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Genitourinary Cancers (S Gupta, Section Editor)

Management of Metastatic Hormone-Sensitive Prostate Cancer (mHSPC): an Evolving Treatment Paradigm

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Opinion statement

Combination systemic therapy is now standard of care for all men with metastatic, hormone-sensitive prostate cancer (mHSPC). Patients with mHSPC should be treated with standard androgen deprivation therapy (ADT) and abiraterone acetate with prednisone or docetaxel (chemohormoanl therapy) unless there are contraindications to combination therapy. Based on the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) study subgroup analysis, chemohormonal therapy may be most beneficial in men with high-volume disease burden, as men with low-volume metastatic disease do not appear to experience a survival benefit with chemohormonal therapy, while abiraterone in combination with ADT appears to be beneficial across both disease volume subgroups. Decisions regarding whether to use chemohormonal therapy or abiraterone and ADT for men with mHSPC should integrate consideration of volume of disease burden, quality of life effects, duration of therapy, and patient preferences for treatment as there is no formally powered prospective head-to-head comparison of these options demonstrating superiority of one approach over the other. Treatment of the primary tumor with radiation should be considered in men with de novo low-volume metastatic disease as radiation is associated with prolonged survival and a tolerable toxicity profile. Men with de novo high-volume metastatic disease do not appear to have improved survival with radiation of the primary tumor. Numerous clinical

trials are ongoing to evaluate treatment approaches that may benefit men with mHSPC. Radical prostatectomy in men with mHSPC in combination with optimal systemic therapy is currently being assessed in a clinical trial, but should not be considered outside of a clinical trial. Metastasis-directed therapy with radiotherapy directed at metastatic lesions is still investigational, but can be considered in clinical trials in men with oligometastatic disease. Multiple studies are enrolling worldwide for men with mHSPC, and these should be considered for all interested patients.

Introduction

Prostate cancer (PCa) is the most common non-cutaneous malignancy in American men and the second most common cause of cancer-related death [1]. Although most men are diagnosed with localized, curable disease, recent epidemiological data has suggested a growing frequency of de novo metastatic PCa (mPCa) [2, 3], perhaps related to changes in guidelines for PCa screening in the USA [4, 5]. Additionally, many men treated for localized PCa will eventually develop cancer recurrence and metastatic disease [6].

The mainstay of treatment for the past several decades for men with metastatic hormone-sensitive PCa (mHSPC) has been to achieve castrate levels of testosterone with either bilateral orchiectomy or through the use of a gonadotropin-releasing hormone (GnRH) analog, termed androgen deprivation therapy (ADT). ADT was previously the only form of treatment available prior to the development of resistance to ADT and progression to castration-resistant PCa (CRPC) [7–9], for which there are now multiple life-prolonging treatment options [10–12]. In recent years, however, several systemic therapies once reserved for metastatic CRPC (mCRPC) have demonstrated efficacy in disease control and tolerability in men with mHSPC [13••, 14••, 15]. Additionally, growing data support the role of treatment directed at the primary tumor [16•, 17, 18•] and potentially treatment of sites of metastases [19•, 20, 21]. Other studies have also advanced our understanding of the adverse health effects of continuous ADT and how to mitigate and monitor those effects [14••, 22–26].

Considering the multidisciplinary approach required in the management of mHSPC, it is important for medical oncologists, radiation oncologists, and urologists to be educated on recent developments in the treatment and monitoring of men with mHSPC.

Defining oligometastatic prostate cancer

Oligometastatic cancer defines a state of low-volume metastatic disease that appears to be prognostically different and potentially amenable to different treatment options that may alter disease trajectory as compared with more widespread cancer [27]. The concept of low-volume metastatic disease was first evaluated as a prognostic tool in PCa literature in the late 1980s [28]. In the original study by Soloway et al., fewer than 6 metastatic bone lesions on bone scan purported an improved overall survival compared with more extensive disease at 2 years of follow-up (94% vs 74%, $p = 0.019$) [28].

