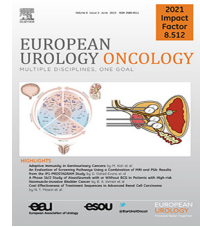


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Does Research from Clinical Trials in Metastatic Hormone-sensitive Prostate Cancer Treatment Translate into Access to Treatments for Patients in the “Real World”? A Systematic Review

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Abstract

Context: Since 2015 there have been major advances in the management of primary metastatic hormone-sensitive prostate cancer (mHSPC) following the publication of key clinical trials that demonstrated significant clinical benefits with docetaxel chemotherapy or novel hormone therapy (NHT) in addition to androgen deprivation therapy (ADT). Despite these advances, there is evidence to show that these treatments are not being utilised for mHSPC in clinical practice.

Objective: To determine the utilisation of docetaxel and NHT in mHSPC in routine practice and the determinants of variation in their use.

Evidence acquisition: MEDLINE and Embase were searched systematically for studies on utilisation of treatments for primary mHSPC that were based on regional or national data sets and published after January 2005. Study results were summarised using a narrative synthesis.

Evidence synthesis: Thirteen papers were included in the analysis, six full-text articles and seven abstracts, on studies that included a total of 166 876 patients. The utilisation rate of treatment intensification with either docetaxel or NHT (enzalutamide, apalutamide, or abiraterone) in addition to ADT ranged from 9.3% to 38.1% across the studies. Younger, White patients with fewer comorbidities and living in more urban settings were more likely to be prescribed treatment intensification. Patients treated in private academic institutions by oncologists were more likely to receive docetaxel or NHT. Socioeconomic status did not impact receipt of systemic therapy. NHT utilisation rates appear to have increased over time.

Conclusions: These results highlight the need to change the approach to the treatment of primary mHSPC in the real world by harnessing the practice-changing results from recent trials in this setting to optimise upfront systemic therapy for this patient population.

Patient summary: We reviewed the use of treatments for primary metastatic hormone-sensitive prostate cancer that showed a benefit in key clinical trials. We found that these treatments are underused, particularly among certain patient groups.

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1. Introduction

The basis of treatment in metastatic hormone-sensitive prostate cancer (mHSPC) has been androgen deprivation therapy (ADT). However, since 2014 there has been a significant shift in treatment options following several practice-changing trials.

In 2015, the CHAARTED trial [1] demonstrated significant improvement in median overall survival (OS) for men treated with docetaxel combined with ADT in comparison to ADT alone (57.6 vs 44.0 mo). The trial found that the treatment benefit was restricted to patients with high-volume disease, defined as the presence of visceral metastases or four or more bone lesions with one or more beyond the vertebral bodies and pelvis. In 2016, the STAMPEDE study [2] also showed that docetaxel given at the time of ADT initiation was associated with better median OS (81 vs 71 mo). This improvement in OS was regardless of metastatic burden [3]. Docetaxel was approved by the European Medicines Agency (EMA) in September 2019.

In 2017, two randomised controlled trials (RCTs), STAMPEDE [4] and LATITUDE [5], revealed an increase in OS for men with mHSPC who received abiraterone in combination with prednisolone in addition to ADT. This treatment was approved by the EMA in November 2017 and the US Food and Drug Administration (FDA) in February 2018. More recently, the ARCHES [6] and ENZAMET [7] studies have shown that enzalutamide in combination with ADT improved OS significantly when given as first-line treatment in the primary mHSPC setting.

The TITAN trial [8] published in 2019 showed that apalutamide in addition to ADT improved the OS rate at 24 mo in comparison to ADT alone (82.4% vs 73.5%). The ARASENS study demonstrated an OS benefit with darolutamide in combination with ADT and docetaxel as a triplet therapy in comparison to ADT and docetaxel [9]. Finally, the PEACE-1 trial [10] explored the benefit of abiraterone in combination with ADT and docetaxel and found that this treatment combination improved OS for patients with high-volume disease.

These studies have influenced national and international evidence-based guidelines, which subsequently recommended the use of treatment intensification with either docetaxel or novel hormonal therapy (NHT) in combination with ADT in the first-line mHSPC setting [11–13]. However, early evidence suggests that not all patients eligible for these treatments are receiving these life-prolonging therapies. For example, the National Prostate Cancer Audit NPCA found that following approval of docetaxel in the first-line setting, only 36% of men diagnosed with mHSPC in England received this agent between April 2018 and March 2019 [14]. However, the determinants of this variation and whether these inequalities affect particular patient groups have yet to be explored. Evidence of poor implementation of trial evidence in routine clinical practice is an important issue given the significant benefit this may provide in terms of OS and quality of life.

The aim of this systematic review was to evaluate evidence on whether research from clinical trials has been translated into access to treatments for patients with

primary mHSPC in the real-world setting. We also sought to understand what patient and clinical factors might influence the utilisation of these systemic treatments in a national or regional population setting.

