Identifiers: NCT04220983
Unique Protocol ID: 19-04020263

Brief Title: **PRAGMA (Prostate Radio Ablation Guided by Magnetic Resonance Imaging Acquisition) in Metastatic Prostate Cancer**

Version 5.0

Version date: 26JUL2023

IRB approval: 01AUG2023

Document History

Document Name	Version number	Version Date
Amendment 4	5.0	26JUL2023
Amendment 3	4.0	03FEB2022
Amendment 2	3.0	05OCT2021
Amendment 1	2.0	24JAN2020
Initial Protocol	1.0	23JUL2019

TITLE: PRAGMA (**P**rostate **R**adio **A**blation **G**uided by **M**agnetic resonance imaging **A**cquisition) in metastatic prostate cancer

IRB Protocol #: 19-04020263
Version 5.0
Version Date : 26JUL2023

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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 WCMC.

List of Abbreviations

All abbreviations used throughout the protocol must be defined.

AE	Adverse Event
AUA	American Urologic Association
CBC	Complete Blood Count
CBCT	Cone Beam Computed Tomography
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
DIN	Dominant intraprostatic nodule
DSMB	Data Safety Monitoring Board
DSMP	Data Safety Monitoring Plan
DVH	Dose Volume Histogram
EPIC	Expanded Prostate Cancer Index Composite Instrument
ERB	Endorectal Balloon
FDA	Food and Drug Administration
Fx	Fraction
GCP	Good Clinical Practice
GI	Gastrointestinal
GTV	Gross Target Volume
Gy	Gray
GU	Genitourinary
HIPAA	Health Insurance Portability and Accountability Act of 1996
HRBFA	Human Research Billing Analysis Form
HRQOL	Health-related Quality of Life
ICF	Informed Consent Form
IG	Image Guided
IMRT	Intensity Modulated Radiation Therapy
IND	Investigational New Drug
I-PSS	International Prostate Symptom Score
IRB	Institutional Review Board
NCCN	National Comprehensive Cancer Network
NLR	Neutrophil lymphocyte ratio
PHI	Protected Health Information
PI	Principal Investigator

PIRADS	Prostate Imaging Reporting and Data System
PSA	Prostate Specific Antigen
PSMA	Prostate Specific Membrane Antigen
PTV	Planning Target Volume
REDCap	Research Electronic Data Capture
RS	Rectal Spacer
RT	Radiation Treatment
SAE	Serious Adverse Event
SBRT	Stereotactic Body Radiation Therapy
SHIM	Sexual Health Inventory Men
SIB	Simultaneous integrated boost
STAMPEDE	Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRUS	Transrectal Ultrasound
UAP	Unanticipated Problem
WCMC	Weill Cornell Medical College

Summary of changes for version 5.0 dated 26JUL2023

Sections	Change	Rationale
Principal Investigator section	Changing Principal investigator from Dr. Ariel Marciscano to Dr. Silvia Formenti	Changing Principal investigator from Dr. Ariel Marciscano to Dr. Silvia Formenti, since Dr. Marciscano will no longer be at WCM.
No changes to the Informed consent since the study is closed to accrual and only in follow up.		

Summary of changes for version 4.0 dated 03FEB2022

Sections	Change	Rationale
Primary Objective	Revising the toxicity measurement timeframe stated in the primary objective from 30 days to 3-6 months post treatment.	Revising the toxicity measurement timeframe stated in the primary objective from 30 days to 3-6 months post treatment and keep it consistent with the study calendar.
Personnel changes	Adding Charles Ekeh to the protocol cover page.	Updating personnel and contact information. Admin amendment approved on 16NOV2021.
No changes to the Informed consent		

Summary of changes for version 3.0 dated 05OCT2021

Sections	Change	Rationale
Principal Investigator section	Changing Principal investigator from Dr. Josephine Kang to Dr. Ariel Marciscano	Changing Principal investigator from Dr. Josephine Kang to Dr. Ariel Marciscano
Personnel changes	Removed Maria Fenton-Kerimian as Nurse practitioner and Viji Nagaraj as study coordinator, Added Jessica Richman. Updated contact details for personnel.	Change of personnel and contact information.
Informed consent changes		
Principal Investigator section	Changing Principal investigator from Dr. Josephine Kang to Dr. Ariel Marciscano	Changing Principal investigator from Dr. Josephine Kang to Dr. Ariel Marciscano

Summary of changes for version 2.0 dated 24JAN2020.

1. **Inclusion Criteria:** Must have metastatic prostate cancer proven on biopsy or imaging
2. **Exclusion Criteria:** Removing criteria # 4 - Evidence of disease progression on bone scan, MR and/or CT
3. Revised accrual ceiling to 25 patients as stated in the IRB application
4. Adding Viji Nagaraj as data manager to the protocol to keep it consistent with the IRB personnel list.
5. Updating QOL – AUA to I-PSS
6. Study Calendar – clarifying that blood/stool collection is optional at all time points as stated in the informed consent.

Informed consent changes:

1. The protocol version date is incorrect - changing the footer of the informed consent.
2. Making study calendar consistent with the protocol.

Document History

Document Name	Version number	Version Date
Amendment 4	**5.0**	**26JUL2023**
Amendment 3	4.0	03FEB2022
Amendment 2	3.0	05OCT2021
Amendment 1	2.0	24JAN2020
Initial Protocol	1.0	23JUL2019

Protocol Summary

PRAGMA (**P**rostate **R**adio **A**blation **G**uided by **M**agnetic resonance imaging **A**cquisition) in metastatic prostate cancer

IRB Protocol #: 19-04020263

Short Title:	MRI-guided prostate SBRT for metastatic prostate cancer
Principal Investigator:	Dr. Ariel Marciscano
Sample Size:	N = 20
Accrual Ceiling:	This study plans to enroll a total of 25 patients
Study Population:	Patients with metastatic prostate cancer
Accrual Period:	2 years
Study Design:	Single-arm study for safety

