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Study Protocol of a Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation (PRIME TRIAL)

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ABSTRACT

INTRODUCTION

There has been an interest in studying the efficacy of extreme hypofractionation in low & intermediate risk prostate cancer utilising the low α/β ratio of prostate. Its role in high risk and node positive prostate cancer, however, is unknown. We hypothesize that a 5 fraction schedule of extreme hypofractionation will be non-inferior to a moderately hypofractionated regimen over 5 weeks in efficacy and will have acceptable toxicity and QOL while reducing the cost implications during treatment.

METHODS AND ANALYSIS

This is a noninferiority, multicentre, randomized trial of two schedules for NCCN high risk &/or node positive non metastatic carcinoma of the prostate. The standard arm is a schedule of 68Gy/25# over 5 weeks while the test arm will be extremely hypofractionated RT with SBRT to 36.25Gy/5# (7-10 days). The block randomization will be stratified by nodal status (N0/N+), hormonal therapy (LHRH therapy/ orchiectomy) and centre. All patients will receive daily IGRT.

The primary endpoint is 4-year Biochemical Failure Free Survival (BFFS). The power calculations assume 4-year BFFS of 80% in the moderate hypofractionation arm. 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). The secondary end points include overall survival, prostate cancer specific survival, acute and late toxicities, quality of life and out of pocket expenditure.

DISCUSSION

The trial aims to establish a therapeutically efficacious and cost-efficient modality for high risk and node positive prostate cancer with an acceptable toxicity profile. Presently, this is the only trial evaluating and answering such a question in this cohort.

ETHICS AND DISSEMINATION

The trial has been approved by IEC-III of Tata Memorial Centre, Mumbai.

TRIAL REGISTRATION

Registered with CTRI/2018/05/014054 (http://ctri.nic.in) on May 24, 2018.

KEYWORDS

High Risk/Node Positive Prostate Cancer, SBRT, Extreme Hypo fractionation, SABR

STRENGTHS & LIMITATIONS

Strengths

1. First study addressing the role of Moderate hypo fractionation and SBRT in High Risk and Node Positive prostate cancer
2. Use of PSMA PET/CT for all patients and risk adapted approach.
3. Out of pocket expenditure will be collected from all patients which will potentially have a huge impact on logistics and resource utilization especially in LMIC like India.

Limitations

1. Non-inferiority margin between standard arm and test arm kept at 9%.
2. No published evidence for role of SBRT in Node positive prostate cancer in the literature

INTRODUCTION

Incidence of high risk/very high risk prostate cancer is on a rising trend across the globe.(1–4) Advanced prostate cancer accounts for 15% of all diagnosed prostate cancers in developed nations whereas in low and low-middle income countries like India the proportion of advanced disease is estimated to be as high as 84%.(5) Radiotherapy in the form of EBRT and/or brachytherapy forms an integral part of management of these patients. Radiobiological studies have shown that prostate cancer has a low alpha /beta ratio in the range of 0.47-4.14.(6) This makes hypo-fractionated radiotherapy radio-biologically superior than conventional fractionated (treatment time 7-8 weeks) schedules as it leads to a considerably higher biologically equivalent dose delivery. Prospective randomized trials have studied the safety and efficacy of moderate hypo-fractionation (treatment time 4-6 weeks) in prostate cancer and is now considered as the standard of care in low and intermediate risk prostate cancer.(7) With the benefit shown with moderate hypo fractionation, there has been a growing interest in the role of extreme hypo fractionation in prostate cancer.

Extreme hypo fractionation (treatment duration 7-10 days) with stereotactic body radiation therapy (SBRT) has an emerging role as an alternative technique to deliver high dose radiotherapy to the prostate comparable to brachytherapy, but with a non-invasive approach. However, the acute and late toxicities remain a concern with SBRT. Multiple single arm series on the use of SBRT as the primary treatment for prostate cancer have suggested the treatment to be safe but these studies have a majority of patients from low /intermediate risk group. The results of HYPO-RT-PC trial published recently supports the safety of SBRT in low/intermediate risk prostate cancer. (8)

The data with regards to extreme hypofractionation for high risk prostate cancer is still sparse. Recently, the early toxicity and quality of life results of a phase I/II Study of stereotactic ablative radiotherapy including regional lymph node irradiation in patients with high-risk prostate cancer (SATURN) has demonstrated the safety of SBRT for these patients.(9) Similarly, a retrospective series of 68 patients reported from India reported equivalent toxicities as compared to moderate hypofractionation in this subset of patients.(10)

Extreme hypo-fractionation (SBRT) for a total duration of 7-10 days, would offer an opportunity to optimize the therapeutic ratio for the treatment of these tumors along with significantly decreasing the overall treatment time which in turn would lead to significantly better quality of life during treatment, early recommencement to daily activities along with lessening the financial burden for these patients. We therefore initiated a randomized phase III trial to establish the non-inferiority of SBRT in high risk and/or node positive prostate cancer.

METHODS/DESIGN

Trial design

This is a prospective, multicenter, two arm randomized control trial with a non-inferiority design led from a tertiary care cancer center in India for high-risk node negative and node positive prostate cancer patients. Randomization will be by stratified randomization method in a 1:1 ratio.

1. Standard Arm/Moderate Hypofractionation: Treatment duration: 5 weeks
2. Test Arm/Extreme Hypofractionation: Treatment duration: 7-10 days

The inclusion criteria for the trial will include patients who are older than 18 years with histologically proven adenocarcinoma prostate localized to prostate and pelvic nodes with high risk /very high risk disease as per NCCN risk stratification (clinical stage T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9-10/Gleason grade group 5, PSA > 20 ng/mL or Very high risk prostate cancer i.e. T3b/T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4 cores, Gleason score 8-10/Gleason grade group 4 or 5). In addition the patients should be fit to receive long term androgen deprivation therapy in the form of either orchiectomy/hormonal therapy and have a baseline KPS of more than equal to 70.The exclusion criteria for the trial includes a distant metastatic disease, a life expectancy of less than 2 years, patient's with previous history of pelvic RT, patients with severe urinary symptoms (IPSS > 15) despite being on hormone therapy for 6 months, patients with obstructive urinary symptoms like stricture, patients with contraindication to EBRT like pelvic inflammatory disease and patients with uncontrolled co-morbidities.

Patient and Public Involvement

Patient / Public were not involved in the research or methodology of this ongoing study. All patients were given an informed consent form (ICF). Only after willingly consenting and understanding all the aspects of participation in the trial, patients were randomized to either of the two arms.

Baseline Evaluation and Radiotherapy Details

The base line evaluation would include standard work up for a locally advanced carcinoma prostate i.e. TRUS guided 12 core biopsy, baseline serum PSA level and CECT, MRI and/or PSMA PET CT for staging.

All patients will receive ADT for a minimum duration of 8 weeks before starting EBRT. All patients will have baseline documentation of Quality of Life (using EORTC QLQ C30 and PR 25 questionnaire) and IPSS score at baseline as well as before starting EBRT.

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

In the test arm of study, patients who are scheduled to receive extreme hypo-fractionated RT (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 fractions to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 30-35 Gy in 5 fractions as a simultaneous integrated boost. 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.

All patients will be treated with IMRT or related techniques (Helical Tomotherapy/VMAT) with daily image guidance in the form of KV-CBCT/MVCT. The contouring of GTV nodes, CTV primary and organs at risk will be done according to standard guidelines on CT/MRI scans.(11) CTV nodes will be contoured by giving a radial margin of 5-7 mm around the common iliac, external iliac, internal iliac, pre sacral and the obturator vessels and editing from muscles and bones. The cranial extent of CTV nodes will be at the level of L5 – S1 vertebra and the caudal extent will be at the level obturator nodes. For patients without seminal vesicle involvement only 1.5 cm of the base of seminal vesicles will be included in CTV primary whereas the entire seminal vesicle will be included in the CTV primary in patients with radiological involvement of seminal vesicle. A PTV margins of 5 mm will be given around the entire CTV primary (including seminal vesicles) and CTV nodes to delineate PTV primary and PTV nodes respectively. The dose volume constraints for the target volume will include a CTV D98 of 98% (both primary and nodes) and a PTV D98 of 95% (both primary and nodes).These contouring guidelines and dose constraints are in accordance with the retrospective series of SBRT for high risk and/or node positive prostate cancer published from the same institute.(10) The dose volume constraints for organs at risk is given in Tables 1 and 2.

Table 1: Dose constraints with moderate hypo fractionation in Arm 1 (Standard arm)

Organ EQD2 α/β 3		**V30 (25.2Gy)**	**V40 (36.8Gy)**	**V50 (50Gy)**	**V60 (64.8Gy)**	**V65 (72.8Gy)**
BLADDER	N+	<60%	<40%	<25%	<15%	<3%
	N-	<25%	<20%	<14%	<10%	<3%
RECTUM	N+	<75%	<50%	<25%	<15%	<5%
	N-	<45%	<30%	<20%	<15%	<5%
Bowel(cc)				80CC		

Table No 2: Dose constraints with extreme hypo fractionation/SBRT in Arm 2 (Experimental arm)

Organ EQD2 α/β 3		**V14 (16.2Gy)**	**V17.5 (22.8Gy)**	**V28 (48.2Gy)**	**V31.5 (58.6Gy)**	**V35 (70Gy)**
BLADDER	N+	<40%	<27%	<20%	-	<3%
	N-	<35%	<20%	<10%	-	<3%
RECTUM	N+	<50%	<40%	<15%	<8%	<3%
	N-	<40%	<30%	<15%	<8%	<3%
F.HEADS		<5%				
Bowel(cc)				80cc		

Assessment/Follow up

Patients will continue (LHRH agonist/antagonist) during radiotherapy. All patients will be monitored during radiotherapy and at every follow up for acute/late toxicities using RTOG and CTCAE 4.03 toxicity grading scales. In addition, out of pocket expenditure of the patient and caregiver for food, travel, stay and for management of treatment related side-effects will be captured using a structured record form along with QOL score, IPSS score and urinary function. All patients will be followed up after 4-6 weeks of completion of radiotherapy and then at 3-6

monthly intervals till 2 years and 6 monthly intervals thereafter. Patients will continue LHRH agonists/antagonist after completion of radiotherapy to complete a total duration of 2 years. Clinical evaluation of the disease will be done at each follow up visit with a serum PSA and clinical examination. Any other investigation will be done at the physician 's discretion.

Statistics

The primary end point of this study will be 4-year **biochemical failure free survival (BFFS)** which will be defined as the time (in months) from the date of randomization to the date of biochemical failure as per Phoenix Criteria (a rise in PSA level of more than 2 ng/ml above the nadir).

This is a non-inferiority (NI) trial and the non-inferiority margin between the standard and the test arms is 9% (delta). To detect this delta difference in the primary endpoint of a 4-year Biochemical Failure Free Survival (80% in standard arm and 71% in the test arm; hazard ratio [HR] 1.53), with a power of 80% and a one sided 5% alpha value, total of 135 events are required, with a minimum number of 422 patients. Non-inferiority of Extreme hypofractionation with SBRT (test arm) versus moderate hypofractionated RT (standard arm) will be concluded if the upper limit of the estimated 95% one sided confidence interval of the hazard ratio obtained lies entirely below 1.53. If the upper limit of the 95% one-sided confidence interval is 1.53 or higher, we do not reject the null hypothesis of inferiority. The trial will accrue patients over a period of six years and all patients will be followed until the end of study. Considering an attrition rate of around 5%, the trial would require a total of 434 patients (217 in each arm). The primary efficacy analysis will be on both ITT basis and per protocol basis.

The secondary end points for the study will be evaluation of the acute and late toxicities (according to RTOG and CTCAE criterion), ascertaining the overall survival and prostate cancer specific survival for these patients, estimation of out of pocket expenditure involved in patients receiving the two treatment schedules and assessment of pre-treatment and post-treatment quality of life of these patients. For this study, overall survival (OS) and prostate cancer specific survival (PCSF) will be defined as time in months between date of randomization and date of death due to any cause or date of death due to prostate cancer respectively.

A planned interim analyses will be done on accrual of 25% (108 patients in both arms combined) patients completing 2 years of follow up. At the 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). We expect 80 patients to be accrued per year in the project with total study duration of about 6 years, with a non-fixed follow up period and a uniform accrual rate.

Quality Assurance

Radiation therapy quality assurance in the setting of a multi-institutional clinical trial has been shown to have a very important bearing on outcomes. The US National Cancer Institute Work Group on Radiotherapy Quality Assurance has laid down guidelines that help individual trials lay

down their QA protocol (Bekelman et al. 2012). The PRIME trial will use these guidelines to formulate a trial specific protocol as outlined below.

Tiered system for Radiotherapy Trial QA

Tier 1 includes General credentialing which comprises of filling a facility questionnaire outlining machine specific and patient specific QA process.

Tier 2 is a Trial specific credentialing consists of a dry run process with oncologists and physicists familiarizing themselves with the contouring protocol and advanced dosimetry checks with multiple plan generation to meet trial constraints.

Tier 3 is an individualized case review of dosimetry and QA datasheet reviewed every monthly in virtual QA meet.

DISCUSSION

The efficacy of SBRT for prostate cancer is supported by a radiobiological basis as well as phase 1 and phase 2 single arm studies. Several single arm series have established the efficacy and safety of SBRT for low and intermediate risk prostate cancer. The results of ongoing phase 3 trials comparing extreme hypofractionation to moderate hypofractionation/conventional fractionation are awaited. (Table 3). The major concern with SBRT is the impact on acute and late toxicities of the patients. The HYPO-RT-PC trial accrued 1200 intermediate risk prostate cancer patients (T1c-T3a, PSA </=20, with one or two of the following risk factors: T3a or Gleason 7 or PSA >10) and tested conventionally fractionated RT against extreme hypofractionation. Preliminary results show no significant differences in the prevalence of physician reported grade

2+ toxicity at 2 years between the two arms for urinary (5.4% vs 4.6%, P=0.59) and bowel (2.2% vs 3.7%, P=0.20) toxicity. (8)

The reports for SBRT as monotherapy for high risk disease are limited as most contemporary series have included very few high risk prostate cancers (Table 4). The dose per fraction given in these series range from 7-8Gy in 4 to 6 fractions given over 7-14 days. The toxicities and outcomes are comparable to that expected with moderate hypo-fraction schedules with the GI and GU RTOG ≥ 2 late toxicities ranging from 2 -14%.

FASTR is a phase 1 feasibility study for SBRT for node positive disease which delivered a dose of 25 Gy to pelvic nodes and 40 Gy to primary over a period of 5 weeks (once weekly fractionation). 9 out of the 15 patients accrued (60%) developed ≥ Gr 2 GI or GU toxicity at 6 months and 4 (30%) ≥ Gr 3 GI or GU toxicity at 6 months. The study was terminated before phase 2 in view of the higher toxicities. (12)Another single arm study (SATURN) evaluated a similar protocol with a dose of 25 Gy to pelvic nodes and seminal vesicle, 40Gy as SIB to the prostate and 33.25 Gy to the prostate PTV delivered over a period of 5 weeks in 5 once weekly fractions. The authors reported a Gr 2 GU toxicity of 52% (baseline 30%) and 32 % GI toxicity (baseline 3.3%) at 6 months. No grade 3 toxicities were reported. The authors attributed the lesser toxicity of this study as compared to the FASTR protocol to the lesser dose prescription to the prostate PTV (40 vs 33.25 Gy), the lesser PTV margins (5 mm vs 3 mm), smaller CTV volumes and better image guidance in SATURN protocol.(9)

In the present trial, the dose to primary PTV will be 36.25Gy in 5 fractions, which is between those given in FASTR and SATURN trials. The efficacy and safety of such a dosing schedule has already been published as a single arm retrospective series from India with an 18-month

biochemical disease free survival of 94% and incidence of ≥ Grade 3 late GU and GI toxicity of 3% and 0% respectively. In addition, the PTV margins are 5 mm which again has been shown to adequate with daily CBCT based IGRT. (17)

This trial aims to establish a therapeutically efficacious and cost-efficient modality for high risk, very high risk and node positive prostate with acceptable toxicity profile which is likely to be a big public health problem in low income/low middle income countries in the coming decade. Presently, this is the only trial evaluating and answering such a question in this cohort of patients.

Table 3: Phase 3 Trials of SBRT in Prostate Cancer

	NRG-GU 005	PACE A & PACE B	Hypo fractionated RT in Prostate Cancer	HYPO-RT-PC	PATRIOT	PRIME
Trial ID	NCT 03367702	NCT 01584258	NCT 01764646	ISRCTN45905321	NCT01423474	NCT03561961
Study/Group	NRG Oncology	Royal Marsden NHS Foundation Trust	Geneva, Switzerland	Scandinavia	Canada	Tata Memorial Hospital, India
Stage/ Eligibility	cT1c or T2a/b (limited to one side of the gland); (AJCC, version 7) or cT1a-c or 2a /2b, stage group IIA or IIB; (AJCC, version 8) Excludes: Definitive T3 on MRI	Low risk: cT1-T2a and Gleason ≤ 6 and PSA < 10 ng/ml, or Intermediate risk: Clinical stage T2b orT2c, PSA 10-20 ng/ml or Gleason 3+4Excludes:	cT1c - cT3a disease with a Low Risk of Nodal Metastases (≤ 20%, Roach Index)	T1c - T3a with one or two of the following risk factors: T3a or Gleason >7, PSA >10 according to the TNM classification system UICC 2002, PSA<20 µg/L	Low or intermediate risk T1-2b, Gleason </=7, PSA <20ng/ml	High risk, Very high risk and node positive prostate cancer as per NCCN definition: T3a-T4 or Gleason score 8/grade group 4 or Gleason score 9/grade group 5 or Primary Gleason pattern 5 or PSA > 20 ng/ml
Target Accrual	606	1716	170	1200	152	434

Interventions	SBRT (36.25Gy in 5 fractions over 12 days) vs Moderate Hypo fractionation (70Gy in 28 fractions over	PACE A: SBRT (36.25Gy in 5 fractions) vs Radical Prostatectomy PACE B: SBRT (36.25Gy in 5 fractions) vs Conventional fractionation (78Gy in 39 fractions)	SBRT (36.25Gy in 5 fractions) every other day over 9 days vs SBRT (36.25Gy in 5 fractions) once a week over 28 days	SBRT (42.7Gy in 7 fractions alternate day over 2.5 weeks) vs Conventional fractionation (78Gy in 39 fractions over 8 weeks)	SBRT (40Gy in 5 fractions) every other day (EOD) over 11 days vs SBRT (40Gy in 5 fractions) once a week (QW) over 29 days	SBRT: 36.25Gy in 5 fractions over 7-10 days; (Node positive disease - 25Gy in 5 fractions) vs Moderate Hypo fractionation: 68Gy in 25 fractions over 5 weeks; (Node positive disease – 50Gy in 25 fractions)
Primary Endpoint	Composite end point of DFS & EPIC-26 urinary and bowel toxicity at 2 years	PACE A: QOL and EPIC score at 2 years PACE B: Biochemical/ Clinical failure at 5 years	Acute and Late urinary, rectal and sexual toxicity at 5 years (CTCAE 3.0)	Freedom from failure (PSA or any clinical), measured 5 years after the end of treatment	EPIC measured bowel related QOL	Biochemical Failure free survival at 4 years
Estimated Completion	December 2028	September 2026	September 2025	Accrual complete	October 2020	March 2028

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Gy), the lesser PTV margins (5 mm vs 3 mm), smaller CTV volumes and better image guidance in SATURN protocol.(9)

In the present trial, the dose to primary PTV will be 36.25Gy in 5 fractions, which is between those given in FASTR and SATURN trials. The efficacy and safety of such a dosing schedule has already been published as a single arm retrospective series from India with an 18-month biochemical disease free survival of 94% and incidence of ≥ Grade 3 late GU and GI toxicity of 3% and 0% respectively. In addition, the PTV margins are 5 mm which again has been shown to adequate with daily CBCT based IGRT. (17)

This trial aims to establish a therapeutically efficacious and cost-efficient modality for high risk, very high risk and node positive prostate with acceptable toxicity profile which is likely to be a big public health problem in low income/low middle income countries in the coming decade. Presently, this is the only trial evaluating and answering such a question in this cohort of patients.

