Adaptive stereotactic body radiation therapy to the prostate and pelvic nodes with simultaneous integrated boost to the MR-detected nodule for patients with high-risk and unfavorable intermediate-risk prostate cancer

Washington University School of Medicine
Department of Radiation Oncology
660 South Euclid Avenue, Campus Box 8224
St. Louis, MO 63110

Protocol #: 202211121
Version Date: August 16, 2024

Principal Investigator: **Amit Bhatt, MD, PhD**
Phone: (314) 747-7236
E-mail: amitb@wustl.edu

Sub-Investigators	**Modality**
Hiram Gay, MD	Radiation Oncology
Eric Laugeman, M.S.	Radiation Oncology – Physics
Jeff Michalski, M.D., MBA, FASTRO	Radiation Oncology
Yi Huang, M.S.	Biostatistics

Study Device: Ethos
NCT#: NCT05628363
Funded by: Varian

CONFIDENTIAL
The information contained in this document is regarded as confidential and, except to the extent necessary to obtain informed consent, may not be disclosed to another party unless law or regulations require such disclosure. Persons to whom the information is disclosed must be informed that the information is confidential and may not be further disclosed by them.

Adaptive stereotactic body radiation therapy to the prostate and pelvic nodes with simultaneous integrated boost to the MR-detected nodule for patients with high-risk and unfavorable intermediate-risk prostate cancer

Protocol Revision History

Initial Approval Version	**10 November 2022**
Amendment #1 Version	**04 April 2023**
Amendment #2 Version	**07 September 2023**
Amendment #3 Version	**19 April 2024**
Amendment #4 Version	**16 August 2024**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Table of Contents

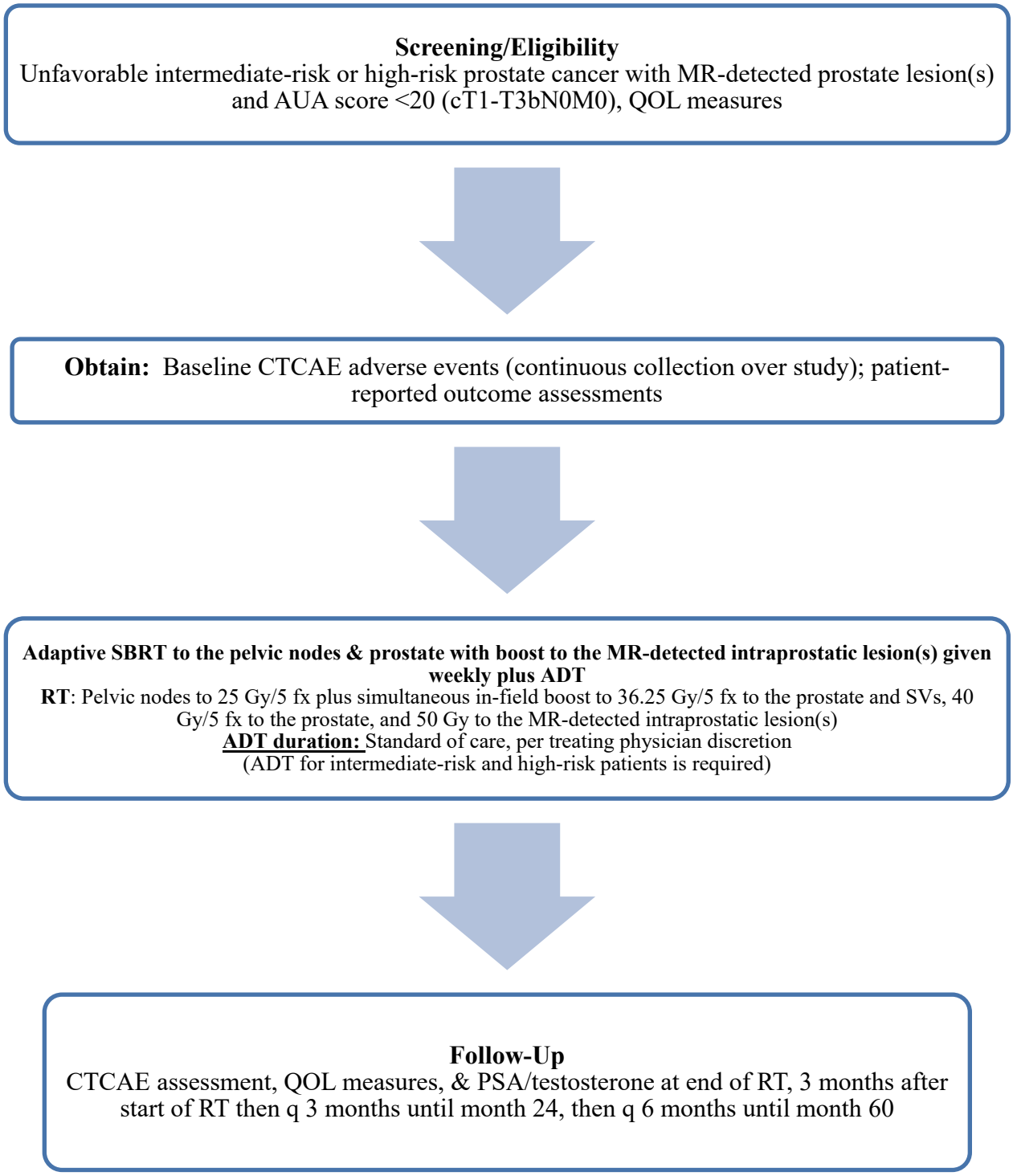
PROTOCOL SUMMARY

Title:	Adaptive stereotactic body radiation therapy to the prostate and pelvic nodes with simultaneous integrated boost to the MR-detected nodule for patients with high-risk and unfavorable intermediate-risk prostate cancer
Study Description:	This trial is a prospective clinical trial designed to demonstrate the safety and feasibility of whole-pelvis adaptive prostate SBRT with a tumor boost to the MR-detected sites of disease. The hypothesis is that this treatment approach will be safe and feasible with <15% of patients experiencing an acute CTCAEv5 grade ≥3 GU or GI adverse event.
Objectives:	Primary Objective: To demonstrate that rates of acute grade ≥3 GI and GU adverse events associated with adaptive prostate SBRT is acceptable (≤15%). Secondary Objectives: 1. To assess patient-reported quality of life changes after adaptive SBRT treatment using EPIC-26 based on comparison to historical controls 2. To determine change in global function after treatment using EQ-5D-5L patient-reported outcome assessment tool 3. To assess physician-reported acute GI/GU CTCAE toxicities and any other acute grade ≥3 AE at least possibly related to radiotherapy Exploratory Objectives: 1. To assess physician-reported late GI/GU CTCAE toxicities and any other late grade ≥3 AE at least possibly related to radiotherapy 2. To assess biochemical recurrence-free survival 3. To assess failure free survival 4. To assess metastasis-free survival 5. To assess prostate cancer-specific mortality 6. To assess overall survival 7. To assess whether the adaptive plan resulted in an improvement in target coverage and/or reduction in dose to critical organs at risk (e.g. rectum, bladder, sigmoid, bowel, penile bulb, femurs) compared to the non-adaptive plan across the course of treatment 8. To assess whether organ-at-risk constraints can be met with a goal of achieving at least >95% of the GTV getting >45 Gy (>112.5% of the 40 Gy prescription dose) and to assess the percentage of the GTV receiving full prescription dose (50 Gy)

	9. To determine the workflow feasibility of adaptive SBRT for prostate cancer (including measuring time on table and frequency of using the adapted vs. original treatment plan for each fraction)
Endpoints:	Primary Endpoint: Rate of acute grade ≥3 GI and GU adverse events within 90 days from the start of radiotherapy (as assessed during weekly on-treatment visits and at the first follow-up visit) Secondary Endpoints: 1. Changes in patient-reported quality of life using EPIC-26. 2. Change in global function after treatment using EQ-5D-5L patient-reported outcome assessment tool 3. Acute GI/GU CTCAE toxicities and any other acute grade ≥3 AE possibly related to radiotherapy Exploratory Endpoints: 1. Late GI/GU CTCAE toxicities and any other late grade ≥3 AE possibly related to radiotherapy 2. Biochemical recurrence free-survival 3. Failure-free survival 4. Metastasis-free survival 5. Prostate cancer-specific mortality 6. Overall survival 7. Dose volume histogram comparison of organs at risk and PTVs a. PTV_4000 V112.5 % > 95% of 40 Gy b. PTV_pX_5000 V100% 8. Workflow feasibility as defined by: a. Time on table b. Fractions adapted versus total fractions
Study Population:	Twenty-five toxicity evaluable adult patients with NCCN high-risk or unfavorable intermediate-risk histologically confirmed adenocarcinoma of the prostate who have not undergone radical prostatectomy or lymph node dissection and who are candidates for definitive radiation therapy and androgen deprivation therapy will be enrolled in this study.
Phase:	N/A
Description of Sites / Facilities Enrolling:	This study will be active at Siteman Cancer Center at Washington University School of Medicine.
Description of Study Intervention:	Treatment consists of adaptive dose-escalated stereotactic body radiotherapy (SBRT) to the pelvic nodes to 25 Gy in 5 once or twice weekly fractions with simultaneous integrated boosts (SIB) to the prostate and proximal seminal vesicles to 36.25 Gy in 5 fractions (full seminal vesicles if involved), to the prostate to 40 Gy in 5

	fractions, and to the involved MR-detected nodule(s) to up to 50 Gy in 5 fractions. Adaptive radiotherapy will allow for safe dose escalation by reducing dose to the organs at risk (especially the bladder wall, rectal wall, and urethra), target the lesion with greater accuracy, and improve overall plan quality. All treatments will be delivered on the Ethos Varian treatment system using an online adaptive approach with SBRT-based treatment planning.
Study Duration:	30 months (recruitment) + 5 weeks (treatment) + 60 months (follow-up) + 12 months (analysis)
Participant Duration:	Approximately 5 years (5 weeks of treatment + 5 years of follow-up)

SCHEMA



Primary Outcome: Acute grade ≥3 GI/GU adverse events

SCHEDULE OF ACTIVITIES

All screening assessments must take place no more than 120 days prior to the start of registration except as noted.

	Screening	**Weekly During RT (Week 1-4)**	**End of RT[7](Week 5)**	**3 months after start of RT (±1 wk)**	**Q3 months until Month 24 (±2 wks)**	**Q6 months until Month 60 (±1 mon)**
Informed consent	X					
H&P (incl. wt, BP)	X		X[5]	X	X	X
Bone imaging[1]	X					
3T MRI of the prostate[8]	X					
Decipher testing	X[4]					
PSA, testosterone	X			X	X	X
ECOG PS	X		X	X	X	X
Concomitant medications	X					
QOL questionnaires[2]	X		X	X	X	
Acute GI and GU adverse event (AE) assessment	X		X	X		
Late AE assessment[3]					X	X
Online adaptive SBRT		X[6]				

1. Either bone scan or prostate cancer-specific PET/CT scan (fluciclovine F-18 PET, gallium-68 PSMA PET, F-18 PSMA PET, or C-11 or 4-18 choline PET)
2. EPIC-26 (Appendix F), EQ-5D-5L (Appendix G)
3. Late AEs are defined as those occurring more than 90 days after the start of RT.
4. Decipher testing is recommended for all patients.
5. Blood pressure does not need to be checked at the end of RT.
6. Online adaptive SBRT is delivered once or twice weekly on the Ethos machine over a total of 5 weeks (barring treatment delays) as described in Section 5. SBRT must start no later than 60 days after the start of ADT.
7. To be completed within +/- 5 days of completion of RT.
8. A PET/CT can be substituted in place of an MRI for baseline planning.

1.0 INTRODUCTION

1.1 Study Rationale

This study aims to leverage the power of adaptive radiotherapy on Ethos to advance prostate cancer radiation therapy to the next level. In this study, high-risk and unfavorable intermediate-risk prostate cancer patients will receive adaptive dose-escalated stereotactic body radiotherapy (SBRT) to the pelvic nodes to 25 Gy in 5 once or twice weekly fractions, with a simultaneous integrated boost (SIB) to the prostate to 40 Gy in 5 fractions and another SIB to up to 50 Gy to the involved MR-detected nodule(s). Adaptive radiotherapy will allow dosing to be safely escalated by reducing dose to the organs at risk (especially the bladder wall, rectal wall, and urethra), targeting the lesion with greater accuracy, and improving overall plan quality. Preliminary results using prostate adaptive SBRT on Ethos to treat 7 patients demonstrated a statistically significant improvement in target coverage to the planned tumor volume (PTV) with a simultaneous 2 Gy reduction in the maximum dose to the rectum, which was significant regardless of whether patients had rectal hydrogel in place or not.

1.2 High-Risk Prostate Cancer

High-risk prostate cancer patients treated with definitive external beam radiation therapy commonly receive standard fractionation to the prostate and seminal vesicles to 79.2 Gy in 44 fractions with IMRT plus long-term androgen deprivation therapy. Many of the large randomized trials in high-risk disease are looking to improve the treatment paradigm by enhancing the systemic therapy or tailoring treatment based on genomic classifiers. However, efforts to improve the quality and effectiveness of radiation therapy for higher-risk disease are important considerations as well. Exciting avenues for investigation to improve radiotherapy quality and convenience include the following: 1) elective nodal radiation to prevent nodal recurrences; 2) dose escalation to the MR-detected lesions; 3) extreme hypofractionation with SBRT; and 4) daily online adaptive radiation therapy to reduce dose to the organs at risk and improve target coverage.