2. Evidence acquisition

2.1. Study eligibility

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist. Studies were eligible for inclusion if they investigated evidence on the rates of utilisation of systemic cancer therapies in clinical practice.

2.2. Search strategy

Search terms were designed to focus on three key concepts: (1) to identify patients with primary mHSPC; (2) to identify specific treatments for prostate cancer; and (3) to assess utilisation or practice patterns for these treatments. The final research strategy is shown in the [Supplementary material](#).

Publications were included for review if they explored the patient population with mHSPC and evaluated interventions involving specific systemic prostate cancer treatments (docetaxel, or NHT with abiraterone, enzalutamide, or apalutamide). Studies reporting on patterns of utilisation of systemic therapy as outcomes and on the determinants of variation were included. Studies were eligible for inclusion if they used regional or national data sets. The review was limited to observational studies published between January 2005 and June 2022 to ensure it reflected contemporary management of prostate cancer. We also evaluated when these treatments received FDA and EMA approval and their indications as recommended in national or international guidelines.

Publications were excluded if they were not written in English; related to nonmetastatic or metastatic castrate-resistant prostate cancer; analysed surgical or radiotherapy treatment interventions; were published as editorials, commentaries, letters, case reports, or the “grey” literature; or used data from a single centre only. If multiple publications were identified describing similar results using the same data set, only the most recent publication was retrieved. Publications that used the same data set but analysed different treatments or determinants of variation were included.

A single author (J.D.) performed electronic searches of two online databases (Embase and MEDLINE) via the OVID platform in June 2022. The titles and abstracts were assessed by two authors (J.D. and A.A.) and all potentially relevant articles were identified for full-text review. The final selection from the set of full-text articles was independently performed by two authors (J.D. and A.A.), with disagreements resolved via discussion with a senior author (J.v.d.M.). Reasons for exclusion included: castration-resistant disease [15–24], no evaluation of treatment utilisation and/or determinants [25–35], incorrect population [36–41], and cost analysis [42]; one abstract was excluded because the full-text paper was included in the review [43].

2.3. Data extraction

Information on study characteristics was extracted by two authors (J.D. and A.A.) and included the article information (eg, first author, publication year), population demographics, study methodology, and key findings. Utilisation rates for each treatment type and any determinants of variation were summarised. The change in utilisation rates over time was also captured.

2.4. Assessment of study quality

The Newcastle-Ottawa Scale (NOS) [44] was used to appraise the quality of each full-text article. There was insufficient information for studies that were published only as abstracts to perform this quality assessment. Given that the studies were exploring rates of utilisation of treatment intensification available for all patients rather than comparing one cohort with another, we used a modified NOS scoring system that appraises noncomparative observational studies on a scale from 0 to 6, rather than from 0 to 9 [45]. A higher score indicates a lower risk of bias and therefore superior study quality. Two authors (J.D. and A.A.) assessed each paper independently, with score discrepancies resolved via discussion.

2.5. Analysis of results

Studies were analysed using a narrative synthesis approach [46]. All studies provided utilisation rates across the time period for evaluation. In addition, some studies provided an utilisation rate either annually or monthly for the study duration. A meta-analysis of overall utilisation rates and predictors was not performed because of the variation in study populations and intervention types in the studies.

The review protocol was registered on PROSPERO (CRD42023316786).

3. Evidence synthesis

3.1. Studies included in the review

The electronic database searches identified 2477 studies. The titles and abstracts of papers identified via this search were screened, and 43 papers were selected for full-text review. Of these, 13 papers met the study eligibility criteria [47–59]. There were six full-text articles and seven abstracts. The study selection steps are presented in Figure 1. Two studies used the same data set and cohort, so were only included once when analysing changes over time, but as the studies explored different determinants, they were included separately in the analysis of determinants of variation [50,52].

3.2. Study characteristics and quality assessment

Table 1 summarises the characteristics of the 13 publications. All papers had a population-based cohort design and used clinical or administrative databases for data acquisition. The studies were conducted in various countries in different health care systems, including eight from the USA [49,50,52–55,57,58], three from Europe [48,51,56],

one from Australia [47], and one from Canada [59]. Nine studies were conducted in a national setting [48–52,54,55,57,58] and four in a regional setting [47,53,56,59]. All studies included patients with primary mHSPC, with a total of 166 876 patients assessed across the 13 papers. All of the studies used cohorts from 2009 to 2021, and three studies included data for patients undergoing treatment during the COVID-19 pandemic in 2020 and 2021. The data sources used in each study varied from cancer registries ($n = 3$) to insurer databases ($n = 5$) and other company databases ($n = 4$). Cancer registries known to capture the majority of prostate cancer cases in a region are less prone to bias than registries maintained by insurers or other companies, which can be less representative of the target population. The quality of the six full-text studies was assessed using the modified NOS. Three studies scored 4 out of 6, and the other three scored 5 out of 6 (Supplementary Table 1).

