Mayo Clinic Radiation Oncology

MC1651: Prospective evaluation of Hypofractionation Proton beam therapy with Concurrent Treatment of the Prostate and Pelvic Nodes for Clinically Localized, Intermediate or High Risk Prostate Cancer

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*Study contributor(s) not responsible for patient care.

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Protocol Resources

Questions:	Contact Name:
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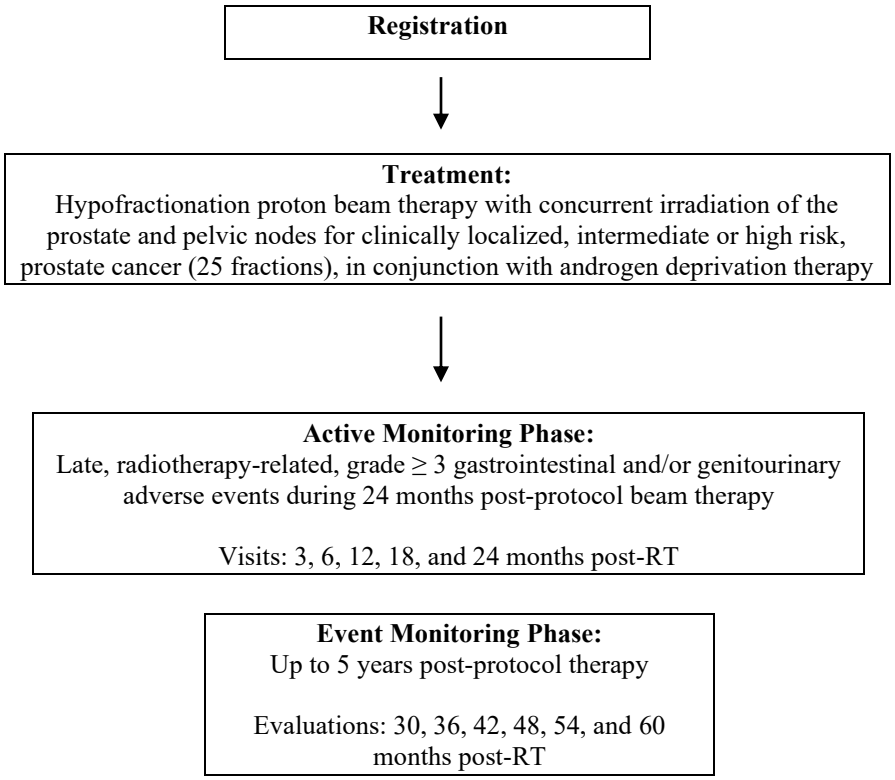
List of Abbreviations

AE	Adverse Event/Adverse Experience
BED	Biologic equivalent dose
CFR	Code of Federal Regulations
CRF	Case Report Form
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GU	Genitourinary
HIPAA	Health Insurance Portability and Accountability Act
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
PHI	Protected Health Information
PI	Principal Investigator
PSA	Prostate Specific Antigen
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
RT	Radiation Therapy

Schema


Registration
Treatment:
Hypofractionation proton beam therapy with concurrent irradiation of the prostate and pelvic nodes for clinically localized, intermediate or high risk, prostate cancer (25 fractions), in conjunction with androgen deprivation therapy
Active Monitoring Phase:
Late, radiotherapy-related, grade ≥ 3 gastrointestinal and/or genitourinary adverse events during 24 months post-protocol beam therapy
Visits: 3, 6, 12, 18, and 24 months post-RT
Event Monitoring Phase:
Up to 5 years post-protocol therapy
Evaluations: 30, 36, 42, 48, 54, and 60 months post-RT

1.0 Background

1.1 Current status of radiotherapy (RT) when elective pelvic nodal irradiation is considered for clinically localized, intermediate and high risk, prostate cancer

Clinically localized prostate cancer is classified as 'high' risk, when there is a clinical stage T3-4, Gleason score 8-10, or Prostate Specific Antigen (PSA) > 20 ng/mL, and as 'intermediate' risk disease, when there is a clinical stage T2b-2c, Gleason score 7, or PSA 10-20 ng/mL. When such high or intermediate risk prostate carcinoma is treated with RT, elective pelvic nodal irradiation is often considered (along with definitive RT to the prostate and seminal vesicles), since there is concern that regional pelvic nodes may harbor occult metastasis.

When regional pelvic nodes are to be irradiated along with RT to the primary tumor in the prostate +/- seminal vesicles, RT is usually delivered in two phases in the current clinical practice. The first phase is to irradiate both regional pelvic nodes and the primary tumor in the prostate +/- seminal vesicles with a dose of 45 Gy in 25 fractions. The second phase involves reducing the clinical target volume to the prostate +/- seminal vesicles and delivering an additional dose of 34.2 Gy in 19 fractions. This entails delivering daily 1.8 Gy per fraction to a total dose of 79.2 Gy over 8.8 weeks.

Adding androgen deprivation therapy to RT is a standard of care for high risk prostate cancer and to a lesser extent for intermediate risk prostate cancer, based on a number of phase III studies demonstrating its overall or disease-free survival benefit. The duration of androgen deprivation therapy is usually 2-3 years for high risk, and 4-6 months for intermediate risk prostate cancer.

1.2 Hypofractionation as dose escalation

Dose escalation in RT can be achieved either adding more fractions (with the conventional dose fraction size of 1.8 to 2 Gy per fraction daily) or altered fractionation schedule (with hypo- or hyper-fractionation). Hypofractionation refers to an altered dose fractionation scheme in which the daily radiation dose is increased beyond the conventional 1.8 to 2 Gy per fraction. Although a total radiation dose is usually lower with hypofractionation, a higher doe per fraction is a method of biologically intensifying the radiation dose over a shorter period of time.

Clinical and laboratory studies have suggested that prostate cancer has a relatively slow rate of proliferation, characterized by a low α/β value (1.5 to 3 Gy) in a linear quadratic model for cell survival after irradiation[1-4]. This implies that a larger radiation dose per fraction (i.e. hypofractionation) is more effective in cell killing for prostate cancer than simply adding more fractions. Another major advantage of hypofractionation is its convenience and lower treatment cost, as it allows a shorter treatment duration with a reduced number of RT fractions.

1.3 Proton beam therapy

Proton beam therapy delivers a radiation dose with positively charged atomic particles (protons), while conventional external beam RT does with photons. Unlike photons, protons have a physical property to deposit most of their energy only when they reach their target. This allows protons to deliver a radiation dose to a target more preferentially,

while minimizing a dose to nearby normal organs. Thus, a delicate balance of delivering a high radiation dose to eradicate prostate cancer while largely sparing the nearby normal organs (such as rectum, bladder, and small bowel) can be achieved much better with proton beam therapy than with conventional RT. A study of dose-volume histogram has shown in the treatment of prostate cancer that proton beam therapy delivers less radiation dose to the dose-limiting normal organs, in comparison to conventional, photon-based, intensity modulated RT (IMRT)[5].

Several studies have reported that proton beam therapy can provide a therapeutic gain by offering at least equivalent (or superior) tumor control while reducing the risk of radiation toxicity, in comparison with conventional photon-based external beam RT, for clinically localized prostate cancer[6-9]. In these studies, proton beam therapy achieved at least equivalent or better biochemical relapse-free rates, while yielding lower incidences of acute and late radiation toxicity, in comparison with conventional RT. In a study comparing patient-reported quality of life between the two prospectively collected databases, Hoppe suggested approximately 50% reduction in significant bowel urgency and frequency in patients treated with proton beam therapy compared with IMRT[10].

In the current proton beam therapy of prostate cancer, the target volume has been mostly limited to the prostate and the adjacent seminal vesicles. There has been no prospective study of proton beam therapy to treat both the primary tumor in the prostate and the regional pelvic nodes simultaneously using a hypofractionation regimen.