Study Intervention Description:
MR-guided Prostate SBRT:
Prostate SBRT has become a standard of care for the treatment of localized prostate cancer. Radiation is delivered to the prostate and seminal vesicles in 5 treatment sessions (fractions). Doses ranging from 35-45 Gy in 5 fractions have demonstrated good outcomes with acceptable toxicity when planning is delivered appropriately.
There is emerging evidence that patients with *non*-localized prostate cancer also derive benefit from radiation (RT) to the primary tumor. The STAMPEDE multiarm British trial recently reported that patients with low burden metastatic prostate cancer have an overall survival benefit from prostate RT. Doses of radiation used in the STAMPEDE trial were either 36 Gy in 6 fractions, or 55 Gy in 20 fractions.
The MRidian ViewRay offers delivery of prostate SBRT with real-time MR guidance, which provides superior soft-tissue differentiation with excellent visualization of the prostate. This ViewRay platform offers the ideal setting for this study, that aims at precisely delivering prostate SBRT with a simultaneous integrated boost (when indicated) to visible nodules.
In this study, we hope to demonstrate the safety of using 36.25 Gy in 5 fractions, plus a simultaneous integrated boost (when indicated), in patients with metastatic prostate cancer.

Hypothesis: Patients with metastatic prostate cancer can undergo MRI-guided prostate SBRT without significant adverse events, similar to what has been reported for patients with localized prostate cancer.

We hypothesize that prostate SBRT will be well-tolerated in metastatic prostate cancer patients, with quality of life outcomes similar to what has been reported in non-metastatic prostate cancer patients.

We also hypothesize that prostate SBRT will impact lymphocyte counts and neutrophil

lymphocyte ratio, as well as the diversity, abundance and composition of the gut microbiome, when baseline datapoints are compared to post-RT and follow up datapoints.

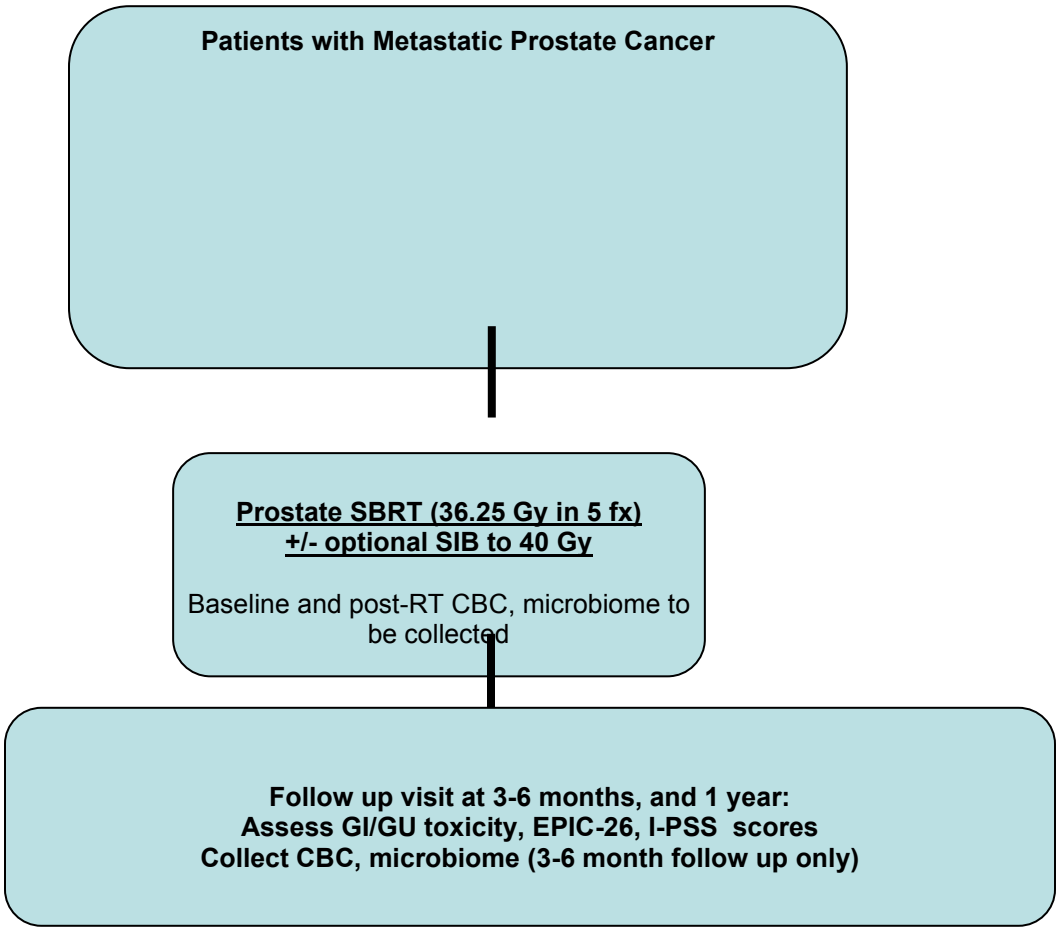
Primary objective: To assess safety of delivering MRI-guided prostate SBRT in patients with metastatic prostate cancer.

Treatment will be deemed safe of there is is no more than 3 acute >G3 likely radiation treatment related GI/GU toxicity within 3-6 months after treatment (CTCAE 5.0 criteria) completion. Given that the treatment plans will meet rigorous normal tissue constraints used for standard prostate SBRT that have been established now with up to 10 year follow up data in patients with localized prostate cancer, we do not anticipate any increased toxicity on this study for metastatic prostate cancer patients.

Secondary objective: To obtain quality of life and toxicity data after prostate SBRT.
We will measure quality of life (HRQOL) using: 1) the Expanded Prostate Cancer Index Composite (EPIC-26) short form questionnaire, 2) International Prostate Symptom Score (I-PSS). QOL assessments will occur at baseline, 3-6 months, and at 9-12 months.
Toxicity data will be measured with CTCAE 5.0 at 3-6 months, and at 9-12 months.

Correlative study objectives:
1. To explore gut microbiome changes associated with prostate radiation
2. To collect complete blood count (CBC) measurements at baseline, post-treatment and 3-6 month followup to assess impact of SBRT on immune correlates and neutrophil lymphocyte ratios.

