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Clinical Protocol: Hypofractionated Image-Guided Radiation Therapy for Localized Adenocarcinoma of the Prostate

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Clinical Protocol: Hypofractionated Image-Guided Radiation Therapy for Localized Adenocarcinoma of the Prostate

Phase: II

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Time required to complete the study: The study was resumed August 2011and is expected to be complete November 2015.

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1.0 BACKGROUND AND RATIONALE

Radiation therapy is an effective and frequently utilized modality for the treatment of clinically localized prostate cancer. Traditionally, external beam radiation has been delivered in a fractionated manner using daily doses of 1.8-2.0 Gy. This daily dose was derived from early animal experiments and clinical experience, supported by mathematical models of normal tissue and tumor response to fraction size. The most widely used of these models is the linear-quadratic formula, which predicts responses to different fraction sizes based on the alpha/beta ratio of any given tissue.[1]

One of the main motivations for delivering a treatment at low dose rate or with many fractions is that late-responding normal tissue are generally more sensitive than early-responding tissues (i.e. tumor) to increases in fraction size. So increasing the number of fractions generally spares late-responding tissues more than the tumor. This can be quantified in terms of the alpha/beta ratio:

- Small alpha/beta ratio (2-4 Gy), typical of late sequelae, means high sensitivity to fractionation changes.
- Large alpha/beta ratio (>8 Gy), typical of tumor control, means low sensitivity to fractionation changes.

It is generally assumed that the mechanistic basis for the different fractionation response of tumors and late-responding normal tissues relates to the larger proportion of cycling cells in tumors. But prostate tumors contain unusually small fractions of cycling cells.[2] Brenner and Hall as well as Duchesne and Peters have reasoned that prostate tumors might not respond to changes in fractionation in the same way as other cancers; both papers hypothesize that prostate tumors might respond to changes in fractionation or dose rate more like a late-responding normal tissue.[3],[4] In mathematical terms, the suggestion is that the alpha/beta ratio for prostate cancer might be low, comparable to that for late-responding tissues or even lower. Previous estimates of alpha/beta ratios of normal tissue and tumor tissue have generally been 3 and 10, respectively. Recent evidence has estimated the alpha/beta ratio of prostate cancer to be as low as 1.5. If these hypotheses are true, then the optimal therapeutic ratio for prostate cancer would be achieved using daily doses higher than 2 Gy.[5]

Several preliminary clinical reports have found reasonable PSA control rates and no increase in late toxicity (90 days of greater following radiation, as defined by RTOG) using doses of 2.5 to 3 Gy. Kupelian from the Mayo Clinic found PSA-free survival rates of 97%, 88%, and 70% in low-, intermediate-, and high-risk patients, respectively. The dose regimen used was 70 Gy in 2.5 Gy daily fractions. Both acute and late toxicity were not higher than seen with typical dose regimens.[6] A group from Christie Hospital reported 82%, 56%, and 39% 5-year biochemical disease free survival rates (low, intermediate, and high risk, respectively) in patients treated with 50 Gy in 16 fractions (3.125 Gy per fraction), with acceptable bowel and bladder toxicity; however, they did find a trend toward general worsening of bowel function at 2 years.[7] More recently, Lock et al. reported on a Phase II study evaluating 63.2 Gy in 20 fractions over 4 weeks. At median follow-up of 36 months, late grade 2 and 3 GU toxicity was 14% and 5%, and late grade 2 and 3 GI toxicity of 25% and 3%[8]. Biochemical disease-free survival at 3 years was 98%. Martin et al. reported from the Princess Margaret Hospital Phase II study of 60 Gy in 20 fractions, and found that only 1/92 patients experienced Grade 3 toxicity at a median

follow-up of 38 months.[9] Rene et al. treated 129 patients with 66 Gy in 22 fractions, and at median follow-up of 51 months the 5-year biochemical control rate was 98%. At last follow-up, there was 2% and 1.5% rates of persistent grade 2 or greater GU and GI toxicity, respectively.[10]

