Weill Cornell Medicine | NewYork-Presbyterian

`TITLE: Randomized Phase II Trial of **S**alvage Radiot**h**erapy f**or** Prosta**t**e Canc**er** in 4 Weeks v. 2 Weeks **(SHORTER)**

IRB Protocol #: 20-03021572
Version Date:13NOV2024
Version #: 8.0

Principal Investigator:

Emily Weg, M.D.
[redacted]

Co-Investigators:

Silvia Formenti, MD
[redacted]

Ariel Marciscano, M.D.
[redacted]

Paul Pagnini, M.D.
[redacted]

Christopher Barbieri, MD PhD
[redacted]

Douglas S. Scherr, MD
[redacted]

Jim Hu, MD MPH
[redacted]

[redacted]

Daniel Margolis, MD
[redacted]

Ana M. Molina, MD
[redacted]

David Nanus, MD
[redacted]

Cora Sternberg, MD
[redacted]

Scott Tagawa, MD MS
[redacted]

Statisticians:
Xi Kathy Zhou, PhD
[redacted]

Xiaoyue Ma, MS
[redacted]

Study Contact: Fabiana Gregucci, [redacted]

Data Coordinators:
Dakota Trick
[redacted]

[redacted]

Maahi Patel

[redacted]

Participating Sites: Weill Cornell Medicine – NewYork-Presbyterian Hospital

Confidentiality Statement

This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, study staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from WCM.

List of Abbreviations

All abbreviations used throughout the protocol must be defined.

AE	Adverse Event
CFR	Code of Federal Regulations
CRF	Case Report Form
CTSC	Clinical Translational Science Center
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
EPIC	Expanded Prostate Cancer Index Composite
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GU	Genitourinary
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HUD	Humanitarian Use Device
ICF	Informed Consent Form
IDE	Investigational Device Exemption
IMRT	Intensity Modulated Radiotherapy
IND	Investigational New Drug
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
QOL	Quality of Life
REDCap	Research Electronic Data Capture
RP	Radical Prostatectomy
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiotherapy
SUSAR	Suspected Unexpected Serious Adverse Reaction
UAP	Unanticipated Problem
VMAT	Volumetric Modulated Arc Therapy
WCM	Weill Cornell Medicine

Document History

Document name	Version Number	Version date
Amendment 8	**8.0**	**13NOV2024**
Amendment 7	7.0	04NOV2022
Amendment 6	6.0	04MAY2022
Amendment 5	5.0	17DEC2021
Amendment 4	4.0	02APR2021
Amendment 3	3.0	29DEC2020
Amendment 2	2.1	14OCT2020
Amendment 1	2.0	24AUG2020
Initial Protocol	1.0	15JUL2020

Summary of changes version 8.0 dated 13NOV2024

Protocol and other Administrative changes		
Section(s)	**Change**	**Rationale**
Personnel changes	Removing Dr. Himanshu Nagar as well as he is no longer WCM employee. Adding Dr. Emily Weg as study PI. Adding Dr. Fabiana Gregucci, Dakota Trick and Maahi Patel. Removing Chandrasekhar, Pragya Yadav, Marvin Campos and Logan Ritchie as well as they are no longer WCM employee. Removing personnel will not affect the integrity of the research.	Adding new personnel and removing personnel who are no longer working on the study.
Informed consent changes		
Consent Footer changes	Updating protocol and consent version and date,	PI change

Summary of changes version 7.0 dated 04NOV2022

Protocol and other Administrative changes		
Section(s)	**Change**	**Rationale**
3.2 Inclusion Criteria	Adding clarity to inclusion Patients with positive pelvic lymph nodes are eligible	Adding clarity to inclusion criteria
3.2 Inclusion Criteria	Patient with no evidence of distant metastatic disease on CT/MRI and bone scan < 9 months prior to enrollment. (changing from < 90 - **180** days)	Increasing imaging requirement window – Administrative Change.

Personnel changes	Adding Co-Investigator Dr. Paul Pagnini to the trial. Adding Marvin Campos and Dr. Logan Ritchie to the study. Removing Co-Investigator Dr. Josephine Kang. Removing Jessica Richman.	Adding new personnel and removing personnel who are no longer working on the study.
Informed consent changes		
Consent Footer changes	Updating protocol and consent version and date,	Administrative change

Summary of changes version 6.0 dated 04MAY2022

Protocol and other Administrative changes		
Section(s)	**Change**	**Rationale**
Patient recruitment	Submitting another patient recruitment video	Additional patient recruitment video
Informed consent changes		
Consent Footer changes	Updating protocol and consent version and date,	Administrative change

Summary of changes Version 5.0 dated 17DEC2021

Protocol and other Administrative changes		
Section(s)	**Change**	**Rationale**
Inclusion Criteria	Removing: Prostatectomy > 6 months before treatment	We are removing this clause from the inclusion criteria to make the regulatory workflow more straightforward. We will add this statement to the Radiation therapy section where it would be more relevant. Patients will continue to be treated > 6months post prostatectomy.
Section 5.4 Radiation Therapy Planning	Prostatectomy > 6 months before treatment	We are removing this clause from the inclusion criteria to make the regulatory workflow more straightforward. We will add this statement to the Radiation therapy section where it would be more relevant. Patients will continue to be treated > 6months post prostatectomy.
Informed consent changes		
What other options are there?	Clarifying Standard of care treatment to be anywhere from 20-40 fractions given in 4-8 weeks	Clarification

Summary of changes Version 4.0 dated 02APR2021

Protocol and other Administrative changes		
Section(s)	**Change**	**Rationale**
Section 3.2 Inclusion criteria	Criteria 4: Patient with no evidence of distant metastatic disease on CT/MRI and bone scan < 90 -**180** days prior to enrollment. (Changing from < 90 days to 90 - 180 days)	Administrative change.
Document history	Updated document history table	For consistency.
No Informed consent changes		

Summary of changes Version 3.0 dated 29DEC2020

Protocol and other Administrative changes		
Section(s)	**Change**	**Rationale**
Section 3.2 Inclusion criteria	Patient with no evidence of distant metastatic disease on PET/CT/MRI or bone scan < 90 days prior to enrollment. Patients with pelvic lymph nodes equivocal or questionable by imaging are eligible if the nodes are ≤ 1.5 cm in the short axis.	PET Scans will be acceptable.
Section 5.1 Schedule of events	Removing the 3month time point for Urocuff assessment	Revising study procedure interval.
Dose/treatment parameters	Added - Optional boost(s) to 40 Gy permitted. Optional boost(s) to 60 Gy permitted.	Treatment specifications
Section 5.3 Imaging studies	Pelvic MRI or CT and Bone Scan must show no evidence of metastatic disease. Next-generation PET scans are permitted but not required and can be substituted for bone scan.	Next-generation PET scans are permitted but not required and can be substituted for bone scan.

Document history	Updated document history table	For consistency.
Informed consent changes		
Schedule of Events	Removing 3months time point for Urocuff assessment. Added PET scan	Revising study procedure interval PET scan will be acceptable.

Summary of changes Version 2.1 dated 14OCT2020

Protocol and other Administrative changes		
Section(s)	**Change**	**Rationale**
Section 4.1	Clarifying patient consenting and QOL completing procedures.	Study team will be coordinating directly with the patients for emailing consents and QOL surveys.
Study team	Added Jessica Richman	Personnel changes
Patient recruitment	Submitting new Patient recruitment video	For recruitment purposes.
Informed consent changes		
Cancelling authorization section.	Page 8 : The word “end.” was cut off from the sentence, “Unless you cancel it, permission for WCMC and/or NYPH researchers to use or share your protected health information for their research will never end.”	Administrative changes only.

Summary of Changes Version 2.0 Dated 24AUG2020

Inclusion Criteria Changes		
Section(s)	**Change**	**Rationale**
Inclusion Criteria #1	Added : **PSA does not need to be detectable for men with pathologically node positive disease.**	Changing PSA from 0.1 to detectable as ulta-sensitive PSAs are more sensitive and do not

	Removed: PSA of at least 0.1ng/ml	want to restrict trial to higher PSAs

Administrative Changes		
Section(s)	**Change**	**Rationale**
Schema foot notes	Removed: “Clinically node positive	Clarity
Section 10 (DSMB)	Removed: The WCMC DSMB may also convene as needed if stopping criteria are met or other safety issues arise that the Principal Investigator and/or IRB would like the WCMC DSMB to address.	As requested by the initial DSMB review dated 20AUG2020. A signed memo has also been submitted as requested by the DSMB.
Section 5.4 - Radiation therapy planning	Made administrative changes for RT planning.	Clarification in terms of RT planning and dose

No Changes to the informed consent.