The therapeutic combination evaluated most frequently was NHT (either abiraterone, enzalutamide, or apalutamide) and ADT ($n = 12$) [47–55,57–59], followed by docetaxel and ADT ($n = 11$) [47,49,50,52–59]. Of the 12 studies evaluating NHT, five reported on abiraterone specifically [48,49,51,58,59]. Triplet therapy comprising docetaxel, NHT, and ADT was evaluated in one study [57]. The comparator treatment in all studies was ADT alone. Some papers also included detail on utilisation of a first-generation nonsteroidal anti-androgen (NSAA) agent (bicalutamide or flutamide) and ADT [49,50,52,53,55,57,58].

3.3. Rates of utilisation of systemic treatments in the management of mHSPC

Table 2 summarises the rates of utilisation of the treatments for mHSPC. The proportion of patients who received any treatment intensification for mHSPC (with either docetaxel or NHT or triplet therapy) ranged from 9.3% to 38.1% across the studies. More specifically, only between 2% and 38.1% of eligible patients received docetaxel and ADT in real-world practice [47,49,50,52,53,55–59]. In studies exploring NHT in addition to ADT, the utilisation rate ranged from 4% to 30% [47,50,52–55,57]. In studies specifically exploring abiraterone and ADT, the utilisation rate ranged from 1.5% to 12% [48,49,51,58,59]. Finally, only one paper assessed triplet therapy, for which the utilisation rate was 0.9% [57]. Of the studies that reported on NSAAs in addition to ADT, the utilisation rate ranged from 14.3% to 30% [49,50,52,53,55,57,58].

3.4. Variation in utilisation rates over time

Ten of the 13 papers analysed variation in the utilisation of treatments over time [47–50,53–55,57–59], as summarised in Table 3. Most papers looked at a time frame after 2015, which correlates with publication of results from the CHARTED trial [1].

Of the ten studies, nine analysed the variation in NHT utilisation over time periods between 2014 and 2021; all found that utilisation rates have increased, with absolute differences in percentage points ranging from a 2.5% to a