SCHEMA


Patients with Metastatic Prostate Cancer
Prostate SBRT (36.25 Gy in 5 fx)
+/- optional SIB to 40 Gy
Baseline and post-RT CBC, microbiome to be collected
Follow up visit at 3-6 months, and 1 year:
Assess GI/GU toxicity, EPIC-26, I-PSS scores
Collect CBC, microbiome (3-6 month follow up only)

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1 STUDY OBJECTIVES

HYPOTHESIS 1: Patients with metastatic prostate cancer can undergo MRI-guided prostate SBRT w/SIB without significant adverse events, similar to what has been reported for patients with localized prostate cancer using CTCAE criteria.

HYPOTHESIS 2: Patients with metastatic prostate cancer who undergo MRI-guided prostate SBRT will report good overall quality of life, similar to what has been reported for patients with localized prostate cancer. This will be measured using EPIC-26, I-PSS questionnaires, which are validated instruments that have been used to report QOL outcomes after prostate RT.

HYPOTHESIS 3: Patients may experience decline in neutrophil:lymphocyte ratios during radiation therapy, that is most prominent at end of treatment, but recovers to baseline by follow up. There will be alterations in the composition, diversity and abundance of microflora during radiation therapy when the microbiome is compared at baseline, to post-treatment, to follow up.

1.1 Primary Objectives

1.11 To assess safety of delivering MRI-guided prostate SBRT in patients with metastatic prostate cancer.

Treatment will be deemed safe of there is is no more than 3 acute >G3 likely radiation treatment related GI/GU toxicity within 3-6 months after treatment (CTCAE 5.0 criteria) completion. Given that the treatment plans will meet rigorous normal tissue constraints used for standard prostate SBRT that have been established now with up to 10 year follow up data in patients with localized prostate cancer, we do not anticipate any increased toxicity on this study for metastatic prostate cancer patients.

1.2 Secondary Objectives

1.21 We will measure quality of life (HRQOL) using: 1) the Expanded Prostate Cancer Index Composite (EPIC-26) short form questionnaire, 2) I-PSS. QOL assessments will occur at baseline, 3-6 months, and at 9-12 months. Toxicity data will be measured with CTCAE 5.0 at 3-6 months, and at 9-12 months.

1.3 Correlative Study Objectives

1.31
To collect complete blood count (CBC) measurements at baseline, post-treatment and 3-6 month followup to assess impact of SBRT on immune correlates and neutrophil lymphocyte ratios.

To describe gut microbiome changes (abundance, composition, diversity) associated with prostate radiation.

2 BACKGROUND

2.1 Radiation to the prostate: Rationale for treating patients with metastatic prostate cancer

Next to skin cancer, prostate cancer is the most commonly diagnosed cancer in men, and second leading cause of cancer death.[4] It is estimated that one out of seven men will be diagnosed with prostate cancer during their lifetime. Due to improvements in diagnostic imaging, monitoring and therapy, an increasing number of patients are being diagnosed with early metastatic prostate cancer, where an aggressive approach is hypothesized to yield improved clinical outcomes.

The appropriate management of patients with metastatic prostate cancer has varied widely and continues to evolve. In the past, local therapy to the prostate (radical prostatectomy, definitive external beam radiation (EBRT)) was offered only to patients with non-metastatic prostate cancer, and systemic therapies such as androgen deprivation therapy (ADT) was administered to patients with disease outside of the prostate. However, new data suggests that treatment of the primary tumor provides clinical benefit to men with metastatic disease. [5,6]

The STAMPEDE (Radiotherapy to the Primary Tumour for Newly Diagnosed, Metastatic Prostate Cancer) trial results demonstrate that select men with metastatic prostate cancer derive an overall survival benefit from prostate-directed EBRT. In this randomized controlled phase 3 study, men with newly diagnosed metastatic prostate cancer were treated with either standard of care, or standard of care plus prostate EBRT. The primary outcome was overall survival. With median follow up of 37 months, it was reported that patients with metastatic prostate cancer had improved overall survival after prostate EBRT versus none, 3 year OS 81% vs 73% (HR 0.68, 95% CI 0.52-0.90, P=0.007). Based on these results, prostate EBRT has become a standard treatment option for patients with low metastatic burden prostate cancer.[5] Low metastatic burden prostate cancer is defined using the CHAARTED (Chemohormonal Therapy in Metastatic Hormone Sensitive Prostate Cancer) and STAMPEDE trial criteria: any metastatic prostate cancer that does not have a) visceral metastases AND/OR b) four or more bone metastases with one or more outside the vertebral bodies or pelvis. Any patients without a) or b) are considered to have low metastatic burden.[5,7] Furthermore, there is retrospective data suggesting that prostate RT improves outcomes in men with metastatic prostate cancer who do not necessarily fit the definition of low metastatic burden.[32-33]

In the STAMPEDE study, patients receiving EBRT were allowed either 20 fractions of radiation to 55 Gy over 4 weeks, or 6 fractions of radiation to 36 Gy over 6 weeks. Neither of these regimens are commonly utilized in the United States. Stereotactic body radiation therapy delivers 36.25 Gy over 5 fractions in 1-2 weeks, completing treatment in a short span of time with a low overall adverse event rate demonstrated in patients with non-metastatic prostate cancer[1-3]. In this study, we hope to demonstrate the safety and feasibility of delivering SBRT in patients with metastatic prostate cancer, using MR-guided treatment delivery.

2.2 Prostate cancer radiotherapy: Rationale for extreme hypofractionation SBRT

In the past, standard fractionation EBRT was delivered over 9-10 weeks, with 1.8 to 2.0 Gy administered daily, in up to 50 treatment sessions. The inconvenience associated with the protracted length of a standard course of prostate treatment has stimulated interest in delivering more radiation dose per session, to reduce the duration of treatment. Compared to conventional fractionation, hypofractionation (higher dose of radiation given in fewer sessions) allows for reduced number of treatment visits, increasing patient convenience while lowering health care costs. This has resulted in the development of extremely hypofractionated regimens, delivered most commonly within 5 fractions, allowing completion of treatment generally within 1-2 weeks. Such treatments are delivered using stereotactic or image-guided IMRT approaches, most commonly referred to as prostate stereotactic body radiation therapy (SBRT).