1.2.1 Elective nodal radiation

Several recent studies support the use of elective nodal radiation for high-risk prostate cancer. The POP-RT randomized trial of prostate only vs. pelvic nodal plus prostate RT from Tata Memorial Hospital reported a statistically significant improvement in biochemical recurrence-free survival and distant metastasis-free survival in favor of elective pelvic nodal RT (Murthy, JCO, 2021) using standard fractionation RT. While 80% of the patients on this trial were staged as cN0 by PSMA PET/CT scan, a recent retrospective study from Washington University in St. Louis of seven patients with unfavorable intermediate-risk or high-risk disease with conventional staging found that pelvic nodal RT was associated with improved overall survival for patients with Gleason 9-10 disease or a ≥10% risk of nodal involvement. Elective pelvic nodal RT is already a standard-of-care approach and is likely to be more widely adopted in the future.

1.2.2 Tumor boost to the MR-detected lesion(s)

Dose-escalated radiation therapy has been shown to improve biochemical control for patients with intermediate and high-risk prostate cancer (Michalski 2019; Morris 2017). Whole-gland dose-escalation with external beam radiation therapy (EBRT) is safe and effective up to 80 Gy with standard fractionation, but doses to the whole gland beyond 80 Gy with external beam radiation are associated with higher toxicity (Beckendorf 2011; Kuban 2008). Whole-gland dose escalation >80 Gy can be achieved with a brachytherapy boost to the whole gland in combination with external beam radiotherapy, and this approach improved biochemical control vs. EBRT without brachytherapy on the ASCENDE RT trial (Morris 2017). However, grade 3 GU toxicity was considerably higher for patients treated with the brachytherapy boost (18% vs. 5%, $p<0.01$) (Rodda 2017), and patient access for this treatment is more limited because of the special expertise and equipment to perform the procedure and the anesthesia requirements which complicate treatment delivery.

A focal boost using external beam radiation therapy to the MR-detected intraprostatic disease has been proposed as a way to improve disease control without the added toxicity of whole-gland dose escalation. There is great interest in this approach as local failure in the prostate as the first site of failure is the predominant pattern of failure after standard dose-escalated whole-gland EBRT, with rates of 10%-15% for unfavorable intermediate-risk disease (Zumsteg 2015). Most local failures occur at the primary tumor site (Cellini 2002). The FLAME trial tested a concurrent focal tumor boost to the MR-detected site(s) of disease in a cohort of mostly high-risk prostate cancer patients treated with standard fractionation and found a statistically significant improvement in biochemical control in favor of the micro-boost arm with no significant difference in toxicity (Kerkmeijer 2021). The FLAME trial also reported that a focal tumor boost was associated with a statistically significant improvement in regional and distant metastasis-free survival (cite).

1.2.3 Stereotactic body radiation therapy

Stereotactic body radiation therapy (SBRT) is gaining in popularity and was recently added to the NCCN guidelines as an acceptable treatment option for high-risk disease. SBRT offers improved convenience for the patient, potential radiobiologic advantages, and promising toxicity outcomes, with late grade 3 GU and GI toxicity of 2.0% and 1.1%, respectively, from a large pooled analysis of prostate SBRT patients (Jackson 2019). While SBRT is being used more commonly for intermediate and high-risk disease, the publication of the Tata Memorial study means that SBRT will likely have to evolve to include pelvic nodal RT for high-risk patients. While there is some data on prostate SBRT including the pelvic nodes, data is limited. The trials reported by Alayed (IJROBP, 2020) demonstrated the feasibility of whole-pelvis prostate SBRT to 25 GY to the pelvic

nodes with a simultaneous integrated boost to the prostate to 40 Gy. In addition, there is great interest in treating patients with SBRT using a tumor boost approach. The HypoFlame trial looked at a similar patient population treated with SBRT to 35 Gy in 5 weekly fractions with a simultaneous boost to up to 50 Gy to the MR-detected nodule. Median dose to the nodule was 44 Gy. The primary endpoint was adverse events and the study reported acceptable acute GI/GU toxicity (Draulans, Radiother & Oncol, 2020) with very low rates of grade 3 adverse events.

1.2.4 Adaptive prostate SBRT

Another exciting area that needs further exploration is adaptive prostate SBRT. Early results of a trial of adaptive SBRT using MR-guided radiotherapy have been reported, though the treatment dose was relatively conservative (36.25 Gy in 5 every-other-day fractions, the current NRG standard) (Bruynzeel, IJROBP, 2019). Online adaptive radiation therapy allows us to dynamically adapt the target structure and the organs at risk based on daily changes in the patient's anatomy, ensuring that the treatment plan optimizes dose to the target with sparing of the organs at risk.

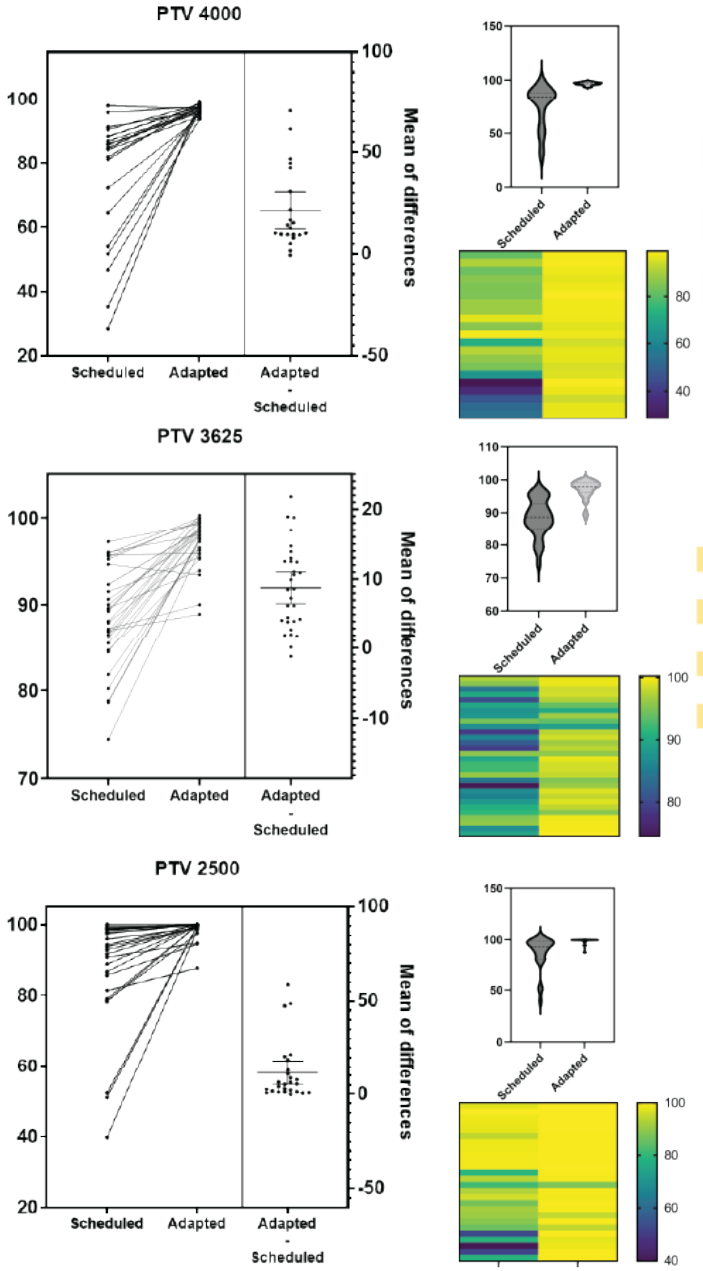
1.3 Study Intervention – Ethos Treatment Planning Platform

Varian's Ethos treatment planning platform (Palo Alto, CA) offers an innovative, highly functional platform for rapid, high-quality adaptive radiotherapy to fit the needs of the clinic to treat prostate SBRT patients. The Ethos CBCT and auto-contour adjustment features allow for adaptive treatments to be delivered safely and effectively in a relatively short amount of time. Prior to each treatment, patients undergo a high-quality CT scan on the treatment machine. The system uses an artificial intelligence algorithm to rapidly generate auto-contours of the relevant normal tissues which are then reviewed by the physician at the machine prior to each treatment. The system also allows the target structures to be accurately propagated to the daily CT scan. Together, these structures are then used to generate a treatment plan that can maximize dose to the target while minimizing dose to the normal tissues, accounting for how the patient's anatomy looks on that particular day and at that particular time with respect to bladder and rectum filling.

1.4 Preliminary Data using Ethos online adaptive prostate SBRT

In a preliminary analysis of seven patients treated with adaptive SBRT to the whole pelvis to 25 Gy in 5 fractions with a simultaneous integrated boost to the prostate and seminal vesicles to 36.25 Gy in 5 fractions and to 40 Gy to the prostate, we found that adaptive planning resulted in significantly improved prescription coverage of the PTV as well as significant reduction in the D0.035cc of the rectum (Waters, ASTRO, 2022) when comparing the adaptive treatments vs. the scheduled plan.

For the adapted plans, the average V100 (% of the target volume receiving 100% of the prescription dose) for the PTV_3625 was 97.2%, an 8.8% improvement over the average



ID	AVERAGE SCHEDULED	AVERAGE ADAPTED	DIFFERENCE
1	74.30%	94.90%	20.60%
3	84.76%	97.40%	12.64%
4	89.18%	97.93%	8.75%
5	86.82%	95.82%	9.00%
7	43.24%	96.40%	53.16%

ID	Average Scheduled	Average Adapted	Difference
1	79.50%	95.70%	16.20%
2	91.79%	99.97%	8.17%
3	89.46%	98.56%	9.10%
4	92.53%	98.60%	6.08%
5	89.26%	92.54%	3.28%
6	84.20%	97.20%	13.00%
7	88.42%	97.82%	9.40%

ID	Average Scheduled	Average Adapted	Difference
1	98.65%	100.00%	1.35%
3	98.94%	99.82%	0.88%
4	97.30%	99.87%	2.57%
5	88.74%	97.66%	8.92%
6	60.00%	99.06%	39.06%
7	88.64%	96.96%	8.32%

Figure 1. *Coverage of PTV comparing scheduled and adapted plans (V100). (**A**) Paired differences between scheduled and adapted plans. (**B, top**) Violin plots of V100 distribution between scheduled and adapted plans. (**B, bottom**) Heatmap of changes in V100 coverage between scheduled and adapted fractions. (**C**) Individual patient 5 fraction averages between scheduled and adapted V100.*

V100 for the scheduled plan of 88.4%. At the individual patient level, the 5-fraction average V100 for the adapted plan ranged from 92.5% to 100% vs. 79.5% to 92.5% for the scheduled plan. For the adapted plans, the average V100 for the PTV_4000 was 96.7% compared to 75.2% for the scheduled plan, an improvement of 21.5%. At the individual patient level, the 5-fraction average V100 for the adapted plan for PTV_4000 ranged from 94.9 – 97.9% vs. 43.2% - 89.2% for the scheduled plan. For the adapted plans, the average V100 for the PTV_2500 was 98.7% vs. 87.2% for the average V100 for the scheduled plans, an improvement of 11.5%. At the individual patient level, the 5-fraction average V100 for the adapted plan for PTV_2500 was 96.9% - 100% vs. 60.0 – 98.9% for the scheduled plans (Figure 1).

All of the V100 PTV differences between adapted and scheduled plans were statistically significant. No clinical factors, including presence of rectal hydrogel spacer were significantly associated with changes in PTV coverage as assessed by multivariable linear regression; however, BMI was inversely correlated with both adapted and scheduled PTV_3625, and positively correlated with the difference between scheduled PTV_3625 and adapted PTV_3625.

With regards to organs at risk, mean rectal D0.03cc was significantly reduced by 38.8 cGy ± 5.95 cGy ($p<0.0001$) per fraction (194 cGy/5 fractions) with the adapted vs. the scheduled plans (Figure 2). Bladder dose was increased with the adapted plans, 10.9 cGy ± 4.93 cGy per fraction (55 cGy/5 fractions) ($p<0.0424$). Though bladder dose was increased with the adaptive plans, bladder dose constraints were met for all of the adaptive treatment plans. There were no statistically significant differences between sigmoid or bowel dose comparing the adapted vs. the scheduled plans. No patients experienced acute CTCAE grade ≥3 GI/GU adverse events with a median follow up of 9.5 months.