Table 4: Published series of SBRT in High Risk Prostate Cancer

Author, Year, Origin	No. of high risk patients	HR definition	Dose	Median FU (y)	ADT/duration	Acute GU	Acute GI	Late GU	Late GI	OUTCOMES
Kang 2011, Korea(13)	29	D'Amico	8 Gy ×4, 8.5Gy x 4 or 9Gy x 4	3.3	Yes/24 months	G2 - 25%	G2 - 25%	G2 - 14%	G2 - 14%	5-y bDFS: 90.9%
King 2013, USA(14)	125	D'Amico	7-8Gy x 5	3	38% HR patients/4 months	NS	NS	NS	NS	5-y bDFS: 81%
Davis 2015, Radiosurgery Society(15)	33	NCCN 2015	7-9.5Gy x 4-5	1.6	15HR patients received ADT/NS	NS	NS	G2 - 8%	G2 - 2%	2-y bDFS: 90% but with PSA >20 ng/mL: 62.5%
Ricco 2016, USA(16)	32	NCCN 2015	7-7.5Gy x 5	4.1	27% of all SBRT patients/ NS	NS	NS	No G3 GU/GI toxicity		6-y bDFS for SBRT: 92%. 4-y bDFS for HR and VHR: 95% and 72%
Katz 2016, USA(17)	38	NCCN 1.2016	7-7.25Gy x 5	7	Yes/NS	G2 - <5%	G2 - <5%	G2 - 9%	G2 - 4%; G3 - 1.7%	8-y bDFS: 65% for HR. Favorable unfavorable intermediate 7-y bDFS ~93% and 68%
Koskela 2017, Finland(18)	111	D'Amico	7-7.25Gy x 5	2	88.3% HR/48% of HR patients ADT >24months	No acute G3 toxicity		Intermediate GU % GI - 1.8 & 0.9%		23-mo bDFS: 92.8%
V Murthy 2018, India(10)	68	NCCN 37 (54%) patients were N1	7-7.25Gy x 5	1.5	Median duration - 15 months	G2 – 12%;	G2 – 4%	G2 - 4.5%; G3 – 2%	G2 – 4%	18-mo bDFS: 94%

Word Count: 3817

ABBREVIATIONS:

EBRT: External Beam Radiotherapy, SBRT: Stereotactic Body Radiotherapy, NCCN: National Cancer Control Network, PSA: Prostate Specific Antigen, KPS: Karnofsky Performance scale, RT: Radiotherapy, TRUS: Transrectal Ultrasonography, CECT: Contrast Enhanced Computerized Tomography, PSMA: Prostate specific Membrane Antigen, PET: Positron Emission Tomography, ADT: Androgen Deprivation Therapy, IPSS: International Prostate Symptom Score, EORTC: European Organization for Research and Treatment of Cancer, QLQ: Quality of Life Questionnaire IMRT: Intensity Modulated Radiotherapy, VMAT: Volumetric Modulated Arc Therapy, KV-CBCT: Kilo Voltage-Cone Beam Computerized Tomography, MVCT: Megavoltage Computerized Tomography, GTV: Gross Tumor Volume, CTV: Clinical Target Volume, MRI: Magnetic Resonance Imaging, PTV: Planning Target Volume, LHRH: Luteinizing hormone releasing hormone RTOG: Radiotherapy Oncology Group, CTCAE: Common Terminology Criteria for Adverse Events, QOL: Quality of Life, BFFS: Biochemical Failure Free Survival, ITT: Intention to treat , OS: Overall survival, PCSF: Prostate Cancer Specific Survival, IGRT: Image Guided Radiotherapy, GI: Gastrointestinal, GU: Genitourinary, DSMC: Data Safety and Monitoring Committee.

DECLARATIONS:

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Signature of the informed consent will be obtained from all patients before inclusion in the study. This ongoing study was approved by Institutional Ethics Committee of Tata Memorial Hospital, Mumbai (TMC IRB Project No: -271/CTRI No: CTRI/2018/05/014054). This study was approved by Institutional Ethics Committee of Tata Medical Center, Kolkata (2018/TMC/134/IRB32). This trial is registered prospectively with CTRI/2018/05/014054 (http://ctri.nic.in)(REF/2018/05/019975) on May 24, 2018.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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AUTHOR CONTRIBUTIONS

Study concept and design: VM, IM; Selection accrual and consenting of patients: VM, IM, AG, SS, RK, TT, AM; Patient examination and clinical evaluation: VM, IM, AG, SS, RK, TT, AM, GB, GP, MP; Radiological evaluation: PP, VR, AA; Pathological evaluation: SM. All authors have read and approved the manuscript.

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Not Applicable

AUTHOR'S INFORMATION

Not applicable

REFERENCES:

1. Time trends and local variation in primary treatment of localized prostate cancer. - PubMed - NCBI [Internet]. [cited 2018 Sep 26]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20124165

2. Punnen S, Cooperberg MR. The epidemiology of high-risk prostate cancer. Curr Opin Urol. 2013 Jul;23(4):331–6.

3. Jain S, Saxena S, Kumar A. Epidemiology of prostate cancer in India. Meta Gene. 2014 Aug 29; 2:596–605.

4. Hariharan K, Padmanabha V. Demography and disease characteristics of prostate cancer in India. Indian J Urol. 2016 Apr 1;32(2):103.

5. Hebert JR, Ghumare SS, Gupta PC. Stage at diagnosis and relative differences in breast and prostate cancer incidence in India: comparison with the United States. Asian Pac J Cancer Prev APJCP. 2006 Dec;7(4):547–55.

6. Vogelius IR, Bentzen SM. Meta-analysis of the Alpha/Beta Ratio for Prostate Cancer in the Presence of an Overall Time Factor: Bad News, Good News, or No News? Int J Radiat Oncol Biol Phys. 2013 Jan 1;85(1):89–94.

7. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol. 2012 Jan;13(1):43–54.

8. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Extreme Hypofractionation versus Conventionally Fractionated Radiotherapy for Intermediate Risk Prostate Cancer: Early Toxicity Results from the Scandinavian Randomized Phase III Trial "HYPO-RT-PC." Int J Radiat Oncol Biol Phys. 2016 Dec 1;96(5):938–9.

9. Musunuru HB, D'Alimonte L, Davidson M, Ho L, Cheung P, Vesprini D, et al. Phase I/II Study of Stereotactic Ablative Radiotherapy Including Regional Lymph Node Irradiation in Patients with High-Risk Prostate Cancer (SATURN): Early Toxicity and Quality of Life. Int J Radiat Oncol Biol Phys. 2018 Jul 30;

10. Murthy V, Gupta M, Mulye G, Maulik S, Munshi M, Krishnatry R, et al. Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer. Clin Oncol R Coll Radiol G B. 2018 Jul;30(7):442–7.

11. Salembier C, Villeirs G, Bari BD, Hoskin P, Pieters BR, Vulpen MV, et al. ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. Radiother Oncol. 2018 Apr 1;127(1):49–61.

12. Bauman G, Ferguson M, Lock M, Chen J, Ahmad B, Venkatesan VM, et al. A Phase 1/2 Trial of Brief Androgen Suppression and Stereotactic Radiation Therapy (FASTR) for High-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2015 Jul 15;92(4):856–62.

13. Management of high-risk prostate cancer with 5-treatment stereotactic body radiotherapy: Long-term results.: Journal of Clinical Oncology: Vol 35, No 6_suppl [Internet]. [cited 2018 Sep 19]. Available from: http://ascopubs.org/doi/10.1200/JCO.2017.35.6_suppl.94

14. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2013 Nov;109(2):217–21.

15. Davis J, Sharma S, Shumway R, Perry D, Bydder S, Simpson CK, et al. Stereotactic Body Radiotherapy for Clinically Localized Prostate Cancer: Toxicity and Biochemical Disease-Free Outcomes from a Multi-Institutional Patient Registry. Cureus [Internet]. [cited 2018 Sep 19];7(12). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4699985/

16. Ricco A, Manahan G, Lanciano R, Hanlon A, Yang J, Arrigo S, et al. The Comparison of Stereotactic Body Radiation Therapy and Intensity-Modulated Radiation Therapy for Prostate Cancer by NCCN Risk Groups. Front Oncol [Internet]. 2016 Aug 23 [cited 2018 Sep 19];6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4994110/

17. Katz A, Kang J. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Risk Stratification for Intermediate- and High-Risk Patients. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2): E250.

18. Koskela K, Palmgren J-E, Heikkilä J, Virsunen H, Sailas L, Auvinen P, et al. Hypofractionated stereotactic body radiotherapy for localized prostate cancer - first Nordic clinical experience. Acta Oncol Stockh Swed. 2017 Jul;56(7):978–83.

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 V 4.03)

Gastro intestinal Disorder					
CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation **Definition:** A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea **Definition:** A disorder characterized by an increase in frequency and/or loose or watery bowel movements	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective	-	-

Definition: A disorder characterized by inability to control the escape of stool from the rectum			operative intervention indicated		
Proctitis **Definition:** A disorder characterized by inflammation of the rectum	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self-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 symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent 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, 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 invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Renal and Urinary Disorder

CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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 invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
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; 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
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 urgency **Definition:** A disorder characterized by a sudden compelling urge to urinate	Present	Limiting instrumental ADL; medical management indicated	-	-	-

Appendix 5: Out of pocket Expenditure: Data Collection Tool
General Information

Case No: _____ Trial No: _____

Type of Radiotherapy: _____

1) Name of Patient _____

Address of Patient

Contact No.

Email id_____

2) Name of Respondent/Caregiver _____

Relation with Patient _____

Contact No._____

3) Religion

a) Hindu b) Muslim c) Sikh

d) Christian f) Others

4) Locality

a) Urban b) Slum c) Rural

5) Educational status

a) Illiterate b) Primary c) Middle

d) Matric e) Senior secondary f) Graduation

g) Post graduation

6) Marital Status

a) Unmarried b) Married

c) Separated/Divorced d) Widow/Widower

7) Type of Insurance

a) BPL free/poor free b) Government employee

c) Private Insurance d) NO

8) Previous history of

a) Smoking b) Alcohol consumption

c) Tobacco chewing d) Any other e) No

Out of pocket expenditure From To		**Date of Follow up visit:**
No. of Care givers:		
Travel expense (Rs):	1) Home town to Mumbai & Return Journey to Home town	
	2) Local Residence to Hospital	
	3) Other Travel related to treatment	
Medicine expense related to cancer or its treatment:	1) Hormone Therapy	
	2) Urinary	
	3) Rectal/ Bowel	
	4) Others	
Tests/ Labs expense:	1) PSA/testosterone/BMD/CBC, etc.	
	2) Scans	
	3) Others	
Surgery Procedure expenses	1) Cystoscopy	
	2) Sigmoidoscopy/APC	
	3) Others	
Food expense for patient + Care giver		
lodging expense for patient + Care giver		
Other Related Payments/ Consultancy fee		
Total for the visit:		

Name: Signature:

APPENDICES

32. INFORMED CONSENT MATERIALS

PATIENT INFORMATION SHEET

You are being invited to participate in a research study. Before you take part, we would like to explain the study purpose is giving you a chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the informed consent form. You will be given a copy of this document to take home with you.

STUDY INFORMATION

DESCRIPTION OF YOUR CONDITION AND THE STUDY

You have been diagnosed with a condition called prostate cancer. The treatment with radiotherapy has been decided by your doctors. This is the standard treatment for your cancer along with hormonal therapy. During radiotherapy, normally the prostate gland is treated to a high dose with radiation with computer-based planning over a period of 5-6 weeks. There is an alternative schedule in which the treatment is delivered over a shorter time of 7-10 days. We intend to study these schedules and find out the side-effects and effectiveness of both the schedules.

The present study: The present research is comparing two different dose schedules of radiotherapy. It is to see whether the shorter duration of treatment results is as effective as the standard duration of treatment and thus possibly help to reduce the treatment time for patients. This will also hopefully reduce the associated cost involved in radiotherapy to patients. The study plans to include about 434 study participants.

STUDY PROCEDURES AND VISIT SCHEDULE

If you agree to take part in this study, before you start treatment, basic tests like blood tests, scans and x-rays will be performed, if not already done. You will be then allocated to one of the treatments by a process known as randomization. Randomization means that the decision will be impartially done by a central computer and your study doctor cannot influence to which treatment you will be assigned. In group A, patients will receive radiotherapy in 25 sittings over 5 weeks. If allotted to group B, patients will receive radiotherapy over 1-2 weeks in 5 sittings. The radiotherapy will be given with the best possible and most advanced technique in both groups to decrease possible side effects and is similar in every way except the duration of treatment. Once the treatment is decided in any group, you will be called for planning of radiation treatment. This will involve undergoing a CT scan which will be done to accurately plan the radiotherapy. You will be followed up on a regular basis to monitor your condition and all other medicines will be similar in both groups. During the follow-up, routine examination and tests by your physician will be done. You will be asked to fill quality of life form regularly to help us to understand the side effects better. You will also be asked questions on your health care expenditure to understand the financial costs borne by you during the treatment. You will need to visit the doctor's clinic 3-6 monthly for 1st year and 6 monthly thereafter. The frequency of visiting the doctor's clinic is the same as normal follow-up visits outside the study.

ALTERNATIVE TREATMENTS

If you choose not to take part in this study, you will be offered RT outside the study over 5-6 weeks. This will be discussed with you in detail by your doctor.

POSSIBLE RISKS AND SIDE-EFFECTS OF RADIOTHERAPY

You will be counselled regarding the possible side effects of radiation which are no different from that of routine radiotherapy. The technique of RT that we will employ will help in reducing the side effects. These include general symptoms like nausea, vomiting, fatigue, mild weakness and loss of appetite. Skin darkening in the treated area, diarrhoea, pain and/or bleeding on passing motion, urinary urgency, increased frequency of urination or bleeding on passing urine as immediate side effects during treatment. Late side effects include increased frequency of urination, burning in urine and mild bleeding from urine and stools. These expected side effects can be treated by simple medicines if needed. Those in the short treatment group may have slightly more side effects as mentioned above compared to those on the 5-week radiotherapy schedule. In case of severe side effects, which may occur in about 2% of patients, the RT may be temporarily stopped.

COST OF TREATMENT AND SIDE EFFECTS

If you are in the standard group with 5 weeks of treatment, the cost of treatment will be borne by you as would have done routinely. In case you are in the short treatment group of 1-2 weeks, the cost will not be charged to you. The doctor will discuss the approximate cost of treatment with you. There will be no extra scans or tests involved.

REIMBURSEMENT FOR PARTICIPATION

No financial reimbursement is planned for participation in the study.

EMERGENCY MEDICAL TREATMENT

In the unlikely event of any medical emergency arising due to the radiotherapy, you will be provided the best possible care as needed. You will have to pay for it in the standard longer treatment arm but not the shorter treatment arm.

POTENTIAL BENEFITS

There may be no direct benefits to you due to participation in the trial. You will receive excellent quality treatment in both arms. If you are in the arm that has radiation with shorter duration of treatment, you may have less out of pocket expenditure and can return home quickly. There is no assurance however that you will benefit from this study. Nevertheless, your participation may contribute to the medical knowledge about the best way to treat patients with disease like yours. Please remember that the many of the most effective treatments used today are the result of clinical trials done in the past.

CONFIDENTIALITY OF STUDY AND MEDICAL RECORDS

The information in the study records will be kept confidential and the clinical charts will be housed in the TMH/CRS/ACTREC. Data will be stored securely and will be made available only to persons conducting the study and to the regulatory authorities. The data will not be made available to another individual unless you specifically give permission in writing. No reference will be made in oral or written reports which could link you to the study. Result of the project will not be communicated to the subject unless deemed necessary.

COMPENSATION FOR PROTOCOL RELATED INJURY

All subjects participating in the study will be covered under institutional insurance for any trial related injury or death.

WHOM TO CONTACT IF YOU HAVE QUESTIONS

If you have questions about this research study and your rights or in the case of any injuries during this study, you may contact the Principal Investigator:

Dr. Vedang Murthy

Department of Radiation Oncology,

Advanced centre for treatment, research and education for cancer (ACTREC),

Tata Memorial Centre, Navi Mumbai 410210, Tel: (022) 27405000

If you have questions about the study or your rights as a participant, you can call the IEC, which is the committee that reviewed and approved this study:

The Chairperson,

Dr R Mulherkar,

IEC III,

Advanced centre for treatment, research and education for cancer (ACTREC),

Tata Memorial Centre,

Navi Mumbai 410210,

Tel:(022)27405154

INFORMED CONSENT FORM (ICF)

Participation

Your participation in this study is voluntary; you may decline to participate at any time without penalty and without loss of benefits to which you are otherwise entitled.

If you withdraw from the study prior to its completion, you will receive the usual standard of care for your disease, and your non-participation will not have any adverse effects on your subsequent medical treatment or relationship with the treating physician

If you withdraw from the study before data collection is completed, your data will not be entered in the study report.

Consent

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject' Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

1. I understand that I am being invited to take part in the research study. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand the risks and potential benefits of this research study that were explained to me. I freely give my consent to take part in research study described in this form.
4. I understand that the Sponsor of the research study, others working on the Sponsor's behalf, IEC and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
5. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
6. I agree to take part in the above study.

   I have read the above information and agreed to participate in this study. I have received a copy of this form.
7. **Informed consent form to participate in a biological sample study**

Study Title:

Study Number:

Participant' Initials: _____

Participant's Name: _____

Date of Birth / Age: _____

Do you consent to biological sample study?

☐ YES, I consent ☐ NO, I do not consent

1. I understand that I am being invited to take part in the research study. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand the risks and potential benefits of this research study that were explained to me. I freely give my consent to take part in research study described in this form.

4. I understand that the investigator of the research study, others working on the Investigator's behalf, IEC and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
5. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
6. I agree to take part in the above study.

Participant's name (print):	
Participant's signature & date:	
Address: Qualification (please attach supporting documentation): _____ Occupation: Student / Self-Employed / Service /Housewife /Others (Please tick as appropriate) and attach supporting documentation Annual Income of the subject (please attach supporting documentation): _____	
Phone Nos.:	
Legally Acceptable Representative name	
Legally Acceptable Representative signature & date:	

Address (capital letters): Phone Nos.:	
Impartial Witness's name:	
Impartial Witness's signature & date:	
Address (capital letters): Phone Nos.:	
Name of PI or Co-PI/Co-I:	
PI or Co-PI/Co-I & date:	

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	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	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube

		requiring analgesics		distended bowel loops)	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 V 4.03)

Gastro intestinal Disorder					
CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation **Definition:** A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea **Definition:** A disorder characterized by an increase in frequency and/or loose or watery bowel movements	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Fecal incontinence **Definition:** A disorder characterized by inability to control the escape of stool from the rectum	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Proctitis **Definition:** A disorder characterized by inflammation of the rectum	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Rectal hemorrhage **Definition:** A disorder characterized by bleeding from the rectal wall	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death

and discharged from the anus					
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, 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 invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Renal and Urinary Disorder

CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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	Urinary, suprapubic or intermittent catheter placement not indicated; able to	Placement of urinary, suprapubic or intermittent catheter placement indicated;	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative	Death

urine within the bladder because of the inability to urinate	void with some residual	medication indicated		intervention indicated	
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; 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
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 urgency **Definition:** A disorder characterized by a sudden compelling urge to urinate	Present	Limiting instrumental ADL; medical management indicated	-	-	-

Appendix 5: Out of pocket Expenditure: Data Collection Tool

General Information

Case No: _____ Trial No: _____

Type of Radiotherapy: _____

1) Name of Patient _____

   Address of Patient

   Contact No.