Single institutional and pooled reports have demonstrated similar efficacy and toxicity to conventionally fractionated regimens. [1-3] The NCCN treatment paradigm currently includes SBRT as an alternative to conventionally fractionated regimens at centers with appropriate technology, physics and clinical expertise.[8] SBRT enables patients to undergo a non-invasive treatment and be finished in five treatments, achieving outcomes equivalent to long-course EBRT or surgery, without a surgical procedure, general anesthesia and the risk of associated complications. As such, it is an excellent option to deliver prostate EBRT in patients with metastatic prostate cancer.

2.3 Biological rationale for SBRT

Proponents of prostate cancer hypofractionation argue that the rectum and bladder are less sensitive to increases in dose per fraction than prostate cancer and that therefore hypofractionation should yield negligible increases in late toxicity while providing improved cancer control. The α/β is a theoretical measure of a tissue's predicted response to a dose of radiation, relative to the size of the dose delivered per fraction. Conventional daily doses of radiation are based on the presumed high α/β ratios of most malignant tumors. Higher α/β ratios mean that tumor response is less dependent on the amount of radiation administered with each fraction when compared to adjacent normal tissue, and therefore that a lower radiation dose per treatment can typically be used. Lower tumor α/β ratios mean that a larger dose of radiation per treatment can provide improved efficacy in terms of therapeutic ratio, tumor control versus risk of complications. A large body of work theorizes that the α/β for prostate cancer is low (~1.5), implying that a hypofractionated schedule could improve prostate cancer control, while maintaining a low risk of severe normal tissue complications (see Table 1). [9] The radiobiological linear-quadratic cell survival model was used to calculate the biologically equivalent doses for tumor control and complications to normal organs, using standard 2 Gy fractions delivered five times a week.[10-12]

Table 1. Equivalent total doses in 2 Gy per fraction (EQD2) based on α/β Biologically Effective Doses (BED)

	α/β (Gy)	EQD2 Standard (1.8 Gy x 45 fx)	EQD2 SBRT (7 Gy x 5 fx)	EQD2 SBRT (7.5 Gy x 5 fx)	EQD2 SBRT (8 Gy x 5 fx)	EQD2 SBRT (8.5 Gy x 5 fx)	EQD2 SBRT (9 Gy x 5 fx)
Total Dose (Gy)		**81**	**35**	**37.5**	**40**	**42.5**	**45**
Tumor	1.5	76.37 Gy	85 Gy	97.65 Gy	110 Gy	123.07 Gy	135 Gy
Fibrosis/stricture	2	76.95 Gy	78.75 Gy	89.06 Gy	100 Gy	111.56 Gy	123.7 Gy
Telangiectasia	4	78.3 Gy	64.17 Gy	71.88 Gy	80 Gy	88.54 Gy	97.5 Gy
Rectum	4	78.3 Gy	64.17 Gy	71.88 Gy	80 Gy	88.54 Gy	97.5 Gy
Bladder	4	78.3 Gy	64.17 Gy	71.88 Gy	80 Gy	88.54 Gy	97.5 Gy

2.4 SBRT Outcomes

To date, results from prospective and retrospective studies demonstrate good biochemical control and low toxicity for SBRT, with commonly used doses ranging from 35-45 Gy in 5 fractions (see Table 2). Randomized data from the phase III PACE trial, comparing standard fractionation EBRT to 78 Gy or moderately hypofractionated EBRT to 62 Gy, versus SBRT to 36.25 Gy in 5 fractions, show no difference in grade 2 or higher acute urinary or bowel toxicity, suggesting SBRT to be a well-tolerated, safe alternative to longer treatment regimens.[13]

SBRT compares favorably to outcomes for standard fractionation EBRT to 81 Gy, which has 10-year biochemical RFS of 91%, 78% and 62%, respectively, for low-, intermediate- and high-risk prostate cancer, and late Grade 3 gastrointestinal (GI) and genitourinary toxicity of 1% and 5%, respectively.[14] There is a lack of consensus regarding the appropriate dose to use for prostate SBRT. Extrapolating from dose escalation studies in conventionally fractionated EBRT,[15,16] a higher dose in SBRT is hypothesized to result in improved local control. However, delivery of higher dose results in small but significant increase in GU toxicity. Katz and Kang showed significantly higher late grade 2-3 GU toxicity with 36.25 Gy compared to 35 Gy (13.2 vs 8.8%, $P<0.05$). With 35 Gy in five fractions, the majority of toxicity was grade 2, and overall toxicity was low without impacting GU quality of life. As shown in Table 2, late grade 3 GU/GI toxicity after SBRT appears to be comparable to that of conventionally fractionated EBRT, ranging from 0.6 – 3% [1,3] with longest median follow-up of 7 years.

Table 2. Biochechemical control after prostate SBRT. *prospective

Study	SBRT Dose (5 fx)	FU	# Pts	Risk Categories	bPFS	Toxicity ≥3
Bolzicco[17]*	35 Gy	36m	71	Low (41%), Int (42%), High (17%)	3y 94.4%	GI 0%, GU 1%
King[18]*	35-36.25 Gy	5y	41	Low, Favorable Int Risk	5y 92.7%	GI 0%, GU 3.5%
McBride[19]*	36.25-37.5 Gy	44.5 m	45	Low	3y 97.7%	GI 4.4%, GU 2.2%
Madsen[20]*	33.5 Gy	41m	40	Low	4y 90%	GI 0%, GU 0%
Fuller[21]*	38 Gy/ 4 fx	60m	259	Low (43%), Int (57%)	5y Low 100%, Int 88.5%	GI 0%, GU 3.1%