Structure	Scheduled	Adapted	p-value
Rectum	805.2	766.4	<0.0001
Bladder	822.4	833.3	0.0424
Sigmoid	536	543.1	0.0603
Bowel	536.8	540.4	0.3355

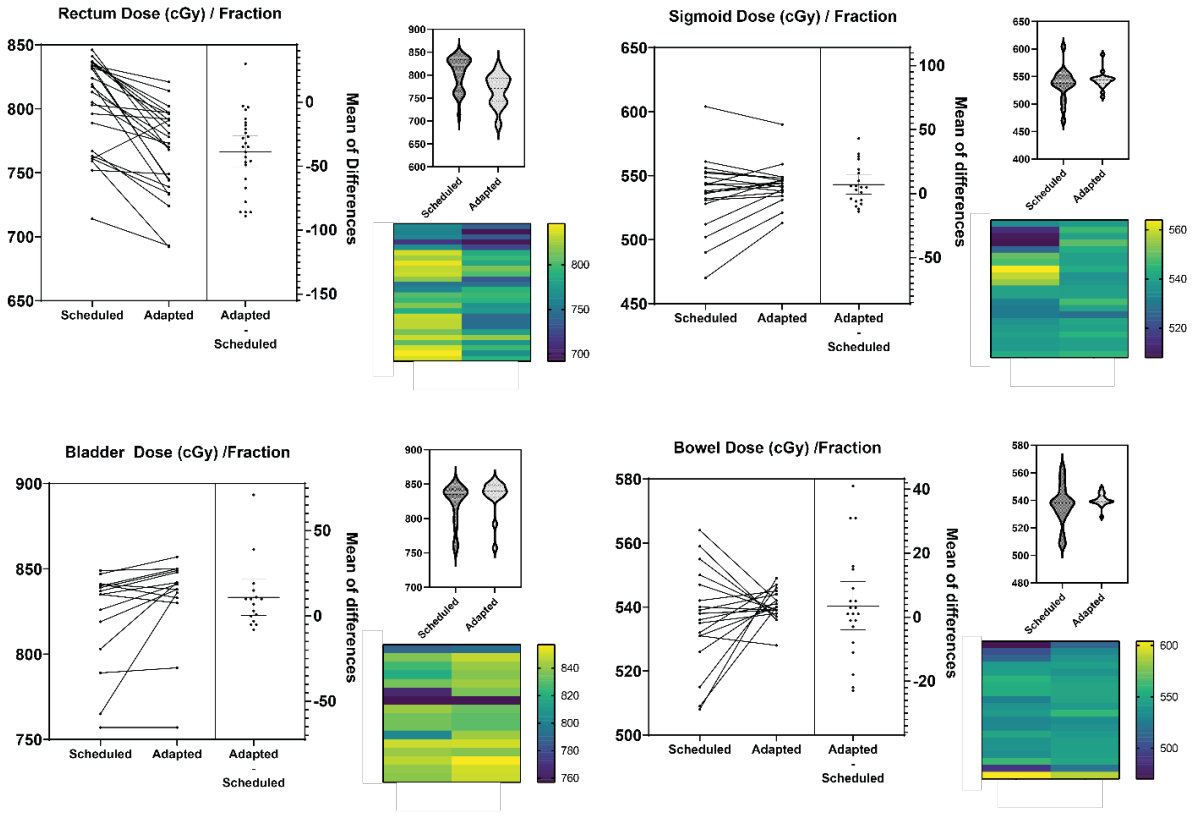


Figure 2*. OAR dosimetry between scheduled vs adapted plans. (**A**) Differences between average per fraction dose between scheduled and adapted plans for given OARs. (**B**) Paired individual fraction Dmax0.03 differences between scheduled and adapted plans, violin plots of Dmax0.03 distribution between scheduled and adapted plans. Heatmap of changes in Dmax0.03 between scheduled and adapted fractions.*

These promising results in a small retrospective pilot study showing improvement in PTV coverage as well as reduced dose to the rectum with the adaptive treatment plan provide the rationale for a larger, prospective study investigating this approach. The adaptive approach is ideally suited for further dose escalating radiation to the MR-detected nodule, which has emerged as a new standard-of-care approach with the publication of the Flame trial.

1.5 Study Design

1.5.1 Overall Design

This is a single-arm prospective clinical trial designed to demonstrate the safety and feasibility of whole-pelvis adaptive prostate SBRT with a tumor boost to the MR-detected sites of disease. The hypothesis is that this treatment approach will be safe and feasible with ≤15% rate of acute grade ≥3 GU and GI adverse events using CTCAEv5.

1.5.2 Scientific Rationale for Study Design

The study is designed as a prospective study to assess the safety/feasibility of this approach. While the Flame trial established a focal boost dose to the intraprostatic lesion(s) as a relatively safe and effective option, the Flame trial used conventional fractionation and did not assess this approach for SBRT patients. The study that did investigate an SBRT boost dose to 50 Gy in 5 fractions (HypoFlame) did not also include elective nodal radiation. We are encouraged that safety/toxicity for HypoFlame was favorable but we need to confirm this in the present study.

1.5.3 Justification for Dose

The doses are taken from the recently opened NRG Oncology GU 010 protocol for patients with unfavorable intermediate-risk prostate cancer and the NRG GU 009 protocol for patients with high-risk prostate cancer. For patients on both trials, elective nodal RT can be performed in combination with SBRT with a recommended dose of 25 Gy in 5 fractions. This is also a standard dose when treating the pelvic nodes for short-course radiation for rectal cancer, with a long track record of safety. The dose to the prostate and seminal vesicles (36.25-40 Gy in 5 fractions) is consistent with NRG 009 and GU 010 as well as current NCCN guidelines. The boost dose to 50 Gy in 5 fractions to the intraprostatic dominant lesion is taken from the HypoFlame trial. This is also the dose for the focal tumor boost that is being used in the NRG GU 010 protocol. 50 Gy in 5 fractions is an effective ablative dose that is used for multiple other malignancies (hepatocellular carcinoma, lung cancer).

1.6 Risk/Benefit Assessment

1.6.1 Known Potential Risks

The known potential risks from this treatment are the same potential risks involved with prostate and pelvic nodal radiation. Acute risks include fatigue, urinary side effects (urinary urgency, frequency, weak stream, increased nocturia, dysuria, hematuria, urinary obstruction) and GI side effects (diarrhea, tenesmus, rectal pain, constipation, rectal bleeding, decreased appetite). Late side effects include long-term changes in GI/GU side effects which include those mentioned in the acute side effects above, as well as erectile dysfunction. More rare but serious late side effects include risk of second cancers, hip/pelvic insufficiency fractures, bowel obstruction, bleeding, perforation, rectal bleeding, dysuria, hematuria, severe urinary urgency/frequency, urinary obstruction. Given that patients would be

treated with dose escalated radiation therapy, the risk of any of these acute or late side effects would be increased somewhat. However, to mitigate risk, the trial requires that each treatment meets strict dose constraints for critical organs at risk. Coverage of the target will be reduced to ensure that dose to critical structures is not exceeded.

1.6.2 Known Potential Benefits

Potential benefits include potential for decreased risk of cancer recurrence from the tumor boost and decreased side effects from androgen deprivation therapy as high-risk patients have the option to be treated on this study with less than 2 years of ADT. Less than 2 years of ADT in combination with dose-escalated radiation therapy is reasonable as this was the approach used on the ASCENDE-RT trial of external beam radiation +/- brachytherapy boost, which reported excellent results for cancer control for the external beam plus brachytherapy boost cohort (better than historical controls treated with EBRT plus 2 years of ADT). ADT has been shown to significantly decrease patient quality of life, leads to weight gain, decreased muscle mass and bone density, loss of libido and erectile function, decreased energy, worsening heart disease, dementia, depression, gynecomastia, among others. Patients will also benefit as the treatment is shorter and more convenient, decreasing inconvenience and financial toxicity for patients.

1.6.3 Assessment of Potential Risks and Benefits

In our opinion, the potential benefits of reduced cancer risk, decreased exposure to ADT, and reduced financial toxicity from a short-course of treatment outweigh the potential risks of increased adverse events. The study is a "safety-first" trial that prioritizes meeting the dose constraints for normal tissues ahead of delivering dose to the target(s).

2.0 OBJECTIVES AND ENDPOINTS

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
To demonstrate that rates of acute grade ≥3 GI and GU adverse events associated with adaptive prostate SBRT are acceptable (≤15%).	Rate of acute grade ≥3 GI and GU adverse events within 90 days from the start of radiotherapy (as assessed during weekly on-treatment visits and at the first follow-up visit)	Grade 3 toxicities are associated with emergency room visits and/or hospitalizations, thus ensuring low rates of grade 3 adverse events is important.
Secondary		

1. To assess patient-reported quality of life changes after adaptive SBRT treatment using EPIC-26 based comparison to historical controls	Minimal clinically important change (MCID) for EPIC 26 QOL instrument for GI and GU and erectile domains from screening to end of radiation treatment, 3 months after start of radiation treatment, and at each 3 month follow-up until Month 24	EPIC 26 is a validated measure of prostate-cancer specific patient-reported outcomes
2. To determine change in global function after treatment using EQ-5D-5L patient-reported outcome assessment tool	Minimal clinically important change (MCID) in EQ-5D-5L QOL instrument from screening to end of radiation treatment, 3 months after start of radiation treatment, and at each 3 month follow-up until Month 24	EQ-5D-5L is a validated measure of patient-reported global functioning.
3. To assess physician reported acute GI/GU CTCAE toxicities and any other acute grade ≥3 AE at least possibly related to radiotherapy	Acute GI/GU AEs less than grade 3 will be collected as well as any other acute grade ≥3 AEs at least possibly related to RT.	Criterion standard assessment for physician-reported adverse events.
Exploratory		
1. To assess physician reported late GI/GU CTCAE toxicities and any other late grade ≥3 AE at least possibly related to radiotherapy	Late GI/GU AEs (defined as those occurring 91 days or more after the start of RT) will be collected along with other late grade ≥3 AEs at least possibly related to RT.	Criterion standard assessment for physician-reported adverse events.
2. To assess biochemical recurrence-free survival	Biochemical recurrence-free survival (time from start of radiotherapy to recurrence of prostate cancer by PSA criteria or radiographically)	Important oncologic endpoint.
3. To assess failure-free survival	Failure-free survival – Time from start of radiotherapy to biochemical relapse, radiographic recurrence with	See above.

	development of local, regional or distant metastases, or death to due to any cause	
4. To assess metastasis-free survival	Metastasis-free survival – Time from start of radiotherapy treatment to radiographic diagnosis of metastatic disease (M1 disease) or death from any cause	See above.
5. To assess prostate cancer-specific mortality	Prostate cancer-specific mortality – Time from start of radiotherapy to death due to prostate cancer.	See above.
6. To assess overall survival	Overall survival – Time from start of radiotherapy to death from any cause	See above.
7. To assess whether the adaptive plan resulted in an improvement in target coverage and/or reduction in dose to critical organs at risk (e.g. rectum, bladder, sigmoid, bowel, penile bulb, femurs) compared to the non-adaptive plan across the course of treatment	Dose volume histogram comparison of organs at risk and PTVs	Dosimetry metrics
8. To assess whether organ-at-risk constraints can be met with a goal of achieving at least >95% of the GTV getting >45 Gy (>112.5% of the 40 Gy prescription dose) and to assess the percentage of the GTV receiving full prescription dose (50 Gy)	PTV_4000 V112.5 % > 95% of 40 Gy PTV_pX_5000 V100%	Dosimetry metrics.
9. To determine the workflow feasibility of adaptive SBRT for prostate cancer (including measuring time on table and frequency of using the adapted vs. original treatment plan for each fraction)	Time on table. This study will be determined to be feasible if the total time on table for patients does not exceed 90 minutes. Fractions adapted versus total fractions. The study will be feasible if more than 90% of	Workflow efficiency metrics

	patients successfully receive an adapted fraction.	

3.0 STUDY POPULATION

3.1 Inclusion Criteria

In order to participate in this study, a patient must meet all of the criteria listed in this section:

1. Pathologically proven adenocarcinoma of the prostate with NCCN high-risk disease or NCCN unfavorable intermediate-risk disease.

2. Patients with unfavorable intermediate-risk disease must meet the following criteria:
   a. At least one intermediate risk factor (IRF):
      i. PSA 10-20 ng/mL
      ii. cT2b-c (AJCC 8th ed.)
      iii. Gleason score 7
   b. At least one "unfavorable" intermediate-risk identifier:
      i. > 1 IRF
      ii. Gleason score 4+3
      iii. ≥ 50% of biopsy cores positive
   c. NO high-risk features

3. Patients with high-risk disease must meet at least one of the following criteria:
   a. cT3a-T3b
   b. PSA > 20
   c. Gleason score ≥ 8

4. MRI scan of the prostate with at least one MR-detectable lesion in the prostate/seminal vesicles. PET/CT which is found to display activity in the prostate consistent with prostate cancer may be substituted per investigator discretion.

5. Planning to undergo concurrent whole-pelvis SBRT and androgen deprivation therapy (ADT). ADT may be initiated at any time per institutional standard, so long as ADT begins within 60 days of the start of radiotherapy.

6. At least 18 years of age.

7. ECOG performance status ≤ 1 (Appendix C).

8. Agreement to adhere to Lifestyle Considerations throughout study duration (see Section 3.4).

9. Able to complete relevant patient-reported quality-of-life questionnaires in the opinion of the treating physician.

10. Able to understand and willing to sign an IRB approved written informed consent document.

3.2 Exclusion Criteria

In order to participate in this study, a patient must not meet any of the criteria listed in this section:

1. Definitive radiologic evidence of nodal (cN+) or metastatic (cM1) disease on conventional imaging (bone scan) or prostate cancer-specific PET/CT scan (NaF PET/CT, Axumin PET/CT, fluciclovine, choline, or PSMA PET/CT scan). Patients with lymph nodes ≥ 1 cm on short axis are ineligible unless the lymph node is read as benign by Radiology.

2. Prior androgen deprivation therapy. (If the onset of androgen ablation is ≤ 60 days prior to treatment start, the patient is eligible.) Baseline PSA and testosterone must be obtained prior to start of treatment.

3. Systemic chemotherapy within 3 years prior to treatment start.

4. Prior radical prostatectomy, pelvic lymph node dissection, prostate cryotherapy, or high-intensity focused ultrasound (HIFU) to the prostate.

5. Prior pelvic radiotherapy.

6. Presence of baseline CTCAE grade ≥ 2 GI or GU toxicity that does not resolve to grade 1 or less with appropriate intervention.

7. cT4 disease.

8. American Urologic Association (AUA) urinary symptom score ≥ 20 (See Appendix B).

9. Prostate gland measuring >90 cc.

10. Unable to get prostate fiducial markers placed for image guided radiation treatment. Rectal hydrogel is optional and is left to the discretion of the treating physician.

11. Hip prosthetic that does not allow for treatment planning visualization.

12. Prior malignancy (except for non-melanoma skin cancer) unless disease-free for at least 2 years. Patients are not eligible if they have had a prior pelvic malignancy (e.g. bladder cancer, rectal cancer).

13. Prior transurethral resection of the prostate (TURP) within 3 months prior to registration.

14. Uncontrolled intercurrent illness precluding RT and/or ADT including, but not limited to, seizures, myocardial infarction in the past 6 months, current severe or unstable angina pectoris, congestive heart failure requiring hospitalization in the past 6 months, uncontrolled active infection, uncontrolled hypertension, or any condition that in the opinion of the investigator would preclude participation in the study.

15. History of uncontrolled inflammatory bowel disease, including ulcerative colitis and Crohn's disease.

16. Presence of anal fissure or history of bowel or bladder fistula.

17. Scleroderma. Patients who are moderately symptomatic from other autoimmune diseases or patients on biologic therapies for autoimmune diseases are also excluded.