The notion that oligometastatic mHSPC is distinct from the more widespread metastatic disease has become more relevant in recent years as clinical trials for mHSPC have stratified their analyses with differences noted in efficacy based on low versus high-burden metastatic disease

Table 1. Recent trials defining low-volume and oligometastatic prostate cancer

Trial (publication year)	Intervention investigated	Definition of oligometastatic prostate cancer	Assessment of metastases
HORRAD (2018) [16•]	ADT with or without radiotherapy to the prostate	< 5 bone lesions	Bone scan
CHAARTED (2015) [15, 29••]	ADT with or without docetaxel	< 4 bone lesions, no bone lesions beyond the vertebral bodies or pelvis, and no visceral metastases	Bone scan and CT
STAMPEDE (2018) [18•]	Standard of care with or without radiotherapy to prostate	< 4 bone lesions, no bone lesions beyond the vertebral bodies or pelvis, and no visceral metastases	Bone scan and CT or MRI
STOMP (2017) [18•]	Observation versus metastasectomy or radiotherapy to metastases	< 4 extracranial metastases	Choline PET-CT

(Table 1). Although no consensus exists for the exact definition of oligometastatic mHSPC, the most commonly used definitions include a lack of visceral metastases and fewer than 4 or 5 bone lesions limited to the axial skeleton or pelvis.

Additionally, most trials have used standard imaging to define the extent of metastatic disease, relying on definitions of metastatic spread by technetium-99m bone scan and computed-tomography (CT) or magnetic resonance imaging (MRI). New developments in positron emission tomography (PET) with radiotracers such as ^{11}C-choline, ^{18}F-fluciclovine, and those based on prostate-specific membrane antigen (PSMA) hold promise in advancing our ability to identify occult metastatic disease, and may increase the frequency with which oligometastatic disease is identified among patients previously believed to be non-metastatic [30–32].

Androgen deprivation therapy: adverse effects and health monitoring

Since the discovery of PCa's dependence on androgen in the 1940s, ADT has been the mainstay of treatment for advanced disease with proven survival benefit in slowing disease progression and reducing complications from metastatic disease [33]. In the past 30 years, repeat dosing of GnRH agonists or antagonists has supplanted orchiectomy as the predominant form of ADT in the USA [34]. Following initiation of ADT, castrate levels of testosterone have historically been defined as ≤ 50 ng/dL (1.73 nmol/L). However, the optimal level of castration has not been definitively prospectively determined [35]. Because it is the backbone of

systemic therapy for PCa, it is critical to recognize both the benefits and potential complications and negative effects on patient quality of life associated with treatment. Several of the medical complications associated with increased morbidity and mortality should be routinely discussed and considered by clinicians and patients initiating therapy, and are reviewed here.

Metabolic dysfunction and cardiovascular risks

Several large prospective, population-based studies demonstrate an association between ADT exposure and the risk of diabetes, increased body fat percentage, hyperlipidemia, and cardiovascular disease [36–39]. In one large claims-based study, the use of a GnRH agonists increased the incidence of diabetes 44%, coronary artery disease by 16%, myocardial infarction by 11%, and sudden cardiac death by 16% compared with controls [38].

For men with cardiac risk factors, preventive strategies such as appropriate blood pressure management, diet strategies that encourage weight loss and are adherent with cardiovascular guidelines, encouragement of exercise, and appropriate management of diabetes have been proposed as mechanisms to counteract morbidity from excess cardiovascular events. The routine use of statins, metformin, and aspirin in men without cardiovascular indications for these medications is not recommended. Lipid abnormalities should be treated per American Heart Association/American College of Cardiology guidelines, and individuals at high risk for developing diabetes should be followed by primary care physicians who follow American Diabetic Association recommendations for screening, diagnosis, and management. Several trials examined whether exercise strategies can counteract metabolic effects of ADT [40]. A recent meta-analysis of 14 studies (N = 1135) concluded that exercise improved lean body mass, upper and lower muscle strength and endurance, and BMI, but had no impact on cardiometabolic markers [40].

Bone health and skeletal-related events

Exposure to ADT is associated with a significant decline in bone mineral density—up to 5–10% within first year of treatment—and increased fracture risk [41]. Bone mineral density loss is due to the effect of low estrogen on bone remodeling shifting the balance between bone formation and resorption in the direction of resorption, as well as indirect effects from muscle loss. Skeletal-related events (SRE) are a significant source of morbidity and increased mortality in men with PCa, and may be particularly detrimental in older men who are at higher risk of both osteoporosis and falls.

Treatment with either the bisphosphonate zoledronic acid or denosumab, a human monoclonal antibody against the receptor activator of nuclear factor-kB ligand that blocks the maturation of osteoclasts, improves BMD and reduces fragility fracture risk in men with osteoporosis and men receiving ADT, respectively [42, 43]. However, these agents did not prevent SREs or delay disease progression in prospective studies of men with mHSPC. A phase 3 randomized trial including the upfront use of zoledronic acid for 2 years in men with mHSPC, node positive, or high risk locally advanced or recurrent hormone-sensitive PCa within 3 months of ADT initiation did not improve overall

survival or reduce the rate of SRE [44].