1.4 Study proposal

In the proposed study, the prostate +/- seminal vesicles will be treated with a hypofractionation regimen using daily 2.7 Gy fractions to 67.5 Gy, while the regional pelvic lymph nodes will be simultaneously treated with daily 1.8 Gy fractions to 45 Gy, using proton beam therapy. Assuming a α/β value of prostate carcinoma between 1.5 and 3 Gy, 67.5 Gy in 2.7 Gy fractions is equivalent to 80.2 Gy to 85.9 Gy in 1.8 Gy fractions. The overall treatment time is 5 weeks, which is about 3.8 weeks shorter than the standard conventional dose fractionation schedule (44 fractions over 8.8 weeks). A high precision RT technique using pencil beam proton therapy and daily on-line targeting of the prostate gland is employed to minimize the dose to adjacent normal organs (bladder, rectum, and small bowel), which will, in turn, reduce the risk of radiation toxicity.

1.5 Biologic equivalent dose (BED) calculation for the proposed hypofractionation RT

Using the linear quadratic model for cell survival after irradiation, a numeric value called biologic equivalent dose (BED) can be calculated. BED is often used when different fractionation regimens are compared with respect to their radiobiologic effects on acute and late responding tissues[11]. A higher BED equates to better tumoricidal effect and, at the same time, higher risk of normal tissue toxicity.

BED = total dose x relative effectiveness

$BED = (nd) \times [1 + d / (\alpha/\beta)]$

n: number of fractions (treatments)

d: dose per fraction

α/β: numeric value reflecting acute or late responding tissue

Table 1 shows BEDs for prostate cancer with the proposed hypofractionation regimen (67.5 Gy at 2.7 Gy per fraction) versus with the conventional dose fractionation scheme (79.2 Gy at 1.8 Gy per fraction), when α/β ratio of prostate cancer = 1.5 or 3. Prostate cancer is considered to have a low rate of proliferation similar to late responding tissues with a α/β ratio ranging from 1.5 to 3 in the linear quadrantic model[1-4]. This means that prostate cancer is more sensitive to a fractionation size (dose per treatment), with a higher dose per treatment resulting in more effective tumor control. As depicted in the Table 1, the hypofractionation regimen provides a higher BED, which means greater tumoricidal effect.

Table 1: BEDs for Prostate Cancer

α/β values	79.2 Gy at 1.8 Gy/fraction	67.5 Gy at 2.7 Gy/fraction*
1.5	174.2	189.0
3	126.7	128.3

*Protocol dose

To properly address a potential therapeutic gain of the proposed hypofractionation regimen, its impact on acute and late responding normal tissues needs to be also addressed. Table 2 compares BEDs between the hypofractionation regimen and the conventional dose fractionation scheme with respect to both acute and late responding normal tissues. The α/β value of acute responding normal tissues (i.e. cells with high turnover) is estimated in the range of 10 (e.g. mucosal tissues), while late responding normal tissues (i.e. cells with low turnover) is considered to have a low α/β value in the range of 3 (e.g. parenchymal cells)[11].

For acute responding normal tissues, BED of the hypofractionation regimen is slightly lower than that of the conventional dose fractionation scheme. This suggests that the likelihood of observing a higher incidence of acute radiation toxicity with the hypofractionation regimen is unlikely. In contrast, for late responding normal tissues, BED of the hypofractionation regimen is slightly higher than that of the conventional dose fractionation scheme. This means that the hypofractionation regimen has potentially a slightly higher probability of late radiation injury (such as radiation proctopathy or cystourethritis), when no other strategy to reduce the risk of radiation toxicity is integrated to the regimen. In order to counterbalance this negative effect on the late responding normal tissues, the proposed study has incorporated high precision RT techniques (pencil beam proton therapy, and daily on-line targeting of the prostate using intraprostatic fiducial markers and computed tomography imaging) that reduce the volume of normal tissues exposed to a high radiation dose. This reduction in the irradiated volume of normal tissues would, in turn, minimize the risk of late radiation toxicity.

Table 2: BEDs for Acute and Late Normal Tissue Toxicity

α/β values	79.2 Gy at 1.8 Gy/fraction	67.5 Gy at 2.7 Gy/fraction*
10 (Acute Responding Tissues)	93.5	85.7
3 (Late Responding Tissues)	126.7	128.3

*Protocol regimen

1.6 Other studies evaluating hypofractionation regimens in photon radiotherapy setting

The efficacy of the proposed hypofractionation regimen in a photon RT setting has been recently reported by Cheung et al [12, 13]. In this prospective study of 97 patients, a hypofractionation regimen of 67.5 Gy in 25 fractions was delivered to the prostate +/- seminal vesicles, along with a simultaneous irradiation of regional pelvic nodes with 45 Gy in 25 fractions, over 5 weeks. The prostate and seminal vesicles were irradiated with intensity-modulated radiotherapy (IMRT) technique, while the regional pelvic nodes were treated with either three-dimensional conformal radiotherapy (3D-CRT; 67 patients) or IMRT (30 patients). The study targeted patients with high risk prostate carcinoma (clinical stage T3, Gleason score 8-10, or PSA ≥ 20). Median age of the cohort was 71 years. The patients received adjuvant androgen deprivation therapy for median duration of 29.8 months

Table 3 shows the incidence of the maximal acute gastrointestinal (GI) and genitourinary (GU) toxicity in the study, using the National Cancer Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Table 3: Incidence of maximal acute GI and GU toxicity (%)					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
GI toxicity	4.3	59.1	36.6	0	0
GU toxicity	7.5	49.5	38.7	4.3	0

Table 4 shows the incidence of maximal late GI and GU toxicity, using the Radiation Therapy Oncology Group (RTOG) late morbidity criteria, with median follow-up of 39 months.

Table 4: Incidence of maximal late GI and GU toxicity (%)					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
GI toxicity	53.8	39.8	6.5	0	0
GU toxicity	82	8	5	3	1

With median follow-up of 62 months, PSA relapse-free rate and survival was 83.7% and 92.2%, respectively, at 5 years. Of the 33 patients who underwent a 5-year prostate biopsy, only 4 (12.1%) had a positivity showing viable malignant cells.

Pollack et al. reported a phase III study comparing 76 Gy in 38 fractions (2 Gy per fraction; conventional fractionation regimen) with 70.2 Gy in 26 fractions (2.7 Gy per fraction; hypofractionation regimen) for low- to high-risk prostate cancer[14]. Clinical target volume of radiotherapy was limited to the prostate and seminal vesicles for low- and intermediate-risk prostate cancer, while regional pelvic nodes were included, along with the prostate and seminal vesicles, for high-risk prostate cancer. Patients were treated with IMRT technique. Adjuvant androgen therapy was variable, depending on the risk category. There were a total of 307 patients randomized between the two fractionation regimens. With median follow-up of 68.4 months, there was no difference in the rate of PSA relapse and/or clinical disease recurrence at 5 years: 21.4% for the conventional fractionation arm vs. 23.3% for the hypofractionation arm. There were no statistically significant differences in acute and late toxicity between the two arms. Table 5 shows late

GI and GU toxicity, using modified LENT (Late Effects of Normal Tissues)/RTOG criteria.