18. Known history of HIV or chronic hepatitis B or C. Testing to evaluate for the presence of HIV and/or hepatitis B or C is not required in patients who do not carry the diagnosis.

19. Poorly visualized bladder and bowel on diagnostic CT or CT simulation (either due to body habitus or artifact).

20. Unable to spend 30 minutes lying on the radiation therapy treatment couch due to significant urinary frequency/urgency or other comorbidities.

3.3 Inclusion of Women and Minorities

Men and transgender women who have prostate cancer and members of all races and ethnic groups are eligible for this trial.

3.4 Lifestyle Considerations

Patients must agree to use condoms (even if S/P vasectomy) and another effective method of birth control if engaging in heterosexual intercourse with a woman of childbearing potential. Patients must agree to use condoms if engaging in heterosexual intercourse with a woman who is pregnant. These restrictions are in place throughout treatment and for 3 months following the last radiation treatment.

4.0 REGISTRATION AND ENROLLMENT PROCEDURES

The following steps must be taken before enrolling patients on this study:

1. Registration of consented patient in the Siteman Cancer Center OnCore database

2. Assignment of unique patient number (UPN)
3. Confirmation of patient eligibility

Patients must not start any protocol intervention or procedures prior to signing of informed consent.

4.1 Registration in OnCore Database

Patient registration to the Siteman Cancer Center OnCore database must occur within one business day of the patient signing consent.

4.2 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.3 Confirmation of Patient Eligibility and Enrollment

Patient eligibility will be confirmed using the information listed below:

1. Completed eligibility checklist, signed and dated by a member of the study team
2. Copy of appropriate source documentation confirming patient eligibility

4.4 OnCore Subject Status Definitions

Note: subject status should not be updated in OnCore until the subject is actively in that status; future dates are not allowed.

Subject Status	Definition
Consented	Patient has signed an IRB approved consent for the trial.
Eligible	Patient eligibility has been confirmed by Washington University PI or delegate.
Not Eligible	Patient did not meet eligibility criteria for the trial. Note that if a patient is determined to be eligible but never initiates study participation, they are not considered a screen fail.
On Study	Patient is confirmed eligible for the study and enrolled.
On Treatment	Patient is receiving study therapy. On Treatment date should be the date of the first study treatment.
Off Treatment	Patient has discontinued study therapy. Off Treatment date should be the last day any study treatment was administered.
On Follow Up	Patient has completed RT and entered the protocol-required follow-up.
Off Study	Patient has fully discontinued all study procedures (including any follow-up procedures and/or review of medical record for outcomes data).

4.5 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently entered in the study (status of On Study). A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.6 Strategies for Recruitment and Retention

Patients will be evaluated for enrollment by Washington University radiation oncologists at the main Barnes and the satellite facilities. Clinical research associates will also assist in pre-screening new consult visits for potential eligibility. Most unfavorable intermediate-risk and high-risk patients will be eligible. In our experience, patients are very interested in the idea of adaptive radiation therapy as a way to give a more personalized and potentially less toxic treatment that adjusts for differences in their anatomy each day. We think this will help to boost recruitment. In addition, since patients will be treated with a much shorter course of treatment (5 fractions), than we currently offer off-trial when treating the elective nodes (28-44 fractions), we think the added convenience and reduced financial toxicity will help with patient recruitment and retention. In addition, we think that patients will be willing to travel from a greater distance to be treated on this trial given that fewer treatments are involved, allowing us to recruit patients for the study who may not have elected to receive their treatment at WashU. We will work hard to identify potential minority patients for accrual and will work with patient advocates to develop a strategy to improve recruitment of all patients, including minority patients.

5.0 TREATMENT PLAN

5.1 Study Intervention

5.1.1 Treatment Targets

The prostate and at least the proximal 1 cm of the seminal vesicles and elective nodes must be treated. The prostate should receive full prescription dose (40 Gy). The MR-detected dominant intraprostatic lesion (DIL) will be prescribed a dose of 50 Gy but the delivered dose will be reduced as necessary to meet organ at risk dose constraints, with target coverage sacrificed to meet critical OAR constraints. Given the proximity of the seminal vesicles to the bowel for some patients, the seminal vesicles may receive less than full prescription dose in order to meet normal tissue constraints. Ideally any gross disease in the seminal vesicle should receive full prescription dose.

Radiotherapy treatment will consist of **once or twice weekly treatment** with stereotactic body radiation therapy given over 5 weeks (total of 5 fractions). During each treatment, 4 separately defined targets will be simultaneously treated, each to a different dose, using a simultaneous integrated boost technique. The targets include 1) the elective pelvic lymph nodes, 2) the prostate and seminal vesicles, 3) the prostate plus gross disease, 4) MR-detected prostate lesion(s). The dose levels and target volumes are summarized as follows:

- 25 Gy in 5 fractions: elective pelvic nodes (up to the aortic bifurcation at ~L4/L5)
- 36.25 Gy in 5 fractions: prostate and proximal 1-1.5 cm of seminal vesicles or prostate and full seminal vesicles (if seminal vesicles are involved or if full seminal vesicle coverage is recommended by the treating physician)
- 40 Gy in 5 fractions: Prostate plus gross disease
- 50 Gy in 5 fractions: MR-detected lesion(s)

All treatments should be delivered on the Ethos Varian treatment system using an online adaptive treatment approach with SBRT-based treatment planning (using Arc therapy or fixed beam IMRT).

5.1.2 EBRT Immobilization and Target Localization

Patients will be positioned supine on a flat tabletop. Patient setup reproducibility must be achieved using appropriate clinical devices using an alpha cradle, vac lock or similar device. For particularly obese patients where an alpha cradle is not advisable, it is acceptable to treat these patients flat on the tabletop but all efforts should be made to ensure immobilization and reproducibility (e.g. knee/foot lock). Degree of bladder fullness should be made to duplicate the degree of fullness anticipated for daily treatment. Prostate fiducial markers are required. Rectal balloons may be used but are not required. Rectal hydrogel spacer may be utilized but is not required.

5.1.2.1 Immobilization

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

5.1.2.2 Target Localization for Treatment

All patients shall undergo daily cone beam CT prior to each treatment with fiducial markers to assist with target localization and alignment of the CTV_3625, CTV_4000, and PTV_5000. A “PTV_fiducial” structure will be created which is a 2 mm expansion from the fiducial contours to assist with target alignment, with the goal that all of the fiducials are aligned within the PTV_fiducial volume.

5.1.3 EBRT Simulation Imaging

The treatment planning CT and MRI (or PET/CT per investigator discretion) will be acquired with the patient setup in the same position as planned for daily treatments and stored in the Varian/Ethos treatment planning system along with the target and organ-at-risk contours.

5.1.3.1 CT-based simulation imaging

The primary volumetric imaging modality for target delineation and dose calculation purposes is CT. The field of view (FOV) and superior-inferior extent of the primary planning image shall be large enough so as to encompass the target volume, the entirety of the organs at risk (OARs), and any regions through which treatment beams may propagate through the patient, with sufficient margin to accurately account for lateral scatter in the treatment planning system. Ideally, the CT will consist of 1.5 mm thick (or less) axial slices, and will extend from the top of L2 to either 2 cm below the ischial tuberosity or the level of the lesser trochanter (whichever is more inferior) caudally. If 1.5 mm or less slice thickness is not possible for the entire scan, the reconstructed axial slice thickness shall, in the vicinity of the target volumes, be sufficient to enable accurate dose calculation resolution. The protocol recommends a reconstructed slice thickness of 2 mm or less in this region. For regions of the patient either superior or inferior to the target-volume region, a greater slice thickness may be used (up-to 5 mm). Fiducial length may also mandate smaller slice thickness within the region encompassing the fiducial markers. Ideally, at least two slices should intersect each fiducial marker.

5.1.3.2 MR-based simulation imaging

The primary volumetric image acquired for target delineation and dose calculation purposes may be MR imaging, provided that the voxel-by-voxel density-assignment techniques are accommodated. The FOV and superior-inferior extent of the primary planning image shall be large enough so as to encompass the target volume, the entirety of the OARs, and any regions through which treatment beams may propagate through the patient.

The reconstructed axial slice thickness shall, in the vicinity of the target volumes, be sufficient to enable accurate dose calculation resolution. The protocol recommends a reconstructed slice thickness of 3 mm or less in this region. For regions of the patient either superior or inferior to the target-volume region, a greater slice thickness may be used (up to 5 mm), with the scan range extending superiorly and inferiorly from the boundaries of the target volume.

For MRI simulation the following imaging protocol is recommended:

- Patient setup should represent treatment conditions (bowel prep, bladder prep, immobilization devices, etc.).
- Bladder filling should be comfortable to reduce image blurring.
- Field of view should generally be >14 cm, to include prostate and SV and skin surface.
- Each imaging sequence should strive to minimize acquisition times (< 5 minutes if possible) to minimize image blurring due to motion.
- Utilize optimal MR sequences for prostate such as T2W, T2W TSE/FSE, DWI, DCE, 3DFFE, T2 cube etc.
- A synthetic CT may be generated for treatment planning.

5.1.3.3 Imaging for Structure Definition, Image Registration/Fusion and Follow-up

MRI should be used as part of staging and to assist in volume delineation in all eligible patients.

5.1.4 Bladder and Bowel Preparation

The subject will be instructed to drink water to fill their bladder so it is comfortably full or approaching comfortably full when they present for treatment. They will also be instructed to place an enema and have a bowel movement prior to each treatment to ensure that the rectum is empty. Detailed written instructions will be provided to the patient per standard institutional protocols. For subjects with persistent gas in the rectum/bowels, medications/dietary modifications are encouraged to reduce gas.

5.1.5 Target Volumes to Contour

Standard Name	Description	Detailed Specification
CTV_Pros+SV_3625	Prostate and seminal vesicles Required	Includes the entire prostate and the proximal 1-1.5 cm of the seminal vesicles. For patients with involvement of the seminal vesicles, the entire seminal vesicles should be included. The entire seminal vesicles can be treated in the absence of seminal vesicle involvement per provider preference.
CTV_SV	Seminal vesicles	The proximal 1-1.5 cm of seminal vesicles (or entire seminal vesicles for patients with seminal vesicle involvement or based on provider preference)

Standard Name	Description	Detailed Specification
CTV_Pros_4000	Prostate	Includes the prostate and any gross disease
GTV_pX_5000 when more than one MR-detected nodule is contoured (X= nodule #1-5) in volume name GTV_p1_5000 GTV_p2_5000, etc.	Grossly involved MR-detected nodule(s) Required	Includes all PIRADS 4 or 5 intraprostatic or seminal vesicle lesions as noted on MRI and all PIRADS 3 lesions with MR-fusion biopsy pathologic confirmation. Inclusion of additional PIRADS 3 lesions without MR-fusion biopsy pathologic confirmation is recommended but is not required, provided the combined GTV_5000 volume does not exceed 50% of the prostate by volume.
GTV_sum_5000	The sum of all grossly involved MR-detected nodules(s) Required	GTV_p1_5000 + GTV_p2_5000 + GTV_p3_5000. The volume of this structure as calculated in Eclipse should be ≤50% of the volume of CTV_Pros+SV_3625.
CTV_LNPelv_2500	Elective pelvic nodal region Required	Includes the full common iliac, external iliac, internal iliac, presacral (S1-S3), and obturator nodes **(see contouring guidelines section**)
PTV_Pros+SV_3625	PTV expansion for CTV_Pros+SV_3625	Non-uniform expansion from CTV to generate PTV: 0.5 cm (sup/inf/lateral) and 0.3 cm anterior and posterior
PTV_Pros_4000	PTV expansion for CTV_Pros_4000 Required	Non-uniform expansion from CTV_Pros_4000 to generate PTV: 0.2 cm (sup/inf/lateral) and 0.0 cm anterior and posterior
PTV_pX_5000 when more than one MR-detected nodule is contoured (X= nodule #1-5) in volume name PTV_p1_5000 PTV_p2_5000, etc.	PTV for GTV_pX_5000	PTV_pX_5000 is equal to GTV_pX_5000 with zero expansion from GTV to PTV. PTV_pX_5000 = GTV_pX_5000
PTV_LNPelv_2500	PTV expansion for CTV_LNPelv_2500	Uniform 0.5 cm expansion from CTV to PTV

5.1.6 Normal structures to contour for initial plan based on CT simulation

Standard Name	Description	Validation Required
Rectum	Rectum	Required
Bladder	Bladder	Required
Bladder-CTV	Entire bladder minus CTV_Pros+SV_3625	Required
Urethra	Urethra	Required
Urethra_PRV	Urethra plus 2 mm uniform expansion	Required
Femur_Head_L	Left femoral head	Required
Femur_Head_R	Right femoral head	Required
Femurs	Femur_Head_L + Femur_Head+R	Required
Sigmoid	Sigmoid colon	Required
Bowel-Sigmoid	Small and large bowel (not including rectum or sigmoid) extending 2 cm cranial to the highest PTV	Required
Penile Bulb	Entire penile bulb	Required
Fiducials	Intraprostatic fiducial markers (at least 3)	Required
PTV_Fiducials	Fiducials + 2 mm circumferential margin	Required
External	External contour	Required
E-PTV	External minus PTVs	Required

5.1.7 Detailed specifications

- Bladder, rectum, sigmoid, small bowel, femoral heads, urethra, penile bulb will be considered as solid organs rather than just contouring the walls for each organ.
- **Bladder** should be contoured from its base to the dome.
- **Rectum** should be contoured from the anus (at the level of ischial tuberosities) for a length of 11-15 cm or to the recto sigmoid flexure. This generally is below the bottom of the sacroiliac joints. Sigmoid and small bowel should be excluded from this volume.
- **Femur Head L/R**: should be considered separately. Each femoral head should be outlined down to the interface between the greater and less trochanters.
- **Sigmoid**: Contour from the recto-sigmoid flexure to the beginning of the descending colon.
- **Bowel-Sigmoid** (Bowel excluding rectum and sigmoid): Bowel loops should be contoured encompassing small and large bowel, outlined on each axial CT slice, up to at least 2 cm superior to all PTVs. Contours should include the loops of bowel on the periphery and in and around the target structures. Individual loops of bowel do not have to be contoured inside a mass of bowel

and can be combined into a bowel bag-like structure, so long as the bowel loops along the periphery and close to the target are contoured.

