Randomised controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation

[PRIME Trial]

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TRIAL SUMMARY

PROTOCOL TITLE	Randomised controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation (PRIME trial).
RATIONALE	Extreme hypofractionated radiotherapy is a shorter duration treatment with probable similar clinical efficacy as moderately hypofractionation Radiotherapy. Given the potential positive economic impact with shorter duration treatment with similar clinical outcomes and probable similar toxicity profile, SBRT (extreme hypo-fractionation) in prostate cancer can be offered as a treatment option, especially in a limited-resource setting.
AIM	The aim of the study is to compare the efficacy with SBRT and moderate hypo-fractionation in high risk and node positive prostate cancer
PRIMARY STUDY OBJECTIVES	To assess whether extreme hypo-fractionation with SBRT in high risk prostate cancer is non inferior to moderately hypo-fractionated standard radiotherapy
STUDY DESIGN	Two arm, Prospective Randomized Trial with a non-inferiority design
TRIAL POPULATION	**Inclusion criteria:** 1. Age: above 18 years. 2. Participants must be histologically proven, adenocarcinoma prostate 3.Localised to the prostate or pelvic lymph nodes 4. High risk prostate cancer as per NCCN definition clinical stage T3a or Gleason score 8/Gleason grade group4 or Gleason score 9-10/gleason grade group 5, PSA > 20 ng/mL. or Very high risk prostate cancer as per NCCN definitioni.e T3b-T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4cores Gleason score 8-10/Gleason grade group 4 or5 5. Ability to receive long term hormone therapy/ orchidectomy 6. KPS >70 (see appendix 7. No prior history of therapeutic irradiation to pelvis 8. Patient willing and reliable for follow-up and QOL. 9.Signed study specific consent form **Exclusion criteria:** 1. Evidence of distant metastasis at any time since presentation 2. Life expectancy <2 year 3. Previous RT to prostate or prostatectomy. 4. Severe urinary symptoms or with severe IPSS score inspite of being on hormonal therapy for 6mnths which in the opinion of the physician precludes RT 5. Patients with known obstructive symptoms with stricture. 6. Any contraindication to radiotherapy like inflammatory bowel disease. 7. Uncontrolled comorbidities including, but not limited to diabetes or hypertension 8. Unable to follow up or poor logistic or social support
	Arm 1-[standard arm]

TREATMENT REGIMEN	**Moderate hypofractionated RT,** Will receive a total dose of 68Gy in 25# to the primary over 5 weeks, with treatment being delivered daily. Patients with node positive disease will receive a dose of 50Gy in 25# to the pelvic nodes.Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66Gy/25# as a simultaneous integrated boost (SIB). An option of equivalent biological dose using 60-62.5 Gy in 20# may be allowed for multi-centric accrual in the future. **Arm 2 –[Experimental Arm]** **Extreme hypofractionation with SBRT,** will receive a course of 5 fractions of radiation; each fraction size will be 7.25 Gy. The total dose will be 36.25 Gy. Patients with node positive disease will receive a dose of 25Gy in 5 # to the pelvic nodes. The 5 treatments will be scheduled to be delivered alternate day over approximately 7-10 days. An option of equivalent biological dose using 35-36.25 Gy in 5 weekly fractions may be allowed for multicentric accrual in the future. Dose Coverage The 95% isodose line used for the prescription dose should cover a minimum of 95% of the PTV
RECRUITMENT TARGET	434 total number of patients with 217 patients in experimental arm and 217 patients in standard arm. 65 patients to be accrued per year in the project with a total study duration of about 8 years, with a 4-year follow up period and a uniform accrual rate.
PRIMARY ENDPOINT	1. To assess the 4 year Biochemical Failure free Survival (BFFS) between the two arms.
KEY SECONDARY ENDPOINTS	1. To evaluate acute and late toxicity with both treatments. 2. To find theProstate cancer specific survival and overall survival of patients receiving moderately hypofractionated RT and SBRT. 3. To estimate the out of pocket expenditureinvolved in patientsreceiving the two treatment schedules. 4. To assess quality of life
FOLLOW UP	• 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 monthly thereafter. At baseline and every follow-up data will be collected and recorded in CRF • Physician assessment of toxicity with RTOG toxicity criteria and CTCAE ver4.03 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.

