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A Randomized, Parallel Phase II Trial Of Hypofractionated Proton Therapy Or IMRT For Recurrent, Oligometastatic Prostate Cancer Involving Only Pelvic And/or Para-aortic Lymph Nodes Following Primary Localized Treatment

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Mayo Clinic Radiation Oncology

Radiotherapy with Hypofractionated Abdomino-Pelvic Salvage for Oligonodal Disease Study (RHAPSODY): MC1851 A Randomized, Parallel Phase II trial utilizing Proton Therapy or IMRT

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Protocol Resources

Questions:	Contact Name:
Patient eligibility, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, protocol document, consent form, regulatory issues, forms completion and submission	Mayo Clinic Radiation Oncology Study Coordinator group.

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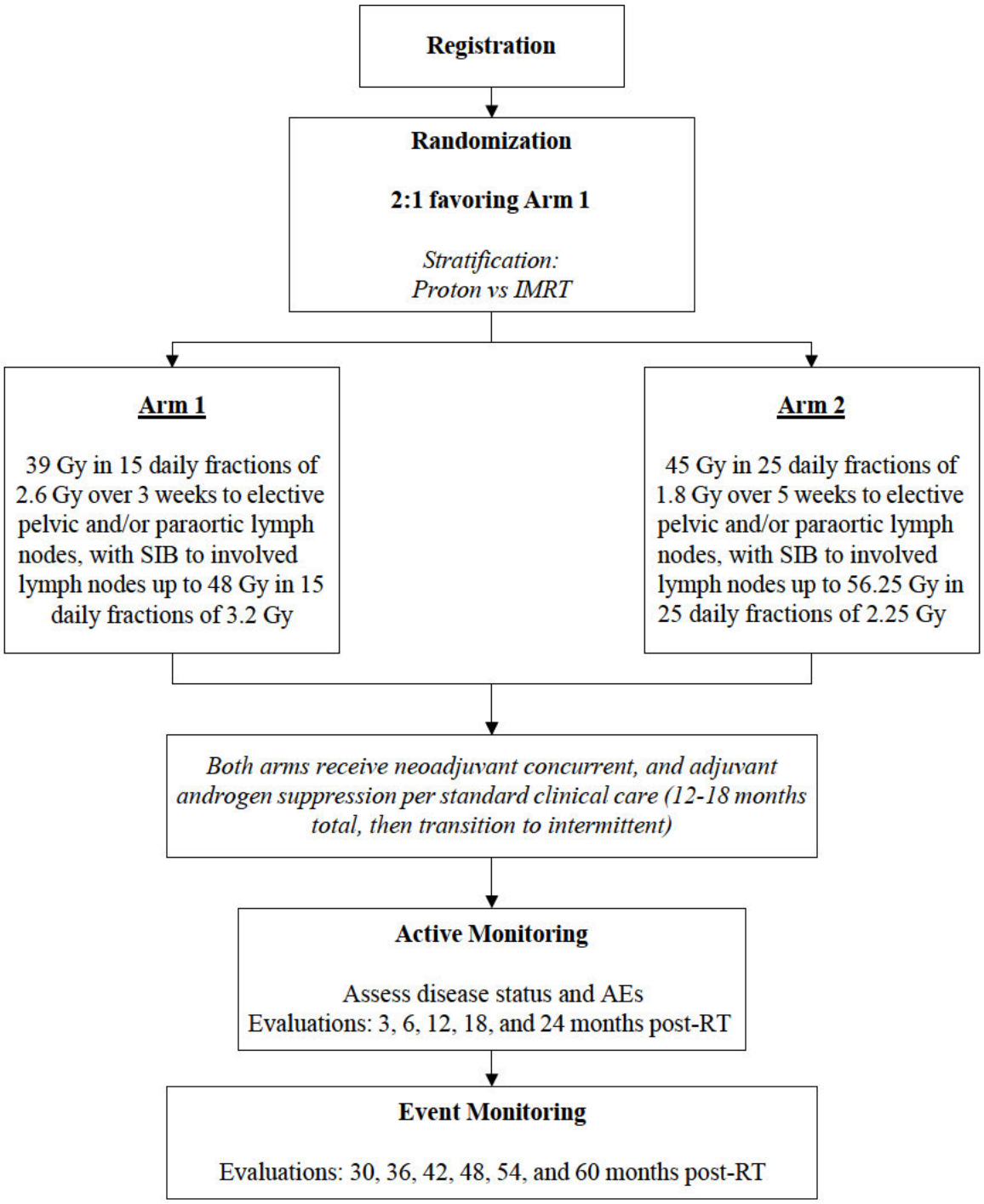
List of Abbreviations

AE	Adverse Event/Adverse Experience
BED	Biologically effective dose
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computed Tomography
DNA	Deoxyribonucleic Acid
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GETUG	Groupe d'Études des Tumeurs Uro-Génitales
GI	Gastrointestinal
GU	Genitourinary
HIPAA	Health Insurance Portability and Accountability Act
IMRT	Intensity Modulated Radiation Therapy
IRB	Institutional Review Board
PET	Positron Emission Tomography
PHI	Protected Health Information
PI	Principal Investigator
PSA	Prostate Specific Antigen
RT	Radiation Therapy
SAE	Serious Adverse Event/Serious Adverse Experience
SIB	Simultaneous Integrated Boost
SOP	Standard Operating Procedure

Schema


Registration
Randomization
2:1 favoring Arm 1
Stratification:
Proton vs IMRT
Arm 1
39 Gy in 15 daily fractions of 2.6 Gy over 3 weeks to elective pelvic and/or paraortic lymph nodes, with SIB to involved lymph nodes up to 48 Gy in 15 daily fractions of 3.2 Gy
Arm 2
45 Gy in 25 daily fractions of 1.8 Gy over 5 weeks to elective pelvic and/or paraortic lymph nodes, with SIB to involved lymph nodes up to 56.25 Gy in 25 daily fractions of 2.25 Gy
Both arms receive neoadjuvant concurrent, and adjuvant androgen suppression per standard clinical care (12-18 months total, then transition to intermittent)
Active Monitoring
Assess disease status and AEs
Evaluations: 3, 6, 12, 18, and 24 months post-RT
Event Monitoring
Evaluations: 30, 36, 42, 48, 54, and 60 months post-RT

Summary: This is a prospective, randomized trial of parallel design evaluating conventionally and hypo-fractionated proton beam therapy or IMRT for patients with oligometastatic prostate cancer at Mayo Clinic-Rochester.