- **Penile Bulb**: The entirety of the penile bulb should be contoured. The penile bulb is the portion of the bulbous spongiosum of the penis immediately inferior to the GU diaphragm. The fused MRI scan(s) should be used to assist with contouring the penile bulb. The penile bulb is bright on T2-weighted MRI scans.
- **Urethra**: Urethra will be contoured longitudinally as a 6 mm diameter circle, using the MRI scan to assist with contour delineation.
- **Urethra PRV**: Urethra plus a 2 mm circumferential expansion.
- **External**: The skin encompassing all CT slices from 1.5 cm inferior to superior of the radiation fields
- **E-PTV**: External patient contour minus all PTV volumes

Target coverage goals for initial CT-simulation planning

Target Standard Name	**Dose (Gy)**	**Fraction Size (Gy)**	**# of fractions**
PTV_LNPelv_2500	25	5	5
PTV_Pros+SV_3625	36.25	7.25	5
PTV_Pros_4000	40	8	5
PTV_pX_5000	50*	10*	5

5.1.8 Dose constraints for initial planning

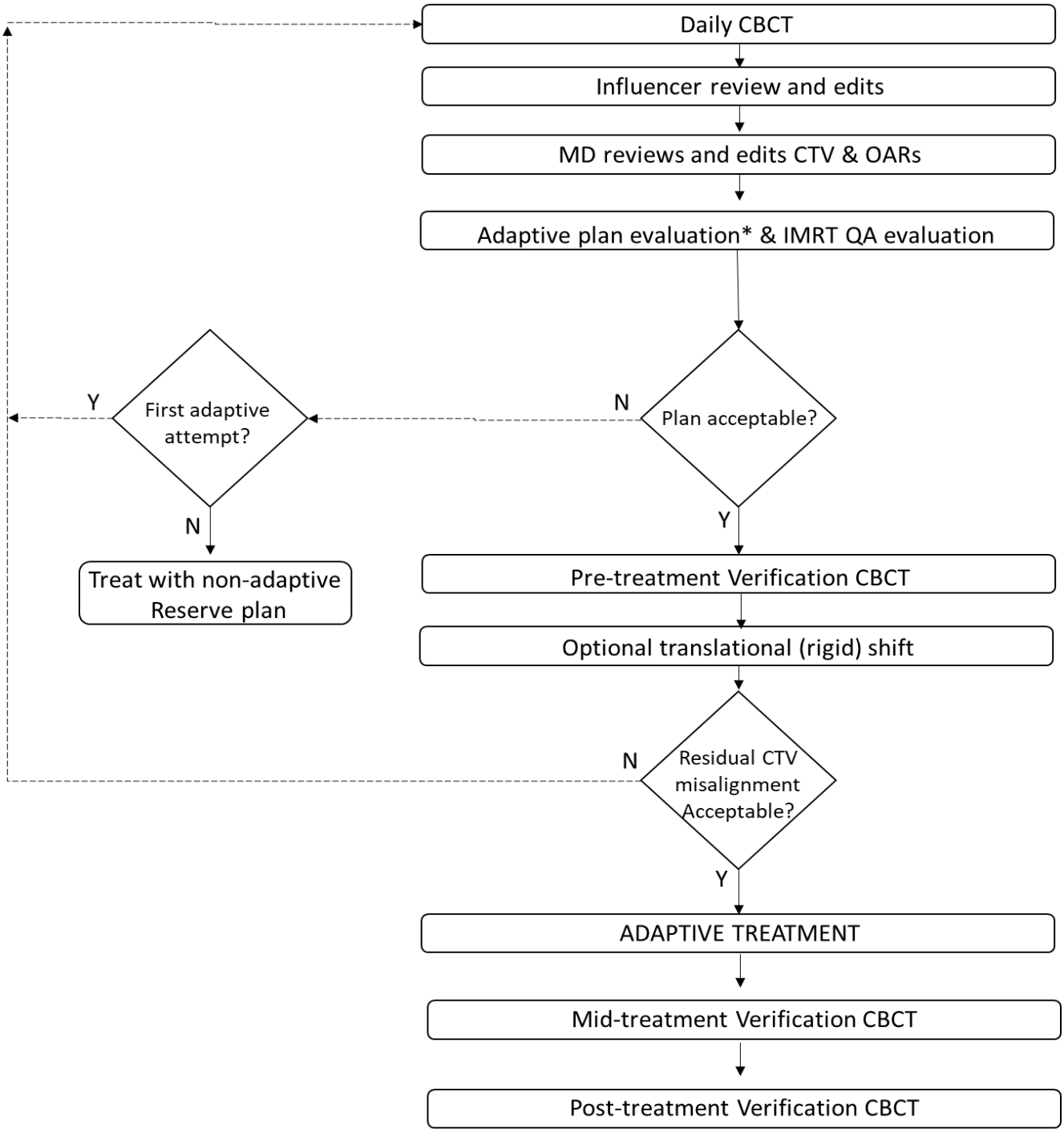
Name of Structure	**Dosimetric parameter**	**Per Protocol**	**Acceptable Variation**
PTV_2500 and PTV_3625	V100% [%]	≥ 98%	≥ 95%
	D99% [%]	≥ 95%	≥ 93%
PTV_4000	V100% [%]	≥ 96%	≥ 90%
PTV_5000	V100% [%]	≥ 85%	No hard limit
	V95% [%]	≥ 95%	No hard limit *Goal is for ≥ 95% of the PTV to receive ≥ 45 Gy (112.5% of the 40 Gy prescription dose)

Initial Treatment Planning Dose Constraints			
Name of Structure	**Dosimetric parameter***	**Per Protocol**	**Variation Acceptable**
Rectum	D0.03cc[Gy]	<=41.2 Gy	-
	V38.5Gy [cc]	<=1cc	<=1.5cc
	V34.4 Gy [cc]	<=3cc	
	V29Gy[%]	<=20%	<=30%
	V18.1[Gy]	<=50%	<=60%
Bladder	D0.03cc[Gy]	<=43.5Gy	-
	V37Gy[cc]	<=10cc	<=20cc
	V18.1Gy[%]	<=40%	<=60%
Femur_Head_L Femur_Head_R	V14.5 Gy[%]	<=5%	<=15%
PenileBulb	Mean[Gy]	<=29.5 Gy *Guideline only; adherence to this threshold should not compromise coverage of target volume*	-
Urethra	V43.5Gy[cc]	0.03cc	-
Small bowel (if in-field)	D0.03cc	<=32 Gy	
Sigmoid (if in-field)	D0.03cc	<=40 Gy	

5.2 Online Adaptive Treatment for every fraction

CBCT adaptation with Ethos represents the core intervention of this study. This section outlines the procedure for utilizing Ethos to perform daily adaptation, as well as review and approval criteria for daily adapted treatments.

5.2.1 Adaptive Procedure



The sequence of steps in the online adaptive workflow are as follows:

1. *Influencer structure review:* After capture of daily CBCT, the Ethos system will initiate Deep Learning autosegmentation to generate influencer contours (bladder, bowel, and rectum). These should be reviewed through all slices

where the contour is present for accuracy before proceeding to the next step. **Visible contouring discrepancies for rectum and bladder >2 mm must be corrected**. It is recommended that most normal contour adjustments be performed at the same time as CTV edits as the tools for editing structures are more robust.

The bowel contour generated by the Ethos autosegmentation should represent detailed small and large bowel loops.

2. OAR review: The auto-segmentation of the femurs, bowel, rectum, sigmoid, bladder, should be reviewed.
   - **Bowel** (including small bowel and large bowel) should be edited as needed anywhere that bowel extends within the low-dose contouring ring (**Ring_Low_Dose**) which is an automatic expansion of the PTV_2500 nodal treatment volume. The edge of bowel adjacent to the target structures should be contoured as a bowel loop. Individual loops of bowel do not have to be contoured inside a mass of bowel and can be combined into a bowel bag-like structure, so long as the bowel loops along the periphery and close to the target are contoured.
   - **Sigmoid** should be contoured wherever sigmoid appears within the separate high-dose contouring ring (**Ring_High_Dose**) which is an automatic expansion from the PTV_3625. Sigmoid that exists outside of the high-dose ring does not have to be separately contoured as sigmoid and should instead be contoured as bowel. An automated program will subtract sigmoid out of bowel to create the Bowel-Sigmoid structure (bowel minus sigmoid).
   - **Bladder** – Entire bladder contour should be reviewed and edited as needed.
   - **Rectum** – Entire rectum contour should be reviewed and edited as needed with particular attention to the anterior rectal wall. The rectum should not extend into the rectal hydrogel if rectal hydrogel is present.
   - **Femurs** – Both the left and right femurs should be reviewed and edited.
   - **Urethra** – The urethra is difficult to see on CBCT scan. The urethra is co-registered to the fiducial markers and the prostate CTVs and will be rigidly propagated with the target structures. The urethra can be edited as needed, although in most cases editing is not needed.

3. CTV review: It is recommended that all CTV volumes be rigidly registered rather than deformed. The CTV_2500 (pelvic nodal volume) should be aligned separately from the other structures using bony anatomy primarily. The CTV_2500 should be reviewed to ensure that anterior coverage is appropriate, particularly with respect to the external iliac nodal region. The CTV_3625, CTV_4000, and CTV_5000 are all linked to the fiducial marker and PTV fiducial marker contours, along with the urethra contour. The fiducial marker volumes should be aligned with the fiducial markers seen on the CBCT. The CTV_3625 (prostate and seminal vesicles), the CTV_4000 (prostate only), and CTV_5000 (prostate nodule(s)) should be carefully reviewed and edited as

needed. These structures should not extend into rectum or bladder unless physician provides instructions to say otherwise. **Visible contouring discrepancies for all CTVs must be corrected.**

While there have not been any observed instances where the CTV segmentation corrections have required more than 15 minutes, the goal of the adaptive workflow is to complete the entire sequence prior to optimization in approximately 20 minutes. However, there is no upper limit prescribed by the protocol. If the CTV editing will extend the subject's time on the table beyond a clinically acceptable level, or if subject's comfort/motion dictates that he/she be taken off the table before delivering adaptive radiotherapy, it is recommended the subject be treated with the standard margin non-adaptive plan for that day.

If normal structure and CTV editing precludes adaptation for more than three sequential treatment fractions, the participating site should contact study advisors and sponsor to discuss whether the subject should be treated with standard-of-care non-adaptive RT for the remainder of his/her treatments.

PTVs will be automatically generated after CTV review. A PTV_3625_opt will also be created which crops PTV_3625 out of sigmoid, rectum, and bladder.

4. *Adapted plan review:* After target approval, Ethos will automatically reoptimize the case according to the contours of the day. When optimization and dose calculation are complete, Ethos will present the plan for review and allow comparison to the initially approved plan, including all target and normal tissue evaluation metrics in Section 5.2.5. Specific DVH metrics might change depending on the daily anatomy; emphasis in review should be on ensuring target coverage. The adapted plan should then be approved by the attending physician or physicist.

5. *Pre-treatment QA:* After plan approval, the physicist should review the calculation-based patient-specific QA in the Mobius3D system on the Ethos console. The recommended patient specific QA criterion is that 90% of the comparison points pass a ±3%/3 mm Gamma Index analysis.

6. *Verification CBCT:* A verification CBCT prior to treatment is required. Rigid shifts will be possible but no further contour/dose adaptation can occur. After applying the shifts, the prostate should be well-aligned within the PTV_3625 and the fiducial markers should be aligned within the PTV_fiducial volume. If the prostate is outside of the PTV_3625 volume or there is significant change in the rectal position such that the rectal dose to the anterior rectal wall is considerably different, the subject should be removed from the table to re-fill their bladder and/or empty their rectum of stool/gas. If the issue is gas only, a rectal probe can be placed to evacuate gas.

7. Mid-treatment CBCT: A verification CBCT will be obtained mid-treatment to ensure that the targets remain well-aligned, with particular attention to the fiducial marker alignment.

8. Post-treatment CBCT: A post-treatment verification CBCT is required. This scan will be used to assess organ motion and to allow for adjustment in the PTV margin.

5.2.2 Real-time MD review

This is the first observation of the subject on treatment and, most critically, the performance of the Ethos CBCT-based auto-segmentation on that subject's anatomy. Radiation therapists, medical physicists/planners, and attending radiation oncologist should be present for the first treatment fraction and all subsequent fractions, as per institutional practice. The presence and identity of the attending radiation oncologist and medical physicist will be logged in the Varian treatment planning system during each fraction. The role of the attending physician is to review the Ethos contours and OARs, the adapted/scheduled plan, and the post-planning, pre-treatment verification CBCT scan. **We strongly suggest rigidly propagating the CTV volumes rather than using deformable registration**.

5.2.3 Adaptive Compliance Criteria

The following tables outline the dosimetric criteria that will be presented to the user at the treatment console. As there are no plan refinement options once the daily contours are set, acceptable daily variations to protocol DVH criteria are listed below. In such instances where the adapted plan is not within the criteria in *Table 14* and *Table 15*, the attending physician will communicate with the treatment team whether to treat with the adaptive or the non-adaptive plan. The attending physician will review the delivered treatment plan prior to the next treatment fraction.

Table 1. Daily adaptive target volume constraints and compliance criteria.

