Management of metastatic castration-resistant prostate cancer in Middle East African countries: Challenges and strategic recommendations

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Abstract

Despite the reliance on Western guidelines for managing prostate cancer (PC), there are wide variations and gaps in treatment among developing countries such as the Middle East African (MEA) region. A multidisciplinary team of experts from the MEA region engaged in a comprehensive discussion to identify the real-world challenges in diagnostics and treatment of Metastatic Castration-Resistant Prostate Cancer (mCRPC) and provided insights on the urgent unmet needs. We present a consensus document on the region-specific barriers, key priority areas and strategic recommendations by experts for optimizing management of mCRPC in the MEA. Limited access to genetic testing and economic constraints were highlighted as major concerns in the MEA. As the therapeutic landscape continues to expand, treatment selection for mCRPC needs to be increasingly personalized. Enhanced genetic testing and judicious utilization of newer therapies like olaparib, articulated by reimbursement support, should be made accessible for the underserved populations in the MEA. Increasing awareness on testing through educational activities catalyzed by digital technologies can play a central role in overcoming barriers to patient care in the MEA region. The involvement of multidisciplinary teams can bridge the treatment gaps, facilitating holistic and optimal management of mCRPC. Region-specific guidelines can help health-care workers navigate challenges and deliver personalized management through collaborative efforts – thus curb health-care variations and drive consistency. Development of region-specific scalable guidelines for genetic testing and treatment of mCRPC, factoring in the trade-off for access, availability, and affordability, is crucial.

Keywords: Genetic testing, metastatic castration-resistant prostate cancer, Middle East African region, multidisciplinary care

INTRODUCTION

Prostate cancer (PC), the fifth-leading cause of mortality worldwide, is a heterogeneous disease with an indolent course of progression.[1] Over the past few years, the
landscape of PC care has undergone dynamic changes due to evolving diagnostic approaches and novel therapies. Although most developing countries lean on Western guidelines for the management of PC, there are wide differences in practice patterns, resulting in treatment gaps. To identify the current challenges in diagnostics and treatment of metastatic castration-resistant prostate cancer (mCRPC) in the Middle East African (MEA) region, a multidisciplinary meeting with experts from different counties across the MEA region was convened. The panel aimed to gain insights on the real-world treatment practices in the MEA region in the mCRPC domain, to view them in the light of international guidelines and unify best practices across MEA. The panel deliberated on the region-specific priority needs and provided strategic recommendations for optimizing PC management through collaborative efforts.

**CONSENSUS METHODOLOGY**

The steering committee meeting held on December 12, 2020 included a multidisciplinary panel of eight members with a broad range of expertise in the diagnosis and management of PC across the MEA region (Saudi Arabia \[n = two\], Egypt \[n = two\], Morocco \[n = one\], United Arab Emirates \[n = one\], Lebanon \[n = one\], and Turkey \[n = one\]) [Figure 1].

Key areas including current practices for managing mCRPC, implications of genomic analysis and communicating its importance to urologists, perspectives on multidisciplinary care, and strategic recommendations for improving management were discussed in moderator-led sessions. The members provided insights on the real-world challenges in their region and provided recommendations on ways to overcome the limitations for improving PC care based on their discretion and experience. The meeting concluded with the prioritization of urgent unmet needs and actionable elements to improve patient outcomes in the MEA region. The opinions and responses of the expert committee were assimilated and a thematic qualitative analysis was conducted to systematically categorize the region-specific recommendations and action plans.

**BURDEN AND EPIDEMIOLOGY IN MIDDLE EAST AFRICAN**

Globally, PC has an age-standardized incidence (ASIR) (per 100,000) and mortality rates (per 100,000) of 30.7 and 7.7, respectively.\(^1\) PC is one of the most common cancers in the MEA region. ASIR of PC is lower in the Arab countries compared to North American and European regions; however, it is rising steadily\(^2,3\) [Table 1].\(^4\) A study from a tertiary referral center in Lebanon reported that 22.6% of the patients presented with advanced stage 4 disease at diagnosis.\(^5\) Late-stage PC has poor survival outcomes, with the American Cancer Society estimating a 5-year relative survival rate of 30% for distant PC.\(^6\)

Herein, we present the challenges, recommendations, importance of multidisciplinary care and the way forward in diagnosis and management of PC in the MEA region.

**CURRENT CHALLENGES AND RECOMMENDATIONS FOR PROSTATE CANCER DIAGNOSIS IN MIDDLE EAST AFRICAN**

Although most experts reported wide availability of diagnostic approaches such as prostate-specific membrane antigen-positron emission tomography with computerized tomography (PSMA-PET-CT scan), their scarcity was highlighted in Saudi Arabia and Morocco [Table 2]. All the experts (except Saudi Arabia) reported conducting BRCA and homologous recombination repair (HRR) testing in an mCRPC setting; however, lack of insurance cover was an important

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**Table 1: Age-standardized incidence and mortality rates of prostate cancer**

| Country            | ASIR (per 100,000) | ASMR (per 100,000) |
|--------------------|--------------------|--------------------|
| Morocco            | 23.6               | 11.8               |
| United Arab Emirates| 13.4              | 3.4                |
| Turkey             | 42.5               | 11.3               |
| Lebanon            | 28.5               | 9.7                |
| Egypt              | 13.9               | 7.9                |
| Saudi Arabia       | 7                  | 2.5                |
| United States      | 72.0               | 8.2                |
| United Kingdom     | 77.9               | 12.4               |