Table 5: Late GI and GU toxicity: Crude incidences (%)								
	76 Gy in 38 fractions				70.2 Gy in 26 fractions			
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 0	Grade 1	Grade 2	Grade 3
GI toxicity	18.5	58.9	20.5	2	28.2	53.7	16.1	2
GU toxicity	2	50.3	44.4	3.3	3.4	51.7	40.9	4

Another phase III study compared 80 Gy in 40 fractions (2 Gy per fraction over 8 weeks) with 62 Gy in 20 fractions (3.1 Gy per fraction over 5 weeks) for high-risk prostate cancer[15, 16]. Clinical target volume of radiotherapy was limited to the prostate and seminal vesicles. Patients were treated with 3D-CRT technique, and received 9-month adjuvant androgen deprivation therapy. A total of 168 patients were randomized between the two fractionation regimens. With median follow-up of 70 months, there was no statistical difference in the rate of PSA relapse (15% for 62 Gy/20 fractions vs. 26% for 80 Gy/40 fractions, $p = 0.065$), local recurrence, and distant metastasis at 5 years. Table 6 shows acute GI and GU toxicity, using the RTOG/EORTC scale. Table 7 shows late GI and GU toxicity, using a modified LENT–SOMA scale.

Table 6: Acute GI and GU toxicity: Crude incidences (%)				
	80 Gy in 40 fractions		62 Gy in 20 fractions	
	Grade ≥ 2	Grade 3	Grade ≥ 2	Grade 3
GI toxicity	21	0	35	0
GU toxicity	40	1.2	47	1.2

Table 7: Late GI and GU toxicity: Crude incidences (%)				
	80 Gy in 40 fractions		62 Gy in 20 fractions	
	Grade ≥ 2	Grade 3	Grade ≥ 2	Grade 3
GI toxicity	12	0	14	1.2
GU toxicity	6	2.4	8	0

1.7 High precision RT techniques in the proposed study

Mayo Clinic conducted a prospective study to examine the motion of the prostate and the stability of intraprostatic gold fiducial markers, using an electronic portal imaging device[17]. The study found that gold fiducial markers were stable within the prostate and that there was a significant prostate motion between radiation fractions (i.e. inter-fraction motion). It demonstrated that fiducial markers in the prostate gland allowed a significant margin reduction for planning target volume (PTV) when used for on-line localization of the prostate. Margins of 5-7.3 mm around the prostate for inter-fraction prostate motion could be reduced to 3 mm by daily on-line localization of the prostate using intraprostatic gold fiducial markers. As a result of this study, the implant of fiducial markers in the prostate gland, the application of a reduced margin for PTV, and the use of IMRT (to achieve better conformity around the prostate) have been a standard of care for photon RT of prostate cancer at Mayo Clinic.

When RT is delivered using daily setup based on prostate position, uncertainty arises about the dose coverage of pelvic nodes in the setting of simultaneous irradiation of the prostate and pelvic nodes, because the motion of pelvic nodes can be independent of prostate motion. The Stanford group reported that in the absence of a significant systemic offset, there were negligible changes in dose coverage of the pelvic nodes or normal tissue sparing when prostate fiducial markers were used for daily localization in the IMRT setting[18]. In another study, Adamczyk retrospectively evaluated the impact of correcting inter-fraction prostate motion upon the dose delivered to pelvic nodes in 28 patients, based on 253 cone beam computed tomography (CBCT) taken during the radiotherapy[19]. In this study, the target (prostate) was matched based on CBCT imaging, and there were no fiducial markers in the prostate. Shifting treatment fields on CBCT prostate matching influenced minimum, maximum, and mean dose of pelvic nodes in the range of 0.17% - 2.63%. At our own center, there are currently two prostate cancer patients receiving pencil beam proton beam therapy to the pelvic nodes as well as to the prostate. In these patients, proton beam therapy was delivered after a treatment set-up was established by matching prostate carbon markers using kV orthogonal imaging. During the course of proton beam therapy, they had verification CT scans in order to assess whether clinical target volumes including the pelvic nodes were adequately covered. One patient had three verification CT scans and the other had one. All of the verification scans showed that > 95% of the clinical target volume encompassing the pelvic nodes received the prescription dose (45 Gy), and that the standard deviation in the volume covered by 45 Gy was 1.5%. These findings as well as the aforementioned studies indicate that setting up the RT field using the fiducial markers in the prostate or CBCT matching of the prostate does not significantly jeopardize a dosimetric coverage of the pelvic nodes, and can be utilized for the simultaneous irradiation of the prostate and pelvic nodes.

In the proposed study, high precision RT techniques using pencil beam proton therapy and daily on-line targeting of the prostate and pelvic nodal region are employed to ensure the accurate delivery of radiation to the intended targets, while minimizing the dose to the adjacent normal organs (such as bladder, rectum, and small bowel). The goal of these precision RT techniques is to minimize the risk of radiation toxicity as much as possible. Proton beam therapy provides a dosimetric advantage, in comparison with photon RT, since it deposits the bulk of its energy to the target while delivering minimal dose to healthy tissues around the target. The delivery of proton beam therapy is further refined by pencil beam scanning technology in which proton is more precisely delivered in accordance to the depth and contour of the tumor, thus further reducing unnecessary radiation to the surrounding healthy tissues. Daily on-line targeting of the intended targets is achieved with two independent methods: 1. Carbon fiducial markers implanted into the prostate, which can be visualized on an onboard imaging. Using the carbon markers as a surrogate for prostate position, the treatment field is adjusted daily to be aligned with the position of the carbon markers in order to ensure that the prostate is in the proper treatment coordinates. 2. Limited computed tomography imaging to confirm that the prostate and pelvic nodal chains are within the planning target volumes. Computed tomography imaging allows a volumetric conformation that the prostate and pelvic nodes are within the planning target volumes.

1.8 Significance of the proposed study

If the proposed RT regimen proves to be safe and effective, it will have a major impact in the current radiotherapy of prostate cancer. It may demonstrate not only its therapeutic

efficacy, but also its cost effectiveness and convenience as it allows a shorter treatment duration with a reduced number of RT fractions. This can be particularly appealing to prostate cancer patients who otherwise face 8.8 weeks of daily treatment in the conventional dose fractionation schedule. A shorter treatment course with a reduced number of RT fractions also means substantial cost savings to the health care system. Additionally, the outcome of this study can be a basis for a large phase III clinical trial comparing the hypofractionation regimen to a standard conventional dose fractionation schedule.

2.0 Goals

2.1 Primary

2.1.1 To assess late ≥ grade3 GI and/or GU toxicity of interest with the hypofractionation proton beam therapy regimen

2.2 Secondary

2.2.1. Late grade ≥ 2 GI and/or GU toxicities of interest within 24 months after the protocol RT, using the CTCAE v4.0.

2.2.2. Acute grade ≥3 GI and/or GU toxicities of interest during and within 3 months after the protocol RT, using the CTCAE v4.0.

2.2.3. Disease-free survival including freedom from PSA relapse at 5 years

2.2.4. Disease-specific survival at 5 years

2.2.5. Overall survival at 5 years

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1. Male; Age ≥ 18 years.

3.1.2. Histological confirmation of adenocarcinoma of the prostate within 6 months of study enrollment.

3.1.3. Clinical stage T1-2 N0 M0, Gleason Score ≤ 7, PSA 20-100 ng/mL, or
Clinical stage Any T N0 M0, Gleason Score 8 -10, PSA ≤ 100 ng/mL, or
Clinical stage T3-4 N0 M0, any Gleason Score, PSA ≤ 100 ng/mL, or
Clinical stage T1-2 N0 M0, Gleason Score 4 + 3, PSA 10-20 ng/mL

3.1.4. Zubrod performance score (PS) ≤ 1(Appendix 1).

3.1.5. Total bilirubin, AST, ALP, and serum creatinine: < 2 x upper normal limit

3.1.6. Signed informed consent.

3.2 Exclusion Criteria

3.2.1. Any known nodal (N1) or distant metastasis (M1)

3.2.2. Previous androgen deprivation therapy lasting more than 6 months

3.2.3. History of inflammatory bowel disease

3.2.4. Presence of a hip prosthesis

3.2.5. Prior pelvic radiotherapy or prostatectomy

3.2.6. Prior or concurrent antineoplastic agents (chemotherapy)

3.2.7. Previous or concurrent malignancy other than non-melanoma skin cancer within 5 years of diagnosis of prostate cancer.