Name of Structure	Dosimetric parameter	Per Protocol	Acceptable Variation
PTV_2500 and PTV_3625	V100% [%]	≥ 98%	≥ 95%*
	D99% [%]	≥ 95%	≥ 93%
PTV_3625_opt	V100% [%]	≥ 98%	≥ 95%
PTV_4000	V100% [%]	≥ 96%	≥ 90%
PTV_5000	V100% [%]	≥ 85%	No hard limit
	V95% [%]	≥ 95%	No hard limit *Goal is for ≥ 95% of the PTV to receive ≥ 45 Gy (112.5% of the 40 Gy prescription dose)

	D0.03cc	≤107%	≤110%

% is calculated with prescription dose for that dose level.
* if PTV_3625 coverage objectives not met, plan is acceptable if "PTV_3625_opt" coverage objectives are met.

Table 2. Daily adaptive normal structure constraints and compliance criteria.

Daily Adaptive Treatment Planning Dose Constraints			
Name of Structure	**Dosimetric parameter***	**Per Protocol**	**Variation Acceptable**
Rectum	D0.03cc[Gy]	<=41.2 Gy	-
	V38.5Gy [cc]	<=1cc	<=1.5cc
	V34.4 Gy [cc]	<=3cc	
	V29Gy[%]	<=20%	<=30%
	V18.1[Gy]	<=50%	<=60%
Bladder	D0.03cc[Gy]	<=43.5Gy	-
	V37Gy[cc]	<=10cc	<=20cc
	V18.1Gy[%]	<=40%	<=60%
Femur_Head_L Femur_Head_R	V14.5 Gy[%]	<=5%	<=15%
PenileBulb	Mean[Gy]	<=29.5 Gy *Guideline only; adherence to this threshold should not compromise coverage of target volume*	-
Urethra	V43.5Gy[cc]	0.03cc	-
Small bowel (if in-field)	D0.03cc	<=32 Gy	
Sigmoid (if in-field)	D0.03cc	<=40 Gy	

5.2.4 Treatment Interruption, Modification, or Discontinuation

Radiotherapy interruptions are acceptable as long as treatments are no more than 16 days apart. Since radiation treatments are given weekly, this means that

treatment can be delayed for 9 additional days beyond the patient's next scheduled weekly treatment due to machine problems, unrelated medical reasons, vacation, weather, or other extenuating circumstances, at the discretion of the treating physician. To avoid a gap between fractions longer than 16 days due to machine problems, patients should receive their next fraction with non-adaptive SBRT on a different treatment machine. In that instance, the boost dose to 50 Gy will be omitted for that fraction and the maximum prescription dose will be 40 Gy (8 Gy per fraction), which is consistent with NCCN guidelines for standard-of-care SBRT. Once machine issues are resolved and provided the patient has not received more than 1 fraction of radiation on a different machine, patients should resume per-protocol adaptive treatment on the Ethos machine. Patients who receive more than 1 fraction on a different treatment machine should complete their remaining treatments with standard, non-adaptive SBRT.

Treatment can also be interrupted due to grade 2 GI or GU adverse events, if such a delay is warranted in the opinion of the treating physician, and as long as the next fraction is given within 16 days of the previous fraction. For patients who develop a grade 3 GI or GU adverse event during radiation therapy (the primary outcome of interest), dose-escalated adaptive SBRT should be halted. Radiation treatments can be resumed at the discretion of the treating physician using standard-of-care treatment (standard dose, non-adaptive SBRT), with a recommended maximum dose of 7.25 Gy/fraction to the prostate (which represents the low end of the acceptable dose per fraction in NCCN guidelines) if using SBRT to complete the treatments. For patients who experience a grade 3 GI or GU adverse event, treatment can be resumed using a more fractionated approach (more fractions, each to a lower dose) if this approach is felt to be in the patient's interests at the discretion of the treating physician, per institutional guidelines.

5.3 Assessments during Radiation

Patients will be assessed according to the study calendar. H&P, ECOG performance status assessment, QOL forms, and assessment of CTCAE GI/GU adverse events should be performed during the last week of treatment at week 5.

5.4 Systemic Therapy

Androgen deprivation therapy (ADT) will be administered to study patients according to institutional standard. Radiation must start no later than 60 days after the start of ADT. ADT is defined as a GnRH agonist/antagonist (leuprolide, goserelin, degarelix, or relugolix). Patients treated with leuprolide, goserelin, or degarelix should also receive an androgen receptor antagonist (flutamide or bicalutamide) for 30 days from the start of GnRH agonist/antagonist or until the end of radiation, depending on institutional standard and physician preference.

Agent selection is per treating physician discretion and will be administered per institutional standard and FDA-approved labeling.

Unfavorable intermediate-risk disease and high-risk disease must receive ADT, but duration of ADT will be at the discretion of the treating physician.

5.5 Definitions of Evaluability

Objective	In order to be evaluable for this objective a patient must have…
Primary	
To demonstrate that rates of acute grade ≥3 GI and GU adverse events associated with adaptive prostate SBRT are acceptable (≤15%).	Received at least 1 fraction of adaptive SBRT. Patients who receive > 1 fraction of non-adaptive radiation on a different treatment machine are not evaluable unless the patient was switched to non-adaptive radiation due to grade 3 acute GI/GU toxicity that is thought to be at least possibly related to the adaptive treatment.
Secondary	
To assess patient-reported quality of life changes after adaptive SBRT treatment using EPIC-26 based comparison to historical controls.	Received at least 5 fractions of adaptive SBRT, completed the screening EPIC-26, and completed at least one post-treatment EPIC-26.
To determine change in global function after treatment using EQ-5D-5L patient-reported outcome assessment tool.	Received at least 5 fractions of adaptive SBRT, completed the screening EQ-5D-5L, and completed at least one post-treatment EQ-5D-5L.
To assess physician-reported acute GI/GU CTCAE toxicities and any other acute grade ≥3 AE at least possibly related to radiotherapy.	Acute: Received at least 1 fraction of adaptive SBRT. Patients who receive > 1 fraction of non-adaptive radiation on a different treatment machine are not evaluable unless the patient was switched to non-adaptive radiation due to grade 3 acute GI/GU toxicity that is thought to be at least possibly related to the adaptive treatment.
Exploratory	
To assess physician-reported late GI/GU CTCAE toxicities and any other late grade ≥3 AE at least possibly related to radiotherapy	Late: Received at least 5 fractions of adaptive SBRT and are still in follow-up as of Day 91 post-radiation treatment. Patients who receive > 1 fraction of non-adaptive radiation on a different treatment machine are not evaluable unless the patient was switched to non-adaptive radiation due to grade 3 acute GI/GU toxicity that is thought to be at least possibly related to the adaptive treatment.

To assess biochemical recurrence-free survival	Received at least 5 fractions of adaptive SBRT, have a pre-treatment PSA assessment, and at least one post-radiation treatment PSA assessment.
To assess failure-free survival	Received at least 5 fractions of adaptive SBRT, have a pre-treatment PSA, and at least one post-radiation PSA.
To assess metastasis-free survival	Received at least 5 fractions of adaptive SBRT, have a pre-treatment radiographic disease assessment, and at least one post-radiation radiographic disease assessment.
To assess prostate cancer-specific mortality	Received at least 5 fractions of adaptive SBRT.
To assess overall survival	Received at least 5 fractions of adaptive SBRT.
To assess whether the adaptive plan resulted in an improvement in target coverage and/or reduction in dose to critical organs at risk (e.g. rectum, bladder, sigmoid, bowel, penile bulb, femurs) compared to the non-adaptive plan across the course of treatment	Received at least 5 fractions of adaptive SBRT.
To assess whether organ-at-risk constraints can be met with a goal of achieving at least >95% of the GTV getting >45 Gy (>112.5% of the 40 Gy prescription dose) and to assess the percentage of the GTV receiving full prescription dose (50 Gy)	Received at least 5 fractions of adaptive SBRT.
To determine the workflow feasibility of adaptive SBRT for prostate cancer (including measuring time on table and frequency of using the adapted vs. original treatment plan for each fraction)	Been enrolled in the study.

5.6 Concomitant Therapy and Supportive Care Guidelines

It is recommended that patient initiate tamsulosin prior to the start of SBRT to reduce risk of acute urinary obstruction. Other related medications can be used in lieu of tamsulosin at the discretion of the treating provider. Finasteride is discouraged as it can affect PSA levels.

Supportive care will be as per standard institutional practices.

5.7 Duration of Therapy

If at any time the constraints of this protocol are considered to be detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, the protocol therapy should be discontinued and the reason(s) for discontinuation documented in the case report forms.

In the absence of treatment delays due to adverse events, protocol treatment may continue for 5 once or twice weekly fractions or until one of the following criteria applies:

- Documented and confirmed disease progression
- Intercurrent illness that prevents further administration of treatment
- Death
- Unacceptable adverse event(s)
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Serious noncompliance with the study protocol
- Lost to follow-up (defined in Section 5.9)
- Patient decides to withdraw from the study
- The Siteman Cancer Center decides to close the study

Patients who prematurely discontinue treatment for any reason will still be followed as indicated in the study calendar.

Refer to Section 4.4 for definitions of when a patient is considered Off Treatment and Off Study.

5.8 Duration of Follow-up

Patients will be followed 3 months after the start of radiation therapy and then every 3 months thereafter for 2 years and then every 6 months for the next 3 years (total of 5 years) 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.

5.9 Lost to Follow-Up

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study team.

The following actions must be taken if the participant fails to return to clinic for a required study visit:

- The study team will attempt to contact the participant and reschedule the missed visit within 14 days and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix D for definitions and Appendix E for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 5 years after discontinuation of treatment. GI and GU adverse events and any grade ≥3 adverse event that is at least possibly related to radiation will be captured weekly during radiation treatment and at all study follow-ups as listed in the study calendar. Acute adverse events are defined as those occurring within 90 days of the start of radiation therapy. Late adverse events are defined as those occurring 91 days through 5 years from the start of radiation therapy. All treatment-emergent adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Pre-existing medical conditions (baseline adverse events), defined as conditions identified during baseline assessment; these are not considered AEs and therefore should not be recorded on the toxicity CRF but shall instead be recorded on the medical history CRF; if a pre-existing condition worsens in severity, it should be reported in the toxicity CRF as an AE

Refer to the data submission schedule in Section 7 for instructions on the collection of AEs in the EDC.

Reporting requirements for WUSM study team may be found in Section 6.1.

6.1 WUSM PI Reporting Requirements

6.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

6.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

6.2 Exceptions to Expedited Reporting

Events that do not require expedited reporting as described in Section 6.1 include:

- planned hospitalizations
- hospitalizations < 24 hours
- respite care
- events related to disease progression

Events that do not require expedited reporting must still be captured in the EDC.

7.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Treatment Form	Week 1, Week 2, Week 3, Week 4, Week 5
PSA and Testosterone Form	Screening, 3 months after start of RT, then Q3M until Month 24, then Q6M until Month 60
QOL Form	Screening, End of RT, 3 months after start of RT, then Q3M until Month 24
Toxicity Form	Continuous
Treatment Summary Form	End of RT
Follow Up Form	Q3M until Month 24, then Q6M until Month 60
Concomitant Medications Form	Screening,
Progression Form	Time of disease progression
Death Form	Time of death
MedWatch Form	See Section 7.0 for reporting requirements

7.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 6.0) must be captured in the Toxicity Form. Baseline AEs should be captured on the Medical History Form.

Participant death due to disease progression should be reported on the Toxicity Form as grade 5 disease progression. If death is due to an AE (e.g. cardiac disorders: cardiac arrest), report as a grade 5 event under that AE. Participant death must also be recorded on the Death Form.

8.0 MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated following completion of treatment with PSA testing. Additional diagnostic scans beyond the baseline scans will only be performed in the event of a PSA rise indicating biochemical recurrence or for pain or other symptoms.

Definitions of disease assessment:

- Biochemical recurrence free survival: Defined as a >2 ng/mL rise in the PSA above the nadir post initial treatment or evidence of radiographic progression.
- Metastasis-free survival by conventional imaging: Events are first occurrence of distant metastatic disease or death from any causes. Subjects with biochemical recurrence or initiation of another prostate cancer treatment (radiation/ surgery/ hormone therapy /chemotherapy) should undergo CT (or MRI) abdomen and pelvis and bone scan OR a prostate-cancer specific PET/CT scan. A metastasis by conventional imaging event will only be scored if the metastasis can be detected by CT, bone scan, or MRI. Equivocal bone scan findings should be confirmed by radiographic or pathologic methods. For a node to count as a distant metastasis, it must be at least 1.5 cm on short axis and be above the iliac bifurcation. The patient has only met the primary endpoint if a metastasis is detectable by conventional imaging (CT, MRI, or bone scan). Assessment of bone disease will be done by whole-body radionuclide bone scan. Radiographic metastatic progression for bone disease is defined as the appearance of 1 or more metastatic lesions on bone scan. When bone lesions are found in a single region on the bone scan, confirmation with a second imaging modality (plain film, CT, or MRI) will be required. Appearance of metastatic lesions in 2 or more of the areas on a bone scan will not require confirmation with a second imaging modality. Assessment of soft tissue metastatic disease will be done by CT or MRI. To count for endpoint of the trial, a soft-tissue metastasis seen on a PET-CT must be visible by RECIST 1.1 size criteria on the CT portion (if soft-tissue), or must meet the size criteria listed above on the CT portion (if nodal), or must be visible as a bony lesion on the CT portion (if a bony metastasis), or has to be confirmed by conventional imaging (bone scan, MRI, or CT). Imaging can also be performed as clinically indicated, e.g. when patients develop pain suggesting possible metastasis.
- Metastasis-free survival including PET imaging: Same as above except seen by PET imaging will also be counted as an MFS event.
- Loco-regional progression: Local or regional recurrence is defined as recurrence within the pelvis including lymph nodes below the iliac bifurcation, or prostate bed. Lymph node recurrence is defined radiographically as any lymph node which measures at least 1.5 cm

short axis dimension as measured by cross sectional imaging with CT or MRI. Biopsy confirmation of recurrence is strongly encouraged but not required.