1.0 Background

1.1 Rationale

Metastatic prostate cancer is presently incurable, but the natural history is highly variable. For patients with limited sites of metastatic disease (oligometastatic), better treatment options may be enabled by technologic advances in radiographic imaging (e.g., C-11 Choline PET/CT) and highly conformal RT. While data to guide management of oligometastatic recurrences following receipt of prior therapy are limited, several recent, large observational series report improved clinical outcomes associated with RT and/or surgery for patients with lymph node involvement at initial diagnosis.[1-3] It is well established that salvage radiotherapy (RT) to the prostate fossa is potentially curative for biochemical recurrence after prostatectomy.[4,5] However, the likelihood of cure decreases as PSA values rise, presumably due to increased risk of metastatic spread beyond the fossa itself.

C-11 choline PET/CT identifies specific sites of metastatic spread at lower PSA values than conventional imaging techniques, which has led to identification of a clinically distinct cohort of patients with oligometastatic disease beyond the prostate fossa but involving sites, such as pelvic lymph nodes, that are readily treatable with curative-intent doses of highly conformal RT.[6-9] Several small, retrospective series of metastasis-directed RT have been reported,[10] serving as rationale for an initial phase II study in Europe evaluating a 6-week regimen of conventionally fractionated IMRT with androgen suppression for oligometastatic pelvic nodal relapses, for which accrual is complete (GETUG P07 [NCT02274779]).[11] Additionally, a phase II study by Ost et al. showed prolonged androgen suppression-free survival (median 21 months vs. 13 months) in patients with biochemical recurrence after primary curative prostate cancer treatment, with 3 or fewer extracranial metastases on choline PET, who received metastasis-directed therapy (RT or surgery).[12]

It remains to be established whether technical advances in RT, such as hypofractionation and proton beam therapy, will further improve the therapeutic ratio for patients with oligometastatic prostate cancer.

1.2 Hypofractionation

With technical improvements in RT delivery, utilization of higher-than-conventional dose (>2 Gy) once-daily fractions has increased, allowing treatment courses to be completed in less time, thereby increasing patient convenience while lowering treatment cost. Randomized trials have shown that modest hypofractionation (2.5-3.0 Gy per fraction) for primary prostate cancer does not appear to compromise clinical outcomes or meaningfully increase toxicity.[13,14] However, no studies have evaluated hypofractionation in the oligometastatic setting, which often requires RT to be delivered to pelvic or intra-abdominal lymph nodes at doses nearing the accepted tolerance of small bowel.

1.3 Proton beam therapy

Proton beam therapy is an exceptionally conformal RT technique owing to the physical properties of charged atomic particles (protons), which enable significantly better sparing of normal tissues than photon-based techniques (i.e., IMRT) in the treatment of prostate cancer.[15] In comparison to high energy x-rays, proton beams yield no exit dose and thus generally improve the conformity index of treatment. Several studies suggest that for treatment of primary prostate cancer, proton beam therapy improves the therapeutic ratio as compared with IMRT by achieving equivalent clinical outcomes while reducing RT-related toxicity.[16-20] Dosimetric studies concerning other cancers in which lymph nodes are targeted in the pelvis and retroperitoneum have shown that protons are able to achieve reduced dose to bowel as compared with photon techniques.[21,22] For oligometastatic prostate cancer, no studies have evaluated whether the physical advantages of proton beam therapy would translate into reduced toxicity.

1.4 Study proposal

We propose a phase II randomized trial to assess toxicity and clinical outcomes for patients with oligometastatic prostate cancer involving only pelvic and/or retroperitoneal lymph nodes (no bone or visceral metastases) receiving hypofractionated or conventionally fractionated RT with proton beam therapy or IMRT.

The hypofractionated regimen will be 39 Gy in 15 daily fractions to elective nodal basins with SIB to involved lymph nodes up to 48 Gy in 15 fractions. The conventionally fractionated regimen will be 45 Gy in 25 fractions to elective nodal basins with SIB to involved lymph nodes up to 56.25 Gy in 25 fractions.

The randomization will be 2:1 favoring the hypofractionated arm, stratifying such that proton therapy and IMRT techniques are evenly balanced, and all patients will receive proton beam therapy with state-of-the-art pencil-beam scanning, also known as intensity modulated proton therapy (IMPT). All patients will be treated with daily image guidance to ensure optimal setup and RT delivery.

1.5 BED calculations for proposed hypofractionated RT

The linear-quadratic model of cellular response to RT enables biologically effective dose (BED) calculations, which provide a framework for comparing different fractionation regimens with respect to acute and late responding tissues (high and low α/β ratios, respectively).[23] Higher BED values are associated with greater cell kill, which may result in improved oncologic outcomes and/or increased toxicity.

Table 1 shows BEDs for the proposed study regimens at α/β ratios of 1.5 Gy and 3 Gy, which represent the range of possible values associated with prostate cancer.[24] Since the α/β ratio of prostate cancer is relatively low, hypofractionation is posited to be advantageous from a treatment perspective based on the linear-quadratic model. As such, the investigational regimen in Arm 1 is expected to result in similar efficacy at an α/β ratio of 3 Gy and potentially better efficacy at an α/β of 1.5 Gy.