Background

Prostate cancer is one of the most common cancers seen in the western population and is also seen on a rising trend in India. It is the fourth most common cancer in both sexes combined and the second most common cancer in men worldwide[1] *[GLOBOCON 2012]* and is the second leading site of cancer among males in large Indian cities like Delhi, Kolkata, Pune and Thiruvananthapuram, third leading site of cancer in cities like Bangalore and Mumbai and it is among the top ten leading sites of cancers in the rest of the PBRCs of India.[2]

High risk prostate cancer is an aggressive form of prostate cancer,defined by NCCN as cases with at least one of thefollowing features: Gleason score of 8–10, clinical stage T3a or higher,or PSA > 20 ng/mL[3]*[NCCN].* The standard of care for locally advanced high risk cancer is external beam radiotherapy alongwithlong term hormonal therapy. [4-6].Long term clinical and biochemical control is achievable with dose escalation in radiotherapy in prostate cancer. With advances in high precision technology in radiotherapy, it is possible to target and deliver higher doses to the tumour with sparing of the normal tissue.

The radiobiological studies have shown that prostate cancer has a low alpha / beta ratio in the range of (0.9-2.2) [7,8].Thismeans increased fraction size may improve biochemicalcontrol without significantly increased toxicity tonearby tissues (bladder, rectum).Thus a low α:β ratio of prostate cancer has high sensitivity to dose per fraction. This makes hypo-fractionated radiotherapy radio-biologically superior than conventional fractionated schedules as it leads to a considerably higher biologically equivalent dose delivery.

Various prospective randomised trials have studied the safety and efficacy of moderate hypo-fractionation in prostate cancer and has been now considered as the standard of care [9-11]. With the benefit shown with moderate hypofractionation, there has been a growing interest in the role of extreme hypofractionation in prostate cancer.

Extreme hypofractionation with stereotactic body radiation therapy (SBRT) has an emerging role as an alternative technique to deliver high dose radiotherapy to the prostate through a non-invasive approach, comparable to HDR brachytherapy, but with a non-invasiveapproach [12-15].SBRT is defined by the American Society for Radiation Oncology and the American College of Radiology as a treatment method to deliver a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body.

Multiple single-institution studies on the use of SBRT as the primary treatment for prostate cancer have suggested the treatment to be safe and quicker alternative to prolongedfractionation schedules [17-26]. However the number of patients with high risk prostate cancer included in these studies was low. This is predominantly because of large numbers of low and intermediate risk cancer in the west as opposed to the high risk group prostate cancer patients commonly seen in Indian scenario.

Table 1 gives a brief summary of various moderate and extreme hypofractionation schedules used in prostate cancer radiotherapy. The safety and toxicity evaluated in extreme hypofractionationin these studies have been comparable to moderate hypofractionation.

Therefore with advance techniques in radiotherapy planning and delivery, it is imperative to use SBRT in the treatment of prostate cancer.

The standard duration of treatment with radiotherapy is 8weeks in conventional fractionation; 5-6 weeks with moderate hypo-fractionation, while it is only 1- 2weeks with extreme hypo-fractionation (SBRT).The health costs and out of pocket expenditure involved in the conventional hypo-fractionated radiotherapy treatmentlargely depends on the overall treatment duration. This involves expenditure not only for the patient but also the caretaker.Moreover most of these patients presenting to a tertiary care centre from different parts of the country, have logistic issues of accommodation, food, travelalong with the treatment costs. Also for patients staying away from family, 5weeks treatment without considerable family support has a psychological impact, especially on elderly group of patients commonly seen with prostate cancer.This further leads to a major cause of distress among these patients, especially in a resource limited setting as ours. [27]

Extreme hypo-fractionation with a total duration of 2weeks, would offer an opportunity tooptimize the therapeutic ratio taking advantage of the potential therapeutic gain due to low alpha/beta for prostate to higher dose/fraction(compared to surrounding organs at risk). Moreover, shortened overall treatment time,would lead to less distressing and early recommencement of their daily activities for the patients,with an obvious impact in improving the quality of life andhealth costs.

Given the potential positive economic impact with shorter duration treatment with similar clinical outcomesand probable similar toxicity profile, SBRT (extreme hypo-fractionation) in prostate cancer is an attractive treatment option, especially in a limited-resource setting and can have a large and positive impact on the patient care.

Table no 1: Reported studies using moderate and extreme hypofractionation dose schedules in prostate cancer.