Protocol Summary

Full Title:	Randomized Phase II Trial of **S**alvage Radiot**h**erapy f**or** Prosta**t**e Canc**er** in 4 Weeks v. 2 Weeks (SHORTER)
Short Title:	SHORTER
Clinical Phase:	II
Principal Investigator:	Himanshu Nagar
Sample Size:	N = 136
Accrual Ceiling:	This study will enroll up to 150 subjects
Study Population:	Men requiring salvage radiotherapy after prostatectomy
Accrual Period:	5 years
Study Design:	Randomized, Phase II, Non-Inferiority
Study Duration:	Patients will remain on study for 5 years
Intervention Description:	Radiotherapy in 4 weeks (20 fractions) or 2 weeks (5 fractions).
Primary Objective:	The primary objective is to demonstrate that 5 days of ultra-hypofractionated radiotherapy does not significantly increase patient-reported GI and GU symptoms over 20 days of hypofractionated radiotherapy 2 years after treatment completion.
Secondary Objectives:	1. Compare patient-reported GI symptoms using the EPIC at end of RT and 3, 6, 12, 24, and 60 months from end of treatment. 2. Compare patient-reported GU symptoms using the EPIC at end of RT and 3, 6, 12, 24, and 60 months from end of treatment. 3. Compare time to progression (TTP) where progression is defined as the first occurrence of biochemical failure (BF), local failure, regional failure, distant metastasis (DM), institution of new unplanned anticancer treatment, or death from prostate cancer (PCSM). 4. Compare freedom from biochemical failure (FFBF) and TTP rates with an alternate PSA ≥ PSA nadir + 2 ng/mL definition of BF. 5. Compare local failure, regional failure, salvage therapy (i.e. institution of new unplanned anticancer treatment), DM, PCSM, and overall survival (OS) rates.
Exploratory Objectives:	1. Compare utilities for health outcomes using the EQ-5D. 2. Assess percentage of fractions requiring adaptive planning on 5 fraction arm. 3. Paraffin-embedded tissue block, serum, plasma, and whole blood will be collected for translational research analyses for predictors of cancer control and toxicity following hypofractionated or ultra-hypofractionated post-prostatectomy radiotherapy.

Table of Contents

SCHEMA 15

1 STUDY OBJECTIVES 16

1.1 PRIMARY OBJECTIVE 16
1.2 SECONDARY OBJECTIVES 16
1.3 EXPLORATORY OBJECTIVES 16

2 BACKGROUND 16

2.1 DISEASE 16
2.2 RATIONALE 17
2.3 RISK/BENEFIT ASSESSMENT 19
2.4 CORRELATIVE STUDIES BACKGROUND 21

3 SUBJECT SELECTION 21

3.1 STUDY POPULATION 21
3.2 INCLUSION CRITERIA 21
3.3 EXCLUSION CRITERIA 22

4 REGISTRATION PROCEDURES 22

4.1 PATIENT REGISTRATION 22

5 STUDY PROCEDURES 22

5.1 TABLE 1. SCHEDULE OF TRIAL EVENTS 22
5.2 SCREENING VISIT 23
5.3 IMAGING STUDIES 23
5.4 RADIATION TREATMENT PLANNING 23
5.5 TRIAL PROCEDURES 25
5.6 GENERAL CONCOMITANT MEDICATION AND SUPPORTIVE CARE GUIDELINES 26
5.7 DURATION OF THERAPY AND CRITERIA FOR REMOVAL FROM STUDY 26
5.8 DURATION OF FOLLOW UP 26

6 CORRELATIVE/SPECIAL STUDIES 26

7 DATA REPORTING / REGULATORY CONSIDERATIONS 27

7.1 DATA COLLECTION 27
7.2 REDCAP 27
7.3 DATA MANAGEMENT 27
7.4 REGULATORY CONSIDERATIONS 28

8 STATISTICAL CONSIDERATIONS 28

8.1 STUDY DESIGN/ENDPOINTS 28
8.2 SAMPLE SIZE/ACCRUAL RATE 28
8.3 STRATIFICATION FACTORS 28
8.4 ANALYSIS OF ENDPOINTS 29

9 ADVERSE EVENT REPORTING REQUIREMENTS 30

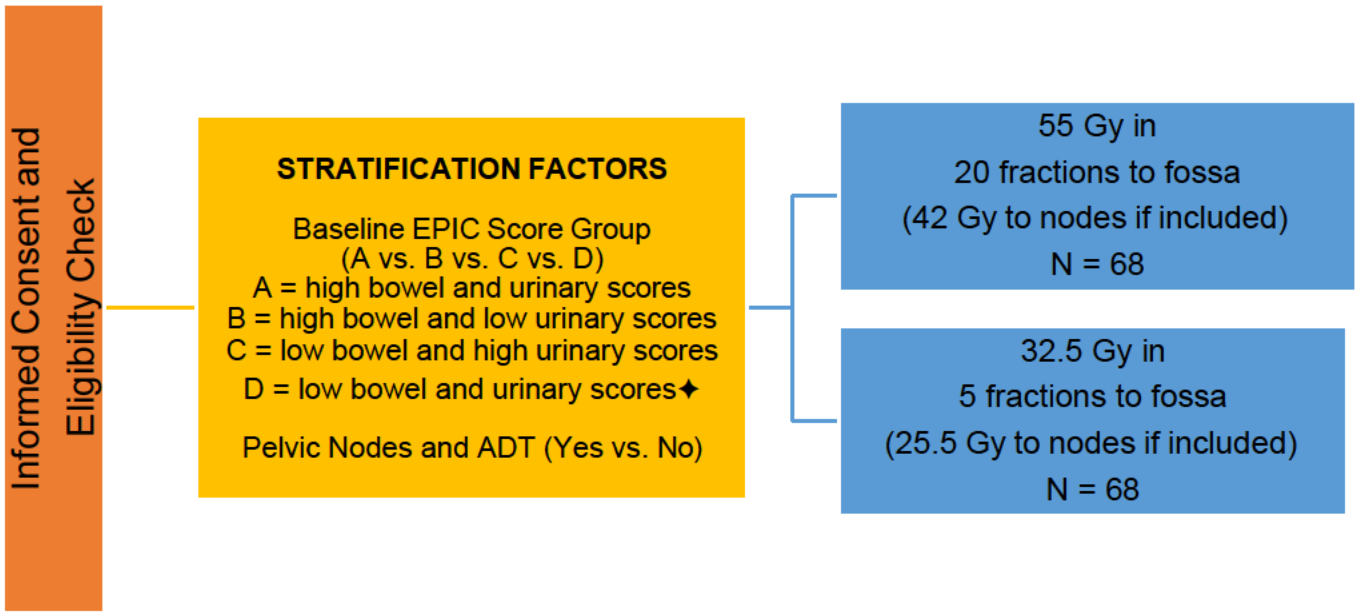
9.1 ASSESSING AND RECORDING ADVERSE EVENTS 30
9.2 DEFINITION OF SAE 31

10 DATA AND SAFETY MONITORING PLAN (DSMP) 31

11 APPENDIX **32**

12 REFERENCES **33**

SCHEMA



EPIC, EQ-5D and IPSS QOLs are collected at baseline, end of treatment, at 3 month, 6 month, 12 month, 24 month and 60 month follow up.

✦ High bowel score >96, low bowel score <= 96, high urinary score > 84, low urinary score <=84.

Patients with PSA > 0.4 ng/ml, high Decipher scores, or pathologically node positive will receive nodal RT and ADT.

1 Study Objectives

1.1 Primary Objective

The primary objective is to demonstrate that 5 days of ultra-hypofractionated radiotherapy does not significantly increase patient-reported GI and GU symptoms compared to 20 days of hypofractionated radiotherapy 2 years after treatment completion.

