

**North Carolina Prostate Cancer Comparative Effectiveness &
Survivorship Study (NC ProCESS)**

National Clinical Trial (NCT) Identification Number: NCT02564120

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Study Protocol

Brief Summary:

NC ProCESS is a cohort of patients from diverse backgrounds diagnosed with early prostate cancer, who were enrolled from January 2011-June 2013. These patients were recruited throughout North Carolina, and also in partnership with institutions across the country. Patients enrolled before they start treatment, and are then followed prospectively through treatment and then afterwards. This observational study collects information on quality of life, cancer control, and health care received inclusive of treatment and management of subsequent effects including complications and recurrence. The objective of this study is to examine comparative outcomes among different modern prostate cancer treatment options in this cohort of patients.

Detailed Description:

Localized prostate cancer treatment options is consistently a "highest priority" comparative effectiveness research (CER) topic according to the Institute of Medicine, Agency for Healthcare Research and Quality (AHRQ), and other summary reports. Patients urgently need information on the comparative outcomes of modern treatment options to guide decision-making for this disease that causes significant burden based on its high prevalence, mortality and treatment effects on quality of life. The status quo as it pertains to prostate cancer is significant overtreatment causing potential patient harm, rapid diffusion of new/expensive technologies without proven benefit and patients lacking high quality research evidence to balance direct-to-consumer advertising and guide individualized decision-making.

NC ProCESS is a population-based cohort designed specifically to address well-described knowledge gaps. It was designed in close collaboration with the unique AHRQ consortium stakeholder group, which included representatives from patients, clinicians and policymakers. Stakeholders helped define study design to emphasize "real-world" patients and select patient-centered and relevant outcomes, and have been involved throughout assembly of this patient cohort. The diverse cohort is well-represented by "hard to reach" patients; enrollment before treatment avoids biases with participation and recall. As clinical trials are not feasible to address the central questions in prostate cancer CER, this prospective study will yield the

highest level of evidence to inform patients and other stakeholders. With an assembled cohort, this study is necessary to examine comparative outcomes.

Study Design:

Study Type:	Observational
Actual Enrollment:	1656 participants
Observational Model:	Cohort
Time Perspective:	Prospective
Study Start Date:	January 2011
Estimated Primary Completion Date:	December 2018
Estimated Study Completion Date:	December 2018

Outcome Measures:

Primary Outcome Measure:

1. Patient Reported Outcomes [Time Frame: 4 years]
Directly compare patient-reported prostate-cancer specific and global quality of life (QOL), anxiety regarding prostate cancer and decisional regret in a cohort of men with localized prostate cancer managed by active surveillance, radical prostatectomy, radiation therapy, and brachytherapy.
2. Disease-Free Survival [Time Frame: 5 years]
Directly compare the disease-free survival among different treatment options for prostate cancer.
3. Directly compare health care utilization among different treatment options for prostate cancer from review of medical records [Time Frame: 4 years]
For each treatment group (radiation therapy, prostatectomy, active surveillance), we will describe the cumulative utilization for each category of health care. These categories are physician/specialty visits, hospitalizations, diagnostic tests/procedures, medications, and prostate cancer treatments (for the initial cancer and for recurrence).
Measurements will be attained by review of medical records.

Eligibility Criteria:

Ages Eligible for Study:	35 Years to 80 Years
Sexes Eligible for Study:	Male

Accepts Healthy Volunteers: No
Sampling Method: Non-Probability Sample

Study Population

Newly-diagnosed, early stage (localized, non-metastatic) prostate cancer patients

Inclusion Criteria:

- Newly-diagnosed, histologically-proven, localized prostate adenocarcinoma.
- Completion of baseline interview prior to initiating therapy.
- Patient ability to complete study interview: no cognitive impairment, language or hearing problems.
- Not diagnosed with prostate cancer through transurethral resection of the prostate (TURP).
- Age 35-80.
- English speaking.
- Has telephone.

Exclusion Criteria:

- Initiation of treatment for prostate cancer prior to completion of baseline interview.
- Cognitive impairment.
- Hearing problems.
- Inability to speak or understand English.

Analytical and Statistical Approaches

Aim 1: Consistent with the prostate cancer QOL literature, we treated each patient-reported outcome measure as a continuous variable. We described the mean, standard deviation, and range of each measure at each time point, as well as the change from each time point compared to the baseline measure. Differences among treatment groups were compared using t-tests. A unique aspect of the PCSI instrument is that scores in each domain (Urinary Incontinence, Urinary Obstruction/Irritation, Bowel Problems, Sexual Dysfunction) are translatable into functional categories: normal, intermediate, and poor.^{2,37} Thus, we explored QOL measures using functional categories to facilitate creation of patient-friendly dissemination materials that summarize study findings. Further, to examine differences in outcomes across treatments, we conducted linear regression models applying propensity scores; a separate model was constructed for each outcome measure. We used generalized estimating equations (GEE) to account for correlation of the outcome measured repeatedly over time. In addition, we included time as a categorical variable and added a time*treatment interaction in the models to account for a non-linear change in outcome over time.