In addition to vitamin D and calcium supplementation for all men on ADT, treatment with either denosumab (60 mg subcutaneously every 6 months), zoledronic acid (5 mg intravenously annually), or alendronate (70 mg orally weekly) for men with a 10-year risk of hip fracture ≥ 3% based on the Fracture Risk Assessment Tool (FRAX) algorithm released by the World Health Organization should be offered to reduce the risk of fragility fracture [45]. A baseline bone mineral density scan should also be obtained in these high-risk men with surveillance scans after 1 year of therapy for men on long-term ADT to assess an individual's risk of fragility fracture during treatment with ADT.

Cognitive impairment

Various studies have established that androgens, specifically testosterone and its metabolites, play a significant role in maintaining cognitive function [46, 47]. Prospective studies examining the impact of ADT on cognitive function have demonstrated conflicting results. One prospective study of 78 patients with locally advanced or metastatic PCa on continuous ADT for 12 months identified significant deficits in cognitive function in domains including language, short-term memory, mental flexibility, and inhibitory control [48]. However, a study by Alibhai et al. that enrolled 241 men with PCa treated with ADT, PCa and no ADT, or healthy controls without PCa did not find an association between ADT and significant changes in cognitive function over time compared with healthy controls [49]. Currently the evidence remains inconclusive regarding the association between ADT and decline in cognitive function, and studies are ongoing to better characterize the relationship.

Advances in systemic therapies

Recent landmark studies have altered the standard of care for men with mHSPC by incorporating therapies approved for mCRPC earlier in the treatment algorithm.

Chemohormonal therapy

Several trials have investigated the addition of chemotherapy to standard ADT for mHSPC without significant improvement in survival but at the cost of added morbidity [50]. The GETUG-AFU 15 trial was the first phase III study investigating 9 cycles of docetaxel for mHSPC [51]. In this trial, median overall survival was not improved (HR 1.01, $p = 0.9$), and there was increased treatment morbidity associated with chemotherapy. Post hoc analyses of these data suggested a trend toward a survival benefit in men with high-volume mHSPC, although this study was not powered to detect this advantage (HR 0.78, $p = 0.14$) [52].

The Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED) trial randomized 790 men with mHSPC to ADT with or without 6 cycles of docetaxel [15]. Docetaxel was associated with improved overall survival (57.6 months versus 44.0 months, HR 0.61, $p < 0.001$). Notably, only men with high-

volume disease, defined as the presence of visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the axial skeleton, appeared to benefit in terms of overall survival in the pre-planned subgroup analysis (low volume: HR 0.60, 95% CI 0.32–1.13; high volume: HR 0.60, 95% CI 0.45–0.81). These findings were confirmed after longer follow-up (low volume: HR 1.04, $p = 0.86$; high volume: HR 0.63, $p < 0.001$) [29••].

The Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial takes advantage of a continuously enrolling standard of care treatment arm and various comparison treatment arms to test new therapies for locally advanced or mHSPC [13••, 53]. Data from arm C of STAMPEDE compared 6 cycles of docetaxel to standard ADT [14••]. Men with locally advanced PCa or mHSPC who received docetaxel had a median survival of 81 months compared with 71 months for controls (HR 0.78, $p = 0.006$). Median progression-free survival also improved with docetaxel from 20 months to 37 months (HR 0.61, $p < 0.001$) [14••]. Although the STAMPEDE trial did not stratify their results by burden of mPCa, subgroup analysis demonstrates that the improvement in survival associated with docetaxel is significant in the mHSPC setting but not for men with locally advanced disease, though the latter analysis is underpowered.

Meta-analyses of the data from these three trials support the use of early docetaxel for mHSPC [54]. In addition, an analysis of patient-reported outcomes from the CHAARTED trial demonstrated that while overall quality of life was poorer at 3 months for men receiving chemohormonal therapy compared with standard ADT, long-term quality of life at 12 months was superior for those who received chemohormonal therapy. However, neither of the differences at these time points met the threshold for minimal clinically important difference [55]. Thus 6 cycles of docetaxel with ADT is a standard of care for men with mHSPC who are healthy enough to receive chemotherapy, with a majority of clinicians using chemohormonal therapy primarily in men with high-volume metastatic disease.

