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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?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/yoda_project_coi_form_mr.pdf

https://yoda.yale.edu/system/files/yoda_project_coi_form_dl1.pdf

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](#)

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

Research Proposal

Project Title

Prognostic relevance of prior local therapy, time to metastasis and time to castration resistant prostate cancer (CRPC) in metastatic CRPC (mCRPC)

Narrative Summary:

Hormone therapy is the usual treatment for metastatic prostate cancer (cancer cells have spread to bones, lung or liver). After some months of this treatment, patients stop responding to hormone therapy. This condition is known as CRPC.

The aim of this study is to find if patients with metastatic CRPC who received treatment with surgery (radical prostatectomy) or radiation when they were first diagnosed of prostate cancer, do better than those treated initially with hormone therapy. Furthermore, the study will try to find if time to develop metastasis and time to CRPC diagnosis influence the outcomes of the patients.

Scientific Abstract:

Background: The role of prior local therapy (PLT) on the outcomes of men with metastatic prostate cancer (PC) is a subject of growing interest. Retrospective studies have suggested an improved survival in metastatic hormone sensitive prostate cancer (mHSPC) patients who underwent PLT with radical prostatectomy (RP) or radiation therapy (RT). The effect of PLT in newly diagnosed mCRPC patients and its prognostic significance remains unknown.

Objective: to evaluate the incidence and prognostic significance of PLT with RP or RT, time to metastasis and time to CRPC on overall survival (OS) in chemo-naïve mCRPC patients treated with AA/placebo + prednisone

Study design: retrospective cohort study

Participants: mCRPC patients in the COU-AA-302 trial

Main Outcome Measures: Overall survival

Statistical Analysis: Patients will be categorised based on PLT (PR or RT or both). OS will be estimated by the Kaplan-Meier method. Cox proportional hazards regression models will be used to test the association of PLT, time to metastasis and time to CRPC with OS.

Brief Project Background and Statement of Project Significance:

Despite the decrease in incidence of metastases at PC diagnosis from over 50% in the 1970s to currently less than 10%, the population of patients with metastatic disease at diagnosis accounts for half of PC mortality (1). A median time to CRPC of 16 months and an OS of 5.2 years was observed in men with detectable metastasis at diagnosis that died of mCRPC. The other half of patients who died of mCRPC had localized PC at diagnosis (64% of which were classified as high-risk PC), with a median OS of 8.8 years (1). Data suggest that the notion of an initially indolent disease slowly progressing to the metastatic phase and death is valid in only approximately half of patients who die of PC.

While different retrospective studies have suggested a survival benefit of local therapy (cytoreductive prostatectomy or radiation therapy) in metastatic PC (2,3,4), the impact of PLT on OS in mCRPC has been scarcely addressed. One recent retrospective study conclude that men who progressed from non-metastatic CRPC (nmCRPC) to mCRPC and had undergone RP +/- RT for localised disease had improved survival compared with those who were treated with androgen deprivation therapy (ADT) alone. This survival benefit is not seen in men treated with RT alone. Selection of patients in this study was based on non-metastatic CRPC, excluding patients with positive imaging for distant metastases before the CRPC diagnosis (5).

The impact of time to metastasis on OS in patients with PC has also been retrospectively studied. In a recent study, authors conclude that due to the shortest time from diagnosis to CRPC, patients with "de novo" metastasis have the worst OS compared with those who were free of metastasis initially but developed metastasis before or after becoming castration-resistant. Once CRPC was reached, no difference in survival time was observed between groups. Authors suggested that efforts aimed to prolong the development of CRPC seem to be essential to improve survival time (6).

Consequently, efforts must be aimed to:

1. Define the optimal treatment strategy for patients with upfront metastatic disease. Currently, the most controversial approach is the indication of treatment to the primary tumor. Recently a survival benefit was seen with

RT to the primary tumor for newly diagnosed prostate cancer with a low metastatic burden (7). No evidence exists for surgery in this setting.

2. Identify patients with localised PC with a higher likelihood of dying of the disease, who could potentially benefit from alternative treatment modalities other than extended surgery and conventional adjuvant therapies. Novel endocrine therapies such as apalutamide, for instance, are being currently tested in the neoadjuvant setting. We intend to evaluate the incidence of PLT with RP or RT and assess the impact on OS in mCRPC patients treated with AA/placebo + prednisone in the COU-AA-302 trial (8)

Specific Aims of the Project:

SPECIFIC AIMS:

1. To determine the proportion of chemo-naïve mCRPC patients with PLT (RP +/- RT or RT) treated with abiraterone/placebo + prednisone in the COU-AA-302 trial.
2. To determine the number of patients that were diagnosed of mCRPC by PSA progression or by radiographic progression (with or without PSA progression).
3. To determine the number of patients with newly diagnosed mCRPC who were metastatic at diagnosis, metastatic before CRPC or metastatic after CRPC.

To evaluate:

1. To evaluate the impact of PLT on OS in abiraterone + prednisone and placebo + prednisone treated patients with chemo-naïve mCRPC
2. To evaluate the impact of time to metastasis and time to CRPC on OS in abiraterone + prednisone and placebo + prednisone treated patients with chemo-naïve mCRPC

SPECIFIC HYPOTHESES:

We hypothesized that PLT, time to metastasis and time to CRPC could be prognostic factors on OS in chemotherapy naïve mCRPC patients.

