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Systematic or Meta-analysis Studies

Management of advanced prostate cancer: A systematic review of existing guidelines and recommendations

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ABSTRACT

The therapeutic landscape of advanced prostate cancer is continuously changing under the light of new available treatment options and the improved understanding of the molecular characteristics of the disease. The lack of high quality evidence regarding the sequencing of these treatments along with the earlier implementation of these therapeutic approaches during the course of the disease have created issues of dispute regarding the optimal treatment of patients with advanced prostate cancer. Therefore, we conducted a systematic review of the existing guidelines and recent randomized trials not included in these guidelines, and present a comprehensive analysis of the available treatment options in each of the stages of advanced prostate cancer, as well as the supportive treatments available for these patients.

Introduction

Prostate cancer (PC) is the most frequently diagnosed neoplasia among men in the Western countries and the third more frequent cause of death [1,2]. In Greece, it represents the second most frequently diagnosed neoplasia and cause of death among men, behind only of lung carcinomas [1]. Prostate cancer epidemiology has changed dramatically during the last two decades as a result of the incorporation of PSA testing as a screening method for prostate cancer in males aged over 50. This led to a dramatic increase in the prostate cancer incidence in mid-90s [3], which was followed by a gradual decline [4], after the publication of two large screening trials [5,6] not supporting its unselected application. Despite increase in early diagnosis, the number of patients diagnosed with metastatic disease or progressing to the incurable castration resistant state has not altered significantly [7].

In parallel to the screening efforts, there has been a significant improvement in therapy both of localized and metastatic disease in the last decade. Currently six new agents are available for the treatment of metastatic prostate cancer (mPC) [8–13] and our therapeutic armamentarium is continuously being enriched. Molecular characterization of prostate carcinomas [14,15] has identified novel targets for future treatments, while better understanding of the natural history of the disease has led to the earlier introduction of efficacious treatments, associated with survival benefit [16–19].

Under this perspective, several national and international urological and medical oncology societies and associations have published guidelines on metastatic prostate cancer management [20–28]. Nevertheless, their utility in everyday practice may be associated with a variety of limitations. Practical issues and a difficulty for clinicians in the community to follow all the new available information have been suggested as possible causes. In addition, issues associated with the development of guidelines may limit adherence in everyday practice. For example, variation in the definition of the levels of evidence (LoE) and grading of recommendations (GoR) result in differences in the strength of recommendations regarding the various treatment modalities. This variation underlines the considerable heterogeneity in the development and reporting of guidelines. Our group also reported similar findings for guidelines on bladder and renal cancer [29,30].

Apart from their wide and timely distribution, the identification of common statements as well as discrepancies among existing guidelines might be of further value. Areas of agreement represent recommendations that should be applied in order to improve the management of prostate cancer patients, and this sets clear targets for our efforts at local, national, and international level. In contrast, issues associated with uncertainty represent the targets for future research and shift the balance from evidence-based medicine to justified clinical practice

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based on personal experience and regional conditions and expertise. This need is highly relevant in a rapidly evolving field, such as the treatment of mPC. We hereby present the results of a systematic review of the current mPC guidelines and the critical evaluation of the evidence produced by this review.

Methods

Search strategy and data abstraction

A systematic review was performed in accordance with the PRISMA guidelines [31]. Eligible articles were identified by a search of MEDLINE bibliographical database for the period from January 1, 2012 up to May 31, 2018. The search strategy included the following keywords: (recommendation [ti] OR recommendations [ti] OR consensus [ti] OR guideline [ti] OR guidelines [ti] OR consultation [ti]) AND ((prostate OR prostatic) AND (carcinoma OR carcinomas OR cancer OR cancers OR neoplasm OR neoplasms OR adenocarcinoma) AND (metastatic OR resistant OR refractory)).

