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MINI-REVIEW

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Recent progress and controversies in the treatment of metastatic hormone-sensitive prostate cancer

Wei-hua Liu[1,2,†], Jia-tao Yao[1,†], Shi-jie Ye[1], Peng-cheng Hu[1], Xin Fei[1], Qi Ma[3,4,5,*], Hai-chao Chen[6,*]

[1]Health Science Center, Ningbo University, 315211 Ningbo, Zhejiang, China
[2]Department of Urology, Beilun People's Hospital, 315800 Ningbo, Zhejiang, China
[3]Comprehensive Genitourinary Cancer Center, The First Affiliated Hospital of Ningbo University, 315010 Ningbo, Zhejiang, China
[4]Translational Research Laboratory for Urology, The First Affiliated Hospital of Ningbo University, 315010 Ningbo, Zhejiang, China
[5]Yi-Huan Genitourinary Cancer Group, 315010 Ningbo, Zhejiang, China
[6]Department of Urology, The First Affiliated Hospital of Ningbo University, 315010 Ningbo, Zhejiang, China

***Correspondence**
fychenhaichao@nbu.edu.cn
(Hai-chao Chen);
fyymaqi@nbu.edu.cn
(Qi Ma)

† These authors contributed equally.

Abstract

Androgen deprivation therapy (ADT) has long been the only treatment for metastatic hormone-sensitive prostate cancer (mHSPC). In recent years, with the use of docetaxel chemotherapy and the emergence of various novel hormone therapy drugs, such as Abiraterone, Enzalutamide, Apalutamide, Darolutamide, and Rezvilutamide, the treatment strategies for mHSPC have been greatly changed. Furthermore, local treatment has been added to the treatment of low tumor burden mHSPC and triple therapy has been regarded as an important treatment choice for high tumor burden mHSPC. The survival rate of mHSPC patients has increased significantly and the quality of life also improved with these new treatment strategies. This article reviews the latest advances and controversies in the current treatment of mHSPC. Ongoing clinical trials are introduced and further directions are also discussed in this mini-review.

Keywords

Metastatic hormone-sensitive prostate cancer; Novel hormone therapy; Androgen deprivation therapy; Triple therapy; Combination therapy; Prostate cancer

1. Background

Worldwide approximately 1.414 million new cases of prostate cancer had been reported leading to 375,000 deaths in 2020 [1]. Metastatic hormone-sensitive prostate cancer (mHSPC) is an important stage in the development of prostate cancer. Even after the metastasis, androgen deprivation therapy (ADT) is quite effective for most of the newly diagnosed prostate cancer patients. However, traditional treatment methods such as androgen deprivation therapy (ADT) alone, or androgen deprivation therapy (ADT) combined with first-generation androgen receptor blockers such as bicalutamide, are not sufficient to increase survival rates of mHSPC patients. The emergence of various new therapeutics and changes in treatment strategies, has increased the treatment efficacy of mHSPC significantly. Table 1 shows previous and current treatment strategies for mHSPC, and this article provides a brief review of the recent progress and controversies in the treatment of mHSPC.

2. Androgen deprivation therapy (ADT) and new hormone therapy (NHT)

2.1 Androgen deprivation therapy and abiraterone

Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE) is a multicenter, randomized controlled, double-blind phase III clinical trial [2]. Total 1199 patients were randomly recruited for ADT + AAP (Abiraterone acetate + Prednisone) treatment group and the ADT + Placebo group in a 1:1 ratio. The trial mainly included treatment-naive patients with high-risk of metastatic prostate cancer. The primary result of the study was the assessment of overall survival (OS). In the final analysis [3], the median follow-up time was 51.8 months. The median overall survival (OS) in the ADT + AAP treatment group was 53.3 months which was significantly longer than the ADT + Placebo group whose overall survival was 36.5 months, with a 34% reduced risk of death ($p < 0.0001$). The most common adverse reaction of the treatment was hypokalemia, with the most common Grade 3–4 adverse reaction being hypertensive. These results suggest that ADT + AAP has significantly prolonged the overall survival rate and has good safety for newly diagnosed high-risk mHSPC patients. Adverse reactions in ADT + AAP

TABLE 1. Previous and current treatment for mHSPC.