1.2 Secondary Objectives

1. Compare patient-reported GI symptoms using the EPIC at end of RT and 3, 6, 12 and 60 months from end of treatment.
2. Compare patient-reported GU symptoms using the EPIC at end of RT and 3, 6, 12 and 60 months from end of treatment.
3. Compare time to progression (TTP) where progression is defined as the first occurrence of biochemical failure (BF), local failure, regional failure, distant metastasis (DM), institution of new unplanned anticancer treatment, or death from prostate cancer (PCSM).
4. Compare freedom from biochemical failure (FFBF) and TTP rates with an alternate PSA ≥ PSA nadir + 2 ng/mL definition of BF.
5. Compare local failure, regional failure, salvage therapy (i.e. institution of new unplanned anticancer treatment), DM, PCSM, and overall survival (OS) rates.

1.3 Exploratory Objectives

1. To compare utilities for health outcomes using the EQ-5D.
2. Assess percentage of fractions requiring adaptive planning on the 5 fraction arm.
3. Paraffin-embedded tissue block, serum, plasma, and whole blood will be collected for translational research analyses for predictors of cancer control and toxicity following hypofractionated or ultra-hypofractionated post-prostatectomy radiotherapy.

2 Background

2.1 Disease

Prostate cancer is the most common non-cutaneous cancer in men and the second leading cause of cancer death in men [1]. It is predicted that the number of cases will almost double by 2030 (GLOBOCAN 2012). Radical prostatectomy is the most common treatment for prostate cancer according to the National Cancer Institute's Pattern of Care study from 14 regional cancer registries with the proportion of men undergoing prostatectomy was 70% for age <60 years, 51% for 60-64 years, and 39% for 65-75 years [2]. After radical prostatectomy a third of patients relapse with a rise in serum prostate-specific antigen (PSA) concentration without evidence of clinical or radiographic disease and, in the absence of salvage treatment, develop distant metastases [3]. Metastasis-free survival rates are 67% at 5 years and 48% at 10 years in patients with PSA recurrence after radical prostatectomy without salvage treatment [4]. The standard treatment for most patients with biochemical recurrence after radical prostatectomy is radiotherapy. Radiotherapy delays the need for chronic, non-curative treatment, such as long-term androgen suppression, and is the only potentially curative treatment of some biochemical recurrences after prostatectomy.

2.2 Rationale

Indications for Post-Operative Radiotherapy

After prostatectomy, features suggesting risk for local recurrence include high grade disease, extra-capsular extension or seminal vesicle invasion (pT3 disease) and positive surgical margins [5]. Post-operative radiotherapy and has been shown to reduce the risk of recurrence in three randomized trials [6-8]. As such, adjuvant radiotherapy after prostatectomy is a recommendation for patients with pT3 disease, positive margins or Gleason Grade 8-10 [9]. Recently, three trials, RADICALS (ISRCTN40814031), GETUG-AFU 17 (NCT00667069) and RAVES (NCT00860652) and a combined meta-analysis of these trials (ARTISTIC) compared adjuvant versus early salvage radiotherapy for patients at high-risk for local failure (pT3 disease or positive margin). Early data from the three trials and the combined meta-analysis suggest that adjuvant and salvage radiotherapy offer similar outcomes for event free survival.

Lessons from Intact Prostate Cancer

Experience in definitive radiotherapy management of low and intermediate-risk prostate cancer with SBRT demonstrates good biochemical control and low toxicity with commonly used doses ranging from 35-45 Gy in 5 fractions. In the largest study to date, Kishan et al. reported on 2142 patients across 10 institutional studies and 2 multi-institutional trials demonstrating that SBRT for low and intermediate-risk disease was associated with low rates of severe toxic events and high rates of biochemical control with a 7-year cumulative incidence of severe genitourinary toxic events of 2.4% and of severe gastrointestinal toxic events of 0.4%. [10]. Our group recently showed increasing use of prostate SBRT from 2010 – 2015: rates of SBRT have tripled in low risk (4% to 12%) and favorable intermediate-risk disease (3% to 10%), have doubled in unfavorable intermediate-risk disease (3% to 7%) and have remained stable in high-risk disease (2%), globally demonstrating a growing acceptance of this approach [11].

Indications for Nodal Coverage

Currently, there are no modern guidelines to include or forego nodal coverage with radiotherapy in the salvage setting. GETUG-AFU 16 which tested the benefit of ADT in the salvage setting mandated nodal coverage for patients that did not have a nodal dissection at time of prostatectomy or the risk of nodal involvement was greater than 15% according to the Partin table [12]. In the modern era, men undergo nodal dissection and the Partin table assesses risk of nodal involvement at time of prostatectomy but not at time of recurrence. More recently, RTOG 0534 reported a benefit of adding nodal radiotherapy to prostate fossa radiotherapy and ADT but has not provided guidance as to which patients benefit from this addition. Consequently, physicians in the current era are electing to add nodal radiotherapy at their discretion based upon PSA values and advanced PET imaging if available as not universally covered. Therefore, it is important to test ultra-hypofractionation for nodal radiotherapy in the salvage setting.

Radiobiology of Prostate Cancer and Hypofractionation

Tissues with low α/β values are particularly sensitive to fraction size, with higher doses resulting in disproportionate increases in cell death. Although most tumors have high α/β values, recent ultra-hypofractionation trials in the intact setting and a large meta-analysis has shown that prostate cancer has an estimated α/β value of 2.7 Gy [13,14]. With a lower α/β value, prostate cancer should have an improved therapeutic ratio with hypofractionation. Furthermore, if the α/β formalism and assumed values for prostate cancer are correct and one maintains a constant biologically effective dose for normal tissues, there is the potential for increased tumor control with hypofractionation in this setting. Based on prostate, bladder and rectum α/β values and 2 Gray Equivalent Dose (EQD_2) calculations of standard dose fractionation for prostate fossa (66.6 Gy in 1.8 Gy/fraction), 6.5 Gy x 5 fractions and 2.75 Gy x 20 fractions to the prostate fossa demonstrates the conversions as demonstrated in the table below (see risk/benefit assessment section for dose selection). The proposed study explores an alternative RT dose-

fractionation schedule that exploits the radiobiological properties of prostate cancer to shorten overall treatment time called hypofractionation. Hypofractionation uses larger daily fraction sizes to deliver radiotherapy over a shorter duration.

Prostate Fossa Doses

Comparison of 1.8 Gy x 37 (66.6 Gy) to 2.75 Gy x 20 (55 Gy)

Organ	Dose (Gy)	BED (Gy)	EQD_2		Dose (Gy)	BED (Gy)	EQD_2
Prostate (α/β = 2.7)	66.6 (1.8 Gy x 37)	111	64		55 (2.75 Gy x 20)	**111**	**64**
Bladder (α/β = 3)	66.6 (1.8 Gy x 37)	107	64		55 (2.75 Gy x 20)	**105**	**63**
Rectum (α/β = 5)	66.6 (1.8 Gy x 37)	91	65		55 (2.75 Gy x 20)	**85**	**61**

Comparison of 1.8 Gy x 37 (66.6 Gy) to 6.5 Gy x 5 (32.5 Gy)

Organ	Dose (Gy)	BED (Gy)	EQD_2		Dose (Gy)	BED (Gy)	EQD_2
Prostate (α/β = 2.7)	66.6 (1.8 Gy x 37)	111	64		32.5 (6.5 Gy x 5)	**111**	**64**
Bladder (α/β = 3)	66.6 (1.8 Gy x 37)	107	64		32.5 (6.5 Gy x 5)	**103**	**62**
Rectum (α/β = 5)	66.6 (1.8 Gy x 37)	91	65		32.5 (6.5 Gy x 5)	**75**	**53**

Pelvic Nodes Doses

Comparison of 1.8 Gy x 25 (45 Gy) to 5.1 Gy x 20 (42 Gy)

Organ	Dose (Gy)	BED (Gy)	EQD_2		Dose (Gy)	BED (Gy)	EQD_2
Prostate (α/β = 2.7)	45 (1.8 Gy x 25)	**75**	**43**		42 (2.1 Gy x 20)	**75**	**43**

Comparison of 1.8 Gy x 25 (45 Gy) to 5.1 Gy x 5 (25.5 Gy)

Organ	Dose (Gy)	BED (Gy)	EQD_2		Dose (Gy)	BED (Gy)	EQD_2
Prostate (α/β = 2.7)	45 (1.8 Gy x 25)	**75**	**43**		25.5 (5.1 Gy x 20)	**74**	**42**

<u>Advances in Image Guidance</u>

Modern radiotherapy for prostate cancer has additional advantages beyond that of hypofractionation. The convergence of improved target delineation with multiparametric MRI and image-guided radiotherapy allow for larger dose delivery in fewer fractions with tighter margins [15]. These advances are further enhanced by the availability of real-time MR-image guided radiotherapy technology allowing for daily real-time adaptive target delineation. As opposed to other linear accelerators which are computed tomography based and require fiducial marker placement to track treatment areas during radiotherapy, the MRI linear accelerator uses real-time intra-fraction MRI sequences to track the anastomosis, bladder, rectum and vasculature controlling for dose delivery during movement and adapting for inter-fractional changes to decrease dose to adjacent structures.