For purposes of comparison to standard fractionation results, Zelefsky et al. reported 17% grade 2 or greater GI and 13% grade 2-3 GU toxicity in patients receiving 75.6 Gy in standard fractionation; Storey et al. reported 21% 5-year grade 2 or greater GI and 9% grade 2 or greater GU toxicity using 78 Gy in 2 Gy fractions[11],[12]. Therefore, although our prior regimen of 67.2 Gy in 21 fractions was not well tolerated (see section 2.0 below), many other published series suggest that a slightly lower dose or a slightly more protracted course appears to have similar toxicity and control rates to a traditional 8 week regimen.

These results, although promising, require further validation. If the hypothesis that prostate cancer alpha/beta ratio is lower than normal tissue is correct, then the optimal fractional dose may be even higher than the doses tested thus far, but if incorrect, the result may be increased normal tissue toxicity.

2.0 OBJECTIVES

This will be a Phase II study evaluating the effectiveness and toxicity of a regimen of 3.6 Gy daily fractions to a total dose of 57.6 Gy. This choice of daily dose is based on the prior published experiences showing safety and efficacy of hypofractionated regimen of 2.5 Gy, 2.7 Gy, 3.0, and 3.63 Gy daily fractions. The total dose is calculated to be iso-effective for late effects to a conventionally fractionated total dose of 79.2 Gy, which has been shown to be effective and safe in large prospective studies.[13] ,[14] If the alpha/beta ratio for prostate is between 1.5-3.0, then this regimen should be at least as effective for tumor control as 79.2 Gy given in conventional 1.8 Gy fractions, a dose within the range of evidence-based standard practice[14],[15]. This dose has been modified from a prior version of this protocol which treated patients to 67.2 Gy in 21 fractions. In this experience, 16 patients were enrolled and treated; 4 patients have experienced Grade 3 urinary symptoms, and 4 patients have experienced Grade 2 rectal bleeding. Based on the urinary Grade 3 toxicity rate as well as the persistence of the urinary toxicity in the patients who developed Grade 3 symptoms, the dose has been reduced to one that is has a biological equivalent dose for late effects (BED = 3) of 127 (compared to 139 for the prior regimen). Also, in contrast to our prior dose regimen which tested a dose regimen which was novel, this dose is within the range of doses used in a prior Phase II study which reported acceptable toxicity and early efficacy results[16]. Other modifications which should ameliorate toxicity include the delivery of 4 fractions per week instead of 5 (based on reports from Stanford which found that increasing the overall time to complete treatment resulted in reduced toxicity, while other data suggest that modest prolongations of treatment course do not significantly impact control rates in prostate cancer)[17],[18], and the use of nominal doses prescribed to the mean, rather than minimal doses to a volume. Also, a run-in safety phase has been added (section 2.1).

Given the change in dose, the patients enrolled on the prior dose regimen will be considered separately from those enrolled onto the new regimen; however, they will still be monitored in follow-up according to the current version of the protocol. Sample size/accrual goals will pertain to the new dose regimen.

Comparison of Biologically Equivalent Doses for Different Regimens

	Fraction Size	# Fractions	Acute (10)	Prostate (1.5)	Prostate (3)	Late (3)	Total Dose
Conventional Fraction	1.8	44	93	174	127	127	79.2
Cleveland Clinic	2.5	28	88	187	128	128	70
Fox Chase	2.7	26	89	197	133	133	70.2
Christie	3	20	78	180	120	120	60
Prior Dose this Study	3.2	21	89	211	139	139	67.2
Proposed Regimen	3.6	16	78	176	127	127	57.6

2.1 Run-In Safety Phase

Although this regimen is based upon already published experience, given the unpredicted toxicity encountered on the previous dose regimen, a 'run-in' phase will be incorporated so that the accrual will be held if the rate of Grade 3+ toxicities at 6 month follow-up visits convincingly exceeds 5% in evaluable patients. Given this stopping guideline, the study regimen will be assessed using a one-sided exact binomial 95% confidence bound. Accrual will be held after 10 patients are treated, until these patients all reach minimum follow-up of 6 months. The protocol will either be modified or terminated if 3 out of first 10 evaluable patients experience G3+ toxicity at a minimum follow up of 6 months (corresponding to lower one-sided 95% confidence bound of 8.7%).