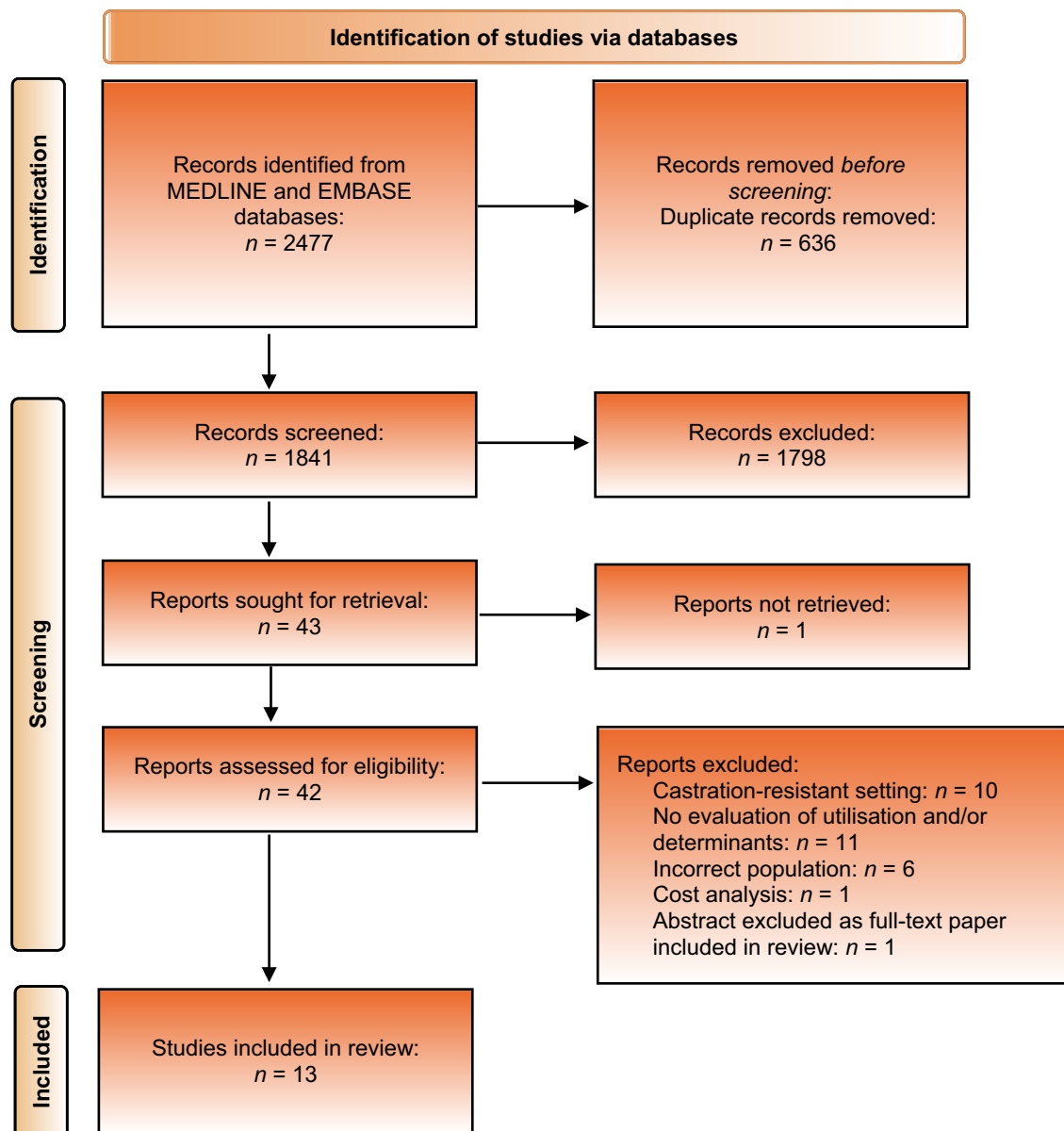


Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram of the search strategy and study selection process [73].

24% increase [48–50,53–55,57–59]. The variation in utilisation of NHT over time is summarised in Figure 2.

Eight studies also assessed the variation in docetaxel utilisation over time periods between 2014 and 2020: five found that the utilisation rate increased, while three identified a decrease, with absolute differences in percentage points ranging from a 13% increase to a 2% decrease [47,49,50,53,55,57–59]. One paper assessed utilisation of triplet therapy over time and found that this increased from 0.4% in 2014 to 1.8% in 2019 [57]. Conversely, rates of utilisation of NSAAs in addition to ADT decreased in all six studies assessing time trends between 2014 and 2020, with absolute differences in percentage points ranging from a 2.6% to a 27% decrease [49,50,53,55,57,58].

3.5. Determinants of variation in utilisation rates

Nine studies evaluated age as a determinant of variation for receipt of systemic therapy, as summarised in Table 2. Seven of these studies [47,49,52,56–59] found that docetaxel was utilised more frequently for younger patients (eg, median age 78 yr for ADT alone vs 67 yr for docetaxel [47]) and two studies [48,51] found that abiraterone was also utilised more frequently for younger patients in comparison to the control group receiving ADT alone.

Three of the four studies evaluating ethnicity [49,50,58] found that docetaxel and/or NHT was utilised more frequently for White patients: of the patients receiving docetaxel and ADT, 72% were White and 21% Black, while of those receiving ADT alone, 64% were White and 28% were

Table 1 – Key characteristics of studies selected for the systematic review

Study (year)	Country	Unit	Cohort	Dataset	N	Treatments in addition to ADT evaluated
Gedeborg 2022 [51]	Sweden	National	2018–2019	National Prostate Cancer Register Sweden	1511	Abi
Joyce 2022 [54]	USA	National	2015–2021	IQVIA database	63 289	NHT vs NSAA vs Doc
Azad 2022 [47]	Australia	Regional	2014–2018	Prostate Cancer Outcomes Registry Victoria	1014	Doc vs NHT
Fallara 2021 [48]	Sweden	National	2018–2020	National Prostate Cancer Register Sweden	2041	Abi
Wallis 2021 [59]	Canada	Regional	2014–2019	Institute for Clinical Evaluative Sciences database	3556	Doc vs Abi
Freedland 2021 [49]	USA	National	2013–2018	Veterans Health Administration	1395	Doc vs Abi vs NSAA
George 2021 [53]	USA	Regional	2014–2019	Concert AI Oncology	858	Doc ± NSAA vs NHT ± NSAA vs NSAA
Mar 2021 [55]	USA	National	2015–2020	IQVIA database	16 768	NHT vs NSAA vs Doc
Freedland 2021 [50] ^a	USA	National	2009–2018	Medicare	35 195	Doc vs NSAA vs NHT
George 2021 [52] ^a	USA	National	2009–2018	Medicare	35 195	Doc vs NSAA vs NHT
Swami 2021 [57]	USA	National	2014–2019	Optum health insurance claims	4221	Doc vs NSAA vs NHT vs Doc/NHT
Tagawa 2020 [58]	USA	National	2014–2018	Veterans Health Administration	1553	Doc vs NSAA vs Abi
Rulach 2018 [56]	Scotland	Regional	2015–2016	Electronic patient record/chemocare	280	Doc

Doc = docetaxel; Abi = abiraterone; Apa = apalutamide; NHT = novel hormonal therapy; NSAA = nonsteroidal antiandrogen; ADT = androgen deprivation therapy.

^a These studies used the same data set but explored different determinants.

Black [49]. One study found no significant difference in utilisation by ethnicity [53].

Five studies assessed comorbidities and/or performance status [48,49,51,56,59] and found that both docetaxel and abiraterone were used in patients with fewer comorbidities or better performance status in comparison to use of ADT alone (eg, 58% of patients receiving docetaxel had a performance status of zero, in comparison to 5% of patients receiving ADT alone [56]). Socioeconomic deprivation was analysed in two studies (one from Australia and one from Canada) that revealed no significant variation in receipt of systemic therapy [47,59].