Table 1: BEDs for Prostate Cancer (all values in Gy).

α/β values	Arm 1		Arm 2	
	Elective Nodes	Involved Nodes	Elective Nodes	Involved Nodes

	39 Gy in 15 fractions	48 Gy in 15 fractions	45 Gy in 25 fractions	56.25 Gy in 25 fractions
1.5	106.6	150.4	99	140.6
3	72.8	99.2	72	98.3

Improvements in efficacy as a result of increased BED must be weighed against potential increases in normal tissue toxicity. Early and late responding tissues are typically assumed to have α/β ratios of 10 Gy and 3 Gy, respectively. Table 2 shows BED values anticipated for each of these tissue types based on the RT regimens proposed.

Table 2: BEDs for normal tissues (all values in Gy).

α/β values	**Arm 1**		**Arm 2**	
	Elective Nodes	**Involved Nodes**	**Elective Nodes**	**Involved Nodes**
	39 Gy in 15 fractions	48 Gy in 15 fractions	45 Gy in 25 fractions	56.25 Gy in 25 fractions
10	49.1	63.4	53.1	68.9
3	72.8	99.2	72	98.3

For early responding tissues (α/β = 10 Gy), increased dose per fraction has the effect of reducing BED as compared with conventionally fractionated regimens, suggesting that hypofractionation might improve the therapeutic index with regard to early responding tissues. The reverse is true for late responding tissues (α/β = 3 Gy); however, since the α/β ratio for these is probably equal or similar to that of prostate cancer, fraction size manipulation is unlikely to be a good strategy for improving the therapeutic index as it relates to those tissues. Rather, other strategies are needed, such as high-precision techniques for RT delivery. As such, this study will incorporate proton beam therapy with state-of-the-art pencil beam scanning, or IMRT, and daily image guidance to ensure that all normal tissues are maximally spared.

1.6 Significance of the proposed study

If safe and at least equally effective, the proposed RT regimen will provide a new, more convenient and cost-effective option for patients with oligometastatic prostate cancer. As imaging for prostate cancer continues to improve, as with choline PET/CT, the number of patients identified to have oligometastatic disease will increase, such that optimizing treatment for this clinical scenario will grow increasingly important. Mayo Clinic is uniquely positioned in terms of technology, clinical volume, and resources to investigate whether a hypofractionated regimen with proton beam therapy or IMRT should be the RT technique of choice for these patients.

2.0 Goals

2.1 Primary

2.1.1 To assess late ≥ grade 3 GI and/or GU toxicity of interest with the hypofractionated regimen with proton beam therapy or IMRT (late defined as 3 to 24 months after protocol RT)

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. Compare the rates of late ≥ grade 3 GI and/or GU toxicity between the 2 treatment schedules

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.1.1. Male; Age ≥ 18 years.

3.1.2. Histological confirmation of prostate adenocarcinoma.

3.1.3. Recurrent prostate cancer after prior receipt of primary radiotherapy to the prostate (can also include treatment of SVs and LNs) or salvage RT to the prostate fossa (can also include prior pelvic RT).

3.1.3. Oligometastatic extent of disease
3.1.3.1. Recurrent disease involving lymph nodes as diagnosed with choline PET/CT or other advanced PET imaging (PSMA or flucyclovine)
3.1.3.2. Limited to pelvic and/or retroperitoneal/para-aortic lymph nodes

