Prostate Cancer Screening, Molecular Diagnostics, and Therapy Prediction: Toward Personalized Care

Ph.D. Thesis Booklet

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1. Introduction

1.1. What is the topic?

Prostate cancer (PCa) is the second most common solid tumor in men with more than one million new cases worldwide in 2020, placing a significant burden on health care systems. Notably, the five-year relative survival of localized and locoregional disease is nearly 100%, however, it is only 32% for distant metastatic disease, highlighting the need for improvement in early detection, diagnostics, and development of prognostic and predictive biomarkers to aid clinical decision-making.

1.2. What is the problem to solve?

Despite the mortality benefits of prostate-specific antigen (PSA)-based screening, this approach is limited by overdiagnosis and overtreatment of clinically insignificant cancers. Magnetic resonance imaging (MRI) has emerged as a promising tool to refine PCa detection, however its optimal role in population-based screening remains unclear. At the same time, advances in genomics have identified *BRCA* mutations as key biomarkers with both prognostic and predictive importance, particularly in the setting of metastatic castration-resistant prostate cancer (mCRPC), where novel agents such as poly (ADP-ribose) polymerase inhibitors

(PARPi) and platinum-based chemotherapies offer potential therapeutic benefit.

1.3. What is the importance of the topic?

Our research seeks to address two critical gaps: (1) synthesizing evidence on the role of MRI in PCa screening, and (2) evaluating the treatment efficacy of standard and later-line therapies including abiraterone, enzalutamide, PARPi, taxane and platinum chemotherapy in *BRCA*-positive mCRPC.

1.4. What would be the impact of our research results?

This work is essential for informing clinical decision-making, guiding future screening strategies, and optimizing treatment selection for patients with advanced PCa. The results of our investigations could potentially impact patient outcomes by reducing unnecessary interventions, promoting targeted screening, and advancing precision oncology in PCa care.

2. Objectives

2.1. Project I – Investigating the integration of MRI in prostate cancer screening

In our first project, we aimed to comprehensively synthesize evidence to inform clinical practice and help devise a PCa screening strategy incorporating MRI information. Particularly, our goal was to summarize the currently available literature on the performance of PCa population-based screening strategies incorporating MRI, and to compare them to PSA-only-based screening.

2.2. Project II – Investigating the therapy predictive value of *BRCA* mutations in mCRPC

In our second project, we aimed to assess the therapy predictive utility of *BRCA* mutations in patients with mCRPC. Specifically, we assessed the efficacy of various treatment modalities, including abiraterone, enzalutamide, taxane-based chemotherapy (docetaxel, cabazitaxel), PSMA-ligand therapies, platinum-based chemotherapy, and PARPis in *BRCA*-positive mCRPC.

3. Methods

To address our objectives, we performed systematic reviews and meta-analyses according to the recommendations of the PRISMA 2020 guideline. The study protocols were registered on PROSPERO (Project I: CRD42023423945; Project II: CRD42021285267; CRD42022287005).

3.1. Project I

We included studies of men in the general population (population), who underwent MRI examination as part of the screening (intervention) and were compared with men screened for PCa using PSA alone (comparison). The primary endpoint was the cancer detection rate (CDR) of clinically significant PCa (csPCa), defined as an International Society of Urological Pathology (ISUP) grade of 2 or higher (outcome). Secondary endpoints included the CDR of insignificant PCa (defined as ISUP grade 1), positive predictive values (PPVs) for detecting significant PCa, MRI and biopsy indication and adherence rates.

We queried the MEDLINE (via PubMed), Embase, Cochrane/Central, Scopus, and Web of Science databases through May 5, 2023. Randomized clinical trials and prospective cohort studies were eligible if they reported data on the diagnostic utility of

prostate MRI in the setting of PCa screening. Study selection and data extraction were performed independently by two review authors. The generalized mixed-effect approach with pooled odds ratios (OR) with 95% confidence intervals (CI) and random-effect models was used to compare the MRI-based and PSA-only screening strategies. Separate analyses were performed based on the timing of MRI (primary/sequential after PSA test) and cut-off (Prostate Imaging Reporting and Data System (PI-RADS) ≥3 or ≥4) for biopsy indication.

3.2. Project II

The primary endpoint of the studies was the PSA response rate, defined as at least a 50% decrease in serum PSA level during treatment (PSA50). Our secondary endpoints were PFS (composite of clinical, radiographic, biochemical progression or death), and OS.