Prostate Globocan factsheet 2020. Available from [https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf](https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf). Accessed Jan 2021. ASIR: Age-standardized incidence rate, ASMR: Age-standardized mortality rates
Table 2: Challenges and recommendations for diagnosis and genetic testing of prostate cancer in Middle East Africa

| Availability and adequate timing of genomic testing | Challenges | Recommendations |
|-----------------------------------------------------|------------|----------------|
| Egypt                                               | Testing for BRCA essential and available, however testing needed for somatic as well as germline mutations Timing for testing is crucial; testing in early disease stage might be better | Tissue suitability: Concern over availability of suitable tissue at early stages of disease, after prolonged ADT and re-biopsy in irradiated prostate. In addition, tissue may not be available in case of prostatectomy Special preparation of bone in case of bone biopsy Reimbursement: BRCA not reimbursed by the government | For generalized genomic profiling, preferable to have recent biopsy, as quality of DNA can degrade over time Liquid test can be used for BRCA, in future to evaluate discordance between blood test and somatic test from tumor tissue Streamlined approach for genetic testing in the urology clinic |
| Lebanon                                             | Access to genetic testing for BRCA and HRD crucial Next generation genetic sequencing available Testing at an early stage might be useful | Long duration for obtaining results Concern over the type of genetic testing to be evaluated Bone metastasis testing difficult owing to complex bone preparation Reimbursement: Testing not reimbursed by social security, government or private insurance | Need refined definitive guideline Imperative to sensitize urologist for genetic testing early in the disease Need virtual molecular biology board for interpretation of results |
| Morocco                                             | DNA alterations, BRCA testing performed in castration phase | PSMA PET not available BRCA mutation testing not reimbursed and not performed in all public hospitals Long time lag to obtain results, thus delaying treatment Due to tumor instability, DNA alterations may change over time with metastatic disease progression Ethnic variations | Essential to understand the type of DNA alterations to be evaluated - for germline and somatic mutations BRCA testing is crucial. Although general genomic profiling may not be essential, MSI may be required Urologists need better access to reliable results and interpretation. Crucial to support urologists for genetic testing for BRCA mutation In addition, differences in ethnicity need to be considered Virtual genetic counseling clinics are needed Need of MDT Need reflex genetic testing from pathology to molecular labs Need virtual genetic counseling clinics |
| Turkey                                              | BRCA and MSI test are reimbursed for all patients with prostate cancer, however they are not widely available in common practice yet Testing conducted at onset of castration resistant prostate cancer. However, conducting it earlier would be beneficial | Long duration for obtaining results for BRCA testing Currently, BRCA testing can’t be validated Region-specific testing algorithm not available, mostly international guidelines followed | Genomic profiling is essential for prognosis and to optimize the treatment at diagnosis of CRPC or at failure of first-line therapy Genomically driven trials with better companion diagnostics will help in advancing precision medicine Genomic profile summary predicting response to ADT, sensitivity to chemotherapy, and neuroendocrine differentiation can help identify the best therapy and sequence for the patient Optimal timing at mCRPC stage is crucial Need virtual genetic counseling clinics |
| UAE                                                 | BRCA and HRR testing used in mCRPC setting | Although BRCA and HRR testing used in the mCRPC setting, concern over long time for obtaining results and cost May lead to patient anxiety Region-specific testing algorithm not available Though biopsied tissue is preserved optimally, patient mobilization to international places may lead to scarcity of detailed report | For generalized genomic profiling, preferable to have recent biopsy, as quality of DNA can degrade over time Liquid test can be used for BRCA, in future to evaluate discordance between blood test and somatic test from tumor tissue Streamlined approach for genetic testing in the urology clinic |
| Saudi Arabia                                        | Only few centers, tertiary care facilities offer HRD testing | Government centers do not perform PSMA Limited availability of PSMA PET and HRD testing | No comments |

ADT: Androgen deprivation therapy, BRCA: Breast cancer gene, HRD: Homologous repair deficiency, PC: Prostate cancer, HRR: Homologous recombination repair, mCRPC: Metastatic castration-resistant PC, MDT: Multidisciplinary team, MSI: Microsatellite instability, PSMA PET: Prostate-specific membrane antigen positron emission tomography with computerized tomography.
effect of bone-targeted agents on biopsy and the problem of calcifications while bone testing, especially if the patient received bone-targeted agents previously, need to be explored further. Regarding tissue preservation and archiving optimization, the experts deliberated that though biopsied tissues were preserved optimally, the mobilization of patients to international places led to scarcity of detailed reporting.