If the study is not stopped by the above rule in the first 10 patients, then protocol accrual will continue to study completion (108 subjects). At the final analysis, a sample size of 108 patients will allow a Grade 3+ toxicity estimate of +/- 4.5% if observed toxicity is 5%, and +/- 6.2% if observed rate is 10%, respectively.

2.2 Primary Objective

Assess the incidence of grade 2 and 3+ GU and GI toxicity and self-reported quality of life data with image-guided radiation therapy in doses of 3.6 Gy per day to a total dose of 57.6 Gy (16 fractions).

2.3 Secondary Objectives

1) Assess biochemical, clinical, and pathologic control rates associated with the hypofractionated dose regimen.
2) Collect dose/volume and imaging data to allow normal tissue complication probability modeling and targeting assessment for patients treated with hypofractionated radiation therapy.

3.0 PATIENT SELECTION

The target population will be patients with a diagnosis of adenocarcinoma of the prostate who are seen in consultation in the Department of Radiation Oncology (approximately 360 patients per year).

3.1 Inclusion Criteria

- Histologically confirmed adenocarcinoma of the prostate
- Clinical stages T1a-T2b

- PSA of less than 10 ng/ml
- Gleason score of 3+4 or lower
- The patient has decided to undergo external beam radiation as treatment choice for his prostate cancer.
- Signed study-specific consent form prior to registration

3.2 Exclusion Criteria

- Clinical stages T3-4 disease.
- Gleason (4+3) or higher score.
- PSA > 10 ng/ml.
- History and/or clinical evidence of lymph node involvement *(N1).*
- History and/or clinical evidence of distant metastases *(M1).*
- Radical surgery for carcinoma of the prostate.
- Previous Chemotherapy or pelvic radiation therapy.
- Previous or concurrent cancers other than basal or squamous cell skin cancers or superficial bladder cancer unless disease free for at least □5 years.
- History of inflammatory bowel disease.
- Major medical or psychiatric illness which, in the investigator's opinion, would prevent completion of treatment and would interfere with follow up.
- Androgen suppression therapy within past year. Defined as: LHRH agonist or antagonist, or androgen blocker, not 5-alpha reductase inhibitor.

4.0 PRETREATMENT EVALUATIONS

4.1 Subject Screening Procedures

- History and physical (including digital rectal examination).
- Histological diagnosis and Gleason score provided on the pathology report. All patients, per institutional policy, will have pathology reviewed at Johns Hopkins.
- Prostate specific antigen *(PSA)* within 6 months prior to registration.
- Quality of life measures: IPSS, and EPIC bowel and sexual questionnaires (See Appendix 1 for questionnaires).
- Patients will not be required to have pelvic lymph node imaging (i.e. CT scan) or a bone scan if they have not previously had them performed, given the low incidence of positive findings in this population and the current standard of care for work-up.

4.2 Registration Procedures

4.2.1 Subject Identification

Patient confidentiality will be maintained in accordance with Health Information Portability and Accountability Act (HIPAA) guidelines. All participants must sign an informed consent that will describe the objectives of the study and potential risks. All patient data reported on the case reports forms will be identified by the patient's initials and study code number only. Patients shall not be identified by name. This should serve to protect the confidentiality of subjects enrolled on the trial. Clinical data and records for all subjects studied including history and physical findings, laboratory data, and results of interventions are to be maintained by the

investigators in a secure, locked location. Computerized data will require password authorization(s) for access.