3.2.8. Inability to start the protocol treatment within 1 month after study enrollment.

3.2.9. Medical or psychiatric conditions that preclude informed decision-making or compliance with the protocol treatment or follow-up

4.0 Test Schedule

Tests and procedures	Active Monitoring Phase					Event Monitoring Phase
	≤ 120 days prior to registration	Within 2 weeks prior to RT	During RT (weekly)	End of RT (+/- 5 days)	Post-RT month[3]: 3, 6, 12, 18, and 24	Post-RT month[3]: 30, 36, 42, 48, 54, and 60
History, Physical exam, ECOG	X				X	X[7]
PSA	X				X	X
Serum total testosterone	X				X[2]	X[2]
CBC, AST, ALP, Total Bilirubin, Creatinine	X				X[4]	X[4]
Path review[1]	X					
CT scan of abdomen and pelvis, or MRI of pelvis	X				X[4]	X[4]
Bone scan	X				X[4]	X[4]
GI and GU toxicity assessment (CTCAE v4.0)		X	X	X	X	X
Questionnaires[5]	X[6]			X	X	X

1. Optional; For outside prostate biopsy only
2. Serum total testosterone: to be performed post-RT month 12, 24, 36, 48, and 60
3. Month: targeted month +/- 1 month
4. Only when relapse occurs
5. Questionnaires [including Patient-Reported Outcomes version of the CTCAE, EPIC-26, American Urologic Association Symptom Index score *(paper),* and International Index of Erectile Function – Erectile Function Domain *(paper)*], which are currently parts of a routine clinical practice, will be administered electronically to patient in conjunction with the Registry and IRB# 15-000136.

6. Baseline questionnaires should be completed prior to patient starting hormone therapy if possible.
7. Only at 36, 48, and 60 months

5.0 Stratification Factors

None

6.0 Registration Procedures

Registration to the study will take place when a patient has met eligibility criteria, signed an informed consent, and has been logged into Research Participant Tracking (Ptrax).

7.0 Protocol Treatment

Protocol treatment consists of proton beam therapy, in combination with 28 months of androgen deprivation therapy (or 4-6 months of androgen deprivation therapy for intermediate risk prostate cancer).

7.1. Proton beam therapy

7.1.1 Treatment planning

7.1.1.1. Preparation prior to simulation

A minimum of 1 day prior to a scheduled CT simulation, a total of four carbon markers are implanted into the prostate gland (two in the left and two in the right lobe of the prostate gland), via transperineal approach, under a transrectal ultrasound guidance by a radiologist. These implanted carbon markers are used for daily image-guided proton beam therapy.

Bladder preparation: A patient is to void one hour before simulation or treatment. Right after voiding, he drinks 250 or 500 mL (8.5 or 16.9 oz) of water over the following 15 minutes. Then he does not void until he completes a CT simulation or treatment. This systemic approach is to minimize day-to-day variation of bladder volume as much as possible.

7.1.1.2. Simulation

A planning CT scan will be performed with a patient in supine position. A custom vacuum lock bag is to be used for immobilization during simulation and treatment. It should be built up around the patient's feet to reduce the variation in foot rotation. An indexed knee cushion may be added to the setup, if desired.

An inflated endorectal balloon is optional, and can be used for prostate immobilization. An endorectal balloon is to be inflated with 100 mL of diluted contrast (consisting of 5 mL Gastroview mixed with 95 mL normal saline). At the time of CT simulation, the insertion depth of endorectal balloon will be recorded at the level of anal verge. The same insertion depth will be applied when an endorectal balloon is inserted during the course of proton beam therapy.

Bladder contrast may or may not be used at the time of CT simulation at the discretion of attending physician. When bladder contrast is to be used, the

following steps are to be taken: (1) Insert a Foley catheter into the bladder, (2) Drain 40-50 mL of urine, (3) Replace the drained amount of urine with the same volume of diluted contrast (made of 5 mL of Omnipaque mixed with 55 mL of sterile water) into the bladder via a Foley catheter, (4) Remove the Foley catheter thereafter.

A bladder scanner will be used to measure a bladder volume at the time of CT simulation. The target bladder volume to be achieved at the time of MR simulation and during the course of proton beam therapy will be the measured volume at the time of CT simulation +/- 25%.

CT simulation scanning will be performed from immediately above the iliac crests through at least the ischial tuberosities with 1 - 2.5 mm slice thickness.

Shortly after CT simulation is completed, MRI of the pelvis (MR simulation)will be obtained with the same set-up described above. No contrast should be used for bladder or an endorectal balloon. When an endorectal balloon is used, it should be inflated with normal saline (100 mL). MR imaging will be fused with the planning CT imaging, using the implanted carbon markers as references.

7.1.1.3. Target volumes

7.1.1.3.1 Clinical target volume (CTV)

There are two clinical target volumes: CTV1 and CTV2.

CTV1 is the prostate plus a portion of or entire seminal vesicles. The extent of seminal vesicles to be included in CTV1 is at the judgement of the attending physician and based on clinical and pathologic features of a given malignancy.

CTV2 is the regional pelvic nodes. CTV2 includes the obturator, external iliac, proximal internal iliac and common iliac nodes, up to a level corresponding to the sacral promontory so that most of the common iliac nodes are included. Please refer to the pelvic nodal atlas at the RTOG Web site (Pelvic Lymph Node Volumes for Prostate Cancer Atlas; [redacted] The presacral nodes from the sacral promontory to S3 may be included, depending on whether the dose constraints to the rectum are achievable. The inferior extent of the external iliac lymph nodes is generally at the top of the femoral heads. The inferior extent of the obturator lymph nodes is generally at the top of the symphysis pubis. CTV2 will include a 7 mm margin in 3-dimensions to the iliac vessels, and a 10 mm margin anteriorly from the anterior sacral bone for prescaral nodes. Adjacent normal organs (such as small bowel, large bowel, bladder, and rectum), pelvic musculature, and bones are carved out from CTV2.

7.1.1.3.2. Internal target volume (ITV)

ITV is an additional margin around CTV to ensure proper dose coverage of CTV, given changes in the dose distribution caused by target motion.

ITV1: CTV1 + 4-5 mm expansion for superior, inferior, anterior, and posterior directions, and 5-6 mm expansion in the lateral direction.

ITV2: CTV2 + 5 mm expansion in all directions

7.1.1.3.3 Optimization target volume (OTV): A volume constructed by a dosimetrist under the guidance of a physicist. The OTV is a volume used by the treatment-planning-dose-optimization algorithm to ensure that the ITVs and CTVs are treated with a planned radiation dose. It includes set-up and range uncertainties of 3 mm and 3 %, respectively. The OTV is to provide a robust coverage of CTV and ITV. The evaluation of a proton plan is based on a robust coverage of CTV and ITV. The OTV should not be considered when evaluating the treatment plan.

7.1.1.4 Normal Critical Structures

Normal critical structures to be defined on the treatment planning CT scan include the bladder, rectum, large bowel, small bowel, bilateral femora (to the level of ischial tuberosity), penile bulb, and skin. The structures will be contoured and considered as solid organs. The bladder should be contoured from its base to the dome, and the rectum from the anus (at the level of the ischial tuberosity) to the rectosigmoid flexure. Any small bowel within the primary beam aperture should be defined. Please refer to the RTOG web site [redacted] view the normal pelvis atlas for examples of target and normal tissue contours.

7.1.1.5 Treatment planning for critical structures

Plan quality and acceptability will be assessed in accordance to dose-volume histogram (DVH) parameters of target volumes and organs at risk (OAR) using the constraints shown in the following Table.

