Principal Investigator

First Name: Yao
Last Name: Zhu
Degree: MD
Primary Affiliation: Fudan University Shanghai Cancer Center
E-mail: xdni18@fudan.edu.cn
Phone number:
Address: dongan road

City: Shanghai
State or Province: Shanghai
Zip or Postal Code: 200032
Country: China
SCOPUS ID: 22955119300

General Information

Key Personnel (in addition to PI):
First Name: Xudong
Last name: Ni
Degree: MD
Primary Affiliation: Fudan University Shanghai Cancer Center

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/20230322coizy.pdf
https://yoda.yale.edu/system/files/20230322conflict_of_interest_of_yoda.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. NCT00638690 - COU-AA-301 - A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients With Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy
2. 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
3. NCT01715285 - 212082PCR3011 - A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High-Risk, Metastatic Hormone-naive Prostate Cancer (mHNPC)
4. 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-naive Metastatic Castration-resistant Prostate Cancer (mCRPC)
5. NCT01946204 - ARN-509-003 - A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase III Study of ARN-509 in Men With Non-Metastatic (M0) Castration-Resistant Prostate Cancer
6. NCT02489318 - 56021927PCR3002 - A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Apalutamide Plus Androgen Deprivation Therapy (ADT) Versus ADT in Subjects With Metastatic Hormone-sensitive Prostate Cancer (mHSPC)

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

Research Proposal

Project Title

The association between antibiotics exposure and outcomes in men with prostate cancer

Narrative Summary:

Antibiotics are commonly used for urinary tract infection caused by urinary tract obstruction or other systematic infection in men with prostate cancer. However, the association of antibiotics exposure with overall survival (OS) and radiographic progression-free survival (rPFS) in prostate cancer remain unclear. In this study, we plan to use patient level data from clinical trials of prostate cancer at different stages to evaluate the association between antibiotic exposure and clinical outcomes.

Scientific Abstract:

Background:
The association of antibiotics exposure with overall survival (OS) and radiographic progression-free survival (rPFS) in prostate cancer remain unclear.

Objective:
We aim to use the antibiotics exposure record and survival data from men with prostate cancer at different stages to explore the association between antibiotics exposure and clinical outcomes.

Study design
Patients with prostate cancer at different stages will be classified according to their antibiotics exposure during the treatment. OS and rPFS will be estimated using Kaplan-Meier methods and compared using the log rank test. Time-dependent Cox model will be used to calculate the hazards ratio of antibiotics exposure by groups. We will explore whether there are differences in clinical outcomes between antibiotic exposed patients and non-antibiotic exposed patients at different stages.

Participants:
Patients with prostate cancer enrolled in NCT00638690, NCT00887198, NCT01715285, NCT02257736, NCT01946204 and NCT02489318.

Primary and Secondary Outcome Measure(s)?
Overall survival & Radiographic progression free survival

Statistical Analysis?
Patients enrolled will be stratified by antibiotics exposure. Baseline variables will be summarized by the exposure of antibiotics. We will examine for any differences between groups using the Chisq test for categorical variables and Kruskal-Wallis test for non-normally distributed continuous type variables. Kaplan–Meier survival analysis will be used to compare OS and rPFS. Hazard ratios will be calculated using a multivariable time-dependent Cox non-proportional hazard model. All analyses were 2-sided with a significance threshold of p=0.05.

Brief Project Background and Statement of Project Significance:

In the past decades, novel hormone therapy (NHT) such as abiraterone, enzalutamide and apalutamide have become the first-line treatments for men with advanced prostate cancer. However, the prognosis for patients after NHT failure is dismal. Therefore, it remains important to find new treatments to prolong the survival of patients or to extend the effective duration of NHT.
Antibiotics are commonly used for urinary tract infection caused by urinary tract obstruction or other systematic infection in men with prostate cancer. Preclinical study has shown that in mouse model fed with high-fat diet, oral administration of antibiotics mixture reduced the progression of prostate cancer[1]. Meanwhile, the stool diversity and specific species of bacteria in the gut can have a direct impact on the progression of prostate cancer. In vivo, transplantation with stools of CRPC patients accelerated the PCa progression while stools of HSPC patients inhibited cancer progression[2]. Gut bacteria that produce androgens and their derivatives or convert androgens to active forms may be responsible for accelerating the progression of prostate cancer[3-4]. In the previous study, the genotype of HSD3B1, which encoded enzyme 3?-hydroxysteroid dehydeogenase-1(3?-HSD), was associated with clinical outcomes in men with low-volume prostate cancer[5], while recent study has shown that some gut microbes, such as Mycobacterium neoaurum, can express 3?-HSD[4]. As antibiotic exposure can alter the gut microbiome, there has been interest in evaluating the impact of antibiotic exposure in men with mCRPC.
In this study, we will use data of men with prostate cancer at different stages from randomized phase 3 clinical trials on NHT to evaluate the association of antibiotic exposure on overall survival (OS) and radiographic progression-free survival (rPFS).