First, to assess the proportion (PSA50) and median values (PFS, and OS), we used the CoCoPop framework, where the endpoints (Co-condition) were evaluated in the context of administered treatments (Co-context) in the population with mCRPC (Pop-population). Then, to compare time-to-event data, we used the PICO framework, where the population (P) was mCRPC patients with *BRCA* mutations; the interventions and controls (I and C) were

abiraterone/enzalutamide /docetaxel and PARPi/platinum/cabazitaxel/PSMA-ligand therapies; and the outcomes were PFS (O1) and OS (O2).

The Embase, MEDLINE (via PubMed) and CENTRAL databases were searched on the 17th of October 2021 for studies of abiraterone, enzalutamide and docetaxel, and on the 23rd of February 2022 for those assessing PARPi, platinum, cabazitaxel and PSMA-ligand therapies. We performed data synthesis by using both proportional and individual patient data. For PSA50 evaluation, we pooled event rates with 95% CIs. Time-to-event data (PFS and OS) analyses with individual patient data were performed with the mixed-effect Cox proportional hazard model and single-arm random-effect analysis, providing pooled medians.

4.Results

4.1. Project I

We synthesized data from 80,114 men from 12 studies. Compared to standard PSA-based screening, the MRI pathway (sequential screening, PI-RADS ≥3 cut-off for biopsy) was associated with higher odds of csPCa when tests results were positive (OR: 4.15; 95% CI: 2.93-5.88, P ≤ 0.001), decreased odds of biopsies (OR: 0.28; 95% CI: 0.22-0.36, P ≤ 0.001) and insignificant cancers detected (OR: 0.34; 95% CI: 0.23-0.49, P = 0.002), without significant differences in the detection of csPCa (OR: 1.02; 95% CI: 0.75-1.37, P = 0.9). Implementing a PI-RADS ≥4 threshold for biopsy selection led to a further reduction in the odds of detecting insignificant PCa (OR: 0.23; 95% CI: 0.05-0.97, P = 0.048), and biopsies performed (OR: 0.19; 95% CI: 0.09-0.38, P = 0.01), without differences in csPCa detection (OR: 0.85; 95%-CI: 0.49-1.45, P = 0.2). The pooled MRI rate was 8.5% (95% CI: 2.6%-24.8%) among the screened individuals, and the adherence for biopsy indication was higher when MRI was utilized (OR: 4.61; 95% CI: 2.39-8.89, *P* = 0.01)

4.2. Project II

Our meta-analysis of first-line available treatments included 16 eligible studies with 348 *BRCA*-positive mCRPC patients. In the first treatment line, response rates for abiraterone, enzalutamide and docetaxel were 52% (95% CI: 25-79%), 64% (95% CI: 43-80%) and 55% (95% CI: 36-73%), respectively. Analyses of individual patient data revealed a PFS (HR: 0.47; 95% CI: 0.26-0.83, P = 0.01) but no OS (HR: 1.41; 95% CI: 0.82-2.42, P = 0.2) benefit for enzalutamide compared to abiraterone-treated patients.

In our study assessing later-line treatments, we included 23 eligible studies with 901 *BRCA*-positive mCRPC patients. PSA50 response rates for PARPi and platinum were 69% (CI: 53-82%), and 74% (CI: 49-90%), respectively. Analyses of OS data showed no difference between PARPi and platinum treatments (HR: 0.86; CI: 0.49-1.52; P = 0.6). The single-arm OS and PFS analyses revealed similarities among different PARPi compounds; pooled PFS and OS medians were 9.7 months (95% CI: 8.1-12.5) and 17.4 months (95% CI: 12.7-20.1), respectively.

5. Conclusions

5.1. Project I

Our results suggest that prostate MRI with targeted biopsies is an effective strategy for the early detection of PCa. We found that MRI mitigates pitfalls of standard PSA-based strategies, as it is associated with fewer unnecessary biopsies and helps to avoid the detection of insignificant cancers while not compromising clinically significant disease detection. Considering these results, we need to reassess our approach to population-based PCa screening. However, the optimal setup of MRI and biopsy scheme in the screening process requires further evaluation.

5.2. Project II

Our findings confirm that *BRCA*-positive mCRPC patients respond to standard first-line treatments, including abiraterone, enzalutamide, and docetaxel, with enzalutamide showing the most favorable outcomes in terms of PSA response and PFS. However, this observation requires validation in prospective, molecularly selected interventional trials. We also demonstrated that different PARPis yield comparable PFS and OS, and that their efficacy appears similar to that of platinum-based chemotherapy in this

patient population. These results support platinum as a valid treatment option for *BRCA*-mutated mCRPC. Nevertheless, head-to-head comparisons in biomarker-driven prospective trials are essential to establish the optimal therapeutic strategy.

6. Bibliography

Publications related to the thesis:

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