Treatment Burden

Patients are recommended to undergo salvage radiotherapy to eradicate biochemical disease delivered in approximately 35-40 fractions over the course of 7-8 weeks in the United States and 4-7 weeks in Europe and Australia, representing a high burden of therapy, which may be related to lower utilization of salvage radiotherapy [16]. In prostate cancer specifically, ultra-hypofractionated radiotherapy has the added potential of not increasing toxicity with shorter treatment times [17].

2.3 Risk/Benefit Assessment

Trials with Moderate Hypofractionation in the Post-Operative Setting

Multiple trials have examined the role of hypofractionated radiotherapy in a post-operative setting. As seen in the tables below, trials with mild hypofractionation schemes show tolerable acute and late genitourinary and gastrointestinal adverse events [18]. More recently, the completed RADICALS trial comparing adjuvant to early salvage radiotherapy allowed two schedules: 1) 66 Gy given in 33 fractions over 6.5 weeks or 2) 52.5 Gy given in 20 fractions over 4 weeks. Additionally, Chin et al. published their 10-year outcomes for 112 patients treated to 52.5 Gy over 20 fractions demonstrating long term disease control comparable to conventionally fractionated radiotherapy.

Treatment characteristics.

Study (No. pts.)	Design	Setting	Treatment techniques	Total dose (Gy)	Dose/fraction (Gy)	NTD_{2Gy} α/β = 1.5 Gy (prostate cancer)	NTD_{2Gy} α/β = 3 Gy (late toxicity)
Syndikus et al. (n = 115) [18]	Prospective	Adj./Salv.	2D/3D-CRT	52 (50–55)	2.76 (2.0–3.1)	62	59
Lee et al. (n = 37) [16]	Retrospective	Salv.	3D-CRT	51.2 (50–52.5)	2.5	57	55
Wong et al. (n = 50) [21]	Retrospective	Salv.	IMRT HT	65	2.5	74	71
				70	2.5	80	77
Ippolito et al. (n = 25) [19]	Prospective	Adj.	SIB-IMRT	56.7	2.27	61	60
				59.7	2.39	66	64
				61.2	2.45	69	67
				62.5	2.5	71	69
Kruser et al. (n = 108) [20]	Retrospective	Salv.	IMRT HT	65	2.5	74	71
Koukourakis et al. (n = 48) [26]	Prospective	Adj./Salv.	3D-CRT	51	3.4	71	65
Massaccesi et al. (n = 49) [29]	Prospective	Adj./Salv.	SIB-IMRT	62.5	2.5	71	69
Alongi et al. (n = 84) [30]	Retrospective	Adj./Salv.	IMRT	70–71.4	2.5–2.55	80–83	77–79
Cozzarini et al. (n = 247) [17/27]	Retrospective	Adj./Salv.	IMRT HT	58	2.9	73	66
				65.8*	2.35*	71*	70*
				72.1 (71.4–72.8)	2.55	83	80
Katayama et al. (n = 39) [23]	Prospective	Adj./Salv.	HT	54	3	70	65
Gladwish et al. (n = 30) [22]	Prospective	Adj./Salv.	IMRT	51	3	66	61
Lewis et al. (n = 56) [24]	Prospective	Adj./Salv.	IMRT	65 (57.5–65)	2.5	74	71
Fersino et al. (n = 125) [25]	Prospective	Adj./Salv.	VMAT	66 (65.5–71.4)	2.3 (2.2–2.4)	72	70

Abbreviations: Adj., adjuvant; Salv., salvage; 3D-CRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; HT, Helical Tomotherapy; VMAT, volumetric-modulated arc therapy; SIB-IMRT, simultaneous integrated boost IMRT; NTD_{2Gy}, normalized total dose in 2 Gy per fraction.

* Data for subgroup from the 2008 phase I-II prospective trial by Cozzarini et al. (n = 50).

Toxicities and outcomes.

Study (No. pts.)	Median follow-up (months)	Scoring system	Acute GU toxicity (%)	Acute GI toxicity (%)	Late GU toxicity (%)	Late GI toxicity (%)	Therapeutic outcome bRFS %
Syndikus et al. (n = 115) [18]	89 (Adj.) 26 (Salv.)	RTOG	Not reported	Not reported	G3:14 G4:7	G2:9 ≥ G3: 0	54 (10y Salv.)
Lee et al. (n = 37) [16]	36	RTOG	≥G2: 0	≥G2: 0	≥G2: 0	G2:3 ≥G3: 0	74 (3y)
Wong et al. (n = 50) [21]	19	RTOG Modified Fox Chase scale	G2:8 ≥G3: 0	G2:2 ≥G3: 0	G2:4 ≥G3: 0	G2:4 ≥G3: 0	72.9 (2y)
Ippolito et al. (n = 25) [19]	19	RTOG	G2: 36 ≥G3: 0	G2: 20 ≥G3: 0	Not reported	Not reported	Not reported
Kruser et al. (n = 108) [20]	32	Modified RTOG Modified Fox Chase scale	G2:6 G3:1	G2:14 ≥G3: 0	G2:15 ≥G3: 0	G2:4 ≥G3: 0	67 (4y)
Koukourakis et al. (n = 48) [26]	41	CTCAE v 4.0	≥G2: 0	G2:30 ≥G3: 0	≥G2: 0	≥G2: 0	85 (3y)
Massaccesi et al. (n = 49) [29]	–	RTOG	G2:9.6 G3: 0 G4:2	G2:29.7 ≥G3: 0	Not reported	Not reported	Not reported
Alongi et al. (n = 84) [30]	23	RTOG	G2:10 ≥G3: 0	G2:20 ≥G3: 0	G2:8 G3:3	≥G2: 0	Not reported
Cozzarini et al. (n = 247) [17]	98	RTOG	G2:10 * G3: 2 *	G2:4 * ≥G3: 0 *	G3:46.5 G4: 2	Not reported	Not reported
Katayama et al. (n = 39) [23]	–	CTCAE v4.0	G2: 10.3 ≥G3: 0	G2:11 ≥G3: 0	Not reported	Not reported	Not reported
Gladwish et al. (n = 30) [22]	24	CTCAE v3.0	G2: 3 G3:3	≥G2: 0	≥G2: 3	≥G2: 6	>90 (2y)
Lewis et al. (n = 56) [24]	48	CTCAE v4.0 Late toxicities RTOG	G2:4 ≥G3: 0	G2:4 ≥G3: 0	G2:39 G3: 27	G3: 3.6	75 (4y)
Fersino et al. (n = 125) [25]	18	CTCAE v4.0	G2:12.8 G3:0.8	G2:8.8 ≥G3: 0	G2:10.4 G3:1.6	G2:8 ≥G3: 0	94 (3y Adj.) 77 (3y Salv.)

Abbreviations: G, grade; GU, genitourinary; GI, gastro-intestinal; Salv, salvage; Adj., adjuvant; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; bRFS, biochemical relapse-free survival; y, years.
* Data for subgroup from 2008 phase 1–2 prospective trial by Cozzarini et al. n = 50.

