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Review Article

Management of Patients with Nonmetastatic Castration-Resistant Prostate Cancer: Recommendations of a Multidisciplinary Panel of Experts from South America

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Most prostate cancer patients who undergo androgen-deprivation therapy or orchiectomy will eventually develop castration-resistant prostate cancer (CRPC), often preceded by a nonmetastatic CRPC state known as M0CRPC. The recent development of second-generation antiandrogens provides clinicians with efficacious and safe treatments for M0CRPC. However, the complexity of these patients, who typically have to deal with underlying comorbidities and polypharmacy, often challenges therapeutic decisions in this setting. The recent development of novel imaging techniques also provides clinicians with tools for detecting metastases with high sensitivity and specificity. However, the lack of evidence on the early detection of metastases and the corresponding impact on therapeutic decisions makes these techniques a double-edged sword that must be managed appropriately. Here, we present the expert view of the rapidly evolving concept of M0CRPC and provide recommendations for the identification of these patients, the appropriate use of the emerging imaging modalities, and patients' management, particularly considering their clinical complexity and the recent development of next-generation antiandrogens.

1. Introduction

Prostate cancer is the second most frequently diagnosed cancer in men, accounting for 15% of all cancers diagnosed worldwide [1]. In Colombia, prostate cancer is the second leading cause of death due to malignancies in men, and its incidence has shown an increasing trend over the last decades [2]. In patients with advanced disease, androgen-deprivation therapy (ADT) or orchiectomy induces an initial regression of the disease. However, nearly all patients will eventually develop castration-resistant prostate cancer (CRPC), with 34–60% of them progressing towards a metastatic disease within five years following CRPC state [3].

The transition from nonmetastatic to metastatic disease is rather heterogeneous and encompasses different progression profiles. Nevertheless, many patients will experience a disease state known as nonmetastatic CRPC (nmCRPC) or M0CRPC state, defined by rising PSA levels despite castrate levels of testosterone and absence of detectable metastases on conventional imaging techniques (e.g., bone scintigraphy and computed tomography of the chest and abdomen) [4].

The primary therapeutic goal in patients with M0CRPC is the delay of metastasis formation, which is expected to increase their overall survival and quality of life. The recent approval of three novel (second-generation) androgen

receptor antagonists (i.e., apalutamide, enzalutamide, and darolutamide) with favorable safety profile and proven efficacy in delaying metastasis in patients with M0CRPC has remarkably changed the therapeutic landscape of this state [5–7]. However, clinical evidence regarding patients' profile that is better suited for each agent is scarce, and clinicians have limited information for choosing the best therapeutic option in the complex and often multimorbid scenario of M0CRPC.

The pivotal trials of the three second-generation antiandrogens included patients without evidence of metastatic disease in conventional imaging techniques, which are currently recommended for the surveillance of M0CRPC patients. However, in the recent years, novel positron emission tomography (PET) radiotracers have become available for detecting metastases in patients with prostate cancer. Among them, ^{68}gallium-labeled ligands of the prostate-specific membrane antigen (PSMA) (^{68}Ga-PSMA) provide early detection of metastasis in patients with biochemically recurrent hormone-sensitive prostate cancer [8]. While providing clinicians with higher accuracy in the diagnosis of metastatic disease, the advent of next-generation imaging modalities such as ^{68}Ga-PSMA has raised concerns about the definition of the M0CRPC state, a concept built upon a bulk of evidence based on conventional imaging techniques [9]. The therapeutic attitude is driven by the results of the three aforementioned phase 3 clinical trials.

In this study, we present the expert view of the rapidly evolving concept of M0CRPC and provide recommendations for the identification of these patients, the appropriate use of the emerging imaging modalities, and patients' management, particularly considering their clinical complexity and the recent development of next-generation antiandrogens. The recommendations presented are based on a thorough review of the literature and the conclusions drawn by the authors from two consecutive focus group discussion.