- Failure-free survival: Events include biochemical recurrence, radiographic recurrence with development of local, regional, or distant disease, or death due to any cause.
- Castrate resistance: PSA increase >25% and more than 2ng/mL above nadir on study in the setting of a serum testosterone <50ng/mL, confirmed by repeat measurements at least 2 weeks later.
- Salvage therapy is defined as a non-protocol intervention in response to a rising PSA.
- Serum testosterone recovery is assessed as follows: Testosterone above castrate (>50 ng/dL) and time to recover above 200 ng/dL.
- Prostate cancer specific survival: Death due to prostate cancer.

9.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, the Principal Investigator will provide a Data and Safety Monitoring (DSM) report to the Washington University Quality Assurance and Safety Monitoring Committee (QASMC) semi-annually. The first report is required either 30 days after the enrollment of the 5th participant (if sooner than 6 months after study activation) or 6 months after study activation (provided at least one patient has been enrolled; if zero patients have been enrolled at the 6-month mark, the first report will be required one year after accrual opens provided at least one patient has been enrolled).

The Principal Investigator will review all patient data at least every six months, and provide a semi-annual report to the QASMC. This report will include:

- Study demographic information (local protocol number, protocol title, list of primary study team members, study sites, primary and secondary sponsors, IND/IDE status, date of most recent QA audit, and study status and history (including activation and suspension dates)
- Accrual information, including study-wide target accrual and actual accrual, anticipated and/or actual accrual end date
- Subject status information presented in both cumulative format (total number of subjects who consented, enrolled, screen failed, started intervention, discontinued intervention, went off study, expired) and current format (number of subjects in screening, on intervention, in follow-up, or off study at time of report)
- Protocol objectives and the number of participants who are evaluable for each objective
- History of study (including summaries of substantive amendments, accrual suspensions and reasons, protocol exceptions, errors, and breaches of confidentiality)
- Summary of exceptions, noncompliance reports, and unanticipated problems reported to the IRB
- Early stopping rules and data describing whether the stopping rules have been met
- Interim analysis plans and the results of the interim analysis
- Separate SAE and worst grade toxicity tables
- Participant-level response and survival data

- Summary of specimen collection (percentage of participants who have had specimens collected at each required time point)
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety of participants or the ethics of the study

Standardized DSM report tables are generated out of OnCore; study-specific DSM report tables are located in Appendix H.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

This is a prospective pilot study designed to demonstrate the safety and feasibility of whole-pelvis adaptive prostate SBRT with a tumor boost to the MR-detected sites of disease in patients with unfavorable intermediate- and high risk prostate cancer.

10.2 Endpoints

The primary endpoint is acute grade ≥3 GU and GI adverse event (AE) rates, which will be graded by CTCAE v5.0 and evaluated during the evaluation window from 90 days from the start of RT.

The secondary endpoints include changes in patient reported QoL (EPIC-26 and EQ-5D-5L), acute GI/GU AEs and any acute AEs grade 3 or higher at least possibly related to RT. Exploratory endpoints include late GI/GU AEs and any late AEs grade 3 or higher at least possibly related to RT, patient survival outcomes (biochemical recurrence free survival (bRFS), metastasis-free survival (MFS), prostate cancer-specific survival (PCSS), overall survival (OS), dose volume histogram comparison of organs at risk and PTVs, PTV_4000 V112.5 % > 95% of 40 Gy, PTV_pX_5000 V100%, time on table, and fractions adapted versus total fractions.

The EPIC-26 is used to assess health related quality of life among persons with prostate cancer. It contains 5 domains of urinary incontinence, urinary irritability/obstructive, bowel, sexual, and hormonal. Response options for each EPIC item form a Likert scale, and multi-item scale scores are transformed linearly to a 0-100 scale, with higher scores representing better health related quality of life. The EQ-5D-5L is a commonly used and reliable questionnaire used to assess patient perception of their current health state. Patients are asked about their levels of difficulty with mobility, self-care, and usual activities, and about their pain/discomfort and anxiety/depression levels on a 5-point scale where the response “I have no problems” = 1 and “I am unable/have extreme” = 5.

10.3 Statistical Hypotheses

This study is motivated by the favorable safety/toxicity results from the HypoFlame trial which investigated an SBRT boost dose to 50 Gy in 5 fractions to the MR-detected lesion(s). This study adopts doses based on the recently opened NRG Oncology GU 010 protocol and the HypoFlame trial and further expand SBRT with focal boost to the MR-detected lesions to include elective nodal treatment as well as adaptive SBRT. Based on our small pilot study of 7 patients, this novel adaptive treatment will improve effectiveness with better coverage to the target than non-adaptive treatment and reduced dose to the rectum compared to using conventional techniques delivering the same doses.

This study using adaptive radiation expects to reduce toxicities for elective nodal SBRT with a focal boost to 50 Gy compared to the toxicities that would be observed with these prescription dose levels using conventional SBRT techniques (25/36.25/40/50 Gy). Because this approach with these prescription dose levels has been not been reported to our knowledge using either conventional SBRT or adaptive SBRT, we need to assess the safety feasibility of this approach. The HypoFlame trial did evaluate SBRT with a focal boost but the dose to the entire prostate was lower (35 Gy) than current NCCN recommendations and lower than what we are using on this study (36.25 – 40 Gy). In addition, they did not treat the elective nodes on the HypoFlame study, whereas we are treating the elective nodes. It is therefore possible that the rates of acute grade ≥3 GU and GI adverse events may be higher than what was reported using SBRT with a conventional technique but treating a small target and treating to a lower dose. We think that the AE rate is likely to be higher than the conventional technique (ranging 1~5%).

The primary hypothesis is that the adaptive SBRT treatment proposed in this study will be safe and feasible with acute grade ≥3 GU and GI AE rates ≤15%.

10.4 Sample Size Determination

The primary objective of this pilot study is safety and feasibility. Thus, the sample size is primarily determined based on clinical feasibility rather than statistical power. Based on an extensive simulation regarding the sample size for translational and pilot studies, Piantadosi[1] recommended that a sample size of 10 to 20 patients is reasonable for providing preliminary information in translational clinical trials. We therefore expect that the proposed sample size of 25 toxicity evaluable patients will be adequate in assessing toxicities and feasibility, as well as providing preliminary efficacy estimates.

N=25 should suffice the safety evaluation purpose. If the study's acute grade ≥3 GU and GI AE rate is at the maximally acceptable rate of 15%, then the probability of observing at least 3 such AEs among 25 evaluable patients is ~74.6%, but the probability of observing at least 9 such AEs is only ~0.008. Note that 9 is the critical minimum boundary that corresponds to excessive events derived according to Pr(# of such AEs among N=25 patients ≥9 | rate= 0.15)≤0.05) based on the approach proposed by Ivanova et. al.[2]

10.5 Sequential toxicity monitoring

For sequential toxicity monitoring, dose limiting toxicity (DLT) will include treatment-related acute grade ≥3 GI/GU adverse events, grade 2 treatment-related GI/GU adverse events that caused delay >16 days or forced the patient to stop treatment.

To ensure patient safety, we will sequentially monitor for the DLT rate using a Pocock-type boundary for repeated testing for toxicity when at least 5 patients are evaluable and the rate will be evaluated on every cohort of 5 patients (i.e., at n=5, 10 15, 20) to ease practical implementation. This boundary is equivalent to testing the null hypothesis, after each patient, that the acute DLT rate is 15%, using a one-sided level 0.020611 test. The accrual will be halted if excessive numbers of severe adverse events are seen, that is, if the number of DLTs is equal to or exceeds boundary (b_n) out of a total of n patients treated and at the completion of evaluation (see table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary ≤0.05 (i.e., the probability of early stopping) when the rate is equal to the acceptable rate of 0.15, i.e., Pr(# of excessive events among n patients ≥ b_n | treatment-related DLT rate = 0.15)≤0.05).

Because the very similar HypoFlame trial evaluating a simultaneous integrated boost to 50 Gy in 5 fractions using SBRT to the MR-detected disease (the same dose employed in this trial) reported no acute grade 3 GI/GU adverse events in a cohort of 100 patients (Draulans, 2020), we expect a very low rate of DLT and so will conduct sequential monitoring without pausing enrollment while we wait for toxicity evaluation of patients on treatment.

Number of Patients (*n*)	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**	13	14	**15**	16	17	**18**	19	20
Boundary (b_n)	-	-	**3**	3	4	**4**	4	5	**5**	5	5	**6**	6	6	**6**	7	7	**7**	7	8
Number of Patients (*n*)	**21**	22	23	**24**	25															
Boundary (b_n)	**8**	8	8	**8**	9															

10.6 Population for Analyses

- Safety Analysis Dataset: refers to patients who received at least 1 fraction of the SBRT treatment.
- Efficacy Analysis Dataset: refers to patients who have received all 5 SBRT adaptive treatments

10.7 Statistical Analyses

10.7.1 General Approach

All data will be analyzed as recorded and no data imputation will be performed. Baseline demographic, clinical-pathological and lab tests will be summarized using summary statistics. For summary statistics, continuous variables will be summarized with mean/median and standard deviation/inter-quartile range at each time point. Qualitative variables will be summarized by counts and percentages.

10.7.2 Analysis of Primary Endpoint

The treatment-related acute grade ≥3 GU and GI adverse event (AE) rate will be estimated with 95% Wilson-type CI.

10.7.3 Analysis of Secondary Endpoints

All types of AE, overall and by attribution and by grade will be summarized as counts and percentages. Epic-26 and EQ-5D-5L global function score will be summarized by descriptive statistics, including mean, median, standard deviation and interquartile range, at each time point, as well as the percentage change of each time point from baseline. The individual patients' longitudinal trajectories will be plot against time with median trajectory connecting the medians from each time point. QoL and global function score at on- and post-treatment time point will be compared against baseline by Wilcoxon signed rank test.

10.7.4 Analysis of Exploratory Endpoints

All types of late AEs, overall and by attribution and by grade will be summarized as counts and percentages. Time to event outcomes (bRFS, DMFS, PCSS, OS) will be analyzed by the Kaplan-Meier method to estimate empirical survival probability and median PFS with 95% Brookmeyer and Crowley confidence intervals. The survival difference between patient subsets of interest will be compared by log rank test. Adaptive plan OAR sparing and target coverage will be evaluated directly through DICOM images and comparison plans will be used to assess goals. Workflow will be captured and compared to established workflow with Adaptive treatment with respect to time and patient ability to complete treatments.

10.7.5 Safety Analyses

AEs will be coded according to the CTCAE v5.0. Each AE will be counted once only for a given participant. The severity, frequency, and relationship of AEs will be presented by System Organ Class (SOC). AEs will be reported with the following information: start date, stop date, severity, attribution/relationship, expectedness, outcome, and duration. Adverse events leading to premature discontinuation from the study intervention and serious treatment-emergent AEs will be presented in a table.

All acute grade ≥3 GU and GI adverse events will be reviewed regularly by the study team. In any concerns of excessive treatment-related adverse events, enrollment will be temporarily discontinued and all available data on adverse events will be assessed by a review committee in order to make a recommendation of continuation of accrual, suspension followed by formal amendment and reactivation, or study closure.

10.7.6 Sub-Group Analyses

The analyses proposed above will be performed by patient subsets such as intermediate/high risk patients, Gleason grade, toxicity grades.

10.7.7 Tabulation of Individual Participant Data

Toxicity data of individual participant will be separately listed.

11.0 REFERENCES

Alayed Y, Davidson M, Liu S, et al. Evaluating the Tolerability of a Simultaneous Focal Boost to the Gross Tumor in Prostate SABR: A Toxicity and Quality-of-Life Comparison of Two Prospective Trials. Int J Radiat Oncol Biol Phys 2020;107:136-142. PMID: 31987962

Beckendorf V, Guerif S, Le Prise E, et al. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. Int J Radiat Oncol Biol Phys 2011;80:1056-1063. PMID: 21147514

Cellini N, Morganti AG, Mattiucci GC, et al. Analysis of intraprostatic failures in patients treated with hormonal therapy and radiotherapy: implications for conformal therapy planning. Int J Radiat Oncol Biol Phys 2002;53:595-599. PMID: 12062602

Draulans C, van der Heide UA, Haustermans K, et al. Primary endpoint analysis of the multicentre phase II hypo-FLAME trial for intermediate and high risk prostate cancer. Radiother Oncol 2020;147:92-98. PMID: 32247206

Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal Boost to the Intraprostatic Tumor in External Beam Radiotherapy for Patients With Localized Prostate Cancer: Results From the FLAME Randomized Phase III Trial. J Clin Oncol 2021;39:787-796. PMID: 33471548

Kuban DA, Tucker SL, Dong L, et al. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. Int J Radiat Oncol Biol Phys 2008;70:67-74. PMID: 17765406

Mahal BA, Chen YW, Muralidhar V, et al. National sociodemographic disparities in the treatment of high-risk prostate cancer: Do academic cancer centers perform better than community cancer centers? Cancer 2016;122:3371-3377. PMID: 27434225

Michalski JM, Moughan J, Purdy J, et al. Effect of Standard vs Dose-Escalated Radiation Therapy for Patients With Intermediate-Risk Prostate Cancer: The NRG Oncology RTOG 0126 Randomized Clinical Trial. JAMA Oncol 2018;4:e180039. PMID: 29543933

Morris WJ, Tyldesley S, Rodda S, et al. Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (the ASCENDE-RT Trial): An Analysis of Survival Endpoints for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost to a Dose-Escalated External Beam Boost for High- and Intermediate-risk Prostate Cancer. Int J Radiat Oncol Biol Phys 2017;98:275-285. PMID: 28262473

Rodda S, Tyldesley S, Morris WJ, et al. ASCENDE-RT: An Analysis of Treatment-Related Morbidity for a Randomized Trial Comparing a Low-Dose-Rate Brachytherapy Boost with a Dose-Escalated External Beam Boost for High- and Intermediate-Risk Prostate Cancer. Int J Radiat Oncol Biol Phys 2017;98:286-295. PMID: 28433432

Waters M, Price A, Laugeman E, Henke L, Hugo G, Stowe H, Brenneman R, Hao Y, Green O, Robinson C, Gay HA, Michalski JM, Baumann BC. CT-Based Online Adaptive Prostate SBRT Improves Target Coverage and reduces rectal dose [Abstract]. Int J Radiat Oncol Biol Phys 2022 (in press).