Trials with SBRT in the Post-Operative Setting

More recently, two phase I dose escalation trials explored further hypofractionation and stereotactic post-operative radiotherapy to the prostate fossa [19,20]. Ballas et al. reported on 24 patients with indications for adjuvant or salvage radiotherapy (6 patients at Dose Level 1 and 2; 12 patients at Dose Level 3). Tested dose levels (DLs) were 3.6 Gy x 15 fractions (DL1); 4.7 Gy x 10 fractions (DL2); and 7.1 Gy x 5 fractions (DL3). All patients had at least 6 months of follow-up (median follow-up, 14.1 months). No grade 3 GI or GU toxicity was seen at any dose level (2 of 6 patients in the DL1 group, 3 of 6 in DL2, and 7 of 12 in DL3 experienced grade 2 GI toxicity during RT). Except in 1 patient, all acute grade 2 GI toxicity resolved by 10 weeks. Three of 12 patients reported an increase to grade 1 and grade 2 GU toxicity in the 2 weeks after RT in groups DL1 and DL2 and 1 of 12 patients in DL3. At week 2 after RT, decline in the 26-item Expanded Prostate Cancer Index Composite bowel domain met criteria for a minimally important difference in 71% of patients. At week 10, 1 of 6, 2 of 6, and 7 of 11 patients at DLs 1, 2, and 3, respectively, still met minimally important difference criteria. International Prostate Symptom Scores worsened 2 weeks after treatment but improved by 6 to 10 weeks. Sampath et al. included patients with organ-confined, node-negative prostate cancer who had biochemical failure. Doses delivered were 35 Gy, 40 Gy, and 45 Gy in 5 fractions, given every other day. Dose-limiting toxicity (DLT) was defined as CTCAE version 4.0 grade 3 or higher GI or GU toxicity within 90 days of treatment. Maximum tolerated dose was the highest dose to be tested where fewer than 2 of the patients experienced DLT. Patients completed QOL questionnaires at regular time intervals. Twenty-six patients completed treatment between October 2013 and December 2017. Three patients received 35 Gy, 8 patients received 40 Gy, and 15 patients received 45 Gy. The median follow-up was 60 months for 35 Gy, 48 months for 40 Gy, and 33 months for 45 Gy. No acute DLT events were observed. Late grade 2 and 3 gastrointestinal toxicity occurred in 11% and 0%, respectively, and late grade 2 and 3 GU toxicity occurred in 38% and 15%, respectively. No difference was observed in late GU toxicity between 40 Gy and 45 Gy. In all patients, the crude rate of PSA control (<0.2 ng/ml) was 11 out of 26 (42%).

Therefore, based on the: 1) radiobiology of prostate cancer, 2) safety data from moderately hypofractionated trials, 3) data from phase I SBRT trials and 4) advent of real-time MR image guidance

and adaptive planning, the dose and fractionation schedules to compare are 55 Gy in 20 fractions to 32.5 Gy in 5 fractions. The current trial has the potential benefit of limiting radiation dose received by normal tissues, namely the bladder and rectum, with advanced MR image guidance, real-time volume adaptability and dose delivery techniques.

This trial is important because:

- It is one of the only Phase II randomized trials in the world exploring SBRT in the salvage setting.
- It lays the foundation to potentially redefine the standard of care to include SBRT. The potential advantages of SBRT are:
    - Increase access for patients to postprostatectomy radiotherapy because of fewer treatment days,
    - Increase convenience to patients because of fewer treatment days,
    - Reduced cost to patients because of fewer travel expenses and copays,
    - Improved resource utilization for physicians because fewer number of treatments per patient and overall,
    - Reduced cost to society,
    - Increased RT utilization.

2.4 Correlative Studies Background

Paraffin-embedded tissue block, serum, plasma, and whole blood will be collected for translational research analyses for predictors of cancer control and toxicity following hypofractionated or ultra-hypofractionated post-prostatectomy radiotherapy. A total of 10%–20% of patients develop long-term toxicity following radiotherapy for prostate cancer. Identification of common genetic variants associated with susceptibility to radiotoxicity might improve risk prediction and inform functional mechanistic studies. Additionally, genomic risk stratification may provide insight for patients that benefit from different fractionation schedules of radiotherapy, nodal radiotherapy and/or ADT with subsequent development of biomarker candidates.

3 Subject Selection

3.1 Study Population

Subjects with a diagnosis of prostate cancer who meet the inclusion and exclusion criteria will be eligible for participation in this study.

3.2 Inclusion Criteria

1. Men aged ≥ 18 with histologically confirmed prostate cancer after prostatectomy with detectable PSA. PSA does not need to be detectable for men with pathologically node positive disease.
2. KPS ≥ 70
3. Patient with no evidence of distant metastatic disease on PET/CT/MRI or bone scan < 9 months prior to enrollment. Patients with positive pelvic lymph nodes are eligible.
4. Ability to receive MRI-guided radiotherapy.
5. Equivocal evidence of metastatic disease outside the pelvis on standard imaging requires documented negative biopsy.
6. Ability to complete the Expanded Prostate Cancer Index Composite (EPIC) questionnaire.

3.3 Exclusion Criteria

1. Prior history of receiving pelvic radiotherapy.
2. Patient with inflammatory bowel disease.
3. Patients with a prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment of ultra-hypofractionated radiotherapy.
4. History of bladder neck or urethral stricture.

4 Registration Procedures

4.1 Patient Registration

1. Following an in-person consult, the patients are given a hard copy of the consent . Following a video visit, the consent document will be emailed by the study team to the patients to review. To randomize and register patients efficiently, we request the patients to scan the signed informed consent back to us. Upon receipt, the Principal investigator/Treating physician will sign the document and will complete the informed consent process. Patients will bring in the hard copy of the signed document at their next appointment.
2. Once the consent is signed, please notify the Radiation Oncology Clinical Trials Office (ROCTO) at rocto@med.cornell.edu. Once the informed consent and the eligibility are verified ROCTO will register the patient in Oncore.
3. Patients will be given an option to complete QOL surveys either via the online link from REDCAP or using hard copies. The online link from REDCAP will be sent by the study team directly to the patient.

Subjects will be centrally registered within the WRG-CT as per the standard operating procedure for Subject Registration.

5 Study Procedures

5.1 Table 1. Schedule of trial events

	Screening	First Day of RT	Last Day of RT	Follow up at 3 months	Follow up Q6 months for 2 years	Follow up Q12 Months for 3 Years
Informed Consent	X					
Demographics/ Medical History	X					
Physical Exam	X			X	X	X
Vital Signs, Height, Weight	X				X	X
Post-Prostatectomy PSA	X			X	X	X
Pelvic MRI	X					
Bone or PET Scan	X					
Prostate 22-Gene Test	X					
Whole blood, serum, plasma		X	X			
Urodynamic Testing (optional)	X				X	X

EPIC	X	X	X	X	X	X
IPSS	X	X	X	X	X	X
EQ-5D	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

5.2 Screening Visit

- Informed Consent
- Demographics/Medical History
- Physical Exam, Vital Signs, Height, Weight
- Post-Prostatectomy PSA
- Pelvic MRI and Bone Scan
- EPIC
- IPSS
- EQ-5D
- Urodynamic Testing

5.3 Imaging Studies

Pelvic MRI or CT and Bone Scan must show no evidence of metastatic disease. Next-generation PET scans are permitted but not required and can be substituted for bone scan.

5.4 Radiation Treatment Planning

After consent and eligibility verification, patients will undergo CT/MRI simulation/radiotherapy planning. Patients will receive treatment to the prostate fossa +/- nodes in either 32.5 Gy in 5 fractions or 55 Gy in 20 fractions. **Patients receiving 32.5 Gy in 5 fractions cannot be treated on consecutive days.**

Please note: Patients will be treated 6 months post Prostatectomy.

Treatment Technology
Photon energies ranging from 6 MV and 10 MV are recommended. IMRT planning is mandated.

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices.

Immobilization of the hips and feet using a cradle should be considered. Each patient will be positioned in the supine position. Prone positioning for treatment is not permitted.

Simulation

Treatment planning MRI will be performed with vac loc immobilization. Patients will be advised to drink 2-3 cups of water 30 minutes prior to the MRI simulation to allow for a comfortably full bladder, as tolerated.

Rectal Filling - An overly distended rectum can introduce a systematic positioning error that may increase the probability of missing the clinical target volume (CTV). Patients should be simulated with the rectum as empty as possible and <3 cm in the anterior-posterior dimension is ideal. Rectal balloons for planning and treatment are not permitted. Enema may be necessary for subjects.