2. Consensus Development

This document was developed using a focus group approach for reaching consensus regarding the items of interest and the expert recommendations on these items. Owing to the COVID-19 health emergency and the distance between experts' locations (deliberately heterogeneous to capture the routine practice across the territory), all meetings were held online. Two consecutive meetings were foreseen at the project start. The first meeting, held on July 03, 2020, was aimed at identifying the main topics to be addressed regarding the routine practice of patients with nmCRPC. Based on this list of contents, a state-of-art document that summarized the available information in the literature was prepared and distributed among experts. In a second meeting, held on September 10, 2020, the experts discussed and agreed on the list of recommendations regarding the preselected topics, which were based on the literature evidence and their experience in routine practice. The output of the second meeting, alongside the state-of-art of nmCRPC, was used to prepare a first manuscript draft, which was subsequently revised by all co-authors.

3. Recommendations

3.1. Diagnosis. CRPC is primarily diagnosed by a progressive increase of PSA serum concentration despite castrate levels of testosterone; the absence of metastatic lesions in conventional imaging techniques is necessary to confirm the M0 or nonmetastatic state [4, 10]. The type of image to be chosen to rule out metastasis is at the physician's discretion; nevertheless, conventional imaging techniques such as bone scintigraphy, computed tomography, and magnetic resonance are currently considered the modality of choice [2].

Novel (also referred to as next-generation) imaging techniques have shown good performance in identifying the presence of metastasis, irrespective of the doubling time of PSA (lower/higher than 10 months) or the Gleason score (lower/higher than 8) [11, 12] (Table 1). One of the most remarkable examples is ^{68}Ga-PSMA-11 PET, which showed a high positive predictive value for detecting metastases in patients with biochemically recurrent prostate cancer, with increasingly higher detection rates as PSA concentrations rise [8, 13].

However, observational studies with population profiles mirroring those of the pivotal trials of second-generation antiandrogens found that up to 98% of patients classified as nmCRPC using conventional imaging techniques had positive results on PSMA-PET scans [12, 14]. This finding suggests that therapy with second-generation antiandrogen should not be ruled out in patients with metastatic disease on PSMA-PET, but staged as M0 on conventional imaging techniques [12]. Accordingly, most guidelines on prostate cancer—including those of the Colombian Society of Urology [2]—highlight the importance of choosing imaging techniques based on their usefulness on further therapeutic decisions. The fact that current evidence on the efficacy and safety of second-generation antiandrogens rely on conventional imaging techniques [5–7] discourages the use of next-generation imaging modalities for making therapeutic decisions in the M0CRPC setting. Box 1 summarizes the expert recommendations regarding the diagnosis of M0CRPC.

3.2. Treatment. Before 2018, therapeutic options for the M0CRPC scenario were limited to observation and treatment with first-generation androgen receptor inhibitors, such as bicalutamide or flutamide, estrogens, or ketoconazole; however, none of these improved patients' survival [15]. The recent development of second-generation antiandrogens apalutamide [6], enzalutamide [7], and darolutamide [5] has considerably shifted the therapeutic landscape of M0CRPC. All three drugs showed efficacy in delaying the occurrence of metastasis in M0CRPC. Furthermore, although data in long-term use are still limited, evidence available so far suggests a class-related overall survival benefit [16, 17].

Table 1: Diagnostic performance of novel imaging techniques.

	Sensitivity (95% CI)	Specificity (95% CI)
PET^{11}C-choline	85% (79–89)	88% (73–95)
PET^{18}F-fluciclovine	87% (80–92)	66% (56–75)
PET^{68}Ga-PMSA PET/CT	86% (37–98)	86% (3–100)

CI, confidence interval; PET, positron emission tomography; PMSA, prostate-specific membrane antigen. Adapted from Gupta et al. [4].

(i) Conventional imaging techniques (e.g., bone scintigraphy and computed tomography of the chest and abdomen) should remain the gold standard for staging and driving therapeutic decisions in patients with M0CRPC
(ii) Current guidance on the treatment of patients with M0CRPC does not allow making evidence-based therapeutic decisions in patients with metastasis found in exams with next-generation imaging modalities such as PSMA-PET scans that cannot be seen in conventional imaging techniques
(iii) Although novel imaging techniques have higher sensitivity and specificity than conventional ones, there is no evidence indicating that early detection of relapse and the corresponding change in patients' management improve survival of these patients
(iv) Novel imaging techniques should be used for locating the disease in patients with biochemical relapse before salvage surgery or radiotherapy

Box 1: Recommendations regarding the diagnosis of M0CRPC.