Genomic profiling is pivotal for upfront prognosis and treatment optimization – highlighting the need for a streamlined roadmap and more refined definitive guideline for genetic testing [Table 2]. Genomically driven trials with better companion diagnostics for advancing precision medicine and genomic profile summary predicting response to ADT, sensitivity to chemotherapy, and neuroendocrine differentiation can help identify best therapy and sequence for the patient. Optimal timing at the mCRPC stage was also deemed as a crucial aspect. Although testing is usually conducted at the onset of castration-resistant PC, the experts opined that conducting the tests at an early stage might be useful. As PC evolves over a longer period (except a small proportion of patients who develop rapidly), the experts concurred for conducting a new biopsy when patients develop metastatic disease. Furthermore, in the case of generalized genomic profiling, the experts recommended conducting a recent biopsy as the quality of DNA may degrade over time. The PROFOUND and PROPEL trials had no time limitation for the next-generation sequencing test and used archived issues. Liquid biopsy can be used for BRCA testing in future as it will be helpful to evaluate discordance between blood tests and somatic tests from tumor tissue. It is imperative to sensitize urologists for genetic testing early in the disease and provide them enhanced access to reliable results and interpretation. Virtual molecular biology board, multidisciplinary panels for interpretation of results from genetic testing, and formulation of genetic counseling clinics are critical.

**EVIDENCE SUPPORTING THE STRATEGIC RECOMMENDATIONS**

**Overview of molecular landscape in Metastatic Castration-Resistant Prostate Cancer**

The molecular profile of mCRPC is highly heterogeneous, encompassing different germline and somatic genetic alterations such as homologous repair deficiency (HRD) (e.g., BRCA1, BRCA2, ataxia telangiectasia mutated (ATM), BRIP1, CHEK2, NBN, BARD1, RAD51C, MRE11A, and PALB2), mismatch repair (MMR) deficiency (e.g., MLH1, MSH2, MSH6, and PMS2) and microsatellite instability (MSI).[8,9] The DNA damage response (DDR), an essential pathway for survival of normal and malignant prostate cells, includes crucial genes, such as breast cancer susceptibility gene (BRCA) 1/2, ATM and partner and localizer of BRCA2 (PALB2). A study identified common deleterious DNA-repair gene mutations in 16 genes, including BRCA2 (5.3%), ATM (1.6%), CHEK2 (1.9%), BRCA1 (0.9%), RAD51D (0.4%), and PALB2 (0.4%).[10] A systematic review showed that the prevalence of DDR germline and/or somatic mutations (among unselected patients) was 22.67% in mCRPC, with BRCA2 having the highest mutation rate – warranting testing of all patients with metastatic disease and not just those with the familial disease.[11] Poly (ADP)-ribose polymerase inhibitors (PARPi) inhibit DNA repair pathways and cause apoptosis of cancer cells, especially in HR-deficient cells.[12] PARPi have emerged as a therapeutic approach to target the DDR pathway harboring genetic mutations (e.g., BRCA1/2 mutations). Many ongoing clinical trials are exploring the benefit of PARPi alongside other targeted therapeutic agents such as pembrolizumab for mutations in the HRD or MMR genes. The FDA has approved two PARPi, olaparib and rucaparib for BRCA-mutated mCRPC.[13,14] Recent guidelines have recommended olaparib and rucaparib for patients with deleterious germline or somatic HRR gene-mutated mCRPC. Pembrolizumab was approved by the FDA in 2017 and is recommended for the treatment of all solid tumors, including PC that have mutations in MMR genes and or MSI in the tumor.[15] Given the high proportion of patients with actionable mutations and the evolution of novel therapies, genetic testing is now an important standard of care. Guidelines such as the National Comprehensive Cancer Network (NCCN) have reflected on the importance of DDR mutation testing in mCRPC and have recommended germline genetic testing for patients with high-risk or metastatic disease or family history of known germline DNA repair gene abnormalities (especially BRCA2 mutation) – for obtaining clarity on prognosis, therapeutic choices, in addition to informing the patient about personal and familial risk.[16,17]

The Germline Genetics Working Group (GGWG) described that integrating genetic testing into oncology and urology clinical scenarios is challenging due to the increased burden of patients requiring testing and the limited access to genetics providers.[18] It is crucial to have trained genetic providers to assess genetic risk, order appropriate testing, and interpret test results; however, majority of the workforce are centered in urban areas.
and academic institutions. Due to the scarce availability of such specialists, it is prudent that other health care providers such as oncologists, urologists, and primary care physicians are sufficiently trained in the area of molecular genetics. A survey of U.S. (n = 132) urologists revealed that only 12% perform germline testing, 44% refer to a genetic counselor, 11% do both, and 33% do not test/refer. The survey highlighted that only 4% had formal education in genetics, but specializing in PC/oncology was significantly associated with recommending germline testing (P = 0.0009). Similarly, a provider survey from Birmingham showed that only 39% of eligible patients were referred, while testing was completed in 11%. About 70% of respondents cited that lack of genetics workforce and lack of knowledge (60%) were barriers to genetic testing. The 2019 Philadelphia Prostate Consensus Guidelines advocated the utilization of digital health technologies such as phones and video telemedicine for facilitating access. It also recommends using hybrid service models encompassing balanced responsibilities between physicians and geneticists, alongside multidisciplinary collaboration between geneticists and clinicians to determine the best approach.