Bladder Filling - Patients should also have a comfortably full bladder (the patient should not be uncomfortable at simulation because it is likely that he will have more difficulty maintaining a full bladder during treatment). Cunningham clamp may be used for subjects with variable incontinence.

Contours

All contouring should be done in general accordance with the RTOG consensus recommendations for the prostate bed (Michalski 2010) and normal pelvic structures (Gay 2012). The RTOG contouring atlas for the prostate fossa and pelvic structures can be accessed at:
http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePostOp.aspx
http://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx

The prostate fossa will be contoured as the clinical target volume (CTV). The contouring of the prostate fossa should be in general accordance with the RTOG consensus guidelines (Michalski 2010). Briefly, the CTV should extend superiorly from the level of the caudal vas deferens remnant to >8-12 mm inferior to vesicourethral anastomosis (VUA). Below the superior border of the pubic symphysis, the anterior border extends to the posterior aspect of the pubis and posteriorly to the rectum, where it may be concave at the level of the VUA. At this level, the lateral border extends to the levator ani. Above the pubic symphysis, the anterior border should encompass the posterior aspect of the bladder wall; posteriorly, it is bounded by the mesorectal fascia. At this level, the lateral border is the sacrorectogenitopubic fascia. Seminal vesicle remnants, if present, should be included in the CTV. The planning target volume (PTV) expansion for the CTV will be 2-3 mm depending on physician discretion. The bladder should not be included in the CTV and a Boolean function may assist this function.

The nodal CTV will include the obturator, external iliac, proximal internal iliac and common iliac nodes, estimated using the vascular structures, up to the level of L5-S1. The recommended volumes are on the NRG Oncology/RTOG website under the “Core Lab/Contouring Atlases” menu (http://www.rtog.org/CoreLab/ContouringAtlases/ProstatePelvicLymphNodes.aspx). The nodal CTV is described as being 7 mm around the iliac vessels, carving out bowel, bladder and bone, which translates into just contouring the iliac/obturator areas with essentially no extra margin because of the proximity to these structures (this is well-illustrated in the contouring Atlas). Thus, the PTVn margins described above are the margins that venture into the potential bowel space, bladder and bone.

The rectum will be drawn from the bottom of the ischial tuberosities to the sigmoid flexure.

The bladder, bladder wall, femoral heads, penile bulb will also be contoured as normal structures.

Dose/Treatment Planning Parameters for 32.5 Gy in 5 fractions

PTV will be treated to the prescribed dose 32.5 Gy in 5 fractions.

Optional boost(s) to 40 Gy permitted.

VPrescription Dose (volume of the PTV receiving Prescription Dose) should be ≥ 95% and not exceed 110% (hotspot)

Structure	Dosimetric Parameter	Per Protocol
Rectum	V25 Max Point Dose	< 20 cc < 38 Gy
Bladder Wall	V18.3 V25 Max Point Dose	< 15 cc < 18 cc < 38 Gy
Femoral Heads	V30	< 10 cc

Dose/Treatment Planning Parameters for 55 Gy in 20 fractions

PTV will be treated to the prescribed dose 55 Gy in 20 fractions.

Optional boost(s) to 60 Gy permitted.

VPrescription Dose (volume of the PTV receiving Prescription Dose) should be ≥ 95% and not exceed 115% (hotspot)

Structure	Dosimetric Parameter	Per Protocol
Rectum	V24 V32 V40 V48 V55	< 80 cc < 70 cc < 60 cc < 50 cc < 40 cc
Bladder	V40 V48	< 80 cc < 50 cc
Femoral Heads	D44 Gy[%]	< 10

Adaptive Planning for 5 Fraction Arm

1. Prior to treatment, each patient will undergo set up MRI scan.
2. 2D shifts will be performed to align relevant anatomy (bladder wall, rectum, prostatic fossa).
3. Simulation contours will be rigid copied to set up scan and recontoured if CTV delineation changes.
4. Predict dose algorithm will determine if treatment dose parameters meeting planning dose parameters.
5. Patients will undergo adaptive planning if treatment dose parameters do not meet planning parameters AND per protocol planning parameters in the tables above.

5.5 Trial Procedures

The Study Procedures Section 5.1 summarizes the trial procedures to be performed at each visit. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Description of studies are in the appendix.

Definition of Disease Assessments

- Biochemical failure: Two definitions of biochemical failure will be assessed:
    - Primary: PSA ≥ 0.4 ng/mL and rising (i.e. PSA ≥ 0.4 ng/mL followed by a value higher than the first by any amount) or initiation of salvage hormones.

- Alternate: PSA ≥ PSA nadir + 2 ng/mL where nadir is the lowest post-RT PSA level.

- Local failure: development of a new biopsy-proven mass in the prostate bed, after enrollment in the protocol
- Regional failure: radiographic evidence (CT or MRI) of lymphadenopathy within the pelvis (lymph node size ≥ 1.5 cm in the short axis) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy
- Distant metastases: radiographic evidence of hematogenous spread (e.g., bone scan, CT, MRI)
- Progression: first occurrence of biochemical failure, local failure, regional failure, distant metastasis, initiation

5.6 General Concomitant Medication and Supportive Care Guidelines

Androgen deprivation therapy (ADT)

ADT will be administered for patients with PSA >0.4 ng/ml, high Decipher score, or pathologic positive lymph nodes. ADT should consist of LHRH agonist or antagonist and be initiated prior to and within 6 months of starting radiotherapy and not exceed 24 months in duration.

Urinary: A proportion of patients undergoing prostate radiotherapy can expect increase in urinary frequency or urgency. If this becomes bothersome to the patient, medication to alleviate symptoms can be prescribed at the discretion of the treating radiation oncologist and documented in patient chart.

Gastrointestinal: Serious bowel symptoms during time of prostate radiotherapy are rare. If patients develop rectal urgency, tenesmus or diarrhea, medication to alleviate symptoms can be prescribed at the discretion of the treating radiation oncologist and documented in patient chart.

5.7 Duration of Therapy and Criteria for Removal from Study

Radiotherapy will be delivered in a total of 5 fractions in 2 weeks or 20 fractions in 4 weeks.

In the absence of treatment delays due to adverse event(s), treatment may continue or until one of the following criteria applies:

- Patients unable to tolerate radiotherapy
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.8 Duration of Follow Up

Patients will be followed for 5 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6 Correlative/Special Studies

Paraffin-embedded tissue block, serum, plasma, and whole blood will be collected for translational research analyses for predictors of cancer control and toxicity following hypofractionated or ultra-

hypofractionated post-prostatectomy radiotherapy. A total of 10%–20% of patients develop long-term toxicity following radiotherapy for prostate cancer. Identification of common genetic variants associated with susceptibility to radiotoxicity might improve risk prediction and inform functional mechanistic studies. Additionally, genomic risk stratification may provide insight for patients that benefit from different fractionation schedules of radiotherapy, nodal radiotherapy and/or ADT with subsequent development of biomarker candidates.

7 Data Reporting / Regulatory Considerations

7.1 Data Collection

The data collection plan for this study is to utilize REDCap to capture all treatment, toxicity, efficacy, and adverse event data for all enrolled patients.

7.2 REDCap

REDCap (Research Electronic Data Capture) is a data management software system that is fully supported by the Weill-Cornell Medical Center CTSC. It is a tool for the creation of customized, secure data management systems that include Web-based data-entry forms, reporting tools, and a full array of security features including user and group-based privileges, authentication using institution LDAP system, with a full audit trail of data manipulation and export procedures. REDCap is maintained on CTSC-owned servers that are backed up nightly and support encrypted (SSL-based) connections. Nationally, the software is developed, enhanced and supported through a multi-institutional consortium led by the Vanderbilt University CTSA.

7.3 Data Management

All patient data will be entered and maintained in REDCap. These data include clinical data and all patient safety data. The REDCap provides audit trails that track creation and modification of records that include user ID and timestamp. Once entered, the data is subjected to validation procedures that are executed either immediately or upon saving the eCRF page or during the batch validation process. Validation failures that are identified before the page is saved can be corrected immediately. Validation failures during saving of the eCRF page and during batch validation processes will generate a discrepancy. Depending on the database account privileges, the data managers may be able to correct a discrepancy or if not, route it to the project data manager at WCMC who can take appropriate action to correct the problem. Once the discrepancy is closed, by marking “resolved” or “irresolvable”, the data is marked clean and an audit trail is generated by the system.