The heterogeneity of the M0CRPC state challenges making decisions regarding the adequate time to start therapy with second-generation antiandrogens. Current FDA recommendations for the use of these drugs as first-line therapy for M0CRPC do not establish a risk threshold based on the doubling time of PSA values to start therapy [18]. However, the pivotal trials of the three second-generation antiandrogens included patient cohorts with PSA doubling times of 10 months or less [5–7]. Subanalyses of time to metastasis in the subgroup of patients with PSA doubling times below 6 months suggest that these treatments remain efficacious in patients at higher risk.

Owing to the recent development of second-generation antiandrogens, comparative information regarding their effectiveness is still scarce. Post hoc analyses of the pivotal trials suggest similar efficacy of the three agents [19–21]. However, the lower permeability of the blood-brain barrier for darolutamide might result in a better safety profile, particularly regarding adverse events associated with the central nervous system. Hence, in the absence of more detailed information regarding the relative efficacy of second-generation antiandrogens, the safety profile and quality of life associated with therapy might drive prescription behaviors in some patients [22].

Antiandrogen therapies for M0CRPC typically coexist with concomitant treatments for diseases with high prevalence among older people, including cardiovascular, neurological, and respiratory diseases [23]. Hence, clinicians should take into account the contribution of treatments for M0CRPC to the therapeutic burden of prostate cancer patients when making decisions in this setting. Taken together, the idiosyncratic features of the M0CRPC state encourage a comprehensive appraisal of the therapeutic approach that better suits each patient. Box 2 summarizes the experts' recommendations regarding the treatment of patients with M0CRPC.

3.3. Management of Adverse Events. Treatment with second-generation antiandrogens is considered overall safe and well-tolerated, particularly bearing in mind that patients in the M0 stage are usually asymptomatic. In the three pivotal trials of these drugs, the most frequent treatment-related adverse event was fatigue, which occurred in 30%, 33%, and 16% of patients treated with apalutamide, enzalutamide, and darolutamide, respectively [5–7]. The different methodologies used for reporting adverse events in the three trials preclude direct comparisons regarding the relative frequency of adverse events between second-generation AR inhibitors [24]. Of note, the reduced permeability of the blood-brain barrier to darolutamide encouraged the allowance of 12 patients with a history of seizures in the ARAMIS trial, whereas these patients were excluded from the PROSPER and SARTAN trials. Regardless of the selection criteria, the incidence of seizure episodes in the three trials was lower than 1%.

Besides fatigue and seizures, the effects of second-generation AR inhibitors on the central nervous system might increase the risk of cognitive impairment or decline in these patients. Again, the way these events were reported in the pivotal trials is highly heterogeneous and precludes direct comparisons between the drugs (e.g., "mental impairment," "memory impairment," "cognitive disorder," and "change in mental status") [18]. However, the inaccessibility of darolutamide to the central nervous system could minimize the risk of treatment-related cognitive disorders. Irrespective of the adverse events profile of each second-generation antiandrogen, clinicians should be watchful of their possible effects on the mental health of patients with M0CRPC and not underestimate signs suspicious of cognitive decline (Box 3).

3.4. Drug-Drug Interactions. The frequency of prostate cancer has a remarkable age increasing trend, reaching a

(i) Patients with M0CRPC with PSA doubling times ≤10 months are those that can benefit most from second-generation antiandrogens
(ii) In M0CRPC patients with PSA doubling times >10 months, we recommend watchful waiting and two to three yearly determinations of PSA levels and a multidisciplinary approach to establish therapy
(iii) A comprehensive assessment with validated geriatric and comorbidity burden scales should precede the establishment of therapy in patients with M0CRPC
(iv) Extending metastasis-free survival, prospectively associated with increased overall survival, is considered a suitable therapeutic goal in the routine management of patients with M0CRPC

Box 2: Recommendations regarding the treatment of M0CRPC.

