 (no improvement)
Posterior threshold λ	0.95
Bayesian power threshold γ	0.80
Minimum events d_{\min}	5
Accrual period	3 years
Minimum follow-up per patient	5 years
Total study duration	8 years
Assumed attrition	10%
Analysis prior (primary)	Gamma(10, 12.78), centred at $\theta^*=0.783$
Design prior (primary)	$\sigma = 0.109$, interval [88%, 92%] FFBF
Simulation replicates N	10,000 for final protocol

2.4 Required sample size results

Scenario	N eval	N recruit	Bay. power
Horiguchi: informative + degenerate design prior	90	100	80.1%
Horiguchi: informative + narrow design prior ($\sigma=0.109$) ★	95	105	82%
Horiguchi: informative + wide design prior ($\sigma=0.20$)	110	122	80%
Horiguchi - Single-prior Bayesian (moderate ESS=20, no design prior)	70	78	81%

Required N = 95-110 evaluable; study targets N = 122 recruited to accommodate a wider design prior (ceiling N = 130), 3-year accrual + 5-year minimum follow-up and a minimum of 5 events.

Calculator app: https://imallick.shinyapps.io/bayesian_samplesize_tte_horiguchi_shiny_app_1/

2.5 R code — efficacy posterior

```
lambda0 <- -log(0.83)/5      # historical hazard: 0.0373/yr
a_pr <- 10; b_pr <- 12.78    # primary Gamma(a,b) analysis prior
```

```
d <- 12 # observed FFBF failure events
U <- sum(lambda0 * obs_times) # transformed person-time (obs_times in years)
a_post <- a_pr + d; b_post <- b_pr + U
pp <- pgamma(1, shape=a_post, rate=b_post) # P(HR < 1 | data)
cat('P(HR<1|data):', round(pp,4), '| Decision:', ifelse(pp>=0.95 & d>=5, 'MET', 'NOT MET'))
```

3. Safety Monitoring — Bayesian Adaptive Design

3.1 Beta-Binomial conjugate model

Objective:

An ongoing review of acute toxicities will be performed for safety monitoring of this protocol using a Bayesian approach. The study uses a Beta-Binomial conjugate model with sceptical priors anchored to a historical cohort of over 500 patients treated without focal boosting in the PRIME trial, in whom acute Grade ≥ 2 GU and GI toxicity rates were 25% and 15% respectively, and Grade 3 toxicity was $<2\%$ for both endpoints.²³

Formal interim analyses are performed after every cohort of 15 patients, beginning at n=15 for descriptive reporting and from n=30 onward for all decision rules, giving seven analyses in total. At each interim, twelve posterior probabilities are computed and reported across four endpoint strata: Grade ≥ 2 GU, Grade ≥ 2 GI, Grade 3 GU, and Grade 3 GI.

The trial operates a four-criterion stopping framework and a parallel four-trigger safety review framework, all evaluated from n=30. Enrolment is immediately halted if any one of the following co-primary stopping criteria is met based on posterior probability $\geq 95\%$ that:

- Grade ≥ 2 GU toxicity exceeds 40% (Criterion A),
- Grade ≥ 2 GI toxicity exceeds 30% (Criterion B),
- Grade 3 GU toxicity exceeds 10% (Criterion C),
- Grade 3 GI toxicity exceeds 10% (Criterion D).

An internal safety committee (ISC) (comprising an independent radiation oncologist + a statistician) review is mandated if the posterior probability reaches $\geq 95\%$ that Grade ≥ 2 GU exceeds 35% or GI exceeds 25% corresponding to an absolute excess of more than 10 percentage points above historical rates — or that Grade 3 toxicity in either site exceeds 5%.

If none of the stopping criteria are met across all seven interims, the safety monitoring will complete at 105 patients and the final analysis will characterise the full posterior distributions for all endpoints under both primary sceptical priors and pre-specified sensitivity priors.

Plan:

At each interim, x events in n evaluable patients: $\mathbf{x} \mid \boldsymbol{\theta}, n \sim \text{Binomial}(n, \boldsymbol{\theta})$. With conjugate Beta prior, the posterior is exact: $\boldsymbol{\theta} \mid \mathbf{x}, n \sim \text{Beta}(\boldsymbol{\alpha}_0 + \mathbf{x}, \boldsymbol{\beta}_0 + n - \mathbf{x})$. No MCMC required.

Sceptical priors anchor to the historical cohort with pseudo-N = 100 (~20% of n=500), deliberately downweighted to account for cross-study heterogeneity:

Endpoint	Prior	Prior Mean	Pseudo-N	Historical Rate
GU Grade ≥ 2 (Co-primary)	Beta(25, 75)	25%	100	25%
GI Grade ≥ 2 (Co-primary)	Beta(15, 85)	15%	100	15%
GU Grade 3 (Co-primary)	Beta(2, 98)	2%	100	$<2\%$
GI Grade 3 (Co-primary)	Beta(2, 98)	2%	100	$<2\%$

3.2 Decision rules

Seven planned interims (n=15, 30, 45, 60, 75, 90, 105). The first (n=15) is **descriptive only**. Formal rules apply from **n=30** (minimum enrolment before early stopping).

