Adjuvant and Salvage Therapy

An estimated 15-25% of prostatectomy patients will develop a prostate specific antigen (PSA) recurrence. (Stephenson 2012) High-risk features for recurrence include extra-capsular extension and/or seminal vesicle invasion (pT3 disease) and positive surgical margins, which occur in an estimated 20% and 16% of patients, respectively. (Tewari 2012) Post-prostatectomy radiotherapy (RT) to the prostate bed for pT3 disease or positive surgical margins has been shown to reduce the risk of recurrence in three randomized trials: Southwest Oncology Group (SWOG) (Thompson 2006); European Organization for Research and Treatment of Cancer (EORTC) (Bolla 2012); and Auckland Radiation Oncology (ARO). (Wiegel 2009) As a result, post-prostatectomy RT is a well-accepted practice standard for adverse pathologic features following surgery or at the first sign of PSA recurrence. (Prostate Cancer 2016, Thompson 2013)

Rationale for Dose Escalation

2.1.1 Lessons From Intact Prostate RT

Central to the success of RT for intact prostate cancer has been dose escalation where an additional 8 - 10 Gy in 2 Gy fractions has been shown to effectively reduce the risk of biochemical failure (BF) [Dearnaley 2007, Fuks 1991, Kuban 1987, 1989, 2008, 2011, Zietman 2010], as well as prevent distant metastasis and death (Kuban 2011). The eradication of local disease for intact prostate cancer has also been shown to reduce the risk of distant metastasis and death from prostate cancer (Coen 2002, Zelefsky 2008, Kuban 1987, Fuks 1991). Rectal complications have been the primary dose limiting toxicity with dose escalation.

2.1.2 Post-prostatectomy Dose Escalation

Radiotherapy dose escalation is rooted in the fundamental radiobiological principle that higher doses are needed to eradicate an increasing burden of disease (Hall 2012). A biochemical tumor control probability (TCP) analysis of dose–response curves for adjuvant and salvage post-prostatectomy RT has estimated a 3%/Gy improvement in FFBF with dose escalation (2.6%/Gy, 95% CI, 2.3–3.0 for adjuvant; 3.8%/Gy, 95% CI, 2.5–7.6 for salvage) [King 2008]. Various treatment planning studies have shown that adequate rectal sparing for dose escalation in the > 70 Gy in 2 Gy fraction range is achievable with modern RT techniques employing image guidance [Bernard 2010, De Meerleer 2008, King 2008, Harrison 2011]. Several studies have indicated a benefit to dose escalation post-prostatectomy (King 2008b, King 2008a, Cozzarini 2009, Valicenti 1998, Anscher 2000). And clinical studies have indicated the risk of toxicity with RT dose ≥ 70 Gy in 2 Gy fractions is low with less than 3% of late grade 3 proctitis or genitourinary side effects, respectively (De Meerleer 2008, Wiegel 2009, Van Der Poel 2008, Feng 2007, Hunter 2012).

2.2 Rationale for Hypofractionation

2.2.1 Hypofractionation Definition

Post-prostatectomy RT has traditionally been delivered in conventional fractionation (i.e. 1.8 or 2.0 Gy per fraction) that can take as long as 6 to 8 weeks to deliver (Thompson 2009, Bolla 2005, Wiegel 2009). The proposed study explores an alternative RT dose-fractionation schedule that exploits the radiobiological properties of prostate cancer to shorten overall treatment time called hypofractionation. Hypofractionation uses larger

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Operations Center by phone, 215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.3.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting Requirements, a CTEP-AERS 24-hour notification must be submitted with 24 hours of learning of the adverse event.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and contact the NRG Operations Center (215-574-3191) for source document submission information.

A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.3.2 Expedited Reporting Requirements for Adverse Events

For Arm 1: Any Phase Study Utilizing Standard of Care Radiation Therapy[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected

2. Patient-reported genitourinary (GU) symptoms using the EPIC at the end of RT, 6 months, 1 and 5 years.
3. Freedom from biochemical failure (FBF)
4. Time to progression (TTP) where progression is defined as the first occurrence of, BF, local failure, regional failure, distant metastasis (DM), institution of new unplanned anticancer treatment, or death from prostate cancer (PCSM)
5. Local failure, regional failure, salvage therapy (i.e. institution of new unplanned anticancer treatment), DM, PCSM, and OS rates.
6. Adverse events using the Common Terminology Criteria for Adverse Events (CTCAE v. 4.0).

14.2.3 Exploratory endpoints

1. Measured utilities for health outcomes using the EQ5D.
2. Paraffin-embedded tissue block, serum, plasma, whole blood, and urine for future translational research analyses for predictors of toxicity following hypofractionated or conventionally fractionated post-prostatectomy radiotherapy.