Previous treatment of mHSPC	Current treatment of mHSPC
Androgen deprivation therapy (ADT)	Low-tumor burden
ADT + Docetaxel	ADT + external beam radiation therapy (EBRT)
	ADT + Abiraterone + Prednisone
	ADT + Apalutamide
	ADT + Enzalutamide
	High-tumor burden
	ADT + Abiraterone + Prednisone
	ADT + Apalutamide
	ADT + Enzalutamide
	ADT + Rezvilutamide (in China)
	ADT + Docetaxel + Abiraterone
	ADT + Docetaxel + Darolutamide

mHSPC: Metastatic hormone-sensitive prostate cancer.

group were generally mild and largely related to excess of mineralocorticoid (*i.e.*, hypertension, hypokalemia, edema), hormonal effects (*i.e.*, fatigue, hot flushes) and hepatic toxicity [2].

The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trials are multi-arm multi-stage platform studies with a series of concurrent or sequential phase 3 trials to test whether additional treatments could improve the survival of patients with ADT as an initial treatment [4]. Its G arm aimed to assess the efficacy and safety of combining the abiraterone acetate along with the prednisone (AAP) to ADT as compared to ADT alone in the initial systemic treatment of mHSPC. The present study included a total of 1917 patients. Among them 52% had metastatic prostate cancer disease. Patients were randomly distributed into two treatment groups, *i.e.*, ADT + AAP group and the ADT-alone group with median follow-up time of 40 and 36 months respectively. The overall survival rate was 83% and 76% for the ADT + AAP group and the ADT-alone group, respectively ($p < 0.001$). The *post hoc* analysis revealed that regardless of stratifying according to the "high-risk" or "low-risk" prostate cancer criteria established by the LATITUDE trial or according to the "high-tumor burden" or "low-tumor burden" criteria established by the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial, the survival benefit was present in all mHSPC patients with the treatment of ADT + AAP [5].

2.2 ADT plus apalutamide

The TITAN study is a randomized, double-blind, placebo-controlled phase III clinical trial aimed to evaluate whether the combination of apalutamide with ADT can extend the survival of mHSPC patients as compared to ADT monotherapy [6]. In the present study, 1052 mHSPC patients were enrolled who were further randomized into two groups, *i.e.*, the ADT + apalutamide group (n = 525) and the ADT + placebo group (n = 527). The TITAN study included greater sample size from actual population. It allowed the inclusion of mHSPC patients who had previously undergone other treatment or docetaxel chemotherapy. The death risk decreased by 35% (Hazard Ratio (HR) = 0.65, $p < 0.0001$) in ADT + apalutamide as compared to the ADT + placebo group. The median overall survival rate in two groups was (ADT + apalutamide) and 52.2 months (ADT + placebo), respectively [7]. Additionally, apalutamide has significantly prolonged the time to prostate-specific antigen (PSA) progression and castration. The combination of apalutamide with ADT exhibited superior therapeutic efficacy and maintained a good quality of life in mHSPC patients as compared to ADT and placebo treatment [8]. These results support the use of apalutamide in combination with ADT for mHSPC, providing the patients with optimal treatment outcomes. The most common adverse reactions were rashes, hypertension, fatigue and anemia [9].

2.3 Combination of androgen deprivation therapy and enzalutamide

ENZAMET [9] is a multicenter, open-label, randomized, phase III clinical trial. For these trials, 1125 mHSPC patients were recruited. The patients were randomized (1:1) into the enzalutamide group and the standard non-steroidal antiandrogen group (standard treatment group). Both groups received ADT as combination therapy. Patients who had received docetaxel chemotherapy combined with enzalutamide were also included in the study. The primary endpoint was overall survival, and the secondary endpoints was PSA-progression-free survival, progression-free survival (PFS) and adverse reactions. Three years overall survival rates in the ADT + enzalutamide and standard treatment groups were 80% and 72%, respectively. Enzalutamide significantly prolonged overall survival reducing the death risk by 33%. The study grouped the patients based on tumor burden (CHAARTED criteria) and prior Docetaxel therapy. The analysis of the subgroups for tumor burden, metastasis location, and prior docetaxel therapy confirmed the improvement in PFS when treated with enzalutamide.