(i) Second-generation antiandrogens are considered overall safe, provided that treatment is prescribed according to current indications
(ii) Signs of cognitive decline should be proactively watched out for during treatment with second-generation antiandrogens
(iii) The inclusion of specific questionnaires for monitoring cognitive function in M0CRPC patients treated with second-generation antiandrogens may be useful to enhance the safety of these therapies

Box 3: Recommendations regarding adverse events in the treatment of patients with M0CRPC.

prevalence of 59% (95% CI: 48–71%) among men older than 79 years [25]. Consequently, patients in the M0CRPC stage are typically older and have to deal with a list of comorbidities, particularly cardiovascular and metabolic [23]. The comorbidity burden of these patients entails a polypharmacy scenario, which increases the risk of drug-drug interactions. Most of these interactions occur due to an inhibitory effect of a common metabolic pathway and may result in an abnormal and potentially harmful increase of plasma levels in some drugs.

Owing to the novelty of second-generation antiandrogens currently used in the management of M0CPRC patients, phase IV data regarding drug-drug interactions are scarce, therefore having to rely on in vitro studies and post hoc analyses of the pivotal trials. In vitro studies showed that both enzalutamide and apalutamide induce cytochrome P450 (CYP) 3A4, thus potentially reducing the plasma concentration of drugs metabolized through this CYP [15, 26]. Conversely, darolutamide showed no inhibitory activity on either CYP or glycoprotein P (P-gp), and therefore, no metabolic interactions via these two enzymes are expected. These in vitro findings were consistent with the results of a post hoc analysis of the ARAMIS trial, which did not find relevant interactions with other drugs metabolized via CYP [27].

Regardless of the nature of the interaction, the list of drugs with potential interactions provided in the summary of product characteristics of second-generation antiandrogens is extensive. Although all of them should be considered when prescribing treatments for M0CRPC, particular attention should be given to those drugs frequently included in the medication plan of these patients. Our recommendations in this regard are summarized in Box 4.

3.5. Quality of Life. Both, prostate cancer and treatments associated with this disease, have a relevant impact on the quality of life (QoL) of patients and caregivers [2]. Thus, although patients in the M0CRPC stage typically present no symptoms associated with the disease, maintaining (i.e., preventing worsening of) their quality of life at the time of M0CRPC diagnosis should be considered as a therapeutic goal. According to an international survey conducted in 2018, more than half of patients with advanced prostate cancer—and their caregivers—felt challenged when managing the side effects associated with the treatment [28]. In addition to the common effects of prostate cancer and its management on quality of life, patients in the M0CRPC state often have to deal with rising values of PSA concentration, which have been associated with a dose-dependent increased risk of experiencing distress [29].

The pivotal clinical trials of second-generation antiandrogens found no changes in QoL during treatment; however, the tools for assessing it were rather heterogeneous, thus challenging direct comparisons (EQ-5D-3 L and FACT-P in the SPARTAN trial [6], EQ-5D-5 L and QLQ-PR25 in the PROSPER trial [7], and FACT-P, EQ-5D-3 L, and EORTC-QLQ-PR25 in the ARAMIS trial [5]). The overall acceptable QoL of M0CRPC patients reported in randomized-controlled trials seems to mirror that observed in routine practice. Conversely, the metastatic state of CRPC patients is associated with a rapid decline of patients' QoL. Therefore, delaying the advent of metastasis seems to be a mainstay for maintaining patients' QoL, rather than thorough monitoring of QoL, which is challenged in day-to-day practice by the length of validated scales. The adequate management of adverse events associated with M0CRPC therapy will also contribute to maintaining QoL of these patients (Box 5). To date, various tools have been validated for measuring patient-reported experiences and outcomes in routine care [30–32].