The selection of appropriate patients for testing is critical. NCCN and other consensus guidelines elucidate key criteria such as metastatic disease or strong family history to screen and identify patients. GGWG suggests that patient-completed family history questionnaires or automated electronic medical records can facilitate referral and testing processes. Insurance and out-of-pocket cost for patients are crucial elements for propagating genetic testing. The Philadelphia consensus outlined that targeted testing for selected individuals might be beneficial in this regard. Complete and detailed family histories can ensure that the most informative, cost-effective testing is performed; however, it may be prudent to include other associated genetic tests as well. The NCCN guidelines recommend considering BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, and PMS2 for testing; however, the Philadelphia consensus included HOXB13 and DNA MMR genes. GGWG recommends that factors such as insurance networks, laboratory billing practices, follow-up testing options for family members, turnaround times, and availability of genetic counseling services are deciding factors for genetic testing. Evidence has shown low awareness and knowledge of genetic counseling, and testing for cancer susceptibility among ethnic minority groups and socioeconomically disadvantaged individuals may result in anxiety. Considering the evolving therapeutic landscape of PC, it is essential to make strategies for minimizing disparities for optimizing treatment and improving outcomes. Increased awareness for genetic testing through counseling for PC, involving shared decision making between provider and patient; discussion of benefits, risks, financial implications; and genetic discrimination laws are important.

**MANAGEMENT OF METASTATIC CASTRATION RESISTANT PROSTATE CANCER**

Overview of international guidelines for the management Recent guidelines have recommended novel agents such as olaparib for patients with deleterious or suspected deleterious germline or somatic HRR gene-mutated mCRPC after prior anti-androgen therapy (enzalutamide or abiraterone) [Table 3]. A summary of ongoing or completed trials of novel therapies for mCRPC is presented in Table 4.

Current treatment practices for Metastatic Castration-Resistant Prostate Cancer in Middle East African region and their comparison with the Western world A real-world study from the U.S. reported that abiraterone/prednisone accounted for 65% of first-line, enzalutamide for 54% of second-line therapies, and docetaxel 24% of third-line therapy; the median overall survival was longer in patients who received abiraterone/prednisone, enzalutamide, and docetaxel therapies (23.7 months) than those who did not (10.1 months). PROXIMA (Treatment Patterns in Patients with Metastatic Castration-Resistant Prostate Cancer Previously Treated With Docetaxel-Based Chemotherapy) a multicenter, prospective registry including patients from Asia, Europe, Latin America, and MEA highlighted regional influences, with chemotherapy being more frequently prescribed in MEA countries (52.3%) compared to Europe (27.1%) – attributed to the unavailability of other agents in these countries. The study showed that median overall survival for all patients was 15.1 months (95% confidence interval, 14.0–17.6). ASPIRE-PCa, a global study including patients from the Middle East and North Africa in late-stage PC reported ADT as the treatment of choice, gonadotropin-releasing hormone agonist with anti-androgen for flare protection only was the most selected ADT (leuprolide [48%]; bicalutamide [48%] and abiraterone [8%]) were most common, while enzalutamide was less frequently chosen [3%]. The APCCC Satellite Meeting for the Middle East presented resource-stratified consensus recommendations for the management of patients with high-risk and advanced PC [Table 5].
### Table 3: Summary of major recommendations for the management of metastatic castration-resistant prostate cancer

| International guidelines[16,23] | Regional guidelines[24] |
|-------------------------------|------------------------|
| **No prior docetaxel/no prior novel hormone therapy:** | **Patients who did not receive chemohormonal therapy:** |
| Preferred: Abiraterone, docetaxel, enzalutamide | For symptomatic patients and rapidly progressing disease: Docetaxel with prednisone |
| In certain circumstances: Sipuleucel-T, radium-223 (symptomatic bone metastasis) | For patients with no or mild symptoms and no visceral metastases: Abiraterone and prednisone |
| Other secondary hormone therapy | For patients with no or mild symptoms: Enzalutamide |
| Prior novel hormone therapy/no prior docetaxel: | For patients with only symptomatic bone metastases: Radium223 |
| Preferred regimens: Docetaxel, Sipuleucel-T | Progressed on or after docetaxel: Cabazitaxel with prednisone, abiraterone with prednisone, enzalutamide, other secondary hormone therapy |
| In certain circumstances: Olaparib (HRRm), cabazitaxel/carboplatin, pembrolizumab (MSI-H/dMMR), radium-223, rucaparib (BRCAm) | For patients with CRPC should continue ADT indefinitely |
| Other: Abiraterone, abiraterone+dexamethasone, enzalutamide, other secondary hormone therapy | |
| Prior docetaxel/no prior novel hormone therapy: | |
| Preferred: Abiraterone, cabazitaxel, enzalutamide | |
| In certain circumstances: Mitoxantrone for palliative therapy, cabazitaxel/carboplatin, radium-223, pembrolizumab (MSI-H/dMMR), Mitoxantrone, rucaparib (BRCAm) | |
| Other: Sipuleucel-T, other secondary hormone therapy | |
| Prior docetaxel and prior novel hormone therapy: | |
| Preferred: Cabazitaxel, docetaxel | |
| In certain circumstances: Olaparib (HRRm), cabazitaxel/carboplatin, radium-223, pembrolizumab (MSI-H/dMMR), Mitoxantrone, rucaparib (BRCAm) | |
| Other: Abiraterone, enzalutamide, other secondary hormone therapy | |
| **Prior novel hormone therapy/no prior docetaxel:** | |
| Preferred regimens: | |
| In certain circumstances: Olaparib (HRRm), cabazitaxel/carboplatin, radium-223, pembrolizumab (MSI-H/dMMR), Mitoxantrone, rucaparib (BRCAm) | |
| Other: Abiraterone, enzalutamide, other secondary hormone therapy | |