All key end points will be source verified by a second person at each site and errors will be corrected. Once the data is verified and all discrepancies are closed, the data can be locked/frozen. Locking and freezing can be done at different granular levels and will follow institutional SOPs and any specific requirements for the project.

Security measures that will be taken in order to protect patient data will include firewall technology and database level security which will be achieved by assigning roles and privileges to different levels of users and by requiring that the users authenticate themselves using user id and password. Additional security for data transfer between remote clients and servers will be achieved by using digital certificates/SSL. All data will be backed-up to tape periodically according to the Institutional SOPs. All data will be stored for at least 5 years following the termination of this study.

7.4 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator.

8 Statistical Considerations

8.1 Study Design/Endpoints

This is a randomized phase II non-inferiority trial comparing 5 days of ultra-hypofractionated radiotherapy versus 20 days of hypofractionated radiotherapy in the salvage setting for prostate cancer patients after prostatectomy. Patients will be stratified based on pre-specified stratification factors and randomized 1:1 to receive 5 days or 20 days using permuted block randomization. The primary endpoint is the change in patient-reported GI and GU symptoms as measured by EPIC at two years from end of treatment. Secondary endpoints will include both the safety endpoints including change in GI and GU symptoms at 3, 6, 12 and 60 months from end of treatment, and multiple efficacy endpoints including time to progression, prostate cancer specific survival and overall survival.

8.2 Sample Size/Accrual Rate

The primary goal of this phase II study is to determine if 5 days of radiotherapy does not increase GI or GU toxicity over 20 days of radiotherapy. The primary endpoints are change scores in the bowel (GI) or urinary (GU) domains of the EPIC. The change scores will be based on the 2-year score minus the pretreatment (baseline) score. The hypothesis for this endpoint is that the EPIC mean change score is no worse in the 5 day arm than it is in the 20 day arm for either type of toxicity. Appendix contains more information about the EPIC, such as validation information, number of questions, possible responses, and ranges of the scores.

The sample size is calculated based on a non-inferiority design. The non-inferiority margins are set to be a change score of 6 points for the GI symptoms and 5 points for the GU symptoms. The standard deviation of the change scores are assumed to be 13.2 for the GI symptoms and 10.5 for the GU symptoms based on estimates generated in RTOG 0415 trial. This level of change in scores are deemed as clinically meaningful. For example, 6 points of change score for GI symptoms corresponds to two symptoms worsening by 1 level (i.e. loose stools and frequency of bowel movements change from “no problem” to “very small problem”) or one of the symptoms worsening by 2 levels (i.e. loose stool change from “no problem” to “small problem”).

A sample size of 122 with 61 in each cohort (30 in each arm) will ensure 80% power for GI endpoint and 83% power for GU endpoint to detect non-inferiority using a one-sided two-sample t-test at the significance level of 0.05. Adjusting for a projected 10% EPIC/non-compliance rate, 136 patients (68 per arm) will be randomized.

The projected accrual rate is 4 patients per month. Based on this information, it is projected that the study will complete accrual in about 34 months. The primary endpoint analysis will occur approximately 4 years from study activation.

8.3 Stratification Factors

Patients will be stratified according to baseline EPIC bowel and urinary domain scores (high bowel score and high urinary score vs. high bowel score and low urinary score vs. low bowel score and high urinary score vs. low bowel score and low urinary score) and pelvic radiotherapy and androgen deprivation therapy (yes vs. no) which are expected to be associated with the primary outcome.

8.4 Analysis of Endpoints

Analysis of the Primary Endpoints:

The co-primary endpoints are GI and GU toxicity as measured by the bowel and urinary EPIC domains, respectively. The change scores, calculated as baseline score subtracted from 2-year score, will be analyzed using a non-inferiority t-test based on the prespecified non-inferiority margins with a significance level of 0.05. If the data are determined to be non-normal, a Wilcoxon test may be used instead. All patients with EPIC bowel and urinary domain scores will be included in the primary endpoint analysis. The EPIC scoring manual will be followed which requires ≥ 80% of items in a domain to be completed in order to obtain a score for that domain.

Interim futility analysis:

An interim futility analysis will be carried out when 1/3 of patients have 6 months follow-up. If the upper 95% confidence limit of the mean difference in 6-months change scores between the treatment arms is less than the pre-specified non-inferiority margins, i.e. < -6 for GU and < -5 for GI, the 5 day arm will be deemed inferior to the 20 day arm. Early reporting of the treatment results will be recommended to the DMC, who will review these results. This approach has a minimal effect on statistical power.

Analysis of secondary safety endpoints:

All safety endpoints as measured by change in EPIC scores will be calculated as baseline score subtracted from follow-up score. Difference between study arms will be examined using t-test or Wilcoxon rank sum test where appropriate. The follow-up time points of interest are end of RT, 3, 6, 12, 24 and 60 months from the start of treatment. A longitudinal analysis incorporating all follow-up time points, will be conducted separately for each domain score using a linear mixed-effects model, adjusting for baseline domain score, treatment arm, Gleason score, baseline PSA, T-stage, age, and race. These analyses will be conducted regardless the outcomes of the primary t-test. For the comparison of primary endpoints at 2 years adjusting for other variables using, especially stratification variables, the analysis of covariance (ANOVA) will be used. The results from the covariate adjusted analysis are expected to be similar to those of the primary analyses. In the rare case when of different results, the impact of missing data and covariates will be examined to help make meaningful conclusions.
If any of the domains are found to differ significantly between arms, analysis of that domain's subscales will be undertaken to assess which particular subscale is driving the significant difference. The subscales are function in terms of both incontinency and irritative/obstructive for the urinary domain, and function and bother for the bowel domain.

The impact of the missing data on the analysis results will be evaluated using multiple strategies (Fairclough 2010, Verbeke 2000) including 1) adjustment of patient characteristics that are associated with missingness at any time point for the EPIC bowel and urinary domain scores in the mixed effects model assuming that the data are missing at random (MAR); 2) using a joint model that allows a shared parameter between the repeated measurements and time to death or drop out if data are found to be missing not at random (MNAR) due to the high number of patient deaths or dropouts (Rizopoulos 2012) or using pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

Secondary Efficacy Endpoints

For competing-risk endpoints such as PCSM, LF, RF, TTP, and DM, Gray's cumulative incidence method will be used with death as a competing risk for LF, RF and DM and death not due to prostate cancer for PCSM and TTP. OS and FFBF will be estimated by the Kaplan-Meier method and compared between arms with the log-rank test. Cox regression will be used to obtain hazard ratios (HRs) for OS and TTP. Fine and Gray's regression will be used for the endpoints with competing risks. Adjusted HRs and the respective 95% confidence interval will be computed. Baseline PSA, stratification variables (baseline EPIC score and ADT status), age, race, and other covariates (Gleason, T-stage), will be adjusted for as appropriate in this analysis.

9 Adverse Event Reporting Requirements

Adverse events (AEs) will be recorded REDCAP for the duration of the trial, regardless of whether or not the event(s) are considered related to the trial. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

Adverse events will be recorded for the duration of a patient's participation in the trial. All adverse events (except grade 1 and 2 laboratory abnormalities unless a dose treatment modification, delay or therapeutic intervention is required), regardless of causal relationship, are to be recorded in the case report form and source documentation. Pre-existing conditions at baseline will be recorded. If a pre-existing condition does not change, it does not have to be reported on subsequent cycles.

The investigator must determine the toxicity of adverse events according to the CTCAE version 5.0 and their causal relationship.

9.1 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure.
CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

Attribution of the AE:
- Definite – The AE is clearly related to the study treatment.
- Probable – The AE is likely related to the study treatment.
- Possible – The AE may be related to the study treatment.
- Unlikely – The AE is doubtfully related to the study treatment.
- Unrelated – The AE is clearly NOT related to the study treatment.

9.1.1 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

9.1.2 Recording of Adverse Events

All adverse events will be recorded on a patient specific AE log. The AE log will be maintained by the research staff and kept in the patient's research chart. The AEs are documented in REDCAP database.

