

## Principal Investigator

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## General Information

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**Are external grants or funds being used to support this research?:** No external grants or funds are being used to support this research.

**How did you learn about the YODA Project?:** Scientific Publication

## Conflict of Interest

[https://yoda.yale.edu/system/files/coi\\_malone\\_1\\_0.pdf](https://yoda.yale.edu/system/files/coi_malone_1_0.pdf)

[https://yoda.yale.edu/system/files/coi\\_morgan\\_1.pdf](https://yoda.yale.edu/system/files/coi_morgan_1.pdf)

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## Certification

**Certification:** All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

**Data Use Agreement Training:** As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. [NCT00887198 - COU-AA-302 - A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate \(CB7630\) Plus Prednisone in Asymptomatic or Mildly Symptomatic Patients With Metastatic Castration-Resistant Prostate Cancer](#)
2. [NCT02257736 - 56021927PCR3001 - A Phase 3 Randomized, Placebo-controlled Double-blind Study of JNJ-56021927 in Combination With Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone in Subjects With Chemotherapy-naïve Metastatic Castration-resistant Prostate Cancer \(mCRPC\)](#)

**What type of data are you looking for?:** Individual Participant-Level Data, which includes Full CSR and all supporting documentation

## Research Proposal

### Project Title

Comparison of Outcomes in Patients treated with prior radical prostatectomy versus prior radiation therapy – a pooled analysis of ACIS and COU-AA302

### Narrative Summary:

Preclinical or animal studies have shown that primary local therapy directed to prostate triggers some subcellular level changes in the prostate cancer cells. However, it is unknown whether these changes translate into any clinically meaningful difference in outcomes when systemic therapies are initiated after progression to a metastatic stage in patients treated with prior local therapy. Our secondary analysis will clarify this ambiguity and will provide robust evidence whether receipt of primary local therapy and the modality of primary local therapy affect overall outcome including response to subsequent lines of therapy in men with metastatic castrate resistant prostate cancer.

### Scientific Abstract:

**Background:** Preclinical studies suggest that receipt of definitive local therapy (LT) might bear substantial effect on subsequent systemic therapy in metastatic prostate cancer. However, there is lack of concrete clinical evidence which shows differential impact of prior local therapy on subsequent lines of systemic therapy. **Objectives:** We plan to perform a pooled analysis of ACIS and COU-AA-302 trial to compare the radiographic progression-free survival (rPFS) and overall survival (OS) in patients treated with prior local therapy compared to those who had no prior local therapy. We also plan to compare rPFS and time to progression in patient treated with prior radical prostatectomy (RP) versus those who were treated with prior radiation therapy (RT).

**Design and Participants:** A pooled analysis with patients in the ACIS trial (NCT02257736) and COU-AA-302 (NCT00887198). **Main outcome:** The primary endpoint will be rPFS. The secondary endpoints will include OS, time to progression and cumulative incidence of progression.

**Main exposure variable:** Receipt of prior LT vs no LT.

**Statistical Plan:** Separate multivariable cox proportional hazard regression models will be applied to estimate adjusted hazard ratios for each of the endpoints. Interaction terms will be added for the receipt of prior local therapy and randomized treatment regimen to determine the heterogeneity of treatment effect on OS and rPFS after adjustment for covariables. To determine the adjusted association of LT with time-to-event endpoints, multivariable Cox regression models will be built.

