Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-145-z Darolutamid

Stand: Juni 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Darolutamid
[zur Behandlung des metastasierten hormonsensitiven Prostatakarzinoms]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	• Orchiektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: • Abirateronacetat: Beschluss vom 07.06.2018 • Apalutamid: Beschluss vom 20.08.2020 • Enzalutamid: Beschluss vom 19.11.2021
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Darolutamid L02BB06 Nubeqa	<u>Anwendungsgebiet laut Zulassung:</u> NUBEQA wird angewendet zur Behandlung erwachsener Männer mitmetastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit Docetaxel und einer Androgendeprivationstherapie.
Antiandrogene	
Bicalutamid L02BB03 generisch	• ist angezeigt entweder als alleinige Therapie oder adjuvant zu radikaler Prostatektomie oder Strahlentherapie bei Patienten mit lokal fortgeschrittenem Prostatakarzinom und hohem Progressionsrisiko • zur Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration.
Cyproteron-acetat G03HA01 generisch	• Zur palliativen Therapie des metastasierenden oder lokal fortgeschrittenen, inoperablen Prostatakarzinoms, wenn sich die Behandlung mit LHRH-Analoga oder der operative Eingriff als unzureichend erwiesen haben, kontraindiziert sind oder der oralen Therapie der Vorzug gegeben wird. • Initial zur Verhinderung von unerwünschten Folgeerscheinungen und Komplikationen, die zu Beginn einer Behandlung mit LHRH-Agonisten durch den anfänglichen Anstieg des Serum -Testosteron hervorgerufen werden können. • Zur Behandlung von Hitzewallungen, die unter der Behandlung mit LHRH-Agonisten oder nach Hodenentfernung auftreten. • […]
Flutamid L02BB01 generisch	Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist • Initialtherapie in Kombination mit einem LHRH-Analogon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LHRH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist • zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprachen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist.
GnRH-Antagonist	
Degarelix L02BX02 Firmagon	FIRMAGON ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Relugolix L02BX04 Orgovyx	Orgovyx ist indiziert zur Behandlung von erwachsenen Patienten mit fortgeschrittenem hormonsensitivem Prostatakarzinom.
GnRH-Analoga	
Buserelin L02AE01 Profact	• ist angezeigt bei Erwachsenen zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. • ist jedoch nicht angezeigt nach beidseitiger Orchiektomie, da es in diesem Fall zu keiner weiteren Absenkung des Testosteronspiegels kommt.
Goserelin L02AE03 Zoladex	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist.
Leuprorelin L02AE02 Trenantone	• Zur Behandlung des fortgeschrittenen hormonabhängigen Prostatakarzinoms. • Zur Behandlung des lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie. • Zur Behandlung des lokalisierten hormonabhängigen Prostatakarzinoms bei Patienten des mittleren und Hoch-Risikoprofils in Kombination mit der Strahlentherapie • […]
Triptorelin L01AA06 Pamorelin	ist indiziert zur Behandlung des • lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. • des lokalisierten Hochrisiko- oder lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms in Kombination mit Strahlentherapie. • […]
Weitere Hormontherapeutika	
Abirateron-acetat L02BX03 Zytiga	ZYTIGA ist indiziert mit Prednison oder Prednisolon: • zur Behandlung des neu diagnostizierten Hochrisiko-metastasierten hormonsensitiven Prostatakarzinoms (mHSPC) bei erwachsenen Männern in Kombination mit Androgenentzugstherapie (androgen deprivation therapy, ADT) • […]
Apalutamid L02BB05 Erleada	Erleada ist indiziert: • zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (mHSPC) in Kombination mit Androgendeprivationstherapie (ADT). • […]

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Enzalutamid L02BB04 Xtandi	Xtandi ist angezeigt: • zur Behandlung erwachsener Männer mit metastasiertem hormonsensitivem Prostatakarzinom (metastatic hormone-sensitive prostate cancer, mHSPC) in Kombination mit einer Androgenentzugstherapie • […]
Zytostatika	
Docetaxel L01CD02 Taxotere	TAXOTERE ist in Kombination mit einer Androgendeprivationstherapie, mit oder ohne Prednison oder Prednisolon, zur Behandlung von Patienten mit metastasiertem hormonsensitivem Prostatakarzinom angezeigt. […]

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2022-B-145-z (Darolutamid)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	28. März 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AA	Abiraterone Acetate
AAP	abiraterone acetate plus prednisone / prednisolone
ADT	Androgen Deprivation Therapy
AE	Adverse Events
APA	Apalutamide
ARAT	Androgen receptor-axis-targeted therapies
ASCO	American Society of Clinical Oncology
AST	Androgen suppression therapy
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CAB	complete andogen blockade
CI	Confidence interval
CSS	cancer-specific survival
CUOG	Canadian Urologic Oncology Group
EAU	European Association of Urology
EBRT	External Beam Radiation Therapy
ESMO	European Society for Medical Oncology
ESTRO	European Society for Radiotherapy & Oncology
DOC	Docetaxel
DGU	Deutsche Gesellschaft für Urologie e. V
ECRI	ECRI Guidelines Trust
EK	Expertenkonsens
ENZ	Enzalutamide
FFS	failure-free survival
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GnRH	Gonadotropin-releasing hormone agonist
GoR	Grade of Recommendations
Gy	Gray
HR	Hazard Ratio
HSPC	Hormone-Sensitive Prostata Cancer
HVD	High volume disease
IGRT	image-guided radiation therapy
IMRT	intensity-modulated radiation therapy
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall

LoE	Level of Evidence
LHRH	Luteinizing Hormone-Releasing Hormone
LVD	low volume disease
mCNPC	metastatic castration-naive prostate cancer
mCSPC	metastatic castration sensitive prostate cancer
MD	mean difference
MDT	metastasis-directed
mHSPC	metastatic Hormone-Sensitive Prostate Cancer
mHNPC	metastatic hormone-naive prostate cancer
mCRPC	metastatic Castration-Resistant Prostate Cancer
NICE	National Institute for Health and Care Excellence
NMA	Netzwerkmetaanalyse
NSAA	non-steroidal anti-androgen
OR	Odds Ratio
OS	Overall Survival
P	Prednisone
PCa	Prostate Cancer
PCSM	PCa-specific mortality
PFS	Progression-Free Survival
PLND	pelvic lymph node dissection
PSA	Prostate-Specific Antigen
PSA-PFS	prostate-specific antigen progression-free survival
QoL/QOL	Quality of Life
RoB	Risk of bias
rPFS	radiographic progression-free survival
RP	Radical Prostatectomy
RR	Relatives Risiko
RT	Radiotherapy
SABR	stereotactic ablation Radiation Therapy
SAEs	serious adverse events
SBRT	Stereotacitc Body Radiation Therapy
SIGN	Scottish Intercollegiate Guidelines Network
SOC	Standard of care
SRT	Salvagestrahlentherapie
SSE	Symptomatic Skeletal Event
SUO	Society of Urologic Oncology
TRIP	Turn Research into Practice Database
WHO	World Health Organization
WW	Wachtful Waiting

1 Indikation

Behandlung des Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinoms bei Erwachsenen.

Hinweis zur Synopse: ,,Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt''.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Prostatakarzinom* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.startpage.com) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 11.09.2020 durchgeführt, die folgenden am 23.04.2021 und 04.01.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 2341 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 26 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Sathianathen NJ et al., 2018 [19].

Taxane-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer

Fragestellung

To assess the effects of early taxane-based chemohormonal therapy for newly diagnosed, metastatic, hormone-sensitive prostate cancer.

Methodik

Population:

- newly diagnosed metastatic hormone-sensitive prostate cancer
- (…) men with a confirmed histological diagnosis of adenocarcinoma of the prostate and radiologic evidence of metastases as determined by cross-sectional imaging (computer tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) with or without bone scans. This included both men who had and had not undergone local therapy.
- We excluded men with advanced prostate cancer who received chemotherapy without known metastases, and those who received prior chemotherapy of any agent for their prostate cancer.

Intervention:

- taxane-based chemotherapy with systemic androgen deprivation therapy (ADT) within 120 days of beginning ADT

Komparator:

- ADT alone at the time of diagnosis of metastatic disease

Endpunkte:

- Primary outcomes
  - Time to death due to any cause.
  - Grade III to V adverse events.
- Secondary outcomes
  - Time to death due to prostate cancer (analyzed as prostate cancer-
  - specific death, see Differences between protocol and review).
  - Time to progression.
  - Discontinuation due to adverse events.
  - All adverse events.
  - Quality of life.

Recherche/Suchzeitraum:

- comprehensive search using multiple databases (the Cochrane Library, MEDLINE, Embase, Scopus, Google Scholar, and Web of Science), trials registries, other sources of grey literature, and conference proceedings,
- up to 10 August 2018.
- We applied no restrictions on publication language or status.

Qualitätsbewertung der Studien:

- Cochrane's 'Risk of bias' assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- three studies in which 2261 participants

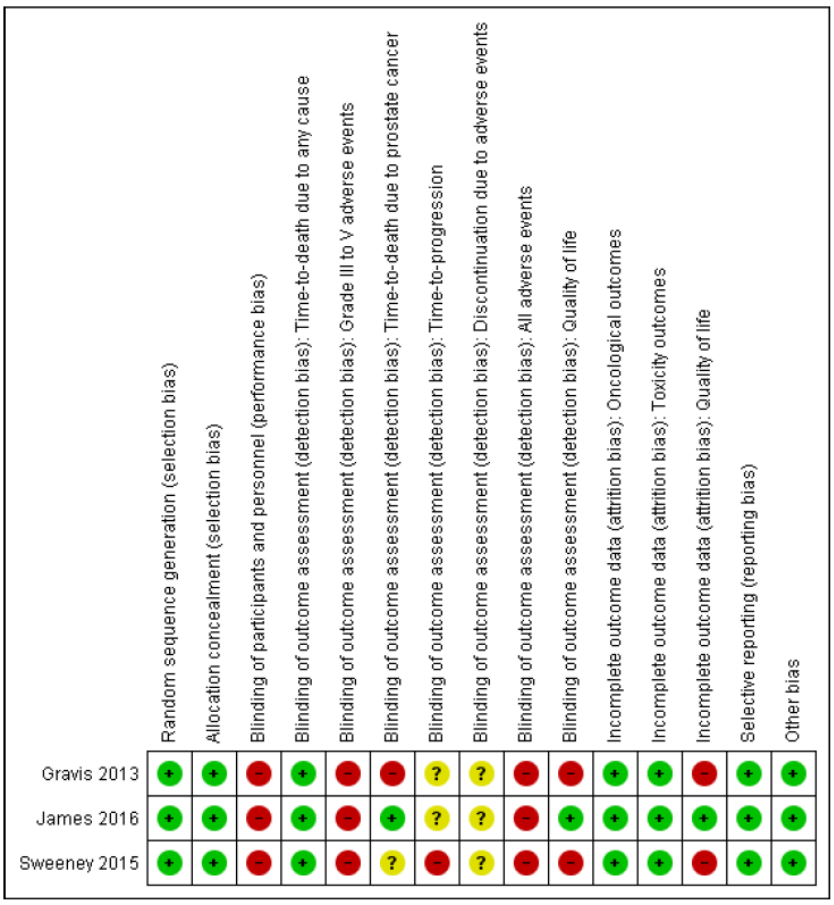
Charakteristika der Population:

This review includes a total of 2,261 randomized participants with metastatic hormone-sensitive prostate cancer, of whom 951 received docetaxel in addition to androgen deprivation therapy (ADT). One trial also enrolled 1,145 participants with non-metastatic disease but we did not include this subgroup in the review (James 2016). The median age and prostate-specific antigen (PSA) level at randomization of participants ranged from 63 to 64 years old and 25.8 nanograms per milliliter (ng/mL) to 50.9 ng/mL, respectivel (Gravis 2013; Sweeney 2015). Separate demographic characteristics for participants with metastatic diease were not reported in James 2016. The proportion of participants with high-volume metastases ranged from 48% to 65% (Gravis 2013; Sweeney 2015); this information was not reported in James 2016. The majority of participants had an initial Gleason score above seven in all trials.

The proportion of participants with prior local treatment before the diagnosis of metastatic disease ranged from 4% to 28% (Gravis 2013; James 2016; Sweeney 2015). Participants over the age of 18 years old were eligible for inclusion in the trials if they had a pathological diagnosis of prostate cancer and radiological evidence of metastatic disease (Gravis 2013; James 2016; Sweeney 2015). One trial also included individuals without a histological diagnosis as long as they had a clinical scenario that was consistent with prostate cancer (Sweeney 2015). Participants were also required to have an adequate functional status, defined as Eastern Cooperative Oncology Group (ECOG) score of zero to two in all trials, and be fit for chemotherapy. Prior neoadjuvant or adjuvant hormone therapy (or both) was allowed in the included studies if it was completed at least 12 months prior to randomization.

The receipt of any previous chemotherapy in the adjuvant or neoadjuvant setting (or both) was an exclusion criterion in two trials (James 2016; Sweeney 2015), but this was permitted in the third trial if the course of chemotherapy had been completed at least 12 months prior to randomization and there had not been any evidence of PSA or disease progression (or both) for at least one year (Gravis 2013).

Qualität der Studien:



Studienergebnisse:

- OS

  Early treatment with taxane-based chemotherapy in addition to ADT probably reduces death from any cause compared to ADT alone (hazard ratio (HR) 0.77, 95% confidence interval (CI) 0.68 to 0.87; moderate-certainty evidence); this would result in 94 fewer deaths per 1,000 men (95% CI 51 to 137 fewer deaths). We downgraded the certainty of evidence due to study limitations related to potential performance bias. Based on the results of one study with 375 participants, the addition of taxane-based chemotherapy to ADT may increase the incidence of Grade III to V adverse events compared to ADT alone (risk ratio (RR) 2.98, 95% CI 2.19 to 4.04; low-certainty evidence); this would result in 405 more Grade III to V adverse events per 1,000 men (95% CI 243 to 621 more events). We downgraded the certainty of evidence due to study limitations and imprecision.

- Secondary outcomes

  Early taxane-based chemotherapy in addition to ADT probably reduces the risk of prostate cancer-specific death (RR 0.79, 95% CI 0.70 to 0.89; moderate-certainty evidence). We downgraded the certainty of evidence due to study limitations related to potential performance and detection bias. The addition of taxane-based chemotherapy also probably reduces disease progression compared to ADT alone (HR 0.63, 95% CI 0.56 to 0.71; moderate-certainty evidence). We downgraded the certainty of evidence because of study limitations related to potential performance bias. The addition of taxane-based chemotherapy to ADT may result in a large increase in the risk of

treatment discontinuation due to adverse events (RR 79.41, 95% CI 4.92 to 1282.78; low-certainty evidence). We downgraded the certainty of evidence due to study limitations and imprecision. This estimate is derived from a single study with no events in the control arm but a discontinuation rate of 20% in the intervention arm. Taxane-based chemotherapy may increase the incidence of adverse events of any grade (RR 1.11, 95% CI 1.06 to 1.17; low-certainty evidence). We downgraded our assessment of the certainty of evidence due to very serious study limitations. There may be a small improvement, which may not be clinically important, in quality of life at 12 months with combination treatment (mean difference (MD) 2.85 on the Functional Assessment of Cancer Therapy—Prostate scale, 95% CI 0.13 higher to 5.57 higher; low-certainty evidence). We downgraded the certainty of evidence for study limitations related to potential performance, detection and attrition bias.

- Summary of findings for the main comparison:

Early taxane-based chemotherapy and ADT compared to ADT only for metastatic hormone-sensitive prostate cancer

Participants: men with metastatic hormone-sensitive prostate cancer

Setting: multicenter

Intervention: early docetaxel with androgen deprivation therapy

Control: androgen deprivation therapy only

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with ADT only	Risk difference with taxane-based chemotherapy and ADT
Time to death due to any cause (absolute effect size estimates based on all-cause mortality at 5 years) Follow-up: median 43 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE [3]	HR 0.77 (0.68 to 0.87)	Study population[1]	
				610 per 1,000	94 fewer per 1,000 (137 fewer to 51 fewer)
				General Population[2]	
				702 per 1,000	96 fewer per 1,000 (141 fewer to 51 fewer)
Grade III to V adverse events Follow-up: median 50 months	375 (1 RCT)	⊕⊕⊖⊖ LOW [4]	RR 2.98 (2.19 to 4.04)	Study population	
				204 per 1,000	405 more per 1,000 (243 more to 621 more)

Prostate cancer-specific death[5] Follow-up: median 29 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE [6]	RR 0.79 (0.70 to 0.89)	Study population[7]	
				512 per 1,000	108 fewer per 1,000 (154 fewer to 56 fewer)
Time to progression (absolute effect size estimates based on progression rate at 5 years) Follow-up: median 43 to 84 months	2,261 (3 RCTs)	⊕⊕⊕⊖ MODERATE [6]	HR 0.63 (0.56 to 0.71)	Study population[8]	
				822 per 1,000	159 fewer per 1,000 (202 fewer to 116 fewer)
Discontinuation due to adverse events Follow-up: median 50 months	385 (1 RCT)	⊕⊕⊖⊖ LOW [9]	RR 79.41 (4.92 to 1282.78)	Study population	
				0 per 1,000	41 more per 1,000 (25 more to 1000 more)
All adverse events Follow-up: median 50 months	375 (1 RCT)	⊕⊕⊖⊖ LOW [4]	RR 1.11 (1.06 to 1.17)	Study population	
				898 per 1,000	99 more per 1,000 (54 more to 153 more)
Quality of life at 12 months (measured with the Functional Assessment of Cancer Therapy-Prostate (FACT-P) scale, higher score is better)	790 (1 RCT)	⊕⊕⊖⊖ LOW [10]	-	The mean quality-of-life (FACT-P) score in the control arm was 116.4	MD 2.85 higher (0.13 higher to 5.57 higher)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: Confidence interval; **HR:** hazard ratio; **RR:** Risk ratio; **OR:** Odds ratio; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certaintv: Our confidence in the effect estimate is limited: The true effect mav be substantiallv different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Baseline risk of death for any cause was calculated from the 5-year event rate of control group from CHAARTED trial (Kyriakopoulos 2018).
[2] Population data from SEER registry, prostate cancer stage IV 5-year survival (70.2%) in the pre-docetaxel era (2007 to 2013).
[3] Severe concerns regarding study limitations (high risk of performance bias) contributed to our decision to downgrade by one level overall.
[4] Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide CI consistent with both large and very large increase in grade III to V adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall.
[5] We planned to assess this as a time-to-event outcome (time to prostate cancer-specific death), but we evaluated this as a dichotomous outcome due to insufficient data.
[6] Severe concerns regarding study limitations (high risk of performance bias and unclear risk of detection bias) contributed to our decision to downgrade by one level overall.
[7] Baseline risk of prostate cancer-specific death was calculated from the 5-year event rate of control group from the GETUG-AFU15 trial.
[8] Baseline risk of progression was calculated from the 5-year event rate of control group from CHAARTED trial (Kyriakopoulos 2018).
[9] Severe concerns regarding study limitations (high risk of performance and detection bias), imprecision (wide confidence intervals suggesting small and very large increase in treatment discontinuation due to adverse events), and additional concerns about selective reporting (outcome only adequately reported by one of three trials) contributed to our decision to downgrade by two levels overall.
[10] Very severe concerns regarding study limitations (high risk of detection, performance and attrition bias) contributed to our decision to downgrade by two levels overall.

Anmerkung/Fazit der Autoren

Compared to ADT alone, the early (within 120 days of beginning ADT) addition of taxane-based chemotherapy to ADT for hormone-sensitive prostate cancer probably prolongs both overall and disease-specific survival and delays disease progression. There may be an increase in toxicity with taxane-based chemotherapy in combination with ADT. There may also be a small, clinically unimportant improvement in quality of life at 12 months with taxane-based chemotherapy and ADT treatment.

3.2 Systematische Reviews

Wang L et al., 2021 [25].
Comparison of Systemic Treatments for Metastatic Castration-Sensitive Prostate Cancer
A Systematic Review and Network Meta-analysis

Fragestellung

To compare the effectiveness and safety determined in randomized clinical trials of systemic treatments form CSPC.

Methodik

Population:

- mCSPC

Intervention:

- docetaxel, abiraterone acetate, apalutamide, enzalutamide

Komparator:

- any active drug, placebo, or no treatment—all in addition to ADT
- Androgen-deprivation therapy includes orchiectomy, luteinizing hormone-releasing hormone agonists and antagonists, and estrogen

Endpunkte:

- overall survival (OS)
- radiographic progression-free survival (rPFS), defined as time from randomization to radiographic progression or death from any cause, whichever occurred first.
- The safety outcome of interest was any serious adverse events (SAEs).

Recherche/Suchzeitraum:

- We searched bibliographic databases (MEDLINE [PubMed interface], EMBASE[OVID interface]), the Cochrane CentralRegister of Controlled Trials (CENTRAL,Wiley interface), trial registries (ClinicalTrials.gov and the EU Clinical Trials Register), and regulatory documents (US Food and Drug Administration and EuropeanMedicinesAgency review packets) frominception toNovember 5, 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool (version 2.0)

Ergebnisse

Anzahl eingeschlossener Studien:

- Seven trials with 7287 patients comparing 6 treatments (abiraterone acetate, apalutamide, docetaxel, enzalutamide, standard nonsteroidal antiandrogen, and placebo/no treatment) were analyzed (Table 1)

Charakteristika der Population:

- multicenter phase 3 RCTs published between 2013 and 2019, involving a total of 7287 patients

Qualität der Studien:

- Risk of bias was noted for 4 trials with open-label design, 3 trials with missing data, and 2 trials with potential unprespecified analyses.

Table 2. Risk of Bias Within Trials

Trial	Added to ADT: Experimental	Added to ADT: Comparator	Randomization process	Deviation from intended intervention	Missing outcome data[a]	Measurement of outcome[b]	Selection of reported result[c]	Overall bias[d]
Overall survival								
GETUG-AFU15[34,38]	Docetaxel	No treatment	Low	Low	Low	Low	Some concerns	Some concerns
CHAARTED[5,36,37]	Docetaxel	No treatment	Low	Low	Low	Low	Low	Low
STAMPEDE[6,8,10,33,42]	Arm 1, docetaxel; arm 2, abiraterone	No treatment	Low	Low	Some concerns	Low	Low	Some concerns
LATITUDE[7,9,39,40]	Abiraterone	Placebo	Low	Low	Some concerns	Low	Low	Some concerns
TITAN[12,41]	Apalutamide	Placebo	Low	Low	Low	Low	Some concerns	Some concerns
ARCHES[11]	Enzalutamide	Placebo	Low	Low	Some concerns	Low	Low	Some concerns
ENZAMET[35]	Enzalutamide	Standard nonsteroidal antiandrogen[e]	Low	Low	Low	Low	Low	Low
Radiographic progression-free survival[f]								
GETUG-AFU15[34,38]	Docetaxel	No treatment	Low	Low	Low	Some concerns	Some concerns	Some concerns
CHAARTED[5,36,37]	Docetaxel	No treatment	Low	Low	Low	Some concerns	Low	Some concerns
STAMPEDE[6,8,10,33,42]	Arm 1 docetaxel; arm 2 abiraterone	No treatment	Low	Low	Some concerns	Some concerns	Low	Some concerns
LATITUDE[7,9,39,40]	Abiraterone	Placebo	Low	Low	Some concerns	Low	Low	Some concerns
TITAN[12,41]	Apalutamide	Placebo	Low	Low	Low	Low	Some concerns	Some concerns
ARCHES[11]	Enzalutamide	Placebo	Low	Low	Some concerns	Low	Low	Some concerns
ENZAMET[35]	Enzalutamide	Standard nonsteroidal antiandrogen	Low	Low	Low	Some concerns	Low	Some concerns

Abbreviation expansions appear in footnotes to Table 1.

[a] Concerns raised for missing outcome data when (1) number of patients with missing data was more than 10% the number of events and distributed unevenly between treatment groups, (2) missing data may relate to outcome and treatment effect, (3) no analysis to correct for bias due to missing data, and (4) no sensitivity analysis to show that results were little changed under different assumptions about the association between missing data and their true value.

[b] Concerns raised for measurement of the outcome when the outcome assessors were unmasked and the assessment of the outcome could have been influenced.

[c] Concerns raised for selection of the reported results when the trial protocol (statistical analysis plan) was finalized after the data cutoff date, the trial was open-label, or the trial was double-blind but the protocol specified unblinding for the analysis leading to the reported results.

[d] Overall bias: low if all domains were low, high if at least 1 domain was high and there were some concerns in multiple domains, and some concerns otherwise.

[e] Nonsteroidal antiandrogen agents included bicalutamide, nilutamide, or flutamide.

[f] Radiographic progression-free survival included progression-free survival in the STAMPEDE trial and clinical progression-free survival in the CHAARTED and ENZAMET trials.

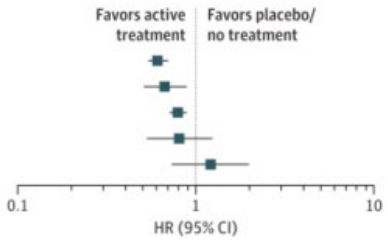
Studienergebnisse:

- Ordered from the most to the least effective determined by results of clinical trials, treatments associated with improved overall survival when added to ADT included abiraterone acetate (hazard ratio [HR], 0.61; 95% credible interval [CI], 0.54-0.70), apalutamide (HR, 0.67; 95% CI, 0.51-0.89), and docetaxel (HR, 0.79; 95% CI, 0.71-0.89);
- treatments associated with improved radiographic progression-free survival when added to ADT included enzalutamide (HR, 0.39; 95% CI, 0.30-0.50), apalutamide (HR, 0.48; 95% CI, 0.39-0.60), abiraterone acetate (HR, 0.51; 95% CI, 0.45-0.58), and docetaxel (HR, 0.67; 95%CI 0.60-0.74).
- Docetaxel was associated with substantially increased SAEs (odds ratio, 23.72; 95% CI, 13.37-45.15), abiraterone acetate with slightly increased SAEs (odds ratio, 1.42; 95% CI, 1.10-1.83), and other treatments with no significant increase in SAEs.

Figure 2. Treatment Ranking and Relative Effect

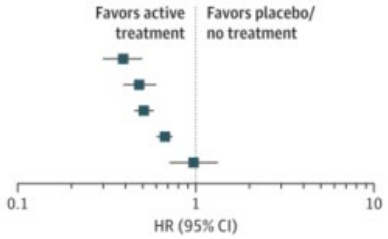
A Overall survival

Median rank	Active treatment	HR (95% CI)
1	Abiraterone acetate	0.61 (0.54-0.70)
2	Apalutamide	0.67 (0.51-0.89)
3	Docetaxel	0.79 (0.71-0.89)
4	Enzalutamide	0.81 (0.53-1.24)
5	SNA	1.21 (0.73-1.99)



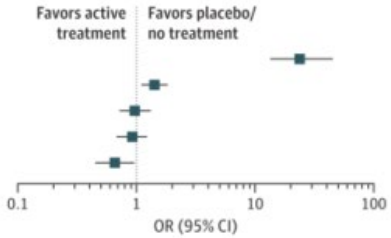
B Radiographic progression-free survival

Median rank	Active treatment	HR (95% CI)
1	Enzalutamide	0.39 (0.30-0.50)
2	Apalutamide	0.48 (0.39-0.60)
3	Abiraterone acetate	0.51 (0.45-0.58)
4	Docetaxel	0.67 (0.60-0.74)
5	SNA	0.97 (0.71-1.33)



C Serious adverse events

Median rank	Active treatment	OR (95% CI)
5	Docetaxel	23.72 (13.37-45.15)
4	Abiraterone acetate	1.42 (1.10-1.83)
3	Apalutamide	0.97 (0.72-1.32)
2	Enzalutamide	0.92 (0.68-1.23)
1	SNA	0.66 (0.45-0.96)



CI indicates credible interval; HR, hazard ratio; OR, odds ratio.

