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Effectiveness of Docetaxel for Metastatic Hormone-sensitive Prostate Cancer in Clinical Practice

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Article info

Abstract

Background: Addition of docetaxel to androgen deprivation therapy (ADT) for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) has been proved to be effective with an overall survival (OS) benefit in phase III clinical trials. The effectiveness of docetaxel with ADT in the general patient population remains unknown.

Objective: The purpose of this study is to report the clinical experience in mHSPC patients treated with 3rd-weekly docetaxel plus ADT in routine practice at two Danish institutions.

Design, setting and participants: A two-center retrospective study including consecutive mHSPC patients treated with 3rd-weekly docetaxel plus ADT was conducted.

Outcome measurements and statistical analysis: Outcomes of interest were OS, and biochemical and clinical progression-free survival.

Results and limitations: A total of 173 consecutive patients with mHSPC who received docetaxel every 3rd week plus ADT between June 2015 and February 2018 were included. Most patients had high-volume disease (85%). All six planned docetaxel cycles were delivered in 149 cases (86%). Of the patients, 106 (61%) were alive at the last follow-up. At a median follow-up of 42 (37.8–58.6) mo, the median OS was 51.6 (41.5–56.3) mo. Castration-resistant prostate cancer (CRPC) developed in 46% within 1 yr, with a median time to CRPC of 15.6 (13.0–18.1) mo. Prostate-specific antigen nadir ≤ 0.2 ng/l was achieved in 15% of patients after 6 mo of ADT and in 19% after 12 mo.

Conclusions: The effect of docetaxel for mHSPC patients treated in routine practice appears comparable with the overall efficacy reported in the literature. Selection of patients will influence the results in clinical practice and clinical studies.

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Patient summary: In this report, we looked at the clinical effectiveness of docetaxel combined with androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer (mHSPC) in a Danish population. We found the effect of docetaxel treatment for mHSPC in the general population to be comparable with the overall efficacy reported in published studies.

1.   Introduction

Worldwide, prostate cancer (PCa) is the second most common cancer and the fifth leading cause of cancer-related death in men [1]. The majority of patients have localized or locoregional disease. Patients with metastatic disease at the time of PCa diagnosis represent 5–15% of all PCa diagnoses but account for about one-third of PCa-related deaths [2,3].

For 75 yr, targeting the androgen pathway has been the cornerstone in the management of metastatic hormone-sensitive prostate cancer (mHSPC) [4]. Although most men initially respond to androgen deprivation therapy (ADT), progression occurs within a median of 18–24 mo [5].

Three large randomized trials, GETUG-AFU 15 [6], CHAARTED [7], and STAMPEDE (arms C and E) [8], explored the benefit of using docetaxel in conjunction with ADT in terms of overall survival (OS), and biochemical and clinical progression-free survival. Despite differences between trials [9], the evidence in favor of adding docetaxel in high-volume mHSPC has led to its incorporation in guidelines [10], and docetaxel for mHSPC was introduced as a standard of care in Denmark in June 2015.

The effectiveness of docetaxel with ADT in routine practice remains unknown. The aim of this study is to verify the effect of docetaxel in mHSPC, when used in routine practice.

2.   Patients and methods

2.1.   Patients

The study population consisted of a consecutive cohort of patients who received docetaxel for mHSPC between June 2015 and February 2018 either at the Department of Oncology, Rigshospitalet, or at the Department of Oncology, Herlev Hospital. Metastatic HSPC was defined according to the CHAARTED criteria [7]. Patients who received docetaxel had a pathological diagnosis of PCa or a clinical scenario consistent with PCa with an elevated prostate-specific antigen (PSA) level, radiological evidence of metastatic disease, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) score of 0, 1, or 2 (in patients with a score of 2, docetaxel was indicated only if the decrement in functioning was due to PCa).

Patients were identified using local databases recording all chemotherapy regimens administered during the study period. Patient files were reviewed to confirm eligibility. Patients were defined eligible if they had received at least one dose of docetaxel for mHSPC and had complete treatment records.

2.2.   Data collection

Data were retrieved from medical records, and patients were followed until July 1, 2020 or death, whichever came first. We reviewed individual records for baseline patient characteristics: age, ECOG PS (defined by scores of 0–4, where 0 indicates no impairment and 4 complete disability), and comorbidities, including any previous malignancies, Gleason score, pretreatment PSA, number of bone metastasis, presence of visceral disease, and previous PCa treatments. Volume of disease (high vs low) was defined applying the CHAARTED criteria [7]. Treatment characteristics, including time from ADT to the first cycle of docetaxel, number of cycles given, and early discontinuation (and reason why), were extracted. Subsequent treatments for castration-resistant prostate cancer (CRPC) were also extracted.