ARCHES is a multicenter, double-blind, randomized, placebo-controlled phase III trial in which 1150 mHSPC are enrolled. The patients were randomly assigned to receive ADT + Enzalutamide (n = 574) or ADT + Placebo (n = 576). The primary endpoint was radiographic progression-free survival (rPFS) and the secondary endpoints were the time to prostate-specific antigen (PSA) progression, time to castration resistance, time to first symptomatic skeletal event (SSE), time to initiation of new antitumor therapy and overall survival. The study showed that enzalutamide significantly reduced the PSA progression, risks of death and castration resistance as compared to placebo. Regarding safety, the incidence of Grade 3–4 adverse reactions was 24.3% and 25.6% in the enzalutamide group and the control group respectively. The main side effects were fatigue and seizures [10]. *Post-hoc* analysis of ARCHES showed that enzalutamide was effective in all mHSPC patients, but the benefit was smaller for patients with visceral metastases [11]. The most common adverse reactions associated with enzalutamide in these trials are fatigue, seizures, and hypertension [1].

2.4 Combination of ADT and rezvilutamide

Rezvilutamide is a second-generation Androgen Receptor (AR) antagonist which was independently developed in China. As compared to enzalutamide, it has made an important innovation in the molecular structure of the drug by introducing hydroxyl groups to improve hydrophilicity. It has higher plasma concentration exposure and lower blood-brain barrier penetration. Rezvilutamide shows a low central nervous system toxicity maintaining high AR inhibition activity due to its low penetration to the brain. Rezvilutamide exhibited good tolerance, safety and anti-tumor activity. The CHART study (a multicenter, randomized phase III clinical trial) showed the efficacy and safety of rezvilutamide in combination with ADT compared to bicalutamide plus ADT. The study included 654 patients with high tumor burden mHSPC who had not previously received ADT, chemotherapy, surgery, or any other treatment. Among them, 90.4% patients were recruited from China. The main endpoints of the study were rPFS and overall survival. Patients receiving rezvilutamide plus ADT had significantly prolonged rPFS, with a 56% reduced risk of radiographic progression (Not Reached (NR) *vs.* 25.1 months, HR = 0.44, 95% CI (Confidence interval) 0.33–0.58) as compared to the bicalutamide group. It also reduced the risk of death by 42% and its safety was controllable [12]. The data did not represent a true picture of non-Chinese population. So, the conclusions of this study currently can only be applied to Chinese population. The most common grade 3 or worse treatment related adverse reactions were hypertension, hypertriglyceridemia, and weight gain [12].

3. ADT combined with docetaxel

In CHAARTED trial [13] 790 mHSPC patients were included who were divided into two groups. In this study, “high tumor burden” was defined as the presence of visceral metastasis or the presence of ≥4 bone metastatic lesions, from which at least 1 bone metastasis located outside the axial skeleton (*i.e.*, pelvis or spine). Whereas “low tumor burden” was defined as a disease without above mentioned factors. Two treatment groups were established. One group was ADT plus docetaxel therapy (75 mg/m^2, at most 6 periods), and the other was ADT monotherapy group. After the median follow-up time of 28.9 months, it was found that the median overall survival in ADT and docetaxel had been extended by 13.6 months as compared to ADT. Further analysis of the OS of patients with “high-tumor burden” and “low-tumor burden” indicated an extended median follow-up time of 53.7 months for the patients with “high-tumor burden”. The median OS of ADT combined with docetaxel therapy group is 57.6 months whereas the median OS of monotherapy docetaxel is 47.2 months ($p < 0.001$) [14]. However, for the patients with “low-tumor burden”, the ADT plus docetaxel therapy did not show increased survival rate. The trial indicates that ADT plus docetaxel therapy could significantly prolong the OS of mHSPC patients with “high-tumor burden”.