Anmerkung/Fazit der Autoren

As add-on treatments to ADT, abiraterone acetate and apalutamide may provide the largest OS benefits with relatively low SAE risks among patients with mCSPC in RCTs. Although enzalutamide may improve rPFS to the greatest extent, longer follow-up is needed to examine its OS benefits.

Kommentare zum Review

- Es liegen weitere NMAs zu dieser Fragestellung mit derselben Schlussfolgerung vor
  - Mori et al. 2021 [15] (NMA) ARAT vs. Docetaxel; Vorteil ARAT
  - Ferro et al. 2020 [7] (NMA) ARAT+ADT vs. Docetaxel+ADT; Vorteil ARAT gegenüber Docetaxel
  - Sathianathen NJ et al. 2020 [18] (NMA) ARAT und Docetaxel vs. ADT alone; Vorteil Kombi gegenüber ADT
  - Kassem L et al. 2018 [9] (NMA) Docetaxel+ADT vs. AA+ADT; Vorteil AA+ADT
  - Feyerabend S et al., 2018 [8] (NMA) Abi vs. Docetaxel; Conclusion: Our findings suggest that AA + P + ADT is at least as effective as DOC + ADT in reducing the risk of death in men with mHSPC and better at preventing disease progression and improving QoL
  - Rydzewka LHM et al. 2017 [17] (SR und MA) AAP zu ADT Conclusion: AAP Vorteil gegenüber ADT

Wang Y et al., 2020 [26].

Comparative Efficacy of Combined Radiotherapy, Systemic Therapy, and Androgen Deprivation Therapy for Metastatic Hormone-Sensitive Prostate Cancer: A Networkn Meta-Analysis and Systematic Review

Fragestellung

Although many combined treatment approaches have been shown to be effective, there are no data on the comparative efficacy of systemic and local therapies combined with ADT.

Methodik

Population:

- patients with mHSPC aged ≥ 18 years. Studies of patients with localized or castrationresistant PC were excluded.

Intervention/Komparator:

- ADT monotherapy
- ADT + APA
- ADT + AAP
- ADT + DOC
- ADT+ ENZ
- ADT + RT.

Endpunkte:

- overall survival (OS)
- prostatespecific antigen progression-free survival (PSA-PFS)
- time to symptomatic skeletal events (SSE) ->keine Ergebnisse
- time to pain progression →keine Ergebnisse
- time to chemotherapy

Recherche/Suchzeitraum:

- PubMed/MEDLINE, EMBASE, Cochrane library, and clinicaltrials.gov) and gray literature (American Society of Clinical Oncology) were searched to identify all relevant publications up to May 7, 2020.

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 RCTs with 11,194 participants were included in our analysis

Charakteristika der Population:

- Although we assumed that the transitivity assumption was satisfied in our study, this was difficult to validate owing to the paucity of the baseline data in several of the included trials.

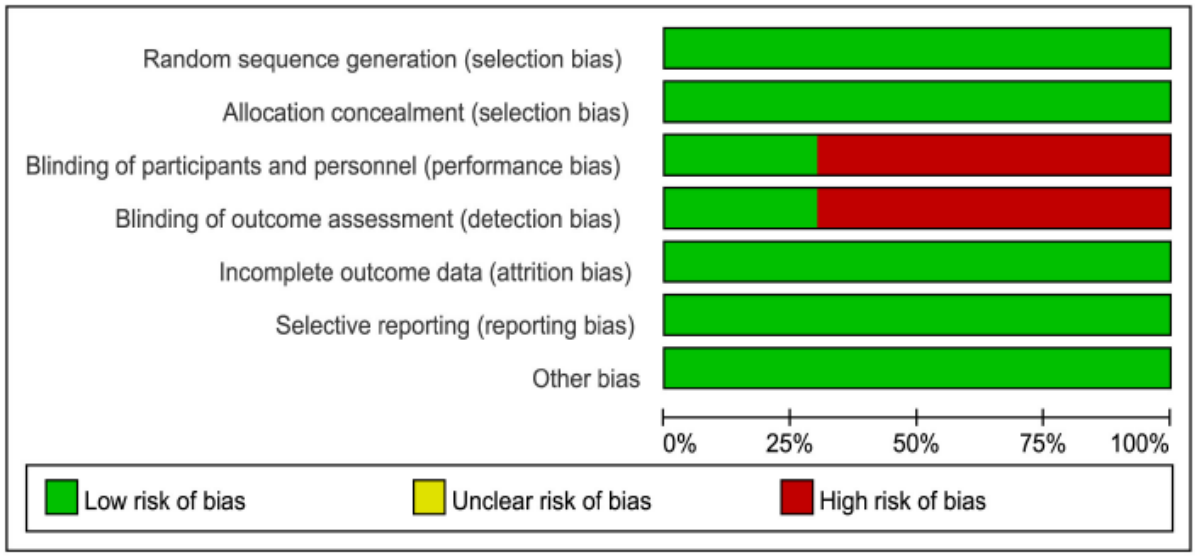
TABLE 1 | Characteristics of included randomized clinical trials in this analysis.

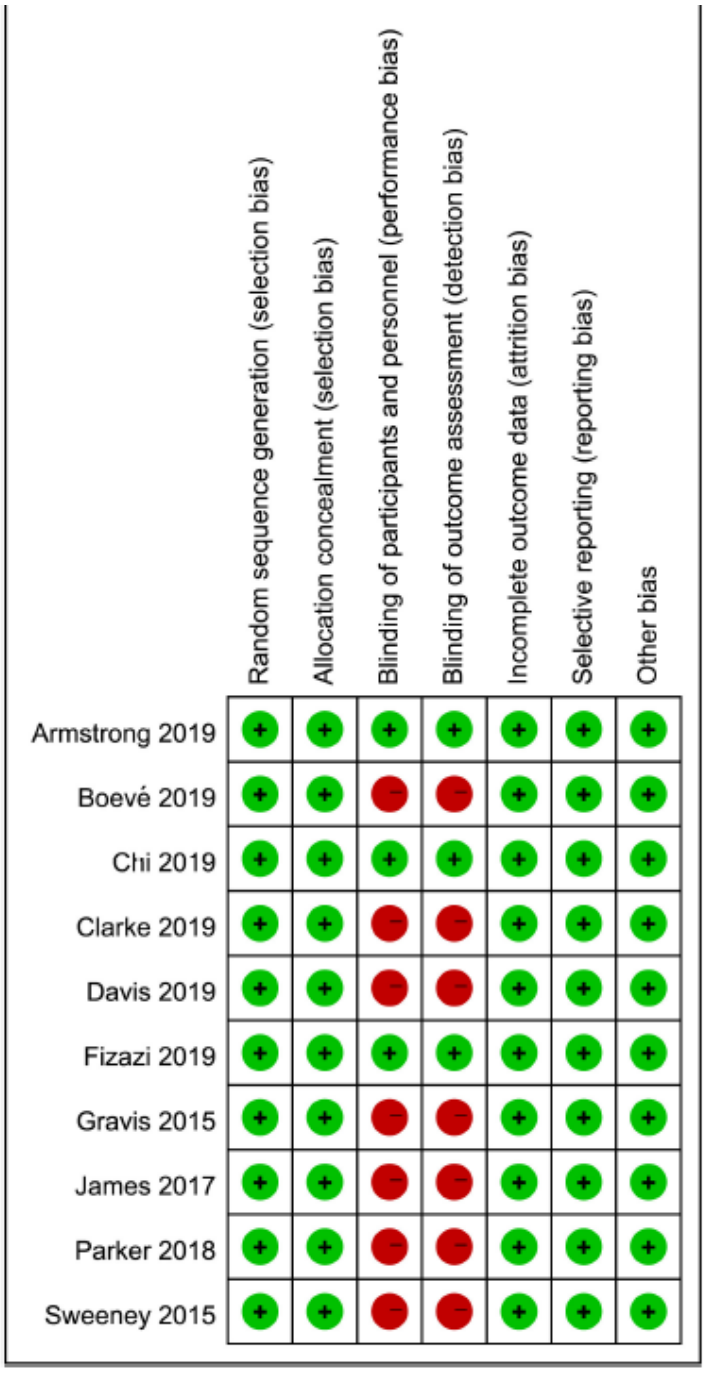
References	Study name	Samples (experiment/control)	Intervention (experiment group)	Intervention (control group)	Primary outcome
Chi et al. (5)	TITAN	525/527	ADT + Apalutamide (240 mg/d)	ADT	OS, rPFS
James et al. (2)	STAMPEDE-G arm	960/957	ADT + Abiraterone (1,000 mg/d) + Prednisolone (5 mg/d)	ADT	OS, FFS
Fizazi et al. (15)	LATITUDE	597/602	ADT + Abiraterone (1,000 mg/d) + Prednisolone (5 mg/d)	ADT	OS, rPFS
Gravis et al. (16)	GETUG-AFU-15	192/193	ADT + Docetaxel (75 mg/m^2 for 21 d, up to 9 cycles)	ADT	OS
Sweeney et al. (12)	CHAARTED	397/393	ADT + Docetaxel (75 mg/m^2 for 21 d, up to 9 cycles)	ADT	OS
Clarke et al. (17)	STAMPEDE-C arm	592/1,184	ADT + Docetaxel (75 mg/m^2 for 21 d, up to 6-cycle)	ADT	OS
Davis et al. (4)	ENZAMET	563/562	ADT + Enzalutamide (160 mg/d)	ADT	OS, PFS
Armstrong et al. (6)	ARCHES	574/576	ADT + Enzalutamide (160 mg/d)	ADT	rPFS
Boevé et al. (8)	HORRAD	216/216	ADT + external beam radiation therapy	ADT	OS
Parker et al. (9)	STAMPEDE-H arm	1,032/1,029	ADT + external beam radiation therapy	ADT	OS, FFS

OS, Overall survival; rPFS, radiographic progression-free survival; PFS, progression-free survival; FFS, failure-free survival; bPFS, biochemical progression-free survival; ADT, androgen deprivation therapy.

Qualität der Studien:

- Seven out of 10 studies were open-label trials and lacked blinding in the study design. All other aspects of the selected articles were determined to be of high quality according to our assessment.




Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Blinding of outcome assessment (detection bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Armstrong 2019
Boevé 2019
Chi 2019
Clarke 2019
Davis 2019
Fizazi 2019
Gravis 2015
James 2017
Parker 2018
Sweeney 2015

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Studienergebnisse:

The treatment network is shown in Figure 3, with the thickness of each line in the network plot proportional to the number of comparisons. Based on the DIC value, the random-effects model was applied to the analysis of PSA-PFS, time to SSE, andOS in the Gleason score ≥ 8 subgroup; the fixed-effects model was applied to the other comparisons.

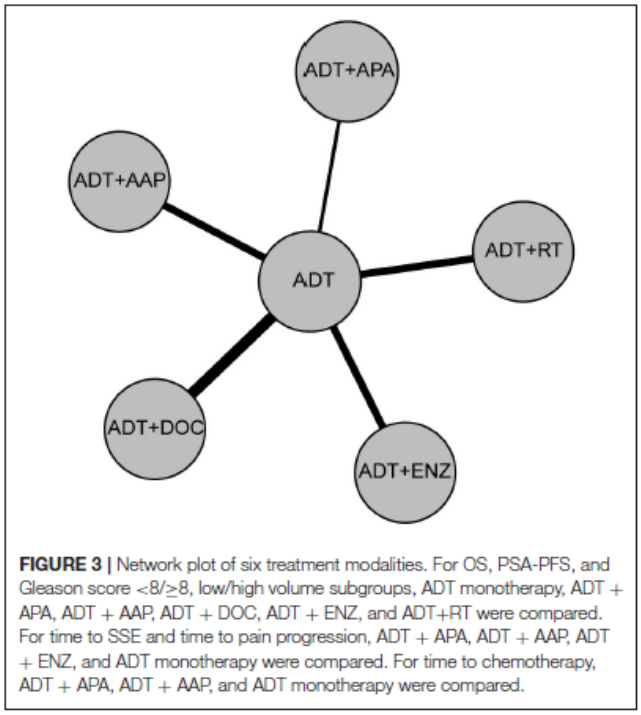


FIGURE 3 | Network plot of six treatment modalities. For OS, PSA-PFS, and Gleason score <8/≥8, low/high volume subgroups, ADT monotherapy, ADT + APA, ADT + AAP, ADT + DOC, ADT + ENZ, and ADT+RT were compared. For time to SSE and time to pain progression, ADT + APA, ADT + AAP, ADT + ENZ, and ADT monotherapy were compared. For time to chemotherapy, ADT + APA, ADT + AAP, and ADT monotherapy were compared.

- Indirect Comparisons of OS
  - Compared to ADT monotherapy, ADT + AAP (HR = 0.64, 95% CI 0.56–0.73), ADT + APA (HR = 0.67, 95% CI 0.51– 0.89), ADT + DOC (HR = 0.78, 95% CI 0.69–0.88), and ADT + ENZ (HR = 0.53, 95% CI 0.37–0.75) all showed statistically significant survival benefits, while no advantages were observed in comparisons between the four combined treatment regimens. ADT + RT had the highest HR compared to ADT monotherapy (HR=0.96, 95%CI 0.85–1.1) and was inferior to every combined systemic therapy. Ranking results indicated a high likelihood that ADT + ENZ was superior (78.58%) to the other regimens in prolonging OS.
- Indirect Comparisons of PSA-PFS
  - Nine of the 10 trials were included in the analysis of PSA-PFS. ADT + AAP (HR = 0.30, 95% CI: 0.26–0.35), ADT + APA (HR = 0.26, 95% CI: 0.21–0.32), ADT + DOC (HR = 0.67, 95% CI: 0.54–0.84), ADT + ENZ (HR = 0.34, 95% CI: 0.26– 0.44), and ADT + RT (HR = 0.86, 95% CI: 0.69–1.1) conferred a survival benefit over ADT monotherapy. ADT + APA was the most effective combined treatment regimen (83.17%) whereas ADT + RT (84.20%) ranked last.
- Indirect Comparisons of Health-Related QoL Outcomes
  - We compared two health-related QoL outcomes; the results of indirect comparisons are shown in Table 2 and detailed ranking results are shown in Figure 5, Table 3. Four regimens (ADT + APA, ADT + AAP, ADT + ENZ, and ADT monotherapy) were compared in terms of time to SSE. The combined treatments had longer times to SSE than ADT monotherapy, although the differences were not statistically significant. ADT + ENZ (HR = 0.51, 95% CI: 0.20–1.3) was the most effective regimen compared to ADT

monotherapy according to rank, whereas ADT + APA had the highest HR (0.80, 95% CI: 0.33–2.0). However, these findings were not statistically significant. The four regimens (ADT + APA, ADT + AAP, ADT + ENZ, and ADT monotherapy) were compared in terms of time to pain progression; all three combined therapies were found to be superior to ADT monotherapy but only ADT + AAP showed a statistically significant difference (HR = 0.72, 95% CI: 0.61– 0.86). ADT + AAP was the highest-ranking regimen (79.90%), although all indirect comparisons yielded non-significant results.

- Indirect Comparisons of Time to Chemotherapy
  - Two trials (TITAN and LATITUDE) were included in the analysis. Indirect comparisons revealed that both ADT + AAP (HR = 0.51, 95% CI: 0.41–0.63) and ADT + APA (HR = 0.39, 95% CI: 0.27–0.56) prolonged the time to chemotherapy compared to ADT monotherapy (Table 2). ADT + APA ranked highest (89.31%) among the three treatment regimens in time to chemotherapy, but this result was non-significant

TABLE 2 | The meta-analysis results of all comparisons.

	ADT + APA vs. ADT	ADT + AAP vs. ADT	ADT + DOC vs. ADT	ADT + ENZ vs. ADT	ADT + RT vs. ADT	ADT + AAP vs. ADT + APA	ADT + DOC vs. ADT + APA	ADT + ENZ vs. ADT + APA	ADT + RT vs. ADT + APA	ADT + DOC vs. ADT + AAP	ADT + ENZ vs. ADT + AAP	ADT + RT vs. ADT + AAP	ADT + ENZ vs. ADT + DOC	ADT + RT vs. ADT + DOC	ADT + RT vs. ADT + ENZ
OS [HR (95%CI)]	**0.67 (0.51, 0.89)**	**0.64 (0.56, 0.73)**	**0.78 (0.69, 0.88)**	**0.53 (0.37, 0.75)**	0.96 (0.85, 1.1)	0.95 (0.70, 1.30)	1.20 (0.85, 1.60)	0.78 (0.50, 1.2)	**1.4 (1.1, 1.9)**	1.20 (1.0, 1.50)	0.82 (0.57, 1.2)	**1.5 (1.3, 1.8)**	**0.68 (0.47, 0.99)**	1.2 (1.0, 1.5)	**1.8 (1.3, 2.7)**
PSA-PFS	**0.26 (0.21, 0.32)**	**0.30 (0.26, 0.35)**	**0.67 (0.54, 0.84)**	**0.34 (0.26, 0.44)**	0.86 (0.69, 1.1)	1.2 (0.9, 1.5)	**2.6 (1.9, 3.5)**	1.3 (0.94, 1.8)	**3.3 (2.4, 4.5)**	**2.2 (1.7, 2.9)**	1.1 (0.84, 1.5)	**2.9 (2.2, 3.7)**	**0.50 (0.36, 0.71)**	1.3 (0.94, 1.8)	**2.6 (1.8, 3.6)**
Time to SSE	0.80 (0.33, 2)	0.76 (0.32, 1.8)	NA	0.51 (0.20, 1.3)	NA	0.94 (0.27, 3.3)	NA	0.64 (0.17, 2.3)	NA	NA	0.68 (0.19, 2.4)	NA	NA	NA	NA
Time to pain progression	0.83 (0.65, 1.1)	**0.72 (0.61, 0.86)**	NA	0.91 (0.78, 1.1)	NA	0.88 (0.65, 1,2)	NA	1.1 (0.83, 1.5)	NA	NA	1.3 (1.0,1.6)	NA	NA	NA	NA
Time to chemotherapy	**0.39 (0.27, 0.56)**	**0.51 (0.41, 0.63)**	NA	NA	NA	1.3 (0.85, 2)	NA	NA	NA	NA	NA	NA	NA	NA	NA
OS for high-volume subgroup	**0.68 (0.50, 0.92)**	**0.62 (0.50, 0.74)**	**0.73 (0.62, 0.86)**	**0.64 (0.42, 0.99)**	1.1 (0.92, 1.2)	0.91 (0.64, 1.3)	1.1 (0.76, 1.5)	0.95 (0.56, 1.6)	**1.6 (1.1, 2.2)**	1.2 (0.93, 1.5)	1.0 (0.65, 1.7)	**1.7 (1.4, 2.2)**	0.88 (0.56, 1.4)	**1.5 (1.2, 1.8)**	**1.7 (1.1, 2.6)**
OS for low-volume subgroup	0.67 (0.34, 1.30)	0.72 (0.47, 1.1)	0.81 (0.64, 1.0)	**0.38 (0.21, 0.69)**	**0.68 (0.54, 0.87)**	1.1 (0.49, 2.4)	1.2 (0.59, 2.5)	0.57 (0.23, 1.4)	1.0 (0.50, 2.1)	1.1 (0.69, 1.8)	0.53 (0.25, 1.1)	0.95 (0.58, 1.5)	**0.47 (0.25, 0.89)**	0.84 (0.60, 1.2)	1.8 (0.95, 3.4)
OS for GS<8 subgroup	**0.56 (0.33, 0.95)**	0.44 (0.15, 1.3)	**0.71 (0.54, 0.92)**	0.59 (0.30, 1.2)	1.1 (0.84, 1.5)	0.78 (0.23, 2.6)	1.3 (0.70, 2.3)	1.1 (0.45, 2.5)	**2.0 (1.1, 3.7)**	1.6 (0.54, 4.8)	1.4 (0.38, 4.8)	2.6 (0.85, 7.7)	0.83 (0.4, 1.7)	**1.6 (1.1, 2.4)**	1.9 (0.92, 4.0)
OS for GS ≥8 subgroup	0.73 (0.36, 1.5)	0.67 (0.35, 1.3)	0.78 (0.53, 1.2)	0.70 (0.35, 1.4)	0.90 (0.48, 1.7)	0.92 (0.35, 2.4)	1.1 (0.48, 2.4)	0.95 (0.35, 2.5)	1.2 (0.48, 3.2)	1.2 (0.54, 2.5)	1.0 (0.4, 2.6)	1.4 (0.55, 3.4)	0.89 (0.40, 2)	1.2 (0.55, 2.5)	1.3 (0.5, 3.4)

OS, Overall survival; HR, hazard ratio; 95%CI, 95% confidence intervals; PSA-PFS, prostate specific antigen progression-free survival; SSE, symptomatic skeletal events; GS, Gleason score; ADT, androgen deprivation therapy; APA, apalutamide; AAP, abiraterone and prednisolone; DOC, docetaxel; ENZ, enzalutamide; RT, radiotherapy; NA, not available. Comparison in bold refers to the statistically significant comparison.

Anmerkung/Fazit der Autoren

In summary, ADT + RT demonstrated superiority over ADT monotherapy in our analysis of OS and the low volume subgroup of mHSPC patients. Furthermore, ADT + RT showed comparable efficacy to most combined systemic treatment regimens in the low-volume subgroup. The combined systemic therapies showed a significant advantage over ADT monotherapy in all comparisons performed in this study, with ADT + ENZ identified as the optimal treatment in most cases. Based on limited data, we also showed that patients receiving combined therapies experienced less of a decline in QoL compared to those treated with ADT monotherapy. Based on these findings, the selection of an appropriate treatment approach for mHSPC patients by the physician should be made based on discussions regarding potential toxicities as well as the duration and cost of treatment.

Di Nunno V et al., 2020 [5].

Systemic Treatment for Metastatic Hormone Sensitive Prostate Cancer: A Comprehensive Meta-Analysis Evaluating Efficacy and Safety in Specific Sub-Groups of Patients

Fragestellung

Several systemic treatments are available for metastatic hormone sensitive prostate cancer (mHSPC) including docetaxel (D), abiraterone and prednisone (A + P) and new anti-androgens (NA). In our study we performed a systematic review and meta-analysis assessing efficacy outcomes (survival and radiological-free survival), safety and survival on specific subgroups of patients.

Methodik

Population:

- metastatic hormone sensitive prostate cancer (mHSPC)

Intervention:

- new hormonal agent or other compounds in addition to ADT

Komparator:

- nicht definiert

Endpunkte:

- Risk of death, biochemical and radiological progression among all patients.
- Risk of death according to different pathological/clinical features.
- Evaluation of the relative risk (RR) and risk difference of serious toxicity defined as adverse events (AEs) with grade ≥ 3 specific AEs.

Hazard ratios (HRs) and RR were measures adopted for endpoints.

Recherche/Suchzeitraum:

- published between 01 January 2012 to 15 September 2019

Qualitätsbewertung der Studien:

- Cochrane tool for risk of bias assessment in randomized trials

Ergebnisse

Anzahl eingeschlossener Studien:

- eight randomized trials were included in meta-analysis for a total of 9987 patients
- all perspective, randomized Phase III clinical trials

Charakteristika der Population:

Overall, 9987 patients were included in this meta-analysis. Of these, 4994 patients received ADT monotherapy, while 4993 received ADT plus experimental compounds. In particular, among 4993 patients included in experimental arms, 1774 received docetaxel (593 also received zoledronic acid), 1557 received abiraterone, 1662 were treated with enzalutamide (n = 1137) and apalutamide (n = 525).

Of note, in the STAMPEDE trials, we considered only patients with metastatic disease for bPFS, rPFS, OS and subgroup analyses (Table 2).

Table 1 Description of studies included in meta-analysis

GETUG-AFU-15 [5, 6]

Randomized, open-label, Phase 3 trial evaluating androgen-deprivation therapy (ADT) ± docetaxel (75 mg/m^2) in patients with radiologically proven mHSPC
Primary endpoint: overall survival (OS)
Secondary endpoints: clinical progression-free survival (cPFS), biochemical progression-free survival (bPFS)

No. of patients
192 in ADT + Docetaxel arm, 193 in ADT alone arm

Median follow-up
83.9 months

Primary endpoint (mOS)
Hazard ratio (HR): 0.88 (95% CI, 0.68–1.14, $p = 0.3$)

Secondary endpoints (bPFS, rPFS)
0.69 (95% CI, 0.55–0.87; $p = 0.002$);
HR: 0.67 (95% CI, 0.54–0.84; $p < 0.001$)

CHAARTED [7, 8]

Randomized, open-label, Phase 3 trial evaluating androgen-deprivation therapy (ADT) ± docetaxel (75 mg/m^2) in patients with radiologically proven mHSPC
Primary endpoint: overall survival (OS)
Secondary endpoints: time to development of castration resistant prostate cancer (TCRPC). Two amendments were made in this study: the first allowed the inclusion of patients with low volume metastatic disease (high volume metastatic disease was defined as: presence of visceral metastases or 4 or more bone lesions with one or more lesions beyond vertebral bodies and pelvis) and the second which expanded the initial overall cohort to 780 patients

No. of patients
397 in ADT + docetaxel arm, 393 in ADT alone arm

Median follow-up
53.7 months

Primary endpoint (mOS)
HR: 0.72 (95% CI, 0.59–0.89; $p = 0.0018$)

Secondary endpoints (TCRPC)
HR: 0.61 (95% CI, 0.52–0.73; $p < 0.001$)

STAMPEDE [9]

STAMPEDE is a multi-arm, multistage trial evaluating multiple distinct strategies in parallel against a single control arm. In this stage, patients with high risk, locally advanced, metastatic or recurrent hormono sensitive prostate cancer were randomized to receive ADT, ADT + zoledronic acid (ZA, 4 mg every 28 days), ADT + ZA + docetaxel (75 mg/mq) or ADT + docetaxel. Primary outcome was OS, secondary outcome failure free survival (FFS)

No. of patients
1184 ADT arm, 593 ADT + ZA, 593 ADT + ZA + docetaxel, 592 ADT + docetaxel

Median follow-up
43 months

Primary endpoint (mOS)
ADT vs ADT + ZA (HR = 0.94, 95% CI 0.79–1.11; $p = 0.45$)
ADT vs ADT + docetaxel (HR = 0.78, 95% CI 0.66–0.93; $p = 0.006$)
ADT vs ZA + docetaxel (HR = 0.82, 95% CI 0.69–0.97; $p = 0.022$)

Secondary endpoints (FFS)
ADT vs ADT + ZA (HR = 0.92, 95% CI 0.81–1.04, $p = 0.198$)
ADT vs ADT + docetaxel (HR = 0.61, 95% CI 0.53–0.70, $p < 0.001$)
ADT vs ZA + docetaxel (HR = 0.62, 95% CI 0.54–0.70; $p < 0.001$)

LATITUDE [10]

Double-blind, placebo-controlled, Phase 3 trial comparing ADT alone to ADT + abiraterone (1000 mg daily) + prednisone (5 mg daily). All patients enrolled in this study had a diagnosis of mHSPC. Moreover only patients with two of these risk factors have been enrolled: (1) Gleason of 8 or more, (2) visceral metastases, (3) three or more bone metastases
Primary endpoints: OS, rPFS
Secondary endpoints: time to the next "skeletal-related event", bPFS, time to next treatment, time to initiation of chemotherapy and time to pain progression

Table 1 (continued)

No. of patients
602 ADT + placebo + placebo arm, 597 ADT + abiraterone + prednisone arm

Median follow-up
30.4 months

Primary endpoints (1. mOS, 2. rPFS)
1. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.62, 95% CI, 0.51–0.76, $p < 0.001$)
2. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.47, 95% CI, 0.39–0.55, $p < 0.001$)

Secondary endpoints (1. time to the next "skeletal-related event", 2. bPFS, 3. time to next treatment, 4. time to initiation of chemotherapy and 5. time to pain progression)
1. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0. 70, 95% CI 0.54–0.92, $p = 0.009$)
2. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.30, 95% CI 0.26–0.35, $p < 0.001$)
3. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.42, 95% CI 0.35–0.5, $p < 0.001$)
4. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.44, 95% CI 0.35–0.56, $p < 0.001$)
5. ADT + placebo + placebo vs ADT + abiraterone + prednisone (HR = 0.70, 95% CI 0.58–0.83, $p < 0.001$).