2.3.   Outcomes

We recorded the OS, and biochemical and clinical progression-free survival in men with mHSPC treated with docetaxel plus ADT in routine practice.

PSA response was defined as a decrease in baseline value by at least 50%; PSA progression was defined as a rise in PSA from nadir of at least 50%, confirmed after 1 mo, with the absolute value being >2 ng/ml. PSA values after 6 and 12 mo (closest value within 6 wk) were specifically recorded. All time-based endpoints (eg, time to CRPC and OS) were defined with respect to the date of initiation of ADT. OS was defined as the time until death from any cause. The time to CRPC was defined as the time until documented clinical, serological, or radiographic progression, whichever occurred first, with a testosterone level of <50 ng/dl. The time to clinical progression was defined as the time until increasing symptoms of bone metastases; progression according to RECIST, version 1.1; or clinical deterioration due to cancer according to the investigator's opinion. Treatment failure was defined as PSA progression, or clinical or radiological progression according to Prostate Cancer Working Group 2 (PCWG2) [11] criteria, initiating new PCa-related treatment.

2.4.   Statistical analysis

Descriptive statistics for categorical variables were reported as percentages, and continuous variables were reported as medians and ranges. Categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann-Whitney U test. For a comparison of Kaplan-Meier estimates, the Cox-Mantel log-rank test was used to perform pairwise comparisons.

All statistical tests were two sided, and statistical significance was defined as $p < 0.05$. Analyses were carried out using SPSS for Windows version 25.0 and MedCalc version 18.11.6. Time-based endpoints were analyzed with the method of Kaplan-Meier.

3.   Results

3.1.   Patient and disease characteristics

A total of 173 patients who received docetaxel for mHSPC between June 2015 and February 2018 were identified; patient characteristics are summarized in Table 1. The median age at the start of docetaxel was 68.8 yr (range

Table 1 – Baseline characteristics of all patients (N = 173)

Age (yr)[a]	
Median	68.8
Range	45.0–79.7
IQR	63.7– 72.4
ECOG PS, no. (%)	
0	136 (78.6)
1	33 (19.1)
2	4 (2.3)
Volume of metastases[b], no. (%)	
Low	26 (15.0)
High	147 (85.0)
Visceral metastases, no. (%)	29 (16.8)
Bone metastases, no. (%)	
0	5 (2.9)
1–3	6 (3.5)
4–10	14 (8.1)
11–20	90 (52.0)
>20	58 (33.5)
Gleason score, no. (%)	
≤6	1 (0.6)
7	24 (13.9)
8–10	139 (80.3)
NA	9 (5.2)
PSA level at start of ADT (pretreatment PSA; ng/ml)	
Median	320
Range	1.6–10 819
IQR	86–827
Time from start of ADT to docetaxel initiation (mo)	
Median	1.2
Range	0.1–4.6
IQR	0.7–1.8
NA	173

ADT = androgen deprivation therapy; IQR = interquartile range; ECOG PS = Eastern Cooperative Oncology Group performance status; NA = not available; PSA = prostate-specific antigen.
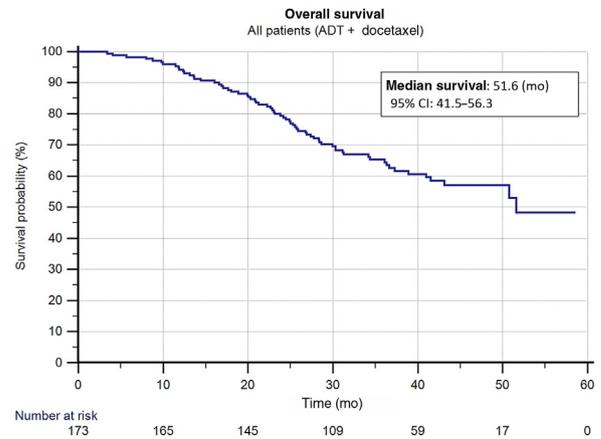[a] At docetaxel initiation.
[b] A high volume of metastases was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis.