Zumsteg ZS, Spratt DE, Romesser PB, et al. Anatomical Patterns of Recurrence Following Biochemical Relapse in the Dose Escalation Era of External Beam Radiotherapy for Prostate Cancer. J Urol 2015;194:1624-1630. PMID: 26165583

We would like to thank the Alvin J. Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital in St. Louis, Missouri, for the use of the Clinical Trials Core which provided protocol development services. The Siteman Cancer Center is supported in part by an NCI Cancer Center Support Grant #P30 CA91842.

APPENDIX A: MSK Prostate Cancer Nomogram

https://www.mskcc.org/nomograms/prostate/pre_op

APPENDIX B: American Urological Association (AUA) urinary reporting form

American Urological Association - Symptom Score (AUA-SS)

Name _____ **Date** _____

Please fill out this short questionnaire to help us find out more about any urinary problems you might have; for questions 1 through 7, circle the number under the column that best describes your situation.

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost Always
1. INCOMPLETE EMPTYING: Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. FREQUENCY: Over the past month, how often have you had to urinate again less than 2 hours after you finished urinating?	0	1	2	3	4	5
2. INTERMITTENCY: Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
3. URGE TO URINATE: Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. WEAK STREAM: Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. STRAINING: Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5
	None	1 time	2 times	3 times	4 times	5+ times
7. URINATING AT NIGHT: Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

Symptom Score:
1-7 Mild, 8-19 Moderate, 20-35 Severe Total: _____

BOTHERSOME SCORE DUE TO URINARY SYMPTOMS							
	Delighted	Pleased	Mostly Satisfied	Mixed	Mostly Dissatisfied	Unhappy	Terrible
QUALITY OF LIFE DUE TO URINARY SYMPTOMS: How would you feel if you had to live with your urinary condition the way it is now – no better, no worse – for the rest of your life?	0	1	2	3	4	5	6

APPENDIX C: ECOG Performance Status Scale

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX D: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Unexpected Suspected Adverse Reaction (SUSAR)

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death

- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX E: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days.	

	If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

APPENDIX F: EPIC-26

Patient ID: _____Visit:_____ Date:_____

EPIC-26
The Expanded Prostate Cancer Index Composite

Short Form

This questionnaire is designed to measure Quality of Life issues in patients with Prostate cancer. To help us get the most accurate measurement, it is important that you answer all questions honestly and completely.

Remember, as with all medical records, information contained within this survey will remain strictly confidential.

Today's Date (please enter date when survey completed): Month_____Day_____Year_____

Name (optional): _____

Date of Birth (optional): Month_____Day_____Year_____

Patient ID: _____ Visit: _____ Date: _____

Do Not Mark in This Space

1. Over the **past 4 weeks**, how often have you leaked urine?

   More than once a day..... 1
   About once a day..... 2
   More than once a week..... 3 (Circle one number) 23/
   About once a week..... 4
   Rarely or never..... 5

2. Which of the following best describes your urinary control **during the last 4 weeks**?

   No urinary control whatsoever..... 1
   Frequent dribbling..... 2 (Circle one number) 26/
   Occasional dribbling..... 3
   Total control..... 4

3. How many pads or adult diapers per day did you usually use to control leakage **during the last 4 weeks**?

   None 0
   1 pad per day..... 1
   2 pads per day..... 2 (Circle one number) 27/
   3 or more pads per day..... 3

4. How big a problem, if any, has each of the following been for you **during the last 4 weeks**?

   (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Dripping or leaking urine	0	1	2	3	4	28/
b. Pain or burning on urination.....	0	1	2	3	4	29/
c. Bleeding with urination.....	0	1	2	3	4	30/
d. Weak urine stream or incomplete emptying.....	0	1	2	3	4	31/
e. Need to urinate frequently during the day.....	0	1	2	3	4	33/

5. Overall, how big a problem has your urinary function been for you **during the last 4 weeks**?

   No problem..... 1
   Very small problem..... 2
   Small problem..... 3 (Circle one number) 34/
   Moderate problem..... 4
   Big problem..... 5

EPIC-SF 6.2002

Copyright 2002. The University of Michigan. All rights reserved.

Do Not Mark in This Space

6. How big a problem, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Urgency to have a bowel movement	0	1	2	3	4	49/
b. Increased frequency of bowel movements	0	1	2	3	4	50/
c. Losing control of your stools	0	1	2	3	4	52/
d. Bloody stools	0	1	2	3	4	53/
e. Abdominal/ Pelvic/Rectal pain	0	1	2	3	4	54/

7. Overall, how big a problem have your bowel habits been for you **during the last 4 weeks**?

No problem 1
Very small problem 2
Small problem ..... 3 (Circle one number) 55/
Moderate problem 4
Big problem 5

8. How would you rate each of the following **during the last 4 weeks**? (Circle one number on each line)

	Very Poor to None	Poor	Fair	Good	Very Good	
a. Your ability to have an erection?	1	2	3	4	5	57/
b. Your ability to reach orgasm (climax)?	1	2	3	4	5	58/

9. How would you describe the usual QUALITY of your erections **during the last 4 weeks**?

None at all 1
Not firm enough for any sexual activity 2
Firm enough for masturbation and foreplay only ..... 3 (Circle one number) 59/
Firm enough for intercourse 4

10. How would you describe the FREQUENCY of your erections **during the last 4 weeks**?

I NEVER had an erection when I wanted one 1
I had an erection LESS THAN HALF the time I wanted one 2
I had an erection ABOUT HALF the time I wanted one ..... 3 (Circle one number) 60/
I had an erection MORE THAN HALF the time I wanted one 4
I had an erection WHENEVER I wanted one 5

EPIC-SF 6.2002

Copyright 2002. The University of Michigan. All rights reserved.

Do Not Mark in This Space

11. Overall, how would you rate your ability to function sexually **during the last 4 weeks**?

Very poor	1		
Poor	2		
Fair	3	(Circle one number)	64/
Good	4		
Very good	5		

12. Overall, how big a problem has your sexual function or lack of sexual function been for you **during the last 4 weeks**?

No problem	1		
Very small problem	2		
Small problem	3	(Circle one number)	68/
Moderate problem	4		
Big problem	5		

13. How big a problem **during the last 4 weeks**, if any, has each of the following been for you? (Circle one number on each line)

	No Problem	Very Small Problem	Small Problem	Moderate Problem	Big Problem	
a. Hot flashes	0	1	2	3	4	74/
b. Breast tenderness/enlargement	0	1	2	3	4	75/
c. Feeling depressed	0	1	2	3	4	77/
d. Lack of energy	0	1	2	3	4	78/
e. Change in body weight	0	1	2	3	4	79/

THANK YOU VERY MUCH!!

EPIC-SF 6.2002

Copyright 2002. The University of Michigan. All rights reserved.

APPENDIX G: EQ-5D-5L

Patient ID: _____Visit:_____ Date:_____

Health Questionnaire (EQ-5D-5L)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- ☐ 1 I have no problems in walking about
- ☐ 2 I have slight problems in walking about
- ☐ 3 I have moderate problems in walking about
- ☐ 4 I have severe problems in walking about
- ☐ 5 I am unable to walk about

SELF-CARE

- ☐ 1 I have no problems washing or dressing myself
- ☐ 2 I have slight problems washing or dressing myself
- ☐ 3 I have moderate problems washing or dressing myself
- ☐ 4 I have severe problems washing or dressing myself
- ☐ 5 I am unable to wash or dress myself

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- ☐ 1 I have no problems doing my usual activities
- ☐ 2 I have slight problems doing my usual activities
- ☐ 3 I have moderate problems doing my usual activities
- ☐ 4 I have severe problems doing my usual activities
- ☐ 5 I am unable to do my usual activities

PAIN / DISCOMFORT

- ☐ 1 I have no pain or discomfort
- ☐ 2 I have slight pain or discomfort
- ☐ 3 I have moderate pain or discomfort
- ☐ 4 I have severe pain or discomfort
- ☐ 5 I have extreme pain or discomfort

ANXIETY / DEPRESSION

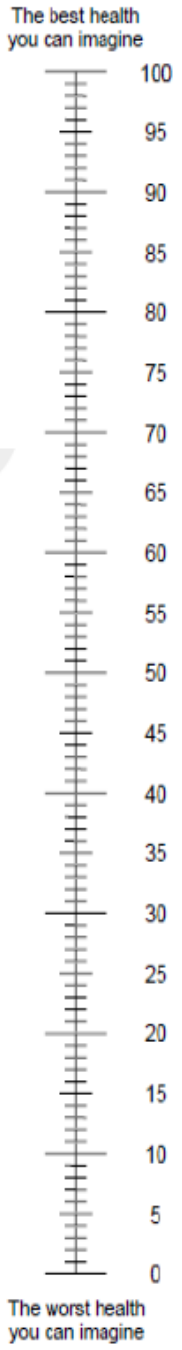
- ☐ 1 I am not anxious or depressed
- ☐ 2 I am slightly anxious or depressed
- ☐ 3 I am moderately anxious or depressed
- ☐ 4 I am severely anxious or depressed
- ☐ 5 I am extremely anxious or depressed

UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

Health Questionnaire (EQ-5D-5L)

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is **TODAY**
- Now, please write the number you marked on the scale in the below.

YOUR HEALTH TODAY = ☐



UK (English) © 2009 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

APPENDIX H: STUDY-SPECIFIC DSM Tables

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
To demonstrate that rates of acute grade ≥3 GI and GU adverse events associated with adaptive prostate SBRT are acceptable (≤15%).	
Secondary	
To assess patient-reported quality of life changes after adaptive SBRT treatment using EPIC-26 based comparison to historical controls	
To determine change in global function after treatment using EQ-5D-5L patient-reported outcome assessment tool	
To assess physician reported acute GI/GU CTCAE toxicities and any other acute grade ≥3 AE at least possibly related to radiotherapy	
Exploratory	
To assess physician reported late GI/GU CTCAE toxicities and any other late grade ≥3 AE at least possibly related to radiotherapy	
To assess biochemical recurrence-free survival	
To assess failure-free survival	
To assess metastasis-free survival	
To assess prostate cancer-specific mortality	
To assess overall survival	
To assess whether the adaptive plan resulted in an improvement in target coverage and/or reduction in dose to critical organs at risk (e.g. rectum, bladder, sigmoid, bowel, penile bulb, femurs) compared to the non-adaptive plan across the course of treatment	
To assess whether organ-at-risk constraints can be met with a goal of achieving at least >95% of the GTV getting >45 Gy (>112.5% of the 40 Gy prescription dose) and to assess the percentage of the GTV receiving full prescription dose (50 Gy)	
To determine the workflow feasibility of adaptive SBRT for prostate cancer (including measuring time on table and frequency of using the adapted vs. original treatment plan for each fraction)	

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? No
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? Yes
If yes, please insert text describing early stopping rules from the protocol

For sequential toxicity monitoring, dose limiting toxicity (DLT) will include treatment-related acute grade ≥3 GI/GU adverse events, grade 2 treatment-related GI/GU adverse events that caused delay >16 days or forced the patient to stop treatment.

To ensure patient safety, we will sequentially monitor for the DLT rate using a Pocock-type boundary for repeated testing for toxicity when at least 5 patients are evaluable and the rate will be evaluated on every cohort of 5 patients (i.e., at n=5, 10 15, 20) to ease practical implementation. This boundary is equivalent to testing the null hypothesis, after each patient, that the acute DLT rate is 15%, using a one-sided level 0.020611 test. The accrual will be halted if excessive numbers of severe adverse events are seen, that is, if the number of DLTs is equal to or exceeds boundary (b_n) out of a total of n patients treated and at the completion of evaluation (see table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary ≤0.05 (i.e., the probability of early stopping) when the rate is equal to the acceptable rate of 0.15, i.e., Pr(# of excessive events among n patients ≥ b_n | treatment-related DLT rate = 0.15)≤0.05).

Because the very similar HypoFlame trial evaluating a simultaneous integrated boost to 50 Gy in 5 fractions using SBRT to the MR-detected disease (the same dose employed in this trial) reported no acute grade 3 GI/GU adverse events in a cohort of 100 patients (Draulans, 2020), we expect a very low rate of DLT and so will conduct sequential monitoring without pausing enrollment while we wait for toxicity evaluation of patients on treatment.

Number of Patients (*n*)	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**	13	14	**15**	16	17	**18**	19	20
Boundary (b_n)	-	-	**3**	3	4	**4**	4	5	**5**	5	5	**6**	6	6	**6**	7	7	**7**	7	8
Number of Patients (*n*)	**21**	22	23	**24**	25															
Boundary (b_n)	**8**	8	8	**8**	9															

If yes, please provide data describing whether any patients have met the stopping rules:

UPN	**Relevant AE** (Grade and CTCAE event name)	**# of days tx delayed (or N/A)**	**Did pt stop tx due to AE?**	**Date of AE**	**# of pts enrolled at time of AE**

Response					
UPN	**On Tx Date**	**# of fractions completed**	**Patient replaced? (y/n)**	**DLT? (y/n)**	**Biochemical recurrence? (y/n)**

Treatment Discontinuation and Survival				
UPN	**Off Tx Date**	**Reason for discontinuation of treatment**	**Vital status**	**If dead, cause**

Summary of Specimen Collections			
Type of specimen	**Time point**	**# of patients eligible for collection at this time point**	**% of patients who have reached this time point and had the specimen collected**
No specimen collections per protocol.			