EDITORIAL

Best of 2022 in prostate cancer and prostatic diseases

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Prostate cancer (PCa) is the most common cancer among men. Worldwide in 2020, 1,414,259 men were diagnosed of PCa and 375,304 died of PCa. Primary prevention in PCa has always been challenging considering that the three main risk factors (age, ethnicity, and family history) are non-modifiable. Several authors have explored the role of life-style, diet, and physical activity on PCa incidence however results are still controversial. To date no specific recommendation on lifestyle or diet can reduce the risk of developing PCa.

In terms of PCa diagnosis, an individualized risk-adapted strategy for early detection may still be associated with a substantial risk of over-diagnosis. It is essential to remember that breaking the link between diagnosis and active treatment is the only way to decrease over-treatment, while still maintaining the potential benefit of individual early diagnosis for men requesting it. For instance, men with a life expectancy <15 years are unlikely to benefit from any kind of screening. In the past years, several tools including mpMRI, new serum and urine biomarkers, risk calculators, and genetic classifiers have been developed to better select patients needing prostate biopsies. Notwithstanding all these new tools, detection rates of significant cancer and insignificant cancer are still suboptimal. As well, once patients are scheduled for prostate biopsies, the number and distribution of biopsy cores is still an important area of debate.

Finally, in the last decades, new androgen pathway targeting agents (ARTA) have significantly changed the outcome of metastatic castration-resistant PCa (mCRPC) patients. ARTAs, initially used to manage mCRPC patients, are now approved in different PCa settings such as non-metastatic CRPC and metastatic hormone-naïve PCa. As well, they are under investigation in non-metastatic patients as adjuvant and neo-adjuvant treatments. Although these treatments have completely changed the treatment landscape in metastatic and CRPC management, several unmet needs remain in this area. Particularly, mechanisms of resistance, role of next-generation imaging, optimal therapeutic sequencing, accessibility, costs, role of patients' preferences, and clinician experience are still far to be defined [1].

In this 2022 collection, we selected the most significant articles published in our Jounal on PCa diagnosis, staging, and treatment.

PSA DENSITY IS COMPLEMENTARY TO THE PROSTATE MRI PI-RADS SCORING SYSTEM FOR RISK STRATIFICATION

Frisbie et al. have evaluated the role of PSA density together with MRI to stratify PCa risk. The authors enrolled a consecutive series of 327 patients undergoing fusion biopsies and estimated an accuracy of 0.67 for PSA density (PSAd) and of 0.72 for PIRADS score to predict clinically significant cancer (Gleason ≥7) [2]. Using a cut-off of 0.10 ng/ml for PSA density together with PIRADS score an AUC of 0.82 for the prediction of clinically significant (CS) PCa was observed. Their results underline the important clinical utility of PSAd in terms of CSPC diagnosis as well as in terms of upgrading of MRI lesions. Notwithstanding the limitations of the study such as sample size, selection bias, and MRI reading, the authors propose a simple strategy to better select patients needing prostate biopsies using only MRI and PSAd.

CLINICAL USE OF THE MRNA URINARY BIOMARKER SELECTMDX TEST

Visser et al. evaluated, in ten European countries, over 5000 patients undergoing Select MDx test, a urinary-based biomarker test, and showed how 40.72% of patients could avoid prostate biopsies [3]. More specifically, in intended to use population of patients with PSA levels between 3 and 10 ng/ml, Select MDx could potentially reduce prostate biopsies in 45% of the cases. Interestingly in patients with PSA < 3 ng/ml only 25% presented a positive result while in patients with PSA > 15 ng/ml 95% presented a positive result on SelectMDx test. As well, patients older than 85 years old presented a positive result in 100% of the cases. Although this study suggests Select MDx test may reduce the number of unnecessary biopsies, how to manage and follow-up patients and how to integrate this test in routine clinical practice remains an open debate particularly when MRI findings are controversial.