Seven studies analysed the impact of metastatic burden on choice of systemic therapy. Two studies found that abiraterone was used more frequently for patients with four or more bone metastases [48,51]. Five studies found that docetaxel and/or NHT were used more often in the presence of bone and/or visceral metastases [47,49,52,57,58].

Regional variation was analysed in five studies. Two of these [47,59] found that patients treated in urban areas were more likely to receive docetaxel and ADT in comparison to men in rural areas (eg, of patients receiving docetaxel and ADT, 91% were from urban settings, while of those receiving ADT alone, 89% were from urban settings [59]). Two other studies [48,51] assessed utilisation rates across a country and found variation in abiraterone use by region. For example, the rate of abiraterone utilisation in Sweden varied between 0% and 39% across different regions [48].

The institutional setting was also identified as a determinant of variation in two studies [47,55], with docetaxel utilised more frequently in private or academic settings than in public or community settings in comparison to ADT alone. For example, of those receiving docetaxel plus ADT, 39% were in private settings, while of those receiving ADT alone, 26% were in private settings [47]. The specialist prescribing the treatment was investigated as a determinant of variation in two studies [54,55]. Oncologists were more likely to prescribe NHT than their urologist colleagues (36% vs 15%) [54].

3.6. Discussion

Our review revealed evidence of considerable variation in the utilisation of treatment intensification of systemic therapy for primary mHSPC in a number of countries, despite evidence from multiple RCTs showing the efficacy of docetaxel, abiraterone, enzalutamide, and apalutamide when combined with ADT. We found that across the 13 studies carried out in five countries between 2009 and 2021, the rate of utilisation of treatment intensification with either docetaxel or NHT ranged from 9.3% to 38.1%. This demonstrates that these treatments, deemed to be a modern standard of care, are not being implemented effectively in the population with primary mHSPC. However, there is evidence suggesting that there is an increasing trend for treatment utilisation over time across most studies, which is probably because the studies explored a time frame consistent with the implementation phase following clinical trial publication. In addition, it is too early to explore the uptake of triplet therapy regimes given that combination treatment with ADT, docetaxel, and darolutamide was only approved towards the end of 2022, so future research should explore the uptake of triplet therapies in real-world populations [60].

While rates of utilisation of docetaxel and NHT are low across all settings identified in this systematic review, there are patterns of underuse in certain patient groups and in particular settings. Treatment intensification utilisation is consistently lower for elderly patients and patients with more comorbidities. Similarly, docetaxel and NHT are more commonly prescribed to patients of White ethnicity or in urban, private, or academic settings in comparison to patients of Black ethnicity or in rural, public, or community settings. There are no differences by deprivation or socioeconomic status.

Similar patterns of underuse according to certain patient and health care characteristics have been observed in other studies in nonmetastatic prostate cancer. Previous research [61] found that the proportion of men with high-risk or

Table 2 – Treatment utilisation and determinants of variation

Study (year)	Treatment in addition to ADT				Determinants							
	Doc	Any NHT	Abi	NSAA	Age	Ethnicity	CMBs or PS	ADT	Region	Institution/setting	Prescribing specialty	Metastatic burden
Gedeborg 2022 [51]	N/A	N/A	10%	N/A	Abi ↑ younger	– ^b	Abi ↑ fewer CMBs	– ^b	Regional variation 5–17%	– ^b	– ^b	Abi ↑ >4 bone mets
Joyce 2022 [54]	– ^a	30%	– ^a	– ^a	– ^b	– ^b	– ^b	– ^b	– ^b	– ^b	NHT ↑ Onc vs Uro	– ^b
Azad 2022 [47]	25%	4%	N/A	N/A	Doc ↑ younger	– ^b	– ^b	↔	Doc ↑ urban vs rural	Doc ↑ private vs public	– ^b	Doc ↑ visceral
Fallara 2021 [48]	N/A	N/A	12%	N/A	Abi ↑ younger	– ^b	Abi ↑ fewer CMBs	– ^b	Regional variation 0–39%	– ^b	– ^b	Abi ↑ >4 bone mets
Wallis 2021 [59]	11.2%	N/A	1.5%	N/A	Doc ↑ younger	– ^b	Doc ↑ fewer CMBs	↔	Doc ↑ urban vs rural	– ^b	– ^b	– ^b
Freedland 2021 [49]	8%	N/A	5%	24%	Doc ↑ younger	Doc ↑ White	Doc ↑ fewer CMBs	– ^b	– ^b	– ^b	– ^b	Doc ↑ visceral/bone
George 2021 [53]	16.4%	19.2%	N/A	26.3%	– ^b	↔	– ^b	– ^b	– ^b	– ^b	– ^b	– ^b
Mar, 2021 [55]	2%	16%	N/A	30%	– ^b	– ^b	– ^b	– ^b	National ↑ ADT California ↑ NSAA	NHT ↑ ACA vs COM	NHT ↑ Onc vs Uro	– ^b
Freedland 2021 [50] ^c	4.8%	4.5%	N/A	14.3%	– ^b	Doc/NHT ↑ White	– ^b	– ^b	– ^b	– ^b	– ^b	– ^b
George 2021 [52] ^c	4.8%	4.5%	N/A	14.3%	Doc ↑ younger	– ^b	– ^b	– ^b	– ^b	– ^b	– ^b	Doc/NHT ↑ visceral//bone
Swami 2021 [57]	8.2%	NHT 13.7% (TPT 0.9%)	N/A	21.1%	Doc/TPT ↑ younger	– ^b	– ^b	– ^b	– ^b	– ^b	– ^b	Doc ↑ visceral
Tagawa 2020 [58]	8%	N/A	6%	25%	Doc ↑ younger	Doc ↑ White	– ^b	– ^b	– ^b	– ^b	– ^b	Abi/Doc ↑ bone
Rulach 2018 [56]	38.1%	N/A	N/A	N/A	Doc ↑ younger	– ^b	Doc ↑ fewer CMBs	– ^b	– ^b	– ^b	– ^b	– ^b