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

3.1.5. Signed informed consent.

3.2 Exclusion Criteria

3.2.1. Bone or visceral metastases present at the time of treatment (consolidative radiotherapy allowed).

3.2.2. Lymph node metastases beyond the pelvis and/or retroperitoneum.

3.2.3. Contraindications to RT (e.g., uncontrolled inflammatory bowel disease).

3.2.4. Contraindications to androgen suppression.

3.2.5. Concurrent cytotoxic chemotherapy.

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

3.2.7. Inability to start the radiation portion of the protocol treatment within 6 months after study enrollment.

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

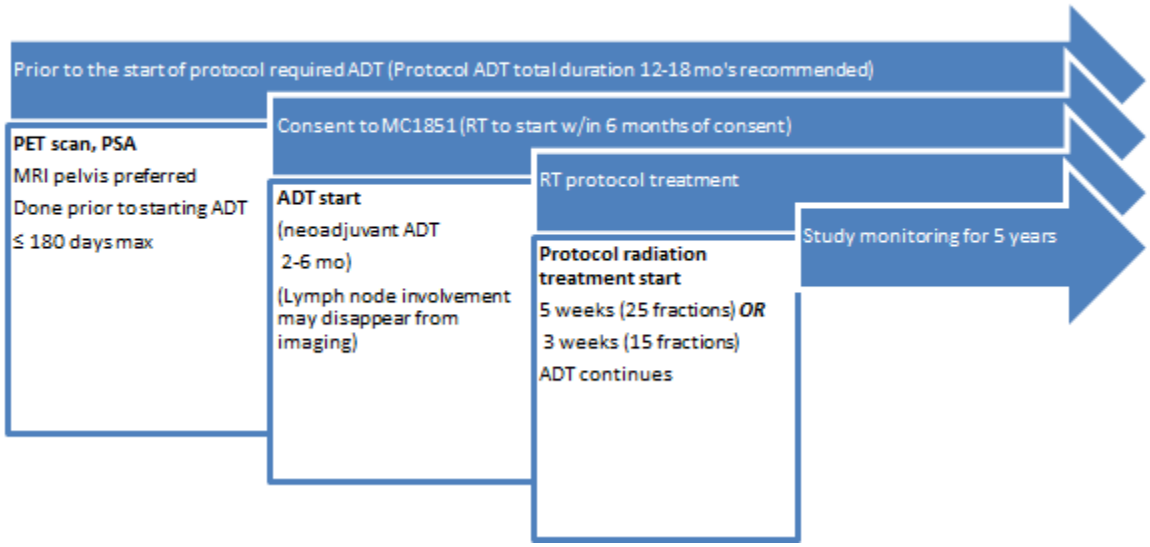
4.0 Test Schedule

Tests and procedures	Active Monitoring Phase[10]					Event Monitoring Phase
	≤ 180 days of beginning ADT	≤ 90 days prior to registration	During RT (weekly)	End of RT (+/- 5 days)	Post-RT month: 3- 6, 12, 18, and 24 (+/-2 mo)	Post-RT month: 30, 36, 42, 48, 54, and 60 (+/-3 mo)
History, Physical exam (Height[1] & Weight[1]), ECOG Performance Status[1]		X	X[1]	X[1]	X[1]	X[5]
PSA	X	X[6]			X	X
Serum total testosterone		X			X[2]	X[2]
CBC w/Diff, Creatinine		X[3]			X[3]	X[3]
MRI of pelvis	X[7]				X[5]	X[5]
Choline PET/CT or other advanced PET imaging	X[8]				X[5]	X[5]
GI and GU toxicity assessment (CTCAE v4.0)	X[9]	X	X	X	X	X
Questionnaires[4]	X[9]	X		X	X	X

1. Height will be recorded at the first visit only; Weight and ECOG will be recorded at only baseline and last week of RT. Physical exam unnecessary if remote follow up.
2. Serum total testosterone to be performed post-RT month 12, 24, 36, 48, and 60.
3. Required before RT start. Optional at follow up time points, per physician's discretion.
4. Questionnaires, including Patient-Reported Outcomes version of the PRO-CTCAE and EPIC/EPIC-26, are part of standard practice and will be administered to patients electronically. Baseline questionnaires should be completed prior to RT start and prior to patient starting hormone therapy if possible. Follow-up questionnaires will be administered clinically at 3 to6, 12, 24, 36, 48, and 60 months.
5. Only at 36, 48, and 60 months.
6. PSA should be ≤ 40 days of registration

7. MRI ≤ 180 days prior to ADT initiation and no more than 1 week after starting ADT; MRI is preferred but not mandatory.
8. PET scan mandatory ≤ 180 days of starting ADT, and no more than 1 week after starting ADT.
9. Recommended, if possible.
10. Follow up in person at the 3 to 6 months and one year time point is preferred but not mandatory. Follow up, including QOL questionnaires, can be completed in person, virtually, by phone and/or electronically via patient portal and with mail-in PSA/testosterone kits.

Sample of patient timeline:



5.0 Stratification Factors

Treatment technique: Proton beam therapy vs. IMRT

6.0 Registration/Randomization Procedures

6.1 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).

6.2 After stratification, patients will be randomized between hypofractionation and standard therapy using a 2:1 randomization favoring hypofractionation. The treatment arms will be balanced based on the 2 stratification factors of interest: proton beam therapy vs. IMRT. The balancing algorithm that we will use is a dynamic allocation procedure that is part of Medidata Rave, known as Balance.

7.0 Protocol Treatment

Protocol treatment consists of proton beam therapy or IMRT, in combination with up to 28 months of androgen deprivation therapy.

7.1. Proton beam therapy

7.1.1 Treatment planning

7.1.1.1. Preparation prior to simulation

An empty bladder will be used for simulation and daily treatment. The patient will void immediately prior to simulation and treatment.

7.1.1.2. Simulation

A planning CT scan will be performed with the patient in supine position. An indexable knee cushion is to be used for immobilization during simulation and treatment.

No contrast will be used for the primary CT treatment planning scan for patients receiving proton radiation. Bladder, rectal, oral and/or IV contrast, are optional at the discretion of the treating radiation oncologist as a second scan.

CT simulation scanning will be performed through the anatomic areas of interest with 1-2.5 mm slice thickness.

7.1.1.3. Target volumes

7.1.1.3.1 Gross tumor volume (GTV) is gross disease as determined by all available radiographic and clinical information, including C11 choline PET/CT and MRI.

GTV metastasis is all lymph nodes involved with gross disease and equals GTV4800 in Arm 1 or GTV5625 in Arm 2. Pre-ADT C11 choline PET/CT and MRI imaging should be fused to the planning CT scan to facilitate accurate contouring of GTV metastasis.

7.1.1.3.2 Clinical target volume (CTV) accounts for potential microscopic disease.

CTV4800 in Arm 1 or CTV5625 in Arm 2 equals the corresponding GTV (no additional expansion).

CTV3900 in Arm 1 or CTV4500 in Arm 2 covers elective lymph nodes, contoured as recommended by the RTOG Prostate Cancer Atlas (rtog.org), typically including obturator, external iliac, internal iliac, and common iliac nodes bilaterally up to the bifurcation of the aorta excluding regions of prior radiation as described below, and incorporating a 7 mm margin around vessels as indicated in the Atlas. In addition, the presacral and perirectal nodes from the sacral promontory to S5 will be included if the rectal dose constraints are met, and are generally covered by a volume extending 1 cm from the anterior surface of the sacrum.

When at least a single pelvic or paraaortic lymph node is involved, all pelvic lymph nodes in the RTOG Atlas, with additional volumes as noted below, will be treated up to the level of the aortic bifurcation or to the level of the most superiorly involved lymph node plus a 1.5 cm superior margin, whichever is the most superior. These volumes may

include paraaortic lymph nodes up to the level of the diaphragm. The CTV to encompass pelvic and paraaortic nodal chains should extend 7 mm circumferentially from the outer surface of the aorta and IVC, cropped out of small and large bowel, bone, bladder and rectum. An acceptable alternative to contouring out bone will be to limit the posterior margin from lymph nodes to CTV to 2 to 4 mm.