14.3 Primary Objectives Study Design

14.3.1 Primary Hypothesis and Endpoints

1. Hypofractionated postprostatectomy radiotherapy (HYPORT) delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GI symptoms, as measured by the EPIC bowel domain, compared to conventionally fractionated postprostatectomy radiotherapy (COPORT) delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed.
2. HYPORT delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GU symptoms, as measured by the EPIC urinary domain, compared to COPORT delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed.

14.3.2 How Primary Endpoints Will Be Analyzed

Analysis of the Primary Endpoints

The co-primary endpoints are GI and GU toxicity as measured by the bowel and urinary EPIC domains, respectively. The change scores, calculated as baseline score subtracted from 2-year score, will be analyzed using a t-test with a significance level of 0.025. If the data are determined to be non-normal, a Wilcoxon test may be used instead. Missing data will be assessed and is described in more detail in Section 14.6.2. All patients will EPIC bowel and urinary domain scores will be included in the primary endpoint analysis. The EPIC scoring manual will be followed which requires ≥ 80% of items in a domain to be completed in order to obtain a score for that domain.

14.3.3 Sample Size and Power Calculations:

The primary goal of this phase III study is to determine if HYPORT does not increase GI and GU toxicity over COPORT. The primary endpoint is based on change scores from the bowel (GI) and urinary (GU) domains of the EPIC. The change scores will be based on the 2-year score minus the pretreatment (baseline) score. The hypothesis for this endpoint is that the EPIC mean change score is no worse in the HYPORT than it is in the

COPORT arm for either type of toxicity. Section 11.1.2 contains more information about the EPIC, such as validation information, number of questions, possible responses, and ranges of the scores.

RTOG 0534 has a similar population to this study, however it did not collect EPIC scores at 2 years. Therefore, data from the conventionally-fractionated arm of RTOG 0415 was used to aid in calculation the sample size for this study. To verify that RTOG 0415 data is similar to the patient population in this study, EPIC data from the conventionally-fractionated arm of RTOG 0415 was compared to the results of a recent paper where conventionally-fractionated post-prostatectomy patients were surveyed with the EPIC questionnaire as to their quality of life (Pinkawa 2008). Pretreatment and 1-year results were compared. For the post-prostatectomy paper, the reported pretreatment and 1-year, respectively, mean bowel function scores are 92 and 91, respectively, while for the RTOG 0415 control arm, the mean bowel function scores at the corresponding time points are 93.0 and 90.2, respectively. For post-prostatectomy, the pretreatment and 1-year mean bowel bother scores are 94 and 90, respectively, while for RTOG 0415 control, the corresponding time point scores are 94.1 and 89.5, respectively.

From the conventional arm of RTOG 0415, in an analysis of 170 eligible patients with the bowel domain completed at both baseline and 2 years from the start of RT, the mean change (2-years minus baseline) in EPIC bowel domain score was -4.3 points (SE=13.2). In a similar analysis of 173 eligible patients with the urinary domain completed at both baseline and 2 years, the mean EPIC urinary domain change score was 0.42 (SE=10.5).

Based on these results an EPIC bowel domain mean change-score of -4 will be hypothesized for the COPORT arm, with a non-inferiority margin of 6 for the HYPORT arm corresponding to a bowel domain change score at 2 years of -10 in the HYPORT arm. An EPIC urinary domain score of 0.4 is hypothesized for the COPORT arm, with a non-inferiority margin of 5 for the HYPORT arm corresponding to a urinary domain change score at 2 years of -4.6 in the HYPORT arm. So, if the mean bowel or urinary domain change score for the HYPORT arm is no more than 6 points worse for bowel or 5 points worse for urinary than the mean change score for the COPORT arm, then the HYPORT arm will be considered non-inferior. For the primary endpoint, the null hypothesis (H_0) of this test is that the mean change score of HYPORT (Δ_2) is worse than the mean change score of COPORT (Δ_1). The alternative hypothesis (H_A) is that the mean change score of HYPORT is not worse than the mean change score of COPORT.

The non-inferiority margin is based on 0.5*SE from the RTOG 0415 analysis due to 0.5*SD being the cutoff for clinical difference (Barry 1999). To put the non-inferiority margins in context, a change score of 6 points corresponds to two symptoms worsening by 1 level (i.e. loose stools and frequency of bowel movements change from “no problem” to “very small problem”) or one of the symptoms worsening by 2 levels (i.e. loose stool change from “no problem” to “small problem”).