Fig. 1 – Kaplan-Meier curve for overall survival. Median overall survival from the date of androgen deprivation therapy (ADT). CI = confidence interval.
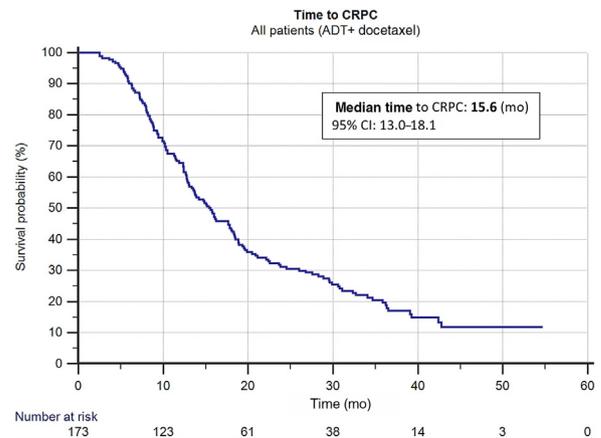
Fig. 2 – Kaplan-Meier curve for time to castration-resistant prostate cancer (CRPC). Time to CRPC is defined as the time from androgen deprivation therapy (ADT) until documented clinical, serologic, or radiographic progression, whichever occurs first, with a testosterone level of <50 ng/dl (1.7 nmol/l). Patients without documented progression were censored at the date of last clinical disease evaluation. CI = confidence interval.

45.0–79.7 yr). Of the patients, 79% had an ECOG PS score of 0, 85% met the CHAARTED definition for high-volume disease, and 80% had a Gleason score of ≥8. Patients had a median PSA level of 320 ng/ml at the start of ADT. Of the 173 patients enrolled in the study, 169 (98%) had received no prior local therapy for PCa and four patients had metastatic relapse after previous radical prostatectomy. The median time from ADT start to initiation of docetaxel was 1.2 mo (range 0.1–4.6 mo).

3.2. Outcomes

In all, 106 patients (61%) were alive at the last follow-up. The median OS was 51.6 (41.5–56.3) mo (Fig. 1). Increasing PSA was recorded as the first sign of progression in 90.8% of the men. After a median follow-up time of 42 (37.8–58.6) mo, 142 patients (82%) had developed castration resistance (Fig. 2). The median time to the development of CRPC was 15.6 (13.0–18.1) mo (Table 2 and Fig. 2). The median time to clinical progression was 30.4 (25.1–36.3) mo (Fig. 3). The median time to treatment failure was 22.2 (18.9–24.6) mo (Supplementary Fig. 2).

PSA nadir ≤0.2 ng/ml was achieved in 15% of patients after 6 mo and in 19% after 12 mo. At 6 mo, proportions of patients with PSA levels of >0.2–≤4.0 and >4.0 ng/ml were 49% and 34%, respectively. At 12 mo, a PSA level was sustained at >0.2–≤4.0 ng/ml for 35% of the patients, 46% of patients had developed CRPC, and 90% of patients were still alive.

Kaplan-Meier curves for OS, time to CRPC, and time to clinical progression are shown in Figures 1, 2, and 3, respectively. Subgroup analyses of PSA-level prognostic groups (≤0.2, >0.2–≤4.0, and >4.0 ng/ml) and high-volume disease patients with respect to time to CRPC are shown in Figure 4 and Supplementary Figure 1, respectively.

3.3. Treatment delivery and toxicity

A total of 149 patients (86%) received the planned six cycles of docetaxel, 19 patients (11%) discontinued treatment due to adverse events, and five patients (3%) progressed while on treatment. Two patients died while on chemotherapy,

Table 2 – Summary of outcomes for all patients

	N	%
OS at 1 yr	156	90.2
PSA (ng/l) at 6 mo		
≤0.2	26	15.0
0.2–4.0	84	48.6
>4.0	59	34.1
NA	4	2.3
PSA (ng/l) at 12 mo		
≤0.2	33	19.1
0.2-4.0	60	34.7
>4.0	58	33.5
NA	22	12.7
Development of CRPC		
Median time to CRPC (mo)	15.6	
95% CI for the median	13.0–18.1	
Total patients after ADT start	142	82.1
<6 mo	16	9.2
6–12 mo	45	26.0
>12 mo	81	46.8

ADT = androgen deprivation therapy; CI = confidence interval; CRPC = castration-resistant prostate cancer; NA = not available; OS = overall survival; PSA = prostate-specific antigen.
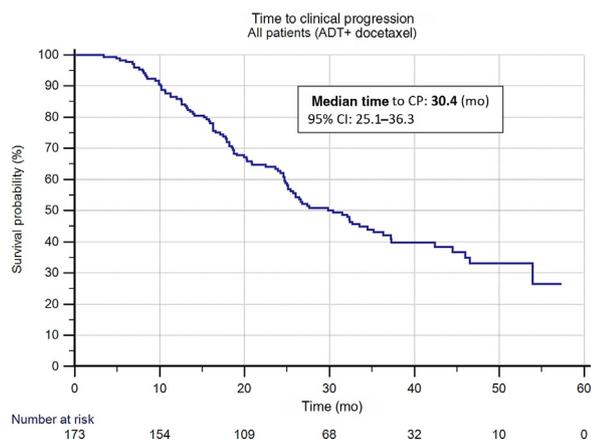
Fig. 3 – Kaplan-Meier curve for time to clinical progression (CP). Time to CP was defined as the time from androgen deprivation therapy (ADT) to CP. Patients without CP were censored at the date of last clinical disease evaluation. CP is defined by increasing symptoms of bone metastases or clinical deterioration due to cancer according to the doctor's opinion. CI = confidence interval.

one death was due to cancer progression, and one death was due to myocardial infarction, probably unrelated to treatment toxicity.