Additional lymph node volumes that differ from the RTOG Atlas include pre-sacral and para-rectal lymph node regions where there is > 5 mm distance between the posterior rectum/sigmoid and the coccyx/sacrum. The inferior border of the protocol treatment field should be superior enough to avoid overlap of the 10 Gy isodose line from the prior treatment with the following isodose lines from the protocol treatment: 27 Gy in Arm 1 or 30 Gy in Arm 2. Small areas of greater overlap are allowed for the purposes of treating gross disease if dose constraints to OARs are satisfied.

7.1.1.3.3 Optimization target volume (OTV): A volume constructed by a dosimetrist under the guidance of a physician and physicist. The OTV is a volume used by the treatment planning, dose-optimization algorithm to ensure that the CTVs receive robust coverage at the intended dose level. It includes set-up and range uncertainties of 3 mm and 3%, respectively. When evaluating the treatment plan, the clinician should leave the OTV unmodified and is typically an expansion of 5 mm from the CTV in axial directions with zero margin in the cranial direction such that the demarcation at the superior edge of the field is lends itself more readily to future matching of additional radiation fields as necessary.

7.2. IMRT

7.2.1 Treatment planning

7.2.1.1. Preparation prior to simulation

An empty bladder will be used for simulation and daily treatment. The patient will void immediately prior to simulation and treatment.

7.2.1.2. Simulation

A planning CT scan will be performed with the patient in supine position. An indexable knee cushion is to be used for immobilization during simulation and treatment.

No contrast will be used for the primary CT treatment planning scan for proton patients. Bladder, rectal, oral and IV contrast, are optional at the discretion of the treating radiation oncologist as a second scan or as the primary scan in patients undergoing IMRT.

CT simulation scanning will be performed through the anatomic areas of interest with 1-2.5 mm slice thickness.

7.2.1.3. Target volumes

7.2.1.3.1 Gross tumor volume (GTV) is gross disease as determined by all available radiographic and clinical information, including C11 choline PET/CT and MRI.

GTV metastasis is all lymph nodes involved with gross disease and equals GTV4800 in Arm 1 or GTV5625 in Arm 2. Pre-ADT C11 choline PET/CT and MRI imaging should be fused to the planning CT scan to facilitate accurate contouring of GTV metastasis.

7.2.1.3.2 Clinical target volume (CTV) accounts for potential microscopic disease.

CTV4800 in Arm 1 or CTV5625 in Arm 2 equals the corresponding GTV (no additional expansion).

CTV3900 in Arm 1 or CTV4500 in Arm 2 covers elective lymph nodes, contoured as recommended by the RTOG Prostate Cancer Atlas (rtog.org), typically including obturator, external iliac, internal iliac, and common iliac nodes bilaterally up to the bifurcation of the aorta excluding regions of prior radiation as described below, and incorporating a 7 mm margin around vessels as indicated in the Atlas. The presacral nodes from the sacral promontory to S3 may be included if the rectal dose constraints are achieved, and are generally covered by a volume extending 1 cm from the anterior surface of the sacrum.

When at least a single pelvic lymph node is involved, all pelvic lymph nodes in the RTOG Atlas, with additional volumes as noted below, will be treated up to the level of the aortic bifurcation or to the level of the most superiorly involved lymph node plus a 1.5 cm superior margin, whichever is the most superior. These volumes may include paraaortic lymph nodes up to the level of the diaphragm. The CTV to encompass paraaortic nodal chains should extend 7 mm circumferentially from the outer surface of the aorta and IVC, cropped out of small and large bowel, bone, bladder and rectum. An acceptable alternative to contouring out bone will be to limit the posterior margin from lymph nodes to CTV to 2 to 4 mm.

Additional lymph node volumes that differ from the RTOG Atlas include pre-sacral and para-rectal lymph node regions where there is > 5 mm distance between the posterior rectum/sigmoid and the coccyx/sacrum . The inferior border of the protocol treatment field should be superior enough to avoid overlap of the 10 Gy isodose line from the prior treatment with the following isodose lines from the protocol treatment: 27 Gy in Arm 1 or 30

Gy in Arm 2. Small areas of greater overlap are allowed for the purposes of treating gross disease if dose constraints to OARs are satisfied.

7.2.1.3.3 Planning target volume (PTV): A volume constructed by expanding 5 mm isometrically from the CTV in axial directions with zero margin in the cranial direction such that the demarcation at the superior edge of the field is lends itself more readily to future matching of additional radiation fields as necessary. The PTV accounts for geometric uncertainty inherent to external beam delivery of IMRT. When evaluating the treatment plan, the clinician should leave the PTV unmodified.

7.3 Normal critical structures

Normal critical structures to be defined on the treatment planning CT scan include the following structures: bladder, rectum, large bowel, small bowel, bilateral femoral heads (to the level of ischial tuberosities), penile bulb, cauda equine and skin. If paraaortic lymph nodes are involved, then the following structures may also be included as normal structures if they are at the level of treatment in the cranial-caudal direction: spinal cord, kidneys, liver, stomach and lung. 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 tuberosities) to the rectosigmoid flexure. Small bowel should be contoured as a "bowel bag" that encompasses all of the loops evident on the planning CT. For examples of normal tissue contouring, please refer to the RTOG website: http://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx

7.4 Treatment plan evaluation

Plan quality and acceptability for both proton beam therapy and IMRT will be assessed in accordance to dose-volume histogram (DVH) parameters of target volumes and OARs using the constraints shown in the following Table.