Target DVH Objectives			Priority
CTV	Max[Gy]		Report
	Max[%]		Report
	Min[Gy]		Report
	Min[%]		Report
	Mean[Gy]		Report
	D2%[%]		Report
	D5%[%]		Report
	D95%[%]		Report
	D98%[%]	100% (via normalization)	Report

	V110%[cc]		Report
	V98%[%]		Report
	V99%[%]		Report
	V100%[%]	98% (via normalization)	1
	V107%[%]		Report
	Volume[cc]		Report
	CV98%[%]		Report
	CV98%[cc]		Report
ITV	Max[Gy]		Report
	Max[%]	< 105%	1
	Min[Gy]		Report
	Min[%]	>90%	3
	Mean[Gy]		Report
	D2%[%]	<= 104 %	3
	D5%[%]		Report
	D95%[%]	>= 95 %	3
	D98%[%]		Report
	V110%[cc]	0 cc	1
	V98%[%]	>= 98 %	1
	V99%[%]	>= 98 %	2
	V100%[%]	>= 95 % (or 95%)	2 (or 1, normalization)
	V107%[%]	<= 2 %	1
	Volume[cc]		Report
	CV98%[%]	<= 2 %	1
	CV98%[cc]		Report

Normal Tissue DVH Objectives			**Priority**
Bladder	D2cc[Gy]	< 72.91 Gy	1
		< 72.14 Gy	2
	V36Gy[cc]		Report
	V57Gy[cc]		Report
	V61Gy[cc]		Report
	V66Gy[cc]		Report
	V36Gy[%]	33%	1
		17%	2
	V57Gy[%]	15%	1
		9%	2
	V61Gy[%]	11%	1
		8%	2
	V66Gy[%]	8%	1
		5%	2
	Volume[cc]		Report
Right femoral head	Max[Gy]	< 34.96 Gy	1
		< 32.69 Gy	2
	Mean[Gy]	<= 23.95 Gy	1
		<= 18.28 Gy	2
	V32Gy[%]	<= 5%	1
		<= 2%	2

	V14Gy[%]	<= 91% <= 66%	1 2
Left femoral head	Max[Gy]	< 34.96 Gy < 32.69 Gy	1 2
	Mean[Gy]	<= 23.95 Gy <= 18.28 Gy	1 2
	V32Gy[%]	<= 5% <= 2%	1 2
	V14Gy[%]	<= 91% <= 66%	1 2
Rectum	D2cc[Gy]	< 71.54 Gy < 71.19 Gy	1 2
	V44Gy[cc]		Report
	V53Gy[cc]		Report
	V57Gy[cc]		Report
	V61Gy[cc]		Report
	V66Gy[cc]		Report
	V44Gy[%]	24% 18%	1 2
	V53Gy[%]	17% 14%	1 2
	V57Gy[%]	15% 11%	1 2
	V61Gy[%]	12% 9%	1 2
	V66Gy[%]	9% 6%	1 2
Penile bulb	Mean[Gy]		Report
	D50%[Gy]	<= 47 Gy	2
	D70%[Gy]	<= 36 Gy	3
Large bowel	D2cc[Gy]		Report
	V44Gy[cc]		
	V53Gy[cc]		
	V57Gy[cc]		
	V61Gy[cc]		
	V44Gy[%]	24% 18%	1 2
	V53Gy[%]	17% 14%	1 2
	V57Gy[%]	15% 11%	1 2
	V61Gy[%]	12% 9%	1 2
	V66Gy[%]	9% 6%	1 2
Small bowel	Max[Gy]	< 52 Gy	3
	D2cc[Gy]		Report
	V30Gy[cc]	< 300 cc	3
	V45Gy[cc]	< 150 cc	2
	V50Gy[cc]	< 2 cc	3

Body - OTV	V50%[cc]		Report
	V100%[cc]		Report
	V105%[cc]	0 cc	1

For purposes of compliance, up to a 5% absolute increase in the volume of critical structure receiving a specified dose (or higher) will be considered acceptable and called “minor deviation”. When there is a ≥ 5% absolute increase in the volume of critical structure receiving a specified dose (or higher), it will be considered unacceptable and called a “major deviation”. [Example: rectum V66Gy < 14%, but > 9%: minor deviation; rectum V66Gy ≥ 14% major deviation]

Of note, the penile bulb constraint is to be regarded as a guideline, and adherence to this should not, in any way, result in a reduction of the prescription dose or a compromised dose coverage of the target volume.

The deviations in dose constraints described above are considered planning deviations only and will not constitute protocol deviations. Treatment plans that include minor planning deviations may be delivered as part of this protocol. Treatment plans that include major planning deviations may be delivered on this protocol with the review and approval of the attending physician prior to treatment. All relevant DVH data regarding doses to critical structures will be maintained in the study database for analysis.

7.1.2 Target Dose

A prescribed dose of 67.5 Gy in 25 fractions (2.7 Gy per fraction per day, 5 days a week) is delivered to ITV1, while ITV2 is concurrently treated to a dose of 45 Gy in 25 fractions (1.8 Gy per fraction).

7.1.3 Treatment Administration

An optimal, pencil beam, proton therapy plan is prepared to achieve proper dose coverage of ITVs. Plan quality and acceptability is assessed, based on dose-volume histogram parameters of target volumes and organs at risk.

7.1.4 Treatment localization and verification

7.1.4.1 Patient set-up for daily proton beam therapy is identical to the CT simulation set-up, including bladder preparation and the application of endorectal balloon, if used. An endorectal balloon is inflated with 100 mL of normal saline (or, if necessary, diluted contrast consisting of 10 mL Gastroview mixed with 90 mL normal saline).

7.1.4.2 On-line target localization and image-guided proton beam therapy:
7.1.4.2.1 Use of implanted carbon fiducial markers
Daily kV orthogonal imaging of the implanted, intra-prostatic, carbon markers (from an on-board imager) should be used to

confirm the treatment set-up and to account for inter-fraction motion. A patient's position should be adjusted, using the fiducial markers as references.

7.1.4.1.2 Use of volumetric imaging with CT on a rail

The use of volumetric imaging with CT on a rail is strongly encouraged, if available, but not mandatory. Volumetric imaging is taken with a CT scan on a rail, after a treatment set-up is established using kV orthogonal imaging of the fiducial markers. This is to verify that ITV is properly covered volumetrically. Volumetric imaging is taken daily for the first 5 treatments and then twice weekly (every Monday and Thursday) thereafter.

7.2 Concurrent androgen deprivation therapy

As part of the standard of care, adjuvant androgen deprivation therapy is added to proton beam therapy for 2-3 years for high risk prostate cancer, and 4-6 months for intermediate risk prostate cancer. Androgen deprivation therapy usually starts 2 months prior to the beginning of proton beam therapy. It consists of bicalutamide 50 mg PO once daily for 2-16 weeks (given at the start of androgen deprivation therapy) and a LHRH agonist (gosereline or leuprolide). The first injection of a LHRH agonist is usually given within 7 days after the initiation of bicalutamide.

8.0 Radiotherapy Dose Modifications Based on Adverse Events

With judicious use of ancillary treatment (see Section 9.0) and/or treatment interruption, it is anticipated that a dose reduction should rarely be necessary. This study has no pre-specified dose reduction due to adverse events. However, if adverse events are severe enough that administration of full dose is considered contraindicated by the attending Radiation Oncologist, the study chair [redacted] should be notified.

Treatment interruption(s) are permitted only when radiation-related adverse events are not reduced to an acceptable level with the use of ancillary treatment (see Section 9.0), or when acute grade ≥3 AEs occur. The reason(s) for the interruption must be documented. The duration of treatment interruption should be minimized, but proton beam therapy should not resume until AEs are grade <3.

9.0 Ancillary Treatment/Supportive Care

Supportive measures such as antiemetic or antidiarrheal medications, steroid-containing topical preparations, topical bladder analgesic (e.g., phenazopyridine HCl) or anti-spasmodic (e.g., α-adrenergic blockers) agents may be administered in accordance with manufacturer recommendations as deemed necessary.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions

Adverse Event- An untoward or undesirable experience associated with the use of a medical product (i.e. drug, device, biologic) in a patient or research subject.