Owing to limited phase IV clinical data on second-generation antiandrogens and the multimorbid profile of patients with M0CRPC, clinicians should carefully review potential drug-to-drug interactions when prescribing therapies in this setting
Particular attention should be given to drugs frequently present in the therapeutic plan of M0CRPC patients and to suspected or confirmed interactions with some second-generation antiandrogens

Hypertension

Diltiazem (CYP3A4 inhibitor)
Carvedilol, verapamil (P-gp inhibitor)

Dyslipidemia

Lovastatin, simvastatin (CYP3A4 substrate)
Rosuvastatin (BCRP substrate)
Gemfibrozil (CYP2C8 inhibitor)

Cardiac disease

Clopidogrel (CYP2C8 inhibitor)
Amiodarone, carvedilol, verapamil (P-gp inhibitor)
Amiodarone, diltiazem (CYP3A4 inhibitor)
Dabigatran, digoxin (P-gp substrate)
Warfarin (CYP2C9 substrate)
Rivaroxaban (CYP3A substrate)

Pain management in CRPC

Oxycodone (CYP3A4 substrate)
Fentanyl (CYP3A4 substrate)
Midazolam (CYP3A4 substrate)

Box 4: Recommendations regarding the management of drug-drug interactions in patients with M0CRPC.

(i) Treatment of patients with M0CRPC should aim at delaying the decline of their quality of life, which is likely achieved by delaying the occurrence of metastases
(ii) The adequate management of adverse events is a mainstay for preventing a therapy-driven decline in quality of life
(iii) Whenever possible, the patients' quality of life should be assessed in routine practice. This assessment should rely on validated patient-reported experience measures (PREMs) or validated patient-reported outcome measures (PROMs).

Box 5: Recommendations regarding the management of quality of life in patients with M0CRPC.

4. Concluding Remarks

The M0CRPC stage is a heterogeneous and rapidly evolving scenario. The cumulative evidence and experience with second-generation antiandrogens and next-generation imaging modalities is shifting the way clinicians manage patients with CRPC. While these advances undoubtedly enhance treatment outcomes, the limited guidance regarding some aspects of patient management adds to the complexity of making therapeutic decisions in the M0CRPC setting. In this manuscript, we captured the key—and often controversial—features of M0CRPC management that clinicians face in their day-to-day practice. Between-country differences regarding drug costs and reimbursement policies, the structure of the healthcare system, and the uneven availability of imaging modalities encourage the development of country-specific recommendations that may complement official guidelines. Our recommendations are particularly suitable for countries with limited guidance on the management of M0CRPC patients and expanding deployment of novel imaging techniques in the urology setting.

Data Availability

No data were used to support this study.

Disclosure

The funder was not involved in drawing conclusions nor manuscript writing/review.

Conflicts of Interest

RM has received honoraria as speaker from Sanofi, Astellas, Bayer, Janssen, and as an advisory board member from Sanofi, Astellas, Bayer, Janssen. RB has received honoraria as speaker from Bristol Myers Squibb, MSD, Pfizer, Roche, Astra Zeneca, and Merck Sharp and Dohme, and as advisory

board member from Bristol Myers Squibb, MSD, Merck Sharp and Dohme, Novartis, Roche, Astra Zeneca, and Pfizer; he has also received research funding from MSD, Bristol Myers Squibb, Roche, and Novartis. JJC has received honoraria as speaker from Bayer, Janssen, Sanofi, and Astra Zeneca, and received research funding from Bayer, Janssen, and Bristol Myers Squibb. JR has received honoraria as advisory board member and speaker from Bayer. DR has received honoraria as speaker from Biopas, Bristol Myers Squibb, Janssen, Astra Zeneca, and MSD. NV has served as consultor for Astra Zeneca, Ferring, Merck Sharp and Dohme, Janssen, Bayer, Bristol Myers Squibb, Gen-Cell, Dr Reddy's, and Sanofi, and has received honoraria as speaker from Tecnoquimicas, Merck Sharp and Dohme, Janssen, Bayer, Sanofi, Astellas, Biopas, Astra Zeneca, Tecnofarma, Ferring, Novartis, and Amgen.

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References

[1] J. Ferlay, I. Soerjomataram, R. Dikshit et al., "Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012," *International Journal of Cancer*, vol. 136, no. 5, pp. E359–E386, 2015.

[2] Sistema General de Seguridad Social en Salud – Colombia, *Guía de práctica clínica (GPC) para la detección temprana, diagnóstico, tratamiento, seguimiento y rehabilitación del cáncer de próstata [Internet]*, Guía para profesionales de la salud, Colombia, Available from: https://www.minsalud.gov.co/sites/rid/Lists/BibliotecaDigital/RIDE/INEC/IETS/Cancer-prostata-fina-Prof-Salud.pdf, 2013.