STAMPEDE [11]

STAMPEDE is a multi-arm, multistage trial evaluating multiple distinct strategies in parallel against a single control arm. In this stage, patients with newly diagnosed and metastatic, node-positive, or high-risk locally advanced (defined with the presence of two of these risk factors: T3–4, Gleason 8–10, PSA of 40 ng/mL or more) or patients with high-risk disease relapsing after radiation therapy or surgery (defined as a PSA > 4 ng/mL, with a doubling time < 6 months, PSA level > 20 ng/mL, nodal or metastatic relapse or < 12 months of total ADT with an interval of > 12 months without treatment) were randomized to receive ADT alone or ADT + abiraterone (1000 mg) + prednisone (5 mg). Of note, this was not a placebo-controlled trial. Primary outcome was OS while FFS was the intermediate primary endpoint. Adverse events, symptomatic skeletal events, PFS, prostate cancer specific survival and quality of life were secondary endpoints

No. of patients
957 ADT arm, 960 ADT + abiraterone + prednisone arm

Median follow-up
40 months

Primary endpoints (1. mOS, 2. FFS)
1. ADT vs ADT + abiraterone + prednisone (HR = 0.63, 95% CI 0.52–0.76, $p < 0.001$)
2. ADT vs ADT + abiraterone + prednisone (HR = 0.29, 95% CI 0.25–0.34, $p < 0.001$)

Secondary endpoints (1. adverse events, 2. symptomatic skeletal events, 3. PFS, prostate cancer specific survival and 4. quality of life)
1. ADT vs ADT + Abiraterone + prednisone (Grade 3–5 AEs occurred in 33% and 47% respectively)
2. ADT vs ADT + abiraterone + prednisone (HR = 0.46, 95% CI 0.37–0.58, $p < 0.001$)
3. ADT vs ADT + abiraterone + prednisone (HR = 0.40, 95% CI 0.34–0.47, $p < 0.001$)
4. Not reported

ARCHES [14]

Phase III randomized, placebo-controlled clinical trial comparing ADT + placebo vs ADT + enzalutamide (160 mg) in patients with mHSPC. Primary endpoint was rPFS and OS. Secondary endpoints are: bPFS, time to new anticancer treatment, PSA undetectable rate, objective response rate (ORR), time to deterioration in urinary symptoms. To date only data of rPFS final analysis and interim OS analysis have been published

No. of patients
576 ADT + placebo arm, 574 ADT + enzalutamide arm

Median follow-up
Not reported

Primary endpoints (1. mOS, 2. rPFS)
1. Only result of interim analysis reported (immature follow up)
2. ADT + placebo vs ADT + enzalutamide (HR = 0.39, 95% CI 0.30–0.50, $p < 0.0001$)

Secondary endpoints (1. bPFS, 2. time to new anticancer treatment, 3. PSA undetectable rate, 4. objective response rate, 5. time to deterioration in urinary symptoms):
1. ADT + placebo vs ADT + enzalutamide (HR 0.19, 95% CI 0.13–0.26, $p < 0.0001$)
2. ADT + placebo vs ADT + Enzalutamide (HR 0.28, 95% CI 0.20–0.40, $p < 0.0001$)
3. ADT + placebo vs ADT + enzalutamide (17.6% vs 68.1%, $p < 0.0001$)
4. ADT + placebo vs ADT + enzalutamide (63.7% vs 83.1%, $p < 0.0001$)
5. Not reported

Table 1 (continued)

ENZAMET [13]

Open-label, randomized, Phase 3 trial investigating the combination between enzalutamide (160 mg) and ADT versus ADT alone in patients with mHSPC. Primary endpoint was OS while bPFS, clinical PFS, radiological PFS and safety were secondary outcomes. After the enrollment of 88 patients, the early administration of docetaxel with testosterone suppression was permitted. Up to two cycles of docetaxel were permitted before randomization. Randomization was performed considering also the presence of high or low volume disease (high volume disease defined as defined as the presence of visceral metastases or at least four bone lesions with at least one lesion located beyond the vertebral bodies and pelvis)

No. of patients:
562 ADT, 563 ADT + enzalutamide arm

Median follow-up:
34 months

Primary endpoints (1. mOS, 2. PFS):
1.ADT vs ADT + enzalutamide arm (HR 0.67, 95% CI 0.52–0.86, $p = 0.002$)
2.ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.40, 95% CI 0.33–0.49 $p < 0.0001$)

Secondary endpoints (1. bPFS, 2. clinical PFS, and 3. safety)
1. ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.39, 95% CI 0.33–0.47 $p < 0.0001$)
2. ADT vs ADT + enzalutamide arm (HR clinical PFS = 0.40, 95% CI 0.33–0.49 $p < 0.0001$)
3 ADT vs ADT + enzalutamide arm (34% vs 42%)

TITAN [12]

Double-blind, Phase 3 trial comparing apalutamide (240 mg) to placebo in addition to standard ADT in patients with mHSPC. Previous docetaxel treatment was allowed. Primary endpoints were OS and rPFS. Secondary endpoint were: time to cytotoxic chemotherapy, time to pain progression, time to chronic opioid use, time to skeletal-related event
Randomization was performed considering also the presence of high or low volume disease (high volume disease defined as defined as the presence of visceral metastases or at least four bone lesions with at least one lesion located beyond the vertebral bodies and pelvis)

No. of patients
527 ADT + placebo, 525 ADT + apalutamide

Median follow-up
22.7 months

Primary endpoints (1. mOS, 2. rPFS)
1. ADT + placebo vs ADT + apalutamide (HR 0.67; 95% CI 0.51–0.89, $p = 0.005$)
2. ADT + placebo vs ADT + apalutamide (HR 0.48, 95% CI 0.39–0.60, $p < 0.001$)

Secondary endpoints (1. time to cytotoxic chemotherapy, 2. time to pain progression, 3. time to chronic opioid use, 4. time to skeletal-related event, 5. bPFS)
1. ADT + placebo vs ADT + apalutamide (HR 0.39, 95% CI 0.27–0.56, $p < 0.0001$)
2. Not performed
3 Not performed
4. Not performed
5. ADT + placebo vs ADT + apalutamide (HR 0.26, 95% CI 0.21–0.32, $p < 0.0001$)

Qualität der Studien:

Table 2 Risk of bias among trials included: + low risk of bias, – high risk of bias, ? uncertain risk of bias

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome and assessment	Incomplete outcome data	Selective reporting	Other bias
GETUG-AFU-15 [5, 6]	+	+	–	–	+	+	+
CHAARTED [7, 8]	+	+	–	–	+	?	+
STAMPEDE [9]	+	+	–	–	+	+	+
LATITUDE [10]	+	+	+	+	+	+	+
STAMPEDE [11]	+	+	–	–	+	+	+
ARCHES [14]	?	+	+	+	–	–	?
ENZAMET[13]	+	+	–	–	+	+	+
TITAN [12]	+	+	+	+	+	+	+

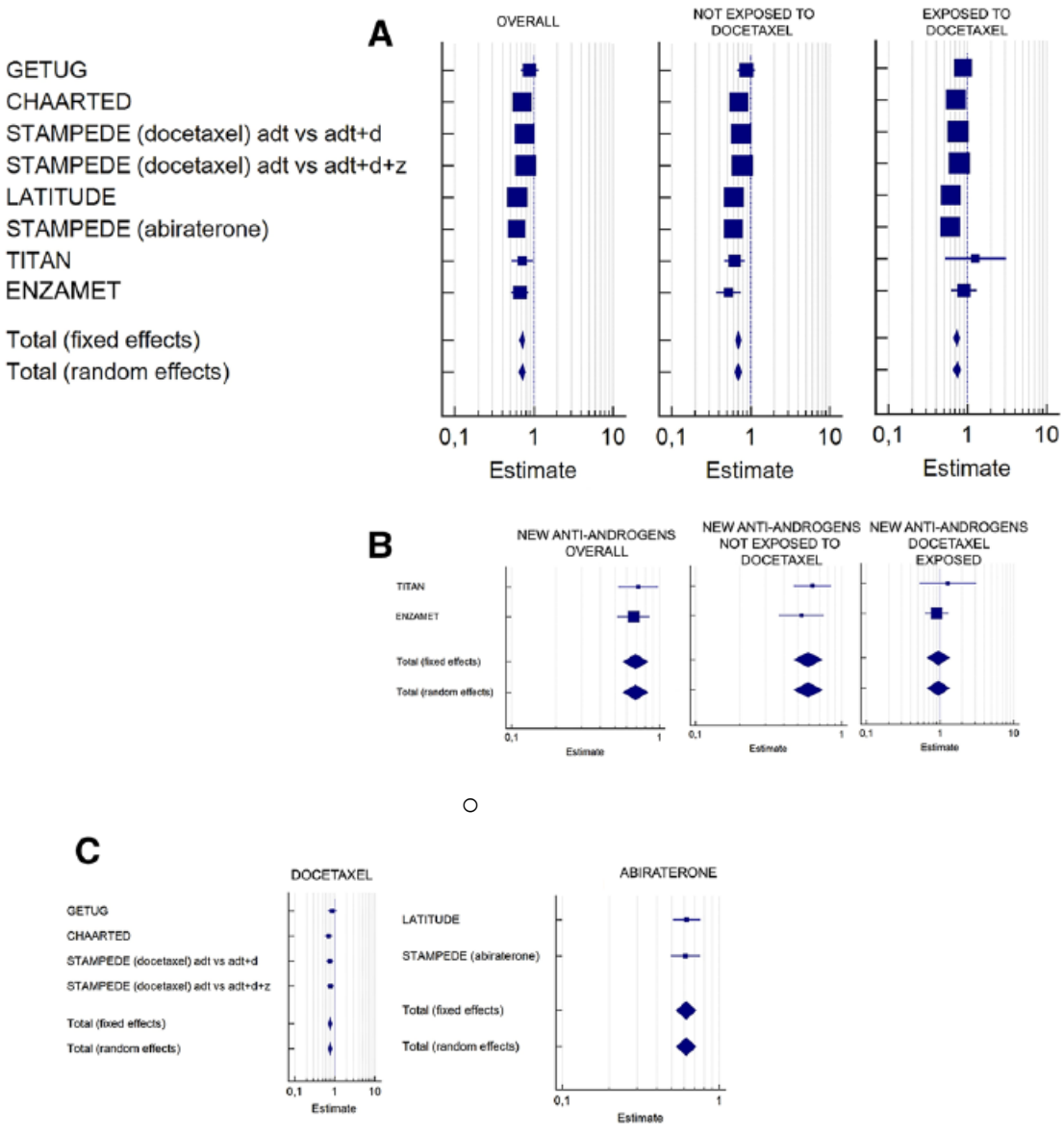
Studienergebnisse:

- Overall survival (OS) analysis among patients with metastatic hormone sensitive prostate cancer.

  a All patients included, including patients not previously exposed to docetaxel, patients previously exposed to docetaxel.

  b New anti-androgens overall, exposed and not previously exposed to docetaxel.

  c OS result among metastatic patients receiving docetaxel; OS result among metastatic patients receiving abiraterone

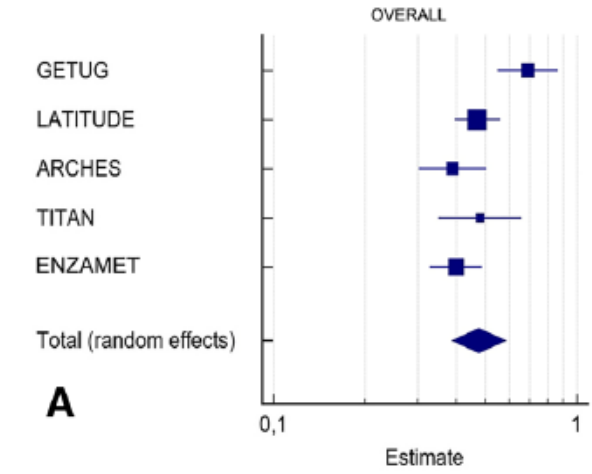


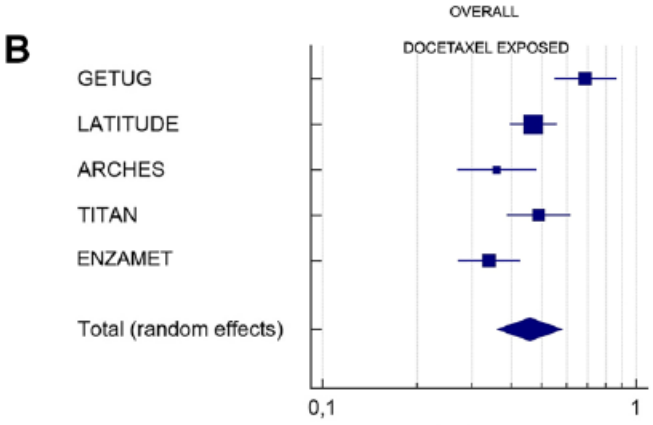
- Radiological progression-free (rPFS) analysis.

  a All studies reporting rPFS.

  b All studies including patients who received docetaxel before experimental treatment, all studies including patients not exposed to docetaxel.

  c New anti-androgen treatment among patients who did not receive docetaxel and among patients previously exposed to docetaxel


OVERALL
GETUG
LATITUDE
ARCHES
TITAN
ENZAMET
Total (random effects)
A
0,1
1
Estimate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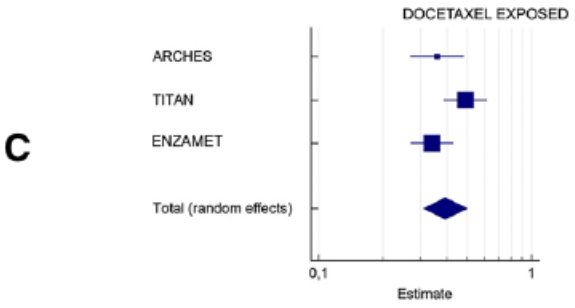
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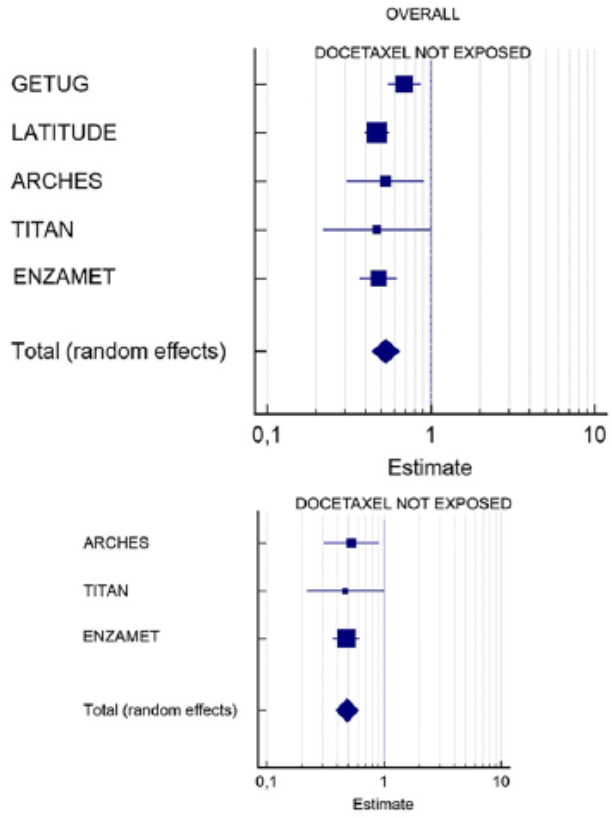

Overall Survival (OS) and Radiological Progression-Free Survival (rPFS) Analysis

Overall, the administration of experimental compounds resulted in a survival advantage (pooled-random HR 0.714; CI 0.656–0.777; p value < 0.001; I2 = 15.66%, p = 0.31; Fig. 2a.1). The survival advantage was confirmed after the inclusion of previously untreated patients (pooled-randommHR 0.697; CI 0.629–0.772; p value < 0.001; I2 = 37.78%, p = 0.13; Fig. 2a.2) and previous docetaxel or concomitant exposed patients (pooled-random HR 0.736; CI 0.662–0.819; p value < 0.001; I2 = 35.59%, p = 0.14; Fig. 2a.3).

Survival benefit was demonstrated in patients treated with docetaxel (pooled-random HR 0.736; CI 0.662–0.819; p value < 0.001; I2 = 0.00%, p = 0.69; Fig. 2c.1), abiraterone (pooled-random HR 0.615, 95% CI 0.532–0.712; p value < 0.001; I2 = 0.00%, p = 0.91; Fig. 2c.2) and new anti-androgens (pooled-random for enzalutamide/apalutamide- treated patients: 0.690, 95% CI 0.568–0.838; pvalue < 0.001; I2 = 0.00%, p = 0.72; Fig. 2b.1).

- Among patients treated with apalutamide or enzalutamide, the survival benefit was confirmed in previously untreated patients (pooled random HR 0.587, 95% CI, 0.467–0.736, p < 0.001, I2 = 0.00%, p = 0.46; Fig. 2b.2) but no survival benefit emerged in patients exposed (concomitant or subsequently) with docetaxel (pooled random HR 0.948, 95% CI 0.671–1.338, p = 0.760, I2 = 0%, p = 0.48; Fig. 2b.3).
- Regarding rPFS analyses, we considered five of eight studies selected [5, 6, 10, 12–14] (three studies did not report data on rPFS [7–9, 11]). Overall, the administration of experimental compounds resulted in prolonged rPFS in overall cohort (pooled random HR: 0.475, 95% CI 0.390–0.579, p < 0.001). Heterogeneity was statistically significant with an I2 value of 74%, p = 0.004 (Fig. 3a). The radiological progression-free advantage was also achievable including patients previously untreated (Fig. 3b.1) and exposed (concomitant or subsequently) with docetaxel to docetaxel (in this case Heterogeneity was statistically significant. I2 value: 81.62%, p = 0.0002; Fig. 3b.2).

- When we consider only the three studies with a cohort of previously treated patients, the rPFS advantage was available in all patients, previously untreated patients (Fig. 3c.2) and previously treated patients (or patients who receivedconcomitant docetaxel) (Fig. 3c.3). An extensive summary of the results achieved for this aim are available in the Supplementary Material.
- In bPFS analyses, we collected data provided by four of eight studies [5, 6, 10, 13, 14]. In this analyses, administration of experimental compounds (docetaxel, enzalutamide or abiraterone) resulted in a significant improvement of bPFS, although heterogeneity was statistically significant (I2 = 93.99%, p < 0.0001). Similar results have been observed when analysis was restricted to patients who received hormonal experimental compounds (I2 = 85.9%, p = 0.0008) or enzalutamide (I2 = 92.38%, p = 0.0003)

Anmerkung/Fazit der Autoren

The addition of chemotherapy, abiraterone or new antiandrogens to ADT improves survival of patients with mHSPC. Our finding is not surprising considering results achieved by each drug in randomized studies. The use of a new anti-androgen may not improve survival of patients receiving concomitant docetaxel or previous docetaxel. However, the large heterogeneity among studies evaluating this issue limits the value of this observation. According to our results, patients with visceral metastases did not seem to show a survival benefit with the administration of new anti-androgens. Initial Gleason score may be related to different outcomes among patients receiving docetaxel or abiraterone. Toxicity profiles of these drugs confirmed the known hematological toxicity of docetaxel and cardio-vascular toxicity associated with abiraterone. High-grade AEs typically associated with new anti-androgens rarely occur during or after treatment.

Results of our meta-analysis suggest that:

• Patient selection is essential before treatment planning. Indeed, some patients do not benefit from a specific treatment (such as docetaxel for patients with low tumor volume or enzalutamide/apalutamide in patients previously exposed to chemotherapy)

• Disease assessment may be an important issue to consider before treatment planning. Low Gleason score may be associated with lowest effect of abiraterone on survival. The presence of visceral metastases should discourage the adoption of apalutamide or enzalutamide.

• Toxicity profile of agents should be carefully considered, and administration of enzalutamide/apalutamide may be a treatment of choice in frail patients. The cardiotoxicity of abiraterone should be considered in patients with high number of cardiovascular comorbidities, while patients with hematopoietic dysfunction or higher risk of infective disease should be discouraged from the adoption of docetaxel in this setting.

Kommentare zum Review

- Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor
  - Buonerba C et al. 2020 [2] In conclusion, our results discourage the sequential or concurrent use of both docetaxel and an ARAT agent regardless of tumor volume or other factors. It is also interesting to note that prior docetaxel use and tumor volume/presence of visceral metastasis were the only factors showing a negative influence on ARAT efficacy among the eight considered, which underlines the need for predictive factors in this setting.
  - Sun G et al. 2018 [21] Abi+ADT vs. Doc+ ADT; Conclusion: Among M1 patients with younger age (<70years), ECOGPS0-1 or aggressive Gleason score (GS≥8), upfront Abi

showed superior-ity to Doc in prolonging FFS. For a subset of populations, Abi may be the first choice for men who start treatment for the first time

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Marchioni M et al., 2020 [14].

New Antiandrogen Compounds Compared to Docetaxel for Metastatic Hormone Sensitive Prostate Cancer: Results from a Network Meta-Analysis

Fragestellung

Docetaxel represent the standard of care in patients with metastatic, hormone sensitive prostate cancer. However, androgen receptor axis targeted therapies have also been shown to be effective. We aimed to analyze findings in randomized controlled trials investigating first-line treatment for hormone sensitive prostate cancer.

Methodik

Population:

- patients with mHSPC

Intervention/ Komparator:

- novel systemic compounds compared to ADT only or in association with any systemic treatment

Endpunkte:

- The primary outcome of interest was OS and secondary outcomes of interest were PFS and high grade (grades 3 to 5) AEs.
- OS followup was defined as the time from treatment initiation to death from any cause or to the last followup available.
- PFS followup was defined as the time from treatment initiation to radiological or clinical progression, death or the last followup.

Recherche/Suchzeitraum:

- In July 2019 we performed a computerized, systematic literature search of studies published up to June 2019 using PubMed, Web of Science, Scopus and ScienceDirect.

Qualitätsbewertung der Studien:

- The RoBs of each study and outcomewere evaluated and then graphically depicted as RoB summaries and graphs using RevMan, version 5.3.

Ergebnisse

Anzahl eingeschlossener Studien:

- n= 13

Charakteristika der Population:

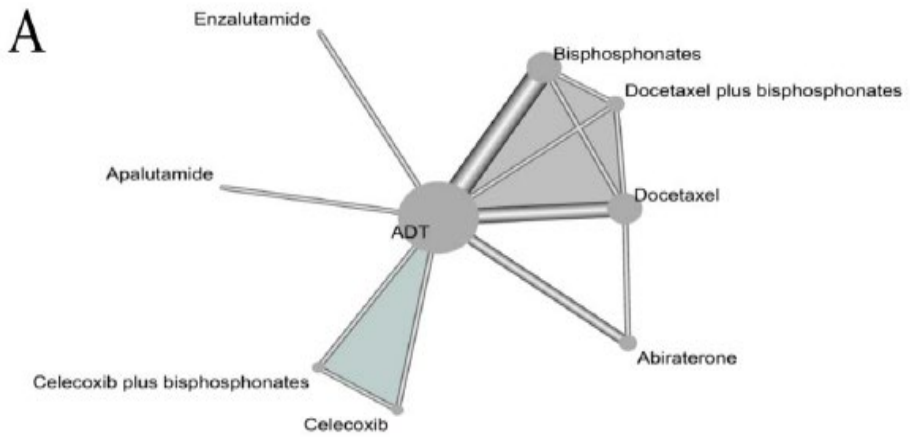
Supplementary Table 1 – Main characteristics of included studies

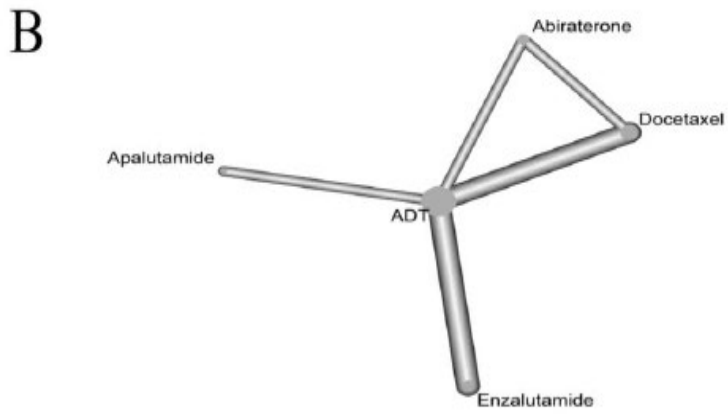
Study	First author (publication year)	Years enrollment	Type of study	Treatment comparison	Primary endpoint	Number of patients
STAMPEDE (Arm G)	James et al. (2017)	2011 - 2014	Open label	ADT+ AA vs. ADT	OS	502 vs. 500
STAMPEDE (Arm B) (Arm C) (Arm E)	James et al (2016)	2005 - 2013	Open label	ADT + ZA vs. ADT ADT + DOC vs. ADT ADT + ZA + DOC vs. ADT	OS	366 vs. 724 362 vs. 724 365 vs. 724
CHAARTED	Kyriakopoulos (2018)	2006 - 2012	Open label	ADT + DOC vs. ADT	OS	393 vs. 397
ARCHES	Armstrong et al. (2019)	2016 - 2018	Double blind	ADT + ENZA vs. ADT	rPFS	576 vs. 574
GETUG AFU 15	Gravis et al. (2016)	2004 - 2008	Open label	ADT + DOC vs. ADT	OS	192 vs. 193
LATITUDE	Fizazi et al. (2019)	2013 - 2014	Double blind	ADT + AA vs. ADT	OS	597 vs. 602
ENZAMET	Davis et al. (2019)	2014 - 2017	Open label	ADT + ENZA vs. ADT	OS	563 vs. 562
TITAN	Chi et al. (2019)	2015 - 2017	Double blind	ADT + APA vs. ADT	rPFS	525 vs. 527
ZAPCA	Kamba et al. (2017)	2008 - 2010	Open label	ADT + ZA vs. ADT	FFS	115 vs. 112
CALGB	Smith et al. (2014)	2004 - 2012	Double blind	ADT + ZA vs. ADT	SREFS	323 vs. 322
MRC-PRO5	Dearnaley et al. (2003)	1994 - 1998	Double blind	ADT + SC vs. ADT	BPFS	155 vs. 156
STAMPEDE (Arm D) (Arm F)	Mason et al. (2017)	2005 - 2011	Open label	ADT + Celecoxib vs. ADT ADT + ZA + Celecoxib vs. ADT	OS	188 vs. 377 190 vs. 377
STAMPEDE (Arm C) (Arm G)	Sydes et al. (2018)	2011 - 2013	Open label	ADT + AA vs. ADT + DOC	OS	227 vs. 115

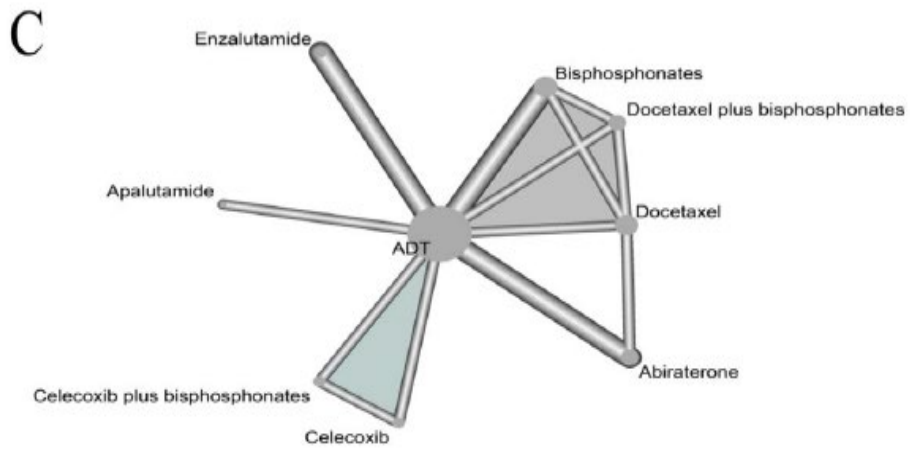
ADT: Androgen deprivation therapy; AA: Abiraterone Acetate; ZA: Zoledronic Acid; DOC: Docetaxel; ENZA: Enzalutamide; APA: Apalutamide; SC: Sodium Clodronate; OS: Overall Survival; FFS: Failure free survival; rPFS: radiographic progression-free survival; SREFS: Skeletal related events-free survival; BPFS: Bone progression-free survival

Figure 1. Evidence networks. A, overall mortality. B, progression. C, high grade adverse events.