3.4. Subsequent treatment for CRPC

At the time of this analysis, 104 patients had progressed and received subsequent systemic treatment for CRPC, with a median time to first subsequent systemic treatment of 25.2 (23.7–31.5) mo. The majority received either enzalutamide (62%) or abiraterone with prednisone (14%). Fifteen patients received chemotherapy for metastatic CRPC (12 cabazitaxel, and three carboplatin and etoposide). Five patients received radium-223.

4. Discussion

Two large phase III trials and one meta-analysis have confirmed the OS benefit of six cycles of docetaxel in men with newly diagnosed mHSPC [7–9]. Thus, ADT plus docetaxel is now considered a standard treatment option in mHSPC.

Data from clinical trials do not necessarily provide adequate information to judge the impact of a new treatment when used in a standard setting [12]. Although randomized controlled phase III trials are the gold standard for the drug-approval process, they invariably have limitations, including "healthy patient" selection bias, and the results may therefore have limited generalizability. In clinical practice, it is likely that a broader range of patients will be exposed to the drug that might subsequently affect both safety and efficacy [13]. Clinical trials are typically done to address the question of efficacy: "Does intervention work in the study setting?" However, clinicians need to know the effectiveness: "Do the results from the clinical trial work in practice?" [14]. The difference in trial and clinical populations could result in lower efficacy. Hence, the purpose of the present study was to assess clinical outcomes in men with mHSPC receiving docetaxel and ADT in routine practice. Second, we wanted to compare results when chemotherapy was used in a routine setting with the reported results from randomized clinical trials. We emphasized on the CHAARTED study, as this study has provided the evidence leading to the routine use of docetaxel in men with HSPC in Denmark [7].

The GETUG-AFU 15 study was the first study to examine docetaxel treatment combined with ADT versus ADT alone in patients with mHSPC [6]. GETUG-AFU-15 enrolled 385 patients and reported with a median follow-up of 84 mo. This showed no improvement in survival by adding docetaxel to ADT over ADT alone (hazard ratio [HR] = 0.88, 95% confidence interval [CI] 0.68–1.14, $p = 0.3$) [6]. The second trial, CHAARTED, enrolled 790 patients and reported with a median follow-up of 54 mo, demonstrating an improvement in survival by the addition of docetaxel (HR = 0.72, 95% CI 0.59–0.89, $p = 0.0018$) [7,15]. This apparent contradiction in results was later explained by the burden of disease at the time of enrollment in the studies [16].

The third trial, STAMPEDE, enrolled 1086 mHSPC patients to evaluate the addition of docetaxel to either ADT or ADT and zoledronic acid. The STAMPEDE trial differed from the previously mentioned trial by including patients with high-risk, locally advanced disease only and patients with nodal disease only [8]. The study showed improved survival associated with the combination of docetaxel and ADT compared with ADT alone after a median follow-up of 78.2 mo (HR = 0.81, 95% CI 0.69–0.95, $p = 0.009$) [17].

A meta-analysis of CHAARTED, GETUG-15, and STAMPEDE studies indicated that docetaxel had significant survival benefits for M1 patients, which increased the 4-yr survival rate by nearly 10% [18]. A subgroup analysis of CHAARTED and GETUG-15 showed less efficacy for low-volume disease [15]. Consequently, docetaxel and ADT have
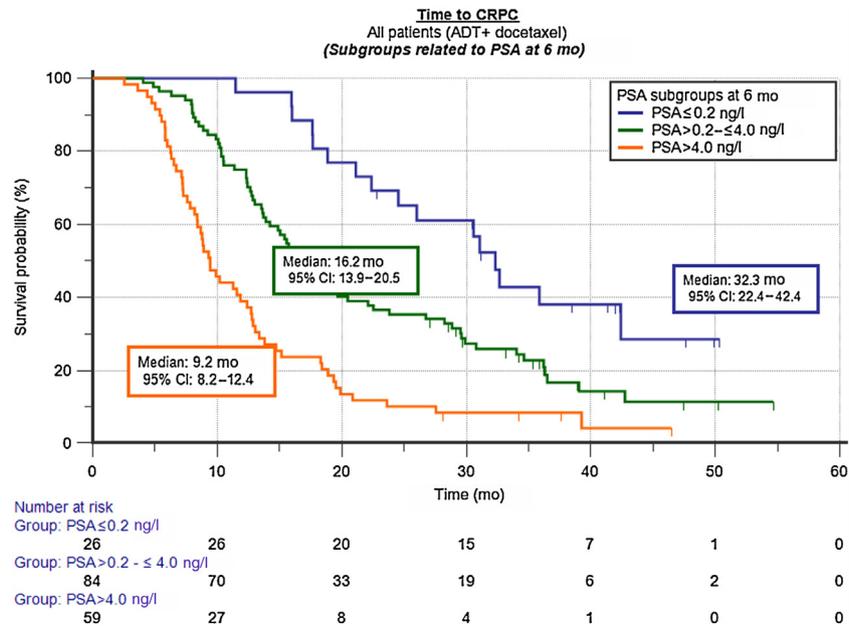
Fig. 4 – Kaplan-Meier curve for time to CRPC by prostate-specific antigen (PSA, ng/ml) status at 6 mo. ADT = androgen deprivation therapy; CI = confidence interval; CRPC = castration-resistant prostate cancer.