4.2.2 Description of the Recruitment Process

Potential subjects will be identified at the time of consultation in the Department of Radiation Oncology by Dr. Song or Dr. DeWeese. All patients meeting above stated eligibility criteria will be offered participation in the study by the consulting physician or by the protocol team study nurse.

4.2.3 Description of the Informed Consent Process

Only physicians who are also investigators or research nurses listed on the project will perform the informed consent interview. The informed consent interview will take place prior to the day the patient is to be treated to ensure that the patient has adequate time to discuss the research project with family, friends, and/or other Health Care providers. During the informed consent interview the interviewer (investigator physician or research nurse) will take as much time as needed to ensure that the potential subject understands the research project and also clearly understands that he does not have to participate in this project to receive his cancer treatment at Johns Hopkins. If the patient decides to enroll into the research project he will sign three copies of the informed consent form. One will be for his own records, one will be kept in the Clinical Research Office at Johns Hopkins, and the third one will be kept in his medical records.

5.0 RADIATION THERAPY AND RESEARCH INTERVENTIONS

Rather than receiving ~ 42 fractions of radiation over 8 ½ weeks, patients enrolling on the study will receive radiation in 16 fractions over 4 weeks. There will be no alteration in what patients experience in a treatment session other than a slightly longer (estimated at 2-3 minutes) duration of beam-on time.

5.1 Simulation procedure

5.1.1

Prior to simulation, patients may undergo transrectal or transperineal insertion of 2-3 Calypso™ transponder beacons, polyethylene glycol hydrogel injection into Denonvilliers' fascia, or gold seeds to improve accuracy in daily prostate alignment and decrease residual positioning errors.[19] Patients may be treated without implanted markers if daily on-board CT imaging is available, or in cases where hydrogel has been injected. In cases where Calypso beacons or hydrogel are not utilized, a rectal balloon will be inserted at simulation and during daily therapy to minimize variability in rectal contents/dosimetry.[20]

5.1.2

Patients will undergo CT simulation in the Department of Radiation Oncology. CT slice thickness of 3mm will be used. For accurate delineation of the prostate, MRI simulation images will be fused with the CT images. MRI will be performed in the Department of Radiation Oncology, with acquisition of T1-weighted (3mm slices) and T2-weighted (1mm slice thickness) images. Image fusion will be performed using the image fusion functionality in Pinnacle treatment planning system.

Simulation is to be performed in the supine position, with either an alpha cradle or adaptable leg bolster. Patients will be instructed to empty their rectum prior to simulation, and to have a moderately full bladder (drink 30 cc of water 30-60 minutes prior to simulation). Oral contrast will be utilized at the discretion of the treating physician, but in general is discouraged given the confounding effect on dose calculation in the radiation planning algorithm due to heterogeneity correction.

In order that extreme rectal filling not be present at the time of the planning CT scan as well as during treatment, patients will be advised to:

a) Take 2 tablespoons of magnesium hydroxide (milk of magnesia) beginning 12 hours before the simulation.
b) Avoid solid food starting at 5PM on the day prior to simulation; clear liquids may be ingested.
c) Take one Fleet's enema the morning of the simulation.

If a patient is determined to have a distended rectum (greater than 3 cm in diameter on any axial CT slice posterior to the prostate or proximal seminal vesicles) at the time of initial scanning, patient will be given opportunity to evacuate and a repeat CT scan performed until treating physician determines it is satisfactory. Otherwise if unsuccessful, the patient will be rescheduled for simulation on another day, with repeated instructions on bowel preparation as noted.