   Email id_____

2) Name of Respondent/Caregiver _____

Relation with Patient _____

Contact No._____

3) Religion

a) Hindu b) Muslim c) Sikh

d) Christian f) Others

4) Locality

a) Urban b) Slum c) Rural

5) Educational status

a) Illiterate b) Primary c) Middle

d) Matric e) Senior secondary f) Graduation

g) Post graduation

6) Marital Status

a) Unmarried b) Married

c) Separated/Divorced d) Widow/Widower

7) Type of Insurance

a) BPL free/poor free b) Government employee

c) Private Insurance d) Any other, specify….

e) NO

8) Previous history of

a) Smoking b) Alcohol consumption

Out of pocket expenditure **From To**		**Date of Follow up visit:**
No. of Care givers:		
Travel expense (Rs):	1) Home town to Mumbai & Return Journey to Home town	
	2) Local Residence to Hospital	
	3) Other Travel related to treatment	
	1) Hormone Therapy	

Medicine expense related to cancer or its treatment:	2) Urinary	
	3) Rectal/ Bowel	
	4) Others	
Tests/ Labs expense:	1) PSA/testosterone/BMD/CBC, etc.	
	2) Scans	
	3) Others	
Surgery Procedure expenses	1) Cystoscopy	
	2) Sigmoidoscopy/APC	
	3) Others	
Food expense for patient + Care giver:		
lodging expense for patient + Care giver:		
Other Related Payments/ Consultancy fee		
Total for the visit:		

c) Tobacco chewing d) Any other e) No

Name: Signature:

33. BIOLOGICAL SPECIMENS

Blood and urine samples and tissue specimens will be collected and preserved for future research with due permission.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-14
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	15
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	15

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15-16
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	16
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	16-17
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	17
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	17
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	17
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	17
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	18
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	18
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	20
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	20
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	20

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	21
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	21
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	21-22
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	22
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	22
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	22
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	23
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	23
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	23
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	23
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	23

	31b	Authorship eligibility guidelines and any intended use of professional writers	24
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary File

STUDY PROTOCOL – PRIME TRIAL

TITLE: Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypo fractionation [PRIME Trial]

2 A. REGISTRY: CTRI/2018/05/014054 (http://ctri.nic.in) (REF/2018/05/019975)

B. WHO Trial Registration Data Set

Data Category	Information
Primary registry and trial identifying number	CTRI/2018/05/014054(http://ctri.nic.in) REF/2018/05/019975
Date of registration in primary registry	May 22, 2018
Secondary identifying numbers	PRIME
Source(s) of monetary or material support	Tata Memorial Centre
Primary sponsor	Tata Memorial Centre (Intramural funding)
Secondary sponsor(s)	-
Contact for public queries	Dr. Vedang Murthy, MD 02224177000 ext 7029
Contact for scientific queries	vmurthyactrec.gov.in
Public title	**PRIME TRIAL**

Scientific title	Randomized controlled trial of Prostate Radiotherapy In High Risk and Node Positive Disease Comparing Moderate and Extreme Hypo-fractionation
Countries of recruitment	**INDIA**
Health condition(s) or problem(s) studied	Prostate Adenocarcinoma, High Risk Prostate Cancer, Node positive Prostate Cancer
Intervention(s)	Radiation: Moderate Hypo-fractionation 68Gy in 25# Radiation: Extreme Hypo-fractionation/SBRT 36.25Gy in 5#
Key inclusion and exclusion 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 5. Ability to receive long term hormone therapy/ orchiectomy 6. KPS >70 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 years 3. Previous RT to prostate or prostatectomy. 4. Severe urinary symptoms or with severe IPSS score (>15) despite being on hormonal therapy for 6 months 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.
Study type	Open Label, Randomized, Interventional
Date of first enrolment	May 28, 2018
Target sample size	434 total number of patients with 217 patients in experimental arm and 217 patients in standard arm.
Recruitment status	**Recruiting**
Primary outcome	4-year biochemical Failure free survival (BFFS) Defined as duration from date of randomization to PSA > 2ng/ml above nadir value. (Phoenix definition)

Key secondary outcomes	Evaluate acute and late toxicity with both treatments. (Time Frame: 2 years) Prostate cancer specific survival and overall survival of patients receiving moderately hypo-fractionated RT and SBRT. (Time Frame: 5 years) Estimate out of pocket expenditure involved in patients receiving the two treatment schedules. Assess quality of life (QLQC30 and PR25)

3. PROTOCOL VERSION

Issue Date: 01.03.2019

Protocol Amendment Number: 2.0

Author(s):

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4. FUNDING

Tata Memorial Centre (Intramural funding)

5. ROLES AND RESPONSIBILITIES

A. CONTRIBUTORSHIP

A. Concept B. Design C. Screening of patients D. Selection & Recruitment and consenting of patients E. Laboratory investigations F. Laboratory report interpretation G. Treatment decision H. Patient evaluation I. AE and SAE management, evaluation and reporting	J. Examination of patients on follow-up K. Data collection and monitoring of data L. Interpretation of data M. Statistical analysis & Interpretation N. Maintaining patients file and master file of project O. Drafting final report P. Publication Z. Any other, please specify

A to P – Vedang Murthy, Indranil Mallick

C to P – Ganesh Bakshi, Abhilash Gavarraju, Shwetabh Sinha, Rahul Krishnatry, Tejshri Telkhade, Arunsingh Moses

C to I, P – Santosh Menon

C, D, G, H, I, J, P – Gagan Prakash, Mahendra Pal, Palak Popat, Venkatesh Rangarajan, Archi Agrawal, Sheetal Kulkarni

B. SPONSOR CONTACT INFORMATION

Trial Sponsor: Tata Memorial Centre (Intramural Funding)

Sponsor's Reference: NA

C. SPONSOR AND FUNDER

Tata Memorial Centre

D. COMMITTEES

DSMSC – Drug Safety Monitoring Committee

6 A. BACKGROUND AND RATIONALE

Prostate cancer is one of the most common cancers seen in the western population and is also seen on a rising trend in India. The standard of care for locally advanced high risk cancer is external beam radiotherapy along with long term hormonal therapy. Long term clinical and biochemical control is achievable with dose escalation in radiotherapy in prostate cancer. The radiobiological studies have shown that prostate cancer has a low alpha / beta ratio in the range of (0.9-2.2). Increased fraction size may improve biochemical control without significantly increased toxicity to nearby tissues (bladder, rectum). 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.

Extreme hypofractionation with a total duration of 2 weeks, would offer an opportunity to optimize 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 and health costs.

Given the potential positive economic impact with shorter duration treatment with similar clinical outcomes and probable similar toxicity profile, SBRT (extreme hypofractionation) 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.

B. CHOICE OF COMPARATORS

Active Comparator: Moderate Hypo-fractionation

In Arm 1 of the study, patients who are randomized to receive moderately hypo-fractionated RT will receive a total dose of 68 Gy in 25# to the primary over 5 weeks, with treatment being delivered daily. Patients with node positive disease will receive a dose of 50 Gy in 25# to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66 Gy/25# as a simultaneous integrated boost(SIB).

Intervention: Radiation: Moderate Hypo-fractionation

Experimental: Extreme Hypo-fractionation

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 30-35 Gy/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 36.5Gy in 5 weekly fractions may be allowed for multicentric accrual in the future.

Intervention: Radiation: Extreme Hypo-fractionation.

Dose Coverage: The 98% isodose line used for the prescription dose should cover a minimum of 95% of the PTV.

7. OBJECTIVES

Hypothesis

Extreme hypofractionation with SBRT in high risk prostate cancer is noninferior to moderately hypo fractionated standard radiotherapy while producing acceptable toxicity and advantage in terms of shortening of treatment duration.

Primary Endpoint

Assess the 4-year biochemical Failure free survival (BFFS) between the two arms.

Secondary Endpoints

Evaluate acute and late toxicity with both treatments.

Prostate cancer specific survival and overall survival of patients receiving moderately hypofractionated RT and SBRT.

Estimate the out of pocket expenditure involved in patients receiving the two treatment schedules.

Assess quality of life.

8. TRIAL DESIGN

Allocation: Randomized, Phase III

Intervention Model: Parallel Assignment (Prospective)

Masking: None (Open Label)

Primary Purpose: Treatment

9. STUDY SETTING

Location: Tata Memorial Hospital and ACTREC, Tata Memorial Centre, Mumbai, India;

Tata Medical Centre, Kolkata, India.

10. 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 group 4 or Gleason score 9 10/Gleason grade group 5, PSA > 20 ng/mL or Very high-risk prostate cancer i.e. T3b-T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4 cores Gleason score 8-10/Gleason grade group 4 or 5
5. Ability to receive long term hormone therapy/Orchiectomy
6. KPS ≥ 70
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) in spite of being on hormonal therapy for 6 months 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.

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

11. INTERVENTIONS

A. INTERVENTIONS

Radiation: Moderate Hypo-fractionation – 68Gy in 25#

Radiation: Extreme Hypo-fractionation/SBRT – 36.25Gy in 5#

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. CT scans will be taken with contrast from 1st Lumber vertebra to 5 cm below ischial tuberosity with a slice thickness of 2.5mm. Laser marks 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 isotropic ally over CTV nodes
- PTV Prostate (and SV): A margin of 5mm will be grown in all directions over the CTV prostate.
- 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.

Clinical Assessment:

1. Objective criteria for toxicity evaluation.

   The RTOG will be used to document acute and late toxicities

   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 the QLQC30 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 to 2 years.
4. All patients will follow up 3-6 weeks from end of radiotherapy. Thereafter follow up visits would be scheduled three to six months 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.

B. MODIFICATIONS

Arm 1 - Patients with node positive disease will receive a dose of 50 Gy in 25# to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66 Gy/25# as a simultaneous integrated boost (SIB).

Arm 2 - Patients with node positive disease will receive a dose of 25 Gy in 5 # to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 30-35 Gy/5# as a simultaneous integrated boost(SIB).

C. ADHERENCE

Appropriate counselling and weekly review of patients on treatment will ensure adherence to study protocol.

D. CONCOMITANT CARE

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 orchiectomy 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.

12. OUTCOMES

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

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

P**rostate 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.

13. PARTICIPANT TIMELINE

Registration

Patients with high risk carcinoma prostate on presentation will be screened for eligibility criteria. They must meet all 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

Stratified block randomization method

Stratification

Stratification will be done for the following parameters

1. Nodal status: N0 Vs N+
2. LHRH agonist/antagonists Vs Bilateral orchiectomy
3. Centre

14. SAMPLE SIZE

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 if the upper limit of the estimated 95% one sided confidence interval of the hazard ratio obtained lies entirely below 1.53. If the upper limit of the 95% one-sided confidence interval is 1.53 or higher, we do not reject the null hypothesis of inferiority. This also accounts for a 5% noncompliance rate as anticipated from experience in previous studies.

15. RECRUITMENT

Patient accrual

Patients will be identified and checked for eligibility from the OPDs at TMH, ACTREC and TMC. 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.

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

16. ALLOCATION

A. SEQUENCE GENERATION - Stratified block randomization method

B. CONCEALMENT MECHANISM - Participants will be randomised using online, central randomisation service. Allocation concealment will be ensured, as the service will not release the randomisation arm until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

C. IMPLEMENTATION - Allocation sequence will be generated applying the stratified randomization method. Enrolment of patients will be done from the outpatient department of Uro-Oncology services under the guidance of the PI and Co-PI.

17. BLINDING

A. MASKING – None (Open Label)

B. EMERGENCY UNBLINDING – NA

18. DATA COLLECTION METHODS

A. DATA COLLECTION

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.

B. RETENTION

Once a patient is enrolled or randomized, the study site will make every reasonable effort to follow the patient for the entire study period. Study site staff are responsible for developing and implementing local standard operating procedures to achieve this level of follow-up.

19. DATA MANAGEMENT

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.

20. STATISTICAL METHODS

A. OUTCOMES

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.

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.

B. ADDITIONAL ANALYSIS

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.

C. ANALYSIS POPULATION AND MISSING DATA

We propose to test non-inferiority using two analysis sets; the intention-to-treat set, considering all patients as randomized regardless of whether they received the randomized treatment, and the "per protocol" analysis set. We expect very few patients will be lost to follow-up. We propose declaring medical management non-inferior to interventional therapy, only if shown to be non-inferior using both the "intention to treat" and "per protocol" analysis sets.

21. DATA MONITORING

A. FORMAL COMMITTEE

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

B. 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)

22. HARMS

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.

23. AUDITING

Regular audit will be carried out by the PI with the assistance of Research Fellow and Trial Co-ordinator to ensure proper adherence to trial protocol, documentation of toxicities during and after treatment and regular follow up of patients post treatment.

24. RESEARCH ETHICS APPROVAL

The protocol and the template informed consent forms 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. After 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.

25. 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. 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.

26. CONSENT OR ASSENT

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.

27. 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.

28. DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

29. 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.

30. ANCILLARY AND POST-TRIAL CARE - NA

31. DISSEMINATION POLICY

A. TRIAL RESULTS

Results will be published in peer reviewed scientific journals along with conference presentations.

B. AUTHORSHIP - NA

C. REPRODUCIBLE RESEARCH

Plan to publish the study protocol in an indexed journal.

BMJ Open

Study Protocol of a Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation (PRIME TRIAL)

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Secondary Subject Heading:	Urology, Health economics, Medical publishing and peer review
Keywords:	Prostate disease < UROLOGY, Radiation oncology < RADIOLOGY & IMAGING, Urological tumours < ONCOLOGY, Clinical trials < THERAPEUTICS

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Study Protocol of a Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation (PRIME TRIAL)

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ABSTRACT

INTRODUCTION

There has been an interest in studying the efficacy of extreme hypofractionation in low & intermediate risk prostate cancer utilising the low α/β ratio of prostate. Its role in high risk and node positive prostate cancer, however, is unknown. We hypothesize that a 5 fraction schedule of extreme hypofractionation will be non-inferior to a moderately hypofractionated regimen over 5 weeks in efficacy and will have acceptable toxicity and QOL while reducing the cost implications during treatment.

METHODS AND ANALYSIS

This is an ongoing, noninferiority, multicentre, randomized trial of two schedules for NCCN high risk &/or node positive non metastatic carcinoma of the prostate. The standard arm is a schedule of 68Gy/25# over 5 weeks while the test arm will be extremely hypofractionated RT with SBRT to 36.25Gy/5# (7-10 days). The block randomization will be stratified by nodal status (N0/N+), hormonal therapy (LHRH therapy/ orchiectomy) and centre. All patients will receive daily IGRT.

The primary endpoint is 4-year Biochemical Failure Free Survival (BFFS). The power calculations assume 4-year BFFS of 80% in the moderate hypofractionation arm. 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). The secondary end points include overall survival, prostate cancer specific survival, acute and late toxicities, quality of life and out of pocket expenditure.

DISCUSSION

The trial aims to establish a therapeutically efficacious and cost-efficient modality for high risk and node positive prostate cancer with an acceptable toxicity profile. Presently, this is the only trial evaluating and answering such a question in this cohort.

ETHICS AND DISSEMINATION

The trial has been approved by IEC-III of Tata Memorial Centre, Mumbai.

TRIAL REGISTRATION

Registered with CTRI/2018/05/014054 (http://ctri.nic.in) on May 24, 2018.

KEYWORDS

High Risk/Node Positive Prostate Cancer, SBRT, Extreme Hypo fractionation, SABR

Strengths & Limitations

Strengths

1. First study addressing the role of Moderate hypo fractionation and SBRT in High Risk and Node Positive prostate cancer
2. Use of PSMA PET/CT for all patients at baseline for staging and risk adapted approach.
3. Out of pocket expenditure will be collected from all patients which will potentially have a huge impact on logistics and resource utilization especially in LMIC like India.

Limitations

1. Non-inferiority margin between standard arm and test arm kept at 9%.
2. No published evidence for role of SBRT in Node positive prostate cancer in the literature

INTRODUCTION

Incidence of high risk/very high risk prostate cancer is on a rising trend across the globe.(1–4) Advanced prostate cancer accounts for 15% of all diagnosed prostate cancers in developed nations whereas in low and low-middle income countries like India the proportion of advanced disease is estimated to be as high as 84%.(5) Radiotherapy in the form of EBRT and/or brachytherapy forms an integral part of management of these patients. Radiobiological studies have shown that prostate cancer has a low alpha /beta ratio in the range of 0.47-4.14.(6) This makes hypo-fractionated radiotherapy radio-biologically superior than conventional fractionated (treatment time 7-8 weeks) schedules as it leads to a considerably higher biologically equivalent dose delivery. Prospective randomized trials have studied the safety and efficacy of moderate hypo-fractionation (treatment time 4-6 weeks) in prostate cancer and is now considered as the standard of care in low and intermediate risk prostate cancer.(7) With the benefit shown with moderate hypo fractionation, there has been a growing interest in the role of extreme hypo fractionation in prostate cancer.

Extreme hypo fractionation (treatment duration 7-10 days) with stereotactic body radiation therapy (SBRT) has an emerging role as an alternative technique to deliver high dose radiotherapy to the prostate comparable to brachytherapy, but with a non-invasive approach. However, the acute and late toxicities remain a concern with SBRT. Multiple single arm series on the use of SBRT as the primary treatment for prostate cancer have suggested the treatment to be safe but these studies have a majority of patients from low /intermediate risk group. The results of HYPO-RT-PC trial published recently supports the safety of SBRT in low/intermediate risk prostate cancer. (8)

The data with regards to extreme hypofractionation for high risk prostate cancer is still sparse. Recently, the early toxicity and quality of life results of a phase I/II Study of stereotactic ablative radiotherapy including regional lymph node irradiation in patients with high-risk prostate cancer (SATURN) has demonstrated the safety of SBRT for these patients.(9) Similarly, a retrospective series of 68 patients reported from India reported equivalent toxicities as compared to moderate hypofractionation in this subset of patients.(10)

Extreme hypo-fractionation (SBRT) for a total duration of 7-10 days, would offer an opportunity to optimize the therapeutic ratio for the treatment of these tumors along with significantly decreasing the overall treatment time which in turn would lead to significantly better quality of life during treatment, early recommencement to daily activities along with lessening the financial burden for these patients. We therefore initiated a randomized phase III trial to establish the non-inferiority of SBRT in high risk and/or node positive prostate cancer.

METHODS/DESIGN

Trial design

This is an ongoing, prospective, multicenter, two arm randomized control trial with a non-inferiority design led from a tertiary care cancer center in India for high-risk node negative and node positive prostate cancer patients. Randomization will be by stratified randomization method in a 1:1 ratio.

1. Standard Arm/Moderate Hypofractionation: Treatment duration: 5 weeks
2. Test Arm/Extreme Hypofractionation: Treatment duration: 7-10 days

Stratification will be done for the following parameters

1. Nodal status: N0 Vs N+
2. LHRH agonist/antagonists Vs Bilateral orchiectomy
3. Centre

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Age: above 18 years 2. Participants must be histologically proven, adenocarcinoma prostate 3. Localized to the prostate or pelvic lymph nodes 4. High risk prostate cancer as per NCCN definition 5. PSMA/PET CT for all patients at baseline for staging 6. Ability to receive long term hormone therapy (2 years)/ orchiectomy 7. KPS >70 8. No prior history of therapeutic irradiation to pelvis 9. Patient willing and reliable for follow-up. 10. Signed study specific consent form	1. Evidence of distant metastasis at any time since presentation 2. Life expectancy < 2 years 3. Previous RT to prostate or prostatectomy. 4. Severe urinary symptoms or with severe IPSS score (>15) despite being on hormonal therapy for 6 months 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.

The inclusion criteria for the trial will include patients who are older than 18 years with histologically proven adenocarcinoma prostate localized to prostate and pelvic nodes with high risk /very high risk disease as per NCCN risk stratification (clinical stage T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9-10/Gleason grade group 5, PSA > 20 ng/mL or Very high risk prostate cancer i.e. T3b/T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4

cores, Gleason score 8-10/Gleason grade group 4 or 5). All patients will be staged with a baseline PSMA PET/CT. In addition, the patients should be fit to receive long term androgen deprivation therapy in the form of either orchiectomy/hormonal therapy (2 years) and have a baseline KPS of more than equal to 70 (Appendix 1). The exclusion criteria for the trial includes a distant metastatic disease, a life expectancy of less than 2 years patient's with previous history of pelvic RT, patients with severe urinary symptoms (IPSS > 15) despite being on hormone therapy for 6 months, patients with obstructive urinary symptoms like stricture, patients with contraindication to EBRT like pelvic inflammatory disease and patients with uncontrolled co-morbidities.

Patient and Public Involvement

Patient / Public were not involved in the research or methodology of this ongoing study. All patients were given an informed consent form (ICF). Only after willingly consenting and understanding all the aspects of participation in the trial, patients were randomized to either of the two arms.

Baseline Evaluation and Radiotherapy Details

The base line evaluation would include standard work up for a locally advanced carcinoma prostate i.e. TRUS guided 12 core biopsy, baseline serum PSA level. PSMA PET/CT will be used at baseline to stage all patients. Nodal involvement by disease will be defined based on size, morphological characteristics and metabolic uptake by a specialist Uro Radiologist (PP) and Nuclear Medicine Specialist (VR, AA).

All patients will receive ADT for a minimum duration of 8 weeks before starting EBRT. Preferably, all patients will have baseline documentation of Quality of Life (using EORTC QLQ C30 and PR 25 questionnaire) and IPSS score at baseline as well as before starting EBRT.

In the standard arm, patients who are randomized to receive moderately hypo-fractionated RT will receive a total dose of 68 Gy in 25 fractions to the primary over 5 weeks, with treatment being delivered daily. Patients with node positive disease will receive a dose of 50 Gy in 25 fractions to the pelvis. Response assessment PSMA PET/CT will be done for all patients with pelvic nodal disease to ascertain the response to ADT based on morphology of the residual node and metabolic uptake as defined by the Uro Radiologist / Nuclear Medicine specialist. Patients with persistent residual nodal disease will be considered for nodal boost. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66 Gy in 25 fractions as a simultaneous integrated boost. An option of equivalent biological dose using 60-62.5 Gy in 20 fractions may be allowed for multicentric accrual in the future. In the test arm of study, patients who are scheduled to receive extreme hypo-fractionated RT (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 fractions to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 30-35 Gy in 5 fractions as a simultaneous integrated boost. 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.