### Table 4: Summary of key ongoing or completed trials of novel therapies for metastatic castration-resistant prostate cancer

| PARPi | Name of study | Population | Outcomes | Result |
|-------|---------------|------------|----------|--------|
| Olaparib | TOPARP-B[23] | mCRPC, HRD selected, previously given taxane | Composite RR (PSA decline ≥50%, objective tumor response, CTC reduction) | Composite RR 54% at 400 mg dose and 39% for 300 mg dose |
| | PROfound[21] | mCRPC, HRD selected, given second-generation hormonal agent and one taxane | Primary outcome: rPFS in cohort A Secondary outcome: rPFS in cohort A+B OS: cohort A | rPFS cohort A versus control 7.4 versus 3.6 months rPFS cohort A+B versus control 5.8 versus 3.5 months OS cohort A versus control 18.15 versus 15.1 months |
| Rucaparib | TRITON2[24,27] | mCRPC, HRD selected, given second-generation hormone agent and taxane | ORR (RECISt/PCWG3) Secondary: PSA decline ≥50% (RECISt) | ORR-BRCA1/2: 43.5-50.8% PSA-BRCA1/2 mutation: 53.8% ORR for other HRD mutation: 28.6% ORR for BRCA/2 mutation 41% |
| | GALAHAD[28] | mCRPC, HRD selected, given second-generation hormone agent and taxane | Composite RR (PSA decline ≥50%, objective tumor response, CTC reduction) | Composite RR for BRCA1/2 mutation 63% |
| Pembrolizumab | KEYNOTE-199[29] | Cohorts 1 and 2: RECISt measurable PD-L1-positive and PD-L1-negative disease, Cohort 3: Bone predominant disease | ORR by RECISt Disease control rate OS | ORR 5% in cohort 1 and 3% in cohort 2 Disease control rate: 10% in cohort 1, 9% in cohort 2, and 22% in cohort 3 Median OS: 9.5 months in cohort 1, 7.9 months in cohort 2, 14.1 months in cohort 3 |
| | LuPSMA trial Phase II[30] | Progressive disease per RECISt or bone scan after standard treatments, with taxane and second-generation anti-androgens | PSA response (≥50% decline from baseline) | 17 (57%) of 30 patients (95% CI 37-75) achieved a PSA decline of 50% or more |

**PARPi:** Poly (ADP-ribose) polymerase inhibitors, mCRPC: Metastatic castration-resistant prostate cancer, RR: Response rate, HRD: Homologous recombination deficiency, CTC: Circulating tumor cells, rPFS: Radiographic progression-free survival, OS: Overall survival, ORR: Objective response rate, RECIST: Response evaluation criteria in solid tumor, BRCA: Breast cancer, PSMA: Prostate-specific membrane antigen, PD-L1: Programmed death-ligand 1, PSA: Prostate-specific antigen
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Table 5: Current treatment practices for metastatic castration-resistant prostate cancer in the middle Eastern region and their comparison with the western world

| US [31] | APCCC Satellite Meeting for Middle East [34] | PROXIMA registry [32] |
|---------|---------------------------------------------|-----------------------|
| First-line (n=1980) | Asymptomatic/minimally symptomatic men who did NOT receive Docetaxel in the castration-sensitive setting: Abiraterone or Enzalutamide: (28%) | First subsequent treatment: Chemotherapy (38.3%); the most frequent were taxanes (26.4%) |
| Abiraterone (37%) | Docetaxel (15%) | Enzalutamide: (87%) |
| Enzalutamide (28%) | Cabazitaxel (1%) | in castration-sensitive setting: Abiraterone or Enzalutamide: (86%) |
| Combination therapy, including radium-223 (7%) | | |
| Second-line (n=969) | Progressive disease to first-line Abiraterone or Enzalutamide: Taxane (85%) | Second subsequent treatments: Chemotherapy (44.8% with 28.8% only chemotherapy) |
| Enzalutamide (34%) | Symptomatic mCRPC and secondary (acquired) resistance (initial response followed by progression) after use of first-line Abiraterone or Enzalutamide: Taxane (100%) | Hormonal therapies (44.4% with 18.8% receiving only hormonal therapy) |
| Abiraterone (20%) | Cabazitaxel (6%) | Palliative radiotherapy (8.7%) |
| Docetaxel (14%) | Radium-223 (3%) | Targeted therapies (6.3%, with 4.5% receiving only targeted therapy) |
| Cabazitaxel (1%) | Sipuleucel-T (2%) | Corticosteroids (6.3%) |
| Combination therapy, including radium-223 (17%) | | Immunotherapy (0.7%) |
| Third-line (n=414) | mCRPC progressing on or after second-line Docetaxel for mCRPC and prior treatment with Abiraterone/Enzalutamide: Cabazitaxel (81%) | Third subsequent treatments: Hormonal therapies (50.6%, with 25.9% only hormonal therapies) |
| Docetaxel (24%) | | Chemotherapy (32.1%, with 21.0% only chemotherapy) |
| Enzalutamide (16%) | Abiraterone (14%) | Palliative radiotherapy (18.5%) |
| Cabazitaxel (11%) | Radium-223 (8%) | Targeted therapies (7.4%, with 4.9% receiving only targeted therapy) |
| Sipuleucel-T (3%) | Combination therapy, including radium-223 (18%) | |
| PC: Prostate cancer, mCRPC: Metastatic castration-resistant PC, PROXIMA: Prospective registry mCRPC previously treated with docetaxel-based chemotherapy |