Thickness of each arm is proportional to number of studies participating in network. Diameter of each junction point is proportional to number of studies including respective treatment. Shadowed areas indicate multi-arm studies.

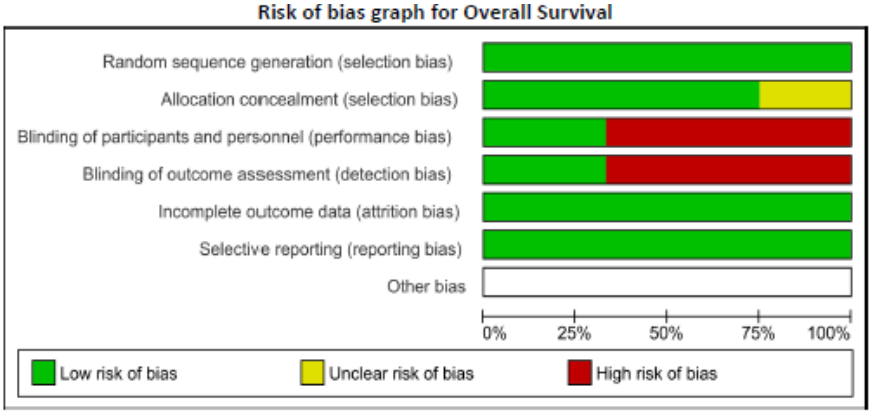




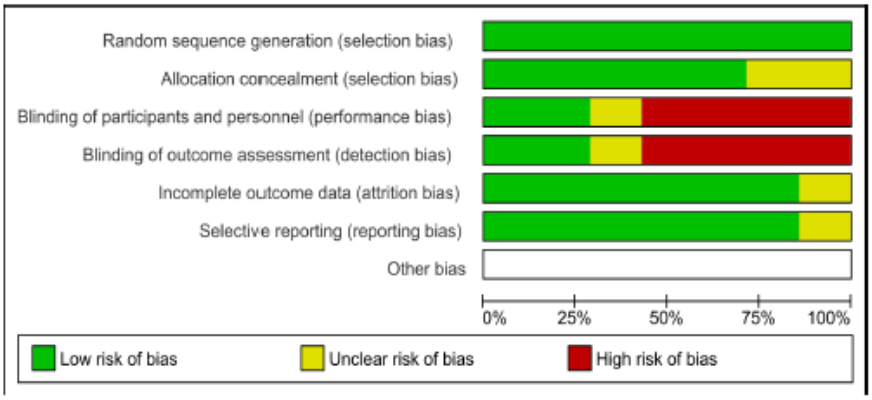


Qualität der Studien:

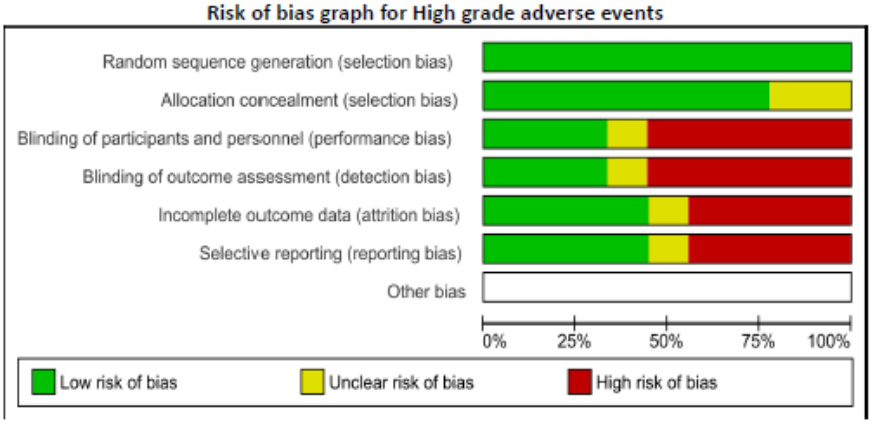
Risk of bias graph for Overall Survival

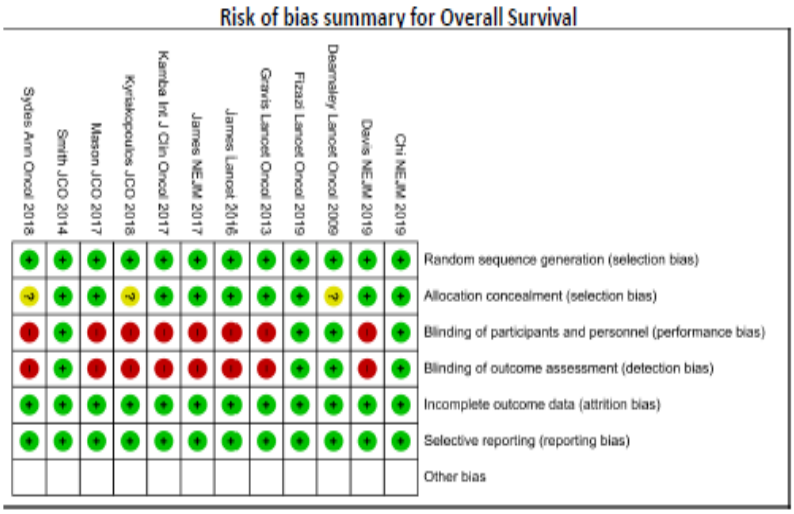


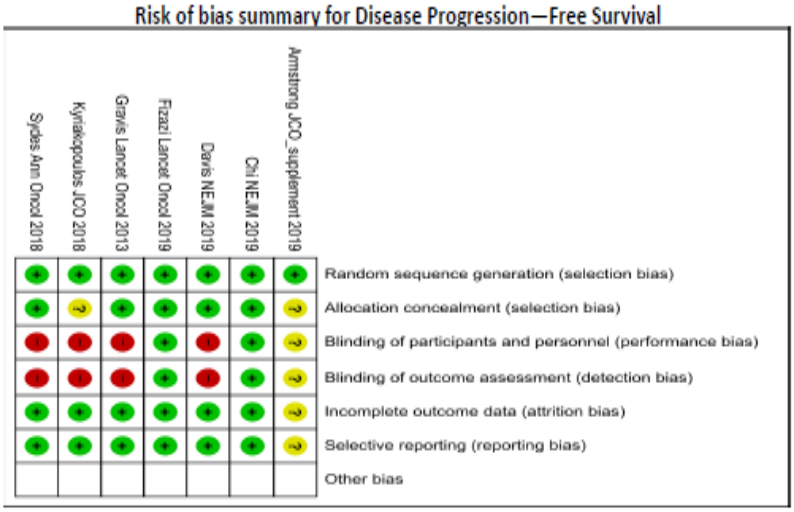
Risk of bias graph for Progression—Free Survival

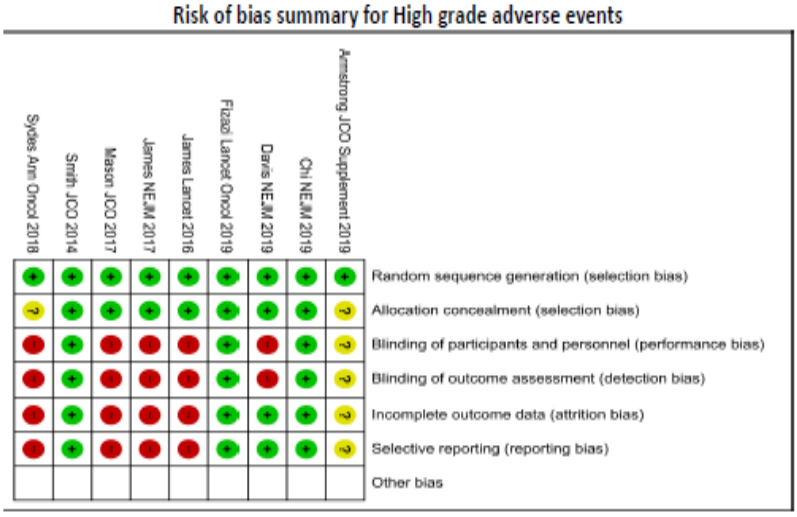


Risk of bias graph for High grade adverse events









The overall quality of included studies was high with a low selection and reporting RoB for the main investigated outcomes but with a high performance and detection RoB. Conversely, there was high attrition and reporting RoB for AEs outcome due to incomplete information on AEs and no stratification by metastatic status.

Studienergebnisse:

- Survival

  Overall. A total of 4,006 deaths were recorded. The pooled effect favored each combination treatment compared to ADT alone except for celecoxib (HR 0.94, 95% CI 0.75-1.18, fig. 2, A). Our analyses failed to demonstrate the superiority of any included treatment compared to docetaxel (fig. 2, B). However, abiraterone, enzalutamide and apalutamide were associated with lower overall mortality rates. On P-score analysis there was a higher probability of being the preferred treatment for abiraterone (85%), enzalutamide (78%) and apalutamide (78%) compared to docetaxel (60%). NMA estimated effects favored docetaxel, abiraterone, enzalutamide and apalutamide over other treatments (supplementary table 2, https://www.jurology.com).

Supplementary Table 2– Head to head comparison of each treatment showing hazard ratios and 95% confidence interval for risk of overall mortality. The lower-left of the table show the results from the network meta-analysis (direct and indirect evidences), the upper-right of the table (gray background) show the results deriving from direct comparisons only. Statistically significant comparisons are reported in bold.

Comparisons should be read from the left to the right in both the lower-left and upper-right of the table. For instance the comparison Abiraterone vs. androgen deprivation therapy (ADT) derived from the meta-analysis of direct comparisons within randomized clinical trials showed an hazard ratio [95% confidence interval]: 0.64 [0.56-0.73] in favor to Abiraterone. Similarly, the comparison of Abiraterone vs. ADT derived from the network meta-analysis, taking into account both direct and indirect comparisons, showed an hazard ratio [95% confidence interval]: 0.66 [0.58-0.75] in favor to Abiraterone.

	Hazard ratios [95%CI] derived from meta-analysis of direct evidences							
Abiraterone	.	.	1.13 [0.77; 1.66]	.	.	.	.	**0.64 [0.56; 0.73]**
0.98 [0.72; 1.33]	**Apalutamide**	.	.	.	.	.	.	**0.67 [0.51; 0.89]**
0.98 [0.74; 1.30]	1.00 [0.69; 1.46]	**Enzalutamide**	.	.	.	.	.	**0.67 [0.52; 0.86]**
0.89 [0.76; 1.05]	0.90 [0.67; 1.22]	0.90 [0.69; 1.19]	**Docetaxel**	0.82 [0.67; 1.00]	0.96 [0.78; 1.18]	.	.	**0.77 [0.68; 0.87]**
0.76 [0.64; 0.90]	0.77 [0.57; 1.04]	0.77 [0.59; 1.02]	**0.85 [0.74; 0.99]**	**Bisphosphonates**	1.18 [0.97; 1.43]	.	.	**0.87 [0.77; 0.98]**
0.86 [0.70; 1.06]	0.87 [0.63; 1.21]	0.87 [0.65; 1.18]	0.97 [0.81; 1.16]	1.13 [0.95; 1.35]	**Docetaxel plus bisphosphonates**	.	.	**0.79 [0.66; 0.95]**
0.70 [0.54; 0.91]	0.71 [0.50; 1.02]	0.71 [0.51; 1.00]	0.79 [0.61; 1.02]	0.92 [0.72; 1.19]	0.82 [0.62; 1.08]	**Celecoxib**	1.21 [0.93; 1.57]	0.94 [0.75; 1.18]
0.84 [0.65; 1.10]	0.86 [0.60; 1.23]	0.86 [0.61; 1.21]	0.95 [0.73; 1.23]	1.11 [0.86; 1.44]	0.98 [0.74; 1.31]	1.21 [0.93; 1.57]	**Celecoxib plus bisphosphonates**	**0.78 [0.62; 0.98]**
0.66 [0.58; 0.75]	**0.67 [0.51; 0.89]**	**0.67 [0.52; 0.86]**	**0.74 [0.66; 0.83]**	**0.87 [0.77; 0.97]**	**0.77 [0.65; 0.91]**	0.94 [0.75; 1.18]	**0.78 [0.62; 0.98]**	**ADT**
Hazard ratios [95%CI] derived from network meta-analysis (direct and indirect evidences)								

Comparisons should be read from the left to the right in both the lower-left and upper-right of the table. For instance the comparison Abiraterone vs. androgen deprivation therapy (ADT) derived from the meta-analysis of direct comparisons within randomized clinical trials showed an hazard ratio [95% confidence interval]: 0.64 [0.56-0.73] in favor to Abiraterone. Similarly, the comparison of Abiraterone vs. ADT derived from the network meta-analysis, taking into account both direct and indirect comparisons, showed an hazard ratio [95% confidence interval]: 0.66 [0.58-0.75] in favor to Abiraterone.

The model failed to show heterogeneity (within design I^2=0%, t2=0, p= 0.664) and inconsistency (between design p= 0.380). The GRADE quality of all direct comparisons was high but it was downgraded to intermediate and low in most cases for the NMA evidence. No statistically significant difference was found between estimates (all p >0.05, supplementary material 4, https://www.jurology.com)

Supplementary material 4 – Quality of evidences comparing treatment on respect to the overall mortality according to the GRADE working Group approach.

	Direct evidence			Indirect evidence			Network Meta-analysis evidence			
comparison	logHR ± SE	p-value	Quality	logHR ± SE	p-value	Quality	logHR ± SE	p-value	p-value for disagreement	Quality
Abiraterone vs ADT	-0.45 ± 0.07	<0.001	⊕⊕⊕⊕	-0.15 ± 0.21	0.456	⊕⊕⊕	-0.42 ± 0.06	<0.001	0.177	⊕⊕⊕
Abiraterone vs Apalutamide	-	-		-0.02 ± 0.16	0.913	⊕⊕	-0.02 ± 0.16	0.913	-	⊕⊕
Abiraterone vs Biphosfonate	-	-		-0.28 ± 0.09	0.001	⊕⊕⊕	-0.28 ± 0.09	0.001	-	⊕⊕⊕
Abiraterone vs Celecoxib	-	-		-0.36 ± 0.13	0.007	⊕⊕⊕	-0.36 ± 0.13	0.007	-	⊕⊕⊕
Abiraterone vs Celecoxib plus bisph	-	-		-0.17 ± 0.13	0.204	⊕⊕	-0.17 ± 0.13	0.204	-	⊕⊕
Abiraterone vs Docetaxel	0.12 ± 0.2	0.533	⊕⊕⊕	-0.17 ± 0.09	0.063	⊕⊕⊕	-0.12 ± 0.08	0.154	0.177	⊕⊕⊕
Abiraterone vs Docetaxel plus bisph	-	-		-0.15 ± 0.11	0.150	⊕⊕⊕	-0.15 ± 0.11	0.15	-	⊕⊕⊕
Abiraterone vs Enzalutamide	-	-		-0.02 ± 0.14	0.906	⊕⊕⊕	-0.02 ± 0.14	0.906	-	⊕⊕⊕
Apalutamide vs ADT	-0.4 ± 0.14	0.005	⊕⊕⊕⊕	-	-		-0.4 ± 0.14	0.005	-	⊕⊕⊕⊕
Biphosfonate vs ADT	-0.14 ± 0.06	0.019	⊕⊕⊕	-0.11 ± 0.25	0.648	⊕⊕	-0.14 ± 0.06	0.017	0.902	⊕⊕⊕
Celecoxib vs ADT	-0.06 ± 0.12	0.593	⊕⊕⊕	-	-		-0.06 ± 0.12	0.593	-	⊕⊕⊕
Celecoxib plus bisph vs ADT	-0.25 ± 0.12	0.033	⊕⊕⊕	-	-		-0.25 ± 0.12	0.033	-	⊕⊕⊕
Docetaxel vs ADT	-0.26 ± 0.06	<0.001	⊕⊕⊕⊕	-0.57 ± 0.17	0.001	⊕⊕⊕	-0.3 ± 0.06	<0.001	0.081	⊕⊕⊕
Docetaxel plus bisph vs ADT	-0.24 ± 0.1	0.014	⊕⊕⊕⊕	-0.39 ± 0.2	0.049	⊕⊕	-0.27 ± 0.09	0.002	0.478	⊕⊕⊕
Enzalutamide vs ADT	-0.4 ± 0.13	0.002	⊕⊕⊕⊕	-	-		-0.4 ± 0.13	0.002	-	⊕⊕⊕⊕
Apalutamide vs bisph	-	-		-0.26 ± 0.15	0.094	⊕	-0.26 ± 0.15	0.094	-	⊕
Apalutamide vs Celecoxib	-	-		-0.34 ± 0.18	0.064	⊕	-0.34 ± 0.18	0.064	-	⊕
Apalutamide vs Celecoxib plus bisph	-	-		-0.15 ± 0.18	0.408	⊕	-0.15 ± 0.18	0.408	-	⊕
Apalutamide vs Docetaxel	-	-		-0.1 ± 0.15	0.512	⊕⊕⊕	-0.1 ± 0.15	0.512	-	⊕⊕⊕
Apalutamide vs Docetaxel plus bisph	-	-		-0.14 ± 0.17	0.415	⊕⊕⊕	-0.14 ± 0.17	0.415	-	⊕⊕⊕
Apalutamide vs Enzalutamide	-	-		0.00 ± 0.19	0.999	⊕⊕⊕	0 ± 0.19	0.999	-	⊕⊕⊕
Biphosfonate vs Celecoxib	-	-		-0.08 ± 0.13	0.536	⊕⊕⊕	-0.08 ± 0.13	0.536	-	⊕⊕⊕
Biphosfonate vs Celecoxib plus bisph	-	-		0.11 ± 0.13	0.418	⊕⊕⊕	0.11 ± 0.13	0.418	-	⊕⊕⊕
Biphosfonate vs Docetaxel	0.20 ± 0.1	0.049	⊕⊕⊕⊕	0.11 ± 0.11	0.343	⊕	0.16 ± 0.08	0.037	0.522	⊕⊕⊕
Biphosfonate vs Docetaxel plus bisph	0.16 ± 0.1	0.102	⊕⊕⊕⊕	-0.09 ± 0.23	0.700	⊕	0.12 ± 0.09	0.179	0.312	⊕⊕⊕
Biphosfonate vs Enzalutamide	-	-		0.26 ± 0.14	0.068	⊕	0.26 ± 0.14	0.068	-	⊕
Celecoxib vs Celecoxib plus bisph	0.19 ± 0.13	0.164	⊕⊕⊕	-	-		0.19 ± 0.13	0.164	-	⊕⊕
Celecoxib vs Docetaxel	-	-		0.24 ± 0.13	0.067	⊕⊕⊕	0.24 ± 0.13	0.067	-	⊕⊕
Celecoxib vs Docetaxel plus bisph	-	-		0.20 ± 0.14	0.159	⊕	0.2 ± 0.14	0.159	-	⊕

- Progression-Free.

  Overall progression was noted in 1,265 cases. The pooled effect was in favor of each treatment included in analysis compared to ADT (fig. 3, A). The largest magnitude in terms of the effect on PFS was an advantage of enzalutamide (HR 0.40, 95% CI 0.34-0.46). This effect was also reflected in the indirect comparison of enzalutamide to docetaxel (HR 0.61, 95% CI 0.49-0.75). However, abiraterone (HR 0.71, 95% CI 0.59-0.86) and apalutamide (HR 0.74, 95% CI 0.57-0.95) also showed an advantage over docetaxel (fig. 3, B). On P-score analysis enzalutamide (96%), followed by abiraterone (67%) and apalutamide (62%) had the highest probability of being the preferred treatment.

  The NMA failed to show a statistically significant difference when comparing abiraterone, apalutamide and enzalutamide to each other (fig. 4).

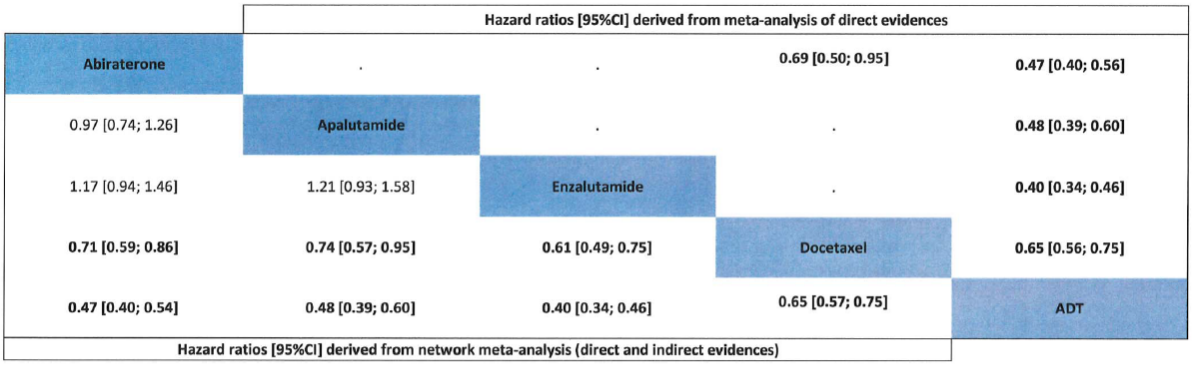


Figure 4. Head-to-head comparison of each treatment shows HR and 95% CI of disease progression risk. Read comparisons from left to right, ie abiraterone vs ADT comparison from direct comparison meta-analysis in RCTs shows HR 0.47 (95% CI 0.40–0.56) in favor of abiraterone. Lower left, network meta-analysis results (direct and indirect evidence). Gray upper right, direct comparison results. Bold indicates statistically significant comparison.

The model also failed to show heterogeneity (within design I^2=0%, t2=0 and p=0.774) and inconsistency (between design p= 0.804). The GRADE quality of all direct comparisons was high but it was downgraded to intermediate and low in most cases for

the NMA evidence. No statistically significant difference was found between estimates (all p >0.05, supplementary material 5, https://www.jurology.com).

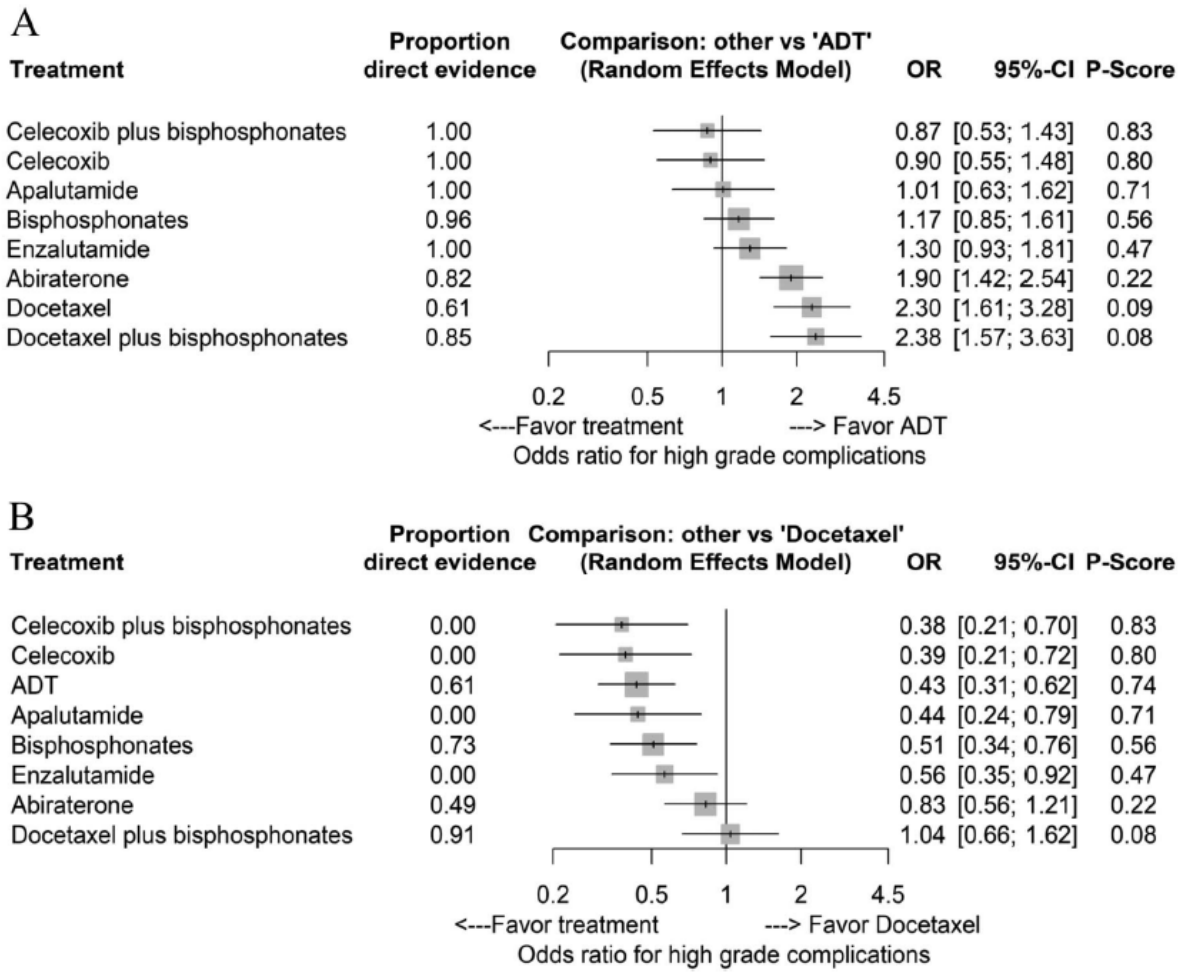
Supplementary material 5 – Quality of evidences comparing treatment on respect to the disease progression according to the GRADE working Group approach.