All studies providing Clinical Practice Guidelines (CPGs)/Expert recommendations regarding the treatment of prostate metastatic carcinoma were considered eligible for this systematic review. Language restrictions were applied (only articles in English, French and Deutsch were considered eligible). Two investigators (FZ and AD), working independently, searched the literature and extracted data from each eligible study. In addition, we checked all the references of retrieved articles, in order to identify additional potentially eligible articles. If a group, association or society produced updated guidelines, only the most recent study was included. CPGs exclusively on pathology, imaging, quality of life, palliative therapies or guidelines for patients were not considered eligible for this analysis. Finally, full length recommendations, if available, were also cross checked against the relevant papers in order to retrieve information not included in the papers. Respective guideline manuals were also reviewed if necessary to clarify methodological or ethical issues.

Data synthesis and development of a therapeutic algorithm

Following the completion of identifying eligible papers, we also reviewed literature for recent publications on randomized clinical trials (RCTs), systematic reviews on RCTs and meta-analyses of RCTs in order to take into consideration level 1 evidence not included in the published guidelines. Since the more recent guidelines had been published in 2018, we searched literature for non-included LoE 1 data published in year 2018. Finally, we synthesized available guidelines in order to produce an algorithm of management of prostate carcinoma.

Results

The search strategy retrieved 77 articles providing possibly CPGs/Expert recommendations regarding the treatment of metastatic prostate carcinoma. Of these articles, 19 were irrelevant, 34 were excluded due to restrictions (i.e, language restrictions, existence of updated publications, etc.) and 24 were considered as eligible according to our predefined inclusion criteria [20–24,26,27,32–47]. After searching the references of all reviews and remaining articles, 3 additional articles were also included [25,48,49]. Overall, 27 papers, published between 2012 and 2018 were eligible for the systematic review (Table 1). The aforementioned stages are illustrated in detail in Fig. 1.

Twenty of the 27 eligible papers were clinical practice guidelines published by national or international societies [20–28,33,36,40,42,43,45–48], while the remaining were recommendations by panels of experts [32,34,35,37–39,41,44]. Nine publications referred only to metastatic castration resistant stage of the disease [20–23,28,33,35,38,39], while the remaining referred either to prostate cancer in general or to metastatic disease.

Data synthesis

Hormone-Naïve disease

Androgen deprivation therapy. Historically, androgen deprivation therapy (ADT) either medical with the use of luteinizing hormone releasing hormone (LHRH) agonists or antagonists or surgical by bilateral orchiectomy constitute the mainstay of treatment in newly diagnosed metastatic prostate cancer. This is accepted in all publications as level I evidence despite hormonal treatment in metastatic prostate cancer is based on relative old unpowered RCTs [50]. There is no preference in the method of castration among publications. It should be noted though that patients with impending spinal cord compression would rather be treated with either a bilateral orchidectomy, or LHRH antagonists [24] in order to avoid the flare phenomenon associated with the use of LHRH agonists [51]. Bilateral orchiectomy though is recognized as the gold standard method but is associated with negative psychological impact in patients. Therefore, LHRH agonists and antagonists have replaced orchiectomy as the standard of care since they offer reversibility of castration. In a recent survey of urological practice in patients with metastatic prostate cancer, it was demonstrated that 94% of treating physicians prescribe LHRH agonists as initial treatment [40]. Furthermore, all guidelines and expert panels recognize that there is no difference in efficacy among LHRH agonists and antagonists.

Mean testosterone levels in patients subjected to bilateral orchiectomy were at 15 ng/dl. However, the acceptable level of castration in all guidelines and expert panels is defined by levels of testosterone below 50 ng/dl.

Combined androgen blockade. The addition of a non-steroidal antiandrogen (NSAA) to standard ADT was associated with minimal survival benefit and increased toxicity [52,53]. Therefore, combined androgen blockade (CAB) is either omitted from recommendations in guidelines [24,25,32] or when suggested it is considered as an alternative to ADT for selected patients [27,34,37,45].