The study sample size is based on 90% power for GI endpoint and 91% power for the GU endpoint (resulting in 81.9% statistical power to reject the null hypothesis for both

adverse events.

14.5 Accrual/Study Duration Considerations

Based on patient accrual in previous RTOG legacy/NRG Oncology studies, the initial 6 months accrual is projected to be negligible while institutions are obtaining IRB approval. This protocol has a similar patient population (post-prostatectomy) to RTOG 0534. The accrual rate for the QOL component on that study was 11.3 patients per month. Therefore, the projected accrual rate is 11 patients per month. Based on this information, it is projected that the study will complete accrual in about 26 months from the end of the 6-month period of negligibility (32 months from activation). The primary endpoint analysis will occur approximately 5 years from study activation. Accrual will be monitored in accordance to CTEP accrual guidelines.

14.6 Secondary Endpoints

14.6.1 Secondary Hypotheses and Endpoints:

1. Hypofractionated postprostatectomy radiotherapy (HYPORT) delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GI symptoms compared to conventionally fractionated postprostatectomy radiotherapy (COPORT) delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed at the end of RT, and 6 months, 1 and 5 years from the start of RT.
2. HYPORT delivering 62.5 Gy in 25 fractions of 2.5 Gy to the prostate bed is not associated with excess patient-reported GU symptoms compared to COPORT delivering 66.6 Gy in 37 fractions of 1.8 Gy to the prostate bed at the end of RT, and 6 months, 1 and 5 years from the start of RT.
3. Comparison of freedom from biochemical failure (FBF) between the HYPORT arm and COPORT arm.
4. Comparison of time to progression (TTP) where progression is defined as the first occurrence of, BF, local failure, regional failure, distant metastasis (DM), initiation of new unplanned anticancer treatment, or death from prostate cancer (PCSM) between the HYPORT arm and COPORT arm.
5. Comparison of local failure, regional failure, salvage therapy (i.e. initiation of new unplanned anticancer treatment), DM, PCSM, and OS rates between the HYPORT arm and COPORT arm.
6. HYPORT is not associated with excess adverse events (AEs) compared to COPORT

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Additional EPIC Endpoints

All four domains of the EPIC will be analyzed, bowel, urinary, sexual, and hormonal. The change scores, calculated as baseline score subtracted from follow-up score, will be analyzed using a t-test. If the data are determined to be non-normal, a Wilcoxon test may be used instead. The follow-up timepoints of interest are end of RT, 6 months, 1, 2 (for sexual and hormonal domains) and 5 years from the start of treatment. A longitudinal analysis incorporating all follow-up time points, will be conducted separately for each domain score using a general linear model with maximum likelihood estimation, adjusting for baseline domain score, treatment arm, Gleason score, baseline PSA, T-stage, age, and

race. These analyses will be conducted regardless the outcomes of the primary t-test. For the comparison of primary endpoints at 2 years adjusting for other variables using the longitudinal model, especially stratification variables, the results will be similar to those of the primary analysis in general. In the rare case when it is different, we will examine very carefully the impact of missing data and the adjusted variables and make a meaningful conclusion regarding the outcome.

If any of the domains are found to significantly differ between arms, then analysis of that domain's subscales will be undertaken to assess which particular subscale is driving the significant difference. The subscales are function both incontinency and irritative/obstructive for the urinary domain, and function and bother for the bowel, sexual, and hormonal domains.

Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If ≥15% of the data is missing at any time point for the EPIC bowel and urinary domain scores, patient characteristics will be compared between patients with completed assessments and those with missing assessments. If any are found to differ significantly, they will be included in the mixed effects model which assumes that the data is MAR. If the missingness is determined to be non-ignorable, other methods may be performed. Specifically, a joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

Secondary Efficacy Endpoints

OS is defined as a death from any cause and will be measured from the date of randomization to the date of death. BF is defined as a PSA ≥ 0.4 ng/mL and rising (i.e. PSA ≥ 0.4 ng/mL followed by a value higher than the first by any amount) or followed by inititation of salvage hormones. The time of the first occurrence of PSA ≥ 0.4 ng/mL will be considered the event time. An alternative definition of BF will also be assessed: PSA ≥ PSA nadir + 2 ng/mL where nadir is the lowest post-RT PSA value. PCSM will be measured from the date of randomization to the date of death due to prostate cancer. LF is defined as the development of a new biopsy-proven mass in the prostate bed after enrollment in the protocol and will be measured from the date of randomization to the date of documented local failure. RF will be defined as radiographic evidence (CT or MRI) of lymphadenopathy (lymph node size ≥ 1.0 cm in the short axis) in a patient without the diagnosis of a hematologic/lymphomatous disorder associated with adenopathy and will be measured from the date of randomization to the date of documented regional metastasis. DM is defined as radiographic evidence of hematogenous spread (e.g., bone scan, CT, MRI) and will be measured from the date of randomization to the date of documented DM. For LF, RF, and DM, a BF is required prior to the LF, RF, and DM but will not be