	Direct evidence			Indirect evidence			Network Meta-analysis evidence			
comparison	logHR ± SE	p-value	Quality	logHR ± SE	p-value	Quality	logHR ± SE	p-value	p-value for disagreement	Quality
Abiraterone vs ADT	-0.76 ± 0.09	<0.001	⊕⊕⊕⊕	-0.80 ± 0.18	<0.001	⊕⊕⊕	-0.77 ± 0.08	<0.001	0.804	⊕⊕⊕
Abiraterone vs Apalutamide	-	-		-0.03 ± 0.13	0.821	⊕⊕⊕	-0.03 ± 0.14	0.821		⊕⊕⊕
Abiraterone vs Docetaxel	-0.37 ± 0.16	0.023	⊕⊕⊕⊕	-0.32 ± 0.12	0.005	⊕⊕⊕	-0.34 ± 0.09	<0.001	0.804	⊕⊕⊕
Abiraterone vs Enzalutamide	-	-		0.16 ± 0.11	0.151	⊕⊕⊕	0.16 ± 0.11	0.151		⊕⊕⊕
Apalutamide vs ADT	-0.71 ± 0.11	<0.001	⊕⊕⊕⊕	-	-		-0.73 ± 0.11	<0.001		⊕⊕⊕
Docetaxel vs ADT	-0.43 ± 0.07	<0.001	⊕⊕⊕⊕	-0.38 ± 0.19	0.039	⊕⊕⊕	-0.43 ± 0.07	<0.001	0.804	⊕⊕⊕
Enzalutamide vs ADT	-0.93 ± 0.08	<0.001	⊕⊕⊕⊕	-	-		-0.93 ± 0.08	<0.001		⊕⊕⊕
Apalutamide vs Docetaxel	-	-		-0.31 ± 0.13	0.018	⊕⊕⊕	-0.31 ± 0.13	0.018		⊕⊕⊕
Apalutamide vs Enzalutamide	-	-		0.19 ± 0.14	0.158	⊕⊕⊕	0.19 ± 0.14	0.158		⊕⊕⊕
Docetaxel vs Enzalutamide	-	-		0.50 ± 0.11	<0.001	⊕⊕⊕	0.50 ± 0.11	<0.001		⊕⊕⊕

- Adverse Events

  The pooled effect revealed a higher AE rate in patients treated with abiraterone (OR 1.90, 95% CI 1.42-2.54), docetaxel alone (OR 2.30, 95% CI 1.61-3.28) or in combination with bisphosphonates (OR 2.38, 95% CI 1.57-3.63, fig. 5, A). The NMA head-to-head comparison showed a higher AE rate for abiraterone and docetaxel compared to apalutamide or enzalutamide (fig. 5, B, and fig 6). However, the model showed high within design heterogeneity (I^2=66.9%, t2=0.042 and p=0.009).

Figure 5. Forest plot of OR(95%CI) of high grade adverse events of each compound vs ADTalone (A) orADTcombined with docetaxel (B). Within design heterogeneity I2=66.9%, t2=0.042 and p=0.009. Between design test for inconsistency showed low risk of inconsistency (p=0.161).



	Hazard ratios [95%CI] derived from meta-analysis of direct evidences							
Abiraterone	.	.	0.93 [0.54; 1.60]	.	.	.	.	**1.82 [1.32; 2.50]**
1.88 [1.08; 3.27]	**Apalutamide**	.	.	.	.	.	.	1.01 [0.63; 1.62]
1.46 [0.94; 2.28]	0.78 [0.44; 1.39]	**Enzalutamide**	.	.	.	.	.	1.30 [0.93; 1.81]
0.83 [0.56; 1.21]	**0.44 [0.24; 0.79]**	**0.56 [0.35; 0.92]**	**Docetaxel**	**2.29 [1.44; 3.66]**	1.01 [0.63; 1.61]	.	.	**2.28 [1.45; 3.59]**
1.63 [1.08; 2.46]	0.87 [0.49; 1.53]	1.11 [0.70; 1.77]	**1.97 [1.32; 2.94]**	**Bisphosphonates**	0.44 [0.28; 0.70]	.	.	1.19 [0.86; 1.66]
0.80 [0.49; 1.29]	**0.42 [0.23; 0.80]**	**0.54 [0.32; 0.93]**	0.96 [0.62; 1.51]	**0.49 [0.32; 0.76]**	**Docetaxel plus bisphosphonates**	.	.	**2.26 [1.44; 3.56]**
2.11 [1.19; 3.76]	1.12 [0.57; 2.23]	1.44 [0.79; 2.63]	**2.56 [1.39; 4.71]**	1.30 [0.72; 2.35]	**2.65 [1.38; 5.09]**	**Celecoxib**	1.03 [0.61; 1.75]	0.90 [0.55; 1.48]
2.18 [1.22; 3.88]	1.16 [0.58; 2.30]	1.49 [0.82; 2.71]	**2.64 [1.43; 4.87]**	1.34 [0.74; 2.43]	**2.74 [1.43; 5.25]**	1.03 [0.61; 1.75]	**Celecoxib plus bisphosphonates**	0.87 [0.53; 1.43]
1.90 [1.42; 2.54]	1.01 [0.63; 1.62]	1.30 [0.93; 1.81]	**2.30 [1.61; 3.28]**	1.17 [0.85; 1.61]	**2.38 [1.57; 3.63]**	0.90 [0.55; 1.48]	0.87 [0.53; 1.43]	**ADT**
Hazard ratios [95%CI] derived from network meta-analysis (direct and indirect evidences)								

Figure 6. Head-to-head comparison of each treatment shows HR and 95% CI of high grade adverse event risk. Read comparisons from left to right, ie abiraterone vs ADT comparison from direct comparison meta-analysis in RCTs shows HR 1.82 (95% CI 1.32–2.50) in favor of abiraterone. Lower left, network meta-analysis results (direct and indirect evidence). Gray upper right, direct comparison results. Bold indicates statistically significant comparison.

Conversely, tests for between design inconsistency showed a low risk of inconsistency (p= 0.161). The GRADE quality of all direct comparisons was intermediate, although it was downgraded to low in most cases for the NMA evidence. No statistically significant difference was found between estimates (all p >0.05, supplementary material 6, Moreover, sensitivity analysis was performed after excluding the STAMPEDE trial due to the limited information on AEs reported only in patients with metastasis. Our results showed no statistically significant differences in AE rates when comparing ADT to apalutamide (OR 1.01, 95% CI 0.48-2.13), enzalutamide (OR 1.29, 95% CI 0.76-2.19) and

bisphosphonates (OR 1.46, 95% CI 0.77-2.74). Similarly on sensitivity analysis abiraterone demonstrated no statistically significant higher AE rate compared to ADT (OR 1.84, 95% CI 0.87-3.87).

Supplementary material 6 - Quality of evidences comparing treatment on respect to the high grade adverse events according to the GRADE working Group approach.

	Direct evidence			Indirect evidence			Network Meta-analysis evidence			
comparison	logHR ± SE	p-value	Quality	logHR ± SE	p-value	Quality	logHR ± SE	p-value	p-value for disagreement	Quality
Abiraterone vs ADT	0.6 ± 0.16	<0.001	⊕⊕⊕	0.84 ± 0.35	0.017	⊕⊕	0.64 ± 0.15	<0.001	0.593	⊕⊕
Abiraterone vs Apalutamide	-	-		0.63 ± 0.28	0.030	⊕⊕	0.63 ± 0.28	0.026		⊕⊕
Abiraterone vs Bisphosphonates	-	-		0.49 ± 0.21	0.021	⊕⊕	0.49 ± 0.21	0.021		⊕⊕
Abiraterone vs Celecoxib	-	-		0.75 ± 0.29	0.011	⊕⊕	0.75 ± 0.29	0.011		⊕⊕
Abiraterone vs Celecoxib plus bisphosphonates	-	-		0.78 ± 0.29	0.008	⊕⊕	0.78 ± 0.29	0.008		⊕⊕
Abiraterone vs Docetaxel	-0.07 ± 0.28	0.801	⊕⊕⊕	-0.31 ± 0.27	0.253	⊕⊕	-0.19 ± 0.19	0.322	0.533	⊕⊕
Abiraterone vs Docetaxel plus bisphosphonates	-	-		-0.23 ± 0.25	0.354	⊕⊕	-0.23 ± 0.25	0.354		⊕⊕
Abiraterone vs Enzalutamide	-	-		0.38 ± 0.23	0.093	⊕⊕	0.38 ± 0.23	0.093		⊕⊕
ADT vs Apalutamide	-0.01 ± 0.24	0.966	⊕⊕⊕	-	-		-0.01 ± 0.24	0.966		⊕⊕
ADT vs Bisphosphonates	-0.18 ± 0.17	0.296	⊕⊕⊕	0.35 ± 0.82	0.673	⊕⊕	-0.15 ± 0.16	0.347	0.533	⊕⊕
ADT vs Celecoxib	0.11 ± 0.25	0.673	⊕⊕⊕	-	-		0.11 ± 0.25	0.673		⊕⊕
ADT vs Celecoxib plus bisphosphonates	0.14 ± 0.25	0.587	⊕⊕⊕	-	-		0.14 ± 0.25	0.587		⊕⊕
ADT vs Docetaxel	-0.83 ± 0.23	<0.001	⊕⊕⊕	-0.84 ± 0.29	0.004	⊕⊕	-0.83 ± 0.18	<0.001	0.963	⊕⊕
ADT vs Docetaxel plus bisphosphonates	-0.82 ± 0.23	<0.001	⊕⊕⊕	-1.17 ± 0.56	0.035	⊕⊕	-0.87 ± 0.21	<0.001	0.556	⊕⊕
ADT vs Enzalutamide	-0.26 ± 0.17	0.131	⊕⊕⊕	-	-		-0.26 ± 0.17	0.131		⊕⊕
Apalutamide vs Bisphosphonates	-	-		-0.14 ± 0.29	0.620	⊕⊕	-0.14 ± 0.29	0.620		⊕⊕
Apalutamide vs Celecoxib	-	-		0.12 ± 0.35	0.737	⊕⊕	0.12 ± 0.35	0.737		⊕⊕
Apalutamide vs Celecoxib plus bisphosphonates	-	-		0.15 ± 0.35	0.672	⊕⊕	0.15 ± 0.35	0.672		⊕⊕
Apalutamide vs Docetaxel	-	-		-0.82 ± 0.3	0.006	⊕⊕	-0.82 ± 0.3	0.006		⊕⊕
Apalutamide vs Docetaxel plus bisphosphonates	-	-		-0.86 ± 0.32	0.008	⊕⊕	-0.86 ± 0.32	0.008		⊕⊕
Apalutamide vs Enzalutamide	-	-		-0.25 ± 0.3	0.399	⊕⊕	-0.25 ± 0.3	0.399		⊕⊕
Bisphosphonates vs Celecoxib	-	-		0.26 ± 0.3	0.387		0.26 ± 0.3	0.387		⊕⊕
Bisphosphonates vs Celecoxib plus	-	-		0.29 ± 0.3	0.334	⊕⊕	0.29 ± 0.3	0.334		⊕⊕

Anmerkung/Fazit der Autoren

Treatment with ARATs combined with ADT in patients with mHSPC does not provide a statistically significant OS advantage compared to the standard, docetaxel. However, it is associated with a lower disease progression rate. Moreover, apalutamide and enzalutamide offer a better safety profile.

Kommentare zum Review

- Es liegen weitere NMAs zu dieser Fragestellung mit derselben Schlussfolgerung vor
  - Chen J et al. 2020 [4] (NMA); ADT plus docetaxel, abiraterone, enzalutamide, or apalutamide were associated with significantly improved survival in patients with mHSPC
  - Tan P et al. 2018 [22] Hinweis: Vorteil Abi+ADT gegenüber Doc+ADT Grund: Finale Analyse der LATITUDE (A Study of Abiraterone Acetate Plus Low-Dose Prednisone Plus Androgen Deprivation Therapy [ADT] Versus ADT Alone in Newly Diagnosed Participants With High-Risk, Metastatic Hormone-Naive Prostate Cancer [mHNPC]) trial wurden 2019 veröffentlicht
  - Vale CL et al., 2018 [23] (NMA); Our results support the use of AAP or Doc with ADT in men with metastatic hormone-naive prostate cancer. AAP appears to be the most effective treatment, but it is not clear to what extent and whether this is due to a true increased benefit with AAP or the variable features of the individual trials

Kretschmer A et al., 2020 [10].

Health-related Quality of Life in Patients with Advanced Prostate Cancer: A Systematic ReviewTitel des Reviews

Fragestellung

The assessment of “soft” endpoints such as health-related quality of life (HRQOL) is increasingly relevant when evaluating the optimal treatment sequence of novel therapeutic options in patients with advanced prostate cancer (PCa). Objective: To systematically review contemporary data regarding HRQOL outcomes in patients with advanced PCa.

Methodik

Population:

- advanced PCa, defined as mHNPC, nmCRPC, and mCRPC

Intervention:

- nicht präspezifiert

Komparator:

- nicht präspezfiziert

Endpunkte:

- HRQOL outcomes

Recherche/Suchzeitraum:

- between January 2011 and March 2019
- PubMed/Medline Database

Qualitätsbewertung der Studien:

- Risk of bias assessment following current EAU recommendations. EAU = European Association of Urology.

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies evaluating HRQOL in 12 661 patients, darunter n=3 für nicht kastrationsrestistenten PCa (nachfolgend dargestellt)

Charakteristika der Population:

Recently, HRQOL outcomes of three randomized controlled phase III trials have been published. The main features of each study are summarized chronologically in Table 1.

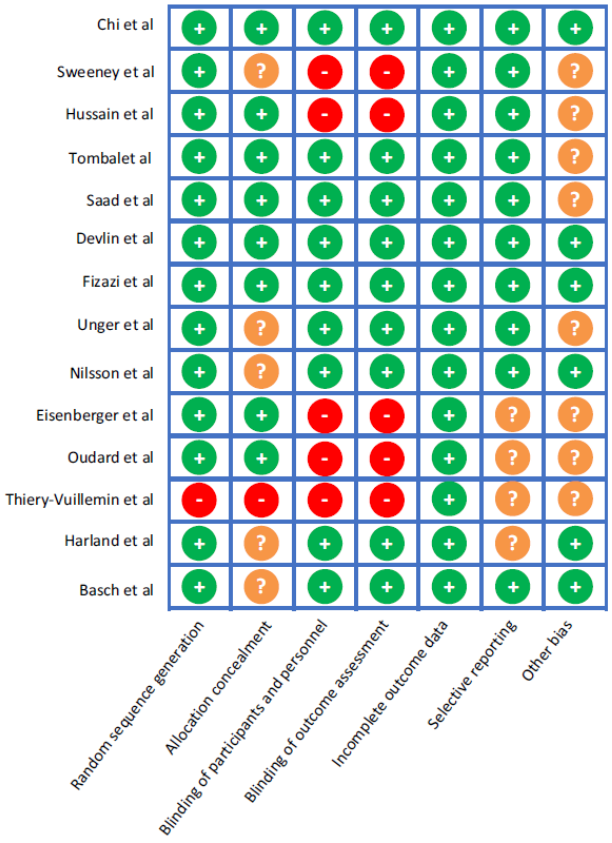
Table 1 – Main features of studies addressing patients with metastatic hormone naive prostate cancer.

Study	Intervention	Phase	*n*	Follow-up	Tool	HRQOL baseline	Main findings
Hussain et al (2013) [16]	IADT vs CADT	III	1162	Up to 15 mo	SWOG QOL questionnaire	NR	Net differences in primary SWOG QOL outcomes after 15 mo: erectile dysfunction −3% (IADT) vs 2% (CADT), p = 0.12; high libido 13% (IADT) vs 3% (CADT), p = 0.46; vitality −2.02 (IADT) vs −3.02 (CADT), p = 0.45; mental health −0.64 (IADT) vs −1.10 (CADT), p = 0.69; physical functioning −2.68 (IADT) vs −5.72 (CADT), p = 0.04
Chi et al (2018) [18] (LATITUDE)	ABI vs PBO	III	1199	Median 30.9 mo (ABI) vs 29.7 mo (PBO)	FACT-P EQ-5D (−5 L)	FACT-P (total): ABI: 113 PBO: 112 EQ-5D−5 L (VAS): ABI: 74 PBO: 74	Median time to deterioration of FACT-P total score 12.9 mo (ABI) vs 8.3 mo (PBO), HR 0.85, 95% CI 0.74–0.99, p = 0.032; EQ-5D VAS: better general health status for ABI vs PBO, same findings for EQ-5D utility score
Morgans et al (2018) [19] (E3805 CHAARTED)	DOC + ADT vs ADT	III	790	Up to 12 mo	FACT-P (FACT-Taxane)	FACT-P (total): DOC: 119 ADT: 119	Net differences in FACT-P total scores after 3 mo: −2.7 (DOC) vs −1.1 (ADT), p = 0.02; net differences in FACT-P total scores after 12 mo: −0.7 (DOC) vs −4.2 (ADT), p = 0.04; changes not considered clinically meaningful

ABI = abiraterone acetate; ADT = androgen deprivation therapy; CADT = continuous androgen deprivation therapy; CI = confidence interval; DOC = docetaxel; EQ-5D = European Quality of Life 5-Dimensions; FACT-P = Functional Assessment of Cancer Therapy-Prostate; HR = hazard ratio; HRQOL = health-related quality of life; IADT = intermittent androgen deprivation therapy; NR = not reported; PBO = placebo; QOL = quality of life; VAS = visual analog scale.

Qualität der Studien:

Risk of bias assessment following current EAU recommendations. EAU = European Association of Urology.



Studienergebnisse:

Metastatic hormone-naive prostate cancer

Hussain et al [16] randomized 1535 patients with newly diagnosed mHNPC to receive either continuous or intermittent ADT. HRQOL outcomes were assessed based on the SWOG HRQOL questionnaire. Net differences in physical functioning favored patients undergoing intermittent ADT (–2.68 vs –5.72, p = 0.04), as did vitality, libido, and mental health, without reaching statistical significance. Since the study was designed as open label, risk of bias assessment showed mixed results with a tendency toward a low risk of bias (Fig. 2).

The randomized controlled phase III LATITUDE trial analyzed oncological [17] as well as HRQOL outcomes [18] in 1199 patients with newly diagnosed high-risk mHNPC. Risk assessment was performed based on Gleason grading as well as PSA doubling time. Patients were randomly assigned to receive standard ADT in combination with placebo or in combination with abiraterone acetate 1000 mg daily (in combination with 5 mg prednisone daily). Regarding HRQOL outcomes, EQ-5D-5L and FACT-P questionnaires were used, and 10% of the data were missing. Regarding general HRQOL, as assessed by the FACT-P total score, the authors found increased time to deterioration of FACT-P total scores for patients who underwent treatment with abiraterone acetate (8.3 vs 12.9 mo, hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.74–0.99, p = 0.032). Similar results were found for remaining subscales [18]. These findings have a low risk of bias (Fig. 2).

The CHAARTED study reported oncological [3] as well as HRQOL outcomes [19] of 790 patients with mHNPC who were randomly assigned to receive either ADT or ADT in combination with docetaxel 75 mg/m2. HRQOL assessment was based on the FACT-P

questionnaire. Missing data were up to 23% at the 12-mo assessment. The authors found a significant decline in FACT-P total scores after 3 mo for patients who underwent combination therapy ($p < 0.001$), with a consecutive rise in the longer-term assessment up to 12 mo. Consequently, patients receiving docetaxel showed significantly lower FACT-P total scores than patients with ADT monotherapy after 3 mo (net differences –2.7 vs –1.1, $p = 0.02$), but significantly higher FACT-P total scores after 12 mo (net differences –0.7 vs –4.2, $p = 0.04$). Notably, CHAARTED was an open-label study. Thus, as illustrated in Fig. 2, risk of bias assessment showed mixed results, especially regarding detection as well as performance bias. Notably, baseline FACT-P total scores were slightly higher within the CHAARTED [19] than in the LATITUDE cohort [17].

Anmerkung/Fazit der Autoren

There is strong evidence from several phase III trials supporting a beneficial effect of current systemic treatment options on HRQOL outcomes in patients with advanced PCa compared with standard androgen deprivation therapy.

Burdett S et al., 2019 [3].

Prostate Radiotherapy for Metastatic Hormone-sensitive Prostate Cancer: A STOPCAP Systematic Review and Meta-analysis

Fragestellung

We aimed to assess the effects of adding prostate radiotherapy to androgen deprivation therapy (ADT) in men with mHSPC.

Methodik

Population:

- men with mHSPC

Intervention/Komparator:

- Comparison A: Prostate radiotherapy + ADT versus ADT
- Comparison B: Prostate radiotherapy + other agent(s) + ADT versus (same) other agents(s) + ADT

Endpunkte:

- primary outcome
  - survival, defined as the time from randomisation to death from any cause.
- Secondary outcomes
  - progression-free survival (PFS), defined as the time from randomisation to first symptomatic clinical or radiological progression or death (excluding biochemical progression);
  - biochemical progression, defined as the time from randomisation to first biochemical (prostate-specific antigen [PSA]) progression; and
  - failure-free survival (FFS), defined as the time from randomisation to first biochemical, clinical, or radiological progression.
  - We also aimed to describe acute toxicity on the radiotherapy arm.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, clinicaltrials.gov, and Cochrane CENTRAL up to June 2018

- published, unpublished, and ongoing trials in mHSPC
- no language restrictions

Qualitätsbewertung der Studien:

Cochrane Collaboration‘s tool RoB

Ergebnisse

Anzahl eingeschlossener Studien:

- Comparison A: 3 RCTs, für die Meta-Analyse werden die RCTs STAMPEDE und HORRAD mit insgesamt 2126 Patienten eingeschlossen. (ongoing PEACE-1 trial)
- Comparison B: 2 RCTs: meta-analysis of comparison B is planned later.

Charakteristika der Population:

Table 1 – Characteristics of trials (or parts of trials) eligible for comparison A

Trial	Years of accrual	Number of men randomised	De novo or relapsed M1?	Treatment	Control	Median follow-up (survival)
				Radiotherapy	ADT	
Radiotherapy + ADT vs ADT						
STAMPEDE A1 [11] (arm H vs arm A)	2013–2016	1694	De novo	36 Gy, 6 fractions over 6 wk or 55 Gy, 20 fractions over 4 wk	ADT (LHRH agonist or antagonist or orchiectomy)	41.9 mo
HORRAD [12]	2004–2014	432	De novo	70 Gy, 35 fractions over 7 wk or 57.76 Gy, 19 fractions over 6 wk	ADT (LHRH agonist or orchiectomy)	47 mo
PEACE-1A1 (NCT01957436)	2013–2018*	234	De novo	74 Gy, 37 fractions within 7–8 wk	ADT (LHRH agonist or antagonist or orchiectomy)	Not yet available

ADT = androgen deprivation therapy; LHRH = luteinising hormone-releasing hormone. *PEACE-1 closed to accrual between submission and acceptance of the manuscript

Qualität der Studien:

Supplementary Table 2: Assessment of risk of bias[10]

Trial ID	Adequate sequence generation	Allocation concealment	Incomplete outcome data addressed	Free of selective reporting
HORRAD[12]	Patients assigned in a 1:1 ratio using a restricted block wise randomisation **Low risk**	Randomisation done centrally by an independent trial office **Low risk**	All randomised patients included in analyses **Low risk**	All outcomes of interest reported **Low risk**
STAMPEDE[11]	A minimisation method with a random element of 80% was used to stratify for a number of clinically important factors **Low risk**	Central telephone randomisation using a computer programme **Low risk**	All randomised patients included in analyses **Low risk**	All outcomes of interest reported **Low risk**

Studienergebnisse:

- Survival results are based on all 2126 men (969 deaths) from HORRAD and STAMPEDE. Overall, there was no evidence that the addition of prostate radiotherapy to ADT improved survival (HR = 0.92, 95% confidence interval [CI] 0.81–1.04, p = 0.195; heterogeneity chi-square = 0.08, degree of freedom = 1, p = 0.78; Fig. 1).
- ThePFS results based on all men(1305 events) also provided no clear evidence that, overall, prostate radiotherapy extended PFS (HR = 0.94, 95% CI 0.84–1.05, p = 0.238; Fig.1).
- Although, in the HORRAD trial, biochemical progression was defined as the time between diagnosis and a PSA increase after the initiation of ADT of >50% of the lowest PSA value

after the start of treatment (with a minimum of 1 ng/ml), and in the STAMPEDE trial as a rise above the lowest PSA within 24 wk of enrolment of 50% to at least 4 ng/ml, we considered them sufficiently compatible to combine.

- Based on all men and 1533 events, we observed a highly statistically significant benefit of prostate radiotherapy (HR = 0.74, 95% CI 0.67–0.82, p = 0.94 x 10^{-8}; Fig. 1) in biochemical progression, which translates to an absolute improvement of 11 (7–14)% at 3 yr from 25% to 36%.
- The FFS results based on all men (1662 events) were very similar (HR = 0.76, 95% CI 0.69–0.84, p = 0.64 x 10^{-7}; Fig. 1).
- Toxicity results are not yet available for HORRAD. Based on the results collected from STAMPEDE, 4% of men who received prostate radiotherapy had severe acute bladder toxicity, and 1% had severe acute bowel toxicity (RTOG scale). Reported STAMPEDE results showed that 4% of men had severe late effects.

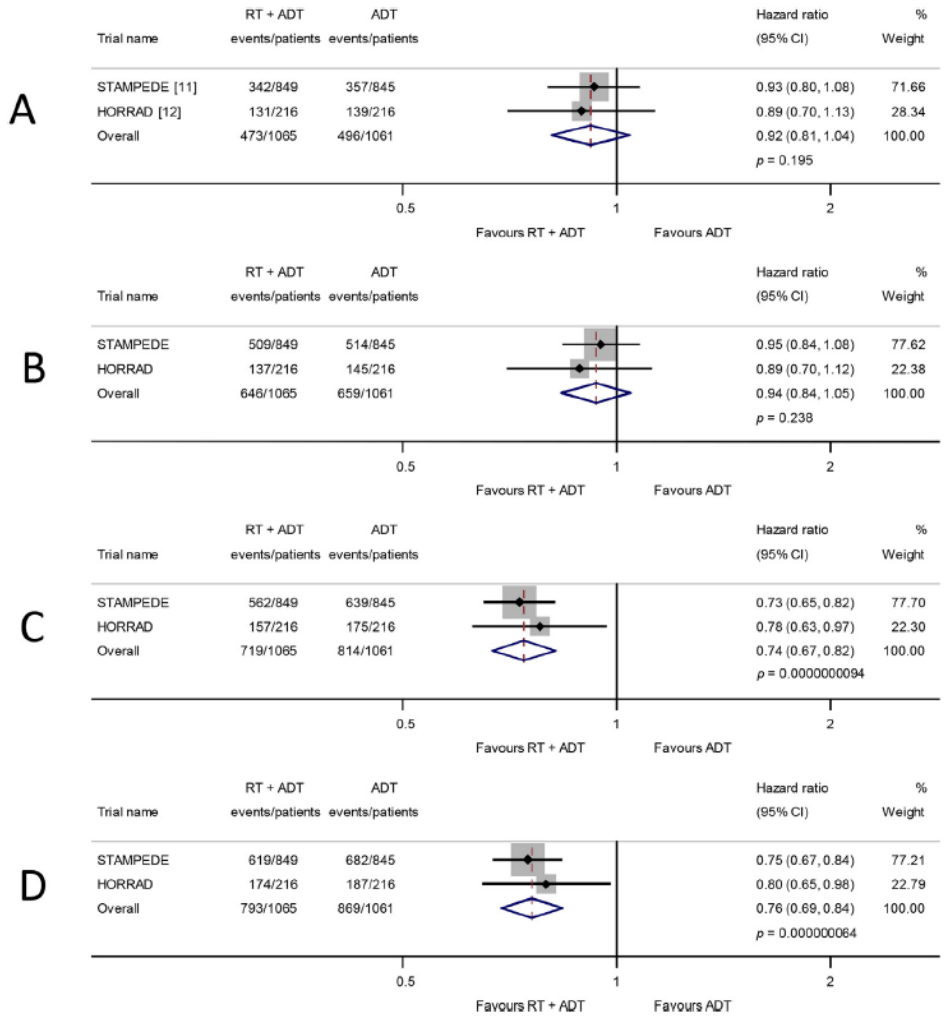


Fig. 1 – Effect of adding prostate radiotherapy to ADT on (A) survival, (B) progression-free survival, (C) biochemical progression, and (D) failure-free survival in men with mHSPC. Each filled square denotes the HR for that trial comparison, with the horizontal lines showing the 95% confidence interval (CI). The size of the square is directly proportional to the amount of information contributed by a trial. The diamond represents a (fixed-effect) meta-analysis of the trial HRs, with the centre of this diamond indicating the HR and the extremities the 95% CI. ADT = androgen deprivation therapy; HR = hazard ratio; RT = radiotherapy.