Abiraterone acetate with prednisone

Arm G in the STAMPEDE trial assessed whether the addition of abiraterone and 5 mg prednisolone in addition to ADT would benefit men with mHSPC [13••]. At 3 years of follow-up, overall survival was 83% in the combination group compared with 76% in the ADT plus placebo group (HR 0.63, $p < 0.001$), an effect that was confirmed in the 1001 men with mPCa (HR 0.61, 95% CI 0.49–0.75).

The LATITUDE trial was a multinational phase 3 study that enrolled patients with high-risk mHSPC from 235 sites across 34 countries [56••]. Unlike arm G of STAMPEDE, LATITUDE required all participants to have high-risk mHSPC defined by having at least two of the following: Gleason score of ≥ 8, ≥ 3 bone metastases, or the presence of visceral metastases. Three-year survival was 66% in the combination group and 49% in the ADT plus placebo group, producing a relative risk of death nearly identical to that seen in the STAMPEDE trial (HR 0.62, $p < 0.001$).

In terms of secondary endpoint, the LATITUDE and STAMPEDE trials demonstrated improvements in radiologic progression, PSA progression, and PCa—specific mortality [13••, 56••]. A meta-analysis from these two trials

demonstrated an improvement in survival associated with abiraterone in addition to ADT vs ADT alone (HR 0.62, $p = 0.55 \times 10^{-10}$) [57]. The analysis also suggested that there was not a difference in benefit associated with Gleason score, performance status, or nodal status [57]. Additionally, post hoc analyses of the LATITUDE trial demonstrated that abiraterone was efficacious in men with either low or high burden of disease based on CHAARTED standards (HR 0.66, $p = 0.041$ and HR 0.54, 95% CI [0.41–0.70]; $p < 0.001$, respectively) [58].

The safety and toxicity profile of abiraterone in the mHSPC setting was similar to that seen in the mCRPC setting, with no unexpected safety signals [13••, 56••, 57]. Patient-reported outcomes from the LATITUDE trial demonstrated abiraterone was associated with improvement in time until pain progression (HR 0.63, < 0.001), longer time to worsened fatigue intensity (HR 0.65, $p = 0.001$), and longer time to deterioration of functional status (HR 0.85, $p = 0.032$) [59].

Comparing chemohormonal therapy with abiraterone acetate

No prospective trial has randomized men with mHSPC to ADT plus abiraterone vs ADT plus docetaxel. However, there was a period of simultaneous enrollment in STAMPEDE in arm C (chemohormonal therapy) and arm G (abiraterone), and the investigators performed a post hoc analysis comparing outcomes between these arms [60]. Perhaps not surprisingly, abiraterone was associated with a longer failure-free (HR 0.56, $p < 0.001$) and progression-free survival (HR 0.69, $p = 0.023$) due to ongoing androgen receptor–directed treatment as failure was driven by rising PSA. However, there was no significant difference between arms in symptomatic skeletal event rate (HR 0.82, $p = 0.648$), overall survival (HR1.13, $p = 0.691$), or PCa-specific survival (HR 1.05, $p = 0.620$) [60].

Recently reported and ongoing studies

The ARCHES trial (NCT02677896) is an international randomized phase 3 trial in which men with mHSPC were treated were randomized to treatment with ADT plus enzalutamide or placebo [61]. Approximately 18% of patients in each arm also received treatment with docetaxel in addition to ADT. The study met its primary endpoint of prolonging radiographic progression-free survival, with a HR 0.39 (95% CI 0.30–0.50) favoring the enzalutamide arm. The overall survival data is not yet mature. The TITAN study (NCT02489318) is a separate international phase 3 trial randomizing men with mHSPC to treatment with ADT with or without apalutamide, a novel antiandrogen. A press release revealed that the study met its primary endpoint of improving radiographic progression-free survival and overall survival, though the data has not yet been released in more detail [62].

Multiple ongoing trials are assessing systemic therapies in the mHSPC setting. The PEACE-1 trial is a four-arm prospective randomized controlled trial in which men with mHSPC are treated with ADT and docetaxel with or without abiraterone, and with or without radiotherapy directed at the primary tumor (NCT01957436). The ARASENS trial includes men with mHSPC receiving ADT plus docetaxel with or without darolutamide, a novel antiandrogen (NCT02799602). ENZAMET (NCT02446405) is an international phase 3 trial in which men with mHSPC receive ADT with or without docetaxel, and are randomized to treatment with enzalutamide or placebo. Finally, the

STAMPEDE trial continues adding treatment arms including arm J which combines abiraterone with enzalutamide [63], arm K investigating metformin [64], and arm L assessing transdermal oestradiol [65].