All patients will be treated with IMRT or related techniques (Helical Tomotherapy/VMAT) with daily image guidance in the form of KV-CBCT/MVCT. No intraprostatic fiducials will be used for IGRT. The contouring of GTV nodes, CTV primary and organs at risk will be done according to standard ESTRO ACROP guidelines(11). CTV nodes will be contoured by giving a radial margin of 5-7 mm around the common iliac, external iliac, internal iliac, pre sacral and the obturator vessels and editing from muscles and bones. The cranial extent of CTV nodes will be at the level of L5 – S1 vertebra and the caudal extent will be at the level obturator nodes. For patients without seminal vesicle involvement only 1.5 cm of the base of seminal vesicles will be included in CTV primary whereas the entire seminal vesicle will be included in the CTV primary in patients with radiological involvement of seminal vesicle. A PTV margins of 5 mm will be given around the entire CTV primary (including seminal vesicles) and CTV nodes to delineate PTV primary and PTV nodes respectively. The dose volume constraints for the target volume will include a CTV D98 of 98% (both primary and nodes) and a PTV D98 of 95% (both primary and nodes). These contouring guidelines and dose constraints are in accordance with the retrospective series of SBRT for high risk and/or node positive prostate cancer published from the same institute (10,12). The dose volume constraints for organs at risk is given in Tables 1 and 2.

Table 1: Dose constraints with moderate hypo fractionation in Arm 1 (Standard arm)

Organ EQD2 α/β 3		**V30 (25.2Gy)**	**V40 (36.8Gy)**	**V50 (50Gy)**	**V60 (64.8Gy)**	**V65 (72.8Gy)**
BLADDER	N+	<60%	<40%	<25%	<15%	<3%
	N-	<25%	<20%	<14%	<10%	<3%
RECTUM	N+	<75%	<50%	<25%	<15%	<5%
	N-	<45%	<30%	<20%	<15%	<5%
Bowel(cc)				80CC		

Table No 2: Dose constraints with extreme hypo fractionation/SBRT in Arm 2 (Experimental arm)

Organ EQD2 α/β 3		**V14 (16.2Gy)**	**V17.5 (22.8Gy)**	**V28 (48.2Gy)**	**V31.5 (58.6Gy)**	**V35 (70Gy)**
BLADDER	N+	<40%	<27%	<20%	-	<3%
	N-	<35%	<20%	<10%	-	<3%
RECTUM	N+	<50%	<40%	<15%	<8%	<3%
	N-	<40%	<30%	<15%	<8%	<3%
F.HEADS		<5%				
Bowel(cc)				80cc		

Assessment/Follow up

Patients will continue (LHRH agonist/antagonist) during radiotherapy. All patients will be monitored during radiotherapy and at every follow up for acute/late toxicities using RTOG and CTCAE 4.03 toxicity grading scales (Appendix 2,3,4). In addition, out of pocket expenditure (Appendix 5) of the patient and caregiver for food, travel, stay and for management of treatment related side-effects will be captured using a structured record form along with QOL score, IPSS score and urinary function. All patients will be followed up after 4-6 weeks of completion of radiotherapy and then at 3-6 monthly intervals till 2 years and 6 monthly intervals thereafter. Patients will continue LHRH agonists/antagonist after completion of

radiotherapy to complete a total duration of 2 years. Clinical evaluation of the disease will be done at each follow up visit with a serum PSA and clinical examination. Any other investigation will be done at the physician's discretion.

Statistics

The primary end point of this study will be 4-year **biochemical failure free survival (BFFS)** which will be defined as the time (in months) from the date of randomization to the date of biochemical failure as per Phoenix Criteria (a rise in PSA level of more than 2 ng/ml above the nadir). This is a non-inferiority (NI) trial and the non-inferiority margin between the standard and the test arms is 9% (delta). To detect this delta difference in the primary endpoint of a 4-year Biochemical Failure Free Survival (80% in standard arm and 71% in the test arm; hazard ratio [HR] 1.53), with a power of 80% and a one sided 5% alpha value, total of 135 events are required, with a minimum number of 422 patients. The assumption of 80% BFFS in the standard arm was based on the results of similar studies of high risk node negative cancer studies (STAMPEDE, James ND et al. JAMA oncology 2016 and PRO 7, J Clin Oncol 2015) and our own data (unpublished) which showed a 5-year BFFS of about 85%. As this study is recruiting high risk and node positive patients also, the upper limit of 80% was chosen. Non-inferiority of Extreme hypofractionation with SBRT (test arm) versus moderate hypofractionated RT (standard arm) will be concluded if the upper limit of the estimated 95% one sided confidence interval of the hazard ratio obtained lies entirely below 1.53. If the upper limit of the 95% one-sided confidence interval is 1.53 or higher, we do not reject the null hypothesis of inferiority. The trial will accrue patients over a period of six years and all patients will be followed until the end of study. Considering an attrition rate of around 5%, the trial would require a total of 434

patients (217 in each arm). The primary efficacy analysis will be on both ITT basis and per protocol basis.

The secondary end points for the study will be evaluation of the acute and late toxicities (according to RTOG and CTCAE criterion), ascertaining the overall survival and prostate cancer specific survival for these patients, estimation of out of pocket expenditure involved in patients receiving the two treatment schedules and assessment of pre-treatment and post-treatment quality of life of these patients. For this study, overall survival (OS) and prostate cancer specific survival (PCSF) will be defined as time in months between date of randomization and date of death due to any cause or date of death due to prostate cancer respectively.

A planned interim analyses will be done on accrual of 25% (108 patients in both arms combined) patients completing 2 years of follow up. At the 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). We expect 80 patients to be accrued per year in the project with total study duration of about 6 years, with a non-fixed follow up period and a uniform accrual rate.

Quality Assurance

Radiation therapy quality assurance in the setting of a multi-institutional clinical trial has been shown to have a very important bearing on outcomes. The US National Cancer Institute Work Group on Radiotherapy Quality Assurance has laid down guidelines that help individual trials lay down their QA protocol (Bekelman et al. 2012)(13). The PRIME trial will use these guidelines to formulate a trial specific protocol as outlined below.

Tiered system for Radiotherapy Trial QA

Tier 1 includes General credentialing which comprises of filling a facility questionnaire outlining machine specific and patient specific QA process.

Tier 2 is a Trial specific credentialing consists of a dry run process with oncologists and physicists familiarizing themselves with the contouring protocol and advanced dosimetry checks with multiple plan generation to meet trial constraints.

Tier 3 is an individualized case review of dosimetry and QA datasheet reviewed every monthly in virtual QA meet.

DISCUSSION

The efficacy of SBRT for prostate cancer is supported by a radiobiological basis as well as phase 1 and phase 2 single arm studies. Several single arm series have established the efficacy and safety of SBRT for low and intermediate risk prostate cancer. The results of ongoing phase 3 trials comparing extreme hypofractionation to moderate hypofractionation/conventional fractionation are awaited. (Table 3). The major concern with SBRT is the impact on acute and late toxicities of the patients. The HYPO-RT-PC trial accrued 1200 intermediate risk prostate cancer patients (T1c-T3a, PSA </=20, with one or two of the following risk factors: T3a or

Gleason 7 or PSA >10) and tested conventionally fractionated RT against extreme hypofractionation. Preliminary results show no significant differences in the prevalence of physician reported grade 2+ toxicity at 2 years between the two arms for urinary (5.4% vs 4.6%, P=0.59) and bowel (2.2% vs 3.7%, P=0.20) toxicity. (8)

The reports for SBRT as monotherapy for high risk disease are limited as most contemporary series have included very few high risk prostate cancers (Table 4). The dose per fraction given in these series range from 7-8Gy in 4 to 6 fractions given over 7-14 days. The toxicities and outcomes are comparable to that expected with moderate hypo-fraction schedules with the GI and GU RTOG ≥ 2 late toxicities ranging from 2 -14%.

Table 3: Phase 3 Trials of SBRT in Prostate Cancer

	NRG-GU 005	PACE A & PACE B (14)	Hypo fractionated RT in Prostate Cancer	HYPO-RT-PC (8)	PATRIOT (15)	PRIME
Trial ID	NCT 03367702	NCT 01584258	NCT 01764646	ISRCTN45905321	NCT01423474	NCT03561961
Study/Group	NRG Oncology	Royal Marsden NHS Foundation Trust	Geneva, Switzerland	Scandinavia	Canada	Tata Memorial Hospital, India
Stage/ Eligibility	cT1c or T2a/b (limited to one side of the gland); (AJCC, version 7) or cT1a-c or 2a /2b, stage group IIA or IIB; (AJCC, version 8) Excludes: Definitive T3 on MRI	Low risk: cT1-T2a and Gleason ≤ 6 and PSA < 10 ng/ml, or Intermediate risk: Clinical stage T2b orT2c, PSA 10-20 ng/ml or Gleason 3+4Excludes:	cT1c - cT3a disease with a Low Risk of Nodal Metastases (≤ 20%, Roach Index)	T1c - T3a with one or two of the following risk factors: T3a or Gleason >7, PSA >10 according to the TNM classification system UICC 2002, PSA<20 µg/L	Low or intermediate risk T1-2b, Gleason </=7, PSA <20ng/ml	High risk, Very high risk and node positive prostate cancer as per NCCN definition: T3a-T4 or Gleason score 8/grade group 4 or Gleason score 9/grade group 5 or Primary Gleason pattern 5 or PSA > 20 ng/ml
Target Accrual	606	1716	170	1200	152	434

Interventions	SBRT (36.25Gy in 5 fractions over 12 days) vs Moderate Hypo fractionation (70Gy in 28 fractions over	PACE A: SBRT (36.25Gy in 5 fractions) vs Radical Prostatectomy PACE B: SBRT (36.25Gy in 5 fractions) vs Conventional fractionation (78Gy in 39 fractions)	SBRT (36.25Gy in 5 fractions) every other day over 9 days vs SBRT (36.25Gy in 5 fractions) once a week over 28 days	SBRT (42.7Gy in 7 fractions alternate day over 2.5 weeks) vs Conventional fractionation (78Gy in 39 fractions over 8 weeks)	SBRT (40Gy in 5 fractions) every other day (EOD) over 11 days vs SBRT (40Gy in 5 fractions) once a week (QW) over 29 days	SBRT: 36.25Gy in 5 fractions over 7-10 days; (Node positive disease - 25Gy in 5 fractions) vs Moderate Hypo fractionation: 68Gy in 25 fractions over 5 weeks; (Node positive disease – 50Gy in 25 fractions)
Primary Endpoint	Composite end point of DFS & EPIC-26 urinary and bowel toxicity at 2 years	PACE A: QOL and EPIC score at 2 years PACE B: Biochemical/ Clinical failure at 5 years	Acute and Late urinary, rectal and sexual toxicity at 5 years (CTCAE 3.0)	Freedom from failure (PSA or any clinical), measured 5 years after the end of treatment	EPIC measured bowel related QOL	Biochemical Failure free survival at 4 years
Estimated Accrual Completion	December 2025	September 2021	Accrual completed	Accrual completed	October 2020	March 2024

FASTR is a phase 1 feasibility study for SBRT for node positive disease which delivered a dose of 25 Gy to pelvic nodes and 40 Gy to primary over a period of 5 weeks (once weekly fractionation). 9 out of the 15 patients accrued (60%) developed ≥ Gr 2 GI or GU toxicity at 6 months and 4 (30%) ≥ Gr 3 GI or GU toxicity at 6 months. The study was terminated before phase 2 in view of the higher toxicities (16). Another single arm study (SATURN) evaluated a similar protocol with a dose of 25 Gy to pelvic nodes and seminal vesicle, 40Gy as SIB to the prostate and 33.25 Gy to the prostate PTV delivered over a period of 5 weeks in 5 once weekly fractions. The authors reported a Gr 2 GU toxicity of 52% (baseline 30%) and 32 % GI toxicity (baseline 3.3%) at 6 months. No grade 3 toxicities were reported. The authors attributed the lesser toxicity of this study as compared to the FASTR protocol to the lesser dose prescription to the prostate PTV (40 vs 33.25 Gy), the lesser PTV margins (5 mm vs 3 mm), smaller CTV volumes and better image guidance in SATURN protocol.(9)

In the present trial, the dose to primary PTV will be 36.25Gy in 5 fractions, which is between those given in FASTR and SATURN trials. The efficacy and safety of such a dosing schedule has already been published as a single arm retrospective series from India with an 18-month biochemical disease free survival of 94% and incidence of ≥ Grade 3 late GU and GI toxicity of 3% and 0% respectively. In addition, the PTV margins are 5 mm which again has been shown to adequate with daily CBCT based IGRT(15).

This trial aims to establish a therapeutically efficacious and cost-efficient modality for high risk, very high risk and node positive prostate with acceptable toxicity profile which is likely to be a big public health problem in low income/low middle income countries in the coming decade. Presently, this is the only trial evaluating and answering such a question in this cohort.

Table 4: Published series of SBRT in High Risk Prostate Cancer

Author, Year, Origin	No. of high risk patients	HR definition	Dose	Median FU (y)	ADT/duration	Acute GU	Acute GI	Late GU	Late GI	OUTCOMES
Kang 2011, Korea(17)	29	D'Amico	8 Gy ×4, 8.5Gy x 4 or 9Gy x 4	3.3	Yes/24 months	G2 - 25%	G2 - 25%	G2 - 14%	G2 - 14%	5-y bDFS: 90.9%
King 2013, USA(18)	125	D'Amico	7-8Gy x 5	3	38% HR patients/4 months	NS	NS	NS	NS	5-y bDFS: 81%
Davis 2015, Radiosurgery Society(19)	33	NCCN 2015	7-9.5Gy x 4-5	1.6	15HR patients received ADT/NS	NS	NS	G2 - 8%	G2 - 2%	2-y bDFS: 90% but with PSA >20 ng/mL: 62.5%
Ricco 2016, USA(20)	32	NCCN 2015	7-7.5Gy x 5	4.1	27% of all SBRT patients/ NS	NS	NS	No G3 GU/GI toxicity		6-y bDFS for SBRT: 92%. 4-y bDFS for HR and VHR: 95% and 72%
Katz 2016, USA(21)	38	NCCN 1.2016	7-7.25Gy x 5	7	Yes/NS	G2 - <5%	G2 - <5%	G2 - 9%	G2 - 4%; G3 - 1.7%	8-y bDFS: 65% for HR. Favorable unfavorable intermediate 7-y bDFS ~93% and 68%
Koskela 2017,Finland (22)	111	D'Amico	7-7.25Gy x 5	2	88.3% HR/48% of HR patients ADT >24months	No acute G3 toxicity		Intermediate GU % GI - 1.8 & 0.9%		23-mo bDFS: 92.8%
V Murthy 2018, India(10)	68	NCCN 37 (54%) patients were N1	7-7.25Gy x 5	1.5	Median duration - 15 months	G2 – 12%;	G2 – 4%	G2 - 4.5%; G3 – 2%	G2 – 4%	18-mo bDFS: 94%

Word Count (including tables): 3833

ABBREVIATIONS:

EBRT: External Beam Radiotherapy, SBRT: Stereotactic Body Radiotherapy, NCCN: National Cancer Control Network, PSA: Prostate Specific Antigen, KPS: Karnofsky Performance scale, RT: Radiotherapy, TRUS: Transrectal Ultrasonography, CECT: Contrast Enhanced Computerized Tomography, PSMA: Prostate specific Membrane Antigen, PET: Positron Emission Tomography, ADT: Androgen Deprivation Therapy, IPSS: International Prostate Symptom Score, EORTC: European Organization for Research and Treatment of Cancer, QLQ: Quality of Life Questionnaire IMRT: Intensity Modulated Radiotherapy, VMAT: Volumetric Modulated Arc Therapy, KV-CBCT: Kilo Voltage-Cone Beam Computerized Tomography, MVCT: Megavoltage Computerized Tomography, GTV: Gross Tumor Volume, CTV: Clinical Target Volume, MRI: Magnetic Resonance Imaging, PTV: Planning Target Volume, LHRH: Luteinizing hormone releasing hormone RTOG: Radiotherapy Oncology Group, CTCAE: Common Terminology Criteria for Adverse Events, QOL: Quality of Life, BFFS: Biochemical Failure Free Survival, ITT: Intention to treat , OS: Overall survival, PCSF: Prostate Cancer Specific Survival, IGRT: Image Guided Radiotherapy, GI: Gastrointestinal, GU: Genitourinary, DSMC: Data Safety and Monitoring Committee.

DECLARATIONS:

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Signature of the informed consent will be obtained from all patients before inclusion in the study. This ongoing study was approved by Institutional Ethics Committee of Tata Memorial Hospital, Mumbai (TMC IRB Project No: -271/CTRI No: CTRI/2018/05/014054). This study was approved by Institutional Ethics Committee of Tata Medical Center, Kolkata (2018/TMC/134/IRB32). This trial is registered prospectively with CTRI/2018/05/014054 (http://ctri.nic.in)(REF/2018/05/019975) on May 24, 2018.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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AUTHOR CONTRIBUTIONS

Study concept and design: VM, IM; Selection accrual and consenting of patients: VM, IM, AG, SS, RK, TT, AM; Patient examination and clinical evaluation: VM, IM, AG, SS, RK, TT, AM, GB, GP, MP; Radiological evaluation: PP, VR, AA; Pathological evaluation: SM; Statistical Analysis and

Interpretation: SK; Data collection and Master File maintenance: SK. All authors have read and approved the manuscript.

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Not Applicable

AUTHOR'S INFORMATION

Not applicable

REFERENCES:

1. Time trends and local variation in primary treatment of localized prostate cancer. - PubMed - NCBI [Internet]. [cited 2018 Sep 26]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20124165

2. Punnen S, Cooperberg MR. The epidemiology of high-risk prostate cancer. Curr Opin Urol. 2013 Jul;23(4):331–6.

3. Jain S, Saxena S, Kumar A. Epidemiology of prostate cancer in India. Meta Gene. 2014 Aug 29; 2:596–605.

4. Hariharan K, Padmanabha V. Demography and disease characteristics of prostate cancer in India. Indian J Urol. 2016 Apr 1;32(2):103.

5. Hebert JR, Ghumare SS, Gupta PC. Stage at diagnosis and relative differences in breast and prostate cancer incidence in India: comparison with the United States. Asian Pac J Cancer Prev APJCP. 2006 Dec;7(4):547–55.

6. Vogelius IR, Bentzen SM. Meta-analysis of the Alpha/Beta Ratio for Prostate Cancer in the Presence of an Overall Time Factor: Bad News, Good News, or No News? Int J Radiat Oncol Biol Phys. 2013 Jan 1;85(1):89–94.

7. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol. 2012 Jan;13(1):43–54.

8. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, Kindblom J, Ginman C, Johansson B, Björnlinger K, Seke M. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. The Lancet. 2019 Jun 18.

9. Musunuru HB, D'Alimonte L, Davidson M, Ho L, Cheung P, Vesprini D, et al. Phase I/II Study of Stereotactic Ablative Radiotherapy Including Regional Lymph Node Irradiation in Patients with High-Risk Prostate Cancer (SATURN): Early Toxicity and Quality of Life. Int J Radiat Oncol Biol Phys. 2018 Jul 30;

10. Murthy V, Gupta M, Mulye G, Maulik S, Munshi M, Krishnatry R, et al. Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer. Clin Oncol R Coll Radiol G B. 2018 Jul;30(7):442–7.

11. Salembier C, Villeirs G, Bari BD, Hoskin P, Pieters BR, Vulpen MV, et al. ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. Radiother Oncol. 2018 Apr 1;127(1):49–61.

12. Murthy V, Sinha S, Kannan S, Datta D, Das R, Bakshi G, Prakash G, Krishnatry R. Safety of Prostate Stereotactic Body Radiation Therapy after Transurethral Resection of Prostate (TURP): A Propensity Score Matched Pair Analysis. Practical Radiation Oncology. 2019 Apr 9.

13. Bekelman JE, Deye JA, Vikram B, Bentzen SM, Bruner D, Curran Jr WJ, Dignam J, Efstathiou JA, Fitzgerald TJ, Hurkmans C, Ibbott GS. Redesigning radiotherapy quality assurance: opportunities to develop an efficient, evidence-based system to support clinical trials—report of the National Cancer Institute work group on radiotherapy quality assurance. International Journal of Radiation Oncology* Biology* Physics. 2012 Jul 1;83(3):782-90.

14. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, Ford D, Tolan S, Jain S, Martin A, Staffurth J. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. The Lancet Oncology. 2019 Sep 17.