Kim[22]	45-50 Gy	42m	47	Low (38%), Int (62%)	4y 98%	GI 0%, GU 0%
Loblaw[23]*	35 Gy	55m	84	Low	5y 98%	GI 1%, GU 1%
Mantz[24]*	40 Gy	60m	102	Low, Fav Int	5y 100%	GI 0%, GU 0%
Chen[25]	35-36.5 Gy	2.3y	100	Low (37%), Int (55%), High (8%)	2y 99%	GI 0%, GU 1%
Katz and Kang[2]	35-36.25 Gy	72m	477	Low (68%), Int (32%)	7y Low 95.6%, Fav Int 93.5%, Unfav Int 79.3%	GI 0%, GU 2%
Katz and Kang[26]	35-36.25 Gy	84m	515	Low (63%), Int (30%), High (7%)	8y Low 93.6%, Int 84.3%, High 65.0%	GI 0%, GU 2%
Katz[27]	35-36.25 Gy	108m	230	Low	10y 93%	GI 0%, GU 2%

Abbreviations: FU, follow up; Gy, Gray; Fx, fractions; m, months; y, years; IQR, interquartile range
*SBRT monotherapy patients
** Heterogeneous SBRT planning such that at least 1% of PTV receives ≥ 150% of prescription dose.

2.5 Rationale for Simultaneous Integrated Boost

Both EBRT and SBRT target the entire prostate gland with radiation. Studies on patterns of failure following conventional EBRT demonstrate that 85-100% of local failures occur in the region of macroscopic tumor.[28,29] Modern treatment planning systems have the ability to selectively target visible lesions within the prostate to a higher dose, resulting in heterogeneous dose distributions that target high-risk nodules to increased dose and surrounding prostate to a lower dose. A phase II trial is currently ongoing in the Netherlands (Hypofractionated focal lesion ablative microboost in prostate cancer, "hypo-FLAME" NCT02853110), to look at feasibility of a focal ablative boost with SBRT, using dose of 35 Gy in 5 fractions with a boost to visible nodules up to 50 Gy. Furthermore, our department has a currently ongoing investigator initiated protocol in patients with non-metastatic prostate cancer ("MRI-guided Stereotactic Body Radiotherapy (SBRT) with Simultaneous Integrated Boost for Prostate Cancer" PI: Josephine Kang, Silvia Formenti IRB Protocol # 1802019010), which utilizes a simultaneous integrated boost in patients with non-metastatic prostate cancer, and has demonstrated the feasibility and safety of such an approach in 9 patients who have thus far enrolled. The dose used for simultaneous integrated boost in this protocol, 40 Gy, remains within the acceptable range of doses for prostate SBRT.

2.6 Need for IGRT in prostate radiotherapy

SBRT delivers high dose to the target with a rapid dose fall-off. Thus, it is important to account for prostate motion as much as possible during treatment delivery (intrafraction motion), and between each treatment fraction (interfraction motion). A small shift in the prostate, if unaccounted for, can result in significantly decreased dose to the target. Position changes are inevitable due to bowel gas/stool fluctuation, bladder filling and/or prostate edema from radiation.[30] There are multiple techniques to account for prostate motion during delivery of SBRT. Such techniques include tracking via implanted radiofrequency transponders (e.g., Calypso), on-board kV imaging of prostate fiducials at 30-60 second intervals (e.g., Cyberknife), and use of multiple cone-beam CTs during treatment. Traditional image-guided radiation is unable to provide real-time feedback of target position. Treating multiple radiation targets (prostate, seminal vesicles, high-risk nodules) with steep dose gradients becomes particularly challenging with standard image guidance systems, because adjustments are made offline or at prolonged select intervals during treatment delivery.

2.7 ViewRay: a unique radiation delivery approach

The ViewRay MRIdian Linac system is a radiation delivery machine that integrates a linear accelerator with real-time MRI imaging. The ViewRay machine allows fusion of MR imaging with treatment planning. The uniqueness of this approach is the image guided delivery component, based on precise MRI-based detection of target and normal tissue during treatment in real-time. The ViewRay will provide real-time MRI imaging to ensure that the high-dose region is precisely targeted. MRI guided radiation has the benefit of not requiring fiducial implantation or excess radiation exposure from multiple cone beam CT. Furthermore, motion monitoring can be performed with images acquired up to 4 frames a second, allowing live feedback of treatment position.

ViewRay offers the ideal system for delivery of prostate SBRT, due to its ability to provide image guidance “live”, during treatment. Real-time MRI imaging allows superior soft-tissue differentiation with excellent visualization of the prostate. This ViewRay platform offers the ideal setting for this study, that aims at precisely delivering prostate SBRT with a simultaneous integrated boost to visible nodules. MRI guided radiation, a property unique to ViewRay, will be exploited in the current trial to deliver precise treatment with resultant lower dose to surrounding normal structures.

The goal of this study is to assess safety of treating patients with metastatic prostate cancer with MRI-guided prostate SBRT. Safety is defined as lack of more than 3 patients with treatment related acute >G3 GI or GU toxicity within 3- 6 months post treatment. The proposed SBRT dose (36.25 Gy in 5 fractions to the whole prostate) has been reported in the literature to be safe and well tolerated (Table 2), with no acute G3 toxicity. The proposed boost dose to 40 Gy in applicable patients is within the range of current standard of care SBRT doses, and is also expected to be well-tolerated. Furthermore, it has been tested in our currently ongoing investigator initiated protocol in patients with non-metastatic prostate cancer (“MRI-guided Stereotactic Body Radiotherapy (SBRT) with Simultaneous Integrated Boost for Prostate Cancer” PI: Josephine Kang, Silvia Formenti IRB Protocol # 1802019010). As of 4/29/19, 15 patients with localized prostate cancer have enrolled on this study with planned accrual of 30 patients, and have demonstrated excellent safety and feasibility with boost doses up to 45 Gy. It

is therefore expected that similar outcomes can be achieved in patients with metastatic prostate cancer, though it is possible that the addition of systemic therapy may alter likelihood of toxicity.

2.8 Rationale for Correlative Studies Background: Microbiome and blood sample collection
Patients accrued to the study will donate a stool specimen and a blood sample both before and after radiation, to study their changes in the microbiome and circulating immune correlates during and after radiotherapy, and at 3-6 month follow up.

