Caption: **New approaches**

Title: **Treatment of metastatic hormone sensitive prostate cancer**

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**Introduction**

Prostate cancer is the second most common cancer among men worldwide, with nearly 1.27 million new cases diagnosed annually.[1] The overall, median five-year survival rate is 87%,[2] but when diagnosed at a metastatic stage (nearly 15% of all new cases in the UK), the five-year survival rate drops to 49%.[2] The reduced survival is primarily due to the transformation of metastatic hormone sensitive prostate cancers (mHSPC) to castration-resistant prostate cancers (CRPC) within 2–3 years of starting standard of care androgen deprivation treatment (ADT). Patients with CRPC have limited treatment options and experience symptoms affecting quality of life.[3] Therefore, it is of paramount importance to identify more effective first-line treatment options for mHSPC.

A number of phase III randomised control trials (RCTs) have now shown improved outcomes for mHSPC patients by combining ADT with additional agent/radiotherapy. ADT has been the mainstay of mHSPC since the mid-twentieth century.[4] It involves use of Gonadotropin-releasing hormone (GnRH) agonists or antagonists, which suppress testosterone directly.

The recent RCTs for mHSPC have added escalated therapies at diagnosis and aim to target cancer cell clones resistant to ADT at the earliest opportunity to delay castration resistance. Some of these trials have stratified mHSPC into several categories (see Table 1). One of the important trials among them is a multi-arm multi-stage STAMPEDE trial.[5] The selection criteria for patients in this trial were high-risk, newly diagnosed non-metastatic node-negative disease, or newly-diagnosed metastatic, or node-positive disease, or previously radically treated and now relapsing disease. The trial opened with six arms (A–F) in 2005, but subsequently five more arms were added (G-L). Each trial arm investigated the benefit of adding a single agent or a combination of agents to standard of care (SOC) treatment. Over a period, STAMPEDE has evaluated the benefit of adding docetaxel, celecoxib, zoledronic acid, radiotherapy, abiraterone and enzalutamide either alone or in different combinations. The trial is on hold for now with the plan to potentially add additional arms to assess PARP inhibitors and oligometastatic disease management.

**Chemotherapy for mHSPC: docetaxel**

The addition of anti-mitotic chemotherapy agent, docetaxel, to ADT was the first combination to provide meaningful benefit for mHSPC patients. The randomised phase III CHAARTED trial showed median overall survival (OS) benefit of 10.4 months for all mHSPC patients treated with ADT plus docetaxel compared to ADT alone (hazard ratio [HR], 0.72; 95%; CI, 0.59 to 0.89; $p$=0.0018),[6,7] with a 53.7 month follow up. This OS benefit was almost exclusively driven by high volume disease, with no significant OS benefit noted in mHSPC patients with low volume disease. The STAMPEDE arm C phase III trial demonstrated an OS benefit of 10 months (HR 0.78; 95% CI, 0.66 to 0.93; $p$=0.006) in ADT plus docetaxel and prednisolone arm over ADT alone for men with metastatic prostate cancer at a median follow-up of 43 months.[8]

Interestingly, a retrospective reclassification in STAMPEDE showed benefit for both high and low volume disease. The common side effects were febrile neutropenia and peripheral neuropathy. This data led NICE to recommend six, three-weekly cycles of docetaxel (with or without daily prednisolone) initiated within three months of starting ADT as a first line standard of care treatment for mHSPC since 2019.

**Abiraterone for mHSPC**

Abiraterone offers a potential advantage over ADT alone in that it inhibits androgen biosynthesis in adrenals and prostate cancer tissue as well. The combination of abiraterone (plus prednisolone) with ADT was first tested in high risk mHSPC patients in the LATITUDE trial.[9,10] It showed a 16.8-month OS advantage over ADT alone (HR 0.66 95% CI 0.56 to 0.78; $p$<0.0001) at median follow up of 51.8 months.