Serious Adverse Event - Adverse events are classified as serious or non-serious. Serious problems/events can be well defined and include;

- death
- life threatening adverse experience
- hospitalization secondary to radiation treatment, RT side effects or problem due to prostate carcinoma
- inpatient, new, or prolonged; disability/incapacity
- persistent or significant birth defect/anomaly

and/or per protocol may be problems/events that in the opinion of the investigator may have adversely affected the rights, safety, or welfare of the subjects or others, or substantially compromised the research data.

All adverse events that do not meet any of the criteria for serious, should be regarded as non-serious adverse events.

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSO) - Any unanticipated problem or adverse event that meets the following three criteria:

- Serious: Serious problems or events that result in significant harm, (which may be physical, psychological, financial, social, economic, or legal) or increased risk for the subject or others (including individuals who are not research subjects). These include: (1) death; (2) life threatening adverse experience; (3) hospitalization - inpatient, new, or prolonged; (4) disability/incapacity - persistent or significant; (5) birth defect/anomaly; (6) breach of confidentiality and (7) other problems, events, or new information (i.e. publications, DSMB reports, interim findings, product labeling change) that in the opinion of the local investigator may adversely affect the rights, safety, or welfare of the subjects or others, or substantially compromise the research data, **AND**
- Unanticipated: (i.e. unexpected) problems or events are those that are not already described as potential risks in the protocol, consent document, or not part of an underlying disease. A problem or event is "unanticipated" when it was unforeseeable at the time of its occurrence. A problem or event is "unanticipated" when it occurs at an increased frequency or at an increased severity than expected, AND
- Related: A problem or event is "related" if it is possibly related to the research procedures.

Preexisting Condition- A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period. At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

10.2 Recording Adverse Events

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site:

[redacted]

10.2.1 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected and if the adverse event is related to the medical treatment or procedure. With this information, determine whether the event must be reported as an expedited report (see Section 10.3).

10.2.2 Assessment of Attribution
When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event is clearly related to the agent(s).
Probable - The adverse event is likely related to the agent(s).
Possible - The adverse event may be related to the agent(s).
Unlikely - The adverse event is doubtfully related to the agent(s).
Unrelated - The adverse event is clearly NOT related to the agent(s).

10.3 Reporting of Serious Adverse Events and Unanticipated Problems

When an adverse event has been identified, the study team will take appropriated action necessary to protect the study participant and then complete the Study Adverse Event Worksheet and log. The sponsor-investigator will evaluate the event and determine the necessary follow-up and reporting required.

Serious Adverse Events will be reported as part of regular adverse event reporting mechanisms via the data capture system and logged for review reporting.

10.3.1 Investigator Reporting: Notifying the Mayo IRB:

The IRB requirements reflect the guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) in early 2007 and are respectively entitled "Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events" and "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection."

10.3.1.1 According to Mayo IRB Policy any serious adverse event (SAE) which the Principal Investigator has determined to

be a UPIRTSO must be reported to the Mayo IRB as soon as possible but no later than 5 working days after the investigator first learns of the problem/event.

10.3.1.2 Non-UPIRTSO – the investigator reports problems or events that do NOT meet criteria of an UPIRTSO in summary format at the time of the next continuing review. The investigator monitors the severity and frequency of subsequent non-UPIRTSOs.

Consider the following information to collect when developing any forms for documentation of adverse events.
Example
Information collected on the adverse event worksheet (and entered in the research database):

- Subject's name:
- Medical record number:
- Disease/histology (if applicable):
- The date the adverse event occurred:
- Description of the adverse event:
- Relationship of the adverse event to the research (drug, procedure, or intervention):
- If the adverse event was expected:
- The severity of the adverse event: (use a table to define severity scale 1-5)
- If any intervention was necessary:
- Resolution: (was the incident resolved spontaneously, or after discontinuing treatment?)
- Date of Resolution:

The investigator will review all adverse event reports to determine if specific reports need to be made to the IRB and FDA. The investigator will sign and date the adverse event report when it is reviewed. For this protocol, only directly related SAEs/UPIRTSOs will be reported to the IRB.

10.4 CTCAE v4.0 is used for the following AEs to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline:

System Organic Class	Adverse events/Symptoms
Gastrointestinal	Diarrhea
	Fecal incontinence
	Proctitis
	Rectal hemorrhage
	Rectal ulcer
	Small intestinal obstruction

	Stricture/Stenosis: Rectum
Renal/Genitourinary	Bladder spasm
	Hematuria
	Urinary frequency
	Urinary incontinence
	Urinary tract obstruction
	Urinary tract pain
	Urinary urgency
	Cystitis noninfective
	Urinary retention
Sexual/Reproductive function	Erectile dysfunction

Acute AEs are defined as those that occur from day 1, or commencement of radiation therapy, through 3 months after the completion of protocol treatment.

All AEs seen after 3 months after the completion of protocol treatment are considered late effects.

10.4.1 Submit via appropriate reporting mechanisms (i.e., paper or electronic) the following AEs experienced by a patient and not specified in Section 10.4:

Grade 5 AEs (Death)

10.4.1.1.1 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to radiation treatment

10.4.1.1.2 Any death more than 30 days after the patients last study treatment or procedure that is felt to be at least possibly related to radiation treatment must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.5 Monitoring and Auditing

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor, and government regulatory agencies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable compliance offices

10.5.1 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his site. This safety monitoring will include careful

assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan. Medical monitoring will include a regular assessment of the number and type of serious adverse events. Any serious adverse events will be followed up by the sentinel event reporting procedure.

10.5.2 Internal Data and Safety Monitoring Board

As an interventional study, this study will be reviewed in conjunction with the Mayo Clinic Cancer Center DSMB processes. The study will also be reviewed by the Radiation Oncology Research Executive Board on a yearly basis to assess accrual, adverse events, and any endpoint problems. Any safety issues requiring protocol changes will be communicated through protocol amendments.

The trial will be reviewed by the Cancer Center Auditing area on a bi-annual or yearly basis, dependent on random study selection. Accrual, adverse events, and any endpoint problems will be assessed. Any safety issues requiring protocol changes will be communicated through protocol amendments.

11.0 Treatment Evaluation

11.1 No evidence of disease: No clinical evidence of tumor recurrence including the freedom from biochemical (PSA) failure (Section 11.2.2.1)

11.2. Recurrence of disease: The site of recurrence will be collected, and classified as biochemical failure, local recurrence, regional recurrence and/or distant recurrence.

11.2.1 Biochemical (PSA) failure: PSA nadir is defined as the lowest PSA value reached after completion of treatment. Biochemical failure is defined as a PSA value that is ≥ PSA nadir + 2.0 ng/mL with the date of biochemical failure set at the date of the PSA value that meets this criterion.

11.2.2 Local recurrence: Local recurrence is defined when one or more of the followings occur: (1) ureteric obstruction at the level of the ureterovesical junction; urethral obstruction that requires prostatic resection (with resected tissue demonstrating prostatic adenocarcinoma) or urinary diversion; or hematuria due to prostate cancer progression, (2) positive prostate biopsy at ≥ 24 months from the completion of protocol treatment (3) ≥ 20% increase in the longest diameter of a target lesion in the prostate gland (for patients with a measurable target lesion at baseline), or a new lesion measuring ≥ 1 cm short axis during follow-up (for patients with non-measurable lesion at baseline) in the setting of biochemical failure

11.2.3 Regional recurrence: Development of nodal metastasis in the pelvis which is defined as a new regional pelvic node that was normal at baseline (< 1.0 cm short axis) and increased to ≥ 1.0 cm short axis during follow-up. Confirmation by biopsy is encouraged.