[3] H. I. Scher, K. Solo, J. Valant, M. B. Todd, and M. Mehra, "Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model," *PLoS One*, S. Filleur, Ed., vol. 10, no. 10, Article ID e0139440, 2015.

[4] R. Gupta, I. Y. Sheng, P. C. Barata, and J. A. Garcia, "Non-metastatic castration-resistant prostate cancer: current status and future directions," *Expert Review of Anticancer Therapy*, vol. 20, no. 6, pp. 513–522, 2020.

[5] K. Fizazi, N. Shore, T. L. Tammela et al., "Darolutamide in nonmetastatic, castration-resistant prostate cancer," *New England Journal of Medicine*, vol. 380, no. 13, pp. 1235–1246, 2019.

[6] M. R. Smith, F Saad, S Chowdhury et al., "Apalutamide treatment and metastasis-free survival in prostate cancer," *New England Journal of Medicine*, vol. 378, no. 15, pp. 1408–1418, 2018.

[7] M. Hussain, K. Fizazi, F. Saad et al., "Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer," *New England Journal of Medicine*, vol. 378, no. 26, pp. 2465–2474, 2018.

[8] W. P. Fendler, J. Calais, M. Eiber et al., "Assessment of 68Ga-PSMA-11 PET accuracy in localizing recurrent prostate cancer," *JAMA Oncology*, vol. 5, no. 6, pp. 856–863, 2019.

[9] C. S. Higano, "Does nonmetastatic castration-resistant prostate cancer still exist?" *Nature Reviews Clinical Oncology*, vol. 15, no. 6, pp. 350-351, 2018.

[10] N. Mottet, *EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer*, vol. 75, European Association of Urology, Available from: https://uroweb.org/wp-content/uploads/EAU-EANM-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Cancer-2019-1.pdf, , pp. 889-890, 2019.

[11] A. Fourquet, C Aveline, O Cussenot et al., "68Ga-PSMA-11 PET/CT in restaging castration-resistant nonmetastatic prostate cancer: detection rate, impact on patients' disease management and adequacy of impact," *Scientific Reports*, vol. 10, no. 1, pp. 2104–2109, 2020.

[12] W. P. Fendler, M. Weber, A. Iravani et al., "Prostate-specific membrane antigen ligand positron emission tomography in men with nonmetastatic castration-resistant prostate cancer," *Clinical Cancer Research*, vol. 25, no. 24, pp. 7448–7454, 2019.

[13] M. S. Hofman, N Lawrentschuk, R. J Francis et al., "Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study," *Lancet*, vol. 395, no. 10231, pp. 1208–1216, 2020.

[14] E. N. Akdemir, M. Tuncel, F. Akyol et al., "68Ga-labelled PSMA ligand HBED-CC PET/CT imaging in patients with recurrent prostate cancer," *World Journal of Urology*, vol. 37, no. 5, pp. 813–821, 2019.

[15] I. Heidegger, M. P. Brandt, and M. M. Heck, "Treatment of non-metastatic castration resistant prostate cancer in 2020: what is the best?" *Urologic Oncology: Seminars and Original Investigations*, vol. 38, no. 4, pp. 129–136, 2020.

[16] B. Bhindi and R. J. Karnes, "Novel nonsteroidal antiandrogens and overall survival in nonmetastatic castration-resistant prostate cancer," *European Urology*, vol. 74, no. 4, pp. 534-535, 2018.

[17] E. J. Small, F. Saad, S. Chowdhury et al., "Apalutamide and overall survival in non-metastatic castration-resistant prostate cancer," *Annals of Oncology*, vol. 30, no. 11, pp. 1813–1820, 2019.

[18] C. Higano, "Enzalutamide, apalutamide, or darolutamide: are apples or bananas best for patients?" *Nature Reviews Urology*, vol. 16, no. 6, pp. 334-335, 2019.

[19] G. Roviello, M. R. Gatta Michelet, A. D'Angelo, S. Nobili, and E. Mini, "Role of novel hormonal therapies in the management of non-metastatic castration-resistant prostate cancer: a literature-based meta-analysis of randomized trials," *Clinical and Translational Oncology*, vol. 22, no. 7, pp. 1033–1039, 2020.