In the contrary, there is a unanimous suggestion that anti-androgen monotherapy should not be offered for metastatic hormone sensitive disease [43].

Intermittent androgen deprivation therapy

Intermittent androgen deprivation therapy (IADT) in patients with metastatic prostatic cancer was considered an approach that could derive equal efficacy to continuous ADT and improve the quality of life of the patients. However, the largest phase III randomized clinical trial that compared intermittent and continuous ADT in metastatic prostate cancer patients [54] failed to demonstrate non-inferiority for the intermittent use of ADT. Under this perspective there is an ongoing discussion over the use of IADT in metastatic prostate cancer patients that is also reflected on the variability of recommendations among guidelines. ESMO and SEOM guidelines do not suggest IADT as an option [25,27], while NCCN and EAU guidelines as well as Japanese urological association and Brazilian recommendations suggest IADT but it is suggested as an alternative for a minority of eligible well informed patients and it is highlighted that the optimal protocol of treatment has yet to be defined [24,45,46] **(**Table 2**)**. There is a trend favoring IADT in terms of quality of life (QoL), especially regarding treatment-related side-effects, such as hot flushes, bone loss, metabolic syndrome and cardiovascular problems [55], although the latter has been challenged [56]. In some cohorts the negative impact on sexual function was less pronounced with IADT [57,58] It should be noted though that in clinical practice, the aforementioned outcomes as well as the lack of any survival benefit in mPC patients, suggest that IADT remains an option for selected well-informed patients for the majority of the treating

Table 1
List of publications included in the systematic review.