11.2.4 Distant recurrence: Development of nodal metastasis outside the pelvis, or a hematogenous (e.g., osseous, hepatic, etc.) lesion. Confirmation by biopsy is encouraged.

11.2.5 Disease-free survival: Disease-free survival duration will be measured from the date of registration to the date of biochemical, local, regional, or distant recurrence or the date of death from any cause.

11.2.6 Disease-specific survival: Disease-specific survival duration will be measured from the date of registration to the date of death due to prostate cancer. Death due to prostate cancer will be defined as:

11.2.6.1 Death attributed to carcinoma of the prostate by the investigator, or

11.2.6.2 Death due to complications of treatment

11.2.7 Overall survival: Survival duration will be measured from the date of registration to the date of death from any cause.

12.0 Descriptive Factors

12.1. Clinical tumor (T) classification: ≤ T2 vs. ≥ T3

12.2. Histologic grade: Gleason score ≤ 7 vs. ≥ 8

12.3. Pre-treatment serum PSA value: ≤ 20 ng/mL vs. >20 ng/mL

This is the PSA value obtained most immediately before the start of neoadjuvant androgen deprivation therapy (see Section 7.2).

12.4. Patient age: ≤70 years vs. >70 years.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

Follow-up data will be collected and entered in accordance to Section 4.0. No follow-up data is required beyond 5 years from the date of study enrolment.

13.1 If a patient fails to complete the entire course of treatment for reasons other than toxicity or prostate cancer progression, he will be regarded as *inevaluable* and will be replaced. Baseline characteristics will be collected in the database. However, no further data collection will be collected.

13.2 A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, he did not satisfy each and every eligibility criteria for study entry.

The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted, and collection of follow-up data will continue in accordance to Section 4.0. Event monitoring will be required per Section 18.0 of the protocol.

13.3 A patient is deemed a *cancel* if he is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.4 A patient is deemed a *major violation*, if protocol requirements regarding treatment are severely violated such that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will continue the active monitoring phase and the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

13.5 When the patient develops a biochemical recurrence only, he will continue on the protocol test schedule until further medical management is implemented at the discretion of his physician.

13.6 When the patient develops a local, regional, or distant recurrence, he will go off study with no further scheduled follow-up tests.

14.0 Body Fluid Biospecimens

Not applicable

15.0 Drug Information

Not applicable

16.0 Statistical Considerations and Methodology

16.1 Overview: This Phase II study will utilize a one-stage binomial design to assess the rate of late grade 3 or higher GI and GU toxicities associated with a hypofractionation proton beam therapy regimen for prostate cancer.

16.1.1 Endpoint: The primary endpoint of this trial is the proportion of patients who experience a late grade 3 or higher GI or GU toxicity. Toxicity will be defined as an adverse event possibly, probably, or definitely related to proton beam therapy. A late GI or GU toxicity will be defined as a GI or GU toxicity that occurs between 3 months and 2 years from the completion of proton beam therapy. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for late toxicity, with the exception of patients determined to be a major violation.

16.2 Statistical Design:

16.2.1 Decision Rule: It is hypothesized that ≤ 5% of patients will encounter a late grade 3 or higher GI or GU toxicity between 3 months and 2 years from the completion of proton beam therapy. The proposed treatment strategy would be considered ineffective in this population if ≥15% of patients experiences a late grade 3 or higher GI or GU toxicity. Subsequent studies with the proposed treatment strategy may be considered in this patient population if ≤5% of patients experiences a late grade 3 or higher GI or GU toxicity. The following one-stage binomial design uses 51 evaluable patients to test the null hypothesis that the rate of late grade 3 or higher GI or GU toxicity is ≥15%.

16.2.1.1 Final Decision Rule: Enter 51 evaluable patients into the study. If 5 or more patients experience late grade 3 or higher GI or GU toxicity in the first 51 evaluable patients, we will consider this regimen ineffective in this patient population. If 4 or more fewer are patients in the first 51 evaluable patients experience late grade 3 or higher GI or GU toxicity, we may recommend further testing of this regimen in subsequent studies in this population.

16.2.1.2 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.3.4.

16.2.2 Sample Size: This study is expected to require a maximum of 51 evaluable patients. We anticipate accruing 5 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, this study is expected to accrue a maximum of 56 patients overall.

16.2.3 Accrual Rate and Study Duration: The anticipated accrual rate is approximately 3-4 patients per month. Therefore, the accrual period for this phase II study is expected to be approximately 1.5 years. The final analysis can begin as soon as the last patient has been observed for 2 years, or at approximately 3.5 years after the study opens to accrual.

16.2.4 Assuming that the number of late grade 3 or higher GI or GU toxicities is binomially distributed, with a significance level of 10%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) under various toxicity proportions can be tabulated as a function of the true toxicity proportion as shown in the table below.

If the true late toxicity rate is…	0.20	0.15	0.10	0.05

Then the probability of declaring that the regimen is promising and warrants further study is…	0.02	0.10	0.41	0.89

16.2.5 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.3 Analysis Plan

16.3.1 Primary Outcome Analyses:

16.3.1.1 Definition: The primary endpoint of this trial is the proportion of patients who experience a late grade 3 or higher GI or GU toxicity. Toxicity will be defined as an adverse event possibly, probably, or definitely related to proton beam therapy. A late GI or GU toxicity will be defined as a GI or GU toxicity that occurs between 3 months and 2 years from the completion of proton beam therapy. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for late toxicity, with the exception of patients determined to be a major violation.

16.3.1.2 Estimation: The proportion of grade 3 or higher GI or GU toxicities will be estimated by the number of patients with a late grade 3 or higher GI or GU toxicity divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the toxicity proportion will be calculated.

16.3.2 Secondary Outcome Analyses:

16.3.2.1 Disease-free survival is defined as the time from registration until the time of the first occurrence of biochemical failure (Section 11.2.1), local recurrence, regional recurrence, distant metastases, or death due to any cause. The distribution of disease-free survival will be estimated using the method of Kaplan-Meier. The disease-free survival rate will be estimated at 2 years and 5 years.

16.3.2.2 Disease-specific survival is defined as the time from registration until the date of death due to prostate cancer (Section 11.2.6). The distribution of disease-specific survival will be estimated using the method of Kaplan-Meier. The disease-specific survival rate will be estimated at 2 years and 5 years.

16.3.2.3 Overall survival is defined as the time from registration until the death due to any cause (Section 11.2.7). The distribution of overall survival will be estimated using the method of Kaplan-Meier. The overall survival rate will be estimated at 2 years and 5 years.

16.3.2.4 An acute adverse event is defined as an adverse event that occurs any time between registration and 3 months after the completion of proton beam therapy. The rate of ≥ grade 3 GI or GU acute adverse events will be estimated by the number of patients with a ≥ grade 3 GI or GU acute adverse event divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true rate of ≥ grade 3 GI or GU acute adverse events will be calculated.

16.3.2.5 A late adverse event is defined as an adverse event that occurs any time between 3 months and 2 years after completion of proton beam therapy. The rate of ≥ grade 2 GI or GU late adverse events will be estimated by the number of patients with a ≥ grade 2 GI or GU late adverse event divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true rate of ≥ grade 2 GI or GU late adverse events will be calculated.

16.3.2.6 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration. Acute and late adverse events (as defined in sections 16.3.2.2 and 16.3.2.3) will be summarized separately.

16.3.3 Correlative Analyses

16.3.3.1 Patients will complete the Expanded Prostate Cancer Index Composite short form (EPIC-26) questionnaire at baseline and at the specified post-treatment time points as shown Section 4.0. Subdomains for urinary, bowel, and sexual function will be evaluted at each time point and summarized descriptively. Changes across time will be evaluated to assess patient function and quality of life after study treatment.