STAMPEDE arm G also investigated the benefit of 'abiraterone and prednisolone' (AAP) and ADT compared to ADT alone for mHSPC.[11] It showed improved five-year survival with AAP+ADT (60%) compared to ADT alone (41%), with benefits observed in both low burden (HR 0.55; 95% CI 0.41 to 0.76) and high burden (HR 0.54; 95% CI 0.43 to 0.69) metastatic disease.[12] The main grade 3/4 side effects were hypertension (20%), hypokalemia (11%), and liver enzymes derangement (5%). Some of these side effects are because abiraterone suppresses cortisol, increasing the concentration of precursors of cortisol with mineralocorticoid activity. Prednisolone is given in combination with abiraterone to lower the incidence and severity of mineralocorticoid-related side effects.

Indirect comparison of AAP+ADT with docetaxel and ADT showed similar OS benefit, but abiraterone plus ADT was found to maintain better quality of life in STAMPEDE analyses. The US food and drug administration (US FDA) approved abiraterone plus prednisolone and ADT for the management of high risk mHSPC based on the LATITUDE data. However, currently NICE only allows switching to abiraterone plus prednisolone with ADT in patients who experienced toxicity to enzalutamide within the first three months of starting the treatment.

**Enzalutamide for mHSPC**

Enzalutamide is a second-generation non-steroidal anti-androgen, which suppresses androgen receptor activity more completely than first-generation anti-androgens (for example, bicalutamide), even in the context of androgen receptor overexpression.

Two key phase III RCTs have evaluated the role of enzalutamide in the context of mHSPC: ARCHES and ENZAMET.[13,14] ARCHES investigated the role of enzalutamide or placebo plus ADT, stratifying patients by disease volume and previous docetaxel use. The primary end point of radiological progression free survival (rPFS) demonstrated a 61% improvement in rPFS in the enzalutamide group (HR=0.39; 95% CI 0.30–0.50; $p$<0.001) at 14.4 months. This was consistent across most pre-specified subgroups, including volume of disease (high volume, HR 0.44, 95% CI 0.33-0.57; low volume, HR 0.24, 95% CI 0.13–0.45) and previous docetaxel (no prior, HR 0.36, 95%CI 0.27–0.48; prior, HR 0.53, 95% CI 0.31–0.92).

ENZAMET investigated the use of enzalutamide versus first-generation non-steroidal anti-androgens with/without early docetaxel use. The use of concurrent docetaxel was permitted due to the then accepted treatment benefit in the hormone sensitive setting. The primary endpoint of OS at three years was 80% in the enzalutamide group, compared to 72% in the standard-care group. The experimental arm demonstrated a 33% reduction in death (HR 0.67; 95% CI 0.52–0.86) and improved

secondary endpoints of clinical and PSA PFS (with HR 0.40; 95% CI 0.33–0.49, and HR 0.39; 95% CI 0.33–0.47, respectively).

Key side-effects of enzalutamide include hypertension and central nervous system-related toxicities: dizziness, fatigue, seizures and falls. Nonetheless, it still requires less intense monitoring compared to abiraterone (see Table 2), and patient-reported outcomes demonstrated that enzalutamide is well tolerated. In 2019 the US FDA approved the use of enzalutamide in the mHSPC setting, and in the wake of COVID-19 pandemic NICE approved the use of enzalutamide with ADT as the first line management for mHSPC.

**Apalutamide for mHSPC**

Apalutamide is another second-generation non-steroidal anti-androgen. It binds directly to the ligand-binding domain of the androgen receptor, thereby preventing androgen-receptor translocation, DNA binding, and androgen receptor–mediated transcription.

Apalutamide's role in mHSPC was assessed in the TITAN study.[15] In this RCT, mHSPC patients received apalutamide or placebo alongside ADT: 62.7% of patients had high volume disease, while a small proportion (10.7%) had received previous docetaxel. The primary endpoints of PFS and OS both demonstrated a significant improvement in the apalutamide arm, with radiological PFS HR 0.48; 95% CI, 0.39–0.60; $p$<0.001, and OS HR 0.67; 95% CI 0.51–089. The benefit was consistent across all sub-group analyses.