5.2 Target and Normal Tissue Volumes

The target volume definitions are, for the most part, based upon the *ICRU Report 58, Dose and Volume Specification for Reporting Interstitial Therapy*.

a) Gross Target Volume (GTV): The GTV is the entire prostate as defined on T2-weighted MRI sequences.
b) Clinical Target Volume (CTV): In the case of intermediate risk disease, the CTV will include the prostate and will also encompass the proximal 1-2 cm of seminal vesicle (overlap of seminal vesicle with 1-2cm expansion on prostate; in Pinnacle this can be accomplished by contouring entire seminal vesicle, then using auto-expand ROI function with prostate as 'source' and seminal vesicle turned on as 'avoid exterior'). For low risk patients the CTV is equal to the prostate GTV.
c) Planning Target Volume (PTV): The PTV is the CTV plus 7mm margin expansion in all directions except posteriorly, for which a 5mm expansion will be utilized.
d) Rectum will be contoured from approximately the level of the bottom of the ischial tuberosities (where the rectum joins the anal canal) superiorly to the rectosigmoid junction (generally below the sacroiliac joints, or until the rectum no longer is adjacent to the sacrum).
e) Penile bulb (contoured on the proximal/superior 3 slices or 1cm on CT)
f) Bladder (entire bladder)
g) Bowel (contoured up to the level of the top of the sacroiliac joints)
h) Femoral heads

5.3 Treatment Planning

Intensity-modulated radiation will be utilized to achieve a plan meeting the criteria for dose coverage of the PTV and minimizing dose to critical structures. Dose-volume histograms (DVHs) must be generated for all critical normal sructures.

5.3.1 Dose

Prescription dose will be 3.6 Gy per fraction x 16 fractions. The nominal dose will be the median dose received by the prostate (or CTV for intermediate risk patients), +/- 0.1 Gy. Minor variation (marginal coverage): Minor variation will be deemed if any portion of PTV receives < 93% of the prescription dose (minimum PTV dose less than 53.6 Gy), or any portion of CTV receives <95% of prescription dose (minimum CTV or prostate dose < 54.7 Gy).

a) Major variation: Major variation will be deemed if any portion of PTV receives <90% of prescription dose (minimum PTV dose less than 51.8 Gy), or any portion of CTV receives <93% of prescription dose (53.6 Gy).

5.3.2 Dose Constraints

Based on an alpha/beta ratio of 3 for rectum and 3 for bladder late toxicity, as well as dose constraints for rectal and bladder toxicity as determined from prior studies with conventional fractionation, dose constraints will be:

a) no more than 20% of rectum receives greater than 51 Gy
b) no more than 40% of rectum receives greater than 43 Gy
c) no more than 30% of bladder receives greater than 47 Gy
d) no more than 10% of femoral heads receive greater than 36 Gy
e) no more than 5% of bowel receives greater than 39 Gy [21,22,23,24]

5.3.3 Dose Heterogeneity

Maximum dose to the PTV volume should not exceed prescription dose by more than 5% (i.e. maximum PTV dose of 60.48 Gy). Maximum point dose to any tissues or other structures outside the PTV including unspecified tissue should not exceed prescription dose by more than 7% (i.e. maximum dose of 61.63 Gy). Entire PTV volume should receive at least 93% of prescription dose (i.e. 53.6 Gy), and entire CTV volume should receive at least 95% of prescription dose (i.e. 54.7 Gy).

5.4 Image-Guided and Adaptive Therapy

5.4.1

If Calypso beacons are utilized, temporary intrafraction motion is expected to occur and will be monitored. Thresholds of prostate/beacon motion of 5mm (3mm in posterior direction) for interrupting therapy will be utilized. If the prostate does not move back to within these thresholds within five minutes (as tolerated by the patient lying on the table) then therapist will perform re-alignment to new position based on transponder

beacon system. If daily on-board CT is utilized, a pre-treatment image will be obtained and necessary positioning adjustments made prior to beam-on.

5.4.2

If gold markers are utilized, a daily pre-treatment lateral and anterior-posterior kV image will be obtained to assess for necessary adjustments in patient positioning. Weekly verification CT simulation may also be performed according to physician discretion.