Specific Aims of the Project:

Objective: Using individual patient data from men with prostate cancer of different stages to analyze prognostic differences between antibiotic-exposed and non-antibiotic-exposed patients.
Hypothesis: Antibiotics exposure favours the prognosis of CRPC patients through remodeling of the gut microbiota, while not affect the prognosis of HSPC patients.

What is your Study Design?:

Meta-analysis (analysis of multiple trials together)

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 on clinical prediction or risk prediction

Research Methods

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

Patients with prostate cancer at different stages from randomized clinical trials: NCT00638690, NCT00887198, NCT01715285, NCT02257736, NCT01946204 and NCT02489318 will be included. Patients in different treatment arm will be classified according to antibiotics exposure. We will use Cox model to adjust the confounding effects of other baseline characteristics including age, PSA, HGB, LDH, ECOG, Gleason score, visceral & bone metastasis. Therefore, patients lacking baseline data will be excluded.

Primary and Secondary Outcome Measure(s) and how they will be categorized/defined for your study:

Primary end points include overall survival and radiographic progression-free survival.
rPFS defined as the time from registered to radiologic progression.
OS defined as the interval between the date of registration and the date of death.

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

Main independent variable: antibiotics exposure during the treatment. The antibiotics exposure will be treated as a time-varying covariate

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:

Baseline variables will be summarized by the exposure of antibiotics. We will examine for any differences between groups using the Chisq test for categorical variables and Kruskal-Wallis test for non-normally distributed continuous type variables. OS and rPFS will be estimated using Kaplan-Meier methods and compared using the log rank test. We will construct a multivariable time-depending Cox model to correct potential immortal time bias. Antibiotics use will be modeled using a time-varying covariate that has a value of 1 after day 30 of systemic antibiotics use and a value of 0 by day 30 (and for patients who did not receive any systemic antibiotics). The HR will also be adjusted for the confounding effects including age, PSA, HGB, LDH, ECOG, Gleason score, visceral & bone metastasis. In the sensitivity analysis, we replaced the 30-day threshold with 14 days. All analyses are 2-sided with a significance threshold of p=0.05 and will be performed using R studio.

Software Used:

RStudio

Project Timeline:

We anticipated start the project In May this year, finish the analysis before 1 May 2024, and draft the manuscript for submission before 1 Nov 2024.

Dissemination Plan:

We plan to submit the project to distinguished journals in medicine or oncology (such as Eclinilical medicine, Clinical Cancer Research).

Bibliography:

[1] Matsushita M, Fujita K, Hayashi T, et al. Gut Microbiota-Derived Short-Chain Fatty Acids Promote Prostate Cancer Growth via IGF1 Signaling. Cancer Res 2021; 81(15): 4014-26.
[2] Pernigoni N, Zagato E, Calcinotto A, et al. Commensal bacteria promote endocrine resistance in prostate cancer through androgen biosynthesis. Science 2021; 374(6564): 216-24.
[3] Li D, Liu R, Wang M, et al. 3?-Hydroxysteroid dehydrogenase expressed by gut microbes degrades testosterone and is linked to depression in males. Cell Host Microbe 2022; 30(3): 329-39.e5.
[4] Mei Z, Yang T, Liu Y, et al. Management of prostate cancer by targeting 3?HSD1 after enzalutamide and abiraterone treatment. Cell Rep Med 2022; 3(5): 100608.
[5] Hearn JWD, Sweeney CJ, Almassi N, et al. HSD3B1 Genotype and Clinical Outcomes in Metastatic Castration-Sensitive Prostate Cancer. JAMA Oncol 2020; 6(4): e196496.

.misc-fixes { display: none; } #admin-region { z-index: 9999999; } #admin-menu { z-index: 99999999; }