- As the HORRAD trial collected the number of bone metastases in three prespecified categories (<5, 5–15, and >15), and the STAMPEDE trial collected the absolute number of metastases up to 9 and then >9, we obtained compatible results from both trials for our planned analyses (<5, ≥5).

- The effect of prostate radiotherapy on survival varied by the number of bone metastases (interaction HR = 1.47, 95% CI 1.11–1.94, p = 0.007; Fig. 3), with a benefit seen in men with fewer than five bone metastases (HR = 0.73, 95% CI 0.58–0.92, p = 0.0071), which translates to an absolute improvement of 7% (95% CI 2–11%) at 3-yr survival (from 70% to 77%). There was no clear evidence of an effect among men with five or more bone metastases (HR = 1.07, 95% CI 0.92–1.26, p = 0.37).
- A similar planned analysis of PFS (interaction HR = 1.32, 95% CI 1.04–1.67, p = 0.021; Fig. 3) and an exploratory analysis of FFS (interaction HR = 1.35, 95% CI 1.10–1.66, p = 0.004; Fig. 3) gave comparable results.

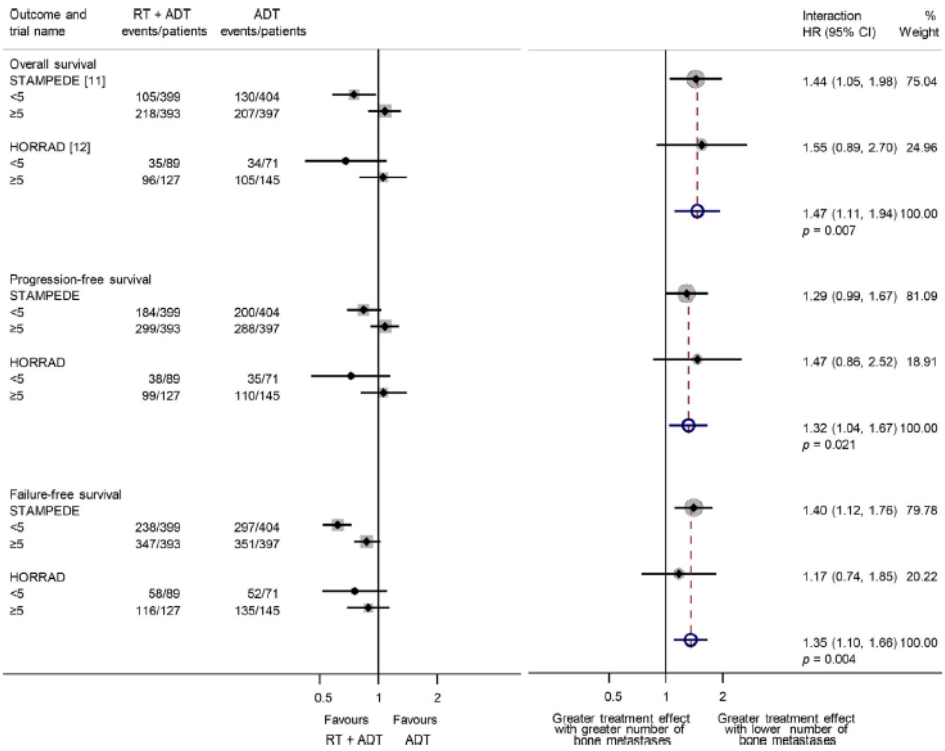


Fig. 3 – Effect of adding prostate radiotherapy to ADT on survival, progression-free survival, and failure-free survival (exploratory) by the number of bone metastases. ADT = androgen deprivation therapy; HR = hazard ratio; RT = radiotherapy.

Anmerkung/Fazit der Autoren

Prostate radiotherapy did not clearly improve survival or PFS in unselected men with mHSPC. However, there was a clear difference in the effect by metastatic burden on survival, with an absolute improvement of 7% in 3-yr survival in men who had four or fewer bone metastases. There was no evidence that the effect of prostate radiotherapy on survival varied by other patient or disease characteristics. Prostate radiotherapy improved 3-yr biochemical progression and FFS by ~10% in unselected men, but the size of effect varied by metastatic burden.

The addition of prostate radiotherapy to ADT should be considered for men with mHSPC who have four or fewer bone metastases.

Kommentare zum Review

Dieser Review wurde in folgenden Leitlinien berücksichtigt:

- Leitlinienprogramm Onkologie (2021)
- European Association of Urology (EAU) (2021) [6]

- So et al. (2020) [20]

3.3 Leitlinien

Leitlinienprogramm Onkologie 2021 [11,12].

Federführende Fachgesellschaft: Deutsche Gesellschaft für Urologie e. V. (DGU)

Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms; Langversion 6.2 Oktober 2021: AWMF Registernummer: 043/022OL

Zielsetzung/Fragestellung

Die interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms ist ein evidenz- und konsensbasiertes Instrument, um Früherkennung, Diagnostik und Therapie des Prostatakarzinoms zu verbessern.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert - die Leitlinie (Version 6.2 Oktober 2021) ist bis zur nächsten Aktualisierung gültig (11.05.2024). Vorgesehen sind regelmäßige modulare Aktualisierungen in einem 3-jährlichen Abstand.

Recherche/Suchzeitraum:

- Bisherige Änderungen an der Version 6 Oktober 2021, Version 6.2: Spezifizierung der Anmerkung zu Qualitätsindikator 12 (Fokale Therapie bei lokal fortgeschrittenem Prostatakarzinom) hinsichtlich fokaler stereotaktischer Bestrahlung. Juli 2021, Version 6.1: Ergänzung der aktualisierten Qualitätsindikatoren, Überarbeitung der Empfehlung 7.10 (Ergänzung von Bicalutamid), Korrektur von Angaben zur ARAMIS-Studie (Hintergrund Empfehlung 7.32)
- Für die Version 6.0 der Leitlinie erfolgten systematische Literaturrecherchen zu insgesamt 16 Fragestellungen nach aggregierter Evidenz sowie randomisierten, kontrollierten Studien, teilweise in Form von Update-Recherchen. Die Recherchen wurden in Medline via Pubmed und der Cochrane-Datenbank durchgeführt. Ergänzend erfolgte eine systematische freie Suche in den Referenzlisten der ermittelten Studien. (Methodikeranmerkung: unterschiedliche Suchzeiträume jeweils angegeben; häufig: 18.09.2020)
- Recherche zur 4. Aktualisierung 2018: Zu allen Fragestellungen erfolgte eine spezifische systematische Literaturrecherche in den Datenbanken Medline (Pubmed) und den

Datenbanken der Cochrane Library (Methodikeranmerkung: unterschiedliche Suchzeiträume jeweils angegeben). Es wurden außerdem Studien berücksichtigt, die in Referenzlisten bekannter Studien oder durch Hinweise aus der Leitliniengruppe identifiziert wurden.

LoE

- Die Klassifikation der Evidenz erfolgte nach den Kriterien des Scottish Intercollegiate Guidelines Network (SIGN) (siehe Tabelle 2).

Tabelle 2: Schema der Evidenzklassifikation des Scottish Intercollegiate Guidelines Network (SIGN)

Klasse	Beschreibung
1++	Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)
1+	Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)
1-	Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)
2++	Qualitativ hochwertige systematische Übersichten von Fall-Kontroll- oder Kohortenstudien oder qualitativ hochwertige Fall-Kontroll- oder Kohortenstudien mit sehr niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und hoher Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2+	Gut durchgeführte Fall-Kontroll-Studien oder Kohortenstudien mit niedrigem Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und moderater Wahrscheinlichkeit, dass die Beziehung ursächlich ist
2-	Fall-Kontroll-Studien oder Kohortenstudien mit einem hohen Risiko systematischer Verzerrungen (Confounding, Bias, „Chance“) und signifikantem Risiko, dass die Beziehung nicht ursächlich ist
3	Nicht-analytische Studien, z. B. Fallberichte, Fallserien
4	Expertenmeinung

GoR

- Die Empfehlungsstärken drücken aus, wie sicher sich die Leitliniengruppe ist, dass der größte Teil der beschriebenen Patienten von einer Intervention profitiert. Dies richtet sich nach:
  - der Aussagekraft der Evidenz, beurteilt an Hand von: Studienqualität bzw. Verzerrungsrisiko, Konsistenz der Studienergebnisse, Übertragbarkeit, ggf. Kenntnis/Wahrscheinlichkeit von nicht veröffentlichten Studien zum selben Thema;
  - dem Nutzen-Schaden-Verhältnis;
  - alternativen Handlungsoptionen;
  - den Behandlungszielen und Präferenzen;
  - der Umsetzbarkeit im klinischen Alltag, in verschiedenen Versorgungssettings/Sektoren;
  - ethische, rechtliche sowie sonstigen Erwägungen

Tabelle 3 Einstufung der Empfehlungen

Empfehlungsgrad	Beschreibung	Ausdrucksweise
A	Starke Empfehlung	Soll
B	Empfehlung	Sollte
0	Empfehlung offen	kann

- Als Expertenkonsens (EK) werden Empfehlungen bezeichnet, zu denen keine Recherche nach Literatur durchgeführt wurde. In der Regel adressieren diese Empfehlungen Vorgehensweisen der guten klinischen Praxis, zu denen keine wissenschaftlichen Studien notwendig sind bzw. erwartet werden können.

Empfehlungen

Kapitel 7: Diagnostik und Therapie des rezidivierten oder metastasierten Prostatakarzinoms

7.3. Therapie des hormonsensitiven, metastasierten Prostatakarzinoms (mHSPC)

Die Therapie des metastasierten (M1), hormonsensitiven Prostatakarzinoms hat sich in den vergangenen Jahren grundlegend geändert. Nachdem die CHAARTED Studie einen Vorteil für die frühe Chemohormontherapie gezeigt hat [787], konnte dies später auch für Kombinationstherapien aus Androgendeprivation (AD) mit Hormonpräparaten der neuen Generation (Abirateron, Enzalutamid, Apalutamid) gezeigt werden [791 – 793 ,789 ,788]. Entsprechende der Situation bei der einfachen Androgendeprivation legen einzelne Studien, bei denen auch lokal fortgeschrittene Hochrisikotumoren eingeschlossen wurden (z.B. STAMPEDE), nahe, dass Patienten bereits in früheren Tumorstadien in ähnlicher Weise von den Kombinationstherapien profitieren könnten.

7.20	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad A	Bei Patienten mit metastasiertem, hormonsensitiven Prostatakarzinom (mHSPC) soll eine Einteilung nach high- und low-volume sowie high- und low-risk erfolgen.	
Level of Evidence 1+ bis 1-	Literatur: [787–789]	
	Gesamtabstimmung: 98 %	

7.21	Evidenzbasierte Empfehlung	geprüft 2021
Empfehlungsgrad A	Bestandteil der Patientenaufklärung über eine alleinige Androgendeprivation oder eine Kombinationstherapie sollen insbesondere folgende Punkte sein: · der palliative Charakter der Therapie; · Einfluss auf die Lebensqualität; · die unerwünschten Wirkungen.	
Level of Evidence 4	Expertenkonsens basierend auf [731,734,729,730,790]	
	Gesamtabstimmung: 98 %	

Zu Empfehlung 7.20

In den Studien, die einen Vorteil für eine kombinierte Hormontherapie mit Docetaxel oder Abirateron (plus Prednison/Prednisolon) beim hormonsensitiven, metastasierten Prostatakarzinom nachweisen konnten, wurden die Studienpopulationen anhand des Metastasierungsmusters bzw. des Gleason Scores auf unterschiedliche Art definiert. Bei der kombinierten Chemohormontherapie (AD+Docetaxel) wurden die Patienten in high und low volume eingeteilt (CHAARTED) [787]. High volume umfasst diejenigen Patienten, bei denen

- mindestens vier Knochenmetastasen, davon mindestens eine außerhalb des Achsenskeletts bzw. Beckens
- und/oder viszerale Metastasen

vorlagen. In die zulassungsrelevante Studie von Abirateron wurden nur Patienten eingeschlossen, die de novo metastasiert waren und folgende high risk Kriterien erfüllten (LATITUDE) [788 ,789]:

mindestens zwei der drei Parameter

- Gleason 8 – 10
- mindestens drei Knochenmetastasen
- viszerale Metastasen.

Untersuchungen, in denen Patienten sowohl nach high und low volume sowie high und low risk eingeteilt wurden, zeigen eine etwas mehr als 80%ige Übereinstimmung zwischen high volume und high risk. Dennoch ist eine Differenzierung bzw. Einteilung von Patienten mit

metastasiertem hormonsensitiven Prostatakarzinom in beide Gruppen sinnvoll, da sich deutliche Vorteile für die Chemohormontherapie vor allem bei high volume Patienten zeigen, und die Zulassung von Abirateron auf high risk Patienten beschränkt ist.

Zu Empfehlung 7.21

Die Empfehlung zur Patientenaufklärung steht vor dem Hintergrund der informierten Entscheidung, wie sie guter klinischer Praxis sowie den Anforderungen des Patientenrechte-Gesetzes entspricht. Patienten sollen gemeinsam mit dem aufklärenden Arzt die schwierige Frage der Risikoabwägung entscheiden. Die in Tabel le 22 und Tabel le 23 (siehe Kapitel 7.7) aufgeführten typischen und häufigen Nebenwirkungen von Androgendeprivation und ggf. kombinierter Chemotherapie bzw. neuer Hormontherapie sind Bestandteil des

7.22	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad **A**	a. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven, Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Apalutamid angeboten werden.	
Empfehlungsgrad **A**	b. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Enzalutamid angeboten werden.	
Empfehlungsgrad **A**	c. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu-diagnostiziertem (de novo), metastasierten (M1), hormonsensitiven, high-risk Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus Prednison / Prednisolon) angeboten werden.	
Empfehlungsgrad **A**	d. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven, high-volume Prostatakarzinom (mHSPC) soll unter Aufklärung über die im Vergleich zu neuen Hormonsubstanzen höhere Toxizität zusätzlich zur Androgendeprivation eine Chemotherapie mit Docetaxel angeboten werden.	
Empfehlungsgrad **0**	e. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven, low-volume Prostatakarzinom (mHSPC) kann zusätzlich zur Androgendeprivation eine Chemotherapie mit Docetaxel angeboten werden.	
Level of Evidence **1+ bis 1-**	Literatur: a. [791,792] b. [793] c. [788,789] d. und e. [787,794,795]	
	Gesamtabstimmung: a. 98 %, b. 92 %, c. 86 %, d. 93 %, e. 95 %	

7.24	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad **A**	a. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Apalutamid, soll die Apalutamidgabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 240 mg/Tag gegeben werden.	
Empfehlungsgrad **A**	b. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Enzalutamid, soll die Enzalutamidgabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 160 mg/Tag gegeben werden.	
Empfehlungsgrad **A**	c. Bei Entscheidung für eine kombinierte Behandlung aus Androgendeprivation und Abirateron, soll die Abiraterongabe innerhalb von 3 Monaten nach Beginn der Androgendeprivation beginnen. Die Therapie soll in einer Dosierung von 1000 mg/Tag in Kombination mit Prednison oder Prednisolon (5 mg/Tag) gegeben werden.	
Empfehlungsgrad **A**	d. Bei Entscheidung für eine kombinierte Behandlung aus Chemotherapie und Androgendeprivation, soll die Docetaxelgabe innerhalb von 4 Monaten nach Beginn der Androgendeprivation beginnen. Es sollen 6 Zyklen alle drei Wochen in einer Dosierung von 75mg/m2 gegeben werden.	
Empfehlungsgrad **A**	e. Gründe für einen Therapieabbruch sollen sein: Patientenwunsch, Progress oder intolerable Nebenwirkungen.	
Level of Evidence a-d **1+ bis 1-** e **4**	Literatur: a. [791] b. [793] c. [789,788] d. [729,730,790,37] e. Expertenkonsens	
	Gesamtabstimmung: a. 97 %, b. 90 %, c. 98 %, d. 98 %, e 97 %	

Zu Empfehlung 7.22 a-e und 7.24 a-e

Der nachfolgende Absatz fasst die Datenlage für die Kombinationen aus AD und Docetaxel bzw. den Hormonpräparaten der neuen Generation (Abirateron, Apalutamid und Enzalutamid) beim mHSPC zusammen. Bei den Kombinations-Hormontherapien beruhen die Empfehlungen auf den jeweiligen Zulassungsstudien und den daraus resultierenden Zulassungstexten; diese berücksichtigen die eingeschlossenen Patientenpopulationen, die sich in den Studien teils erheblich unterschieden und deshalb nachfolgend jeweils detailliert dargestellt werden.

Obwohl z.B. die Daten der STAMPEDE-Studie nahelegen, dass Abirateron über die Patientengruppe mit high-risk Kriterien hinaus wirksam ist, wurde von den Leitlinienexperten angesichts der zahlreichen Therapiealternativen keine Notwendigkeit gesehen, eine über die Zulassung hinausgehende Empfehlung auszusprechen. Entsprechend berücksichtigen die Empfehlungen 7.19 und 7.21 die Indikationsstellung und Therapiekonstellation der Zulassungsstudien, für die dementsprechend Daten aus RCTs vorliegen.

Die Empfehlungen 7.24a (Apalutamid) und 7.24b (Enzalutamid) berücksichtigen jeweils eine Zeitdauer von 3 Monaten zwischen Beginn der AD und der Einleitung der Apalutamid-

bzw. Enzalutamid-Therapie. In den jeweiligen Studien war aber ein Zeitraum für die Androgentherapie von 6 Monaten erlaubt, sofern die Patienten vor Studientherapiebeginn noch eine Docetaxel-Chemotherapie (bis zu 6 Zyklen) erhielten. Der Anteil der Patienten mit vorheriger Docetaxel-Chemotherapie betrug 11 und 18 %, so dass die Subgruppenanalysen keine Aussage erlauben, ob eine zusätzliche Chemotherapie vor Beginn des neuen Androgenrezeptorblockers sinnvoll ist.

Die Therapiedauer ist für alle Hormon-Kombinationstherapien langfristig angesetzt, jedoch gemäß guter klinischer Praxis bei Krankheitsprogress oder dem Auftreten intolerabler Nebenwirkungen abzubrechen oder zu modifizieren.

Zu 7.22 a und 7.24 a (Apalutamid)

Die Kombination aus Apalutamid in Ergänzung zu einer AD wurde in TITAN, einer randomisierten, doppelt-verblindeten, placebo-kontrollierten Phase 3 Studie mit insgesamt 1.052 Patienten untersucht [791]. Eingeschlossen wurden Patienten mit dokumentiertem mHSPC mit einem ECOG Performance Status von 0 oder 1, die eine vorherige AD von bis zu 3 Monaten oder bis zu sechs Zyklen Docetaxel mit AD von bis zu 6 Monaten erhalten haben [791]. In die Studie wurden auch Patienten mit Metastasierung nach kurativ intendierter lokaler Therapie (z.B. Prostatektomie, lokale Strahlenbehandlung) eingeschlossen, sofern diese mindestens ein Jahr vor der Randomisierung abgeschlossen war [791]. Ausgeschlossen wurden u.a. Patienten mit schwerer Angina Pectoris, Herzinfarkt, Herzinsuffizienz, thromboembolischen Ereignissen oder ventrikulären Arrhythmien [791].

Patienten der Interventionsgruppe erhielten Apalutamid ergänzend zur AD, Patienten der Kontrollgruppe Placebo ergänzend zur AD [791]. Primärere Endpunkte waren radiographisches progressionsfreies Überleben (rPFS) sowie Gesamtüberleben (OS); als sekundäre Endpunkte wurden die Zeit bis zu einer Chemotherapie, die Zeit bis zu einer Verschlechterung von Schmerz, die Zeit bis zur Langzeitanwendung von Opioiden sowie die Zeit bis zu skelettassoziierten Ereignissen benannt [791].

Insgesamt zeigt sich ein signifikanter Vorteil für die Kombination aus Apalutamid + AD in den primären Studienendpunkten rPFS und OS. Die Gesamtzahl der unerwünschten Ereignisse (AEs) sowie die Grad 3-5 AEs unterschieden sich nur gering zwischen Interventions- und Kontrollgruppe. Hautausschläge wurden mit Apalutamid deutlich häufiger beobachtet. Eine Zusammenfassung der Ergebnisse einschließlich Nebenwirkungen findet sich in Tabelle 19 [791 ,792].

Apalutamid in der Indikation mHSPC wurde auch einer Nutzenbewertung nach §35a SGB V durch das IQWIG unterzogen. In diesem Verfahren wurde vom G-BA als zweckmäßige Vergleichstherapie (zVT) die Chemohormontherapie mit Docetaxel oder für Patienten mit high risk Kriterien Abirateron festgelegt. Da eine direkte vergleichende Studie zwischen zVT und Apalutamid nicht vorliegt, erfolgte ein adjustierter indirekter Vergleich (AD als „Brückenkomparator“), um Apalutamid mit den Docetaxel-Daten aus der STAMPEDE-Studie zu vergleichen. Insgesamt fand sich kein statistisch signifikanter Unterschied im Gesamtüberleben, aber es konnte ein positiver Effekt für Apalutamid in Bezug auf die Nebenwirkungen gezeigt werden. Das IQWIG sah insgesamt daher einen Anhaltspunkt für einen nicht quantifizierbaren Zusatznutzen [799 ,800]. Der G-BA sah dagegen einen Zusatznutzen als nicht belegt an, da lediglich für den Endpunkt schwerwiegende unerwünschte Ereignisse ein Vorteil für Apalutamid im indirekten Vergleich gesehen wurde und dies nicht mit hinreichender Sicherheit erlaube, einen Zusatznutzen abzuleiten [801].

Tabelle 19 Ergebnisse der RCT TITAN zur Kombinationstherapie mit Apalutamid, mediane Beobachtungszeit 22,7 Monate [791,792]

Patientenzahl: n=1052		AD + Apalutamid	AD + Placebo	Hazard Ratio (HR) (Konfidenzintervall), Signifikanz
Nutzen:	rPFS nach 2 Jahren (95 % KI)	68,2 % (62,9 – 72,9)	47,5 % (42,1-52,8)	HR 0,48 (0,39-0,60), p<0,001
	Gesamtüberleben nach 2 Jahren (95 % KI)	82,4 % (78,4-85,8)	73,5 % (68,7-77,8)	HR 0,67 (0,51-0,89), p=0,005
Schaden:	Nebenwirkungen	42,2 %	40,8 %	Grad 3-4 Ereignisse
		27,1 %	8,5 %	Hautausschlag
		22,7 %	16,3 %	Hitzewallungen
		19,7 %	16,7 %	Fatigue
		17,7 %	15,6 %	Bluthochdruck
		17,4 %	19,4 %	Rückenschmerz
		17,4 %	14,8 %	Arthralgie
	Todesfälle im Verlauf der Behandlung	10 (1,9 %)	16 (3,0 %)	

Zu 7.22 b und 7.24 b (Enzalutamid)

Die Kombination aus Enzalutamid in Ergänzung zu einer AD gegenüber einer alleinigen AD wurde in ARCHES, einer randomisierten, doppelt-verblindeten, placebokontrollierten Phase 3 Studie mit insgesamt 1.150 Patienten mit pathologisch bestätigtem mHSPC untersucht [793]. Eingeschlossen wurden erwachsene Patienten mit einem ECOG Performance Status von 0 oder 1, die eine vorherige AD von bis zu 3 Monaten oder bis zu sechs Zyklen Docetaxel mit AD von bis zu 6 Monaten in der Vorbehandlung erhalten haben [793]. Ebenso wie in der TITAN-Studie (Apalutamid) war Patienten mit Metastasierung nach kurativ intendierter lokaler Therapie (z.B. Prostatektomie, lokale Strahlenbehandlung) eine Studienteilnahme möglich. Patienten mit klinisch signifikanten, kardialen Erkrankungen (z.B. Myokardinfarkt innerhalb von 6 Monaten vor Einschluss) waren ausgeschlossen [793]. Als primärer Endpunkt wurde das radiographische, progressionsfreie Überleben (rPFS) untersucht [793]. Sekundäre Endpunkte waren die Zeit bis zur PSA Progression, die Zeit bis zur Aufnahme einer neuen antineoplastischen Therapie, die PSA-Rate unter der Nachweisgrenze, die objektive Ansprechrate, die Zeit bis zur Verschlechterung von Symptomen bezogen auf den Harntrakt, Gesamtüberleben (OS), die Zeit bis zu Skelett-bezogenen Symptomen, die Zeit bis zur Kastrationsresistenz, die Zeit bis zur Verschlechterung der Lebensqualität sowie die Zeit bis zur Verschlechterung einer Schmerzsymptomatik [793].

Nach einer medianen Beobachtungszeit von 14,4 Monaten zeigte sich ein signifikanter Vorteil für die Kombination aus Enzalutamid + AD für den primären Studienendpunkt rPFS. Ein Vorteil im OS konnte in diesem Datenschnitt (14. Oktober 2018) nicht gezeigt werden (HR 0,81; 95 % KI 0,53-1,25) [793]. Die Gesamtzahl der unerwünschten Ereignisse (AEs) sowie die Grad 3-5 AEs unterschieden sich nur gering zwischen Interventions- und Kontrollgruppe. Eine Zusammenfassung der Ergebnisse einschließlich weiterer Nebenwirkungen findet sich in Tabelle 20.

Für die Zeit bis zur Verschlechterung der Lebensqualität, einem der sekundären Endpunkte, werden median 11,3 Monate für die Interventionsgruppe sowie median 11,1 Monate für die Kontrollgruppe berichtet (HR 0,96 (0,81-1,14) p=0,6548) [793].

Tabelle 20 Ergebnisse der RCTs ARCHES zur Kombinationstherapie mit Enzalutamid (mediane Beobachtungszeit 14,4 Monate) [793]

Patientenzahl: n=1150		AD + Enzalutamid	AD + Placebo	HR (Konfidenzintervall), Signifikanz
Nutzen:	Medianes rPFS (Monate) (95% KI)	NE	19,0 (16,6 - 22,2)	HR 0,39 (0,30-0,50), p<0,001
	Medianes Gesamtüberleben* (Monate) (95 % KI)	NE	NE	HR 0,81 (0,53-1,25), p=0,3361
Schaden:	Nebenwirkungen	24,3 %	25,6 %	Grad 3-4 Ereignisse
		27,1 %	22,3 %	Hitzewallungen
		19,6 %	15,3 %	Fatigue
		12,2 %	10,6 %	Arthralgie
		7,5 %	10,8%	Rückenschmerz
		8,6 %	6,3 %	Bluthochdruck
		4,5 %	2,1 %	Kognitive Störungen
		6,5 %	4,2 %	Frakturen
		26,4 %	27,7 %	Erkrankungen des Bewegungsapparates
	Todesfälle im Verlauf der Behandlung	14 (2,4 %)	10 (1,7 %)	

* Sekundärer Studienendpunkt; NE – nicht erreicht

Zu 7.22 c und 7.24 c (Abirateron)

Zur Kombinationstherapie von Abirateron und AD liegen Daten aus zwei randomisierten klinischen Studien, STAMPEDE und LATITUDE, vor [788 ,802].