Aim 2: We estimated DFS at 5 years among different treatment groups, using the Kaplan-Meier product-limit estimate of the survival curve. We also used the logrank statistic to assess for differences in DFS among the different treatment groups. Cox proportional hazards models were performed with the application of propensity scores. These Cox models estimated the hazard rate for each treatment type and evaluated differences in rates (rate ratios) between treatments, adjusting for confounding using propensity scores. We examined the proportional hazard assumption in each model and included time-varying covariates or incorporated a time*treatment interaction into the model when this assumption was not met.

Aim 3: We described the cumulative utilization for each category of health care (physician/specialty visits, hospitalizations, diagnostic tests/procedures, medications, prostate cancer treatment) within 4 years by treatment group. Specifically, we examined the proportion of patients in each treatment group who received each category of care (we created a

dichotomous variable indicating whether the patient received the care), and the count of services in each care category. We tested the differences in proportions between treatment groups using chi-square tests and differences in counts between treatment groups using t-tests. In multivariable analyses, we used logistic regression models and propensity score methods to estimate differences among groups in the proportions of patients receiving each category of care. Linear regression models incorporating propensity score methods were used to test differences among groups in the number of services received in each category. When counts of health care utilization were small (e.g., hospitalization) Poisson regression models were used.

Bias and Confounding: The use of the NCCCR RCA enabled all study participants to enroll prior to the initiation of treatment, thereby avoiding potential biases related to participation based on post-treatment outcomes. Furthermore, all baseline QOL data were collected before treatment, avoiding biases inherent to the recall of baseline information due to patient experiences during and after treatment. The following analytical methods were also employed to minimize and account for potential bias and confounding.

1. **Propensity score methods:** We conducted propensity score analysis to assess for potential bias from measured confounders between treatment groups. Specifically, we used logistic regression to estimate the probability of receiving each treatment based on baseline characteristics and compute the propensity score from the model predicted probability of treatment for each participant. We examined the distribution of propensity scores across treatment groups and trimmed observations from the non-overlapping ends of the distribution as appropriate.⁵⁷ We then created inverse probability of treatment weights (IPTW) and stabilized these weights to reflect the sample size of each treatment group. IPTW was used in multivariable analyses to maximize the balance of confounding variables between the treatment groups. Propensity score matching using a “greedy algorithm”⁵⁸ and an alternative “optimal match”⁵⁹ algorithm was also considered as an approach to balance covariates across treatment groups.

2. **Assessment of sample balance:** To ensure balance of sample characteristics, we compared differences between treatment groups in the mean (for continuous variables) or distribution (for categorical variables) of each covariate by applying the generated propensity score weights. In addition, for propensity score-matched samples, we assessed the balance of study covariates using standardized differences across treatment groups. We added interaction terms to the propensity score model for the sample characteristics and risk factors that remained unbalanced after applying initial propensity score methods. When imbalances remained, we included the unbalanced variables in the multivariable outcome model(s) to ensure proper control of these confounding factors.
3. **Instrumental variables (IV):** We explored instrumental variable approaches to estimating the relationship between treatment and outcome while addressing potential unmeasured confounders. This method requires finding an appropriate “instrument” that is related to the exposure (treatment) but not directly related to the outcome, and meets all underlying IV assumptions.⁶⁰
4. **Handling of missing data:** We followed the PCORI standards for handling and minimizing the impact of missing data. First, we carefully examined the pattern of missing data by individual items. We determined whether the missing data is informative, missing not at random (MNAR), missing completely at random (MCAR), or missing at random (MAR) by evaluating patient characteristics (e.g., age, race and ethnicity, treatment). We also compared those patients with missing data to patients with complete data. We then imputed missing data using a widely-employed multiple imputation approach.⁶¹ This method replaces the missing data with a set of m possible values by creating m imputed datasets through Monte Carlo technique. Each imputed dataset was analyzed using the same methods that are used for complete datasets. Results were pooled together to provide valid statistical inferences.⁶¹ These methods enabled us to use data from the entire study sample, including patients with differential follow-up, maximizing the study’s statistical power to detect differences among

treatment groups. Lastly, we conducted sensitivity analyses to examine the impact of the missing data on study results.^{62–65}

5. **Cluster analysis:** We examined for possible clustering within our study sample as data may have been clustered at several levels. For example, patients treated by the same physicians or facilities may have correlated outcomes, and patients living in the same area may share characteristics related to treatment outcomes. To account for clustering in our analysis of DFS (Aim 2), we conducted proportional hazard model using a robust sandwich estimate⁶⁶ and likelihood-based random effect (frailty) model.⁶⁷ For outcomes analyzed by linear and logistic regression models, we used GEE modeling approaches to obtain appropriate standard errors, and/or applied multilevel modeling to explicitly model the clustered data structures and allow for random intercepts of the higher level data structure.

Evaluation of Treatment Outcome Heterogeneity: Our rich cohort comprised a sizable proportion of understudied populations, including patients of racial/ethnic minorities, lower socioeconomics, and rural/underserved areas. Therefore, we sought to assess heterogeneity of treatment effect (HTE) following PCORI guidelines. We performed descriptive HTE analysis to produce effect estimates and standard errors for key confounders (e.g., race and ethnicity, age, disease severity). We also explored subgroup analyses when sample size permitted enough power to detect meaningful differences.