	Authors	Title	Souce/year	Society/panel
1	Basch et al. [23]	Systemic therapy in men with metastatic castration-resistant prostate cancer: American Society of Clinical Oncology and Cancer Care Ontario clinical practice guideline.	J Clin Oncol. 2014	ASCO
2	Cassinello et al. [27]	SEOM clinical guidelines for the treatment of metastatic prostate cancer.	Clin Transl Oncol. 2018	SEOM
3	Climent et al. [21]	Updated recommendations from the Spanish Oncology Genitourinary Group for the treatment of patients with metastatic castration-resistant prostate cancer.	Crit Rev Oncol Hematol. 2015	SOGG
4	Cornford et al. [24]	EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer	Eur Urol 2017	EAU-ESTRO-SIOG
5	European Association of Urology Guidelines [49]	EAU Guidelines on Prostate Cancer 2018 edition	33st annual congress of EAU in Copenhagen. ISBN/EAN: 978-94-92671-01-1.	EAU
6	Fitzpatrick et al. [39]	Optimal management of metastatic castration-resistant prostate cancer: highlights from a European Expert Consensus Panel.	Eur J Cancer. 2014	Expert
7	Gillessen et al. [37]	Management of patients with advanced prostate cancer: recommendations of the St Gallen Advanced Prostate Cancer Consensus Conference (APCCC) 2015.	Ann Oncol. 2015	Expert
8	Gillessen et al. [44]	Management of Patients with Advanced Prostate Cancer: The Report of the Advanced Prostate Cancer Consensus Conference APCCC 2017	Eur Urol 2018	Experts
9	Golabek et al. [32]	Evidence-based recommendations on androgen deprivation therapy for localized and advanced prostate cancer.	Cent European J Urol. 2016	Expert
10	Heidenreich et al.. [40]	Therapies used in prostate cancer patients by European urologists: data on indication with a focus on expectations, perceived barriers and guideline compliance related to the use of bisphosphonates.	Urol Int. 2012	EAU
11	Herden et al.. [35]	Systemic Medical Treatment in Men with Metastatic Castration-Resistant Prostate Cancer: Recommendations for Daily Routine.	Oncol Res Treat. 2015	Expert
12	López Torrecilla et al.. [36]	Uroncor consensus statement: Management of biochemical recurrence after radical radiotherapy for prostate cancer: From biochemical failure to castration resistance	Rep Pract Oncol Radiother. 2015	Uroncor
13	Lowrance et al.. [28]	Castration-Resistant Prostate Cancer: AUA Guideline Amendment 2015.	J Urol. 2016	AUA
14	Ming-Chun et al. [43]	Consensus statements on the management of metastatic prostate cancer from the Hong Kong Urological Association and Hong Kong Society of Uro-Oncology	BJU Int 2018	HKSUO
15	Mohler et al.. [26]	Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines.	J Natl Compr Canc Netw. 2012.	NCCN
16	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines). [48]	Prostate Cancer Version 2.2018	http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf, accessed on 09.05.2018.	NCCN
17	Parker et al.. [25]	Cancer of the prostate: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	Ann Oncol. 2015	ESMO
18	Ponholzer et al..[33]	Austrian recommendations on Targeted Hormone Therapy for metastatic, castration-resistant prostate cancer.	Wien Klin Wochenschr. 2016	Austrian Society of Urology and Andrology
19	Rozet et al.. [42]	CCAFU Recommendations 2017: Prostate cancer.	Prog Urol. 2018	CCAFU
20	Saad et al. [22]	The 2015 CUA-CUOG Guidelines for the management of castration-resistant prostate cancer (CRPC).	Can Urol Assoc J. 2015.	CUA
21	Sasse et al. [46]	First brazilian consensus of advanced prostate cancer: recommendations for clinical practice.	Int Br J Urol 2017	Brazilian Society of Urology
22	Singapore Cancer Network (SCAN) Genitourinary Cancer Workgroup. [20]	Singapore Cancer Network (SCAN) Guidelines for the Management of Advanced Castrate-Resistant Prostate Cancer.	Ann Acad Med Singapore. 2015	SCAN
23	Thomas et al. [34]	Advanced Prostate Cancer Consensus Conference (APCCC) 2015 in St. Gallen :Critical review of the recommendations on diagnosis and therapy of metastatic prostate cancer by a German expert panel.	Urologe A. 2016	Expert
24	Wolff et al. [40]	Drivers for change in the management of prostate cancer - guidelines and new treatment techniques.	BJU Int. 2012.	Expert
25	Woo et al. [37]	Multidisciplinary consensus: a practical guide for the integration of abiraterone into clinical practice.	Asia Pac J Clin Oncol. 2014	Expert
26	Yoshiyuki et al. [44]	Evidenced-based clinical practice guideline for prostate cancer (summary: Japanese Urological Association, 2016 edition)	Int J Urol 2017	JUA
27	Morris et al. [46]	Optimizing Anticancer Therapy in Metastatic Non-Castrate Prostate Cancer: American Society of Clinical Oncology Clinical Practice Guideline	J Clin Oncol 2018	ASCO