15. Quon HC, Ong A, Cheung P, Chu W, Chung HT, Vesprini D, Chowdhury A, Panjwani D, Pang G, Korol R, Davidson M. Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): A phase 2 randomized trial. Radiotherapy and Oncology. 2018 May 1;127(2):206-12.

16. Bauman G, Ferguson M, Lock M, Chen J, Ahmad B, Venkatesan VM, et al. A Phase 1/2 Trial of Brief Androgen Suppression and Stereotactic Radiation Therapy (FASTR) for High-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2015 Jul 15;92(4):856–62.

17. Management of high-risk prostate cancer with 5-treatment stereotactic body radiotherapy: Long-term results.: Journal of Clinical Oncology: Vol 35, No 6_suppl [Internet]. [cited 2018 Sep 19]. Available from: http://ascopubs.org/doi/10.1200/JCO.2017.35.6_suppl.94

18. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2013 Nov;109(2):217–21.

19. Davis J, Sharma S, Shumway R, Perry D, Bydder S, Simpson CK, et al. Stereotactic Body Radiotherapy for Clinically Localized Prostate Cancer: Toxicity and Biochemical Disease-Free Outcomes from a Multi-Institutional Patient Registry. Cureus [Internet]. [cited 2018 Sep 19];7(12). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4699985/

20. Ricco A, Manahan G, Lanciano R, Hanlon A, Yang J, Arrigo S, et al. The Comparison of Stereotactic Body Radiation Therapy and Intensity-Modulated Radiation Therapy for Prostate Cancer by NCCN Risk Groups. Front Oncol [Internet]. 2016 Aug 23 [cited 2018 Sep 19];6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4994110/

21. Katz A, Kang J. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Risk Stratification for Intermediate- and High-Risk Patients. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2): E250.

22. Koskela K, Palmgren J-E, Heikkilä J, Virsunen H, Sailas L, Auvinen P, et al. Hypofractionated stereotactic body radiotherapy for localized prostate cancer - first Nordic clinical experience. Acta Oncol Stockh Swed. 2017 Jul;56(7):978–83.

APPENDICES

32. INFORMED CONSENT MATERIALS

PATIENT INFORMATION SHEET

You are being invited to participate in a research study. Before you take part, we would like to explain the study purpose is giving you a chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the informed consent form. You will be given a copy of this document to take home with you.

STUDY INFORMATION

DESCRIPTION OF YOUR CONDITION AND THE STUDY

You have been diagnosed with a condition called prostate cancer. The treatment with radiotherapy has been decided by your doctors. This is the standard treatment for your cancer along with hormonal therapy. During radiotherapy, normally the prostate gland is treated to a high dose with radiation with computer-based planning over a period of 5-6 weeks. There is an alternative schedule in which the treatment is delivered over a shorter time of 7-10 days. We intend to study these schedules and find out the side-effects and effectiveness of both the schedules.

The present study: The present research is comparing two different dose schedules of radiotherapy. It is to see whether the shorter duration of treatment results is as effective as the standard duration of treatment and thus possibly help to reduce the treatment time for patients. This will also hopefully reduce the associated cost involved in radiotherapy to patients. The study plans to include about 434 study participants.

STUDY PROCEDURES AND VISIT SCHEDULE

If you agree to take part in this study, before you start treatment, basic tests like blood tests, scans and x-rays will be performed, if not already done. You will be then allocated to one of the treatments by a process known as randomization. Randomization means that the decision will be impartially done by a central computer and your study doctor cannot influence to which treatment you will be assigned. In group A, patients will receive radiotherapy in 25 sittings over 5 weeks. If allotted to group B, patients will receive radiotherapy over 1-2 weeks in 5 sittings. The radiotherapy will be given with the best possible and most advanced technique in both groups to decrease possible side effects and is similar in every way except the duration of treatment. Once the treatment is decided in any group, you will be called for planning of radiation treatment. This will involve undergoing a CT scan which will be done to accurately plan the radiotherapy. You will be followed up on a regular basis to monitor your condition and all other medicines will be similar in both groups. During the follow-up, routine examination and tests by your physician will be done. You will be asked to fill quality of life form regularly to help us to understand the side effects better. You will also be asked questions on your health care expenditure to understand the financial costs borne by you during the treatment. You will need to visit the doctor's clinic 3-6 monthly for 1st year and 6 monthly thereafter. The frequency of visiting the doctor's clinic is the same as normal follow-up visits outside the study.

ALTERNATIVE TREATMENTS

If you choose not to take part in this study, you will be offered RT outside the study over 5-6 weeks. This will be discussed with you in detail by your doctor.

POSSIBLE RISKS AND SIDE-EFFECTS OF RADIOTHERAPY

You will be counselled regarding the possible side effects of radiation which are no different from that of routine radiotherapy. The technique of RT that we will employ will help in reducing the side effects. These include general symptoms like nausea, vomiting, fatigue, mild weakness and loss of appetite. Skin darkening in the treated area, diarrhoea, pain and/or bleeding on passing motion, urinary urgency, increased frequency of urination or bleeding on passing urine as immediate side effects during treatment. Late side effects include increased frequency of urination, burning in urine and mild bleeding from urine and stools. These expected side effects can be treated by simple medicines if needed. Those in the short treatment group may have slightly more side effects as mentioned above compared to those on the 5-week radiotherapy schedule. In case of severe side effects, which may occur in about 2% of patients, the RT may be temporarily stopped.

COST OF TREATMENT AND SIDE EFFECTS

If you are in the standard group with 5 weeks of treatment, the cost of treatment will be borne by you as would have done routinely. In case you are in the short treatment group of 1-2 weeks, the cost will not be charged to you. The doctor will discuss the approximate cost of treatment with you. There will be no extra scans or tests involved.

REIMBURSEMENT FOR PARTICIPATION

No financial reimbursement is planned for participation in the study.

EMERGENCY MEDICAL TREATMENT

In the unlikely event of any medical emergency arising due to the radiotherapy, you will be provided the best possible care as needed. You will have to pay for it in the standard longer treatment arm but not the shorter treatment arm.

POTENTIAL BENEFITS

There may be no direct benefits to you due to participation in the trial. You will receive excellent quality treatment in both arms. If you are in the arm that has radiation with shorter duration of treatment, you may have less out of pocket expenditure and can return home quickly. There is no assurance however that you will benefit from this study. Nevertheless, your participation may contribute to the medical knowledge about the best way to treat patients with disease like yours. Please remember that the many of the most effective treatments used today are the result of clinical trials done in the past.

CONFIDENTIALITY OF STUDY AND MEDICAL RECORDS

The information in the study records will be kept confidential and the clinical charts will be housed in the TMH/CRS/ACTREC. Data will be stored securely and will be made available only to persons conducting the study and to the regulatory authorities. The data will not be made available to another individual unless you specifically give permission in writing. No reference will be made in oral or written reports which could link you to the study. Result of the project will not be communicated to the subject unless deemed necessary.

COMPENSATION FOR PROTOCOL RELATED INJURY

All subjects participating in the study will be covered under institutional insurance for any trial related injury or death.

WHOM TO CONTACT IF YOU HAVE QUESTIONS

If you have questions about this research study and your rights or in the case of any injuries during this study, you may contact the Principal Investigator:

Dr. Vedang Murthy

Department of Radiation Oncology,

Advanced centre for treatment, research and education for cancer (ACTREC),

Tata Memorial Centre, Navi Mumbai 410210, Tel: (022) 27405000

If you have questions about the study or your rights as a participant, you can call the IEC, which is the committee that reviewed and approved this study:

The Chairperson,

Dr R Mulherkar,

IEC III,

Advanced centre for treatment, research and education for cancer (ACTREC),

Tata Memorial Centre,

Navi Mumbai 410210,

Tel:(022)27405154

INFORMED CONSENT FORM (ICF)

Participation

Your participation in this study is voluntary; you may decline to participate at any time without penalty and without loss of benefits to which you are otherwise entitled.

If you withdraw from the study prior to its completion, you will receive the usual standard of care for your disease, and your non-participation will not have any adverse effects on your subsequent medical treatment or relationship with the treating physician

If you withdraw from the study before data collection is completed, your data will not be entered in the study report.

Consent

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject' Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

1. I understand that I am being invited to take part in the research study. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand the risks and potential benefits of this research study that were explained to me. I freely give my consent to take part in research study described in this form.
4. I understand that the Sponsor of the research study, others working on the Sponsor's behalf, IEC and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
5. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
6. I agree to take part in the above study.

   I have read the above information and agreed to participate in this study. I have received a copy of this form.
7. **Informed consent form to participate in a biological sample study**

Study Title:

Study Number:

Participant' Initials: _____

Participant's Name: _____

Date of Birth / Age: _____

Do you consent to biological sample study?

☐ YES, I consent ☐ NO, I do not consent

1. I understand that I am being invited to take part in the research study. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand the risks and potential benefits of this research study that were explained to me. I freely give my consent to take part in research study described in this form.

4. I understand that the investigator of the research study, others working on the Investigator's behalf, IEC and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
5. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
6. I agree to take part in the above study.

Participant's name (print):	
Participant's signature & date:	
Address: Qualification (please attach supporting documentation): _____ Occupation: Student / Self-Employed / Service /Housewife /Others (Please tick as appropriate) and attach supporting documentation Annual Income of the subject (please attach supporting documentation): _____	
Phone Nos.:	
Legally Acceptable Representative name	
Legally Acceptable Representative signature & date:	

Address (capital letters): Phone Nos.:	
Impartial Witness's name:	
Impartial Witness's signature & date:	
Address (capital letters): Phone Nos.:	
Name of PI or Co-PI/Co-I:	
PI or Co-PI/Co-I & date:	

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	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	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube

		requiring analgesics		distended bowel loops)	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 V 4.03)

Gastro intestinal Disorder					
CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation **Definition:** A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea **Definition:** A disorder characterized by an increase in frequency and/or loose or watery bowel movements	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Fecal incontinence **Definition:** A disorder characterized by inability to control the escape of stool from the rectum	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Proctitis **Definition:** A disorder characterized by inflammation of the rectum	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Rectal hemorrhage **Definition:** A disorder characterized by bleeding from the rectal wall	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death

and discharged from the anus					
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, 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 invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Renal and Urinary Disorder

CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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	Urinary, suprapubic or intermittent catheter placement not indicated; able to	Placement of urinary, suprapubic or intermittent catheter placement indicated;	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative	Death

urine within the bladder because of the inability to urinate	void with some residual	medication indicated		intervention indicated	
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; 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
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 urgency **Definition:** A disorder characterized by a sudden compelling urge to urinate	Present	Limiting instrumental ADL; medical management indicated	-	-	-

Appendix 5: Out of pocket Expenditure: Data Collection Tool

General Information

Case No: _____ Trial No: _____

Type of Radiotherapy: _____

1) Name of Patient _____

   Address of Patient

   Contact No.

   Email id_____

2) Name of Respondent/Caregiver _____

Relation with Patient _____

Contact No._____

3) Religion

a) Hindu b) Muslim c) Sikh

d) Christian f) Others

4) Locality

a) Urban b) Slum c) Rural

5) Educational status

a) Illiterate b) Primary c) Middle

d) Matric e) Senior secondary f) Graduation

g) Post graduation

6) Marital Status

a) Unmarried b) Married

c) Separated/Divorced d) Widow/Widower

7) Type of Insurance

a) BPL free/poor free b) Government employee

c) Private Insurance d) Any other, specify….

e) NO

8) Previous history of

a) Smoking b) Alcohol consumption

Out of pocket expenditure **From To**		**Date of Follow up visit:**
No. of Care givers:		
Travel expense (Rs):	1) Home town to Mumbai & Return Journey to Home town	
	2) Local Residence to Hospital	
	3) Other Travel related to treatment	
	1) Hormone Therapy	

Medicine expense related to cancer or its treatment:	2) Urinary	
	3) Rectal/ Bowel	
	4) Others	
Tests/ Labs expense:	1) PSA/testosterone/BMD/CBC, etc.	
	2) Scans	
	3) Others	
Surgery Procedure expenses	1) Cystoscopy	
	2) Sigmoidoscopy/APC	
	3) Others	
Food expense for patient + Care giver:		
lodging expense for patient + Care giver:		
Other Related Payments/ Consultancy fee		
Total for the visit:		

c) Tobacco chewing d) Any other e) No

Name: Signature:

33. BIOLOGICAL SPECIMENS

Blood and urine samples and tissue specimens will be collected and preserved for future research with due permission.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19-20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary File

STUDY PROTOCOL – PRIME TRIAL

TITLE: Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypo fractionation [PRIME Trial]

2 A. REGISTRY: CTRI/2018/05/014054 (http://ctri.nic.in) (REF/2018/05/019975)

B. WHO Trial Registration Data Set

Data Category	Information
Primary registry and trial identifying number	CTRI/2018/05/014054(http://ctri.nic.in) REF/2018/05/019975
Date of registration in primary registry	May 22, 2018
Secondary identifying numbers	PRIME
Source(s) of monetary or material support	Tata Memorial Centre
Primary sponsor	Tata Memorial Centre (Intramural funding)
Secondary sponsor(s)	-
Contact for public queries	Dr. Vedang Murthy, MD 02224177000 ext 7029
Contact for scientific queries	vmurthyactrec.gov.in
Public title	**PRIME TRIAL**

Scientific title	Randomized controlled trial of Prostate Radiotherapy In High Risk and Node Positive Disease Comparing Moderate and Extreme Hypo-fractionation
Countries of recruitment	**INDIA**
Health condition(s) or problem(s) studied	Prostate Adenocarcinoma, High Risk Prostate Cancer, Node positive Prostate Cancer
Intervention(s)	Radiation: Moderate Hypo-fractionation 68Gy in 25# Radiation: Extreme Hypo-fractionation/SBRT 36.25Gy in 5#
Key inclusion and exclusion 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 5. PSMA PET/CT for all patients at baseline for staging 6. Ability to receive long term hormone therapy/ orchiectomy 7. KPS >70 8. No prior history of therapeutic irradiation to pelvis 9. Patient willing and reliable for follow-up and QOL 10. Signed study specific consent form

	Exclusion Criteria: 1. Evidence of distant metastasis at any time since presentation 2. Life expectancy < 2 years 3. Previous RT to prostate or prostatectomy. 4. Severe urinary symptoms or with severe IPSS score (>15) despite being on hormonal therapy for 6 months 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.
Study type	Open Label, Randomized, Interventional
Date of first enrolment	May 28, 2018
Target sample size	434 total number of patients with 217 patients in experimental arm and 217 patients in standard arm.
Recruitment status	**Recruiting**
Primary outcome	4-year biochemical Failure free survival (BFFS) Defined as duration from date of randomization to PSA > 2ng/ml above nadir value. (Phoenix definition)

Key secondary outcomes	Evaluate acute and late toxicity with both treatments. (Time Frame: 2 years) Prostate cancer specific survival and overall survival of patients receiving moderately hypo-fractionated RT and SBRT. (Time Frame: 5 years) Estimate out of pocket expenditure involved in patients receiving the two treatment schedules. Assess quality of life (QLQC30 and PR25)

3. PROTOCOL VERSION

Issue Date: 01.03.2019

Protocol Amendment Number: 2.0

Author(s):

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4. FUNDING

Tata Memorial Centre (Intramural funding)

5. ROLES AND RESPONSIBILITIES

A. CONTRIBUTORSHIP

A. Concept B. Design C. Screening of patients D. Selection & Recruitment and consenting of patients E. Laboratory investigations F. Laboratory report interpretation G. Treatment decision H. Patient evaluation I. AE and SAE management, evaluation and reporting	J. Examination of patients on follow-up K. Data collection and monitoring of data L. Interpretation of data M. Statistical analysis & Interpretation N. Maintaining patients file and master file of project O. Drafting final report P. Publication Z. Any other, please specify

A to P – Vedang Murthy, Indranil Mallick

C to P – Abhilash Gavarraju, Shwetabh Sinha, Rahul Krishnatry, Tejshri Telkhade, Arunsingh Moses, Ganesh Bakshi

C to I, P – Santosh Menon

K, L, M, N, O, P – Sadhna Kannan; K, N, O, P – Sheetal Kulkarni

C, D, G, H, I, J, P – Gagan Prakash, Mahendra Pal, Palak Popat, Venkatesh Rangarajan, Archi Agrawal

B. SPONSOR CONTACT INFORMATION

Trial Sponsor: Tata Memorial Centre (Intramural Funding)

Sponsor's Reference: NA

C. SPONSOR AND FUNDER

Tata Memorial Centre

D. COMMITTEES

DSMSC – Drug Safety Monitoring Committee

6 A. BACKGROUND AND RATIONALE

Prostate cancer is one of the most common cancers seen in the western population and is also seen on a rising trend in India. The standard of care for locally advanced high risk cancer is external beam radiotherapy along with long term hormonal therapy. Long term clinical and biochemical control is achievable with dose escalation in radiotherapy in prostate cancer. The radiobiological studies have shown that prostate cancer has a low alpha / beta ratio in the range of (0.9-2.2). Increased fraction size may improve biochemical control without significantly increased toxicity to nearby tissues (bladder, rectum). Extreme hypo fractionation 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.

Extreme hypo fractionation with a total duration of 2 weeks, would offer an opportunity to optimize 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 and health costs.

Given the potential positive economic impact with shorter duration treatment with similar clinical outcomes and probable similar toxicity profile, SBRT (extreme hypofractionation) 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.

B. CHOICE OF COMPARATORS

Active Comparator: Moderate Hypo-fractionation

In Arm 1 of the study, patients who are randomized to receive moderately hypo-fractionated RT will receive a total dose of 68 Gy in 25# to the primary over 5 weeks, with treatment being delivered daily. Patients with node positive disease will receive a dose of 50 Gy in 25# to the pelvis. Response assessment PSMA PET/CT will be done for all patients with pelvic nodal disease to ascertain the response to ADT based on morphology of the residual node and metabolic uptake as defined by the Uro Radiologist / Nuclear Medicine specialist. Patients with persistent residual nodal disease will be considered for nodal boost. Boost to residual gross nodal disease to a dose of 60-66 Gy in 25 fractions as a simultaneous integrated boostIntervention: Radiation: Moderate Hypo-fractionation

Experimental: Extreme Hypo-fractionation

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. Response assessment PSMA PET/CT will be done for all patients with pelvic nodal disease to ascertain the response to ADT based on morphology of the residual node and metabolic uptake as defined by the Uro Radiologist / Nuclear Medicine specialist. Patients with persistent residual nodal disease will be considered for nodal boost. Patients with node positive disease at baseline will receive a dose of 25Gy in 5 fractions to the pelvis. Boost to gross residual nodal disease will be considered to a dose of 30-35 Gy in 5 fractions as a simultaneous integrated boost. The 5 treatments will be scheduled to be delivered alternate day over approximately 7-10 days. An option of equivalent biological dose using 36.25Gy in 5 weekly fractions may be allowed for multicentric accrual in the future.

Intervention: Radiation: Extreme Hypo-fractionation.

Dose Coverage: The 98% isodose line used for the prescription dose should cover a minimum of 95% of the PTV.

7. OBJECTIVES

Hypothesis

Extreme hypo fractionation with SBRT in high risk prostate cancer is noninferior to moderately hypo fractionated standard radiotherapy while producing acceptable toxicity and advantage in terms of shortening of treatment duration.

Primary Endpoint

Assess the 4-year biochemical Failure free survival (BFFS) between the two arms.

Secondary Endpoints

Evaluate acute and late toxicity with both treatments.

Prostate cancer specific survival and overall survival of patients receiving moderately hypofractionated RT and SBRT.

Estimate the out of pocket expenditure involved in patients receiving the two treatment schedules.

Assess quality of life.

8. TRIAL DESIGN

Allocation: Randomized, Phase III

Intervention Model: Parallel Assignment (Prospective)

Masking: None (Open Label)

Primary Purpose: Treatment

9. STUDY SETTING

Location: Tata Memorial Hospital and ACTREC, Tata Memorial Centre, Mumbai, India;

Tata Medical Centre, Kolkata, India.

10. 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 group 4 or Gleason score 9 10/Gleason grade group 5, PSA > 20 ng/mL or Very high-risk prostate cancer i.e. T3b-T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4 cores Gleason score 8-10/Gleason grade group 4 or 5.
5. PSMA PET/CT for all patients at baseline for staging.
6. Ability to receive long term hormone therapy/Orchiectomy
7. KPS ≥ 70
8. No prior history of therapeutic irradiation to pelvis
9. Patient willing and reliable for follow-up and QOL
10. 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) in spite of being on hormonal therapy for 6 months 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.