Total 1086 mHSPC patients were enrolled in the STAMPEDE trial C and E Arm [15]. They were randomized into 2:1 to receive either standard-of-care (SOC, N = 724) or SOC + docetaxel treatment. After a median follow-up time of 43 months, the median OS of SOC was 71 months, whereas the SOC + docetaxel group reached 81 months. This suggests that the combination of docetaxel could improve the prognosis of mHSPC patients. Further analysis at median follow-up time of 78.2 months showed that both the OS and PFS in SOC combined with the docetaxel group were significantly higher than the SOC alone group [16]. Regardless of tumor burden (high or low), all patients benefited from docetaxel chemotherapy. The STAMPEDE trial indicates that the use of docetaxel chemotherapy plus ADT as a first-line therapy for mHSPC patients can provide more survival benefits, irrespective of the level of tumor metastatic burden.

Although the combination of ADT and Docetaxel chemotherapy plays a significant role in the treatment of mHSPC, currently it is not recommended for the treatment of mHSPC alone. With the emergence of the triple therapy approach, ADT plus docetaxel has been replaced by the triple therapy approach. The triple therapy includes ADT, docetaxel, and second-generation hormonal therapy. This approach has become the new treatment option for mHSPC, especially in patients with increased metastasis.

4. Triple therapy

4.1 Combination of androgen deprivation therapy with darolutamide and docetaxel

ARASENS is the world’s first phase III trial which compared the efficacy of triple therapy based on ADT with docetaxel chemotherapy in the treatment of mHSPC. This trial enrolled the 1306 mHSPC patients who were randomly grouped into two groups (1:1) to receive either the combination of ADT-darolutamide and docetaxel or the combination of ADT, placebo, and docetaxel [17]. This triple therapy approach reduced the risk of death by 32.5% (HR 0.68, 95% CI: 0.57–0.80, $p < 0.001$) as compared to docetaxel and ADT. It sig-

nificantly extended the time to progression to mCRPC (HR 0.36, 95% CI: 0.30–0.42, $p < 0.0001$). It also reduced bone-related adverse reactions and cancer-related pain. Regarding adverse reactions, the rate of Grade 3–4 adverse reactions for the triple therapy approach was 66.1% as compared to in the control group (63.5%). No significant difference was observed between these two groups. Therefore, the ARASENS trial confirms the efficacy and safety of the triple therapy approach with ADT, darolutamide and docetaxel for the treatment of mHSPC.

4.2 ADT plus abiraterone and docetaxel

Clinical efficacy of the combination of ADT and docetaxel was assessed and compared with combination of ADT and docetaxel in conjunction with abiraterone for patients with newly diagnosed mHSPC patients in the Abiraterone plus prednisone added to androgen deprivation therapy and docetaxel in de novo metastatic castration-sensitive prostate cancer (PEACE-1) study [18]. The combination of ADT, docetaxel and abiraterone (n = 583) significantly enhanced the radiographic progression-free survival (rPFS) (HR = 0.54; 99.9% CI: 0.41–0.71; $p < 0.0001$) and overall survival (OS) (HR = 0.82; 95.1% CI: 0.69–0.98; $p = 0.030$) as compared to the standard treatment of ADT and docetaxel (n = 589) in whole population. A 50% reduced risk of disease progression was observed in triple treatment group. Further grouping of tumor burden, suggested that triple therapy could reduce the risk of death in high tumor burden patients by 28%, but there was no significant OS benefit for low tumor burden patients. Regarding safety, the incidence of grade $\geq$3 adverse reactions was 63% in the experimental group whereas it was 52% in the standard treatment group. The incidence of neutropenia, febrile neutropenia, fatigue, and neuropathy did not increase in the investigational group as compared to standard treatment group.