CURRENT CHALLENGES AND RECOMMENDATIONS IN TREATMENT OF METASTATIC CASTRATION-RESISTANT PROSTATE CANCER IN MIDDLE EAST AFRICA

Gaps in treatment of Metastatic Castration-Resistant Prostate Cancer

Most experts concurred regarding the availability of major therapeutic agents such as enzalutamide, abiraterone, Lutetium 177 PSMA radionuclide therapy; however, deficiencies were highlighted in Morocco and Saudi Arabia. All the experts reported the unavailability of radium 223 as a therapeutic agent. There were congruent views regarding the lack of robust data from prospective studies for treatment sequencing and lack of data on combination therapy for mCRPC reporting better survival outcomes. Majority of the experts reported the absence of region-specific national guidelines for PC, except Lebanon, where guidelines though available, were not updated. The panel unanimously agreed on primarily using international guidelines like NCCN due to the absence of region-specific national guidelines; however, the experts added that formulation of national guidelines is anticipated in Turkey, Egypt, and Morocco in the near future. Another major area of concern was the lack of reimbursement of therapeutics, especially novel agents such as olaparib. The unavailability of PARPi in government centers was reported as a deficiency in countries such as Saudi Arabia.

Recommendations for Metastatic Castration-Resistant Prostate Cancer treatment

All the experts concurred on building a multidisciplinary collaboration for guideline creation and regular upgradation. The experts elaborated the need for a committee to support continuity and suggested empowering skilled clinicians from private sectors through incentives for regular implementation. The experts discussed the need of a dedicated team, including skilled urologist, oncologist, radiation oncologist, medical oncologist, pathologist, nurse and data management personnel. Emphasis was also laid on understanding the importance of real-world management practices alongside scientific recommendations. Conducting meeting of key opinion leaders, including representatives from government and payers, to facilitate region-specific personalization of guidelines might facilitate access. Easily comprehensible procedures funded by the government were regarded as the pathway for the distribution of new national guidelines to practicing clinicians.

EVIDENCE SUPPORTING THE STRATEGIC RECOMMENDATIONS

Role of multidisciplinary care for Metastatic Castration-Resistant Prostate Cancer management

The experts unanimously concurred regarding the utilization of MDT for optimized PC care and management. Traditional care in PC management carries disadvantages such as
fragmented care, lack of prospective treatment sequencing, rapidly evolving treatment options, and delayed care. Given the complexities of multimodal treatment for patients with PC, the use of multidisciplinary teams can aid the formulation of optimal treatment strategies for individual patients. Different stakeholders in the MDT may include urologist, radiation oncologist, medical oncologist, pathologist, imaging specialist, nurse and data management professional in the core team; medical physicist, palliative care specialist, psychologist, genetic counselor, patient advocate, and clinical trial coordinator in the noncore team. In addition, support services and navigators also play an important role [Figure 2]. MDT approach guarantees a higher probability for the patient to receive adequate information on the disease and on all possible therapeutic strategies, balancing advantages, and related adverse effects. A team approach to PC care can reduce mortality and improve the quality of life for the patient. A real-world study demonstrated that patients treated via the MDT survived on average 16.9 months longer than those in the matched Surveillance, Epidemiology and End Results cohort.[13] Guideline-focused care with improved diagnostic and therapeutic paths, increased patient satisfaction, decreased time from presentation to treatment, reduction in errors or variability, as well as timely access to physical and psycho-emotional rehabilitation programs have been shown to be improved by a multidisciplinary approach to PC care.[36-42]

Importance of region-specific consensus guidelines
The experts discussed the importance of region-specific national clinical guidelines to translate evidence from bench to bedside. Region-specific guidelines can help reduce health-care variation, improve consistency in care delivery across systems and countries, modify physician behavior, promote effective interventions, and discourage the use of less effective therapies. Such tailored guidelines can support advanced practice providers and less experienced trainees for the timely and precise clinical decision process, factoring in the regional challenges for access, availability, and affordability. Developing guidelines in low-income and middle-income countries should entail a strategic approach to conduct reviews, present evidence, and promote transparency of consensus-based procedures through multidisciplinary engagement from government and academia, regulators, and practitioners.[43-49] Definitive guidelines incorporating patient preferences, treatment risks, and comorbidities to guide clinicians’ choices can drive personalized medicine and enhance patient care.[46]

**FUTURE DIRECTIONS FOR METASTATIC CASTRATION RESISTANT PROSTATE CANCER MANAGEMENT**

Defining the best sequencing and combination strategies to delay resistance, decrease toxicities, and improve survival outcomes is warranted for mCRPC. Several ongoing clinical trials are exploring this paradigm, especially in combination with recently introduced agents such as olaparib and pembrolizumab.[47-51] The challenges of tumor instability and DNA alterations over time with disease progression can be mitigated by liquid biopsies, thus developing a roadmap of personalized treatment strategies in future.[52,53] Furthermore, utilization of artificial intelligence in diagnostic and prognostic prediction to facilitate decision-making can open opportunities for personalized treatment in mCRPC.[54,55]