1. Complete history and physical examination
2. Serum PSA < 3 weeks of randomization
3. Laboratory investigations undertaken routinely (complete blood counts, Renal function test, Liver function test and Serum Electrolytes)
4. Staging investigation PSMA PET-CT
5. IPSS scoring
6. Documentation of pre-treatment urinary and rectal symptoms and quality of life

11. INTERVENTIONS

A. INTERVENTIONS

Radiation: Moderate Hypo-fractionation – 68Gy in 25#

Radiation: Extreme Hypo-fractionation/SBRT – 36.25Gy in 5#

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. CT scans will be taken with contrast from 1st Lumber vertebra to 5 cm below ischial tuberosity with a slice thickness of 2.5mm. Laser marks 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 isotropic ally over CTV nodes
- PTV Prostate (and SV): A margin of 5mm will be grown in all directions over the CTV prostate.
- 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.

Clinical Assessment:

1. Objective criteria for toxicity evaluation - The RTOG will be used to document acute and late toxicities

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 the QLQC30 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 to 2 years.
4. All patients will follow up 3-6 weeks from end of radiotherapy. Thereafter follow up visits would be scheduled three to six months 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.

B. MODIFICATIONS

Arm 1 - Patients with node positive disease will receive a dose of 50 Gy in 25# to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66 Gy/25# as a simultaneous integrated boost (SIB).

Arm 2 - Patients with node positive disease will receive a dose of 25 Gy in 5 # to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 30-35 Gy/5# as a simultaneous integrated boost(SIB).

C. ADHERENCE

Appropriate counselling and weekly review of patients on treatment will ensure adherence to study protocol.

D. CONCOMITANT CARE

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 orchiectomy 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.

12. OUTCOMES

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

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

P**rostate 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.

13. PARTICIPANT TIMELINE

Registration

Patients with high risk carcinoma prostate on presentation will be screened for eligibility criteria. They must meet all 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

Stratified block randomization method

Stratification

Stratification will be done for the following parameters

1. Nodal status: N0 Vs N+
2. LHRH agonist/antagonists Vs Bilateral orchiectomy
3. Centre

The trial will accrue patients over a period of six years and all patients will be followed until the end of study.

14. SAMPLE SIZE

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 if the upper limit of the estimated 95% one sided confidence interval of the hazard ratio obtained lies entirely below 1.53. If the upper limit of the 95% one-sided confidence interval is 1.53 or higher, we do not reject the null hypothesis of inferiority. This also accounts for a 5% noncompliance rate as anticipated from experience in previous studies.

15. RECRUITMENT

Patient accrual

Patients will be identified and checked for eligibility from the OPDs at TMH, ACTREC and TMC. 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.

Multicentre approach: The trial will be opened to other centres with access to IMRT/IGRT who may be encouraged to join the study in due course. The choice of conventional

fractionation to 60-62.5Gy in 20# will be allowed with appropriate stratification for individual centres.

16. ALLOCATION

A. SEQUENCE GENERATION - Stratified block randomization method

B. CONCEALMENT MECHANISM - Participants will be randomised using online, central randomisation service. Allocation concealment will be ensured, as the service will not release the randomisation arm until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

C. IMPLEMENTATION - Allocation sequence will be generated applying the stratified randomization method. Enrolment of patients will be done from the outpatient department of Uro-Oncology services under the guidance of the PI and Co-PI.

17. BLINDING

A. MASKING – None (Open Label)

B. EMERGENCY UNBLINDING – NA

18. DATA COLLECTION METHODS

A. DATA COLLECTION

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.

B. RETENTION

Once a patient is enrolled or randomized, the study site will make every reasonable effort to follow the patient for the entire study period. Study site staff are responsible for developing and implementing local standard operating procedures to achieve this level of follow-up.

19. DATA MANAGEMENT

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.

20. STATISTICAL METHODS

A. OUTCOMES

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.

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.

B. ADDITIONAL ANALYSIS

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.

C. ANALYSIS POPULATION AND MISSING DATA

We propose to test non-inferiority using two analysis sets; the intention-to-treat set, considering all patients as randomized regardless of whether they received the randomized treatment, and the "per protocol" analysis set. We expect very few patients will be lost to follow-up. We propose declaring medical management non-inferior to interventional therapy, only if shown to be non-inferior using both the "intention to treat" and "per protocol" analysis sets.

21. DATA MONITORING

A. FORMAL COMMITTEE

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

B. 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)

22. HARMS

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.

23. AUDITING

Regular audit will be carried out by the PI with the assistance of Research Fellow and Trial Co-ordinator to ensure proper adherence to trial protocol, documentation of toxicities during and after treatment and regular follow up of patients post treatment.

24. RESEARCH ETHICS APPROVAL

The protocol and the template informed consent forms 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. After 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.

25. 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. 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.

26. CONSENT OR ASSENT

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.

27. 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.

28. DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

29. 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.

30. ANCILLARY AND POST-TRIAL CARE - NA

31. DISSEMINATION POLICY

A. TRIAL RESULTS

Results will be published in peer reviewed scientific journals along with conference presentations.

B. AUTHORSHIP - NA

C. REPRODUCIBLE RESEARCH

Plan to publish the study protocol in an indexed journal.

BMJ Open

Study Protocol of a Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation (PRIME TRIAL)

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Study Protocol of a Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypofractionation (PRIME TRIAL)

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ABSTRACT

INTRODUCTION

There has been an interest in studying the efficacy of extreme hypofractionation in low & intermediate risk prostate cancer utilising the low α/β ratio of prostate. Its role in high risk and node positive prostate cancer, however, is unknown. We hypothesize that a 5 fraction schedule of extreme hypofractionation will be non-inferior to a moderately hypofractionated regimen over 5 weeks in efficacy and will have acceptable toxicity and QOL while reducing the cost implications during treatment.

METHODS AND ANALYSIS

This is an ongoing, noninferiority, multicentre, randomized trial of two schedules for NCCN high risk &/or node positive non metastatic carcinoma of the prostate. The standard arm is a schedule of 68Gy/25# over 5 weeks while the test arm will be extremely hypofractionated RT with SBRT to 36.25Gy/5# (7-10 days). The block randomization will be stratified by nodal status (N0/N+), hormonal therapy (LHRH therapy/ orchiectomy) and centre. All patients will receive daily IGRT.

The primary endpoint is 4-year Biochemical Failure Free Survival (BFFS). The power calculations assume 4-year BFFS of 80% in the moderate hypofractionation arm. 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). The secondary end points include overall survival, prostate cancer specific survival, acute and late toxicities, quality of life and out of pocket expenditure.

DISCUSSION

The trial aims to establish a therapeutically efficacious and cost-efficient modality for high risk and node positive prostate cancer with an acceptable toxicity profile. Presently, this is the only trial evaluating and answering such a question in this cohort.

ETHICS AND DISSEMINATION

The trial has been approved by IEC-III of Tata Memorial Centre, Mumbai.

TRIAL REGISTRATION

Registered with CTRI/2018/05/014054 (http://ctri.nic.in) on May 24, 2018.

KEYWORDS

High Risk/Node Positive Prostate Cancer, SBRT, Extreme Hypo fractionation, SABR

Strengths & Limitations

Strengths

1. First study addressing the role of Moderate hypo fractionation and SBRT in High Risk and Node Positive prostate cancer
2. Use of PSMA PET/CT for all patients at baseline for staging and risk adapted approach.
3. Out of pocket expenditure will be collected from all patients which will potentially have a huge impact on logistics and resource utilization especially in LMIC like India.

Limitations

1. Non-inferiority margin between standard arm and test arm kept at 9%.
2. No published evidence for role of SBRT in Node positive prostate cancer in the literature

INTRODUCTION

Incidence of high risk/very high risk prostate cancer is on a rising trend across the globe.(1–4) Advanced prostate cancer accounts for 15% of all diagnosed prostate cancers in developed nations whereas in low and low-middle income countries like India the proportion of advanced disease is estimated to be as high as 84%.(5) Radiotherapy in the form of EBRT and/or brachytherapy forms an integral part of management of these patients. Radiobiological studies have shown that prostate cancer has a low alpha /beta ratio in the range of 0.47-4.14.(6) This makes hypo-fractionated radiotherapy radio-biologically superior than conventional fractionated (treatment time 7-8 weeks) schedules as it leads to a considerably higher biologically equivalent dose delivery. Prospective randomized trials have studied the safety and efficacy of moderate hypo-fractionation (treatment time 4-6 weeks) in prostate cancer and is now considered as the standard of care in low and intermediate risk prostate cancer.(7) With the benefit shown with moderate hypo fractionation, there has been a growing interest in the role of extreme hypo fractionation in prostate cancer.

Extreme hypo fractionation (treatment duration 7-10 days) with stereotactic body radiation therapy (SBRT) has an emerging role as an alternative technique to deliver high dose radiotherapy to the prostate comparable to brachytherapy, but with a non-invasive approach. However, the acute and late toxicities remain a concern with SBRT. Multiple single arm series on the use of SBRT as the primary treatment for prostate cancer have suggested the treatment to be safe but these studies have a majority of patients from low /intermediate risk group. The results of HYPO-RT-PC trial published recently supports the safety of SBRT in low/intermediate risk prostate cancer. (8)

The data with regards to extreme hypofractionation for high risk prostate cancer is still sparse. Recently, the early toxicity and quality of life results of a phase I/II Study of stereotactic ablative radiotherapy including regional lymph node irradiation in patients with high-risk prostate cancer (SATURN) has demonstrated the safety of SBRT for these patients.(9) Similarly, a retrospective series of 68 patients reported from India reported equivalent toxicities as compared to moderate hypofractionation in this subset of patients.(10)

Extreme hypo-fractionation (SBRT) for a total duration of 7-10 days, would offer an opportunity to optimize the therapeutic ratio for the treatment of these tumors along with significantly decreasing the overall treatment time which in turn would lead to significantly better quality of life during treatment, early recommencement to daily activities along with lessening the financial burden for these patients. We therefore initiated a randomized phase III trial to establish the non-inferiority of SBRT in high risk and/or node positive prostate cancer.

METHODS/DESIGN

Trial design

This is an ongoing, prospective, multicenter, two arm randomized control trial with a non-inferiority design led from a tertiary care cancer center in India for high-risk node negative and node positive prostate cancer patients. Randomization will be by stratified randomization method in a 1:1 ratio.

1. Standard Arm/Moderate Hypofractionation: Treatment duration: 5 weeks
2. Test Arm/Extreme Hypofractionation: Treatment duration: 7-10 days

Stratification will be done for the following parameters

1. Nodal status: N0 Vs N+
2. LHRH agonist/antagonists Vs Bilateral orchiectomy
3. Centre

Table 1: Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
1. Age: above 18 years 2. Participants must be histologically proven, adenocarcinoma prostate 3. Localized to the prostate or pelvic lymph nodes 4. High risk prostate cancer as per NCCN definition 5. PSMA/PET CT for all patients at baseline for staging 6. Ability to receive long term hormone therapy (2 years)/ orchiectomy 7. KPS >70 8. No prior history of therapeutic irradiation to pelvis 9. Patient willing and reliable for follow-up. 10. Signed study specific consent form	1. Evidence of distant metastasis at any time since presentation 2. Life expectancy < 2 years 3. Previous RT to prostate or prostatectomy. 4. Severe urinary symptoms or with severe IPSS score (>15) despite being on hormonal therapy for 6 months 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.

The inclusion criteria for the trial will include patients who are older than 18 years with histologically proven adenocarcinoma prostate localized to prostate and pelvic nodes with high risk /very high risk disease as per NCCN risk stratification (clinical stage T3a or Gleason score 8/Gleason grade group 4 or Gleason score 9-10/Gleason grade group 5, PSA > 20 ng/mL or Very

high risk prostate cancer i.e. T3b/T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4 cores, Gleason score 8-10/Gleason grade group 4 or 5). All patients will be staged with a baseline PSMA PET/CT. In addition, the patients should be fit to receive long term androgen deprivation therapy in the form of either orchiectomy/hormonal therapy (2 years) and have a baseline KPS of more than equal to 70 (Appendix 1). The exclusion criteria for the trial includes a distant metastatic disease, a life expectancy of less than 2 years, patient's with previous history of pelvic RT, patients with severe urinary symptoms (IPSS > 15) despite being on hormone therapy for 6 months, patients with obstructive urinary symptoms like stricture, patients with contraindication to EBRT like pelvic inflammatory disease and patients with uncontrolled co-morbidities (Table 1).

Patient and Public Involvement

Patient / Public were not involved in the research or methodology of this ongoing study. All patients were given an informed consent form (ICF). Only after willingly consenting and understanding all the aspects of participation in the trial, patients were randomized to either of the two arms.

Baseline Evaluation and Radiotherapy Details

The base line evaluation would include standard work up for a locally advanced carcinoma prostate i.e. TRUS guided 12 core biopsy, baseline serum PSA level. PSMA PET/CT will be used at baseline to stage all patients. Nodal involvement by disease will be defined as SUVmax ≥ 3.0 irrespective of the size but based on morphological characteristics like shape, heterogeneity

and perinodal stranding as determined by expert in Uro Radiology (PP) and Nuclear Imaging (VR, AA).

The duration of neoadjuvant ADT ranges from 8-12 weeks for node negative patients and 6 months for node positive patients. Preferably, all patients will have baseline documentation of Quality of Life (using EORTC QLQ C30 and PR 25 questionnaire) and IPSS score at baseline as well as before starting EBRT.

In the standard arm, patients who are randomized to receive moderately hypo-fractionated RT will receive a total dose of 68 Gy in 25 fractions to the primary over 5 weeks, with treatment being delivered daily. Patients with node positive disease will receive a dose of 50 Gy in 25 fractions to the pelvis. Response assessment PSMA PET/CT will be done for all patients with pelvic nodal disease to ascertain the response to ADT based on morphology of the residual node and metabolic uptake as defined by the Uro Radiologist / Nuclear Medicine specialist. Patients with persistent residual nodal disease will be considered for nodal boost. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66 Gy in 25 fractions as a simultaneous integrated boost. An option of equivalent biological dose using 60-62.5 Gy in 20 fractions may be allowed for multicentric accrual in the future. In the test arm of study, patients who are scheduled to receive extreme hypo-fractionated RT (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 fractions to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 30-35 Gy in 5 fractions as a simultaneous integrated boost. 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.

All patients will be treated with IMRT or related techniques (Helical Tomotherapy/VMAT) with daily image guidance in the form of KV-CBCT/MVCT. No intraprostatic fiducials will be used for IGRT. The contouring of GTV nodes, CTV primary and organs at risk will be done according to standard ESTRO ACROP guidelines(11). CTV nodes will be contoured by giving a radial margin of 5-7 mm around the common iliac, external iliac, internal iliac, pre sacral and the obturator vessels and editing from muscles and bones. The cranial extent of CTV nodes will be at the level of L5 – S1 vertebra and the caudal extent will be at the level obturator nodes. For patients without seminal vesicle involvement only 1.5 cm of the base of seminal vesicles will be included in CTV primary whereas the entire seminal vesicle will be included in the CTV primary in patients with radiological involvement of seminal vesicle. A PTV margins of 5 mm will be given around the entire CTV primary (including seminal vesicles) and CTV nodes to delineate PTV primary and PTV nodes respectively. The dose volume constraints for the target volume will include a CTV D98 of 98% (both primary and nodes) and a PTV D98 of 95% (both primary and nodes). These contouring guidelines and dose constraints are in accordance with the retrospective series of SBRT for high risk and/or node positive prostate cancer published from the same institute (10,12).

The dose volume constraints for organs at risk is given in Tables 2 and 3.

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

Organ EQD2 α/β 3		**V30 (25.2Gy)**	**V40 (36.8Gy)**	**V50 (50Gy)**	**V60 (64.8Gy)**	**V65 (72.8Gy)**
BLADDER	N+	<60%	<40%	<25%	<15%	<3%
	N-	<25%	<20%	<14%	<10%	<3%
RECTUM	N+	<75%	<50%	<25%	<15%	<5%
	N-	<45%	<30%	<20%	<15%	<5%
Bowel(cc)				80CC		

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

Organ EQD2 α/β 3		**V14 (16.2Gy)**	**V17.5 (22.8Gy)**	**V28 (48.2Gy)**	**V31.5 (58.6Gy)**	**V35 (70Gy)**
BLADDER	N+	<40%	<27%	<20%	-	<3%
	N-	<35%	<20%	<10%	-	<3%
RECTUM	N+	<50%	<40%	<15%	<8%	<3%
	N-	<40%	<30%	<15%	<8%	<3%
FEMORAL HEADS		<5%				
Bowel(cc)				80cc		

Assessment/Follow up

Patients will continue (LHRH agonist/antagonist) during radiotherapy. All patients will be monitored during radiotherapy and at every follow up for acute/late toxicities using RTOG and CTCAE 4.03 toxicity grading scales (Appendix 2,3,4). In addition, out of pocket expenditure (Appendix 5) of the patient and caregiver for food, travel, stay and for management of treatment related side-effects will be captured using a structured record form along with QOL score, IPSS score and urinary function. All patients will be followed up after 4-6 weeks of completion of radiotherapy and then at 3-6 monthly intervals till 2 years and 6 monthly intervals thereafter. Patients will continue LHRH agonists/antagonist after completion of

radiotherapy to complete a total duration of 2 years. Clinical evaluation of the disease will be done at each follow up visit with a serum PSA and clinical examination. Any other investigation will be done at the physician's discretion.

Statistics

The primary end point of this study will be 4-year **biochemical failure free survival (BFFS)** which will be defined as the time (in months) from the date of randomization to the date of biochemical failure as per Phoenix Criteria (a rise in PSA level of more than 2 ng/ml above the nadir). This is a non-inferiority (NI) trial and the non-inferiority margin between the standard and the test arms is 9% (delta). To detect this delta difference in the primary endpoint of a 4-year Biochemical Failure Free Survival (80% in standard arm and 71% in the test arm; hazard ratio [HR] 1.53), with a power of 80% and a one sided 5% alpha value, total of 135 events are required, with a minimum number of 422 patients. The assumption of 80% BFFS in the standard arm was based on the results of similar studies of high risk node negative cancer studies (STAMPEDE, James ND et al. JAMA oncology 2016 and PRO 7, J Clin Oncol 2015) and our own data (unpublished) which showed a 5-year BFFS of about 85%. As this study is recruiting high risk and node positive patients also, the upper limit of 80% was chosen. Non-inferiority of Extreme hypofractionation with SBRT (test arm) versus moderate hypofractionated RT (standard arm) will be concluded if the upper limit of the estimated 95% one sided confidence interval of the hazard ratio obtained lies entirely below 1.53. If the upper limit of the 95% one-sided confidence interval is 1.53 or higher, we do not reject the null hypothesis of inferiority. The trial will accrue patients over a period of six years and all patients will be followed until the end of study. Considering an attrition rate of around 5%, the trial would require a total of 434

patients (217 in each arm). The primary efficacy analysis will be on both ITT basis and per protocol basis.

The secondary end points for the study will be evaluation of the acute and late toxicities (according to RTOG and CTCAE criterion), ascertaining the overall survival and prostate cancer specific survival for these patients, estimation of out of pocket expenditure involved in patients receiving the two treatment schedules and assessment of pre-treatment and post-treatment quality of life of these patients. For this study, overall survival (OS) and prostate cancer specific survival (PCSF) will be defined as time in months between date of randomization and date of death due to any cause or date of death due to prostate cancer respectively.

A planned interim analyses will be done on accrual of 25% (108 patients in both arms combined) patients completing 2 years of follow up. At the 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). We expect 80 patients to be accrued per year in the project with total study duration of about 6 years, with a non-fixed follow up period and a uniform accrual rate.

Quality Assurance

Radiation therapy quality assurance in the setting of a multi-institutional clinical trial has been shown to have a very important bearing on outcomes. The US National Cancer Institute Work Group on Radiotherapy Quality Assurance has laid down guidelines that help individual trials lay down their QA protocol (Bekelman et al. 2012)(13). The PRIME trial will use these guidelines to formulate a trial specific protocol as outlined below.

Tiered system for Radiotherapy Trial QA

Tier 1 includes General credentialing which comprises of filling a facility questionnaire outlining machine specific and patient specific QA process.

Tier 2 is a Trial specific credentialing consists of a dry run process with oncologists and physicists familiarizing themselves with the contouring protocol and advanced dosimetry checks with multiple plan generation to meet trial constraints.

Tier 3 is an individualized case review of dosimetry and QA datasheet reviewed every monthly in virtual QA meet.