Preliminary results from our ongoing study "Effect of Radiotherapy Variables on Circulating Effectors of Immnue Response and Local Microbiome" PI: Silvia Formenti, IRB Protocol #: 1708018471 demonstrate depletion of circulating lymphocytes in prostate cancer patients undergoing protracted standard radiation compared to 5-fraction SBRT (which is the regimen we will use on this study) (results submitted to ASTRO). We will study this phenomenon further in patients undergoing SBRT on this study. We have also found a temporary increase in neutrophil:lymphocyte ratio (NLR) during radiation to the prostate in our dataset of patients; patients enrolled on this protocol will also have assessment of NLR at baseline, after RT and at 3-month follow up.

The host microbiome is an emerging topic of investigation, with growing evidence that commensal microbiota impacts anti-tumor immune response, and sensitivity to systemic therapies and immunotherapy. Commensal bacteria outnumber human cells by at least 10-fold, colonizing host mucosal surfaces and playing critical roles in metabolism, defense against pathogens, and crosstalk between the environment and immune system. Preclinical studies suggest that microbiota impact the immune system through a number of mechanisms, including possible modulation of myeloid-derived cells; stimulation of T helper cells, and enhancement of memory T-cell response. Dysbiosis, or shifts in microbial composition, may modulate response to cancer therapy. We hypothesize that the underlying microbial community composition will be impacted by administration of radiation to the prostate. Our preliminary data in mice suggests fluctuations in composition, abundance and diversity after local tumor-directed radiation. We hope to explore this further in patients who are undergoing SBRT by collecting microbiome samples at baseline, upon completion of RT, and at follow up.

3 SUBJECT SELECTION

3.1 Study Population

Men with a histologically confirmed diagnosis of metastatic prostate adenocarcinoma, meeting the inclusion and exclusion criteria below, and electing to undergo definitive radiation treatment with SBRT, will be eligible for participation in this study.

3.2 Inclusion Criteria

1. Biopsy-proven diagnosis of prostate adenocarcinoma
2. Age ≥ 18
3. Must have metastatic prostate cancer proven on biopsy or imaging

3.3 Exclusion Criteria

1. History of prior pelvic radiation (external beam or brachytherapy)
2. Inability to undergo MRI
3. AUA score >20
5. For patients on systemic therapy, enrollment must be within six months of start of therapy unless exception is made by protocol PIs (Drs. Kang, Formenti or Sternberg)

4 REGISTRATION PROCEDURES

4.1 Patient Registration

Before any protocol specific procedures can be carried out, investigators/staff will fully explain the details of the protocol, the study procedures and the aspects of patient privacy regarding research information. Patients will be provided a comprehensive explanation of the proposed treatment including the type of therapy, the rationale for treatment on the protocol, alternative treatments that are available, any known adverse events, the investigational nature of the study and the potential risks and benefits of the treatment. The informed consent document will meet all requirements of the Institutional Review Board (IRB). All subjects/patients are informed in the consent that participation or refusal to participate in the research study will not affect any of the clinical treatment or services to which they would otherwise be entitled.

The physicians who may obtain informed consent are listed on the title page of this protocol. The informed consent form will be signed by the participant and the registering physician. Once signed, a copy will be given to the patient and one will be maintained with the patient's medical record. Once eligibility is confirmed and informed consent is documented, the patient will be registered by the study coordinator/data manager.

Patients will be centrally registered with the Office of Billing Compliance. To register a patient, submit the following documents via the JIRA Registration Process:

- Legible copy of the HRBAF
- Signed informed consent

Registration must be completed within 24 hours of the signing of informed consent.

5 STUDY PROCEDURES

	Pre-Study	Fx 1	Fx2	Fx 3	Fx 4	Fx 5*	Post-RT Visits (3-6 months, 9-12 months s/p RT)
Informed consent	X						
Demographics	X						
PSA	X						X
Acute/Late Toxicity Assessment (CTCAE)	X					X	X
EPIC-26, I-PSS	X						X
Imaging: Planning CT/MR;	X						
Blood draw and microbiome sample	X					X	X**

** no blood draw at 9-12 months.

5.1 Pre-Study Visit

At the initial screening visit, patient will undergo:

- Informed consent
- Medical history
- Baseline EPIC-26 Questionnaire, I-PSS forms

5.2 Imaging Studies

Placement of a rectal spacer is optional. Treatment planning CT and MR will be performed with appropriate immobilization. Patients will be advised to drink approximately 1-2 cups of water 1 hour prior to the CT simulation to allow for a comfortably full bladder, if tolerated; this will be modified according to physicians discretion. A radiation planning MR will be obtained at the physician's discretion.

5.3 Radiation Treatment Planning

5.3.1 Contours

The prostate +/- seminal vesicles (SV) will be contoured as the clinical target volume (CTV) as per usual practice. For patients with identifiable dominant intraprostatic nodules (**Select PIRADS 3-5 and/or PSMA avid (if PSMA PET/MR is available) and/or biopsy positive nodules (chosen based on physician's clinical judgment and correlation with biopsy findings)),** there is the option for DIN to be contoured as gross tumor volume(s) (GTV). There will be no planning target volume (PTV) expansion for the DIN GTV. The PTV expansion for the CTV will be 0-5 mm on the prostate, depending on physician discretion as per standard care.

The rectum will be drawn from the bottom of the ischial tuberosities to the sigmoid flexure. The urethra will be delineated on MRI from the prostatic apex, to entry of urethra into the penile bulb, using a 5-6 mm brush.