5. Combination of systemic therapy and local treatment

The combination of systemic therapy and local treatment (such as prostate radiotherapy, palliative prostatectomy, *etc.*) may improve the survival and prognosis of the mHSPC patients with low-tumor burden [19]. HORmonal therapy versus hormonal therapy plus local external RADiation therapy (HORRAD) trial showed that during the treatment of mHSPC [20], the OS of the patients was not different when compared with ADT monotherapy. The PSA progression-free time was significantly extended (HR: 0.78, 95% CI 0.63–0.97; $p = 0.02$) when combined with prostate radiotherapy. In the H arm of STAMPEDE trial [21], 2061 patients were randomly recruited. Among them, 1029 patients received SOC therapy whereas 1032 patients received radiotherapy for the prostate along with standard of care (SOC). Among the patients who had received radiotherapy, 40% had a low tumor burden and 54% had a high tumor burden. The results indicated that radiotherapy improved failure-free survival but had an influence on OS. However, further subgroup analysis indicated that although prostate radiotherapy did not provide an OS benefit to patients with high tumor burden (HR 1.11, 95% CI 0.96–1.28; $p = 0.164$), it improved OS in patients with low tumor burden when combined with standard treatment (HR 0.64, 95% CI 0.52–0.79; $p < 0.001$) [22].

Heidenreich *et al.* [23] included 113 patients with mHSPC having bone metastasis for cytoreductive prostatectomy. Among these patients, 77.9% had a low tumor burden whereas 22.1% had a high tumor burden. With a mean follow-up of 53.6 months, the 3-year and 5-year survival rates of patients were 87.6% and 79.6%, respectively. The average recurrence-free time was 72.3 months [23]. The Testing Radical prostatectomy in men with prostate cancer and oligo-Metastases to the bone (TRoMbone) bone study is a prospective controlled study that focuses on cytoreductive prostatectomy and pelvic lymph node dissection of patients with oligometastatic bone lesions in mHSPC [24]. The results suggested that cytoreductive prostatectomy could be safely performed on these patients without increasing surgical risks and the impact on the patient's quality of life was comparable to using systemic therapy alone.

6. Controversies in the treatment of mHSPC

The increasing treatment options for mHSPC have led to more questions and controversies. It is unclear that which treatment is the most suitable as first-line of therapy and which treatment sequence is more helpful for metastatic prostate cancer patients [25, 26]. The questions like which patients require local intensive treatment and which patients' systemic treatment is sufficient are also unanswered [27]. How to sort out patients needing triple therapy, from those only require ADT and NHT is yet unclear [28, 29]. Should the treatment be de-escalated for patients with good response and escalated for patients with poor response [30]? Is it necessary to target the oligometastatic lesions in patients with oligometastatic mHSPC for metastasis-directed therapy (MDT) [31]? If the treatment has to be chosen for the primary lesion. Which treatment method, *i.e.*, surgery or radiation is more suitable [32]? For prostate-specific membrane antigen (PSMA) can the "oligometastasis" or "low metastatic burden" detected by traditional imaging still be defined as "oligometastasis" or "low metastatic burden" [33]? Many such questions emerged regarding the treatment of mHSPC in recent years which remain unanswered in the report of the Advanced Prostate Cancer Consensus Conference (APCCC) 2022 [34]. Further clinical studies are needed to answer these questions.

7. Further directions

Increased understanding of the molecular mechanisms related to the occurrence and progression of prostate cancer, has led to numerous clinical trials focused on the treatment of mHSPC, aiming to provide more benefits to patients. As cyclin D overexpression and cell cycle dysregulation [35], homologous recombination repair gene (HRR) mutations [36] and Phosphatase and tensin homolog deleted on chromosome10 (PTEN) loss are common consequences in prostate cancer [37]. These targets can be focused for developing new treatment strategies for mHSPC. Currently phase III clinical trials of novel combinations include: CYCLONE3 (ADT, Abiraterone and