Doc = docetaxel; Abi = abiraterone; Enza = enzalutamide; Apa = apalutamide; NHT = novel hormonal therapy (Abi, Enza, or Apa); NSAA = nonsteroidal antiandrogen; ADT = androgen deprivation therapy; N/A= not applicable; TPT = triplet therapy; CMBs = comorbidities; PS = performance status; ACA = academic; COM = community; Onc = oncology; Uro = urology; mets = metastases; ↑ = used more; ↔ = no difference

^a Treatment utilisation rate not clearly stated in the paper.

^b Determinant not been explored in this study.

^c These studies used the same data set but explored different determinants.

Table 3 – Change in the rate of utilisation of systemic therapy over time^a

Study (year)	Treatment in addition to ADT	Change over time			
		Doc	Any NHT	Abi alone	NSAA
Gedeborg 2022 [51]	Abi	No trend over time			
Joyce 2022 [54]	NHT vs NSAA vs Doc	–	2018: 20% 2021: 30% ↑	N/A	–
Azad 2022 [47]	Doc	2014: 20% 2015: 20% 2016: 25% 2017: 24% 2018: 33% ↑	N/A	N/A	N/A
Fallara 2021 [48]	Abi	N/A	N/A	2018: 4% 2020: 26% ↑	N/A
Wallis 2021 [59]	Doc vs Abi	Pre 2017 12% Post 2017 10% ↓	N/A	Pre 2017 0.5% Post 2017 3% ↑	N/A
Freedland 2021 [49]	Doc vs Abi vs NSAA	2014: 3% 2015: 8% 2016: 12% 2017/18: 9% ↑	N/A	2014: 1% 2015: 2% 2016: 2% 2017/18: 15% ↑	2014: 31% 2015: 30% 2016: 20% 2017/18: 17% ↓
George 2021 [53]	Doc ± NSAA vs NHT ± NSAA vs NSAA	2014: 8.3% 2015: 19.8% 2016: 14.6% 2017: 22.0% 2018: 17.0% 2019: 10.1% ↑	2014: 10.2% 2015: 11.2% 2016: 14.6% 2017: 19.2% 2018: 27.7% 2019: 34.2% ↑	N/A	2014: 42.6% 2015: 31.9% 2016: 31.7% 2017: 20.1% 2018: 19.8% 2019: 16.5% ↓
Mar 2021 [55]	NHT vs NSAA vs Doc	2015: 4% 2016: 10% 2017: 9% 2018: 7% 2019: 5% 2020: 2% ↓	2015: 0% 2016: 0% 2017: 0% 2018: 8% 2019: 14% 2020: 17% ↑	N/A	2015: 53% 2016: 46% 2017: 45% 2018: 38% 2019: 33% 2020: 26% ↓
Freedland 2021 [50] ^b	Doc vs NSAA vs NHT	2014: 2.8% 2015: 5.9% 2016: 6.7% 2017: 4.5% 2018: 4.1% ↑	2014: 0.8% 2015: 0.9% 2016: 0.6% 2017: 6.3% 2018: 12.4% ↑	N/A	2014: 26.7% 2015: 24.3% 2016: 22.8% 2017: 20.1% 2018: 17.4% ↓
Swami 2021 [57]	Doc vs NSAA vs NHT vs Doc/NHT (TPT)	2014/15: 8.5% 2016/17: 8.6% 2018: 7.8% 2019: 7.6% ↓	2014/15: 2.4% 2016/17: 8.9% 2018: 25.1% 2019: 22.6% ↑ Triplet 2014/15: 0.4% 2016/17: 0.9% 2018: 1.1% 2019: 1.8% ↑	N/A	2014/15: 28.1% 2016/17: 23.5% 2018: 14.9% 2019: 15.3% ↓
Tagawa 2020 [58]	Doc vs NSAA vs Abi	2014: 2% 2017: 9% ↑	N/A	2014: 1% 2017: 14% ↑	2014: 30% 2017: 18% ↓
Rulach 2018 [56]	Doc	No trend over time			

Doc = docetaxel; Abi = abiraterone; Apa = apalutamide; NHT = novel hormonal therapy; NSAA = nonsteroidal antiandrogen; ADT = androgen deprivation therapy; ↑ = increase in utilisation over time; ↓ = decrease in utilisation over time; N/A = not applicable; TPT = triplet therapy.