Target DVH Objectives			**Priority**
		Both Arms	
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

Normal Tissue DVH Objectives				**Priority**
		Arm 1	Arm 2	
Bladder	D2cc[Gy]	< 61 Gy	< 72.91 Gy	1
		< 60 Gy	< 72.14 Gy	2
	V36Gy[cc]			Report
	V57Gy[cc]			Report
	V61Gy[cc]			Report
	V66Gy[cc]			Report
	V36Gy[%]	26%	33%	1
		13%	17%	2
	V57Gy[%]	12.6%	15%	1
		7.5%	9%	2
	V61Gy[%]	9.3%	11%	1
		6.75%	8%	2
	Volume[cc]			Report
Right femoral head	Max[Gy]	< 30.6 Gy	< 34.96 Gy	1
		< 28.7 Gy	< 32.69 Gy	2
	Mean[Gy]	≤ 21.4 Gy	≤ 23.95 Gy	1
		≤ 16.6 Gy	≤ 18.28 Gy	2
	V32Gy[%]	≤ 4.4%	≤ 5%	1
		≤ 1.75%	≤ 2%	2
	V14Gy[%]	≤ 83.7%	≤ 91%	1
		≤ 60.7%	≤ 66%	2
Left femoral head	Max[Gy]	< 30.6 Gy	< 34.96 Gy	1
		< 28.7 Gy	< 32.69 Gy	2
	Mean[Gy]	≤ 21.4 Gy	≤ 23.95 Gy	1
		≤ 16.6 Gy	≤ 18.28 Gy	2
	V32Gy[%]	≤ 4.4%	≤ 5%	1
		≤ 1.75%	≤ 2%	2
	V14Gy[%]	≤ 83.7%	≤ 91%	1
		≤ 60.7%	≤ 66%	2
Rectum	D2cc[Gy]	< 50.8 Gy	< 71.54 Gy	1
		< 50.5 Gy	< 71.19 Gy	2

	V44Gy[cc]			Report
	V53Gy[cc]			Report
	V57Gy[cc]			Report
	V61Gy[cc]			Report
	V66Gy[cc]			Report
	V44Gy[%]	20.7%	24%	1
		15.5%	18%	2
	V53Gy[%]	14.5%	17%	1
		12%	14%	2
	V57Gy[%]	12.8%	15%	1
		9.4%	11%	2
	V61Gy[%]	10.2%	12%	1
		7.6%	9%	2
Penile bulb	Mean[Gy]			Report
	D50%[Gy]	≤ 40.4 Gy	≤ 47 Gy	2
	D70%[Gy]	≤ 31.4 Gy	≤ 36 Gy	3
Large bowel	D2cc[Gy]			Report
	V44Gy[cc]			
	V53Gy[cc]			
	V57Gy[cc]			
	V61Gy[cc]			
	V44Gy[%]	20.7%	24%	1
		15.5%	18%	2
	V53Gy[%]	14.5%	17%	1
		12%	14%	2
	V57Gy[%]	12.8%	15%	1
		9.4%	11%	2
	V61Gy[%]	10.2%	12%	1
		7.6%	9%	2
Small bowel	Max[Gy]	< 44.4 Gy	< 52 Gy	3
	D2cc[Gy]			Report
	V30Gy[cc]	< 265 cc	< 300 cc	3
	V45Gy[cc]	< 130 cc	< 150 cc	2
	V50Gy[cc]	< 1.7 cc	< 2 cc	3
Right kidney	V6Gy [%]			Report
	V18Gy [%]	< 9%	< 10%	3
Left kidney	V6Gy [%]			Report
	V18Gy [%]	< 9%	< 10%	3
Kidneys_total	Mean [Gy]	16.3 Gy	< 18 Gy	1
	V12[%]	< 51%	< 55%	3
	V20 [%]	< 54%	< 60%	1

Spinal cord	Max [Gy]	< 39 Gy	< 45 Gy	3
	V35Gy[%]	< 1.75%	< 2%	2
	V45Gy[%]	< 0 %	< 0.1%	1
Body - OTV	V50%[cc]			Report
	V100%[cc]			Report
	V105%[cc]	0 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]

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.

7.4.1 Target Dose

In Arm 1, dose prescriptions are as follow: 39 Gy in 15 fractions to CTV3900 and 48 Gy in 15 fractions to CTV4800. In Arm 2, dose prescriptions are 45 Gy in 25 fractions to CTV4500 and 56.25 Gy in 25 fractions to CTV5625. All RT is delivered 5 days per week. Target dose deviations within 15% of the prescribed dose will be called a "minor deviation"; those exceeding this threshold will be considered a "major deviation."

7.4.2 Treatment Administration

An optimal proton therapy plan utilizing pencil-beam scanning or an optimal IMRT plan is created to achieve adequate prescription dose coverage of CTVs. Plan quality and acceptability is assessed based on DVH parameters of target volumes and OARs.

7.4.3 Treatment localization and verification

7.4.3.1 Patient set-up for daily RT is identical to the CT simulation setup, including bladder preparation and immobilization devices.

7.4.3.2 On-line target localization and image-guided RT:
7.1.4.2.1 For proton beam therapy, daily kV orthogonal imaging should be used to confirm the treatment setup and to account for inter-fraction motion. Patient alignment should be corrected prior to treatment as appropriate. For IMRT, daily kV imaging or daily cone beam CT should be used for the same purpose at the discretion of the treating clinician.

7.4.3.2.1 Routine use of volumetric imaging to verify patient setup throughout the course of proton beam therapy is encouraged but not mandatory. Options include CT on rails in the treatment room or verification CT in the setup room.

7.5 Concurrent androgen suppression

Androgen suppression is routinely administered in patients with metastatic prostate cancer as standard of care. For this protocol, the recommendation is that 2-8 months of androgen suppression be administered prior to RT (neoadjuvant). Androgen suppression should then continue during and after RT for a goal of 12-18 months continuously. Androgen suppression may consist of bicalutamide 50 mg PO once daily for the first 2-16 weeks (given at the start of androgen deprivation therapy) and an LHRH agonist (goserelin or leuprolide).

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 (BJD) 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 RT should not resume until AEs are grade <3.

9.0 Ancillary Treatment/Supportive Care

Supportive measures such as, but not limited to, 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
- inpatient, new, or prolonged; disability/incapacity

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: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

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.

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
	Rectal stenosis
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 RT, 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 or biochemical (PSA) failure (Section 11.2.1).