Study	No of patients	Median Follow-up (months)	Total dose (Gy)	Dose /fraction (Gy)	Free from PSA failure	Definition of failure	Late toxicity		Hormone (%)
							GU ≥2 (%)	GI ≥2 (%)	
Extreme hypofractionation with SBRT									
Madsen [20]	40	41	33.5	6.7	Low, 90% (4 years)	Nadir+2/ASTRO[#]	20	8	No
Freeman [19]	41	60	36.25	7.25	Low, 92.7% (5 years)	Nadir+2	9.5	2.5	No
Tang [21]	30	12	35[‡‡]	7	NA	NA	13 at 6 months	13 at 6 mo	3
Friedland[22]	112	24	35–36	7–7.2	NA	NA	0	0.9	19
Katz[23]	50, 254[§§]	17, 30	35, 36.25	7, 7.25	Low, 99%, Int, 100%, High,83% (last follow-up)	Nadir+2	2, 6.3	0, 2.9	19
Bolzicco[24]	45	20	35	7	Low and Int, 100%	NA	2.2	2.2	38
Jabbari [27]	20	18.3	38	9.5	All risk groups, 100%	NA	13[¶¶]	8[¶¶]	47%
Boike [25]	15, 15, 15[##]	30, 18, 12	45, 47.5, 50	9, 9.5, 10	100%	Nadir+2	13, 20, 7	7,7, 0	22

Moderate hypofractionation									
Pollack [13-14]	50	39	70.2	2.7	Int and High, 83% (5 years)	Nadir+2	25(5years	6(5years)	44
Kupelian	770	45	70	2.5	Low, 94; Int, 83%; High, 72% (5 years	Nadir+2/ASTRO#	7 (5 years)	6 (5 years)	60
CHHiP Dearnaley et al. [25-26]	1065/37 # 1074/20 # 1077/19 #		74 Gy/37# 60 Gy/20# 57 Gy/19 #	2 3 3	15 % low 73 % intermediate 12 % high	NA	5 years G 2 + GU (RTOG, NS) 9.1 % (37 #) 11.7 % (20 #) 6.6 % (19 #)	Acute G2 + GI (p < 0.0001) 25 % (37 #) 38 % (20 #) 38 % (19 #) 5 years G 2+ GI (RTOG, NS) 13.7% (37#x) 11.9% (20 #) 11.3% (19 #)	97
HYPRO Aluwini et al. [12]	397 407	60	78 Gy/39 # 64.6 Gy/19 fx	2G 3.4Gy	27 % intermediate 73 % high	NA	3 years G2+ GU 39 % 3 years G3+ GU12.9 % (3 years G3+ GU p = 0.02) 3years G2+ GU41.3 % 3 years G3+ GU 19.0 %	3 years G2+ GI 17.7 % 3 years G2+ GI 21.9 %	66%

Hypothesis for present study:

Extremehypo-fractionation with SBRT in high risk prostate cancer is non inferior to moderately hypo-fractionated standard radiotherapy while producing acceptable toxicity and advantage in terms of shortening of treatment duration

Aim

The aim of the study is to compare the efficacy with SBRT and moderate hypo-fractionation in high risk and node positive prostate cancer

Objectives:

Primary Endpoint

- ✓ The primary objective of the study is to assess the 4 year biochemical Failure free Survival (BFFS) between the two arms

Secondary Endpoints

- ✓ To evaluate acute and late toxicity with both treatments.
- ✓ To find the Prostate cancer specific survivaland overall survival of patients receiving moderately hypofractionated RT and SBRT.
- ✓ To estimate the out of pocket expenditure involved in patientsreceiving the two treatment schedules.
- ✓ To assess quality of life

Methodology:

Trial design

This will be a 2 arm, Prospective Randomized Trial with anon-inferiority design
Patients will be randomized to one of these below mentioned arms using stratified block randomization method.

Arm 1[standard arm]: Moderatelyhypofractionated Radiotherapy (217 patients)	Arm 2 [Experimental arm]: Extreme hypofractionation with Stereotactic body radiotherapy (217 patients)

Eligibility criteria

Inclusion criteria-

1. Age: above 18 years.
2. Participants must be histologically proven, adenocarcinoma prostate
3. Localised to the prostate or pelvic lymph nodes
4. High risk prostate cancer as per NCCN definition
   clinical stage T3a or Gleason score 8/Gleason grade group4 or Gleason score 9-10/gleason grade group 5, PSA > 20 ng/mL.orVery high risk prostate cancer i.e T3b-T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4cores Gleason score8-10/Gleason grade group 4 or5
5. Ability to receive long term hormone therapy/ orchidectomy
6. KPS ≥ 70 (see appendix)
7. No prior history of therapeutic irradiation to pelvis
8. Patient willing and reliable for follow-up and QOL
9. Signed study specific consent form