5.5 Patient Management During Treatment

All patients will be seen weekly by the radiation oncologist or nurse (weekly on-treatment visit) during treatment, as well as upon completion of radiation. Radiation reactions to be captured:

a) Rectal or small bowel symptomatology (cramping, diarrhea, rectal urgency, hematochezia)
b) Bladder symptomatology (frequency, urgency, nocturia, dysuria)
c) Radiation dermatitis
d) Side effects will be treated based on the discretion of the radiation oncologist, and documentation kept in the medical record. Rectal side effects such as diarrhea may be treated with diphenoxylate or loperamide. Bladder or rectal spasms can be treated with anticholinergic agents or tolterodine. Irritative or obstructive voiding symptoms can be managed with alpha-blockers or phenazopyridine.

6.0 Patient Assessments

6.1 Study Calendar

Parameter	Pre-Study Entry	Weekly during RT	Within 1 week prior to or after finish of RT	Semiannually post-RT (until year 5)
H&P	x			
PSA	x		x	x
Quality of life assessment [a]	x			x[b]
Toxicity assessment using NCI CTC v 4		x		x[b]

a. IPSS, EPIC sexual, EPIC bowel
b. Until 3 years then annually until year 5

6.2 Follow-Up Schedule

6.2.1

Patients will be assessed for Quality of life and Toxicity every 6 months (+/- 30 days) until 3 years following completion of radiotherapy, then annually (+/- 30 days) until year 5. PSA measurements will be obtained every 6 months until year 5. The patient will be off study after 5 years.

6.2.2

Patients who develop a rise in PSA compared to the prior PSA will have PSA drawn every 3 months until PSA either declines, or rises to a value 2 ng/ml or more above the nadir. The nadir PSA is defined as the lowest PSA value after initiation of treatment. Time of failure will be the date of the first PSA that is 2 ng/ml or more above the nadir.

6.2.3

At 2 years post-radiation, patients will be encouraged but not required to undergo biopsy for histopathologic assessment of disease response.

7.0 Data Analysis and Statistical Considerations

7.1 Primary Objective

7.1.1

Assess the incidence of grade 2 and 3 or greater late GU and GI toxicity and self-reported quality of life data with hypofractionated image-guided radiation. Assessment will be performed at median 4 years and again once all patients reach 5 years of follow-up (except for run-in safety phase).

7.2 Secondary Objectives

7.2.1

Assess biochemical and clinical control rates associated with the hypofractionated dose. Assessment will be performed at median 4 years and again once all patients reach 5 years of follow-up.

7.1.1.1

Freedom from Biochemical (PSA) Failure: Measured from the date of enrollment to the date of a rise by 2 ng/ml or more above the nadir PSA.

7.1.1.2

Clinical Disease-Free Survival, measured from the date of enrollment to the date of documented radiographic, clinical evident progression or date of death. Progression may be documented by imaging studies such as CT or bone scan, or biopsies. Patients with new palpable abnormality on digital rectal examination will also be offered biopsy to confirm local failure.

7.2.2

Collect dose/volume and imaging data to allow normal tissue complication probability modeling and targeting assessment for patients treated with hypofractionated radiation therapy.

7.3 Sample Size

7.3.1 Primary Endpoints

The primary goal of the study is to estimate the risk of late grade 2 and 3 or greater GU or GI toxicity. The expected rate of grade 3 or greater toxicity is 5% for GI + GU. A sample size of 108 patients will allow a Grade 3+ toxicity estimate of +/- 4.5% if observed toxicity is 5%, and +/- 6.2% if observed rate is 10%, respectively.

7.3.2 Secondary Endpoints

We seek to estimate the risk of biochemical (PSA) control at 5 years with a confidence interval of +/- 10%. For conventionally fractionated high-dose regimens, the expected rate of control is 93% and 85% for low and intermediate risk groups, respectively.[25] In order to test the null hypothesis that the proportion of patients in our cohort who maintain biochemical control at 5 years is less than or equal to 75%, a sample size of **108** patients will be required. This sample size was determined using the Type I error rate of 0.05 and Type II error rate of 0.2.