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: Consistent with published definitions, biochemical failure is defined as a PSA value that is ≥ 0.2 ng/mL in patients with prior radical prostatectomy, or ≥ PSA nadir + 2.0 ng/mL in those treated with radiation alone, where PSA nadir is defined as the lowest PSA value reached after completion of treatment. The date of biochemical is defined as the date of the PSA value that first meets this criterion.

11.2.2 Local recurrence: Local recurrence for patients receiving involved lymph node treatment is defined as either increase in lymph node diameter or increase in PET avidity (not due to RT) following completion of RT.

11.2.3 Regional recurrence: Development of a nodal metastasis beneath the diaphragm that was < 1.0 cm short axis and PET negative prior to RT but increased to ≥ 1.0 cm short axis or became PET positive during follow-up. Biopsy confirmation is encouraged. Regional recurrences either will be labeled ‘in-field’ if they occur within the 50% isodose volume of the prescription dose of protocol-specified RT or ‘out-of-field’ if they occur beyond.

11.2.4 Distant recurrence: Development of nodal metastasis above the diaphragm, or a hematogenous (e.g., osseous, hepatic, etc.) lesion. Biopsy confirmation 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 mortality: Disease-specific mortality will be measured from the date of registration, as the proportion of patients who die 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. Pre-treatment serum PSA value: ≤ or > 0.5 ng/mL and ≤ or > 2.0 ng/mL
This is the PSA value obtained most immediately before the start of androgen suppression (see Section 7.2).
12.2. Patient age: ≤70 years vs. >70 years.
12.3. RT field size: pelvis only vs. para-aortic only vs. pelvic and para-aortic

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 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.

13.2 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.

13.3 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.

13.4 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.

13.5 A patient's status is deemed in *major violation*, if protocol requirements regarding treatment are severely violated such that evaluability for primary end points is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will remain on study and 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.

13.6 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.

13.7 If a patient develops a local, regional, or distant recurrence, he will continue on-study in the monitoring phase.

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 using the exact test to assess the rate of late grade 3 or higher GI and GU toxicities associated with 2 different dose/fractionation regimens of proton beam therapy or IMRT for prostate cancer.

Primary Endpoint: The primary endpoint is the proportion of patients who experience a late (≥ 90 days after RT start date) grade 3 or higher GI and/or GU AE defined as possibly, probably, or definitely related to RT through 24 months post-RT as compared to baseline for each arm. 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 have a major violation.

The primary goal for Arm 1 is to assess the safety of a more dose intensive radiation therapy given over a shorter time period. The goal of Arm 2 is to assess the safety of the current standard regimen given in a prospective, controlled clinical trial. In a retrospectively defined, serial cohort of 70 men, the Arm 2 regimen had an observed grade 3 or higher GI and/or GU AE rate of 1.4%.

16.2 Patient Groups: There are two separate and independent patient groups as defined by the RT regimen: Arm 1 treated with 39 Gy in 15 daily fractions to elective nodal basins with SIB to involved lymph nodes up to 48 Gy in 15 fractions, and Arm 2 treated with 45 Gy in 25 fractions to elective nodal basins with SIB to involved lymph nodes up to 56.25 Gy in 25 fractions.

Patients will be randomized to a treatment schedule in a 2:1 ratio (Arm 1: Arm 2) using a dynamic allocation procedure. There will be stratification by treatment technique (proton beam therapy vs. IMRT) to ensure these are balanced within arms. Patients with insurance coverage for proton therapy will preferentially receive it. The evaluation of each treatment schedule will be conducted independently of the other arm. That is, the decision to stop accrual to one of these treatment schedules will based on the AEs experienced among patients on that particular treatment schedule.

16.3 Statistical Design:

16.3.1 Decision Rule – Arm 1: Since the hypofractionated regimen may have a slightly higher AE rate than serial cohort observed rate of 1.4%, 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 RT. 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 52 evaluable patients to test the null hypothesis that the rate of late grade 3 or higher GI or GU toxicity is ≥15%.

Decision Rule – Arm 2: Based on a retrospectively defined, serial cohort with an AE rate of 1.4%, it is hypothesized that ≤ 2% of patients will encounter a late grade 3 or higher GI or GU toxicity between 3 months and 2 years from the completion of RT. 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 ≤2% of patients experiences a late grade 3 or higher GI or GU toxicity. The following one-stage binomial design uses 26 evaluable patients to test the null hypothesis that the rate of late grade 3 or higher GI or GU toxicity is ≥15%.

16.3.1.1 Final Decision Rule – Arm 1: Enter 52 evaluable patients into the study. If 5 or more patients experience late grade 3 or higher GI or GU toxicity in the first 52 evaluable patients, we will consider this regimen ineffective in this patient population. If 4 or fewer 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.

Final Decision Rule – Arm 2: Enter 26 evaluable patients into the study. If 2 or more patients experience late grade 3 or higher GI or GU toxicity in the first 26 evaluable patients, we will consider this regimen ineffective in this patient population. If 1 or fewer patients in the first 26 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.

16.3.1.2 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 16.4.4.

16.3.2 Sample Size: This study requires 78 evaluable patients (52 Arm 1 + 26 Arm 2). We anticipate accruing 9 additional patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, this study is expected to randomize a maximum of 84 patients overall (56 Arm 1 and 28 Arm 2). We plan to screen up to 120 patients to get the 84 randomized patients.

16.3.3 Accrual Rate and Study Duration: The anticipated accrual rate is approximately 4 patients per month. Therefore, the accrual period for this phase II study is expected to be approximately 2 years. The final analysis can begin as soon as the

last patient has been observed for 2 years, or at approximately 4 years after the study opens to accrual.

16.3.4 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.