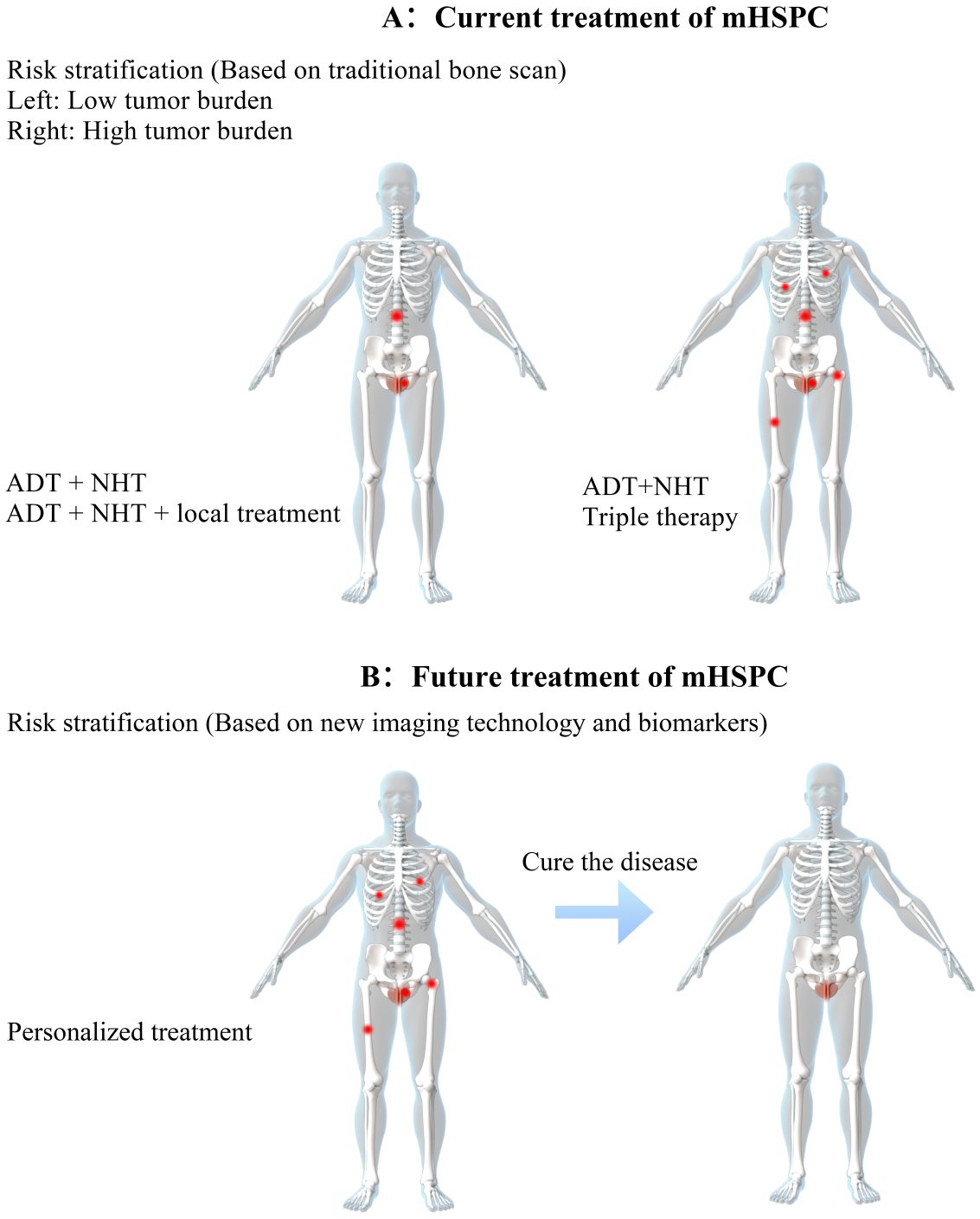

FIGURE 1. Current and further treatment regimens for mHSPC patients. (A) current treatment for mHSPC. Current treatment strategy for mHSPC is based on life expectancy and traditional imaging. For patients with long life expectancy and low metastatic burden, ADT + NHT and effective local treatment is recommended. For patients with long life expectancy and high metastatic burden, ADT + NHT is recommended, and triple therapy (ADT + chemotherapy + Abiraterone/Darolutamide) is also a suitable choice. For patients with short life expectancy, ADT + NHT is recommended. Drug's side effects and patients' quality of life should be considered during the treatment. Treatment escalation or treatment de-escalation may be discussed with patients based on treatment response. Long term follow-up and careful observation of treatment response and disease progress is important for mHSPC patients. (B) Further potential treatment for mHSPC. Advanced imaging technologies, useful biomarkers, novel drugs and drug combinations, new techniques in surgery and radiation, may lead to personalized treatment options for mHSPC patients. Treatment decision may be made based on life expectancy, new imaging evaluation and useful biomarkers. Treatment strategies including surgery, radiation and effective drug and drug combinations may help mHSPC patients to recover from this disease. mHSPC: Metastatic hormone-sensitive prostate cancer; ADT: Androgen deprivation therapy; NHT: new hormone therapy.

CDK4/6 inhibitor Abemaciclib), TALAPRO-3 (ADT, Enzalutamide and PARP inhibitor Talazoparib), AMPLITUDE (ADT, Abiraterone and PARP inhibitor Niraparib), and CAPItello-281 (ADT, abiraterone and AKT inhibitor Capivasertib). The new generation of highly selective PARP inhibitor (AZD5305) is being planned to the conduct international multicenter phase III study. These international multicenter phase III clinical trials are expected to further reshape the clinical treatment landscape of mHSPC in the next 3–5 years.