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

5.3.2 Dose/Treatment Planning Parameters

The CTV (prostate +/- SV) will be treated to dose of 36.25 Gy in 5 fractions. For patients with identifiable DINs, at the physician's discretion, there is an option for a simultaneous integrated boost to PIRADS 3-5 or PSMA avid nodules and/or biopsy positive nodules, delivering 40 Gy to the contoured nodule(s) as a mean dose while respecting normal tissue constraints to rectum and urethra. (If normal tissue constraints to the rectum and urethra can not be achieved, the DIN will be boosted to a lower dose, or not boosted)

Volume of the PTV receiving prescribed SBRT dose should ideally be ≥ 95%; acceptable suggested deviation is dose >85%

Critical organ limits (SBRT monotherapy):

1. Rectum: Maximum dose to 1 cc 38.5 Gy, Max dose to 3 cc 34.4 Gy,, Max point dose 40 Gy. Acceptable deviation is maximum dose to 1 cc 39 Gy, max dose to 3 cc 36 Gy and max point dose of 42 Gy.
2. Bladder: Maximum dose to 1 cc 38.5 Gy, Max point dose 40 Gy. Acceptable deviation is max point dose of 42 Gy.
3. Penile Bulb: No more than 105% of prescription dose; D3cc 25 Gy. This is a soft constraint.
4. Femoral heads: Maximum point dose 30 Gy
5. Small bowel: Maximum point dose 25 Gy
6. Urethra: Max dose 40 Gy. Will allow up to 42 Gy point dose. Urethra planning organ at risk volume (PRV) can be created around the contoured urethra if there is uncertainty

5.4 Supportive Care Guidelines

a. Urinary: A proportion of patients undergoing prostate SBRT 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.

b. Bowel: Bowel symptoms during time of prostate SBRT can occur. 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.

5.5 Duration of Therapy and Criteria for Removal from Study

In the absence of treatment delays, the SBRT is anticipated to complete within 2-3 weeks time. Patients will undergo radiation 2-3 times a week, but treatment can be slowed down to once a week at the physician's discretion; these differing fractionation patterns fall within standard of care for SBRT. Patients can be removed from the study at any point should they decide they no longer wish to participate. They will continue to receive routine medical care as necessary outside the confines of this study.

Patients will be placed in a prospective database patients undergoing prostate SBRT in our department. As per our usual care, they will fill out I-PSS and EPIC-26 quality of life forms at each follow up visit.

5.6 Duration of Follow Up

Patients will be followed as per standard care. For purposes of this study, patients will be followed with CTCAE evaluation, EPIC-26 quality of life questionnaire, I-PSS scores at each follow up visit (3-6 months; 9-12 months); afterwards they will be prospectively followed as per usual care in the Radiation Oncology department with quality of life questionnaires and adverse event evaluation, I-PSS scores.

6 DOSE MODIFICATIONS

None.

7 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug or device under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

7.1 Adverse Event Definition

An adverse event (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with treatment, and does not imply any judgment about causality.

Adverse Event Characteristics and Related Attributions

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for grade 3 or higher AE reporting. A copy of the CTCAE version 4.0 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.

7.2 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.

7.2.1 Reporting of AE to WCMC 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.

7.3 Definition of SAE

SAE's include death, life threatening adverse experiences, hospitalization or prolongation of 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.

7.3.1 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.

7.4 Expedited Adverse Event Reporting

The principal investigator is responsible for monitoring the safety of patients who enroll in the study. All AEs occurring after treatment will be followed until resolution. The descriptions and grading scales found in the revised NCI CTCAE version 4.0 will be used for adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

A serious adverse event (SAE) is any adverse experience that results in any of the following outcomes:

- Death.
- Life-threatening adverse experience.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.

• Important medical events: Defined as AEs that, based upon appropriate medical judgment, may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed above, even though these events may not be immediately life-threatening or result in death or hospitalization.

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.

7.4.1 AE/SAE Follow Up

All SAEs and AEs reported during this study will be followed until resolution or until the investigator confirms that the AE/SAE has stabilized and no more follow-up is required. This requirement indicates that follow-up may be required for some events after the patient discontinues participation from the study.

8 PHARMACEUTICAL INFORMATION

There is no investigative agent used on this protocol.

9 CORRELATIVE/SPECIAL STUDIES

9.1 Correlative Study: Blood draws for immune correlates and microbiome collection

Patients will provide blood draw prior to, at the completion of radiation and at 3-6 months post treatment follow up. They will also be providing a stool sample for microbiome analysis at baseline, end of completion and 3-6 month follow up (last stool sample is optional). This is a correlative study.

Blood Sample Collection and Procedure

Blood samples (40-ml) will be collected in heparinized “Green Top” tubes (for PBMC and plasma isolation) and processed within 4 h of sample receipt. The PBMC will be isolated using a 1.077 g/ml Ficoll layer to enrich the leukocytes and remove the dead cells and any red cells, and cryopreserved in 10% DMSO, 90% human AB serum at 10×10^6

cells/vial and stored in liquid nitrogen for batch analysis. Plasma will also be aliquoted and stored at -80^{0}C for batch analysis. We anticipate analyses of T cell subsets and neutrophil/lymphocyte ratios, as well as cytokine measurement and proliferation analyses (all markers of peripheral immune correlates to assess status over time).

Microbiome collection
Collection of Specimen(s): Patients will be provided with a stool collection container and be instructed on providing a specimen appropriately, which can be done from home or in the clinic.

Handling of Specimens(s): Samples received will be promptly frozen at 20 degrees C, and transferred within the next week to a -80 degree freezer or liquid nitrogen for long-term storage. DNA extractions and 16sRNA analysis will be performed once all samples are collected.

The microbial DNA will be isolated and used to provide DNA sequence information. We will perform taxonomic characterization of bacteria (using 16S rRNA). Prokaryotic diversity will be screened using massively parallel DNA sequencing, exploiting a multiplexing technique to generate 16S rRNA sequence tags, followed by analyses (statistical, clustering, and phylogenetic) to estimate the distribution of phylotypes, differential abundance, and the relative contributions between phylotypes and community dissimilarities to the overall diversity in individuals.

We will examine whether there are metagenome sequence content changes during radiation treatment, and study whether differences in gene content indicate differences in functional pathways between the normal and irradiated microbiome using pathway analysis.

Samples will be collected by the research team and the samples will be stored in -80C freezer in Dr. Silvia Formenti's lab until sample analysis.

10 MEASUREMENT OF EFFECT

This is a safety study.

Treatment will be deemed safe of there are no more than 3 acute greater than grade 3 radiation treatment related GI/GU adverse events within 3-6 months of treatment (CTCAE 5.0 criteria).