The time of failure for the PSA control endpoints will be measured from the date of completion of radiation to the date of documentation of the event of interest. In the presence of multiple endpoints of failure, the time to the first failure of any type would be the most clinically relevant endpoint to the treatment outcome and the first failure will affect subsequent endpoints. Therefore, if a patient experiences a competing event prior to the event of interest, the patient will be censored at the date of first occurrence of the competing event. The survival function of these endpoints will be estimated using the Kaplan-Meier method.

7.3.3 Accrual and Study Duration

Of approximately 66 patients per month seen in consultation for prostate cancer in the department of radiation oncology, we anticipate approximately 25% of patients to be eligible. All eligible patients will be offered enrollment on the study, and we estimate a 35% accrual rate with 5% dropout rate, resulting in an average of 5 patients enrolled per month. If these projections are correct, it should take 20 months for full patient accrual of 108. The study resumption date was August 2011, with a projected closure date of November 2015. *(adjusted October 2013)*

7.3.4 Incidence of Adverse Events

Time to adverse events will be measured from the time that protocol treatment started (i.e., the start of RT) to the time of the worst severity of the adverse event. Adverse events are scored according to the NCI CTCAE v4.0 criteria.[26]

7.3.5 Safety Run-In

See section 2.1

8.0 REPORTING OF SERIOUS OR UNEXPECTED ADVERSE EVENTS

8.1 *The following guidelines will be followed for reporting serious or unexpected adverse events.*

8.1.1

All **fatal** events, both **anticipated and unanticipated**, must be reported to the JHM IRB within a time period as specified by current institutional guidelines after the PI learns of the event, whether or not the PI believes the event to be related to the study. All other events, which are both **serious** and **unanticipated**, must be reported to the JHMI IRB within a time period as specified by current institutional guidelines after the PI learns of the event. Events which are **serious** but **anticipated**, should be reported as part of the continuing review application. If any of these Serious Adverse

Events requires a change to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the JHM IRB.

8.1.2

Important Adverse Events that are **unanticipated** must be reported to the JHM IRB within a time period as specified by current institutional guidelines. If the Important Adverse Event requires changes to the protocol or consent form, the PI must make those changes promptly and submit the revised documents to the JHM IRB.

8.1.3

All other **unanticipated** Adverse Events or changes to the protocol and consent form must be reported to the JHM IRB, within a time period as specified by current institutional guidelines.

8.2 Definitions

Serious Adverse Event: an event that is

- Fatal
- Life-threatening
- Persistent or significantly disabling or incapacitating
- Inpatient hospitalization or prolongation of hospitalization
- Congenital anomaly or defect and/or
- A significant medical incident (considered to be a serious study related event because, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.)

Important Adverse Event: means an event, although not a Serious Adverse Event, which still presents an undesirable occurrence that interferes with the subject's usual activities and may be persistent or require treatment. (For example, serious rash, cough, or fever.)

Unanticipated Adverse Event: means an event that results from a study intervention and was not expected or anticipated from prior experience. This includes expected events that occur with greater frequency or severity than predicted from prior experience.

8.3 Following a Study Related Adverse Event

If a patient experiences an adverse event while on study, the following steps will be taken:

1) Establish the cause and severity of the adverse event and determine if said event is related to study participation.
2) Principal Investigator will decide what treatment(s), if any, is/are required.
3) Depending on the type and severity of adverse event, an appropriate follow-up schedule will be constructed which will allow for determination of event outcome.
4) Patient will be followed by principal investigator until the adverse event has resolved.

9.0 DISPOSITION OF DATA

Clinical records for all subjects studied including history and physical findings, laboratory and clinical data, and operative and dosimetric records are to be maintained by

the investigators in a secure location at Johns Hopkins Cancer Center. Any records that are stored electronically will be password protected and only those who are involved in the research will have a password. These records are to be stored for a minimum of 8 years after last clinical visit.