been strongly recommended by oncological guidelines since 2016, particularly for high-volume mHSPC. Even though CHAARTED and GETUG-15 strongly indicates that only high-volume disease patients benefit from the addition of docetaxel to ADT, the impact of metastatic burden has been debated. The long-term follow-up of the patients included in the STAMPEDE trial stratified by CHAARTED criteria found no significant differences in OS, progression-free survival, and failure-free survival for this regimen between patients with low- and high-volume disease [17]. It has been suggested that the difference between STAMPEDE and other prospective trials with respect to the effect of docetaxel in low-tumor-volume patients might be the number of patients with previous local therapy [17]. Of the patients included in STAMPEDE, 95% were newly diagnosed with M1 PCa, whereas the CHAARTED trial included about 25% of patients with metastatic disease secondary to local therapy [17].

When compared with the populations in the GETUG-AFU 15 [6], CHAARTED [7], and STAMPEDE [8] trials, our study population was skewed toward slightly older age, higher PSA at baseline, higher Gleason scores, and metastatic burden. This is consistent with the bias toward fitter patients in clinical trials. Yet, more patients had a PS score of 0 in our cohort than in the CHAARTED population, which could drive our results in a more positive direction (Table 3). The percentage of patients with high-volume disease was higher than that in the CHAARTED study. Collectively, these factors could suggest a possible imbalance in prognostic factors. Furthermore, a notable difference between our cohort and the clinical trials is that in our cohort, only four had had previous curatively intended therapy, leading to 98% of patients being newly diagnosed with M1 PCa. This difference can likely be

explained by differences in diagnostic strategies and treatment policies [3,19]. Our cohort may reflect the less active screening policy in Denmark than that in other parts of the western world. However, it may be of importance as the time of metastatic presentation (relapsed after prior therapy or primary metastatic) in addition to the volume of disease (low vs high) has an impact on survival. Recent evidence suggests that de novo disease may portend worse survival and potentially a greater benefit to upfront chemotherapy compared with previously localized PCa, which progressed to metastatic disease [20].

In our cohort, we found OS comparable with that of the high-volume patients in the CHAARTED study (Table 4) [15]. Our results are also in line with the recent updated results from the STAMPEDE trial [8,17] reporting a median OS of 59.1 mo for patients treated with docetaxel, with a median duration of follow-up of 78.2 mo.

Comparisons of clinical factors and outcomes between patients receiving docetaxel for mHSPC in clinical practice and in the pivotal phase III trial CHAARTED are shown in Tables 3 and 4, respectively.

Our results show a similar time to CRPC (15.6 mo) to the recent updated analysis of patients with high-volume disease from the CHAARTED study (14.9 mo) [15]. In GETUG-AFU 15 [6], the time to CRPC was 22.9 mo; STAMPEDE (arm C) had a time to CRPC of 37 mo, but this trial also included nonmetastatic patients [8]. The shorter median time to CRPC in our cohort indicates that our patients had disease comparable with that in high-volume patients in CHAARTED, and they were in fact attempted to be selected following the criteria for high-volume disease. Inconsistent with previous trials, patients with low-volume disease had a shorter time to CRPC (13.9 mo). This

Table 3 – Comparison of baseline characteristics of all patients versus CHAARTED patients