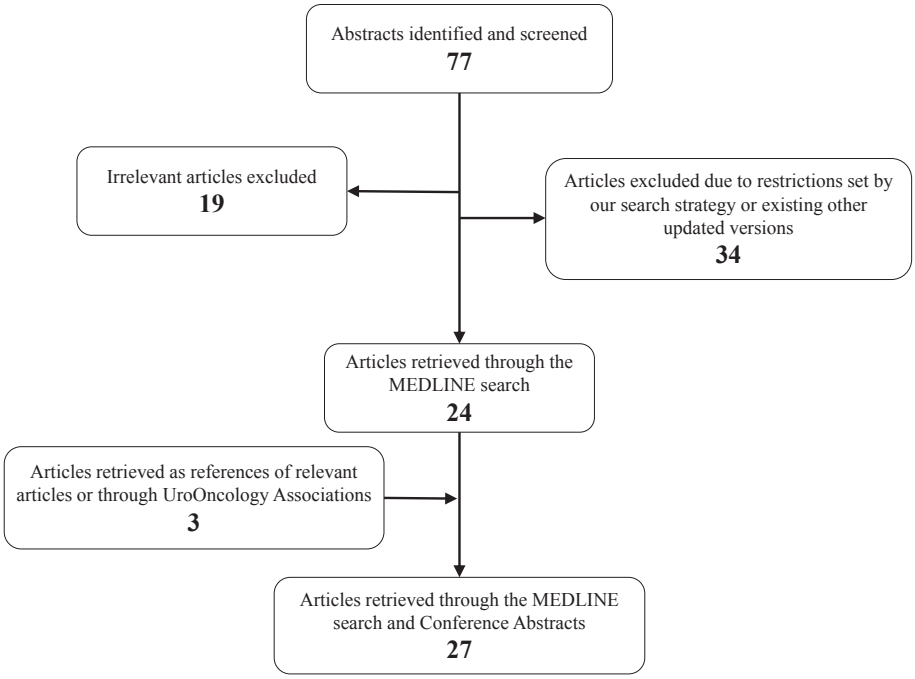

Fig. 1. Diagram depicting selection process for this systematic review.

physicians as suggested by the APCCC 2015 [37].

Docetaxel or abiraterone plus ADT

The role of CAB and IADT possesses decreasing importance in the modern management of hormone-naïve metastatic prostate cancer (mHNPC) since the presentation of randomized trials combining ADT with either docetaxel or abiraterone in this setting [16–19,59,60]. Based on these data ESMO has updated their recommendations and ADT plus either docetaxel or abiraterone plus prednisone are suggested with LoE 1A for the treatment of patients with metastatic hormone-naïve disease (eUpdate in [25]). NCCN and EAU guidelines as well as recommendations from other medical societies and expert panels suggest docetaxel plus ADT as initial treatment of metastatic hormone-naïve prostate cancer with the same LoE [43–45], as well as have incorporated ADT plus abiraterone and prednisone as treatment option for metastatic castration-naive disease [27,49]. Due to the lack of head to head comparisons between these two treatment modalities and the heterogeneity of the populations enrolled in the clinical trials there is an ongoing debate regarding the optimal selections of the patients that derive the maximal benefit from these therapies [61,62]. This is reflected in the opinions of the Experts in the APCCC2017 that voted unanimously in favor of docetaxel plus ADT in newly diagnosed mHNPC patients with high volume disease [44]. However, the panel was more sceptic for the implementation of this treatment in patients relapsing post local treatment and especially in patients with low volume disease [44]. Analogously, recently published ASCO guidelines recognize that either docetaxel plus ADT or abiraterone plus ADT should be the new standard of care only for these patients with high-volume disease [47], ASCO guidelines underline that no recommendation favoring the ADT-docetaxel treatment can be made for patients with low volume disease. On the contrary, it is suggested that ADT plus abiraterone might be considered in low volume patients, since no data exist to refute that these men may benefit [47]. Even more, recently published data from the STAMPEDE trial provide strong evidence that Abiraterone does confer OS benefit even when administered in in low volume or low-risk patients [63]. On the same issue other guidelines suggest that performance status and burden of the disease are considered as factors that should be taken into account by treating physicians prior to initiation of docetaxel-ADT combination for mHNPC disease [43].

Regarding the preference of one treatment over the other, no specific recommendation can be made in the absence of head to head comparisons. A recently presented indirect comparison suggested that PFS analysis favors ADT plus abiraterone while overall survival data ADT plus docetaxel [64]. However, in accordance to the conclusions of this study, ASCO guidelines suggest that factors as drug availability, eligibility of the patient, affordability and duration of the treatment should be taken into account when choosing optimal treatment for mHNPC patients with high volume of disease [47].