Local treatment of the prostate

Recent investigations have suggested that the primary tumor plays a role in disease progression even after the development of metastatic disease [66, 67]. This has sparked renewed enthusiasm for local treatment of the prostate for men with mHSPC.

Radiotherapy

Prior trials demonstrated improved survival with radiotherapy for men with locally advanced PCa [68, 69], and retrospective analyses of large cancer datasets suggested a benefit to radiotherapy for mPCa [17, 70–72]. More recently, prospective studies have evaluated the benefits of radiotherapy.

The HORRAD trial randomized 432 men with mPCa with bony metastases only and PSA > 20 ng/mL to either ADT alone or ADT with EBRT given as either 70 Gy over 35 fractions or 57.76 Gy in 19 fractions [16•]. Radiotherapy in this study did not improve overall survival (45 versus 42 months, adjusted HR 0.90 p = 0.4). Notably, however, time to PSA recurrence was improved in the radiotherapy group from 12 to 15 months (HR 0.78, p = 0.02). Additionally, subgroup analyses suggest the effect of radiotherapy on overall survival may be more pronounced in men with fewer metastatic bone lesions (< 5 lesions; HR = 0.68, 95% CI 0.70–1.14), although the study was not powered to reliably detect this difference.

Soon after the publication of data from the HORRAD trial, data from the STAMPEDE trial's arm H were published in which men were randomized to either standard of care systemic therapy (ADT or ADT plus docetaxel—approximately 18% received ADT plus docetaxel) with or without radiotherapy to the prostate [18•]. In total, over 2000 men were randomized. Notably, the radiation doses in STAMPEDE were lower than typical definitive doses in the USA—either 36 Gy in 6 fractions or 55 Gy in 20 fractions [18•]. Radiotherapy was not associated with a survival benefit in the population overall (median overall survival 46 versus 48 months for no radiation vs radiation, respectively; HR 0.92, p = 0.3). However, a prespecified subgroup analysis demonstrated that radiotherapy to the prostate was associated with improved survival in men with low-volume metastatic disease by the CHAARTED criteria (HR 0.68, p = 0.007) [18•].

Thus, prospective data from STAMPEDE demonstrates radiotherapy to the prostate is associated with prolonged survival for men with low-volume mHSPC [16•, 18•]. As mentioned above, the PEACE-1 trial is a four-arm study randomizing men with mHSPC to ADT plus docetaxel to treatment with or without abiraterone, and then randomizes to receive radiotherapy directed at the prostate or no local therapy (NCT01957436). Radiation doses in the PEACE-1 trial will be 74 Gy given in 37 fractions. PEACE-1 intends to enroll nearly 1200 men with final analyses set for

2030. Prior to then, a North American trial (NCT01751438) will assess PFS in 180 men receiving 6 months of best systemic therapy who are then randomized to receive either local therapy to the prostate or no local treatment (local treatments include radiotherapy to the prostate or radical prostatectomy; NCT01751438).

Radical prostatectomy

Data regarding a potential benefit for cytoreductive radical prostatectomy for men with mHSPC remains limited to retrospective studies. In two large datasets from the USA, radical prostatectomy was associated with improved overall survival for men with newly diagnosed mHSPC (HR 0.51, $p < 0.01$ and HR 0.38, $p < 0.001$) [17, 73]. In a separate dataset from Munich, 5-year overall survival was 55% for men who underwent surgery versus 21% compared with those who did not ($p < 0.01$) [74]. In a recent multi-institutional study of 113 men with bone-only or small (< 3 cm) pelvic lymph node metastatic disease, radical prostatectomy with pelvic lymphadenectomy with ADT resulted in nearly 80% 5-year overall survival and a mean relapse-free survival of 72 months [75]. There was no comparator in this study.

These retrospective data are valuable for hypothesis generation, but may be subject to selection bias as included men had to be fit enough for surgery. Forthcoming prospective trials include the trial of best systemic therapy prior to radical prostatectomy or radiation vs no local treatment (NCT01751438), the TROMBONE feasibility trial (ISRCTN15704862), the LoMP trial which will assess time to development of mCRPC (NCT02138721), and the comparatively larger (predicted accrual ~ 452 men) g-RAMMP trial which will compare cancer-specific survival (NCT02454543) among others (NCT02020070 and NCT01751438).