### Brief Project Background and Statement of Project Significance:

Definitive treatment for men with localized prostate cancer often comprises local therapy (either radical prostatectomy [RP] or radiation therapy [RT]), with or without androgen deprivation therapy (ADT) based on patient and disease characteristics.(1, 2) Despite these curative intent treatments, a proportion of patients, particularly those with high-risk and locally advanced disease, eventually develop recurrence and progression, including to metastatic castrate resistant prostate cancer (mCRPC).(3, 4) At this stage, systemic treatment including chemotherapy, androgen receptor axis targeted therapy (ARAT) remains the cornerstone of management.(5–11) Whether primary local therapy after diagnosis affects response to this subsequent treatment is unclear. Preclinical

studies have shown that fractionated ionizing RT can induce neuroendocrine differentiation in prostate cancer by increasing the nuclear content of phospho-CREB and cytoplasmic accumulation of ATF2.(12) This has significant implications in progression of prostate cancer, androgen-independent growth, and it ultimately portends poor prognosis. In contrast, minimal residual disease after RP could give rise to treatment-resistant clones that can lead to poor response to adjuvant or salvage therapy.(13) In a small Japanese study, initial curative treatment modality was a significant predictor of castration resistance based on a multivariable regression.(14) In another Japanese retrospective study, prior local therapy was associated with a lower risk of overall mortality (hazard ratio [HR]: 0.56, 95% confidence interval [CI]: 0.40–0.79) in patients with CRPC.(15) Similarly, a retrospective study by Patel et al showed that patients with mCRPC who were previously treated with RP with/without postoperative RT had superior overall survival (HR: 0.70, 95% CI: 0.53-0.88) compared to those without prior local therapy.(16) In ACIS (17) and COU-AA-302 trial (18), docetaxel naive patients were randomized to receive single agent or a doublet of second generation anti-androgen regimens (abiraterone in COU-AA-302 while abiraterone + apalutamide in ACIS). In ACIS trial, addition of apalutamide to abiraterone was associated with significant improvement in radiographic progression-free survival (rPFS) (HR: 0.70, 95% CI: 0.60–0.83) while in COU-AA-302 trial, addition of abiraterone alone was associated with significant improvement in rPFS (HR: 0.53, 95% CI: 0.45–0.62).

Herein we propose a pooled analysis of ACIS and COU-AA-302 to compare the outcome with second generation anti-androgen therapy in mCRPC based on receipt of prior local therapy. The response will be compared primarily in terms of rPFS, time to progression, and OS. Our findings will clarify whether the outcome and response to systemic therapy in mCRPC depends on the receipt of prior local therapy and the modality of prior local therapy. This will also provide important information on the fact if receipt of prior local therapy confers any poor prognosis. It will also provide additional information for future risk stratification of these patients.

### **Specific Aims of the Project:**

Objectives:

Primary Objective:

- To compare radiographic progression-free survival in patients treated with prior local therapy to prostate (radical prostatectomy or radiation therapy) as compared to patients with no local therapy to prostate

Secondary Objectives:

- To compare overall survival in patients treated with prior local therapy to prostate (radical prostatectomy or radiation therapy) as compared to patients with no local therapy to prostate
- To compare time to progression in patients treated with prior radical prostatectomy versus those treated with prior radiotherapy to prostate
- To compare the cumulative incidence of progression in patients treated with prior local radical prostatectomy versus prior radiation therapy to prostate considering deaths as competing risk events

### **What is the purpose of the analysis being proposed? Please select all that apply.**

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

## **Research Methods**

### **Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:**

Pooled analysis of individual patient data from ACIS trial (NCT02257736) dataset and COU-AA-302 (NCT00887198) dataset

### **Main Outcome Measure and how it will be categorized/defined for your study:**

- The primary endpoint, radiographic progression-free survival as defined in the trials
- The time to first progression, will be defined as time since randomization to any progression
- Overall survival will be defined as time since randomization to death from any cause

### **Main Predictor/Independent Variable and how it will be categorized/defined for your study:**

Receipt of prior local therapy (radical prostatectomy or radiotherapy to prostate) vs no local therapy. Additional subgroup analyses will be done to compare patients treated with radical prostatectomy and those treated with radiotherapy to prostate.

**Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:**

- Treatment arm: Categorical
- Race: Categorical
- Age: Continuous
- Gleason Score at initial diagnosis: Ordinal
- Prior radical prostatectomy: yes/no (categorical)
- Prior radiation therapy: yes/no (categorical)
- Date of prior radical prostatectomy and prior radiation therapy with indications
- ECOG PS: Ordinal
- Date of randomization
- Prior systemic treatment (ADT) – (categorical)
- Tumor stage at diagnosis
- Nodal stage at diagnosis
- Metastatic stage at diagnosis
- Time from initial diagnosis to randomization in years (continuous)
- Time from initiation of ADT or orchiectomy to randomization in years
- Visceral metastasis (yes or no with sites)
- No. of skeletal metastasis

**Baseline and Post-Baseline Variables:**

- PSA and alkaline phosphatase at time of study entry
- Post-baseline radiographic evaluation (bone scan/CT scan/MRI): categorical
- Time of radiographic, clinical, or PSA progression (date format) – to calculate time to progression
- Deaths (yes/no)
- Time of death (date format) and cause of death
- Time to cytotoxic chemotherapy
- Life prolonging therapy received after progression – (Yes/No) & details (regimen, date)

**Statistical Analysis Plan:**

Descriptive statistics will be used to characterize the data in the study, including means, medians, and analysis of variance and Wilcoxon signed rank for continuous variables and frequency tables and chi-square test for categorical variables. Radiographic progression-free survival, time to any progression, and overall survival will be estimated by Kaplan-Meier's method. Separate multivariable cox proportional hazard regression models will be applied to estimate adjusted hazard ratios for each of the endpoints. Interaction terms will be added for the receipt of prior local therapy and randomized treatment regimen to determine the heterogeneity of treatment effect on OS and rPFS after adjustment for covariables. To determine the association of local therapy with OS and rPFS, multivariable Cox regression models will be built which will include the prior local therapy (radiation therapy or radical prostatectomy vs. no prior therapy), age at randomization, treatment regimens, Gleason score at initial diagnosis, tumor stage at initial diagnosis, nodal stage at initial diagnosis, visceral metastasis, number of skeletal metastasis, PSA at the time of study entry, serum alkaline phosphatase level, receipt and duration of ADT before start of protocol treatment and the time interval between initial diagnosis to time to randomization. For time to progression, a separate multivariable Cox proportional hazard model will be built which will include the modality of prior local therapy (radiation therapy to prostate versus radical prostatectomy), age at randomization, treatment regimen, duration of ADT, Gleason score at initial diagnosis, tumor stage at initial diagnosis, nodal stage at initial diagnosis, site of visceral metastasis, number of skeletal metastasis, PSA at the time of study entry, duration of ADT before start of protocol treatment and the time interval between initial diagnosis to time to randomization in addition to the interaction of treatment regimen with radiation therapy versus radical prostatectomy. For cumulative incidence of progression, we will apply a competing risk regression model to determine the adjusted subdistribution hazard ratio of progression for patients treated with radiation therapy prostate as compared to those with radical prostatectomy (after adjustment for the pre-specified covariables such as age at randomization, treatment regimen, duration of ADT, Gleason score at initial diagnosis, tumor stage at initial diagnosis, nodal stage at initial diagnosis, site of visceral metastasis, number of skeletal metastasis, PSA at the time of study entry, duration of ADT before start of protocol treatment and the time interval between initial diagnosis to time to randomization). Death from any

cause will be considered as a competing event for this competing risk regression model.

Software Used:

RStudio

**Project Timeline:**

- Project submission: July 2022
- Contract: August 2022
- Analysis: September 2022 to February 2023
- Abstract Submission (ASCO 2023 and ASTRO 2023): February 2023
- Paper Draft circulation: March-May 2023
- Paper Submission: May 2023

**Dissemination Plan:**

- Abstract presentation in ASCO 2023 and ASTRO 2023
- Submission of manuscript first-quartile oncology journals: Journal of Clinical Oncology, Journal of National Comprehensive Cancer Network, European Urology, Annals of Oncology

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