Exclusion criteria-

1. Evidence of distant metastasis at any time since presentation
2. Life expectancy < 2 year
3. Previous RT to prostate or prostatectomy.
4. Severe urinary symptoms or with severe IPSS score (>15)inspite of being on hormonal therapy for 6months which in the opinion of the physician precludes RT.
5. Patients with known obstructive symptoms with stricture.
6. Any contraindication to radiotherapy like inflammatory bowel disease.
7. Uncontrolled co-morbidities including, but not limited to diabetes or hypertension
8. Unable to follow up or poor logistic or social support.

Pre-treatment evaluation:

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

- Complete history and physical examination
- Serum PSA < 3 weeks of randomization
- Laboratory investigations undertaken routinely (complete blood counts, Renal function test, Liver function test and Serum Electrolytes)
- Staging investigation including CT scan of the abdomen- pelvis / bone scan/ MRI pelvis/ PSMA PETCTto rule out distant metastasis.
- IPSS scoring
- Documentation of pre-treatment urinary and rectal symptoms and quality of life.

Interventions

Registration

Patients with high risk carcinoma prostate 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.

Subjects must be registered before starting study treatment. Once the registration process has been completed, the subject will be assigned a subject study number. Individuals will only be registered once in this trial following which the patient would be randomized.

Randomisation

Patients will be randomized to one of the below mentioned arms using stratified block randomization method.

Arm 1 (Standard arm): **Moderate hypo-fractionated RT 68Gy/25#**

Arm 2 (Test arm): **Extreme hypo-fractionated RT with SBRT 36.25Gy/5#**

Stratification

Stratification will be done for the following parameters

1. Nodal status: N0 Vs N+
2. LHRH agonist/antagonists Vs Bilateral orchidectomy

Radiotherapy details

In arm 1 of the study, patients who are randomized to receive moderatelyhypofractionated RT will receive a total dose of 68Gy in 25# to the primary over 5 weeks, with treatment being delivered daily. Patients with node positive disease will receive a dose of 50Gy in 25# to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66Gy/25# as a simultaneous integrated boost(SIB). An option of equivalent biological dose using 60-62.5 Gy in 20# may be allowed for multicentric accrual in the future.

In Arm 2 of the study, patients who are scheduled to receive SBRT will receive a course of 5 fractions of radiation; each fraction size will be 7.25Gy. The total dose will be 36.25Gy. Patients with node positive disease will receive a dose of 25Gy in 5 # to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 30-35Gy/5# as a simultaneous integrated boost (SIB).The 5 treatments will be scheduled to be delivered alternate day over approximately 7-10 days. An option of equivalent biological dose using 35-36.25 Gy in 5 weekly fractions may be allowed as per institutional practice for multicentric accrual in the future.

Dose Coverage
The 95% isodose line used for the prescription dose should cover a minimum of 95% of the PTV.

Treatment Planning

Preparation

- Bladder: Patients will be asked to have a comfortably full urinary bladder both during simulation and treatment. 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 45 minutes prior to treatment and to not urinate between this time and treatment.
- Bowel: Patients will be advised to adhere to a low gas, low motility diet commencing 2 days prior to the simulation and treatment. One tablespoon of Milk of Magnesia will be taken the night before the simulation.

Simulation

Computed Tomography (CT)

- Patients will be asked to empty the rectum before the planning CT scan. About 45 min prior of acquiring the helical CT scan; all participants will be asked to void completely and to drink 500 ml of plain water. This protocol of bladder filling will be followed during every day treatment to ensure constant partial bladder filling to achieve lesser volume of bowel in irradiated area and least displacement of internal organs due to variable bladder filling. Patients will be simulated in supine position with hands over chest. Knee rest will be used for immobilisation and reproducibility. Three markers will be placed over skin at laser intersections; one at symphysis pubis and two laterally. CTscans will be taken with contrast from 1st Lumber vertebra to 5 cm below ischial tuberosity with a slice thickness of 2.5mm. Lasermarks will be permanently tattooed for set up.

Magnetic Resonance Imaging (*MRI)*

MRI images are not required but may be used for fusion if available.

Contouring:

- Target Volumes: CTV prostate (and SV): For patients without clinical or radiological involvement of SV, CTV will consist of the whole of prostate gland including any ECE

and the base of seminal vesicles defined as the proximal 0.5 seminal vesicles will be included in the CTV.