Castration resistant prostate cancer (CRPC)

Despite initial treatment, patients treated with ADT will inevitably develop resistance to ADT and progression to castration resistant disease. Castration resistant prostate cancer (CRPC) is defined by disease progression despite ADT and testosterone levels below 50 ng/dl [37,44]. The introduction of novels agents in the management of mCRPC has led to continuous revisions of the guidelines in the treatment of the disease. These guidelines are based in data produced from an era that ADT was the standard of care (SoC) in metastatic hormone naïve setting. The molecular analysis of the mCRPC disease are also based on patients from that era [14]. The introduction of docetaxel and even more abiraterone along with ADT creates a new therapeutic environment that challenges established medical practice. Under this perspective, the issues regarding the mCRPC treatment analyzed in this systematic review have taken into consideration all current updates presented.

Non-metastatic CRPC

A substantial proportion of CRPC patients, estimated around 5% will progress during ADT treatment given for biochemical failure post radical local treatments, without obvious metastatic disease according to conventional CT imaging and bone scintigraphy. No established treatment existed for these patients until recently. Within 2018 two phase III RCTs were presented comparing two novel antiandrogens (enzalutamide and apalutamide) with placebo in this population of patients. Both drugs increased significantly the time to metastatic disease while overall survival data are not yet mature [65,66]. Despite

Table 2
Summary of guidelines and recommendations for intermittent ADT in metastatic prostate cancer patients.

Guideline	Recommendation	LoE	GR	Comment
EAU	In asymptomatic M1 patients, offer intermittent treatment to highly motivated men with a major PSA response after the induction period.	1b	B	In M1 patients, follow the schedules used in published clinical trials on timing of intermittent treatment. Offer combined treatment with LHRH agonists and NSAA.
NCCN	Intermittent ADT can be considered in patients with M1 disease to reduce toxicity	2A		For patients with significant side effects due to ADT impacting QoL and low or intermediate risk, intermittent ADT should be considered after a discussion about the impact on survival
Japanese Urological Association	Intermittent hormone therapy yields the same overall survival as continuous hormone therapy.		C1	
Brazilian Urological Association	Intermittent ADT recommended to asymptomatic patients, with radiologically confirmed metastasis and adequate PSA lowering (usually above 90% and PSA < 4 ng/mL)			
ESMO	No recommendation for intermittent ADT			
SEOM	No recommendation for intermittent ADT			Intermittent ADT may be an option in asymptomatic responding, well informed patients after an induction period.

LoE = Level of Evidence, GR = Grade of recommendation, LHRH = Luteneizing Hormone Releasing Hormone, ADT = Androgen Deprivation Therapy, QoL = Quality of Life, NSAA = Non-steroidal antiandrogen.

that, FDA has already approved apalutamide while enzalutamide has been approved by both FDA and EMA for use in this population and this amendment has already been incorporated in NCCN guidelines [48]. Undoubtedly, further data regarding the effect of these treatments in overall survival as well as the efficacy of subsequent treatments are needed so as to determine a treatment strategy for this group of patients.

The role of older hormonal treatments in the management of mCRPC

Older hormonal treatments including first generation antiandrogens, ketoconazole and steroids as well as strategies as antiandrogen withdrawal were widely used for the treatment of mCRPC prior to the introduction of docetaxel and novel agents. These hormonal manipulation have proven biochemical benefit in about 30% of patients, however they lack data regarding their potential survival benefit. Even more recent phase II studies (TERRAIN and STRIVE) have proven that enzalutamide offers much greater PSA responses and progression free survival in comparison to first generation antiandrogens [67,68]. Most guidelines though still propose with low level of evidence that these agents should be offered to asymptomatic mCRPC patients that do not want or do not have access to novel hormonal treatments or docetaxel due to their favorable cost profile and low toxicity for some of them [20,22,23,25,28,33]. According to the prostate consensus the majority of the panelists voted for first generation antiandrogens followed by dexamethasone [37]. Regarding antiandrogen withdrawal, this strategy is supported mainly by observational studies [69,70] and no survival benefit has been proven [71]. It should be noted that PCWG3 criteria do not consider antiandrogen withdrawal as a separate hormonal intervention [72]. However, clinicians are encouraged to assess for a withdrawal response for 4–6 weeks in patients on long-term antiandrogen therapy with apparent benefit [72].