9.1.3 Reporting of AE to WCM IRB

All AEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

9.2 Definition of SAE

SAE's include death, life threatening adverse experiences, prolonged hospitalization, disability or incapacitation, overdose, congenital anomalies and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

9.2.1 Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy, which can be accessed via the following link:
http://researchintegrity.weill.cornell.edu/forms_and_policies/forms/Immediate_Reporting_Policy.pdf.

10 Data and Safety Monitoring Plan (DSMP)

A medical monitor from the Department of Radiation Oncology will review cumulative study data twice a year to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial.

The WCMC Data and Safety Monitoring Board (DSMB) is the central monitoring board for this study. The WCMC Cancer Institute DSMB is the local monitoring board for WCMC patients. This study will be conducted in accordance with the guidelines in the 2001 NCI approved data Safety and Monitoring plan for the WCMC Cancer Institute and with the WCMC approved data Safety and Monitoring plan for the WCMC Cancer Institute. Reports to the DSMB will include the following information: accruals, targets, responses, adverse events and evidence of reporting to appropriate review committees. The WCMC Data and Safety Monitoring Board (DSMB) will review the IRB approved protocol, the data and safety monitoring plan and any stopping guidelines during protocol initiation.

During the course of the study, the DSMB will review cumulative study data twice a year to evaluate safety, efficacy, study conduct, and scientific validity and integrity of the trial. *Safety reports will be submitted to the DSMB every six months.*

11 Appendix

EPIC (Expanded Prostate Cancer Index Composite)
The Expanded Prostate Cancer Index Composite (EPIC; required assessment) Health Related Quality of Life as measured by the EPIC questionnaire is the primary endpoint in this study. Therefore, every randomized, eligible, analyzable patient on the study will complete the EPIC. Patients will complete the EPIC per the schedule in Section 5. The EPIC is a prostate cancer health-related quality of life (HRQOL) patient self-administered instrument that measures a broad spectrum of urinary, bowel, sexual, and hormonal symptoms related to prostate cancer treatments, including prostatectomy, radiotherapy, and hormonal therapy [21]. Instrument development was based on advice from an expert panel and prostate cancer patients, which led to expanding the 20-item University of California-Los Angeles Prostate Cancer Index (UCLA-PCI) to the 50-item EPIC. Summary and subscale scores were derived by content and factor analyses. Test-retest reliability and internal consistency were high for EPIC urinary, bowel, sexual, and hormonal domain summary scores (each $r \geq 0.80$ and Cronbach's alpha ≥ 0.82) and for most domain-specific subscales. Correlations between function and bother subscales within domains were high $r > 0.60$). Correlations between different primary domains were consistently lower, indicating that these domains assess distinct HRQOL components. The domains were validated separately, and because each domain will be used intact, there is no threat to validity. Response options for each item form a Likert scale with scores transformed linearly to a 0-100 scale. Domain scores are also on a 0-100 scale with higher scores representing better HRQOL. Some items have 5 response options while others have 4. The bowel domain contains 14 questions, the urinary domain contains 12 items, the sexual domain contains 13 questions, and the hormonal domain contains 11 questions.

EuroQol (EQ-5D)
The EQ-5D is a 6-item validated utility assessment instrument that takes less than 5 minutes to complete (van Agt 1994, Conner-Spady 2001, Brooks 1991, Nord 1991). The first part consists of 5 items covering 5 dimensions including: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is graded on 5 levels: 1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, and 5-unable to perform/extreme problems. Health states are defined by the combination of the leveled responses to the 5 dimensions, generating 3,125 health states. The sixth item is a visual analogue scale for overall health. The 5-item index score is transformed into a utility score between 0, “Worst health state,” and 1, “Best health state.” The index score can be used in a quality adjusted survival analysis depending on the health state(s) of interest (Wu 2002). For this study we plan to report the multidimensional utilities for comparative purposes. The measured utility values for each patient on this study will be combined with overall survival to calculate the “QALY” quality-adjusted life years. This will then be used for cost-effectiveness analysis comparing the two arms in this trial.

Urodynamic Testing with UroCuff
The UroCuff is a urodynamic study that can be utilized to non-invasively measure urine flow rate and bladder pressure, as well as aid in the diagnosis of voiding disorders. A small, pneumatic cuff is fitted around a patient’s penis before the bladder is voided. Then, the patient urinates into a portable commode fitted with a flow meter. While the patient is urinating, the cuff is automatically inflated until the patient’s stream of urine is interrupted. This inflation and interruption cycle is repeated until voiding is complete. The pressure applied to the cuff that was required to interrupt urine flow is equivalent to bladder pressure. Optional surface EMG electrodes can be applied to the patient’s perineum or abdomen to monitor sphincter activity or abdominal straining, respectively. At the conclusion of the test, a report is printed which provides pressure-flow data on a modified nomogram.

12 References

1. Haas, G.P., Delongchamps, N., Brawley, O.W., Wang, C.Y. & de la Roza, G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol* **15**, 3866-3871 (2008).
2. Hamilton, A.S.*, et al.* Trends in the treatment of localized prostate cancer using supplemented cancer registry data. *BJU Int* **107**, 576-584 (2011).
3. Pound, C.R.*, et al.* Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* **281**, 1591-1597 (1999).
4. Antonarakis, E.S.*, et al.* The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. *BJU Int* **109**, 32-39 (2012).
5. Tewari, A.*, et al.* Positive surgical margin and perioperative complication rates of primary surgical treatments for prostate cancer: a systematic review and meta-analysis comparing retropubic, laparoscopic, and robotic prostatectomy. *Eur Urol* **62**, 1-15 (2012).
6. Thompson, I.M., Jr.*, et al.* Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA* **296**, 2329-2335 (2006).
7. Bolla, M.*, et al.* Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* **380**, 2018-2027 (2012).
8. Wiegel, T.*, et al.* Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* **27**, 2924-2930 (2009).
9. NCCN Clinical Practice Guidelines in Oncology - Prostate Cancer (Version 2.2017). (2017).
10. Kishan, A.U.*, et al.* Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. *JAMA Netw Open* **2**, e188006 (2019).
11. Mahase, S.S.*, et al.* Trends in the Use of Stereotactic Body Radiotherapy for Treatment of Prostate Cancer in the United States. *JAMA Netw Open* **3**, e1920471 (2020).
12. Carrie, C.*, et al.* Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. *Lancet Oncol* **17**, 747-756 (2016).
13. Widmark, A.*, et al.* Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet* **394**, 385-395 (2019).
14. Vogelius, I.R. & Bentzen, S.M. Dose Response and Fractionation Sensitivity of Prostate Cancer After External Beam Radiation Therapy: A Meta-analysis of Randomized Trials. *Int J Radiat Oncol Biol Phys* **100**, 858-865 (2018).
15. Kang, J.K.*, et al.* Image-guided stereotactic body radiation therapy for localized prostate cancer. *Tumori* **97**, 43-48 (2011).
16. Kalbasi, A.*, et al.* Low rates of adjuvant radiation in patients with nonmetastatic prostate cancer with high-risk pathologic features. *Cancer* **120**, 3089-3096 (2014).
17. Abdel-Wahab, M. & Pollack, A. Radiotherapy: encouraging early data for SBRT in prostate cancer. *Nat Rev Urol* **6**, 478-479 (2009).
18. Picardi, C., Perret, I., Miralbell, R. & Zilli, T. Hypofractionated radiotherapy for prostate cancer in the postoperative setting: What is the evidence so far? *Cancer Treat Rev* **62**, 91-96 (2018).
19. Ballas, L.K.*, et al.* Phase 1 Trial of SBRT to the Prostate Fossa After Prostatectomy. *Int J Radiat Oncol Biol Phys* (2018).
20. Sampath, S.*, et al.* Stereotactic Body Radiation Therapy to the Prostate Bed: Results of a Phase 1 Dose-Escalation Trial. *Int J Radiat Oncol Biol Phys* (2019).
21. Van Andel, G., Visser, A.P., Hulshof, M.C., Horenblas, S. & Kurth, K.H. Health-related quality of life and psychosocial factors in patients with prostate cancer scheduled for radical prostatectomy or external radiation therapy. *BJU Int* **92**, 217-222 (2003).