ID	Decision Rule	Action if Met	Active from	Priority
A	$\Pr(\theta^{\text{GU}}_{\geq 2} > 0.40 \mid \text{data}) \geq 0.95$	HALT enrolment	n = 30	Co-primary STOP
B	$\Pr(\theta^{\text{GI}}_{\geq 2} > 0.30 \mid \text{data}) \geq 0.95$	HALT enrolment	n = 30	Co-primary STOP
C	$\Pr(\theta^{\text{GU}}_{\geq 3} > 0.10 \mid \text{data}) \geq 0.95$	HALT enrolment	n = 30	Co-primary STOP
D	$\Pr(\theta^{\text{GI}}_{\geq 3} > 0.10 \mid \text{data}) \geq 0.95$	HALT enrolment	n = 30	Co-primary STOP
T-A	$\Pr(\theta^{\text{GU}}_{\geq 2} > 0.35 \mid \text{data}) \geq 0.95$	ISC review	n = 30	Safety Trigger

T-B	$\Pr(\theta^{\text{GI}} \geq 2 > 0.25 \mid \text{data}) \geq 0.95$	ISC review	n = 30	Safety Trigger
T-C	$\Pr(\theta^{\text{GU}} \geq 3 > 0.05 \mid \text{data}) \geq 0.95$	ISC review	n = 30	Safety Trigger
T-D	$\Pr(\theta^{\text{GI}} \geq 3 > 0.05 \mid \text{data}) \geq 0.95$	ISC review	n = 30	Safety Trigger

Any single criterion A–D independently halts enrolment. Any trigger T-A to T-D mandates ISC meeting within one month. Grade 3 stopping threshold (10%) = fivefold excess above historical benchmark (<2%); review threshold (5%) = twofold excess.

3.3 Worked example — second interim (n = 30)

Observed: 10 GU Grade ≥ 2 events, 4 GI Grade ≥ 2 events, 0 Grade 3 events. **GU posterior:** Beta(35, 95). Mean = $35/130 = 26.9\%$. $\Pr(\theta^{\text{GU}} > 0.40) = 1 - \text{pbeta}(0.40, 35, 95) \approx 0.01 \rightarrow$ Criterion A **NOT MET**. **GI posterior:** Beta(19, 111). Mean = 14.6% . $\Pr(\theta^{\text{GI}} > 0.30) \approx 0.00 \rightarrow$ Criterion B **NOT MET**. Enrolment continues to n=45.

3.4 R code — safety interim analysis

```
bayes_safety <- function(x_gu2, x_gi2, x_gu3, x_gi3, n) {
  post_gu2 <- function(t) 1-pbeta(t, 25+x_gu2, 75+n-x_gu2)
  post_gi2 <- function(t) 1-pbeta(t, 15+x_gi2, 85+n-x_gi2)
  post_g3 <- function(ep,t) 1-pbeta(t, 2+ep, 98+n-ep)
  list(
    STOP = post_gu2(0.40)>=0.95 | post_gi2(0.30)>=0.95 |
           post_g3(x_gu3,0.10)>=0.95 | post_g3(x_gi3,0.10)>=0.95,
    ISC_review = post_gu2(0.35)>=0.95 | post_gi2(0.25)>=0.95 |
                 post_g3(x_gu3,0.05)>=0.95 | post_g3(x_gi3,0.05)>=0.95,
    probs = c(GU2_40=post_gu2(0.40), GI2_30=post_gi2(0.30),
              GU3_10=post_g3(x_gu3,0.10), GI3_10=post_g3(x_gi3,0.10))
  )
}
bayes_safety(x_gu2=10, x_gi2=4, x_gu3=0, x_gi3=0, n=30)
```

4. Governance, Sensitivity, and Reporting

4.1 Internal Safety Committee

The ISC convenes within one month of each interim report. The n=15 interim is descriptive; formal stopping rules apply from n=30. Emergency ISC review may be convened at any time by the Principal Investigator if unexpected Grade ≥ 3 toxicity patterns emerge.

4.2 Prior sensitivity analysis

All primary conclusions are replicated under three prior specifications:

- **Primary sceptical:** Beta(25,75)/Beta(15,85)/Beta(2,98) for safety; Gamma(10,12.78) for efficacy HR
- **Weakly informative:** Beta(2.5,7.5)/Beta(1.5,8.5) for Grade ≥ 2 safety; Gamma(2,2.56) for efficacy HR
- **Non-informative:** Beta(1,1) for all safety endpoints; Gamma(0.5,0) Jeffreys for efficacy HR

Primary decisions are based on primary sceptical priors only. Discordance across prior specifications will be highlighted in all reports.

4.3 Key model assumptions

- **Proportional hazards (efficacy):** verified by log-log KM plot and Schoenfeld residual test at analysis; Weibull sensitivity analysis if violated
- **Independent censoring:** verified by comparing survival trajectories of censored vs uncensored subgroups
- **Minimum events floor (efficacy):** ≥ 5 observed FFBF events required before declaring the primary objective met
- **Toxicity assessment window (safety):** treatment through 3-month post-completion; patients without 3-month assessment are non-evaluable and do not contribute to Bayesian updates
- **Prior influence monitoring:** ESS/N ratio reported at each interim and final analysis to quantify prior vs data contribution

5.4 References

- [1] Horiguchi G, Yokota I, Teramukai S. Bayesian power-based sample size determination for single-arm clinical trials with time-to-event endpoints. *Pharmaceutical Statistics* 2026;25:e70087.
- [2] Cotterill A, Whitehead J. Bayesian methods for setting sample sizes in phase II trials with time-to-event endpoints. *Statistics in Medicine* 2015;34:1889–1903.
- [3] Wu J. Sample size calculation for the one-sample log-rank test. *Pharmaceutical Statistics* 2015;14:26–33.

[4] Zohar S, Teramukai S, Zhou Y. Bayesian design and conduct of phase II single-arm clinical trials with binary outcomes. *Contemporary Clinical Trials* 2008;29:608–616.

[5] FDA Draft Guidance:

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-bayesian-methodology-clinical-trials-drug-and-biological-products>