First line treatment in mCRPC

Abiraterone plus prednisone, enzalutamide and docetaxel are available treatment options for mCRPC patients in the 1st line setting based on the results of randomized clinical trials [8,10]. It should be noted though that these guidelines are based on clinical trials conducted prior to the introduction of docetaxel plus ADT as the standard of care for metastatic hormone naïve patients. Furthermore, Radium-223 is a treatment option for symptomatic patient with bone only metastases without visceral disease. Therefore, there is an ongoing rivalry regarding the optimal 1st line treatment in mCRPC. Up to now there are no large randomized clinical trials comparing the efficacy of these agents in the first line setting, despite there are sparse evidence that there is no statistical significant difference in the efficacy of abiraterone and enzalutamide in this setting of the disease [73]. Abiraterone provided a 4.4 months overall survival benefit according to the final analysis of the COU-AA-302 study [74], while the corresponding benefit for enzalutamide in the extended analysis of the PREVAIL trial was 4.0 months [75] Guidelines proposals are based on the clinicopathological characteristics of the patients enrolled in the corresponding clinical trials. Therefore, no specific preference between abiraterone and enzalutamide is described in published guidelines [21,22,24,25,27,28,33,37,43,44,46,48] but also both these agents are recommended for asymptomatic or mildly symptomatic mCRPC patients. There are though clinical scenarios that one agent could be preferred over the other and this issue were raised during the APCCC2017 meeting. Experts favored abiraterone in patients with a history of falls, baseline significant fatigue, neurocognitive impairment or stable brain metastases. On the contrary they favored enzalutamide for patients with diabetes mellitus requiring prescription medications, active liver dysfunction and cardiac ejection fraction below 45–50%. The panel of experts was divided for patients with long QTc-syndrome as well as asymptomatic patients with a duration of response to ADT of less than a year. In the last group of patients though, 27% of the experts considered that an alternative treatment should be preferred [44].

Docetaxel is also recommended as treatment for the symptomatic patients with good performance status. Some guidelines differentiate slightly, eg, the American Urological Association suggests docetaxel administration in the 1st line setting with lower grade of recommendation both for asymptomatic and symptomatic patients [28], or the SEOM suggests that docetaxel should be discussed as initial treatment even in asymptomatic patients since it is an active agent in mCRPC [27]. These differences clearly reflect the lack of head to head comparisons among available treatment options and the existing uncertainty regarding the subpopulations of patients that derive the maximal benefit from each treatment.

As it is anticipated, guidelines have not yet incorporated any recommendations regarding patients previously treated with docetaxel or abiraterone and prednisone for their metastatic hormone sensitive disease. It should be highlighted though that patients that received abiraterone in the hormone naïve setting of the disease had poorer responses in AR-targeted therapy in the mCRPC setting in comparison to the docetaxel [17]. In accordance, the majority of experts participating in APCCC2017 voted for abiraterone or enzalutamide treatment in patients previously treated with docetaxel in the mHNPC setting. However, in symptomatic patients with progression within 6 months from docetaxel treatment, 43% of participants voted for alternative treatments mainly cabazitaxel [44]. The above suggest that further clinical research is necessary to delineate optimal treatment sequencing between hormone-naïve and castration–resistant prostate cancer.