**CONCLUSION**

As the list of the therapeutic landscape of mCRPC continues to expand, treatment selection needs to be personalized through enhanced genetic testing. Multidisciplinary care, including stakeholders from different specialties, is critical to deliver optimal care. Formulation of region-specific scalable strategies and guidelines to deliver personalized genetic testing are essential to guide precision medicine and improve patient outcomes. However, insurance for genetic testing and newer therapies like olaparib is pivotal for regular implementation. Guideline sustainability and economical cost are crucial elements for influencing real-world treatment decisions in MEA. In addition, enhancing awareness regarding the need for testing through
educational activities can be pivotal for genetic care delivery. Hybrid methods for educational activities encompassing digital technologies can play a central role in overcoming barriers pertaining to access and availability of mCRPC management in MEA.

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REFERENCES
1. Prostate Globocan; 2020. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf. [Last accessed on 2021 Jan 15].
2. Alshehri BM. Prostate cancer in Saudi Arabia: Trends in incidence, morphological and epidemiological characteristics. Int J Res Med Sci 2020;8:3899.
3. Globocan 2020, Regional Fact Sheets. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/27-Prostate-fact-sheet.pdf. [Last accessed on 2021 Jan 15].
21. Giri VN, Knudsen KE, Kelly WK, Cheng HH, Cooney KA, Cookson MS, et al. Implementation of germline testing for prostate cancer: Philadelphia Prostate Cancer Consensus Conference 2019. J Clin Oncol 2020;38:2798-811.
22. Hann KE, Freeman M, Fraser I, Walker J, Sanderson SC, Rahman B, et al. Awareness, knowledge, perceptions, and attitudes towards genetic testing for cancer risk among ethnic minority groups: A systematic review. BMC Public Health 2017;17:503.
23. Lowrance WT, Breaux RH, Chou R, Chapin BF, Crispino T, Dreicer R, et al. Advanced prostate cancer: AUA/ASTRO/SUO guideline PART II. J Urol 2021;205:22-9.
24. Aljubran A, Abusamra A, Alkhateeb S, Aloaitbi M, Rabah D, Bazarbashi S, et al. Saudi Oncology Society and Saudi Urology Association combined clinical management guidelines for prostate cancer 2017. Urol Ann 2018;10:138-45.
25. Mato J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-repair defects and olaparib in metastatic prostate cancer. N Engl J Med 2015;373:1697-708.
26. Abida W, Campbell D, Patnaik A, Shapiro JD, Sautois B, Vogelzang NJ, et al. Non-BRCA1/2 DNA damage repair gene alterations and response to the PARP-inhibitor rucaparib in metastatic castration-resistant prostate cancer: Analysis From the Phase II TRITON2 Study. Clin Cancer Res 2020;26:2487-96.
27. Abida W, Patnaik A, Campbell D, Shapiro J, Bryce AH, McDermott R, et al. Rucaparib in men with metastatic castration-resistant prostate cancer harboring a BRCA1 or BRCA2 gene alteration. J Clin Oncol 2020;38:3763-72.
28. Smith MR, Sandhu SK, Kelly WK, Scher HI, Efstratiou E, Lara PN, et al. Pre-specified interim analysis of GALAHAD: A phase II study of niraparib in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) and biallelic DNA-repair gene defects (DRD). Ann Oncol 2019;30:v884-5.
29. Antonarolakis ES, Piulats JM, Gross-Goupil M, Goh J, Ojamaa K, et al. Pembrolizumab for treatment-refractory metastatic castration-resistant prostate cancer: Multicohort, open-label phase II KEYNOTE-199 study. J Clin Oncol 2020;38:395-405.
30. Hofman MS, Viollet J, Hicks RJ, Ferdinans J, Thang SP, Akhurst T, et al. LutPSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): A single-centre, single-arm, phase 2 study. Lancet Oncol 2018;19:825-33.
31. George DJ, Saroor O, Miller K, Saad F, Tombal B, Kalinovsky J, et al. Treatment patterns and outcomes in patients with metastatic castration-resistant prostate cancer in a real-world clinical practice setting in the United States. Clin Genitourin Cancer 2020;18:284-94.
32. Akaza H, Procopio G, Pempamonnont C, Facchini G, Fava S, Wheatley D, et al. Metastatic castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy: Treatment Patterns From the PROXIMA Prospective Registry. J Glob Oncol 2018;4:1-12.
33. Clarke NW, Santis MD, Costello AJ, Chang YH, Pickles T, Pompeo AC, et al. Global treatment patterns for late-stage prostate cancer: Updated results from ASPIRE-PCA. Ann Oncol 2016;27:n253.
34. Mukherji D, Youssef B, Dagher C, El-Hajj A, Nasr R, Geara F, et al. Management of patients with high-risk and advanced prostate cancer in the Middle East: Resource-stratified consensus recommendations. World J Urol 2020;38:681-93.
35. Reichard CA, Hoffman KE, Tang C, Williams SB, Allen PK, Achim MF, et al. Radical prostatectomy or radiotherapy for high- and very high-risk prostate cancer: A multidisciplinary prostate cancer clinic experience of patients eligible for either treatment. BJU Int 2019;124:811-9.