Arm 1 statistical power:

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…	0.005	0.10	0.46	0.89

Arm 2 statistical power:

If the true late toxicity rate is…	0.20	0.15	0.10	0.02
Then the probability of declaring that the regimen is promising and warrants further study is…	0.002	0.10	0.57	0.93

16.3.5 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

16.4 Analysis Plan

16.4.1 Primary Outcome Analyses:

16.4.1.1 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. Each arm is analyzed independently.

16.4.1.2 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 90% confidence intervals for the toxicity proportion will be calculated.

16.4.2 Secondary Outcome Analyses:

16.4.2.1 An acute adverse event is defined as an adverse event that occurs any time between registration and 3 months after the completion of RT. 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 90% confidence intervals for the true rate of ≥ grade 3 GI or GU acute adverse events will be calculated. Based on a rate of 4%, the exact binomial 90% CI for Arms 1 and 2 would be 0.7-11.6% and 0.2-17.0%, respectively.

16.4.2.2 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 90% confidence intervals for the true rate of ≥ grade 2 GI or GU late adverse events will be calculated. Based on an anticipated rate of 15%, the exact binomial 90% CI for Arms 1 and 2 would be 7.9-26.1% and 5.4-31.8%, respectively.

16.4.2.3 The proportion of grade 3 or higher GI or GU toxicities will be determined for both treatment arms. The difference between the 2 treatment arm proportions will be determined and exact binomial 90% confidence intervals for the difference in grade 3 or higher GI or GU toxicity rates will be calculated. Based on the anticipated rates of 5% and 2%, the width of the 90% CI would be approximately +/- 10%.

16.4.2.4 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.

16.4.3 Exploratory / Correlative Analyses

16.4.3.1 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.

16.4.3.2 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.

16.4.3.3 Disease-specific mortality is defined as the proportion of deaths due to prostate cancer (Section 11.2.6). The distribution of disease-specific mortality will be estimated using the cumulative incidence function, with death from other causes as the competing event. The disease-specific mortality rate will be estimated at 2 years and 5 years.

16.4.3.4 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.

16.4.4 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.

16.5 Data & Safety Monitoring:

16.5.1 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.

16.5.2 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. The same rule will be applied independently to both arms.

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 3 or more patients in the first 20 treated patients experience an acute grade 3 or higher GI or GU adverse event at least possibly related to treatment at any time within the first 3 months following completion of the protocol treatment.

- After the first 20 patients have been treated: if ≥ 15% of all patients experience an acute grade 3 or higher GI or GU adverse event at least

possibly related to treatment at any time within 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 race or 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	4	0	4
Not Hispanic or Latino	0	80	0	80
Ethnic Category: Total of all subjects*	0	84	0	84
Racial Category				
American Indian or Alaskan Native	0	1	0	1
Asian	0	1	0	1
Black or African American	0	2	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	0	80	0	80
Racial Category: Total of all subjects*	0	84	0	84

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 Data Handling and Record Keeping

18.1.1 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.

18.1.2 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.

18.1.3 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. All data will be entered into electronic case report forms (eCRF's) through the Medidata Rave system. Case report forms will be automatically rolled out based on a predetermined, and visit based schedule to improve study staff workflow and data quality. Data will be exported nightly to a secure FTP for analysis and reporting.

18.1.4 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 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 Department will cover costs related to administrating the study including a clinical research associate. The collaborating laboratory will cover the cost of storing and maintaining the frozen tissue bank.

20.0 Publication Plan

The study chair (BJD) holds primary responsibility for publication of the results of this study and approval from the study chair 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

ECOG PERFORMANCE STATUS	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From http://www.ecog.org/general/perf_stat.html

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 (AUA)

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

Appendix IV

PRO-CTCAE (GI/GU Assessment)

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please mark an X in the one box that best describes your experiences over the past 7 days.

1. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (Diarrhea)?

☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly

2. In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?

☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly

3. In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA)?

☐ None	☐ Mild	☐ Moderate	☐ Severe	☐ Very severe

4. In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?

☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

5. In the last 7 days, how OFTEN did you LOSE CONTROL OF BOWEL MOVEMENTS?

☐ Never	☐ Rarely	☐ Occasionally	☐ Frequently	☐ Almost constantly

6. In the last 7 days, how much did LOSS OF CONTROL OF BOWEL MOVEMENTS INTERFERE with your usual or daily activities?

☐ Not at all	☐ A little bit	☐ Somewhat	☐ Quite a bit	☐ Very much

Appendix V

EPIC-26

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 the number)
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 the number)
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	(Circle the number)
2 pads per day ……	2	
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
b. Pain or burning on urination…	0	1	2	3	4
c. Bleeding with urination…….	0	1	2	3	4

d. Weak urine stream or incomplete emptying…….....	0	1	2	3	4
e. Need to urinate frequently during the day…….....	0	1	2	3	4

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 the number)
Moderate problem.……...	4	
Big problem…..……..	5	

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 Proble
a. Urgency to have a bowel movement…….	0	1	2	3	4
b. Increased frequency of bowel movements...	0	1	2	3	4
c. Losing control of stools…….....	0	1	2	3	4
d. Bloody stools……	0	1	2	3	4
e. Abdominal/Pelvic/Rectal pain…….	0	1	2	3	4

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 the number)
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
b. Your ability to reach orgasm (climax)?.....	1	2	3	4	5

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

None at all…… 1
Not firm enough for sexual activity…… 2
Firm enough for masturbation and foreplay only….. 3 (Circle the number)
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 want 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 the number)
I had an erection MORE THAN HALF the time I wanted one… 4
I had an erection WHENEVER the time I wanted one…… 5

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

Very poor…… 1
Poor…..…….….. 2
Fair…….. 3 (Circle the number)
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 the number)
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
b. Breast tenderness/enlargement…	0	1	2	3	4
c. Feeling depressed……	0	1	2	3	4
d. Lack of energy…….	0	1	2	3	4
e. Change in body weight……	0	1	2	3	4