Sequencing of treatments in mCRPC

Recently, many treatment options have become available for mCRPC patients, but there are no level I evidence to guide the optimal sequencing of these agents. In general, there are retrospective data indicating that sequential administration of AR targeting agents may decrease efficacy of these drugs. In addition, retrospective data have clearly shown that the efficacy of each treatment is affected by the number of treatment that each patient has previously received [76,77]. In this context, patients previously treated with docetaxel may receive any of the survival prolonging agents or receive re-challenge with docetaxel if justified by previous satisfactory response to this agent [24,35]. The latter approach is suggested with low level of evidence [24,27,46]. Some guidelines provide no specific recommendation regarding the sequencing of treatment in mCRPC [20,33]. The SEOM guidelines suggest that treatment with either abiraterone or enzalutamide is efficacious as a third line treatment in patients that have already received docetaxel and one AR-targeting agent [27]. Summarizing the recommendations from various guidelines, the experts' panel in APCCC2015 suggested that sequential treatment of AR-targeting agents is either not recommended or it is recommended in the minority of patients with acquired resistance to the first AR-targeting agent [37]. This panel of experts considered that cabazitaxel is most probably a third line treatment after an AR-targeting agent and docetaxel and this recommendation was confirmed in the 2017 Consensus conference [44]. Independent though of the treatment sequencing, it is considered that the more life-prolonging therapies that a patient receives, the better the outcome will be.

Treatment with Radium-223

Based on the results of the ALSYMPCA trial [12] most guidelines recommend treatment with Radium-223 for mCRPC patients with bone only disease [20,22,24,27,28,35,37,42–44]. They all though recognize that there are no predictive biomarkers or clinicopathological characteristic that would guide treatment decisions for Radium-223 [44]. In the registrational clinical trial were enrolled both docetaxel naïve and pretreated patients. Furthermore, it is an expert opinion that despite ALSYMPCA enrolled only symptomatic patients, the conclusions of the study could be extrapolated for asymptomatic patients with bone only disease as well [37].

Bone targeting agents

Both denosumab and zoledronic acid have gained approval for the prevention of skeletal related events (SREs) in mCRPC patients. Zoledronic has proven superiority in comparison to placebo in the prevention of SREs [78], while denosumab was superior to zoledronic acid for the same outcome [79]. None of these drugs has though proven survival benefit. Both AUA and European (EAU, ESTRO and ESMO) guidelines recommend use of either of these agents for mCRPC patients and osseous metastases [24,25,28], despite the level of recommendation is lower in the American guidelines. However, there are still a debate for the total duration of use of bone targeting agents. Zoledronic acid was used for two years in its registrational trial, while denosumab was used continuously. Duration of treatment is not discussed in the guidelines while the panel of experts was divided in 2015 between continuous use and total duration up to 2 years [37] and this issue remained unresolved in the 2017 update [44]. It should be noted that the beneficial effect of bone targeting agents has not been demonstrated so far in nHNPC patients. More specifically, the STAMPEDE trials showed that the addition of zoledronic acid to LHRH analogue (SoC) provided no difference in both time to treatment failure as well as OS [19]. Furthermore, time to first skeletal event was not improved by the addition of zoledronic acid in this trial [19] and the same was also noted in the randomized study CALGB90202 that used zoledronic acid in the same setting [80]. Since the rate of skeletal related events is low among nHNPC patients, possibly a much larger population should be enrolled in a study to prove the benefit from bisphosphonates.

Conclusions

Growing evidence regarding the biology of the disease and accumulated data from randomized clinical trials have completely and rapidly altered the therapeutic landscape of advanced/metastatic prostate cancer the last few years. As a result many published guidelines become rapidly outdated. In addition, there are many areas of uncertainty regarding the choice of treatment both in mHNPC and CRPC patients and even more regarding the optimal sequence of treatments during the course of the disease. These debates are also reflected in differences noted among the published guidelines. It should also be noted that national recommendations may be influenced by the availability of certain drugs. Regarding this issue, the APCCC recommendations clearly state that experts' responses were based on the idealized assumptions that all diagnostic procedures and treatments mentioned were readily available; there were no treatment contraindications and no option to include the patient in a clinical trial. Under this perspective, this systematic review attempted to comprehensively and critically present all published recommendations in the management of advanced prostate cancer patients. In the era of evidence-based and even more precision medicine, we consider that this could be an additional aid for the clinician to design an optimal treatment strategy for his patients adjusted to possible local limitations according to the recommendations of scientific societies and panels of experts.

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Declarations of interest

None.

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