Baseline characteristics		
	All patients ADT plus docetaxel	CHAARTED ADT plus docetaxel ($N = 397$)
Age (yr)		
Median	68.8	64
Range	45.0–79.7	36–88
ECOG PS, no. (%)		
0	136 (78.6)	277 (69.8)
1	33 (19.1)	114 (28.7)
2	4 (2.3)	6 (1.5)
Volume of metastases[a], no. (%)		
Low	26 (15.0)	134 (33.8)
High	147 (85.0)	263 (66.2)
Visceral metastases, no. (%)	29 (16.8)	57 (14.4)
Gleason score, no. (%)		
≤6	1 (0.6)	21 (5.3)
7	24 (13.9)	96 (24.2)
8–10	139 (80.3)	241 (60.7)
NA	9 (5.2)	39 (9.8)
PSA level at start of ADT (ng/ml)		
Median	320	50.9
Range	1.6–10 818	0.2–8540
Prior treatment for PCa, no. (%)		
No local therapy	169 (97.7)	289 (72.8)
Primary radiation	0 (0.0)	27 (6.8)
Radical Prostatectomy	4 (2.3)	81 (20.4)
Missing data	0	0
Time from start of ADT to docetaxel start (mo)		
Median	1.15	1.2
Range	0.1–4.6	0.03–3.9

ADT = androgen deprivation therapy; ECOG PS = Eastern Cooperative Oncology Group performance status; NA = not available; PCa = prostate cancer; PSA = prostate-specific antigen.
[a] A high volume of metastases was defined by the presence of visceral metastases or four or more bone lesions with at least one beyond the vertebral bodies and pelvis.

unexpected result might be due to a small sample bias of the low-volume series in our cohort.

Men who present with metastatic PCa represent a heterogeneous group of patients. The burden of disease, degree of symptoms, and patterns of spread can vary widely at the time of diagnosis. The course of disease can differ, and patients will vary in their prognoses after several months of ADT based on their response to therapy [7,21,22]. Essentially, there is a vastly heterogeneous outcome, with some prognostic features determined at diagnosis and others established over time. Hence, several prognostic systems for mHSPC have been developed. The original Glass prognostic groups included Gleason score, appendicular versus axial bone metastases, functional status, and PSA levels [23]. Hussain et al [22] used PSA nadir at 7 mo after ADT initiation to develop prognostic PSA groups (≤0.2, >0.2–≤4.0, and >4.0 ng/ml) with widely ranging survival times. Recently, CHAARTED and GETUG-AFU 15 investigators reported outcomes based on the presence of volume of disease (as per the CHAARTED definition) [6,7].

Considering the PSA nadir 6 mo after ADT initiation in the subgroup analysis of our high-volume disease cohort, we found a statistically significantly different time to CRPC between the group of patients with a PSA level of >4.0 ng/ml and the group of patients with a PSA level of ≤4.0 ng/ml ($p < 0.0001$; Supplementary Fig. 1). Performing a parallel subgroup analysis of our low-volume disease cohort could not show a significant difference. In a further subgroup analysis, considering the PSA nadir at 6 mo after ADT initiation and differentiating between PSA-level prognostic groups (≤0.2, >0.2–≤4.0, and >4.0 ng/ml—as defined by Hussain et al [22]), we found a statistically significantly different time to CRPC between the group of patients with a PSA level of >4.0 ng/ml and the group of patients with a PSA level of >0.2–≤4.0 ng/ml ($p < 0.001$; Fig. 4). Similarly, we found a statistically significantly different time to CRPC between the group of patients with a PSA level of >0.2–≤4.0 ng/ml and the patients with undetectable PSA (≤0.2 ng/ml; $p = 0.004$). The median time to CRPC was 9.2 mo (95% CI 8.2–12.4) for the 59 patients with a PSA level of >4.0 ng/ml, 16.2 mo (95% CI 13.9–20.5) for the 84 patients with a PSA level of ≤0.2–≤4.0 ng/ml, and 32.3 mo (95% CI 22.4–42.4) for the 26 patients with undetectable PSA (≤0.2 ng/ml; Fig. 4). These data indicate that our study population is representative of this patient subgroup; consequently, our results may be applicable to others. Together these findings illustrate the heterogeneity of the disease and underline the need for a better understanding of the determinants of this heterogeneity. The ability to assess prognosis individually will help tailor patient therapy and appropriately maximize clinical benefit while minimizing exposure to unnecessary toxicities.