HOW MANY CORES FOR MRI TARGET LESION ARE NEEDED?

Beetz et al. evaluated a consecutive series of 461 patients who underwent 10-core systematic biopsy and MRI-targeted biopsy [4]. The aim of their study was to establish the number of cores needed in the index lesion to establish PCa diagnosis. According to their results, the most relevant diagnosis was made in 97% of patients based on three MRI-targeted biopsy cores. Only three patients (2%) with a PI-RADS score 5 index lesion and 10 patients (6%) with a PI-RADS score 4 index lesion benefitted from a fourth or fifth MRI-targeted biopsy core. Neither PI-RADS score, PSA density, lesion size, zone, nor location independently influenced the prediction of the first MRI-targeted biopsy core. Although the authors clearly state 'more is not always better', the need of standard biopsies or the role of perilesional biopsies should be clarified to definitively reduce the number of unnecessary biopsies.

OPTIMIZING MRI TARGET BIOPSY: THE ROLE OF *PERILESIONAL CORES*

Noujelm et al. evaluated in a consecutive series of 505 patients the cancer detection rate for CSPC of different biopsy strategies: fusion targeted biopsies (TB), standard biopsies (SB), or combined method (TB + SB) [5]. Standing to their results, combined method resulted in a higher detection rate (37% vs. 32%; $p = 0.001$) however when targeted biopsies were associated with perilesional sampling within 10 mm no significant difference was recorded

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(37% vs. 35%; $p > 0.05$). As well avoiding biopsies beyond a 10 mm margin prevented detection of 19% of non-CSPC. Are these results reproducible with a cognitive technique? Will the penumbra sample strategy definitively close the cognitive era? The questions are still there.

EXERCISE IN ADVANCED PROSTATE CANCER ELEVATES MYOKINE LEVELS AND SUPPRESSES IN-VITRO CELL GROWTH

Kim et al. evaluated in twenty-five men with mCRPC if aerobic and resistance exercise induces positive systemic adaptations [6]. Patients were randomized to supervised multimodal exercise vs. self-directed exercise. After 6 months of supervised training, men had higher serum myokine levels and when their serum was applied to DU145 PCa cells in vitro, it decreased growth vs. men randomized to self-directed exercise. Although these data suggest as adequate physical activity could possibly impact on PCa progression, the mechanism behind these findings and the role of myokines on tumor growth should be further investigated.

PREDICTIVE ROLE OF NODE-RADS SCORE IN PATIENTS WITH PROSTATE CANCER CANDIDATES FOR RADICAL PROSTATECTOMY

Lucciola et al. evaluated 150 patients with intermediate-high-risk prostate cancer with indication to lymphadenectomy according to the available nomograms. All patients were as well evaluated with mpMRI to establish the Node-rads score [7]. According to their results, the accuracy of all methods are low with an AUC < 0,60 for all the available methods including nomograms and Node-rads score. The Node-rads score presented a very good PPV (100%) and a very good specificity (100%) however sensitivity is very very low (17%). These discrimination abilities are completely opposite to nomograms which present optimal sensitivity (97–100%) and poor PPV (25–31%). The integration of this new score in the current nomograms could potentially better identify patients at major risk of nodes involvement where an extensive lymph nodes dissection is indicated.

NEOADJUVANT APALUTAMIDE MONOTHERAPY AND RADICAL PROSTATECTOMY

Lee et al. introduce the use of 12 weeks of neo-adjuvant apalutamide in patients with intermediate and high-risk PCa undergoing radical prostatectomy [8]. The objective was to evaluate the complete pathological response (pCR). The study enrolled 30 patients. According to their results, apalutamide was not able to reach a pCR although 21/25 (84.0%) patients achieved a PSA of <0.03 ng/mL at week 24 (secondary endpoint). A tumor volume reduction of 40% was also observed. Although a negative trial, the NEAR study opens new insights on the role of ARTAs as neo-adjuvant treatment in patients with non-metastatic prostate cancer. Further trials are ongoing to evaluate their role as monotherapy or in combination with androgen deprivation therapy in this setting of patients.