to model cost for this analysis. The Medicare reimbursement in dollars/QALY will be calculated as a function of the monetary cost per relative value of each health state and its duration. The EQ-5D-5L index score at 6 months and 5 years will be used for the cost-utility analysis. The z-test will be used to test the hypothesis that the cost-utility in the two treatment arms is the same with significance level of 0.05. The cost-utility using the Medicare reimbursement in dollars/QALY between the two treatment arms after adjusting for the baseline and stratification variables.

14.8 Gender/Ethnicity/Race Distribution (26-APR-2019)

No differences across the patient subsets below are anticipated.

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	2	0	1	3
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	1	0	1	2
Black or African American	0	40	0	3	43
White	0	139	0	10	149
More Than One Race	0	1	0	1	2
Total	0	185	0	16	201

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	1	0	0	1
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	2	0	0	2
White	0	70	0	8	78
More Than One Race	0	0	0	0	0
Total	0	73	0	8	81

daily fraction sizes (i.e. 2 to 5 Gy) to deliver a RT over a shorter duration.

2.2.2 Hypofractionation Advantages

The potential advantages of hypofractionation are: 1) increased convenience to patients because of fewer treatment days, 2) reduced cost to patients because of reduced travel expenses and copays, 3) improved resource utilization for physicians because of the fewer number of treatments per patient and overall, 4) and consequently reduced cost to society. All of these factors may increase the utilization of post-prostatectomy RT, which is estimated to be < 20% for patients with pT3 disease and positive margins who are most likely to benefit, and unaltered by the results of the randomized trials (Ghia 2010, Hoffman 2011). In prostate cancer specifically, hypofractionation has the added potential advantage of not increasing toxicity (primary endpoint of Phase II) compared to standard fractionation, while delivering a higher biological dose and therefore increase efficacy (primary endpoint for Phase III).

2.2.3 Similarities to Breast Hypofractionation

This proposed trial mirrors the practice changing Ontario Clinical Oncology Group (OCOG) [Whelan 2010], UK Standardization of Breast Radiotherapy (START) Trial A (Bentzen 2008a), and START Trial B (Bentzen 2008b) breast cancer trials that sought the advantages of hypofractionation following lumpectomy for early-stage breast cancer and redefined the standard of care (Smith 2011). There are three important comparisons between the current trial and the breast trials: 1) the rationale for hypofractionation, 2) the reduction in overall treatment time, and 3) the primary endpoint. Regarding the rationale, hypofractionation for breast cancer has evolved on an empirical basis, while prostate hypofractionation has evolved more closely rooted to radiobiologic modeling. Furthermore, the magnitude of the radiobiologic advantage for hypofractionation for breast cancer is three times less than that of prostate cancer. Second, the reduction in overall treatment duration with breast hypofractionation is less compared to prostate cancer: 13-14 total treatment days for breast, and 18 days for prostate.

Last, the primary endpoint for the breast trials employed a local control primary endpoint, opposed to a survival based end-point, which is similar to a BF endpoint in prostate cancer because both local and distant recurrences are counted. The publication of the breast cancer hypofractionation trials has led to practice changes in the US and internationally. Therefore, similar if not more enthusiasm is expected for HYPORT that could also change the international standard of care.

2.2.4 Intact Prostate Hypofractionation

Results from definitive in-tact prostate hypofractionation from the Cleveland Clinic Phase II trial (Kupelian 2007, Kupelian 2005), the Fox Chase Phase III trial (Pollack 2011, Pollack 2006), and the Italian Phase III trial (Arcangeli 2012, Arcangeli 2011, Lee 2016) indicate that hypofractionation over 5 weeks is at least as effective and not more toxic than conventional fractionation with fraction sizes of 2.5 Gy, 2.7 Gy or 3.1 Gy, respectively. Therefore, at least similar effectiveness with hypofractionation in the proposed trial is hypothesized.