Table 4 – Comparison of outcomes for all patients versus CHAARTED patients

Outcome comparison						
	All patients		CHAARTED		CHAARTED	
	Copenhagen University Hospital, Denmark				Long-term survival analysis	
	2020		2015		2018	
	ADT plus docetaxel		ADT plus docetaxel		ADT plus docetaxel	
	(N = 173)		(N = 397)		(N = 397)	
	Median time	95% CI	Median time	95% CI	Median time	95% CI
Overall duration of follow-up	42.0	37.8–58.6	28.9		53.7	
Overall survival	51.6	41.5–56.3	57.6	52.0–63.9	57.6	
Time to CRPC						
Overall	15.6	13.0–18.1	20.2	17.2–23.6	19.4	16.8–22.6
High volume	15.8	12.6–18.9			14.9	12.4–17.2
Low volume	13.7	10.5–20.9			31.0	23.1–51.1
Time to clinical progression						
Overall	30.4	25.1–36.3	33.0	27.3–41.2	33.0	29.1–40.9
High volume	26.8	24.7–33.5			27.3	21.9–32.7
Low volume	46.0	15.8–46.5			42.5	34.0–NR
	No.	%			No.	%
Secondary endpoint[a]						
PSA level ≤0.2 ng/ml at 6 mo	26	15.0			127	32.0
PSA level ≤0.2 ng/ml at 12 mo	33	19.1			110	27.7

CI = confidence interval; CRPC = castration-resistant prostate cancer; NR = not reached; PSA = prostate-specific antigen.
[a] Rate of decrease of PSA level to ≤0.2 ng/ml.

Overall the metastatic burden in our patients is comparable with that in the high-volume patients in the CHAARTED study [15]. The median time to clinical progression overall in our study was 30.4 mo, also comparable with that in the high-volume patients in the CHAARTED study [15]. Interestingly, results from our cohort on clinical progression are also comparable with the updated results from STAMPEDE [17] with respect to failure-free survival.

Another possible reason for varying results is subsequent therapies. In the GETUG-AFU15 trial, 85% of patients in the control arm received docetaxel at the time of progression to CRPC [6,21]. One interpretation of this is that it is more important to use docetaxel for metastatic PCa than the specific time point when to use it. In our cohort, the majority of patients receiving subsequent therapies following progression on initial combined ADT and chemotherapy received either enzalutamide (62%) or abiraterone with prednisone (14%). However, the population is too limited to justify further analysis in this study.

Our study demonstrates that the effectiveness of docetaxel in routine practice is in line with recent updates from the CHAARTED [15] and the STAMPEDE [17] trial. These results are encouraging as the use of upfront chemotherapy is expected to increase, as consensus guidelines have been updated to reflect recent landmark trials [24,25]. Interestingly, we report higher OS than that in other recent published reports of data from real-world mHSPC patients who received upfront chemotherapy [26,27].

Despite a tendency toward older patients with a higher tumor burden in our study, most patients (86%) received the planned six cycles of docetaxel, indicating that patient selection in terms of PS/comorbidity must have been relatively well compared with the clinical studies.

Our study carries the inherent limitations of a retrospective chart review, as the rigor of diagnoses and outcome documentation were not protocol prescribed. The reliability of our estimates is challenged by missing data, ascertainment bias, and attribution bias.

The strengths of this study include a reasonable sample size based on two individual institution series; thus, our results may be applicable to other institutions. Follow-up is sufficient, and our study reflects the clinical results when patients with mHSPC are treated with docetaxel.

Following the introduction of docetaxel in the management of patients with mHSPC, other studies have demonstrated that the combination of ADT and abiraterone [28,29] prolongs survival significantly, and a network analysis indicated that abiraterone may, in some cases, be more effective than docetaxel [30,31]. Furthermore, newly introduced second-generation antiandrogens, such as enzalutamide and apalutamide in the ARCHES and TITAN studies, respectively, have demonstrated prolonged survival when introduced in the mHSPC setting [32,33]. No studies have as yet compared the different treatment strategies, ADT + chemotherapy versus ADT + additional endocrine manipulation, head to head. However, importantly, side effects are generally less pronounced when patients are managed with endocrine therapy compared with when they are managed with chemotherapy—an aspect that has to be taken into consideration when consulting patients with newly diagnosed mHSPC.

5. Conclusions

Overall, we found that patients managed in clinical practice were older and had higher PSA values, poorly differentiated PCa more frequently, and a higher metastatic burden than patients included in clinical trials. However, the effect of docetaxel for mHSPC patients treated in routine practice appears comparable with the overall efficacy reported in the literature.

Author contributions: Maria Elisabeth Lendorf 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: Lendorf, Petersen, Brasso.
Acquisition of data: Lendorf, Svendsen.
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Maria Elisabeth Lendorf: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Peter Meidahl Petersen:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing - review & editing. **Andrea Steen Svendsen:** Data curation, Investigation, Methodology. **Henriette Lindberg:** Formal analysis. **Klaus Brasso:** Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euros.2020.12.006.

References

[1] Dy GW, Gore JL, Forouzanfar MH, Naghavi M, Fitzmaurice C. Global burden of urologic cancers, 1990–2013. Eur Urol 2017;71:437–46.

[2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30.