The primary endpoint will be safety, as measured by the percentage of treatments that are delivered without radiation treatment related GI/GU toxicity within 3-6 months from start of treatment. Given that the treatment plans will meet standard normal tissue constraints used for SBRT, and rigorous safety metrics need to be met before radiation is delivered, we do not anticipate any increased toxicity on this study compared to standard SBRT.

11 DATA REPORTING / REGULATORY CONSIDERATIONS

11.1 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.

11.2 REDCap

REDCap (Research Electronic Data Capture) is a free 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.

11.3 Regulatory Considerations

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

11.4 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. Data clarification forms can also be printed out when necessary to be sent to the project data manager at JCTO. 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.

12 STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

12.1.1 Primary Objectives

Safety of this approach will be determined by assessing acute GI/GU toxicity (CTCAE 5). The treatment will be deemed safe if no more than 3 patients experience a grade 4 likely radiation treatment related GI/GU (or higher) adverse event within 3-6 months from the end of treatment.

12.1.2 Secondary Objectives

Secondary objectives include quality of life (HRQOL) measures including: 1) the Expanded Prostate Cancer Index Composite (EPIC) short form questionnaire, 2) International Prostate Symptom Score (I-PSS). These will be assessed at baseline, at the 3-6 month follow-up visit and at the 9-12 month follow-up visit.
Toxicity data will also be assessed at 3-6 months and at 9-12 months follow up visit using CTCAE criteria.

12.1.3 Correlative Study Objectives

Microbiome and labs will be collected for exploratory analyses to see how radiation impacts the host microbiome and peripheral immune correlates found in blood.

12.2 Sample Size/Accrual Rate

We plan to accrue 20 patients over 2 years, or about 4-6 patients every 6 months.

12.3 Analysis of Primary and Secondary Endpoints

Primary Endpoint:

The treatment will be deemed safe if the grade 4+ likely radiation treatment related GI/GU adverse event rate is less than 10% within 3-6 months of the end of treatment. The proportion of patients that experience a >grade 3 GU/GU adverse event will be determined with a binomial

point estimate and corresponding exact 95% binomial confidence interval. If the lower bound of the interval is below 10%, the treatment will be considered safe.

Secondary Endpoints:

QOL measures at baseline and at follow up (3-6 months post treatment start, and 9-12 months) will be summarized numerically and graphically using mean (sd), median (interquartile range), or count (percent) as appropriate, and 95% confidence intervals estimated where possible. The QOL value will be plotted over time with a line for each patient and a smoothed curve super-imposed on the plot. Changes in scoring from pre- to post-treatment will also be determined. EPIC-26 overall scores as well as domain summary scores (urinary incontinence, urinary irritative/obstructive, bowel, sexual, hormonal) and individual item responses will be evaluated. Similarly, overall score as well as individual item responses will be assessed for the I-PSS survey.

Toxicity will be assessed using CTCAE 5.0 criteria at 3-6 months and 9-12 months.

These analyses will be descriptive.

Correlative study endpoints:

Microbiome
Statistical analysis of microbiome and metagenome composition will be performed in the R statistical programming environment using package *phyloseq*, which incorporates and builds upon community ecology packages such as ade4 and vegan and employs the flexible graphic system ggplot2, to easily visualize complex data relationships. For 16S data, we will evaluate the adequacy of sequencing efforts using rarefaction plots. Alpha diversity index for each will be characterized through dominance, equitability, richness, evenness. The diversity metrics will be calculated at OTU and higher taxonomical levels to best characterize the community structure. We will test for associations of each of these alpha diversity metrics with the time relative to radiation exposure, using one-way ANOVA after even-sampling the observations to a depth cut-off maximizing the number of samples and depth. In addition, rank-abundance plots will be used to visualize differences in abundance of dominant taxa in the clinical and phenotypic groups. We will utilize skyline plots to visualize the patterns of community structure in terms of relative abundances in the collected samples between before and after the radiation treatment. Similarly, for metagenomic data, skyline plots will be used to reveal functional compositions of the samples. Heat-maps will be plotted to visualize clustering patterns in the data.

We will study the evolution of microbiome over time as a consequence of the radiation treatment. The relative abundances at each taxonomical level will be first normalized by log-ratio transformation. Then the transformed relative abundance of each individual taxa at multiple time points will be fitted by the linear mixed model along with the time effect and all subject-specific characteristics as the independent covariates. For the nonlinear trend, we will combine the nature splines with linear mixed model in the data analysis. The same model will be applied on the indices calculated in the ecology microbial analysis.

CBC collection
Plasma samples will be collected at three time points: before radiation, following completion, and 3-6 months after completion. We hope to understand the impact of radiation on the distribution and frequency of peripheral immune mediators at these time points. To this effect, NLR will be numerically and graphically summarized in several ways. The average ratio at each time will be estimated, as well as average changes from baseline, and individual trajectories will be plotted in "spaghetti plots." Parallel summaries will be presented dichotomizing N/L ratio at 4%, counting the proportion of patients above this threshold at each time point.

Several markers beyond N/L ratio are of interest in order to thoroughly characterize changes throughout radiation treatment, including continuous (e.g. T cell panel and TREG panel, IL-7, IL-15, IL-6, IL-10, IL-17, IL-2 cytokines), and categorical (e.g. proliferative ability) measures. These will be summarized and analyzed in an exploratory manner in parallel methods to N/L ratio, if funding is secured for these analyses.

13 Data and Safety Monitoring Plan (DSMP)

The WCMC Data and Safety Monitoring Committee (DSMC) is the central monitoring board for this study.

13.1 Monitoring plan

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 Monitoring will occur on a yearly basis from the date the first patient is enrolled. Reports to the Data Safety and Monitoring Committee 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. 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.

13.2 Stopping rules

If more than 2 patients experience a grade 4 likely radiation treatment related adverse event, the study will suspend accrual and the study team will evaluate the adverse events to determine whether they were at least possibly related to treatment. A decision will be made with approval of the DSMB to either modify the protocol or to terminate the trial due to an unacceptable adverse event rate.

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