^a Arrows indicate the direction of change over time using first and last dates only. National utilisation rates are reported. Any blank (–) for the change in treatment utilisation rate over time indicates that the change was not clearly stated in the paper.

^b This abstract and the abstract reported by George et al. [52] used the same data set and cohort, so the cohort was only included once in analysis of the change over time.

locally advanced prostate cancer who received radical local treatment (with surgery or radiotherapy) was lower for older men, men who were from more deprived socioeconomic backgrounds, men with more comorbidities, and men of Black ethnicity.

Our results show that oncologists were more likely to prescribe NHT than their urologist colleagues, which corroborates a recent study [62] that revealed that oncologists are more likely to prescribe NHT than urologists (32% vs 12%). While urologists are heavily involved in the manage-

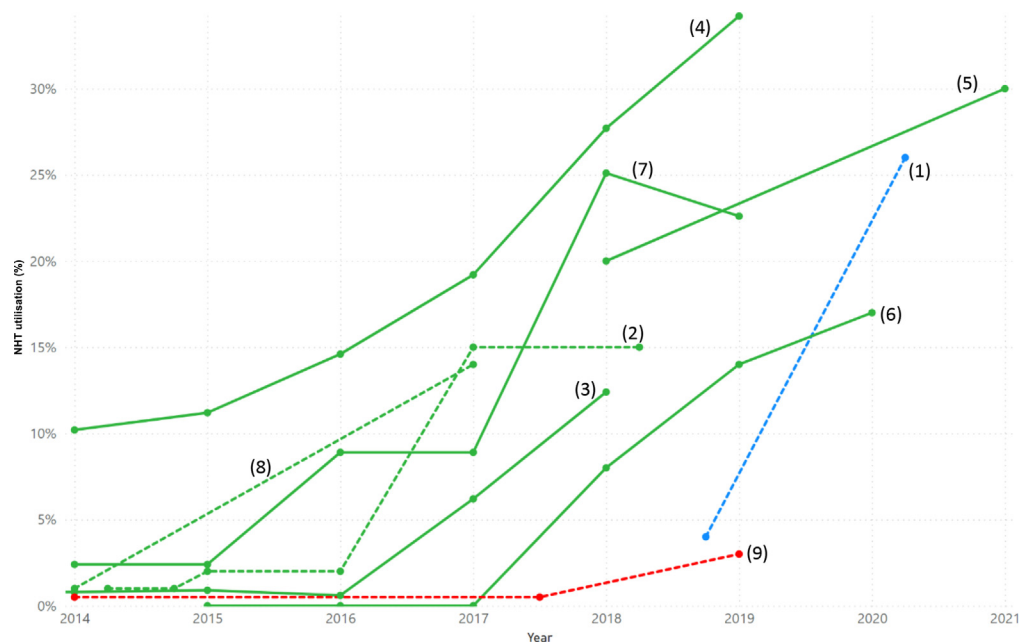


Fig. 2 – Variation in utilisation rates for novel hormonal therapy (NHT) over time. NHT includes enzalutamide, abiraterone, and apalutamide. Solid lines denote trials analysing any NHT, while dashed lines denote trials only analysing abiraterone. Green = USA; blue = Sweden; red = Canada. Published utilisation rates were used to plot the figure. If published results were by specific month or quarter, then the result was plotted at the appropriate point on the x-axis. The curves in the graph correspond to the following studies: (1) Fallara 2021 [48]; (2) Freedland 2021 [49]; (3) Freedland 2021 [50]; (4) George 2021 [53]; (5) Joyce 2022 [54]; (6) Mar 2021 [55]; (7) Swami 2021 [57]; (8) Tagawa 2020 [58]; and (9) Wallis 2021 [59].

ment of localised disease and frequently prescribe ADT for metastatic disease [63], the urologists in our own clinical research team have noted anecdotally that urologists can be discouraged or prevented from prescribing NHT, which may result in fewer patients having access to treatment.

While our study demonstrates that the NHT utilisation rate increased between 2014 and 2021 (ranging from a 2.5% to a 24% increase), there is still scope for greater access to these treatments in clinical practice. Conversely, utilisation of docetaxel peaked around 2015 and 2016 following release of CHARTED and STAMPEDE data in 2015–2016, and subsequently declined in more recent years. This probably coincides with the increasing utilisation of NHT. A recent direct randomised comparative analysis of docetaxel and abiraterone demonstrated no difference in efficacy between the two new treatment standards [64].