[3] Helgstrand JT, Roder MA, Klemann N, et al. Trends in incidence and 5-year mortality in men with newly diagnosed, metastatic prostate cancer—a population-based analysis of 2 national cohorts. Cancer 2018;124:2931–8.

[4] Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. 1941. J Urol 2002;168:9–12.

[5] Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet 2000;355:1491–8.

[6] Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149–58.

[7] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737–46.

[8] James ND, Sydes MR, Clarke NW, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet (London England) 2016;387:1163–77.

[9] Tucci M, Bertaglia V, Vignani F, et al. Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive metastatic prostate cancer: a systematic review and meta-analysis. Eur Urol 2016;69:563–73.

[10] Mottet N, De Santis M, Briers E, et al. Updated guidelines for metastatic hormone-sensitive prostate cancer: abiraterone acetate combined with castration is another standard. Eur Urol 2018;73:316–21.

[11] Anand A, Bjartell A, Danila DC, et al. Translating Prostate Cancer Working Group 2 (PCWG2) progression criteria into a quantitative response biomarker in metastatic castration-resistant prostate cancer (mCRPC). J Clin Oncol 2017;35(6_suppl):170.

[12] Sargent D. What constitutes reasonable evidence of efficacy and effectiveness to guide oncology treatment decisions? Oncologist 2010;15(Suppl 1):19–23.

[13] Glasser SP, Salas M, Delzell E. Importance and challenges of studying marketed drugs: what is a phase IV study? Common clinical research designs, registries, and self-reporting systems. J Clin Pharmacol 2007;47:1074–86.

[14] Djulbegovic B, Paul A. From efficacy to effectiveness in the face of uncertainty: indication creep and prevention creep. JAMA 2011;305:2005–6.

[15] Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018;36:1080–7.

[16] Gravis G, Boher JM, Joly F, et al. Androgen deprivation therapy (ADT) plus docetaxel versus ADT alone in metastatic non castrate prostate cancer: impact of metastatic burden and long-term survival analysis of the randomized phase 3 GETUG-AFU15 trial. Eur Urol 2016;70:256–62.

[17] Clarke NW, Ali A, Ingleby FC, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol 2019;30:1992–2003.

[18] Vale CL, Burdett S, Rydzewska LH, et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol 2016;17:243–56.

[19] Wu JN, Fish KM, Evans CP, Devere White RW, Dall'Era MA. No improvement noted in overall or cause-specific survival for men presenting with metastatic prostate cancer over a 20-year period. Cancer 2014;120:818–23.

[20] Francini E, Gray KP, Xie W, et al. Time of metastatic disease presentation and volume of disease are prognostic for metastatic hormone sensitive prostate cancer (mHSPC). Prostate 2018;78:889–95.

[21] Gravis G, Boher JM, Chen YH, et al. Burden of metastatic castrate naive prostate cancer patients, to identify men more likely to benefit from early docetaxel: further analyses of CHAARTED and GETUG-AFU15 studies. Eur Urol 2018;73:847–55.

[22] Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific antigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984–90.

[23] Glass TR, Tangen CM, Crawford ED, Thompson I. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol 2003;169:164–9.

[24] Gillessen S, Attard G, Beer TM, et al. Management of patients with advanced prostate cancer: report of the Advanced Prostate Cancer Consensus Conference 2019. Eur Urol 2020;77:508–47.

[25] Mohler JL, Antonarakis ES, Armstrong AJ, et al. Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 2019;17:479–505.

[26] Lavoie JM, Zou K, Khalaf D, et al. Clinical effectiveness of docetaxel for castration-sensitive prostate cancer in a real-world population-based analysis. Prostate 2019;79:281–7.

[27] Weiner AB, Ko OS, Li EV, et al. Survival following upfront chemotherapy for treatment-naïve metastatic prostate cancer: a real-world retrospective cohort study. Prostate Cancer Prostatic Dis 2020. http://dx.doi.org/10.1038/s41391-020-00278-0.

[28] Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. N Engl J Med 2017;377:352–60.

[29] James ND, de Bono JS, Spears MR, et al. Abiraterone for prostate cancer not previously treated with hormone therapy. N Engl J Med 2017;377:338–51.

[30] Rydzewska LHM, Burdett S, Vale CL, et al. Adding abiraterone to androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer: a systematic review and meta-analysis. Eur J Cancer 2017;84:88–101.

[31] Vale CL, Fisher DJ, White IR, et al. What is the optimal systemic treatment of men with metastatic, hormone-naive prostate cancer? A STOPCAP systematic review and network meta-analysis. Ann Oncol 2018;29:1249–57.

[32] Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. J Clin Oncol 2019;37:2974–86.

[33] Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. N Engl J Med 2019;381:13–24.