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:

Data Source: COU-AA-302

Inclusion criteria: patients treated with abiraterone + prednisone and placebo + prednisone in the COU-AA-302 trial

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

MAIN OUTCOME MEASURE:

Overall survival, defined as the time (months) from PC diagnosis to death

SECONDARY OUTCOME MEASURES:

- Radiographic progression-free survival (rPFS), which will be defined as the time from study trial treatment initiation to radiographic progression or death
- Clinical progression-free survival (cPFS), which will be defined as the time from time from study trial treatment initiation to clinical progression or death, in months.
- Time to quality of life deterioration will be defined as the time from study trial treatment initiation to clinically significant FACTP or BPI-SF progression.

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

- Prior local therapy (PLT), defined as radical prostatectomy (RP), radiotherapy (RT) or both as definitive treatment for localized disease. PLT will be categorized into two groups: RP +/- RT and RT alone.
- Time to metastasis, which will be defined as time (months) from PC diagnosis to develop of metastatic disease. They will be categorized in metastatic at diagnosis, metastatic before CRPC or metastatic after CRPC
- Time to CRPC, which will be defined as time (months) from start of ADT to CRPC.

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

your study:

Baseline variables:

- Treatment arm: categorical
- Ethnicity: categorical
- Age, height, weight: continuous
- Type of disease progression at baseline: categorical
- Time from LHRH treatment to trial treatment initiation
- Presence of bone, node, liver, other visceral metastases: yes/no
- Gleason Score: ordinal
- Prior surgery or radiation therapy to primary
- Presence of metastatic disease at diagnosis
- Type of metastatic disease at diagnosis

Baseline and at post-baseline time-points:

- Hemoglobin, albumin, alkaline phosphatase, LDH, PSA: continuous.
- ECOG PS: ordinal (0-4)
- BPI-SF score, analgesic score (continuous)
- FACT-P score (continuous)
- Post-baseline radiographic evaluation (BS/CT scan): categorical

Statistical Analysis Plan:

- A descriptive analysis of endpoints and baseline covariates will be performed. Results will be presented as the median and interquartile range (IQR) for continuous variables and as number and percentage frequency for categorical variables.
- The Kaplan-Meier method will be used to estimate median survival times (OS, rPFS, cPFS, PSA-PFS, time to metastases, time to CRPC) and 95% confidence intervals, in months.
- Cox proportional-hazards (Cox-PH) models will be used to test the association of prior local therapy, metastatic disease at diagnosis, time to CRPC and time to metastases with overall survival (primary endpoint), radiographic progression-free survival, biochemical progression-free survival and clinical progression-free survival (secondary endpoints). Other covariates that show a significant ($p < 0.05$) association with survival in the univariable Cox-PH model may be included in the multivariable Cox-PH model. If a skewed distribution is observed in any of the continuous variables, logarithmic transformation may be performed. Tests of proportionality based on Schoenfeld residuals will be applied to test the proportional hazards assumption.

Software Used:

R

Project Timeline:

Project submission: december 2019

Contract: march-april 2019

Analysis: april-june 2020

Abstract submission (AUA 2021): september 2020

Paper draft circulation: october-november 2020

Paper submission: november-december 2020

Dissemination Plan:

Abstract presentation in AUA 2021

Submission of manuscript first-quartile oncology journals: Annals of Oncology, European Urology, Clinical Cancer Research

Bibliography:

1. Patrikidou A, Loriot Y, Eymard J-C, et al. Who dies of prostate cancer?. Prostate Cancer and Prostatic Diseases volume 17, pages348–352 (2014)
2. Reichard CA, Gregg JR, Achim MF et al. Radical prostatectomy in metastatic castration-resistant prostate cancer: feasibility, safety, and quality of life outcomes. Eur. Urol. 2018; 74: 140–3.
3. Løppenbergh B, Dalela D, Karabon P, et al. The impact of local treatment on overall survival in patients with

- metastatic prostate cancer on diagnosis: a national cancer data base analysis. *Eur Urol*, 72 (2017), pp. 14-19
4. Poelaert F, Verbaeys C, Rappe B et al. Cytoreductive prostatectomy for metastatic prostate cancer: first lessons learned from the multicentric prospective local treatment of metastatic prostate cancer (LoMP) trial. *Urology* 2017; 106: 146–52.
 5. Patel DN, Jha S, Howard LE, et al. Impact of prior local therapy on overall survival in men with metastatic castration-resistant prostate cancer: Results from Shared Equal Access Regional Cancer Hospital. *Int J Urol*. 2018 Dec;25(12):998-1004.
 6. Frees S, Akamatsu S, Bidnur S, et al. The impact of time to metastasis on overall survival in patients with prostate cancer. *World J Urol*. 2018 Jul;36(7):1039-1046.
 7. Parker CC, James ND, Brawley CD, et al. Systemic Therapy for Advanced or Metastatic Prostate cancer: Evaluation of Drug Efficacy (STAMPEDE) investigators. Radiotherapy to the primary tumour for newly diagnosed, metastatic prostate cancer (STAMPEDE): a randomised controlled phase 3 trial. *Lancet*. 2018;392:2353-2366.
 8. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in Metastatic Prostate Cancer without Previous Chemotherapy. *N Engl J Med* 2013; 368:138-148