36. Gomella LG, Lin J, Hoffman-Censtis J, Dugan P, Guiles F, Lallas CD, et al. Enhancing prostate cancer care through the multidisciplinary clinic approach: A 15-year experience. J Oncol Pract 2010;6:e5-10.
37. Soukup T, Lamb BW, Arora S, Darzi A, Sevadal N, Green JS. Successful strategies in implementing a multidisciplinary team working in the care of patients with cancer: An overview and synthesis of the available literature. J Multidiscip Healt 2018;11:49-61.
38. Hoffman KE, Madsen LT, Levy J, Petaway C, Pisters L, Choi S, et al. Prostate cancer treatment selection after counseling in a multidisciplinary prostate cancer clinic. Int J Radiat Oncol Bio Phys 2011;81:S563-4.
39. Nazim SM, Fawzy M, Bach C, Ather MH. Multi-disciplinary and shared decision-making approach in the management of organ-confined prostate cancer. Arab J Urol 2018;16:367-77.
40. Hurwitz L, Cullen J, Elsamamoudi S, Kim DJ, Hudak J, Colston M, et al. A prospective cohort study of treatment decision-making for prostate cancer following participation in a multidisciplinary clinic. Urol Oncol 2016;34:233.e17-25.
41. Brown B, Young J, Smith DP, Kneebone AB, Brooks AJ, Egger S, et al. A multidisciplinary team-oriented intervention to increase guideline recommended care for high-risk prostate cancer: A stepped-wedge cluster randomised implementation trial. Implement Sci 2018;13:43.
42. Colasante A, Augurio A, Basilio R, Cotroneo AR, Di Sciascio MB, Gaspari G, et al. A multidisciplinary group for prostate cancer management: A single institution experience. Oncol Lett 2018;15:1823-8.
43. Grol R, Chzeau FA, Burgers JS. Clinical practice guidelines: Towards better quality guidelines and increased international collaboration. Br J Cancer 2003;89 Suppl 1:SA-8.
44. World Health Organization. WHO Handbook for Guideline Development; 2014. Available from: http://apps.who.int/iris/bitstream/10665/145714/1/9789241548960_eng.pdf. [Last accessed on 2021 Feb 07].
45. English M, Irimu G, Nyamai R, Were F, Garner P, Opiyo N. Developing guidelines in low-income and middle-income countries: Lessons from Kenya. Arch Dis Child 2017;102:846-51.
46. Eddy DM, Adler J, Patterson B, Lucas D, Smith KA, Morris M. Individualized guidelines: The potential for increasing quality and reducing costs. Ann Intern Med 2011;154:627-34.
47. Clinical trials.gov. Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel, 2021. Report No: NCT01972217. Available from: https://clinicaltrials.gov/ct2/show/NCT01972217. [Last accessed on 2021 Feb 07].
48. Clinical trials.gov. Phase Ib/II Trial of Pembrolizumab (MK-3475) Combination Therapies in Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-365), 2021. Report No:NCT02861573. Available from: https://clinicaltrials.gov/ct2/show/NCT02861573. [Last accessed on 2021 Feb 07].
49. Clinical trials.gov. Phase 3, Randomized Open-Label Study of Pembrolizumab (MK-3475) Plus Olaparib Versus Abiraterone Acetate or Enzalutamide in Participants With Metastatic Castration-Resistant Prostate Cancer (mCRPC) Who Are Unselected for Homologous Recombination Repair Defects and Have Failed Prior Treatment With One Next-Generation Hormonal Agent (NHA) and Chemotherapy (KEYLYNK-010), 2021. Report No:NCT03834519. Available from: https://clinicaltrials.gov/ct2/show/NCT03834519. [Last accessed on 2021 Feb 07].
50. National Cancer Institute (NCI). Clinical trials.gov. Phase 1/2 Study of Combination Olaparib and Radium-223 in Men with Metastatic Castration-Resistant Prostate Cancer With Bone Metastases (COMRADE), 2021. Report No:NCT03317392. Available from: https://clinicaltrials.gov/ct2/show/NCT03317392. [Last accessed on 2021 Feb 07].
51. Hussain M. Clinica trials.gov. Randomized Phase II Trial of Abiraterone, Olaparib, or Abiraterone+Olaparib in Patients with Metastatic Castration-Resistant Prostate Cancer With DNA Repair Defects, April, 2019. Report No: NCT03012321. Available from: https://clinicaltrials.gov/ct2/show/NCT03012321.
52. Hegemann M, Stenzl A, Bedke J, Chi KN, Black PC, Todenhöfer T. Liquid biopsy: Ready to guide therapy in advanced prostate cancer? BJU Int 2016;118:855-63.

53. Chi KN, Mukherjee S, Saad F, Winquist E, Ong M, Kolinsky MP, et al. Prostate cancer biomarker enrichment and treatment selection (PC-BETS) study: A Canadian cancer trials group phase II umbrella trial for metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2020;38:5551.

54. Van Booven DJ, Kuchakulla M, Pai R, Frech FS, Ramasahayam R, Reddy P, et al. A systematic review of artificial intelligence in prostate cancer. Res Rep Urol 2021;13:31-9.

55. Goldenberg SL, Nir G, Salcudean SE. A new era: Artificial intelligence and machine learning in prostate cancer. Nat Rev Urol 2019;16:391-403.