10.0 PROTOCOL MODIFICATIONS

All revisions or amendments (that are not required for immediate patient safety) to the protocol must be approved by the Johns Hopkins Institutional Review Board prior to implementation.

11.0 DEPARTURES FROM PROTOCOL

If there is a departure from the Clinical Protocol, the Principal Investigator will notify in writing both the local IRB at Johns Hopkins and the HSRRB at the time of annual review (continuing review). The research coordinator will keep a log of all deviations/departures that occur on this project and this log will be reviewed by the research team on a monthly basis. During the review the research team will discuss corrective action plans to minimize future deviations/departures. If there are departures to the protocol that effects patient safety the principal investigator will notify in writing the IRB within 24 hours of discovering the departure/deviation.

12.0 CRITERIA FOR WITHDRAWAL FROM STUDY

Patients may be withdrawn from the study for the following reasons:

a) Consent for participation is withdrawn
b) Noncompliance to study procedures

13.0 ROLES AND RESPONSIBILITIES OF STUDY PERSONNEL

Principal Investigator:

Oversees all aspects of the trial. Recruits and consents patients and administrates protocol specific procedures. Provides medical care to research subjects during the conduct of the study. Follows and advises regarding the treatment of adverse events. Reports SAE's to the IRB within the required time frame. Amends the trial as necessary to reflect unforeseen adverse events, new scientific data and for the general intergrity of the study. Monitors the trial. Is ultimately responsible for the conduct of protocol.

Co-Investigators:

If a physician**:** can recruit and consent patients and can administrate protocol specific procedures. Can provide medical care to research subjects during the conduct of the study. Has input on the course of action for adverse events.

If not a physician**:** Collaborates with the Principal Investigator according to area of expertise.

Research Nurses:

Executes protocol specific procedures requiring nursing qualifications. Provide nursing care to research subjects during the conduct of the study. May consent patients for study enrollment.

Data Manager/Study Coordinator:

Collects data from subject's medical records and codes it onto the study's case report forms. Notifies principal investigator of any deviations that he/she finds while managing

the data. Prepares annual IRB renewals and termination report upon study completion, assists with management of regulatory issues governing the trial. Monitors the trial.

14.0 ETHICAL AND REGULATORY CONSIDERATIONS

14.1

IRB: Prior to initiating the study, the Principal Investigator must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study protocol become necessary, protocol amendment will be submitted in writing to the IRB by the Principal Investigator for IRB approval prior to implementation.

14.2

Informed Consent: All potential candidates for the study will be given a copy to read of the Informed Consent for the study. The investigator will explain all aspects of the study in lay language and answer all the candidate's questions regarding the study. If the candidate desires to participate in the study, he/she will be asked to sign the Informed Consent. No study procedures will be performed on a patient until after they have signed the informed consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

14.3

The principal investigator will ensure that the study is conducted in compliance with the protocol and according ICH Guidelines for Good Clinical Practices, the Declaration of Helsinki, and all regulatory and institutional requirements, including those for patient privacy, informed consent, Institutional Review Board approval and record retention.

15.0 DATA SAFETY AND MONITORING PLAN

Following completion of the run-in phase of the trial (total 15 patients), the independent medical monitor (Dr. Richard Zellars) and study coordinator will review the data on a quarterly basis. The purpose will be to review the level of adverse events, given that the adverse events may occur on a delayed basis after treatment completion. The independent medical monitor may elect at his/her discretion to notify IRB and CRC and/or halt protocol accrual if in his/her estimation there is appears to be an unacceptably high rate of toxicity in the study subjects. In addition, this trial will be audited annually by the central clinical research office at Johns Hopkins as well as the IRB.

16.0 LIST OF DATA COLLECTION SHEETS

IPSS
Sexual Health Inventory for Men
EPIC Bowel

17.0 REFERENCES

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