In die STAMPEDE-Studie wurden nur Patienten in gutem Allgemeinzustand (ECOG 0-1) eingeschlossen (dagegen in LATITUDE auch ECOG 2). Ähnlich wie im Docetaxel-Arm von STAMPEDE (s. 7.19 d) so wurde auch im Abirateron-Arm kein Unterschied bezüglich der Metastasenlast in der Gruppe der metastasierten Patienten gemacht. Im Gesamtüberleben (OS) zeigte sich ein statistisch signifikanter Vorteil für die Kombinationstherapie mit einer hazard ratio (HR) von 0,63 (95% KI 0,52-0,76) [802]. Auch bezüglich des failure-free survivals fand sich ein deutlicher Vorteil zwischen der Therapie- und Placebo-Gruppe (HR 0,29; p<0,001) [802] (siehe Tabelle 21).

In die zulassungsrelevante LATITUDE-Studie wurden Patienten mit neu diagnostiziertem, pathologisch bestätigtem mHSPC (high risk) und ECOG 0-2 eingeschlossen, die mindestens

zwei von drei benannten Risikofaktoren aufwiesen (Gleason Score von 8-10, mindestens drei Knochenläsionen, messbare viszerale Metastasen) [788 ,789].

Ausgeschlossen wurden Patienten, die zuvor eine Chemotherapie, eine Strahlentherapie oder einen operativen Eingriff zur Behandlung eines metastasierten Prostatakarzinoms erhielten, mit Ausnahme einer AD mit luteinisierendem Hormon Releasing Hormon- (LHRH-) Analoga von weniger als drei Monaten, einer Orchiektomie oder palliativer Strahlentherapie beziehungsweise palliativen operativen Eingriffen zur symptomatischen Behandlung [788 ,789].

Als primärer Endpunkt wurden das OS sowie radiographisches, progressionsfreies Überleben (rPFS) betrachtet [788 ,789]. Die Auswertung erfolgte im Rahmen einer ersten Interimanalyse im Oktober 2016, aus deren Ergebnissen eine Entblindung sowie eine Protokollanpassung zu einer offenen Verlängerungsphase der Studie mit der Möglichkeit eines Wechsels der Behandlungsgruppe im Februar 2017 resultierte [788 ,789]. Bei der Endauswertung ist der Wechsel von Patienten der Kontrollgruppe in die Interventionsgruppe nach der Entblindung (cross-over, n=72) zu berücksichtigen [789].

Die Endauswertung erfolgte zum 15. August 2018 mit einer medianen Beobachtungszeit von 51,8 Monaten [789]. Es bestätigte sich der Vorteil bezüglich des Gesamtüberlebens (HR 0,62 bzw. 0,66, s. Tabelle 21). Die Auswertung des rPFS erfolgte nur zur ersten Interimsanalyse mit einem deutlichen Vorteil für die Kombinationstherapie von 33,0 vs. 14,8 Monaten, HR 0,47 [788 ,789].

Die Nebenwirkungen in Tabelle 21 stammen exemplarisch aus der STAMPEDE Studie.

[…]

Tabelle 21 Ergebnisse der RCT zur Kombinationstherapie mit Abirateron [788,789,802]

		AD + Abirateron	AD (Studie)	HR (Konfidenzintervall); Signifikanz
Nutzen:	STAMPEDE			
	Gesamtüberleben nach 3 Jahren *	83 %	76 %	0,63; p<0,001
	LATITUDE			
	Gesamtüberleben nach 3 Jahren (Interimanalyse)	66%	49% (LATITUDE**)	0,62; p<0,001
	Medianes Überleben final, Monate (95 % KI)	53,3 (48,8 – NE)	36,5 (33,5-40,0)	0,66 (0,56-0,78), p<0,0001
	STAMPEDE			
	failure-free survival, Monate	43,9	30,0 (STAMPEDE)	13,9 Mo.; HR 0,29; p<0,001
	LATITUDE			
	progressionsfreies Überleben, Monate (Interimanalyse)	33,0	14,8 (LATITUDE**)	18,2 Mo.; HR 0,47; p<0,001
Schaden:	Nebenwirkungen	47%	33%	Grad 3-5 Ereignisse
	(exemplarisch aus STAMPEDE-Studie, da größeres Patienten-Kollektiv und längeres Follow-up)	14%	14%	endokrine Erkrankungen
		10%	4%	kardiovask. Erkrankungen
		7%	5%	muskuloskeletale Erkrankungen
		5%	4%	gastrointestinale Erkrankungen
		7%	1%	hepatische Erkrankungen
		5%	3%	Allgemeinerkrankungen
		5%	2%	respiratorische Erkrankungen
		4%	2%	abnormale Laborwerte
	Todesfälle im Verlauf der Behandlung	9	3 (STAMPEDE)	
		5	4 (LATITUDE**)	

* jeweils für die gesamte Studienpopulation; LATITUDE und STAMPEDE unterschieden sich in den Einschlusskriterien

** Daten der Interimanalyse

Zu 7.22 d, e und 7.24 d, e (Docetaxel)

Zur Einschätzung der Effektivität einer Kombinationstherapie von Docetaxel und AD wurden drei randomisierte klinische Studien sowie eine Metaanalyse [803] identifiziert. In zwei von drei Studien, die eine Kombinationstherapie von Docetaxel mit gleichzeitiger AD untersuchten, zeigte sich eine signifikante Verlängerung des Gesamtüberlebens (OS) um 15 bzw. 13,6 Monate (60 vs. 45 bzw. 57,6 vs. 44 Monate; 2.962 bzw. 790 Patienten) [787 ,794], die Unterschiede der Ergebnisse einer dritten Studie (OS 62,1 vs. 48,6 Monate; 385 Patienten) waren statistisch nicht signifikant [795]. Das progressionsfreie Überleben (PFS) bzw. das Überleben ohne Therapieversagen war in allen drei Studien durch die Kombinationstherapie signifikant verlängert (Progression: um 10 bzw. 8,5 Monate, Therapieversagen: um 17 Monate). Zwei von drei Studien (CHAARTED und GETUG) führten eine Subgruppenanalyse für Patienten mit hoher Tumorlast durch (in beiden Studien definiert als ‘visceral metastases or ≥4 bone lesions with ≥ 1 beyond vertebral bodies and pelvis‘, bei GETUG nur als post-hoc Analyse) und finden deutlich bessere Ergebnisse für diese Subgruppe. Die Studie mit der größten Population (STAMPEDE) nimmt diese Subgruppenauswertung nicht a priori vor und kommt zu einem signifikanten Ergebnis für

die Gesamtgruppe. In einer retrospektiven Analyse der Bildgebung bei Studieneinschluss mit einer nachträglichen Einordnung nach high und low volume Kriterien (entsprechend CHAARTED) erfolgte auch für die STAMPEDE-Studie noch eine Auswertung im Hinblick auf die Metastasenlast. Im Gegensatz zur CHAARTED-Studie bestand keine Heterogenität zwischen den Behandlungsgruppen mit unterschiedlichem Tumorvolumen (Interaktions-p-Wert: 0,827), d.h. der Vorteil der Chemotherapie war nach Einschätzung der Autoren unabhängig von der Tumorlast

In keiner der drei Studien wurden Subgruppenanalysen hinsichtlich symptomatischen gegenüber asymptomatischen Patienten durchgeführt. Aufgrund der restriktiven Einschlusskriterien der Studien und prognostisch günstigen Faktoren wie einem medianen Alter von 63,5-65 Jahren und den in allen Studien beobachteten vermehrten Grad 3-5 Toxizitäten im jeweiligen Docetaxel-Arm wird die Empfehlung für Patienten in gutem Allgemeinzustand mit ECOG-Werten von 0 oder 1 ausgesprochen, bei denen das Metastasierungsmuster den High Volume Kriterien entspricht.

Widersprüchliche Daten liegen für die Low Volume Metastasierung vor. Während in einigen Studien bzw. Metaanalysen kein Einfluss des „Metastasen-Volumens“ auf die Wirksamkeit der frühen Chemohormontherapie gesehen wird, kann in anderen Auswertungen kein Vorteil für Low Volume Patienten nachgewiesen werden [804 ,805]. Angesichts der mittlerweile zahlreich verfügbaren Therapiealternativen und des Toxizitätsprofils der Chemohormontherapie gegenüber einer kombinierten Homontherapie wurde die Empfehlung für eine Low Volume Metastasierung abgeschwächt („kann“).

[…]

Tabelle 22: Ergebnisse der RCT zur kombinierten Hormon-Chemotherapie

		AD + Docetaxel	AD	(Studie)	Differenz, Signifikanz
Nutzen:	Gesamtüberleben [Monate]	62,1 57,6 60	48,6 44 45	(GETUG) (CHAARTED) (STAMPEDE)	13,5 M., n.s. 13,6 M., p<0,001 15 M., p=0,005
	Subgruppe mit hoher Tumorlast	39,8 49,2	35,1 32,2	(GETUG) (CHAARTED)	4,7 M., n.s. 17 M., p<0,001
	progressionsfreies Überleben/ failure-free survival	22,9 20,2 37	12,9 11,7 20	(GETUG) (CHAARTED) (STAMPEDE)	10 M., p=0,005 8,5 M., p<0,001 17 M., p<0,001
Schaden:	Nebenwirkungen (exemplarisch aus STAMPEDE-Studie, da größtes Patienten-Kollektiv und gute Dokumentation)	52% 15% 12% 10% 8% 7% 6% 5% 4% 3% 3% 1%	32% 1% 0% 12% 3% 4% 6% 2% 6% 3% 2% 0%		Grad 3-5 Ereignisse febrile Neutropenie Neutropenie endokrine Erkrankungen gastrointestinale Erkrankungen Allgemeinerkrankungen muskuloskeletale Erkrankungen respiratorische Erkrankungen renale Erkrankungen kardiale Störungen Erkrankungen des ZNS Nagelveränderungen
	Behandlungs-bedingte Todesfälle	4 1 1	0 0 0	(GETUG) (CHAARTED) (STAMPEDE)	

7.23	Konsensbasierte Empfehlung	modifiziert 2021
EK	Die Therapieentscheidung soll abhängig von Patientenpräferenzen, Nebenwirkungen und Begleiterkrankungen getroffen werden.	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.23

Mittlerweile gibt es zahlreiche Kombinationstherapien beim mHSPC, für die eine Überlegenheit gegenüber der reinen AD nachgewiesen worden ist. Die verschiedenen Therapien unterscheiden sich u.a. bezüglich Zulassungsstatus bzw. Indikation sowie Nebenwirkungsspektrum. Zu den Vorteilen der einen oder der anderen Variante der Kombinationstherapie für spezifische Patientengruppen kann keine Aussage getroffen werden, da es keine direkt vergleichenden Studien gibt. Lediglich in der mehrarmigen STAMPEDE-Studie gab es einen Docetaxel- und einen Abirateron-Arm, und es wurde ein stärkerer Effekt hinsichtlich der Zeit bis zum Therapieversagen unter Abirateron als unter Docetaxel berichtet, ebenfalls jedoch nicht im direkten Vergleich. Ein Unterschied im Gesamtüberleben oder tumorspezifischen Überleben bestand dagegen nicht. Auch für

Apalutamid gibt es einen indirekten Vergleich zum Docetaxel-Arm der STAMPEDE-Studie (s.o.); in einer IQWIG-Bewertung dieses Vergleichs wurde ein Anhaltspunkt für einen nicht-quantifizierbaren Zusatznutzen für Apalutamid aufgrund von Vorteilen in der Kategorie Nebenwirkungen gesehen. Insgesamt scheint bei den Hormonpräparaten der neuen Generation also ein günstigeres Nebenwirkungsprofil zu bestehen, andererseits ist die Therapiedauer länger und für Risikopatienten ist bei Abirateron, die ebenfalls langfristige Gabe von Glucocorticoiden gegenüber der Docetaxel Chemotherapie zu bedenken.

Insgesamt soll daher die Wahl der Therapie bei entsprechender Indikation unter Berücksichtigung der Patientenpräferenzen, möglicher Nebenwirkungen sowie dem bestehenden individuellen Komorbiditätsprofil nach partizipativer Entscheidungsfindung getroffen werden. Dabei ist zu berücksichtigen, dass auch mit einer „einfachen“ AD relativ lange Überlebenszeiten erreicht werden können, so dass z.B. bei mutmaßlich eingeschränkter Lebenserwartung nicht zwingend eine Kombinationsbehandlung verabreicht werden muss. In diesem Sinne ist auch die Einschränkung der Empfehlungen auf Patienten mit gutem Performance-Status (ECOG 0-1) zu verstehen, da bezweifelt werden muss, dass Patienten, die sich unter einer initialen Hormontherapie innerhalb von 3 Monaten nicht im Performance-Status ggf. entsprechend bessern, tatsächlich von einer frühen Kombinationsbehandlung profitieren.

7.25	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad **A**	a. Patienten, die nicht für eine Kombinationsbehandlung in Frage kommen, soll eine Androgendeprivation empfohlen werden.	
0	b. Die Androgendeprivation kann medikamentös oder operativ erfolgen.	
B	c. Die Androgendeprivation sollte kontinuierlich durchgeführt werden, wenn der PSA-Wert nach spätestens 7 Monaten nicht unter 4 ng/mL abfällt.	
0	d. Bei Abfall des PSA-Wertes unter 4 ng/mL kann nach ausführlicher Aufklärung alternativ eine intermittierende Hormontherapie angeboten werden.	
Level of Evidence a-c: **1++** d-e: **1(+)**	Literatur: a. [729-731,734,790] b. [37,729,730,790] c. und d. [796-798]	
	Gesamtabstimmung: 97 %	

Zu Empfehlung 7.25

a) Eine sofortige hormonablative Therapie ist mit einer Verlängerung des progressionsfreien Überlebens verbunden [735]. Wie im Kapitel 6.7 „Primäre hormonablative Therapie und Watchful Waiting“ beim nichtmetastasierten Prostatakarzinom ausgeführt, sind die Ergebnisse jedoch im nichtmetastasierten und ebenso im metastasierten Stadium für das Gesamtüberleben nicht eindeutig. Aufgrund der guten Ansprechraten und der Verlängerung des progressionsfreien Überlebens im symptomatischen metastasierten Stadium wird jedoch eine starke Empfehlung zur sofortigen hormonablativen Therapie ausgesprochen. Die kausale Therapie ist einer symptomatischen Behandlung eindeutig vorzuziehen. Neben einer Verlängerung des progressionsfreien Überlebens gibt es Hinweise darauf, dass eine frühzeitig eingeleitete

Androgendeprivation Komplikationen infolge einer Progression der Grunderkrankung (z. B. durch eine pathologische Fraktur) reduziert [738].

Sowohl bezüglich der Indikationsstellung als auch bezüglich anderer Aspekte der Androgendeprivation (AD) lässt sich auf Basis der publizierten Analysen die Situation von Patienten mit lokalisiertem Prostatakarzinom nicht sicher von der bei Patienten mit metastasiertem PCa differenzieren. Außerdem existiert kein Nachweis dafür, dass sich hormonnaive Patienten in lokalisierten Tumorstadien bezüglich des Ansprechens auf eine AD anders verhalten als solche mit metastasiertem PCa. Demzufolge wurden sowohl in der Metaanalyse von Wilt 2001 [735] als auch in den ASCO-Leitlinien von 2004 bzw. 2007 [738 ,37] sowie in der vorliegenden Leitlinie Studienergebnisse von Patienten mit lokalisierten und fortgeschrittenen Stadien für die Empfehlungen herangezogen [805].

b) Eine ähnliche Empfehlung findet sich im Kapitel Watchful Waiting und alleinige hormonablative Therapie beim nichtmetastasierten Prostatakarzinom. Die Empfehlung zitiert die Substanzen, die in randomisierten kontrollierten Studien wirksam zur AD eingesetzt wurden. Der systematische Review von Kunath et al. 2019 [790] beinhaltet Studien zu Orchiektomie und LHRH-Agonisten. Zusätzlich sind in den Studien der VACURG [740] noch Östrogene bzw. DES eingesetzt worden. Iversen 2006 [729] setzt Bicalutamid ein, Studer 2006 [730] ebenfalls LHRH-Agonisten oder Orchiektomie. Der Einsatz von GnRH-Blockern wird aus der ebenso guten Absenkung des Testosteronspiegels wie durch LHRH-Agonisten abgeleitet. Von den GnRH-Antagonisten sind die Substanzen Abarelix seit 2005 und Degarelix seit Februar 2007 für die Indikation der hormonablativen Therapie des fortgeschrittenen Prostatakarzinoms zugelassen (Jakob et al. 2017/2021) [806]. Eine Monotherapie mit steroidalen Antiandrogenen ist im Vergleich zu einer LHRH-Analogatherapie mit einem kürzeren progressionsfreien Überleben assoziiert und sollte nicht empfohlen werden [37].

c) Grundlage dieser Empfehlung sind zwei Metaanalysen [796 ,797], die jeweils Primärstudien zum Vergleich von kontinuierlicher und intermittierender AD zusammenfassen. Die Mehrheit der eingeschlossenen Studien, inklusive der größten Studie mit mehr als eintausend Patienten [798], hatte als Einschlusskriterium für eine Randomisierung zwischen kontinuierlicher oder intermittierender Therapie das Absinken des PSA-Wertes nach einer mehrmonatigen Induktionsphase (bis zu 7 Monate) unter 4 ng/ml. Für Patienten mit höheren Werten nach der AD-Induktionsphase liegen nach Ansicht der Leitliniengruppe ungenügende Daten zur Wirksamkeit und Sicherheit einer intermittierenden AD vor, sodass sie für diese Indikation nicht empfohlen wird.

d) In den vorliegenden, zusammengefassten Studien überwiegend moderater Qualität wurden Patienten unterschiedlicher Stadien eingeschlossen und keine entsprechenden Subgruppenanalysen durchgeführt. Die Metaanalysen, ebenso wie die größte Studie, welche ausschließlich metastasierte Stadien einschloss, können keine eindeutige Unter- oder Überlegenheit einer der Therapieoptionen hinsichtlich Gesamt- oder Krebs-spezifischem Überleben sowie der Zeitdauer bis zum Fortschreiten der Krankheit belegen. Allerdings zeigt die Hussain-Studie einen nicht signifikanten Überlebensvorteil von median 5,8 vs. 5,1 Jahren für die kontinuierliche AD bei deutlichen Limitationen. Auch bezüglich des Schadenspotentials durch Nebenwirkungen sowie Auswirkungen auf die Lebensqualität ist die Datenlage unklar oder nicht ausreichend vorhanden, deshalb sollen die individuellen Voraussetzungen des Patienten besonders berücksichtigt werden.

7.5. Lokale Therapie bei metastasiertem Prostatakarzinom

7.53	Evidenzbasiertes Statement	neu 2021
Level of Evidence 1-	Unter einem oligometastasierten Prostatakarzinom wird ein Tumor mit maximal 4 in konventioneller Bildgebung (Skelettszintigraphie und CT oder MRT) nachweisbaren Knochenmetastasen ohne extraossäre viszerale Metastasen verstanden.	
	Literatur: [887,888]	
	Gesamtabstimmung: 98 %	

7.5.2. Perkutane Strahlentherapie und radikale Prostatektomie

7.54	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad B	a. Patienten mit einem neu diagnostizierten, oligometastasierten Prostatakarzinom sollten zusätzlich zur systemischen Therapie eine perkutane Strahlentherapie der Prostata erhalten.	
Empfehlungsgrad B	b. Die externe Strahlentherapie (EBRT) sollte hypofraktioniert verabreicht werden, die Strahlendosis sollte eine Äquivalenzdosis von 72 Gy in 2 Gy-Standardfraktionierung nicht überschreiten.	
Level of Evidence 1-	Literatur: [888,887]	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.54: Durch eine zusätzlich zur Androgendeprivation (+/- Docetaxel) durchgeführte perkutane Strahlentherapie der Prostata wird bei Patienten mit einem neudiagnostizierten oligometastasierten Prostatakarzinom die mediane Zeit bis zur PSA-Progression signifikant verlängert. Patienten mit einer „low-volume“-Erkrankung nach CHAARTED-Kriterien (oder bis zu 3 Knochenmetastasen [887]) können darüber hinaus hinsichtlich des Gesamtüberlebens profitieren [887,888] […] Unklar bleibt, ob Patienten durch eine Radiotherapie des Primärtumors auch bei einer geringfügig höheren Anzahl an Knochenmetastasen, die durch PSMA-Hybridbildgebung detektiert werden, gleichermaßen profitieren.

7.55	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad 0	Die perkutane Strahlentherapie der Prostata kann beim oligometastasierten Prostatakarzinom mit einer erweiterten systemischen Therapie kombiniert werden (Androgendeprivation (ADT) simultan, Docetaxel sequentiell).	
Level of Evidence 1-	Literatur: [887]	
	Gesamtabstimmung: 95 %	

Zu Empfehlung 7.55: In der STAMPEDE-Studie wurde eine Minderheit (18 % der Patienten) frühzeitig zusätzlich zur Strahlentherapie des Primärtumors auch systemisch mit Docetaxel behandelt [887]. Wenn eine Docetaxel-Behandlung erfolgt, so wird eine sequentielle Therapie empfohlen; die Androgendeprivation erfolgte dagegen in STAMPEDE „lifelong“, also auch simultan zur Strahlenbehandlung [887].

7.56	Evidenzbasierte Empfehlung / Statement	neu 2021
	a. Die radikale Prostatektomie ist als Therapieoption beim oligometastasierten Prostatakarzinom nicht hinreichend durch Evidenz belegt.	
Empfehlungsgrad **0**	b. Die radikale Prostatektomie kann beim oligometastasierten Prostatakarzinom nach Diskussion in einer interdisziplinären Tumorkonferenz im Rahmen einer multimodalen Therapie angeboten werden.	
Level of Evidence **2++**	a. Expertenkonsens b. Literatur: [891]	
	Gesamtabstimmung: 96 %	

Zu Empfehlung 7.56:

Zum Einsatz der radikalen Prostatektomie beim oligometastasierten Prostatakarzinom gibt es bisher keine abgeschlossenen randomisierten Studien [892] […] Die radikale Prostatektomie beim oligometastasierten Prostatakarzinom wird erwogen, um lokalenprogressionsbedingten Komplikationen im Bereich des unteren Harntraktes vorzubeugen [891,893].

7.57	Evidenzbasierte Empfehlung / Statement	neu 2021
Statement	a. Die metastasengerichtete lokal ablative Therapie beim oligometastasierten Prostatakarzinom ist nicht hinreichend durch Evidenz belegt, insbesondere in Bezug auf onkologische Endpunkte.	
Empfehlungsgrad **0**	b. Die metastasengerichtete lokal ablative Therapie beim oligometastasierten Prostatakarzinom kann zur Verzögerung einer Androgendeprivation und/oder Tumorprogression eingesetzt werden.	
Empfehlungsgrad **B**	c. Eine externe Strahlentherapie (EBRT) als ablative Behandlung sollte hypofraktioniert erfolgen, vorzugsweise als stereotaktische Bestrahlung (SBRT).	
Level of Evidence **2++**	a. Expertenkonsens b. und c. Literatur: [894,231,891]	
	Gesamtabstimmung: 91 %	

7.6. Therapie von Knochenmetastasen

7.58	Evidenzbasierte Empfehlung	modifiziert 2018
Empfehlungsgrad **A**	Die Therapie symptomatischer ossärer Metastasen ist Bestandteil des onkologischen Gesamtkonzeptes (siehe Empfehlungen 7.42, 7.46, 7.49, 7.50). Patienten mit ossären Metastasen soll zusätzlich eine oder mehrere der folgenden Therapieoptionen angeboten werden: · medikamentöse Schmerztherapie · lokale Bestrahlung, siehe Empfehlung 7.59 · operative Intervention (in der Regel in Kombination mit Bestrahlung).	
Level of Evidence bei den jeweiligen Empfehlungen	Literatur: [851,895,896]	
	Gesamtabstimmung: 86 %	

Zu Empfehlung 7.58:

Aufgrund der vorliegenden Daten muss derzeit geschlossen werden, dass eine Lebensverlängerung bei der spezifischen Therapie von Knochenmetastasen auch bei Therapie singulärer Metastasen in der Regel nicht erreicht wird. Einzelnen Studien zum Nutzen der perkutanen Bestrahlung oder zur Gabe von Radionukliden, in denen positive Überlebenszeiteffekte erzielt wurden, stehen andere Studien gegenüber, in denen solche Effekte nicht nachweisbar waren [896].

7.59	Evidenzbasierte Empfehlung	geprüft 2018
Empfehlungsgrad A	Die lokale perkutane Bestrahlung soll bei Knochenmetastasen in folgenden Situationen eingesetzt werden: • persistierende lokalisierte Knochenschmerzen • drohende spinale Kompression (ggf. nach operativer Intervention) • nach operativer Stabilisierung • erhöhtes Frakturrisiko	
Level of Evidence 1++	Literatur: [895]	
	Gesamtabstimmung: 97 %	

Zu Empfehlung 7.59:

Die lokale perkutane Bestrahlung von schmerzhaften singulären Knochenmetastasen ist eine palliative Maßnahme. Die vorliegenden randomisierten kontrollierten Studien zeigen eine partielle oder komplette Schmerzlinderung nach ca. drei bis acht Tagen bei mehr als 80 % der Patienten. Bei mindestens 50 % der Patienten hält diese Schmerzlinderung sechs Monate oder länger an. Eine Einmal-Applikation von mind. 6 Gy (in der Regel 8 Gy) vorausgesetzt, korrelieren der Grad und die Dauer der Schmerzlinderung in den Studien nicht signifikant mit dem eingesetzten Bestrahlungsschema (Einzeldosis versus fraktionierte Gabe) [895,907 ,908]. Die Daten zeigen jedoch nach Einmal-Bestrahlung eine signifikant erhöhte Rate an späterer erneuter Behandlung im Vergleich zu einem fraktionierten Schema [895,909].

[…] Zum Effekt einer Bestrahlung bei tumorbedingter Spinalkanalstenose bzw. bei Rückenmarkskompression liegen Daten aus einer retrospektiven und vier prospektiven Fallserien (mit insgesamt 545 Patienten) vor [895]. Wegweisend für einen möglichen Erfolg der Therapie sind die frühe Diagnose und die Strahlensensibilität des Tumors. Die Studien zeigen eine Besserung der vorliegenden neurologischen Symptomatik bei etwa 25-64 % der Patienten ([895], die Definitionen hierfür sind jedoch heterogen.

Zum Vergleich einer primären kombinierten Therapie mit operativer Dekompression und perkutaner Strahlentherapie (10 x 3 Gy) vs. alleiniger Strahlentherapie liegt ein RCT von 2005 vor [912]. […] Der RCT zeigte bei Patienten (n = 103) mit einer nachgewiesenen Spinalkanalkompression und neurologischen Symptomen < 48 Stunden signifikant bessere Ergebnisse in Bezug auf die Erhaltung oder Wiedererlangung der Gehfähigkeit bei kombinierter Therapie (84 % vs. 57 % und 62 % vs. 19 %). Die Interventionen wurden jeweils innerhalb von 24 h durchgeführt. Eingeschlossen wurden Patienten, deren Symptomatik durch eine unilokuläre komprimierende Metastase eines primär nicht hochstrahlensensiblen Tumors bedingt war. Der chirurgische Eingriff nach erfolgloser Strahlentherapie zeigte in diesem RCT weit schlechtere Ergebnisse als die primäre kombinierte Behandlung. Aufgrund des signifikanten Ergebnisses zugunsten der Kombinationstherapie wurde der RCT nach der Zwischenauswertung nicht weitergeführt.