DISCUSSION

The efficacy of SBRT for prostate cancer is supported by a radiobiological basis as well as phase 1 and phase 2 single arm studies. Several single arm series have established the efficacy and safety of SBRT for low and intermediate risk prostate cancer. The results of ongoing phase 3 trials comparing extreme hypofractionation to moderate hypofractionation/conventional fractionation are awaited. (Table 4). The major concern with SBRT is the impact on acute and late toxicities of the patients. The HYPO-RT-PC trial accrued 1200 intermediate risk prostate cancer patients (T1c-T3a, PSA </=20, with one or two of the following risk factors: T3a or

Gleason 7 or PSA >10) and tested conventionally fractionated RT against extreme hypofractionation. Preliminary results show no significant differences in the prevalence of physician reported grade 2+ toxicity at 2 years between the two arms for urinary (5.4% vs 4.6%, P=0.59) and bowel (2.2% vs 3.7%, P=0.20) toxicity. (8)

The reports for SBRT as monotherapy for high risk disease are limited as most contemporary series have included very few high risk prostate cancers (Table 5). The dose per fraction given in these series range from 7-8Gy in 4 to 6 fractions given over 7-14 days. The toxicities and outcomes are comparable to that expected with moderate hypo-fraction schedules with the GI and GU RTOG ≥ 2 late toxicities ranging from 2 -14%.

Table 4: Phase 3 Trials of SBRT in Prostate Cancer

	NRG-GU 005	PACE A & PACE B (14)	Hypo fractionated RT in Prostate Cancer	HYPO-RT-PC (8)	PATRIOT (15)	PRIME
Trial ID	NCT 03367702	NCT 01584258	NCT 01764646	ISRCTN45905321	NCT01423474	NCT03561961
Study/Group	NRG Oncology	Royal Marsden NHS Foundation Trust	Geneva, Switzerland	Scandinavia	Canada	Tata Memorial Hospital, India
Stage/ Eligibility	cT1c or T2a/b (limited to one side of the gland); (AJCC, version 7) or cT1a-c or 2a /2b, stage group IIA or IIB; (AJCC, version 8) Excludes: Definitive T3 on MRI	Low risk: cT1-T2a and Gleason ≤ 6 and PSA < 10 ng/ml, or Intermediate risk: Clinical stage T2b orT2c, PSA 10-20 ng/ml or Gleason 3+4Excludes:	cT1c - cT3a disease with a Low Risk of Nodal Metastases (≤ 20%, Roach Index)	T1c - T3a with one or two of the following risk factors: T3a or Gleason >7, PSA >10 according to the TNM classification system UICC 2002, PSA<20 µg/L	Low or intermediate risk T1-2b, Gleason </=7, PSA <20ng/ml	High risk, Very high risk and node positive prostate cancer as per NCCN definition: T3a-T4 or Gleason score 8/grade group 4 or Gleason score 9/grade group 5 or Primary Gleason pattern 5 or PSA > 20 ng/ml
Target Accrual	606	1716	170	1200	152	434

Interventions	SBRT (36.25Gy in 5 fractions over 12 days) vs Moderate Hypo fractionation (70Gy in 28 fractions over	PACE A: SBRT (36.25Gy in 5 fractions) vs Radical Prostatectomy PACE B: SBRT (36.25Gy in 5 fractions) vs Conventional fractionation (78Gy in 39 fractions)	SBRT (36.25Gy in 5 fractions) every other day over 9 days vs SBRT (36.25Gy in 5 fractions) once a week over 28 days	SBRT (42.7Gy in 7 fractions alternate day over 2.5 weeks) vs Conventional fractionation (78Gy in 39 fractions over 8 weeks)	SBRT (40Gy in 5 fractions) every other day (EOD) over 11 days vs SBRT (40Gy in 5 fractions) once a week (QW) over 29 days	SBRT: 36.25Gy in 5 fractions over 7-10 days; (Node positive disease - 25Gy in 5 fractions) vs Moderate Hypo fractionation: 68Gy in 25 fractions over 5 weeks; (Node positive disease – 50Gy in 25 fractions)
Primary Endpoint	Composite end point of DFS & EPIC-26 urinary and bowel toxicity at 2 years	PACE A: QOL and EPIC score at 2 years PACE B: Biochemical/ Clinical failure at 5 years	Acute and Late urinary, rectal and sexual toxicity at 5 years (CTCAE 3.0)	Freedom from failure (PSA or any clinical), measured 5 years after the end of treatment	EPIC measured bowel related QOL	Biochemical Failure free survival at 4 years
Estimated Accrual Completion	December 2025	September 2021	Accrual completed	Accrual completed	October 2020	March 2024

FASTR is a phase 1 feasibility study for SBRT for node positive disease which delivered a dose of 25 Gy to pelvic nodes and 40 Gy to primary over a period of 5 weeks (once weekly fractionation). 9 out of the 15 patients accrued (60%) developed ≥ Gr 2 GI or GU toxicity at 6 months and 4 (30%) ≥ Gr 3 GI or GU toxicity at 6 months. The study was terminated before phase 2 in view of the higher toxicities (16). Another single arm study (SATURN) evaluated a similar protocol with a dose of 25 Gy to pelvic nodes and seminal vesicle, 40Gy as SIB to the prostate and 33.25 Gy to the prostate PTV delivered over a period of 5 weeks in 5 once weekly fractions. The authors reported a Gr 2 GU toxicity of 52% (baseline 30%) and 32 % GI toxicity (baseline 3.3%) at 6 months. No grade 3 toxicities were reported. The authors attributed the lesser toxicity of this study as compared to the FASTR protocol to the lesser dose prescription to the prostate PTV (40 vs 33.25 Gy), the lesser PTV margins (5 mm vs 3 mm), smaller CTV volumes and better image guidance in SATURN protocol.(9)

In the present trial, the dose to primary PTV will be 36.25Gy in 5 fractions, which is between those given in FASTR and SATURN trials. The efficacy and safety of such a dosing schedule has already been published as a single arm retrospective series from India with an 18-month biochemical disease free survival of 94% and incidence of ≥ Grade 3 late GU and GI toxicity of 3% and 0% respectively. In addition, the PTV margins are 5 mm which again has been shown to adequate with daily CBCT based IGRT(15).

This trial aims to establish a therapeutically efficacious and cost-efficient modality for high risk, very high risk and node positive prostate with acceptable toxicity profile which is likely to be a big public health problem in low income/low middle income countries in the coming decade. Presently, this is the only trial evaluating and answering such a question in this cohort.

Table 5: Published series of SBRT in High Risk Prostate Cancer

Author, Year, Origin	No. of high risk patients	HR definition	Dose	Median FU (y)	ADT/duration	Acute GU	Acute GI	Late GU	Late GI	OUTCOMES
Kang 2011, Korea(17)	29	D'Amico	8 Gy ×4, 8.5Gy x 4 or 9Gy x 4	3.3	Yes/24 months	G2 - 25%	G2 - 25%	G2 - 14%	G2 - 14%	5-y bDFS: 90.9%
King 2013, USA(18)	125	D'Amico	7-8Gy x 5	3	38% HR patients/4 months	NS	NS	NS	NS	5-y bDFS: 81%
Davis 2015, Radiosurgery Society(19)	33	NCCN 2015	7-9.5Gy x 4-5	1.6	15HR patients received ADT/NS	NS	NS	G2 - 8%	G2 - 2%	2-y bDFS: 90% but with PSA >20 ng/mL: 62.5%
Ricco 2016, USA(20)	32	NCCN 2015	7-7.5Gy x 5	4.1	27% of all SBRT patients/ NS	NS	NS	No G3 GU/GI toxicity		6-y bDFS for SBRT: 92%. 4-y bDFS for HR and VHR: 95% and 72%
Katz 2016, USA(21)	38	NCCN 1.2016	7-7.25Gy x 5	7	Yes/NS	G2 - <5%	G2 - <5%	G2 - 9%	G2 - 4%; G3 - 1.7%	8-y bDFS: 65% for HR. Favorable unfavorable intermediate 7-y bDFS ~93% and 68%
Koskela 2017,Finland (22)	111	D'Amico	7-7.25Gy x 5	2	88.3% HR/48% of HR patients ADT >24months	No acute G3 toxicity		Intermediate GU % GI - 1.8 & 0.9%		23-mo bDFS: 92.8%
V Murthy 2018, India(10)	68	NCCN 37 (54%) patients were N1	7-7.25Gy x 5	1.5	Median duration - 15 months	G2 – 12%;	G2 – 4%	G2 - 4.5%; G3 – 2%	G2 – 4%	18-mo bDFS: 94%

Word Count (including tables): 3849

ABBREVIATIONS:

EBRT: External Beam Radiotherapy, SBRT: Stereotactic Body Radiotherapy, NCCN: National Cancer Control Network, PSA: Prostate Specific Antigen, KPS: Karnofsky Performance scale, RT: Radiotherapy, TRUS: Transrectal Ultrasonography, CECT: Contrast Enhanced Computerized Tomography, PSMA: Prostate specific Membrane Antigen, PET: Positron Emission Tomography, ADT: Androgen Deprivation Therapy, IPSS: International Prostate Symptom Score, EORTC: European Organization for Research and Treatment of Cancer, QLQ: Quality of Life Questionnaire IMRT: Intensity Modulated Radiotherapy, VMAT: Volumetric Modulated Arc Therapy, KV-CBCT: Kilo Voltage-Cone Beam Computerized Tomography, MVCT: Megavoltage Computerized Tomography, GTV: Gross Tumor Volume, CTV: Clinical Target Volume, MRI: Magnetic Resonance Imaging, PTV: Planning Target Volume, LHRH: Luteinizing hormone releasing hormone RTOG: Radiotherapy Oncology Group, CTCAE: Common Terminology Criteria for Adverse Events, QOL: Quality of Life, BFFS: Biochemical Failure Free Survival, ITT: Intention to treat , OS: Overall survival, PCSF: Prostate Cancer Specific Survival, IGRT: Image Guided Radiotherapy*, GI: Gastrointestinal, GU: Genitourinary, DSMC: Data Safety and Monitoring Committee.

*Ghadjar P, Fiorino C, af Rosenschöld PM, Pinkawa M, Zilli T, van Der Heide UA. ESTRO ACROP consensus guideline on the use of image guided radiation therapy for localized prostate cancer. Radiotherapy and Oncology. 2019 Dec 1; 141:5-13.

DECLARATIONS:

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Signature of the informed consent will be obtained from all patients before inclusion in the study. This ongoing study was approved by Institutional Ethics Committee of Tata Memorial Hospital, Mumbai (TMC IRB Project No: -271/CTRI No: CTRI/2018/05/014054). This study was approved by Institutional Ethics Committee of Tata Medical Center, Kolkata (2018/TMC/134/IRB32). This trial is registered prospectively with CTRI/2018/05/014054 (http://ctri.nic.in)(REF/2018/05/019975) on May 24, 2018.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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AUTHOR CONTRIBUTIONS

Study concept and design: VM, IM; Selection accrual and consenting of patients: VM, IM, AG, SS, RK, TT, AM; Patient examination and clinical evaluation: VM, IM, AG, SS, RK, TT, AM, GB, GP, MP; Radiological evaluation: PP, VR, AA; Pathological evaluation: SM; Statistical Analysis and

Interpretation: SaK; Data collection and Master File maintenance: ShK. All authors have read and approved the manuscript.

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Not Applicable

AUTHOR'S INFORMATION

Not applicable

REFERENCES:

1. Time trends and local variation in primary treatment of localized prostate cancer. - PubMed - NCBI [Internet]. [cited 2018 Sep 26]. Available from: https://www.ncbi.nlm.nih.gov/pubmed/20124165

2. Punnen S, Cooperberg MR. The epidemiology of high-risk prostate cancer. Curr Opin Urol. 2013 Jul;23(4):331–6.

3. Jain S, Saxena S, Kumar A. Epidemiology of prostate cancer in India. Meta Gene. 2014 Aug 29; 2:596–605.

4. Hariharan K, Padmanabha V. Demography and disease characteristics of prostate cancer in India. Indian J Urol. 2016 Apr 1;32(2):103.

5. Hebert JR, Ghumare SS, Gupta PC. Stage at diagnosis and relative differences in breast and prostate cancer incidence in India: comparison with the United States. Asian Pac J Cancer Prev APJCP. 2006 Dec;7(4):547–55.

6. Vogelius IR, Bentzen SM. Meta-analysis of the Alpha/Beta Ratio for Prostate Cancer in the Presence of an Overall Time Factor: Bad News, Good News, or No News? Int J Radiat Oncol Biol Phys. 2013 Jan 1;85(1):89–94.

7. Dearnaley D, Syndikus I, Sumo G, Bidmead M, Bloomfield D, Clark C, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer: preliminary safety results from the CHHiP randomised controlled trial. Lancet Oncol. 2012 Jan;13(1):43–54.

8. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, Kindblom J, Ginman C, Johansson B, Björnlinger K, Seke M. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. The Lancet. 2019 Jun 18.

9. Musunuru HB, D'Alimonte L, Davidson M, Ho L, Cheung P, Vesprini D, et al. Phase I/II Study of Stereotactic Ablative Radiotherapy Including Regional Lymph Node Irradiation in Patients with High-Risk Prostate Cancer (SATURN): Early Toxicity and Quality of Life. Int J Radiat Oncol Biol Phys. 2018 Jul 30;

10. Murthy V, Gupta M, Mulye G, Maulik S, Munshi M, Krishnatry R, et al. Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer. Clin Oncol R Coll Radiol G B. 2018 Jul;30(7):442–7.

11. Salembier C, Villeirs G, Bari BD, Hoskin P, Pieters BR, Vulpen MV, et al. ESTRO ACROP consensus guideline on CT- and MRI-based target volume delineation for primary radiation therapy of localized prostate cancer. Radiother Oncol. 2018 Apr 1;127(1):49–61.

12. Murthy V, Sinha S, Kannan S, Datta D, Das R, Bakshi G, Prakash G, Krishnatry R. Safety of Prostate Stereotactic Body Radiation Therapy after Transurethral Resection of Prostate (TURP): A Propensity Score Matched Pair Analysis. Practical Radiation Oncology. 2019 Apr 9.

13. Bekelman JE, Deye JA, Vikram B, Bentzen SM, Bruner D, Curran Jr WJ, Dignam J, Efstathiou JA, Fitzgerald TJ, Hurkmans C, Ibbott GS. Redesigning radiotherapy quality assurance: opportunities to develop an efficient, evidence-based system to support clinical trials—report of the National Cancer Institute work group on radiotherapy quality assurance. International Journal of Radiation Oncology* Biology* Physics. 2012 Jul 1;83(3):782-90.

14. Brand DH, Tree AC, Ostler P, van der Voet H, Loblaw A, Chu W, Ford D, Tolan S, Jain S, Martin A, Staffurth J. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. The Lancet Oncology. 2019 Sep 17.

15. Quon HC, Ong A, Cheung P, Chu W, Chung HT, Vesprini D, Chowdhury A, Panjwani D, Pang G, Korol R, Davidson M. Once-weekly versus every-other-day stereotactic body radiotherapy in patients with prostate cancer (PATRIOT): A phase 2 randomized trial. Radiotherapy and Oncology. 2018 May 1;127(2):206-12.

16. Bauman G, Ferguson M, Lock M, Chen J, Ahmad B, Venkatesan VM, et al. A Phase 1/2 Trial of Brief Androgen Suppression and Stereotactic Radiation Therapy (FASTR) for High-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys. 2015 Jul 15;92(4):856–62.

17. Management of high-risk prostate cancer with 5-treatment stereotactic body radiotherapy: Long-term results.: Journal of Clinical Oncology: Vol 35, No 6_suppl [Internet]. [cited 2018 Sep 19]. Available from: http://ascopubs.org/doi/10.1200/JCO.2017.35.6_suppl.94

18. King CR, Freeman D, Kaplan I, Fuller D, Bolzicco G, Collins S, et al. Stereotactic body radiotherapy for localized prostate cancer: pooled analysis from a multi-institutional consortium of prospective phase II trials. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2013 Nov;109(2):217–21.

19. Davis J, Sharma S, Shumway R, Perry D, Bydder S, Simpson CK, et al. Stereotactic Body Radiotherapy for Clinically Localized Prostate Cancer: Toxicity and Biochemical Disease-Free Outcomes from a Multi-Institutional Patient Registry. Cureus [Internet]. [cited 2018 Sep 19];7(12). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4699985/

20. Ricco A, Manahan G, Lanciano R, Hanlon A, Yang J, Arrigo S, et al. The Comparison of Stereotactic Body Radiation Therapy and Intensity-Modulated Radiation Therapy for Prostate Cancer by NCCN Risk Groups. Front Oncol [Internet]. 2016 Aug 23 [cited 2018 Sep 19];6. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4994110/

21. Katz A, Kang J. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: Risk Stratification for Intermediate- and High-Risk Patients. Int J Radiat Oncol Biol Phys. 2016 Oct 1;96(2): E250.

22. Koskela K, Palmgren J-E, Heikkilä J, Virsunen H, Sailas L, Auvinen P, et al. Hypofractionated stereotactic body radiotherapy for localized prostate cancer - first Nordic clinical experience. Acta Oncol Stockh Swed. 2017 Jul;56(7):978–83.

APPENDICES

32. INFORMED CONSENT MATERIALS

PATIENT INFORMATION SHEET

You are being invited to participate in a research study. Before you take part, we would like to explain the study purpose is giving you a chance to ask questions. Please read carefully the information provided here. If you agree to participate, please sign the informed consent form. You will be given a copy of this document to take home with you.

STUDY INFORMATION

DESCRIPTION OF YOUR CONDITION AND THE STUDY

You have been diagnosed with a condition called prostate cancer. The treatment with radiotherapy has been decided by your doctors. This is the standard treatment for your cancer along with hormonal therapy. During radiotherapy, normally the prostate gland is treated to a high dose with radiation with computer-based planning over a period of 5-6 weeks. There is an alternative schedule in which the treatment is delivered over a shorter time of 7-10 days. We intend to study these schedules and find out the side-effects and effectiveness of both the schedules.

The present study: The present research is comparing two different dose schedules of radiotherapy. It is to see whether the shorter duration of treatment results is as effective as the standard duration of treatment and thus possibly help to reduce the treatment time for patients. This will also hopefully reduce the associated cost involved in radiotherapy to patients. The study plans to include about 434 study participants.

STUDY PROCEDURES AND VISIT SCHEDULE

If you agree to take part in this study, before you start treatment, basic tests like blood tests, scans and x-rays will be performed, if not already done. You will be then allocated to one of the treatments by a process known as randomization. Randomization means that the decision will be impartially done by a central computer and your study doctor cannot influence to which treatment you will be assigned. In group A, patients will receive radiotherapy in 25 sittings over 5 weeks. If allotted to group B, patients will receive radiotherapy over 1-2 weeks in 5 sittings. The radiotherapy will be given with the best possible and most advanced technique in both groups to decrease possible side effects and is similar in every way except the duration of treatment. Once the treatment is decided in any group, you will be called for planning of radiation treatment. This will involve undergoing a CT scan which will be done to accurately plan the radiotherapy. You will be followed up on a regular basis to monitor your condition and all other medicines will be similar in both groups. During the follow-up, routine examination and tests by your physician will be done. You will be asked to fill quality of life form regularly to help us to understand the side effects better. You will also be asked questions on your health care expenditure to understand the financial costs borne by you during the treatment. You will need to visit the doctor's clinic 3-6 monthly for 1st year and 6 monthly thereafter. The frequency of visiting the doctor's clinic is the same as normal follow-up visits outside the study.

ALTERNATIVE TREATMENTS

If you choose not to take part in this study, you will be offered RT outside the study over 5-6 weeks. This will be discussed with you in detail by your doctor.

POSSIBLE RISKS AND SIDE-EFFECTS OF RADIOTHERAPY

You will be counselled regarding the possible side effects of radiation which are no different from that of routine radiotherapy. The technique of RT that we will employ will help in reducing the side effects. These include general symptoms like nausea, vomiting, fatigue, mild weakness and loss of appetite. Skin darkening in the treated area, diarrhoea, pain and/or bleeding on passing motion, urinary urgency, increased frequency of urination or bleeding on passing urine as immediate side effects during treatment. Late side effects include increased frequency of urination, burning in urine and mild bleeding from urine and stools. These expected side effects can be treated by simple medicines if needed. Those in the short treatment group may have slightly more side effects as mentioned above compared to those on the 5-week radiotherapy schedule. In case of severe side effects, which may occur in about 2% of patients, the RT may be temporarily stopped.

COST OF TREATMENT AND SIDE EFFECTS

If you are in the standard group with 5 weeks of treatment, the cost of treatment will be borne by you as would have done routinely. In case you are in the short treatment group of 1-2 weeks, the cost will not be charged to you. The doctor will discuss the approximate cost of treatment with you. There will be no extra scans or tests involved.

REIMBURSEMENT FOR PARTICIPATION

No financial reimbursement is planned for participation in the study.