[20] A. E. Hird, "A systematic review and network meta-analysis of novel androgen receptor inhibitors in non-metastatic castration-resistant prostate cancer," *Clinical Genitourinary Cancer*, pp. 1–8, 2020.

[21] J. Kumar, "Comparative efficacy of apalutamidedarolutamide and enzalutamidefor treatment of nonmetastatic castrate-resistant prostate cancer: asystematic review and network meta-analysis," *Urologic Oncology: Seminars and Original Investigations*, pp. 1–9, 2020.

[22] S. Srinivas, A. F. Mohamed, S. Appukkuttan et al., "Physician preferences for non-metastatic castration-resistant prostate cancer treatment," *BMC Urology*, vol. 20, no. 1, p. 73, 2020.

[23] H. Li, E Hodgson, L Watson, A Shukla, and J. J Nelson, "Comorbidities and concomitant medication use in men with prostate cancer or high levels of PSA compared to matched controls: a GPRD analysis," *Journal of cancer epidemiology*, vol. 2012, Article ID 291704, 13 pages, 2012.

[24] J. Z. Drago, P. W. Kantoff, and K. H. Stopsack, "Adverse event profiles of apalutamide, enzalutamide, and darolutamide in SPARTAN, PROSPER, and ARAMIS: how confident are we about which drug is safest?" *Journal of Clinical Oncology*, vol. 38, no. 6_suppl, p. 318, 2020.

[25] K. J. L. Bell, C. Del Mar, G. Wright, J. Dickinson, and P. Glasziou, "Prevalence of incidental prostate cancer: a systematic review of autopsy studies," *International Journal of Cancer*, vol. 137, no. 7, pp. 1749–1757, 2015.

[26] H. Westdorp, E. J. M. Kuip, I. M. van Oort, C. Kramers, W. R. Gerritsen, and K. C. P. Vissers, "Difficulties in pain management using oxycodone and fentanyl in enzalutamide-treated patients with advanced prostate cancer," *Journal of Pain and Symptom Management*, vol. 55, no. 4, pp. e6–e8, 2018.

[27] N. Shore, C. Zurth, R. Fricke et al., "Evaluation of clinically relevant drug-drug interactions and population pharmacokinetics of darolutamide in patients with nonmetastatic castration-resistant prostate cancer: results of pre-specified and post hoc analyses of the phase III ARAMIS trial," *Targeted Oncology*, vol. 14, no. 5, pp. 527–539, 2019.

[28] L. Drudge-Coates, W. K. Oh, B. Tombal et al., "Recognizing symptom burden in advanced prostate cancer: a global patient and caregiver survey," *Clinical Genitourinary Cancer*, vol. 16, no. 2, pp. e411–e419, 2018.

[29] U. Rönningås, P Fransson, M Holm, and A Wennman-Larsen, "Prostate-specific antigen (PSA) and distress: - a cross-sectional nationwide survey in men with prostate cancer in Sweden," *BMC Urology*, vol. 19, no. 1, pp. 66–68, 2019.

[30] K. Fizazi, *Impact of Darolutamide (DARO) on Pain and Quality of Life (QoL) in Patients (Pts) with Nonmetastatic Castrate-Resistant Prostate Cancer (nmCRPC)*, American Society of Clinical Oncology, Virginia, VA, USA, 2019.

[31] F. Saad, D. Cella, E. Basch et al., "Effect of apalutamide on health-related quality of life in patients with non-metastatic castration-resistant prostate cancer: an analysis of the SPARTAN randomised, placebo-controlled, phase 3 trial," *The Lancet Oncology*, vol. 19, no. 10, pp. 1404–1416, 2018.

[32] B. Tombal, F. Saad, D. Penson et al., "Patient-reported outcomes following enzalutamide or placebo in men with non-metastatic, castration-resistant prostate cancer (PROSPER): a multicentre, randomised, double-blind, phase 3 trial," *The Lancet Oncology*, vol. 20, no. 4, pp. 556–569, 2019.