Metastasis-directed therapy (MDT)

Radiotherapy

Most data related to MDT has been in the form of stereotactic body radiotherapy, defined as high-dose radiotherapy given in few fractions directed at extracranial targets [76]. Although several retrospective series have reported on this topic, the studies are heterogeneous [77–82]. In general, the available data suggest that the toxicities from MDT with radiation are few and mild, and MDT with radiation can provide local control.

A recently published phase II clinical trial, STOMP, randomized 62 men to either MDT in the form of radiotherapy or surgery to lesions identified by PET-CT, or observation after biochemical recurrence following local therapy for non-metastatic PCa [19•]. A majority of men randomized to MDT received radiation (25/31). MDT was not associated with a significant prolongation in ADT-free survival (median 21 versus 13 months; HR 0.060, $p = 0.11$). No men randomized to MDT initiated ADT due to symptomatic progression or local progression, while 10% and 23%, respectively, of men randomized to observation [19•]. Additionally, PSA decreases were seen in 74% of men who received MDT compared with only 42% of men in the observation group. Short-term quality of life was similar between treatment arms.

A separate prospective trial, POPSTAR, reported outcomes similar to those from STOMP [83]. Among 33 men who received radiation, rates of local progression at 2 years were 7%. In men with mHSPC who were off ADT at the beginning of the trial, 48% remained free from ADT at 2 years. A total of 79% had a subsequent decline in PSA following MDT administration and 15% grade 2 toxicities occurred.

Surgery

Besides 6 patients in STOMP treated with surgical MDT, there are no prospective data evaluating surgical MDT for mPCa. Most retrospective studies on this subject have specifically evaluated salvage lymphadenectomy in men with image-confirmed nodal recurrence following radical prostatectomy [20]. In a single-surgeon series of 117 men following radical prostatectomy with biochemical recurrence and nodal disease confirmed by PET/CT, all underwent salvage lymphadenectomy [21]. All but one patient experienced a decrease in PSA while nearly 80% had a PSA nadir < 0.2 ng/mL and over half of men were without radiographic recurrence at 5 years.

In the largest retrospective trial involving 654 men with nodal recurrent PCa, 75% of men remained free of clinical recurrence at 1 year following lymphadenectomy, with a median time to clinical recurrence of approximately 3 years [84].

Ongoing questions

To most effectively guide patients and teams treating oligometastatic mHSPC, forthcoming studies must incorporate conventionally accepted endpoints reflecting disease-specific and overall survival–related endpoints in addition to those describing ADT-free survival. Future trials must also guide consensus on optimal systemic therapy combinations and radiation treatment schedules. There are several ongoing trials that will clarify the role of MDT for mHSPC (NCT03569241, NCT02274779, NCT03143322, NCT02685397, NCT02759783, and NCT02680587).

Developing research and conclusions

Recent advances in the management of mHSPC have been fast and furious in the last decade. As detailed above, combination systemic therapies, including chemohormonal therapy and intensive androgen suppression, have become standard for initial treatment of mHSPC rather than ADT alone. Further, radiation of the primary tumor should be considered a standard of care for men with low-volume metastatic disease, with data still being gathered regarding the impact of surgery in disease control for mHSPC.

Ongoing trials assessing MDT may also shift the landscape, particularly if these studies demonstrate prolongation of disease control and survival endpoints associated with MDT. In addition to data regarding optimal systemic therapy, ongoing work assessing advanced PET imaging is expected to impact the mHSPC landscape due to identification of lower volume oligometastatic disease and stage migration. Overall, the landscape will likely continue to shift, with advances allowing more men with mHSPC to experience longer and better quality of life, and potentially enabling patients with previously incurable

disease to potentially see the possibility of cure.

Compliance with Ethical Standards

Conflict of Interest

Adam B. Weiner declares that he has no conflict of interest. Oluwarotimi S. Nettey declares that she has no conflict of interest. Alicia K. Morgans has received research funding (paid to her institution) from Bayer, and has received compensation for service on advisory boards from Astellas, Bayer, Sanofi, Genentech, AstraZeneca, and Janssen; has received compensation for service as a consultant from AstraZeneca; has received compensation for non-branded talks for education from Astellas; and has received compensation for research collaboration from Sanofi.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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