EMERGENCY MEDICAL TREATMENT

In the unlikely event of any medical emergency arising due to the radiotherapy, you will be provided the best possible care as needed. You will have to pay for it in the standard longer treatment arm but not the shorter treatment arm.

POTENTIAL BENEFITS

There may be no direct benefits to you due to participation in the trial. You will receive excellent quality treatment in both arms. If you are in the arm that has radiation with shorter duration of treatment, you may have less out of pocket expenditure and can return home quickly. There is no assurance however that you will benefit from this study. Nevertheless, your participation may contribute to the medical knowledge about the best way to treat patients with disease like yours. Please remember that the many of the most effective treatments used today are the result of clinical trials done in the past.

CONFIDENTIALITY OF STUDY AND MEDICAL RECORDS

The information in the study records will be kept confidential and the clinical charts will be housed in the TMH/CRS/ACTREC. Data will be stored securely and will be made available only to persons conducting the study and to the regulatory authorities. The data will not be made available to another individual unless you specifically give permission in writing. No reference will be made in oral or written reports which could link you to the study. Result of the project will not be communicated to the subject unless deemed necessary.

COMPENSATION FOR PROTOCOL RELATED INJURY

All subjects participating in the study will be covered under institutional insurance for any trial related injury or death.

WHOM TO CONTACT IF YOU HAVE QUESTIONS

If you have questions about this research study and your rights or in the case of any injuries during this study, you may contact the Principal Investigator:

Dr. Vedang Murthy

Department of Radiation Oncology,

Advanced centre for treatment, research and education for cancer (ACTREC),

Tata Memorial Centre, Navi Mumbai 410210, Tel: (022) 27405000

If you have questions about the study or your rights as a participant, you can call the IEC, which is the committee that reviewed and approved this study:

The Chairperson,

Dr R Mulherkar,

IEC III,

Advanced centre for treatment, research and education for cancer (ACTREC),

Tata Memorial Centre,

Navi Mumbai 410210,

Tel:(022)27405154

INFORMED CONSENT FORM (ICF)

Participation

Your participation in this study is voluntary; you may decline to participate at any time without penalty and without loss of benefits to which you are otherwise entitled.

If you withdraw from the study prior to its completion, you will receive the usual standard of care for your disease, and your non-participation will not have any adverse effects on your subsequent medical treatment or relationship with the treating physician

If you withdraw from the study before data collection is completed, your data will not be entered in the study report.

Consent

Informed Consent form to participate in a clinical trial

Study Title:

Study Number:

Subject' Initials: _____ Subject's Name: _____

Date of Birth / Age: _____

1. I understand that I am being invited to take part in the research study. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand the risks and potential benefits of this research study that were explained to me. I freely give my consent to take part in research study described in this form.
4. I understand that the Sponsor of the research study, others working on the Sponsor's behalf, IEC and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
5. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
6. I agree to take part in the above study.

   I have read the above information and agreed to participate in this study. I have received a copy of this form.
7. **Informed consent form to participate in a biological sample study**

Study Title:

Study Number:

Participant' Initials: _____

Participant's Name: _____

Date of Birth / Age: _____

Do you consent to biological sample study?

☐ YES, I consent ☐ NO, I do not consent

1. I understand that I am being invited to take part in the research study. I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
3. I understand the risks and potential benefits of this research study that were explained to me. I freely give my consent to take part in research study described in this form.

4. I understand that the investigator of the research study, others working on the Investigator's behalf, IEC and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.
5. I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).
6. I agree to take part in the above study.

Participant's name (print):	
Participant's signature & date:	
Address: Qualification (please attach supporting documentation): _____ Occupation: Student / Self-Employed / Service /Housewife /Others (Please tick as appropriate) and attach supporting documentation Annual Income of the subject (please attach supporting documentation): _____	
Phone Nos.:	
Legally Acceptable Representative name	
Legally Acceptable Representative signature & date:	

Address (capital letters): Phone Nos.:	
Impartial Witness's name:	
Impartial Witness's signature & date:	
Address (capital letters): Phone Nos.:	
Name of PI or Co-PI/Co-I:	
PI or Co-PI/Co-I & date:	

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	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	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube

		requiring analgesics		distended bowel loops)	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 V 4.03)

Gastro intestinal Disorder					
CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Constipation **Definition:** A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Diarrhea **Definition:** A disorder characterized by an increase in frequency and/or loose or watery bowel movements	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Fecal incontinence **Definition:** A disorder characterized by inability to control the escape of stool from the rectum	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Proctitis **Definition:** A disorder characterized by inflammation of the rectum	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Rectal hemorrhage **Definition:** A disorder characterized by bleeding from the rectal wall	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death

and discharged from the anus					
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, 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 invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Renal and Urinary Disorder

CTCAE	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
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	Urinary, suprapubic or intermittent catheter placement not indicated; able to	Placement of urinary, suprapubic or intermittent catheter placement indicated;	Elective invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative	Death

urine within the bladder because of the inability to urinate	void with some residual	medication indicated		intervention indicated	
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; 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
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 urgency **Definition:** A disorder characterized by a sudden compelling urge to urinate	Present	Limiting instrumental ADL; medical management indicated	-	-	-

Appendix 5: Out of pocket Expenditure: Data Collection Tool

General Information

Case No: _____ Trial No: _____

Type of Radiotherapy: _____

1) Name of Patient _____

   Address of Patient

   Contact No.

   Email id_____

2) Name of Respondent/Caregiver _____

Relation with Patient _____

Contact No._____

3) Religion

a) Hindu b) Muslim c) Sikh

d) Christian f) Others

4) Locality

a) Urban b) Slum c) Rural

5) Educational status

a) Illiterate b) Primary c) Middle

d) Matric e) Senior secondary f) Graduation

g) Post graduation

6) Marital Status

a) Unmarried b) Married

c) Separated/Divorced d) Widow/Widower

7) Type of Insurance

a) BPL free/poor free b) Government employee

c) Private Insurance d) Any other, specify….

e) NO

8) Previous history of

a) Smoking b) Alcohol consumption

Out of pocket expenditure **From To**		**Date of Follow up visit:**
No. of Care givers:		
Travel expense (Rs):	1) Home town to Mumbai & Return Journey to Home town	
	2) Local Residence to Hospital	
	3) Other Travel related to treatment	
	1) Hormone Therapy	

Medicine expense related to cancer or its treatment:	2) Urinary	
	3) Rectal/ Bowel	
	4) Others	
Tests/ Labs expense:	1) PSA/testosterone/BMD/CBC, etc.	
	2) Scans	
	3) Others	
Surgery Procedure expenses	1) Cystoscopy	
	2) Sigmoidoscopy/APC	
	3) Others	
Food expense for patient + Care giver:		
lodging expense for patient + Care giver:		
Other Related Payments/ Consultancy fee		
Total for the visit:		

c) Tobacco chewing d) Any other e) No

Name: Signature:

33. BIOLOGICAL SPECIMENS

Blood and urine samples and tissue specimens will be collected and preserved for future research with due permission.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1-4
Protocol version	3	Date and version identifier	4
Funding	4	Sources and types of financial, material, and other support	4
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	6
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	13
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	13
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14-15
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	15-16
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	16
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	16
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	16
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	16
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18

Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19-20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21

	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	21
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Supplementary File

STUDY PROTOCOL – PRIME TRIAL

TITLE: Randomized controlled trial of Prostate Radiotherapy In high risk and node positive disease comparing Moderate and Extreme hypo fractionation [PRIME Trial]

2 A. REGISTRY: CTRI/2018/05/014054 (http://ctri.nic.in) (REF/2018/05/019975)

B. WHO Trial Registration Data Set

Data Category	Information
Primary registry and trial identifying number	CTRI/2018/05/014054(http://ctri.nic.in) REF/2018/05/019975
Date of registration in primary registry	May 22, 2018
Secondary identifying numbers	PRIME
Source(s) of monetary or material support	Tata Memorial Centre
Primary sponsor	Tata Memorial Centre (Intramural funding)
Secondary sponsor(s)	-
Contact for public queries	Dr. Vedang Murthy, MD 02224177000 ext 7029
Contact for scientific queries	vmurthyactrec.gov.in
Public title	**PRIME TRIAL**

Scientific title	Randomized controlled trial of Prostate Radiotherapy In High Risk and Node Positive Disease Comparing Moderate and Extreme Hypo-fractionation
Countries of recruitment	**INDIA**
Health condition(s) or problem(s) studied	Prostate Adenocarcinoma, High Risk Prostate Cancer, Node positive Prostate Cancer
Intervention(s)	Radiation: Moderate Hypo-fractionation 68Gy in 25# Radiation: Extreme Hypo-fractionation/SBRT 36.25Gy in 5#
Key inclusion and exclusion 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 5. PSMA PET/CT for all patients at baseline for staging 6. Ability to receive long term hormone therapy/ orchiectomy 7. KPS >70 8. No prior history of therapeutic irradiation to pelvis 9. Patient willing and reliable for follow-up and QOL 10. Signed study specific consent form

	Exclusion Criteria: 1. Evidence of distant metastasis at any time since presentation 2. Life expectancy < 2 years 3. Previous RT to prostate or prostatectomy. 4. Severe urinary symptoms or with severe IPSS score (>15) despite being on hormonal therapy for 6 months 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.
Study type	Open Label, Randomized, Interventional
Date of first enrolment	May 28, 2018
Target sample size	434 total number of patients with 217 patients in experimental arm and 217 patients in standard arm.
Recruitment status	**Recruiting**
Primary outcome	4-year biochemical Failure free survival (BFFS) Defined as duration from date of randomization to PSA > 2ng/ml above nadir value. (Phoenix definition)

Key secondary outcomes	Evaluate acute and late toxicity with both treatments. (Time Frame: 2 years) Prostate cancer specific survival and overall survival of patients receiving moderately hypo-fractionated RT and SBRT. (Time Frame: 5 years) Estimate out of pocket expenditure involved in patients receiving the two treatment schedules. Assess quality of life (QLQC30 and PR25)

3. PROTOCOL VERSION

Issue Date: 01.03.2019

Protocol Amendment Number: 2.0

Author(s):

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4. FUNDING

Tata Memorial Centre (Intramural funding)

5. ROLES AND RESPONSIBILITIES

A. CONTRIBUTORSHIP

A. Concept B. Design C. Screening of patients D. Selection & Recruitment and consenting of patients E. Laboratory investigations F. Laboratory report interpretation G. Treatment decision H. Patient evaluation I. AE and SAE management, evaluation and reporting	J. Examination of patients on follow-up K. Data collection and monitoring of data L. Interpretation of data M. Statistical analysis & Interpretation N. Maintaining patients file and master file of project O. Drafting final report P. Publication Z. Any other, please specify

A to P – Vedang Murthy, Indranil Mallick

C to P – Abhilash Gavarraju, Shwetabh Sinha, Rahul Krishnatry, Tejshri Telkhade, Arunsingh Moses, Ganesh Bakshi

C to I, P – Santosh Menon

K, L, M, N, O, P – Sadhna Kannan; K, N, O, P – Sheetal Kulkarni

C, D, G, H, I, J, P – Gagan Prakash, Mahendra Pal, Palak Popat, Venkatesh Rangarajan, Archi Agrawal

B. SPONSOR CONTACT INFORMATION

Trial Sponsor: Tata Memorial Centre (Intramural Funding)

Sponsor's Reference: NA

C. SPONSOR AND FUNDER

Tata Memorial Centre

D. COMMITTEES

DSMSC – Drug Safety Monitoring Committee

6 A. BACKGROUND AND RATIONALE

Prostate cancer is one of the most common cancers seen in the western population and is also seen on a rising trend in India. The standard of care for locally advanced high risk cancer is external beam radiotherapy along with long term hormonal therapy. Long term clinical and biochemical control is achievable with dose escalation in radiotherapy in prostate cancer. The radiobiological studies have shown that prostate cancer has a low alpha / beta ratio in the range of (0.9-2.2). Increased fraction size may improve biochemical control without significantly increased toxicity to nearby tissues (bladder, rectum). Extreme hypo fractionation 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.

Extreme hypo fractionation with a total duration of 2 weeks, would offer an opportunity to optimize 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 and health costs.

Given the potential positive economic impact with shorter duration treatment with similar clinical outcomes and probable similar toxicity profile, SBRT (extreme hypofractionation) 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.

B. CHOICE OF COMPARATORS

Active Comparator: Moderate Hypo-fractionation

In Arm 1 of the study, patients who are randomized to receive moderately hypo-fractionated RT will receive a total dose of 68 Gy in 25# to the primary over 5 weeks, with treatment being delivered daily. Patients with node positive disease will receive a dose of 50 Gy in 25# to the pelvis. Response assessment PSMA PET/CT will be done for all patients with pelvic nodal disease to ascertain the response to ADT based on morphology of the residual node and metabolic uptake as defined by the Uro Radiologist / Nuclear Medicine specialist. Patients with persistent residual nodal disease will be considered for nodal boost. Boost to residual gross nodal disease to a dose of 60-66 Gy in 25 fractions as a simultaneous integrated boostIntervention: Radiation: Moderate Hypo-fractionation

Experimental: Extreme Hypo-fractionation

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. Response assessment PSMA PET/CT will be done for all patients with pelvic nodal disease to ascertain the response to ADT based on morphology of the residual node and metabolic uptake as defined by the Uro Radiologist / Nuclear Medicine specialist. Patients with persistent residual nodal disease will be considered for nodal boost. Patients with node positive disease at baseline will receive a dose of 25Gy in 5 fractions to the pelvis. Boost to gross residual nodal disease will be considered to a dose of 30-35 Gy in 5 fractions as a simultaneous integrated boost. The 5 treatments will be scheduled to be delivered alternate day over approximately 7-10 days. An option of equivalent biological dose using 36.25Gy in 5 weekly fractions may be allowed for multicentric accrual in the future.

Intervention: Radiation: Extreme Hypo-fractionation.

Dose Coverage: The 98% isodose line used for the prescription dose should cover a minimum of 95% of the PTV.

7. OBJECTIVES

Hypothesis

Extreme hypo fractionation with SBRT in high risk prostate cancer is noninferior to moderately hypo fractionated standard radiotherapy while producing acceptable toxicity and advantage in terms of shortening of treatment duration.

Primary Endpoint

Assess the 4-year biochemical Failure free survival (BFFS) between the two arms.

Secondary Endpoints

Evaluate acute and late toxicity with both treatments.

Prostate cancer specific survival and overall survival of patients receiving moderately hypofractionated RT and SBRT.

Estimate the out of pocket expenditure involved in patients receiving the two treatment schedules.

Assess quality of life.

8. TRIAL DESIGN

Allocation: Randomized, Phase III

Intervention Model: Parallel Assignment (Prospective)

Masking: None (Open Label)

Primary Purpose: Treatment

9. STUDY SETTING

Location: Tata Memorial Hospital and ACTREC, Tata Memorial Centre, Mumbai, India;

Tata Medical Centre, Kolkata, India.

10. 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 group 4 or Gleason score 9 10/Gleason grade group 5, PSA > 20 ng/mL or Very high-risk prostate cancer i.e. T3b-T4 or Primary Gleason pattern 5/Gleason grade group 5 or > 4 cores Gleason score 8-10/Gleason grade group 4 or 5.
5. PSMA PET/CT for all patients at baseline for staging.
6. Ability to receive long term hormone therapy/Orchiectomy
7. KPS ≥ 70
8. No prior history of therapeutic irradiation to pelvis
9. Patient willing and reliable for follow-up and QOL
10. 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) in spite of being on hormonal therapy for 6 months 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.

1. Complete history and physical examination
2. Serum PSA < 3 weeks of randomization
3. Laboratory investigations undertaken routinely (complete blood counts, Renal function test, Liver function test and Serum Electrolytes)
4. Staging investigation PSMA PET-CT
5. IPSS scoring
6. Documentation of pre-treatment urinary and rectal symptoms and quality of life

11. INTERVENTIONS

A. INTERVENTIONS

Radiation: Moderate Hypo-fractionation – 68Gy in 25#

Radiation: Extreme Hypo-fractionation/SBRT – 36.25Gy in 5#

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. CT scans will be taken with contrast from 1st Lumber vertebra to 5 cm below ischial tuberosity with a slice thickness of 2.5mm. Laser marks 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 isotropic ally over CTV nodes
- PTV Prostate (and SV): A margin of 5mm will be grown in all directions over the CTV prostate.
- 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.

Clinical Assessment:

1. Objective criteria for toxicity evaluation - The RTOG will be used to document acute and late toxicities

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 the QLQC30 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 to 2 years.
4. All patients will follow up 3-6 weeks from end of radiotherapy. Thereafter follow up visits would be scheduled three to six months 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.

B. MODIFICATIONS

Arm 1 - Patients with node positive disease will receive a dose of 50 Gy in 25# to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 60-66 Gy/25# as a simultaneous integrated boost (SIB).

Arm 2 - Patients with node positive disease will receive a dose of 25 Gy in 5 # to the pelvis. Boost to gross nodal disease will be considered based on the response to hormonal therapy to a dose of 30-35 Gy/5# as a simultaneous integrated boost(SIB).

C. ADHERENCE

Appropriate counselling and weekly review of patients on treatment will ensure adherence to study protocol.

D. CONCOMITANT CARE

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 orchiectomy 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.

12. OUTCOMES

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

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

P**rostate 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.

13. PARTICIPANT TIMELINE

Registration

Patients with high risk carcinoma prostate on presentation will be screened for eligibility criteria. They must meet all 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

Stratified block randomization method

Stratification

Stratification will be done for the following parameters

1. Nodal status: N0 Vs N+
2. LHRH agonist/antagonists Vs Bilateral orchiectomy
3. Centre

The trial will accrue patients over a period of six years and all patients will be followed until the end of study.

14. SAMPLE SIZE

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 if the upper limit of the estimated 95% one sided confidence interval of the hazard ratio obtained lies entirely below 1.53. If the upper limit of the 95% one-sided confidence interval is 1.53 or higher, we do not reject the null hypothesis of inferiority. This also accounts for a 5% noncompliance rate as anticipated from experience in previous studies.

15. RECRUITMENT

Patient accrual

Patients will be identified and checked for eligibility from the OPDs at TMH, ACTREC and TMC. 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.

Multicentre approach: The trial will be opened to other centres with access to IMRT/IGRT who may be encouraged to join the study in due course. The choice of conventional

fractionation to 60-62.5Gy in 20# will be allowed with appropriate stratification for individual centres.

16. ALLOCATION

A. SEQUENCE GENERATION - Stratified block randomization method

B. CONCEALMENT MECHANISM - Participants will be randomised using online, central randomisation service. Allocation concealment will be ensured, as the service will not release the randomisation arm until the patient has been recruited into the trial, which takes place after all baseline measurements have been completed.

C. IMPLEMENTATION - Allocation sequence will be generated applying the stratified randomization method. Enrolment of patients will be done from the outpatient department of Uro-Oncology services under the guidance of the PI and Co-PI.

17. BLINDING

A. MASKING – None (Open Label)

B. EMERGENCY UNBLINDING – NA

18. DATA COLLECTION METHODS

A. DATA COLLECTION

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.

B. RETENTION

Once a patient is enrolled or randomized, the study site will make every reasonable effort to follow the patient for the entire study period. Study site staff are responsible for developing and implementing local standard operating procedures to achieve this level of follow-up.

19. DATA MANAGEMENT

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.

20. STATISTICAL METHODS

A. OUTCOMES

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.

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.

B. ADDITIONAL ANALYSIS

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.

C. ANALYSIS POPULATION AND MISSING DATA

We propose to test non-inferiority using two analysis sets; the intention-to-treat set, considering all patients as randomized regardless of whether they received the randomized treatment, and the "per protocol" analysis set. We expect very few patients will be lost to follow-up. We propose declaring medical management non-inferior to interventional therapy, only if shown to be non-inferior using both the "intention to treat" and "per protocol" analysis sets.

21. DATA MONITORING

A. FORMAL COMMITTEE

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

B. 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)

22. HARMS

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.

23. AUDITING

Regular audit will be carried out by the PI with the assistance of Research Fellow and Trial Co-ordinator to ensure proper adherence to trial protocol, documentation of toxicities during and after treatment and regular follow up of patients post treatment.

24. RESEARCH ETHICS APPROVAL

The protocol and the template informed consent forms 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. After 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.

25. 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. 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.

26. CONSENT OR ASSENT

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.

27. 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.

28. DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

29. 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.

30. ANCILLARY AND POST-TRIAL CARE - NA

31. DISSEMINATION POLICY

A. TRIAL RESULTS

Results will be published in peer reviewed scientific journals along with conference presentations.

B. AUTHORSHIP - NA

C. REPRODUCIBLE RESEARCH

Plan to publish the study protocol in an indexed journal.