Besides chemical drugs, radionuclide therapy is being increasingly used for the treatment of mHSPC. The PSMAddition study, which is an international multicenter prospective, randomized, open-label phase III clinical trial, is being conducted to evaluate the use of ^{177}Lu-PSMA-617 for the treatment of mHSPC. This study aims to observe whether the addition of ^{177}Lu-PSMA-617 to standard-of-care (SOC) treatment is more beneficial for patients with mHSPC. The KEYNOTE-991 study (ADT, Enzalutamide and PD-1 inhibitor Pembrolizumab) was prematurely terminated due to the failure to achieve anticipated efficacy, however, the exploration of immune therapy for mHSPC never stopped. Research is being conducted on the reversal of the tumor-inhibitory microenvironment of prostate cancer. New therapeutic targets such as B7-H3, LAG-3, IDO-1 and new treatment approaches such as Chimeric Antigen Receptor T-cell (CAR-T) immunotherapy, and Bispecific T-cell engagement antibody (BiTE) immunotherapy [38, 39] are being investigated. Besides, the CONTACT-02 study, a clinical trial for the treatment of metastatic castration-resistant prostate cancer (mCRPC) by the combination of cabozantinib and the PD-L1 inhibitor atezolizumab, has been announced to achieve the primary endpoint of progression-free survival (PFS) of mHSPC patients. This study brings new hope for immunotherapy of prostate cancer and may lead to the treatment of mHSPC in the future.

8. Conclusion

In the previous decade, much progress has been made in the treatment of mHSPC and the treatment options for mHSPC have been greatly improved. However, there is still room for investigation of new therapeutics and strategies to meet the clinical needs. More effective and safer first-line treatment options for newly diagnosed mHSPC patients are needed urgently. Besides all this focus should be on the health-related quality of life of patients. A good treatment prolongs the OS and PFS of patients ensuring their quality of life [26]. Potential mHSPC therapies have been shown in Fig. 1. Increased understanding of the mechanisms of mHSPC, application of image technologies [40] and the multidisciplinary teams (MDTs) model in clinical practice, will lead to better diagnosis and treatment of mHSPC and long-term control of this disease may be achieved successfully in the future.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

QM and HCC—Conception and supervision. WHL, JTY and XF—Manuscript draft. SJY and PCH—Preparation of table and figure. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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