Reasons for underutilisation of treatment intensification for patients with primary mHSPC could include patient preference, prescribing restrictions including financial barriers or access to certain drug treatments, geographic access, educational access, and other patient determinants (eg, patient frailty).

With respect to prescribing restrictions, some commissioning authorities and health technology assessment bodies may mandate specific indications for particular treatments in the metastatic setting. For example, in Sweden, abiraterone for mHSPC is subsidised only for high-volume disease (Gleason score 8–10, ≥ 3 bone metastases, or visceral metastases) in patients not suitable for docetaxel [65]. Similar criteria are likely to be in effect in other countries and regions, which may explain the results observed.

While it is important to consider a patient's performance status, comorbidities, and fitness when considering treatment intensification in mHSPC, especially given the age profile of patients with newly diagnosed mHSPC [66], it is essential not to marginalise patients and preclude them from receiving these treatments. This reinforces the importance of a formal comprehensive geriatric assessment (CGA). A recent study [67] found that CGA led to better functional and quality-of-life scores and lower rates of early treatment cessation. Therefore, referral to geriatric oncology or use of a CGA is important in optimising the use of systemic therapy in older patients. However, even with these assessments, the risks of adverse events and pre-existing comorbidities may preclude the use of these therapies.

Recent work using medical charts from multiple US academic and community practices [68] explored the clinician reasons for treatment choice for patients with mHSPC. The top reasons why clinicians were reluctant to prescribe NHT were perceptions about drug tolerability (38%), lack of clinical trial evidence on OS improvement (31%), lack of reimbursement (26%), patient financial constraints (20%), and questions about sequencing of NHT earlier versus later in the disease course (21%). These findings highlight the need for further clinician education regarding these treatments for mHSPC, particularly during a period of transition following publication of RCT evidence.

Our work highlights the importance of monitoring utilisation of the oncological treatments given to patients with mHSPC. An example of such a monitoring project is the National Prostate Cancer Audit, which since 2013 has enabled providers of cancer services in England and Wales

to compare their data for specific quality indicators against explicit standards and against other providers [69].

Our results highlight the need to monitor access to NHT agents from the moment that RCTs provide data about their effectiveness. Implementation of the trial results will be supported by further research that can provide a better understanding of how implementation of treatment intensification, when its clinical and cost effectiveness is demonstrated, can be facilitated.

3.6.1. Strengths and limitations

A strength of our study is its inclusion of international publications that identify utilisation rates and trends over time, as well as determinants of variation. There are temporal limitations, as we explored papers published only up to June 2022, and included cohorts between 2009 and 2021, which was a period of rapid change in the management of mHSPC. The COVID-19 pandemic has impacted on treatments for all cancers, including prostate cancer [70], and new national guidance has been released in line with this context [71]. With the impact of COVID-19 ongoing, it will be important to do conduct further research on the utilisation of these treatments following the impact of the pandemic. In addition, we did not consider the statistical uncertainty for the published utilisation results when summarising results across studies, but given the numbers of patients included, it is unlikely that the trends highlighted can be explained by random variation.

All studies were conducted in high-income countries (including the USA, Canada, Sweden, Scotland, and Australia) and eight were USA-based [49,50,52–55,57,58] and analysed similar populations. This may have an implication for the generalisability of our findings regarding the factors associated with variation in utilisation rates. A further limitation of our study is the lack of availability of individual patient data to review. Finally, it will be important to assess utilisation of these treatments in low- and middle-income countries, as resource allocation and financial constraints could affect treatment provision in these health care settings [72].

4. Conclusions

In summary, our results highlight the discordance between recent practice-changing trials on treatments for mHSPC and the translation of trial findings into clinical practice. There is clear evidence of low utilisation rates of treatment intensification with docetaxel, abiraterone, enzalutamide, and apalutamide, even though freely available information has been published regarding their effectiveness. With the continued approval of new therapies for mHSPC, it is necessary to understand the timing and speed of the implementation of new evidence and national guidelines on oncological treatment intensification in real-world practice outside a clinical trial setting.

Author contributions: Joanna Dodkins had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dodkins, Aggarwal, van der Meulen.

Acquisition of data: Dodkins, Aggarwal.

Analysis and interpretation of data: Dodkins, Aggarwal.

Drafting of the manuscript: Dodkins.

Critical revision of the manuscript for important intellectual content: Dodkins, Aggarwal, van der Meulen, Nossiter, Cook, Payne, Clarke.

Statistical analysis: Dodkins, Aggarwal.

Obtaining funding: Dodkins, Aggarwal, van der Meulen.

Administrative, technical, or material support: Dodkins.

Supervision: Aggarwal, van der Meulen, Nossiter, Cook, Payne, Clarke.

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Appendix A. Supplementary data

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