OVERALL SURVIVAL AND ADVERSE EVENTS AFTER TREATMENT WITH DAROLUTAMIDE VS. APALUTAMIDE VS. ENZALUTAMIDE FOR HIGH-RISK NON-METASTATIC CRPC

Wenzel et al. evaluates, in a network meta-analysis, OS and AEs of the different pharmacological alternatives available for the management of nmCRPC [9]. The authors compared data from SPARTAN, PROSPER, and ARAMIS trials including 4117 patients. According to their results, all drugs improved OS with HR of 0.79 for Apalutamide, 0.73 for Enzalutamide, and 0.69 for Darolutamide. However, HR varies widely depending on PSA doubling time. In terms of safety (Grade 3+events) Apalutamide showed a better safety profile when compared to Enzalutamide and Darolutamide (AEs likewood respectively: 0.33; 0.51 and 0.59). More effective drugs always represent a better opportunity for patients care, however, as physicians, we must tailor treatments based on several factors including patients/tumor characteristics, availability, and costs.

SURVIVAL OF VETERANS TREATED WITH ENZALUTAMIDE AND ABIRATERONE FOR MCRPC BASED ON COMORBID DISEASES

Schoen et al. retrospectively evaluated survival of patients with mCRPC treated with enzalutamide (ENZA) or abiraterone (ABI) based on comorbidities [10]. Their study evaluated 5822 patients with 43% receiving ENZA and 57% receiving ABI. Overall patients treated with ENZA presented more comorbidities when compared to ABI. In the Overall population ABI was superior to ENZA (24 vs. 22 months; $p < 0.01$) while in the population with comorbidities, ENZA was superior to ABI (23 vs. 20 months; $p < 0.01$) in terms of overall survival. As well, in the propensity score analysis ENZA was superior to ABI in terms of OS (HR: 0.90; $p < 0.01$). A better profile of our patients with CRPC could probably help to identify the right treatment for the right patient, to minimize morbidity, and to possibly improve survival.

REAL-WORLD RADIUM-223 TREATMENT FOR MCRPC (EPIX STUDY)

George et al. in the EPIX study, evaluated the characteristics of patients who survived more than 2 years after Radium 223 treatment [11]. Overall, they compared 775 patients with less than 2 years of OS vs. 185 patients with an OS > 2 years. According to their results Age >75years (HR: 1.46), ECOG status >1 (HR:2.03), presence of visceral M1 (HR:1.61), prior symptomatic skeletal event (HR: 1.19) and prior chemotherapy (HR: 1.57) were independent predictors of poor prognosis. Their results clearly suggest, in a real-world setting, how treating younger patients with a better performance status and a lower disease burden can maximize the Radium 223 efficacy. Patients' selection is always the key.

Authors around the world still fight against the unsolved gaps in prevention, diagnosis, and treatment of PCa. In terms of prevention after years of studies and millions of patients enrolled, we still do not have an answer to those patients asking: What can I do doctor to prevent PCa? Diet and life-style are important but we are still far from a definitive prevention strategy or recommendation. The introduction of MRI in clinical practice has dramatically improved the management of patients at risk of PCa and reduced the number of unnecessary biopsies, but we still need a 100% accurate and non-invasive diagnostic tool for the diagnosis and staging of prostate cancer patients. The introduction of the ARTA in clinical practice represents a milestone in the history of PCa opening new strategies at different stages of PCa management. However, a better-personalized medicine is still needed particularly to define which patients mostly benefit from a specific treatment and in which stage of the disease. The manuscripts summarized in this Editorial are a small part of those published last year in our Journal but they represent some of the mostly investigated topics on PCa management and due to their limitations or perspectives they open new insights in PCa research.

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COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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