- CTV nodes: For patients with node positive disease, will receive radiotherapy to pelvic nodes. Contouring will begin from the level of L4-5. 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 upper external iliac region delineation will also include the lateral and medial pre-sacral nodal area 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 caudal part of the volume will include the distal part of the SV when it is uninvolved clinico-radiologically. 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 1cm thick pre sacral space will be included by joining bilateral nodal CTV up to 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 5mm will be grown isotropically over CTV nodes
- PTV Prostate (and SV): A margin of 5mm will be grown in all directions over theCTVprostate.
- Organs at risk: Whole of 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. The entire bladder will be drawn as a solid structure from the dome to the base including the wall.
- Bowel 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 2 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 pelvis. Both femoral heads will be drawn within the acetabulum without including the neck of the femur.

Treatment planning:

This protocol requires the use of IMRT (DMLC or SMLC) or related techniques (Tomotherapy/VMAT). 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 dose volume constraints are given below in Table 2 and Table 3 for the two dose fractionation schedules and the 2 Gy equivalent doses (EQD2)of each dose fractionation schedule is given in table 4.

Table 2: Dose constraints with moderate hypofractionation in Arm 1 (Standard arm)

Organ	V30	V40	V45	V50	V60	V65	V70
Bowel (cc)			80	30			
Bladder (%)	65	45		25	15		
Rectum (%)	80	60		35	25	15	0.1

Table No 3: Dose constraints with extreme hypofractionation with SBRT in Arm 2 (Experimental arm)

Organ	V14	V17.5	V28	V31.5	V35
Bladder	<40% (N+)	<20% (<27% in N+)			<3%
Rectum		<40%	<15%	<8%	<3%
Femoral head	<5%				

Table 4:EQD2for the different dose-fractionation schedules.

Dose (Gy)	Fractions	Dose/Fraction (Gy)	EQD2 (Gy) Alpha/beta@3Gy	EQD2(Gy) Alpha/beta @1.5Gy
68	25	2.72	78	81
66	25	2.64	74.5	78
64	25	2.56	70	74
60	25	2.4	64.8	66.86
50	25	2	50	50
62.5	20	3.125	76.56	82.59
60	20	3	72	77.14
36.25	5	7.25	78	94
35	5	7	74	85
30	5	6	54	64.29
25	5	5	40	46

Hormone therapy

All patients will receive hormone therapy starting at least 8 weeks prior to the beginning of radiotherapy (LHRH agonist/antagonist). They will continue the hormone therapy during the radiotherapy and later for a total duration of 2 years. Patients who have undergone orchidectomy will also be eligible in this study. The first LHRH agonist/antagonist injection will be covered with a 3-4 week course of anti-androgen to prevent testosterone flare.

Clinical Assessment:

1. Objective criteria for toxicity evaluation.
   The RTOG will be used to document acute and late toxicities (appendix 2-3)
   National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 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.

   a. RTOG toxicity criteria at baseline, 3-6 weeks post RT and at 6 monthly thereafter.

   b. Physician assessment during and end of RT with scoring of toxicity and IPSS scoring.

   c. QOL will be assessed at baseline and 6 monthly using theQLQC30 and PR25 EORTC Questionnaire.

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

3. Out of pocket expenditure of the patient and caregiver on food, travel, accommodation and for management of treatment related side-effects will be captured using a structured record form during treatment and each follow- up upto 2years.

4. All patients will follow up 3-6 weeks from 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.

Statistical consideration: Study Sample Size

The primary endpoint for this study is 4 year BFFS. The power calculations assume a 4-year BFFS of 80% in the moderate hypo fractionation arm (Arm1). On this basis, with a 5% one sided significance and 80% power, a total of 434 patients will be randomized to both arms equally (217 in each arm) and the trial will have the ability to demonstrate non-inferiority of extreme hypo fractionation with SBRT arm (Arm 2), defining non-inferiority as "no worse than 12%" below moderate hypo fractionation arm. This also accounts for a 5% noncompliance rate as anticipated from experience in previous studies.

Interim Analysis

A planned interim analysis for toxicity is built in. The timing of the interim analyses will be based on accrual of patients (25%, n=108) completing 2 years of follow up. At the planned interim analysis, the p-value from the chi-square or fisher exact test assessing treatment efficacy with respect to grade III or higher combined GI and GU RTOG toxicity will be compared in the two arms at one sided alpha of 2.5% and a power of 80%. If the computed p-value is less than or equal to 0.025, then accrual to the trial will be discussed with the DSMC for stopping (if applicable). Otherwise, accrual to the trial or follow-up (as applicable) will continue until the planned sample size (n=434)

Data collection methods

The data of the study would be collected in a pre designed case record form. The data will be filled in excel sheets and then would be transferred in SPSS and/or R studio for requisite analysis.