Overall, apalutamide was well tolerated and health related quality of life was preserved. Grade 3–4 adverse events occurred in 42.2% of patients taking apalutamide versus 40.8% in the standard arm. However, rash of any grade was approximately three times more likely in the apalutamide group. Other reported side effects include CNS toxicities like that of enzalutamide, increased risk of fractures, and hypothyroidism. Although apalutamide was granted US FDA approval for the management mHSPC in 2019, NICE review is currently awaited.

**Prostate radiotherapy for mHSPC**

Historically, radiotherapy to the prostate in the context of metastatic disease was reserved for palliation. The STAMPEDE trial randomised men to standard of care systemic therapy, with or without radiotherapy to the prostate in newly diagnosed mHSPC.[16] Patients with fewer than four bone metastases saw a significantly higher overall survival at three years compared with those who had standard of care (81% versus 73%).

The benefit is thought to be related to the 'soil and seed' theory that the primary tumour plays a role in making certain organs susceptible to metastases. The 'soil' in this case is the metastatic site that is enriched by prostate, which is thought to secrete compounds that create congenial conditions for metastases (the 'seed') to thrive. This means local treatment of the primary tumour inhibits not just new metastases but also the progression of existing metastases. The same benefit was not seen in patients with a high metastatic disease burden – defined as four or more bone metastases with at least one lesion outside the axial skeleton and/or visceral metastases.

**Considerations while choosing treatment options**

Treatment options for mHSPC have expanded rapidly in recent years. Systemic treatments, including androgen-targeted agents and cytotoxic drugs, as well as an increased use of radiotherapy have changed the landscape dramatically. Increasingly, ADT is the building block rather than the mainstay of treatment. Further management approaches are also on the horizon. Second-generation anti-

androgen, darolutamide, was recently approved for use in the non-metastatic castrate-resistant setting and may show benefit in the mHSPC setting, which offer favourable CNS side effect profile.

However, the sequencing of treatments remains controversial. Even in the metastatic setting, prostate cancer can be an indolent disease and there remains a risk of compromising quality of life without providing meaningful survival benefit due to unnecessary overtreatment. More research is needed to examine these new treatments head-to-head, and sequentially. Biomarkers may help inform decisions to prospectively stratify patients into different treatment categories and their identification is a prime research area. The optimal management strategy would depend not only on the weight of the evidence, but also on individual patient factors including co-morbidities, risks of side effects, and patient preference.

**Declaration of interests**

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**Figures/tables**

| **Stratification** | **Criteria** |
|---|---|
| High volume vs low volume (CHAARTED)[7] | High volume disease includes at least 1 of the following:<br>• ≥4 bone lesions with ≥1 beyond the vertebral bodies/pelvis<br>• Visceral metastasis |
| High risk vs low risk (LATITUDE)[9] | High risk disease includes at least 2 of the following:<br>• ≥3 bone lesions<br>• Visceral metastasis<br>Gleason score ≥8 |

Table 1. Stratification of mHSPC

| **Agent** | **Dose and route** | **Monitoring requirements** | **Comments** |
|---|---|---|---|
| Docetaxel | 75mg/$m^2$ IV in six 3-weekly cycles | Hospital administration required | Steroid co-administration needed |

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|---|---|---|---|
| Abiraterone | 1000mg daily PO | Monitor blood pressure, liver enzymes, and electrolytes Every 2 weeks, outpatient | Steroid co-administration needed |
| Enzalutamide | 160mg daily PO | Monitor blood pressure and electrolytes every 4 weeks | Steroid co-administration not needed<br>CYP-inhibitor |
| Apalutamide | 240mg daily PO | Monitor blood pressure, thyroid function tests, and electrolytes every 4 weeks | Steroid co-administration not needed<br>CYP-inhibitor |
| Radiotherapy | STAMPEDE: 55 Gy in 20 fractions or 36 Gy in 6 fractions to prostate | hospital visit required | For low volume metastatic disease only |

Table 2. Summery of current available options