16.3.4 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final endpoint estimates and confidence intervals.

16.4 Data & Safety Monitoring:

16.4.1 The principle investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Radiation Oncology Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least once a year, based on reports provided by the statistical office.

16.4.2 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual if there are unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended, if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy one of the following:

- If 4 or more patients in the first 20 treated patients experience a grade 3 or higher GI or GU adverse event at least possibly related to treatment at any time and after 3 months following completion of the protocol treatment

- After the first 20 patients have been treated: if ≥ 20% of all patients experience a grade 3 or higher GI or GU adverse event at least possibly related to treatment at any time after 3 months following the completion of protocol treatment.

In addition, we will review grade 4 and 5 adverse events deemed "unrelated" or "unlikely to be related", to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting on ClinicalTrials.gov: At study activation, this study will be registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3.5 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 2 years.

16.7 Inclusion of Minorities

16.7.1 This study will be available to all eligible patients, regardless of raceor ethnic origin.

16.7.2 There is no information currently available regarding differential effects of this regimen in subsets defined by race, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.7.3 The geographical region served by Mayo Clinic Cancer Center has a population which includes approximately 3% minorities. Based on prior Mayo Clinic Cancer Center studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and 100% of patients will be men. Expected sizes of racial by gender subsets are shown in the following table:

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	2	0	2
Not Hispanic or Latino	0	54	0	54
Ethnic Category: Total of all subjects*	0	56	0	56
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	0	2	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	0	54	0	54
Racial Category: Total of all subjects*	0	56	0	56

Ethnic Categories: Hispanic or Latino – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”
Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

Not Applicable

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Initial Material(s)

CRF	**Baseline** (Compliance with Test Schedule Section 4.0)
Demographics	≤2 weeks after registration *6 months from accrual
Patient Eligibility	
On-Study	
Adverse Events-Baseline	
PSA and Testosterone Values	
Prostate Radiotherapy Questionnaires	
Androgen Deprivation Treatment	

Test Schedule Material(s)

CRF		**Active-Monitoring Phase[2]** (Compliance with Test Schedule Section 4.0)	**Event-Monitoring Phase[3]** (Compliance with Test Schedule Section 4.0)

	On-Study	At each evaluation during treatment	At end of treatment	Post-RT: 3, 6, 12, 18, and 24 months (Active Monitoring)	Post-RT: 30, 36, 42, 48, and 60 months (Event Monitor)
Adverse Event: Solicited Form	X	X	X	X	X
Adverse Events Other	X	X[1]	X[1]	X[1]	X[1]
Radiation Treatment			X		
Androgen Deprivation Treatment	X	X[4]	X[4]	X[4]	X[4]
End of Active Treatment			X		
PSA and Testosterone Values		X		X[5]	X[5]
Adverse Events: Post Radiation Treatment				X	X
Post Radiation Patient Status/Assessment				X	X[6]
Prostate Radiotherapy Questionnaires				X	X
Consent Withdrawal form		X[1]	X[1]	X[1]	X[1]
Lost to Follow-up		X[1]	X[1]	X[1]	X[1]

1. When applicable
2. Post RT (Active monitoring phase): 3 months (+/- 1 months), 6 months (+/- 1 months), 12 months (+/- 1 months), 18 months (+/- 1 months), and 24 months (+/- 1 months) post RT.
3. Post RT (Event-monitoring phase): 30 months (+/- 1 months), 36 months (+/- 1 months), 42 months (+/- 1 months), 48 months (+/- 1 months), 54 months (+/- 1 months), and 60 months (+/- 1 months) post RT.
4. Coordinator will look to see if patient received Androgen Deprivation Therapy since the previous reporting period. If there was no change, indicate on form.
5. Testosterone is collected at post-RT month 12, 24, 36, 48, and 60 months post RT. However, if one was completed it should be entered into the CRF. Therefore, the form will populate at each visit, and if it wasn't completed because it was not required, indicate "not completed" on form.
6. History, physical exam, and ECOG are not required during Event Monitoring Phase.

18.2 Data Handling and Record Keeping

18.2.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (long term survival status that the subject is alive) at the end of their scheduled study period.

18.2.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. Source documents are kept in a secure location that is locked and requires approved access.

18.3.3 Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. Do not erase or use "white-out" for errors. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it. If the reason for the correction is not clear or needs additional explanation, neatly include the details to justify the correction.

18.3.4 Records Retention

The investigator will maintain records and essential documents related to the conduct of the study. These will include subject case histories and regulatory documents.

The investigator will retain the specified records and reports for;

1. As outlined in the Mayo Clinic Research Policy Manual –"Retention of and Access to Research Data Policy"

[redacted]

19.0 Study Finances

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded: None. All tests and treatments performed in the study are part of routine clinical care.

19.3 Other budget concerns: The Mayo Clinic Radiation Oncology Unit will cover costs related to administrating the study including a clinical research associate.

20.0 Publication Plan

The principal investigators hold primary responsibility for publication of the results of this study and approval from the principal investigators must be obtained before any information can be used or passed on to a third party.

21.0 References

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Appendix I

Zubrod Performance Scale

0 Asymptomatic and fully active

1 Symptomatic; fully ambulatory; restricted in physically strenuous activity

2 Symptomatic; ambulatory; capable of self-care; more than 50% of waking hours are spent out of bed

3 Symptomatic; limited self-care; spends more than 50% of time in bed, but not bedridden

4 Completely disabled; no self-care; bedridden

Appendix II

International Index of Erectile Function Questionnaire (IIEF)

Please circle the appropriate response option to indicate how you were feeling over the past month (4 weeks).

1: During the past month or so, how often were you able to get an erection during sexual activity?

0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

2: During the past month or so, when you had erections with sexual stimulation, how often were your erections hard enough for penetration?

0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

3: During the past month or so, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?

0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

4: During the past month or so, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

5: During the past month or so. during sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

0 = Did not attempt intercourse
1 = Extremely difficult
2 = Very difficult
3 = Difficult
4 = Slightly difficult
5 = Not difficult

6: During the past month or so, how many times have you attempted sexual intercourse?

0 = No attempts
1 = One to two attempts
2 = Three to four attempts
3 = Five to six attempts
4 = Seven to ten attempts
5 = Eleven + attempts

Appendix III

American Urological Association Symptom Index

Please circle the appropriate response option to indicate how you were feeling over the past month (4 weeks).

1: Over the past month or so, how often have you had a sensation of emptying your bladder completely after you finished urinating?

0= Not at all
1 = Less than one time in five
2 = Less than half the time
3= About half the time
4 = More than half the time
5 = Almost always

2: Over the past month or so, how often have you had to urinate again, less than two hours after you finished urinating?

0= Not at all
1 = Less than one time in five
2 = Less than half the time
3= About half the time
4 = More than half the time
5 = Almost always

3: Over the past month or so, how often have you found you stopped and stated again several times when you urinated?

0= Not at all
1 = Less than one time in five
2 = Less than half the time
3= About half the time
4 = More than half the time
5 = Almost always

4: Over the past month or so, how often do you find it difficult to postpone urination?

0= Not at all
1 = Less than one time in five
2 = Less than half the time
3= About half the time
4 = More than half the time
5 = Almost always

5: Over the past month or so, how often have you had a weak urinary stream?

0= Not at all
1 = Less than one time in five
2 = Less than half the time
3= About half the time
4 = More than half the time
5 = Almost always

6: Over the past month or so, how often have you had to push or strain to begin urination?

0= Not at all
1 = Less than one time in five
2 = Less than half the time
3= About half the time
4 = More than half the time
5 = Almost always

7: Over the past month or so, how often did you most typically get up at night to urinate?

0= Not at all
1 = Once every 8 hours
2 = Once every 4 hours
3= Once every 3 hours
4 = Once every 2 hours
5 = At least once every hour