Data monitoring–

The institutional data monitoring and safety board (DSMSC) will be responsible for oversight of the data.

Analysis of population

Patient disposition and efficacy analyses will be performed on data from the intent-to-treat (ITT) population and per protocol analysis. All patients randomized into the study will be classified according to their assigned treatment group, regardless of the actual treatment received. The primary efficacy analysis will be on the ITT basis and per protocol basis.

Statistical Analysis

Qualitative data will be expressed as percentages and compared between the treatment groups using the chi-square test (or the Fisher exact test). Quantitative data will be expressed as means and standard deviation (or medians and range) and compared between the treatment groups using the Student t test (or the Wilcoxon test).

Prostate cancer specific survival and overall survival will be estimated using the Kaplan-Meier method with 95% confidence Intervals. The log-rank test will be used to compare the treatment groups. 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.

Outcome measures

Freedom from biochemical failure [BFFS]: Freedom from biochemical failure will be defined as duration from date of nadir PSA to PSA>2ng/ml over the nadir PSA

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

The **prostate cancer-specific survival** will be calculated from the date of randomization to the date of the death due to prostate cancer.

Quality of life will be assessed using the EORTC QLQ c30 and PR25 questionnaire

Patient accrual

Patients will be identified and checked for eligibility from the OPDs at TMH and ACTREC. Suitable patients will be considered for the study by a member of the investigating team after thoroughly explaining the study process and giving at least 24 hours for thinking over if they need.

We expect 65 patients to be accrued per year in the project with total study duration of about 8 years, with a 4-year follow up period and a uniform accrual rate.

Multicentric approach: The trial will be opened to other centers with access to IMRT/IGRT who may be encouraged to join the study in due course. The choice of conventional fractionation to 60-62.5 Gy in 20# will be allowed with appropriate stratification for individual centres.

Adverse Event reporting guidelines

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed.

The principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the Data Monitoring Committee and Data Management Staff in the CRS within 24 hours of discovery. When reporting it is required that the Principal Investigator should have a relevant material available. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to the DSMSC by the Principal Investigator. This will be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol. The Principal Investigator in consultation with other Investigators will take appropriate and prompt action to inform the IEC of any protocol modifications and/or precautionary measures if this is warranted.

Translational Research

The accrual of patients in the prospective randomized trial will be an excellent opportunity to collect bio-specimen (urine, serum, and paraffin blocks) from the patients for correlative studies in the future with the outcome and toxicity data. Patients will be consented for the same and IEC will be informed before undertaking any future correlative studies using the bio-specimen.

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 12 monthly intervals and within three months of study termination or completion. These reports will

include the total number of participants enrolled and summaries of each DSMSC [data safety and monitoring committee] review of safety and/or efficacy.

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 investigator's' discretion.

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.

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.

Access to data

The Principal Investigator and Co investigators will be given access to the data sets. Project data sets will be housed on the project specific database created for the study, and it will be password protected.

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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: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 pags/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 3: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 bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity < 100 cc); severe hemorrhagic cystitis

Appendix 4:Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

Adverse event	1	2	3	4	5
Proctitis Definition: A disorder characterized by inflammation of the rectum.	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limitingself-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Rectal hemorrhage Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus.	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Rectal mucositis Definition: A disorder characterized by inflammation of the mucous membrane of the rectum.	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Rectal pain Definition: A disorder characterized by a sensation of marked discomfort in the rectal region	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Rectal ulcer Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.	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 operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	death
Urinary frequency Definition: A disorder characterized by urination at short intervals.	Present	Limiting instrumental ADL; medical management indicated	-	-	-

Urinary incontinence Definition: A disorder characterized by inability to control the flow of urine from the bladder.	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Urinary retention Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate.	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 operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Urinary urgency Definition: A disorder characterized by a sudden compelling urge to urinate.	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Urinary tract pain Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract.	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Urinary tract obstruction Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract.	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Appendix 5: 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 5times	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 tourinate 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 difficult to postpone urination?	0	1	2	3	4	5	
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

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 of 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 6: QOL questionnaire (Attached)

Appendix 7: Out of pocket expenditure(Attached)