2.2.5 Preliminary HYPORT Data

The preliminary post-prostatectomy dose-escalated hypofractionation experience from the University of Wisconsin has demonstrated promising efficacy and acceptable toxicity delivering 65 Gy in 26 fractions of 2.5 Gy to the prostate bed. The 4-year actuarial PFS rate was 67.0% with a median overall follow-up of 32.4 months (range, 5.8-70.5) [Kruser

Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day	10 day	24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- Unexpected Grade 4 and all Grade 5 AEs

For Arm 2: Phase III Study Utilizing Radiation Therapy (including chemoRT studies)[1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

endpoints) and a one-sided alpha=0.025 with an overall type I error of 0.05 with a Bonferroni adjustment. With these design parameters, the sample size is 198 patients. Adjusting for a projected 30% EPIC/non-compliance rate, **the required sample size is 282 patients (141 per arm)**.

14.4 Study Monitoring of Primary Objectives

Interim Analysis for the DMC

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

Interim Futility Analysis

There will be a single futility analysis once 50% of patients have 2 years of follow-up. If the upper 95% confidence limit of the mean difference in 2 year change scores between the treatment arms is less than the pre-specified non-inferiority margin, then the HYPORT arm will be deemed inferior to the COPORT arm. Specifically, if the upper 95% confidence limit of the mean difference between arms in 2 year change scores is < -6 for the bowel domain and/or < -5 for the urinary domain, then the HYPORT arm will be deemed inferior to the COPORT arm. Early reporting of the treatment results will be recommended to the DMC, who will review these results. This approach has a minimal effect on statistical power.

Monitoring of EPIC Compliance

Completion rates of the bowel and urinary domains of EPIC will be monitored monthly. Since the study is projected to close within 26 months, 2 year data may not be monitored while the study is open to accrual. Therefore, the rates at 6 months and 1 year will be used to assess feasibility of the primary endpoint analysis. If the EPIC non-compliance rate is $\geq 20\%$ at either of these time points, the study PI and QOL co-chair will work in collaboration with the NRG Oncology Statistics and Data Management Center to contact sites and RAs with delinquent data, assessments completed too early or too late, and assessments not completed due to institution errors. If the EPIC non-compliance rate is $> 40\%$ at either time point, the study will be presented to the DMC for reassessment of feasibility or change in study design.

Interim Analysis to Monitor the Study Progress

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information:

- patient accrual rate with a projected completion date (while the study is still accruing)
- total patients accrued
- distributions of important pre-treatment and prognostic baseline variables
- the frequencies and severity of adverse events by treatment arm

The interim reports will not contain the results from the treatment comparisons with respect to the primary and secondary endpoints, with the exception of reporting of

considered as an event. TTP will be measured from the date of randomization to the date of the first occurrence of BF, LF, RF, DM, of PCSM. Since TTP includes BF as a failure, both definitions of BF will be used resulting in two TTP estimates.

Since baseline PSA level is not a stratification factor, hazard ratios and p-values for all efficacy endpoints will be analyzed and reported after adjustment for baseline PSA. Patients not experiencing an event will be censored at the last known follow-up time. Competing-risk endpoints PCSM, LF, RF, TTP, and DM will treat death as a competing risk (for PCSM and TTP, any death not due to prostate cancer) and be estimated by the cumulative incidence method (Gray 1988). OS and FFBF will be estimated by the Kaplan-Meier method (Kaplan & Meier 1958) and compared with the log-rank test (Mantel 1966). Cox regression (1974) will be used to obtain hazard ratios (HRs) for OS and TTP. Fine and Gray's regression (1999) will be used for the endpoints with competing risks. Adjusted HRs and the respective 95% confidence interval will be computed. Baseline PSA, stratification variables (baseline EPIC score and ADT status), and, as appropriate, age, race, and other covariates (Gleason, T-stage), will be adjusted for in this analysis. Statistical power will be limited for these analyses.

Adverse Events

Adverse events (AEs) will be graded with CTCAE v4. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. A Chi-square test will be used to compare the number of patients with at least 1 grade 3 or higher AE between the treatment arms. A comparison of grade 3 and higher GU and GI events related to treatment (separately) between treatment arms will also be tested using a Chi-square test.

14.7 Exploratory Endpoints

14.7.1 Exploratory Hypotheses and Endpoints

- Measured utilities and cost-effectiveness for health outcomes using the EQ5D.
- Paraffin-embedded tissue block, serum, plasma, whole blood, and urine for future translational research analyses for predictors of toxicity following hypofractionated or conventionally fractionated post-prostatectomy radiotherapy. Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

14.7.2 Definitions of Exploratory Endpoints and How These Will Be Analyzed

Cost effectiveness

The VAS and index scores from the EQ-5D-5L will be calculated at each time point (baseline, end of RT, 6 months, and 1, 2, and 5 years from the start of RT) and compared between treatment arms using a t-test with a 2-sided significance level of 0.05. If there are significant differences, then a cost analysis will be conducted.

Quality-adjusted life years (QALY) is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. A Markov model will be used

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