Unter den eingeschlossenen Patienten waren 19 Patienten mit Prostatakarzinom. Es wird nicht differenziert, ob dieses hormonnaiv oder kastrationsresistent war.

Bei hormonnaiven Patienten mit Symptomen einer spinalen Kompression ohne pathologische Fraktur besteht auch die Möglichkeit einer (notfallmäßigen) Hormonentzugstherapie.

7.61	Evidenzbasierte Empfehlung	neu 2018
Empfehlungsgrad **B**	Zur Prävention von Komplikationen bei Knochenmetastasen im Hormon-naiven Stadium sollten Bisphosphonate nicht eingesetzt werden.	
Statement	Die Wirkung von Denosumab in diesem Stadium kann derzeit nicht beurteilt werden.	
Level of Evidence Zoledronsäure **1+** andere Bisphosphonate, Denosumab **4**	Literatur: Zoledronsäure: [794,897-899] Literatur andere Bisphosphonate, Denosumab: [866,868,900]	
	Gesamtabstimmung: 100 %	

Zu Empfehlung 7.61:

Die Leitliniengruppe entschloss sich im Hinblick auf die Behandlung von Knochenmetastasen zur Verhinderung bzw. Verzögerung symptomatischer skelettaler Ereignisse, sowohl den RANKL Antikörper Denosumab als auch das Bisphosphonat Zoledronsäure zu empfehlen. Diese Empfehlung bezieht sich nur auf Patienten im kastrationsresistenten Stadium. Bei Hormon-naiven Patienten mit Knochenmetastasen wird dagegen von der Gabe osteoprotektiver Substanzen abgeraten: Die identifizierten Studien zeigen mehrheitlich keinen Vorteil des Einsatzes von Zoledronsäure bei hormonnaiven Patienten hinsichtlich der Zeit bis zum Auftreten skelettaler Ereignisse (SRE) und Überleben, zu anderen Bisphosphonaten und Denosumab konnten keine Studien für diese Patientengruppe identifiziert werden. Bei unsicherem bzw. nicht belegtem Nutzen gehen die Wirkstoffe mit potenziellen Risiken einher: Nierenfunktionsstörungen (Zoledronsäure [915] bzw. Kieferosteonekrosen und Hypokalzämie (Denosumab [916,917] (siehe auch Empfehlung 7.63), Auf dieser Grundlage raten die Autoren der Leitlinie vom Einsatz osteoprotektiver Substanzen bei Hormon-naiven Patienten mit Knochenmetastasen ab.

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CLINICAL PRACTICE GUIDELINE GU-010 Version 3

Advanced/ Metastatic Prostate Cancer; Effective Date: November, 2021

Leitlinienorganisation/Fragestellung

- How should advanced/ metastatic prostate cancer be treated?
- How should advanced/ metastatic prostate cancer patients be followed after treatment?

Methodik

Grundlage der Leitlinie

This guideline was originally developed to include early stage prostate cancer in 2005 (updated in January 2009, January 2011, September 2013, October 2014, March 2015) and subsequently split into an advanced/ metastatic only guideline in June 2018.

- Repräsentatives Gremium unklar, keine Patientenvertreter*innen- This guideline was reviewed and endorsed by the Alberta GUTumour Team. Members include surgical oncologists, radiation oncologists, medical oncologists, nurses, pathologists, and pharmacists.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse (Delphi Prozess) und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- For the 2021 guideline update, selected phase III trials were reviewed by the Alberta GU Tumour group (summarized in Appendix A).
- For the 2020 guideline update, selected phase III trials were reviewed by the Alberta GU Tumour group (summarized in Appendix A).
- For the 2018 guideline updates, PubMed was searched; Inclusion criteria: phase III clinical trials, published between January 1, 2010 and June 1, 2018, English language.
- Appendix A: *Table 1. Systemic Therapy Trials for the Treatment of Metastatic Castration Sensitive Prostate Cancer*

Drug	Trial Name	Indication	Arms of Study	PFS	p-value	Median OS	p-value
ADT (Intermittent versus continuous)[5]	INT 0162 (NCT00002651)	Newly diagnosed mCSPC	(n=765) continuous ADT Vs. (n=770) intermittent ADT	N/A	N/A	5.8 years (Continuous) vs. 5.1 years (intermittent)	HR for intermittent 1.10 (90%CI 0.99-1.20)
Abiraterone[12]	LATITUDE (NCT01715285)	Newly diagnosed mCSPC	(N=1199) ADT + placebo Vs. ADT + Abiraterone	ADT+ placebo: 14.8m ADT+ Abiraterone: 33.0 months	HR: 0.47, 95%CI: 0.39-0.55, p<0.001	ADT+ placebo: 34.7 months ADT+ Abiraterone: not reached	HR:0.62, 95%CI 0.51-0.76, P<0.001
Abiraterone[33]	STAMPEDE (NCT00268476)	mCSPC (52%), N1/Nx M0 (20%), N0M0 (28%)	(N=1917) ADT + placebo Vs. ADT + Abiraterone	(3-year) ADT+placebo: 45% ADT+Abiraterone: 75%	HR: 0.29, 95%CI: 0.25-0.34, p<0.001	(3-year) ADT+ placebo: 76% ADT+ Abiraterone: 83%	HR: 0.63, 95%CI: 0.52-0.76, p<0.001, HR for M0: 0.75 HR for M1: 0.61
Docetaxel/ Zoledronic acid[11]	STAMPEDE (NCT00268476)	high-risk, locally advanced, metastatic or recurrent PC, starting long-term hormone therapy	(2:1:1:1 randomization, N=2962) (2)Standard of care (SOC) Vs. (1)SOC + zoledronic acid (ZA) Vs. (1)SOC + docetaxel (Doc) Vs. (1)SOC+ ZA + Doc	SOC: 20m SOC+ZA: 22m SOC+Doc: 37m SOC+ZA+Doc: 36m	SOC+ZA: HR: 0.92, p=0.198 SOC+Doc: HR: 0.61, p<0.001 SOC+ZA+ Doc: HR:0.62, p<0.001	SOC: 71m (5y: 55%) SOC+ZA: not reached (5y:57%) SOC+Doc: 81m (5y: 63%) SOC+ZA+Doc: 76m (5y: 60%)	SOC+ZA: HR: 0.94, p=0.450 SOC+Doc: HR:0.78, p=0.006 SOC+ZA+ Doc: HR:0.82, p=0.022
Docetaxel[10]	CHAARTED (NCT00309985)	mCSPC with bone metastases	(N=790) ADT + placebo Vs. ADT + Docetaxel (Doc)	(Median time to CRPC) ADT+ Placebo: 11.7m ADT+ Doc: 20.2m	HR: 0.61, 95%CI: 0.51-0.72, P<0.001	ADT+ Placebo: 44.0m ADT+ Doc: 57.6m	HR: 0.61, 95%CI: 0.47-0.80, P<0.001
Docetaxel[34]	GETUG-AFU 15 (NCT00104715)	mCSPC	(N=385) ADT + placebo Vs. ADT + Docetaxel (Doc)	(bRFS) ADT+ Placebo: 12.9m ADT+ Doc: 22.9m	HR: 0.72, 95%CI: 0.57-0.91, p=0.005	ADT+ Placebo: 54.2m ADT+ Doc: 58.9m	HR: 1.01, 95%CI: 0.75-1.36, p=0.955
Enzalutamide[14]	ARCHES (NCT02677896)	mCSPC	(N=1150) Enzalutamide + ADT vs. Placebo + ADT	(radiographic) rPFS (events) Enzalutamide+ ADT =15..9% Placebo+ ADT =34.9%	HR: 0.39, 95%CI: 0.30-0.50, p>0.001	Deaths Enzalutamide+ ADT (n=39) Placebo+ ADT (n=45)	HR:0.81, 94%CI: 0.53-1.25, p=0.3361
Enzalutamide[15]	ENZAMET (NCT02446405)	mCSPC	(N=1125) Testosterone suppression plus either Enzalutamide vs. nonsteroidal antiandrogen therapy (Standard care)	PSA Events: Enzalutamide: 174 SOC: 333	HR: 0.39 p<0.001	Deaths: Enzalutamide: 102 SOC: 143	HR: 0.67, 95%CI: 0.52-086, p=0.0002
Apalutamide[35]	TITAN (NCT02489318)	mCSPC	(N=525) Apalutamide+ ADT vs Placebo+ ADT	rPFS at 24 mo Apalutamide: 68.2% Placebo: 47.5%	HR: 0.48, 95%CI: 0.39-0.60, p<0.001	OS at 24 mo Apalutamide: 82.4% Placebo: 73.5%	HR: 0.67, 95%CI: 0.51-0.89, p=0.005

LoE/GoR

- *Anmerkungen FBMed: Zu den Empfehlungen findet sich kein Graduierungssystem (Formulierungen im Text)*
- Critical Appraisal of the Evidence: The Knowledge Management Specialist (KMS) synthesizes the relevant details of the studies included from the literature search into evidence tables. The quality of the included primary studies is rated by the KMS and reviewed with the Guideline Working Group members according to the following criteria:

Level I – evidence from at least one large randomized controlled trial (RCT) of good methodological quality with low potential for bias or meta-analyses of RCTs without heterogeneity

Level II – small RCTs, large RCTs with potential bias, meta-analyses including such trials, or RCTs with heterogeneity

Level III – prospective cohort studies

Level IV – retrospective cohort studies or case-control studies

Level V – studies without a control group, case reports, or expert opinions

- The strength of the recommendations will be rated by the GWG members according to the following criteria originally developed by the Infectious Diseases Society of America and adapted for use by the European Society for Medical Oncology (ESMO):

Grade A – strongly recommended; strong evidence for efficacy with a substantial clinical benefit

Grade B – generally recommended; strong or moderate evidence for efficacy but with a limited clinical benefit

Grade C – optional; insufficient evidence for efficacy or benefit does not outweigh the risks/disadvantages

Grade D – generally not recommended; moderate evidence against efficacy or for adverse outcomes

Grade E – never recommended; strong evidence against efficacy or for adverse outcomes

Empfehlungen

Metastatic Castrate Sensitive Disease (Stage T1-4, N0-1, M+)

Indications include symptomatic disease or asymptomatic disease.

1. Staging

A. Physical Exam.

C. PSA, testosterone, CBC and differential, Aspartate transaminase (AST), Alanine transamine (ALT), creatinine, Blood urea nitrogen (BUN) within the last 1 month.

D. Bone scan (within the last 3 months).

E. CT scan, (abdomen and pelvis, +/- chest) (within the last 3 months).

2. Management

Androgen Deprivation Therapy to achieve a castrate level serum testosterone (<1.7 nmol/L) is the backbone of therapy. Medical and surgical castration are equivalent in terms of efficacy and both are viable options. Lower rates of fracture, peripheral arterial disease, and cardiac-related complications have been reported in surgical castration patients when compared to medical castration patients in a large retrospective cohort study.[4]

A. Castrate level serum testosterone (<1.7 nmol/L) can cause a number of undesirable side effects. For this reason intermittent ADT has theoretical advantages. However, in patients with metastatic prostate cancer continuous ADT is recommended unless survival is considered secondary to quality of life. The phase III intergroup trial reported that intermittent ADT cannot be considered non-inferior compared to continuous ADT in terms of overall survival.[5, 6]

B. Medical castration.

i. Treatment with an LHRH agonist/GnRH antagonist.

a. When first introduced, a non-steroidal antiandrogen (e.g. bicalutamide 50 mg daily, flutamide 250 mg three times a day or nilutamide 300mg daily) should be given concurrently with the first administration of leuprolide, goserelin, or buserelin for 2 weeks to 1 month in order to block the potential initial testosterone flare.

b. The non-steroidal antiandrogen should be administered concurrently with the first LHRH analogue injection and continue for a minimum of 14 days afterward.

c. Medical and surgical castration is equally effective and the risks, benefits, and economic implications should be discussed with the patient.

d. Patients who are intolerant to Leuprolide or unable to achieve castrate testosterone should have a trial of Buserelin.

e. The GnRH antagonist Degarelix is as effective at suppressing testosterone and may achieve testosterone suppression faster[7] than GnRH Agonists. Treatment with a GnRH antagonist (Degarelix) avoids the risk of testosterone 'flare" that occurs with GnRH agonists.[7, 8] A non steroidal antiandrogen is not required to be given concurrently with the first dose of GnRH antagonist.

f. Patients who meet the following criteria are eligible for Degarelix upfront: previous stroke, myocardial infarction, angina, TIA, abdominal aortic disease, previous coronary revascularization, or peripheral arterial disease.

g. if a patient is intolerant to Leuprolide and Buserelin then Degarelix can be tried.

h. Local Drug Access Coordinators or Nurse Navigators can assist with obtaining access to injection clinics for Degarelix.

C. Single agent antiandrogens.

i. Monotherapy with non-steroidal AA is inferior to medical castration with LHRH or GnRH agents. However, it may be considered for rare circumstances. To date there is insufficient data to recommend bicalutamide at 150 mg/day (not Health Canada approved). Options include:

ii. Biclutamide 50 mg orally once a day.

iii. Flutamide 250 mg orally three times daily.

iv. Nilutamide 300 mg orally once a day for one month, then decrease to 150 mg daily.

D. Patients undergoing androgen deprivation therapy for prostate cancer have an improved quality of life if they continue to be physically active. Patients should be counseled on the role of maintaining physical fitness and activity while on hormonal therapy.[9]

F. Ongoing total androgen blockade (e.g. castration with LHRH agonist/antagonist plus a nonsteroidal antiandrogen) is not recommended for patients in this setting.

2. Systemic Therapy

A. All patients presenting with **metastatic castrate sensitive prostate cancer** who are starting ADT should be considered for intensification of systemic therapy beyond ADT. An androgen receptor axis targeted therapy (ie: ARAT - e.g. apalutamide, enzalutamide, abiraterone acetate) is typically used in this setting, with consideration of docetaxel in certain circumstances (see below).

B. Chemotherapy (Docetaxel).

i. Data from the CHAARTED trial[10] demonstrated significant overall survival benefit of 13 months when docetaxel was administered to patients with castrate sensitive metastatic prostate cancer who are about to start or just have recently (within 4 months) started hormonal therapy. The greatest benefit was seen in patients with high volume disease (defined as the presence of visceral metastases or >4 bony lesions with 1 beyond the vertebral bodies and pelvis).

ii. Data from the STAMPEDE trial[11] demonstrated a significant overall survival benefit of 14 months in all patients (low and high volume) with metastatic CSPC.

iii. Patients receiving chemotherapy for this indication should be offered 6 cycles of docetaxel chemotherapy at a starting dose of 75 mg/m$_2$ every 3 weeks (given with or without prednisone). Androgen deprivation therapy as above is continued throughout and after docetaxel completion.

C. Abiraterone Acetate. Patients must meet LATITUDE trial criteria to qualify for this treatment. Currently, this is not available through Cancer Care Alberta or a special access program. Criteria are as listed here.

i. The LATITUDE Inclusion criteria[12]:

a. Adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology.

b. Distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI.

c. At least 2 of the following high-risk prognostic factors: Gleason score ≥8; presence of 3 or more lesions on bone scan; presence of measurable visceral (excluding lymph node disease) metastasis on CT or MRI.

D. Docetaxel plus abiraterone acetate with prednisone 5 mg twice a day may be considered for patients with de novo high volume metastatic disease (defined as the presence of visceral metastases or >4 bony lesions with 1 beyond the vertebral bodies and pelvis), as per the PEACE-1 trial.[13]

E. Enzalutamide (Not publicly funded, special access program required).[14, 15]

F. Apalutamide (All risks/volumes. Not publicly funded, special access program required).[16]

G. There is insufficient evidence to recommend one single agent ARAT strategy over another. Clinical decision making should be based on patient factors and access.

H. For selected men, chemotherapy plus ARAT (either concurrent if Abiraterone or sequential if Enzalutamide/Apalutamide) can be considered. It is highly advised to discuss these cases at tumour board. This strategy is not publicly funded at the time of guideline publication.

3.Radiation Therapy

Referral to RO for consideration of radiation therapy to the prostate for patients with de novo low volume metastatic disease (see Management of Oligometastatic Disease below), as per STAMPEDE.[17]

4. Follow-up

Frequency:

A. If on either docetaxel chemotherapy or ARAT (eg: abiraterone acetate, enzalutamide, apalutamide), patients should be evaluated as per standard protocol.

B. If on ADT alone: q3–6 months following the initiation of therapy to evaluate and then as clinically indicated.

C. Patients should be treated until development of castrate resistant disease

i. Castrate resistance defined as either clinical, biochemical, or radiographic disease progression in the presence of castrate level (<1.7nmol/L) testosterone levels.

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EAU, 2021 [6].

European Association of Urology (EAU)

Prostate cancer.

Zielsetzung/Fragestellung

To assist medical professionals in the evidence-based management of PCa.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium-trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt-trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz-trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt- nur über EAU guideline production handbook (Version March 2022);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert; This 2021 document presents an update of the 2020 PCa Guidelines publication.

Recherche/Suchzeitraum:

- Medline, EMBASE and the Cochrane library April 22, 2020
- A total of 279 new references were added to the 2021 PCa Guidelines.

LoE/GoR

Table 4. EAU Guideline's levels of evidence

Level	Type of evidence
1a	Evidence obtained from meta-analysis of randomised trials
1b	Evidence obtained from at least one randomised trial
2a	Evidence obtained from one well-designed controlled study without randomisation
2b	Evidence obtained from at least one other type of well-designed quasi-experimental study
3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports
4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities

Table 5. EAU Guideline's grades of recommendation

Grade	Nature of recommendations
A	Based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomised trial
B	Based on well-conducted clinical studies, but without randomised clinical trials
C	Made despite the absence of directly applicable clinical studies of good quality

- GRADE
- Each recommendation should be graded as either "strong" or "weak" and justified by using the strongest, clinically relevant data. It is important to point out any flaws in the evidence used to support any given recommendation. The panel can also make a recommendation AGAINST performing a certain action.
- From 2018 onwards, the EAU Guidelines have been using a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for the grading of recommendations. To allow for a transparent assessment of how recommendation statements have been developed, a Summary of Evidence (SOE) table will be provided for each recommendation within the guidelines which will address a number of key elements

Recommendations

6.4.9 *Guidelines for the first-line treatment of metastatic disease*

Recommendations	Strength rating
Offer immediate systemic treatment with androgen deprivation therapy (ADT) to palliate symptoms and reduce the risk for potentially serious sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction) to M1 symptomatic patients.	Strong
Offer luteinising hormone-releasing hormone (LHRH) antagonists, especially to patients with an impending spinal cord compression or bladder outlet obstruction.	Weak
Offer surgery and/or local radiotherapy to any patient with M1 disease and evidence of impending complications such as spinal cord compression or pathological fracture.	Strong
Offer immediate systemic treatment to M1 patients asymptomatic from their tumour.	Weak
Discuss deferred ADT with well-informed M1 patients asymptomatic from their tumour since it lowers the treatment-related side effects, provided the patient is closely monitored.	Weak
Offer short-term administration of an older generation androgen receptor (AR) antagonist to M1 patients starting LHRH agonist to reduce the risk of the 'flare-up' phenomenon.	Weak
Do not offer AR antagonist monotherapy to patients with M1 disease.	Strong
Discuss combination therapy including ADT plus systemic therapy with all M1 patients.	Strong
Do not offer ADT monotherapy to patients whose first presentation is M1 disease if they have no contraindications for combination therapy and have a sufficient life expectancy to benefit from combination therapy and are willing to accept the increased risk of side effects.	Strong
Offer ADT combined with chemotherapy (docetaxel) to patients whose first presentation is M1 disease and who are fit for docetaxel.	Strong
Offer ADT combined with abiraterone acetate plus prednisone or apalutamide or enzalutamide to patients whose first presentation is M1 disease and who are fit enough for the regimen.	Strong
Offer ADT combined with prostate radiotherapy (using the doses from the STAMPEDE study) to patients whose first presentation is M1 disease and who have low volume of disease by CHAARTED criteria.	Strong
Do not offer ADT combined with any local treatment (radiotherapy/surgery) to patients with high volume (CHAARTED criteria) M1 disease outside of clinical trials (except for symptom control).	Strong
Do not offer ADT combined with surgery to M1 patients outside of clinical trials.	Strong
Only offer metastasis-directed therapy to M1 patients within a clinical trial setting or well-designed prospective cohort study.	Strong

Hintergrundinformationen:

6.4.3 First-line hormonal treatment

Primary ADT has been the standard of care for over 50 years [709]. There is no high level evidence in favour of a specific type of ADT, neither for orchiectomy or for an LHRH analogue or antagonist, with the exception of patients with impending spinal cord compression for whom either a bilateral orchidectomy or LHRH antagonists are the preferred options.

6.4.3.1 Non-steroidal anti-androgen monotherapy

Based on a Cochrane review comparing non-steroidal anti-androgen (NSAA) monotherapy to castration (either medical or surgical), NSAA was considered to be less effective in terms of OS, clinical progression, treatment failure and treatment discontinuation due to adverse events [1051]. The evidence quality of the studies included in this review was rated as moderate.

[…]

6.4.4 Combination therapies

All of the following combination therapies have been studied with continuous ADT, not intermittent ADT.

6.4.4.1 'Complete' androgen blockade

The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [1063]. However, results with other anti-androgens or castration modalities have differed and systematic reviews have shown that CAB using a NSAA appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [1064, 1065] beyond 5 years of survival [1066] but this minimal advantage in a small subset of patients must be balanced against the increased side effects associated with long-term use of NSAAs.

6.4.4.2 Androgen deprivation combined with other agents

6.4.4.2.1 Androgen deprivation therapy combined with chemotherapy

Three large RCTs were conducted [801, 1045, 1067]. All trials compared ADT alone as the standard of care with ADT combined with immediate docetaxel (75 mg/sqm, every 3 weeks within 3 months of ADT initiation). The primary objective in all three studies was to assess OS. The key findings are summarised in Table 6.4.3. […]

Based on these data, upfront docetaxel combined with ADT should be considered as a standard in men presenting with metastases at first presentation provided they are fit enough to receive the drug [1070]. Docetaxel is used at the standard dose of 75 mg/sqm combined with steroids as pre-medication. Continuous oral corticosteroid therapy is not mandatory. In subgroup analyses from GETUG-AFU 15 and CHAARTED the beneficial effect of the addition of docetaxel to ADT is most evident in men with *de novo* metastatic high-volume disease [1046, 1047], while it was in the same range whatever the volume in the *post-hoc* analysis from STAMPEDE [1068]. The effects were less apparent in men who had prior local treatment although the numbers were small and the event rates lower. A systematic review and meta-analysis which included these 3 trials showed that the addition of docetaxel to standard of care improved survival [1070]. The HR of 0.77 (95% CI: 0.68‑0.87, p < 0.0001) translates into an absolute improvement in 4-year survival of 9% (95% CI: 5‑14). Docetaxel in addition to standard of care also improves failure-free survival, with a HR of 0.64 (0.58‑0.70, p < 0.0001) translating into a reduction in absolute 4-year failure rates of 16% (95% CI: 12‑19).

6.4.4.2.2 Combination with the new hormonal treatments (abiraterone, apalutamide, enzalutamide)

In two large RCTs (STAMPEDE, LATITUDE) the addition of abiraterone acetate (1000 mg daily) plus prednisone (5 mg daily) to ADT in men with mHSPC was studied [40, 744, 1071]. The primary objective of both trials was an improvement in OS. Both trials showed a significant OS benefit but in LATITUDE in high-risk metastatic patients only with a HR of 0.62 (0.51‑0.76) [744]. The HR in STAMPEDE was very similar with 0.63 (0.52‑0.76) in the total patient population (metastatic and non-metastatic) and a HR of 0.61 in the subgroup of metastatic patients [40]. The inclusion criteria in the two trials differed but both trials were positive for OS. While only high-risk patients were included in the LATITUDE trial a *post-hoc* analysis from STAMPEDE showed the same benefit whatever the risk or the volume stratification [1072]. All secondary objectives such as PFS, time to radiographic progression, time to pain, or time to chemotherapy were positive and

in favour of the combination. […] In three large RCTs (ENZAMET, ARCHES and TITAN) the addition of AR antagonists to ADT in men with mHSPC was tested [742, 743, 1073]. In ARCHES the primary endpoint was radiographic progression-free survival (rPFS). Radiographic PFS was significantly improved for the combination of enzalutamide and ADT with a HR of 0.39 (0.3‑0.5). Approximately 36% of the patients had low-volume disease; around 25% had prior local therapy and 18% of the patients had received prior docetaxel. In ENZAMET the primary endpoint was OS. The addition of enzalutamide to ADT improved OS with a HR of 0.67 (0.52‑0.86). Approximately half of the patients had concomitant docetaxel; about 40% had prior local therapy and about half of the patients had lowvolume disease [743]. In the TITAN trial, ADT plus apalutamide was used and rPFS and OS were co-primary endpoints. Radiographic PFS was significantly improved by the addition of apalutamide with a HR of 0.48 (0.39‑0.6); OS at 24 months was improved for the combination with a HR of 0.67 (0.51‑0.89). In this trial 16% of patients had prior local therapy, 37% had low-volume disease and 11% received prior docetaxel [742]. In summary, the addition of AR antagonists significantly improves clinical outcomes with no convincing evidence of differences between subgroups. The majority of patients treated had de novo metastatic disease and the evidence is most compelling in this situation. In the trials with the AR antagonists, a proportion of patients had metachronous disease (see Table 6.4.5); therefore a combination should also be considered for men progressing after radical local therapy. Lastly, whether the addition of an AR antagonist plus docetaxel adds further OS benefit is currently not observed. Longer follow-up data are needed before a definitive conclusion is possible. At the moment, since toxicity clearly increases, AR antagonists plus docetaxel should not be given outside of clinical trials.

6.4.5 Treatment selection and patient selection

There are no head-to-head data comparing 6 cycles of docetaxel and the long-term use of abiraterone acetate plus prednisone in newly diagnosed mHSPC. However, for a period, patients in STAMPEDE were randomised to either the addition of abiraterone or docetaxel to standard of care. Data from the two experimental arms has been extracted although this was not pre-specified in the protocol and therefore the data were not powered for this comparison. The survival advantage for both drugs appeared similar [1074]. A recent meta-analysis also found no significant OS benefit for either drug [1075]. Limitations of network meta-analyses include variable patient populations with different treatment benefits and follow-up periods. In the STOPCAP systematic review and meta-analysis, abiraterone acetate plus prednisone was found to have the highest probability of being the most effective treatment [1076]. Both modalities have different and agent-specific side effects and require strict monitoring of side effects during treatment. Therefore, the choice will most likely be driven by patient preference, the specific side effects, fitness for docetaxel, availability and cost. There have been several network meta-analyses of the published data concluding that combination therapy is more efficient than ADT alone, but none of the combination therapies has been clearly proven to be superior over another [1077, 1078]. Life expectancy has to be taken into account when deciding on offering a combination therapy vs. ADT alone. Radiographic PFS is significantly prolonged in all trials for the combination therapies, e.g., from 14.8 months to 33 months in the LATITUDE trial, therefore suggesting that men with a life expectancy below 15 months are not likely to profit clinically from receiving a combination therapy. […]

6.4.7 Treatment of the primary tumour in newly diagnosed metastatic disease

The first reported trial evaluating prostate RT in men with metastatic castration-sensitive disease was the HORRAD trial. Four hundred and thirty-two patients were randomised to ADT alone or ADT plus IMRT with IGRT to the prostate. Overall survival was not significantly

different (HR: 0.9 [0.7-1.14]), median time to PSA progression was significantly improved in the RT arm (HR: 0.78 [0.63‑0.97]) [1079]. The STAMPEDE trial evaluated 2,061 men with mCSPC who were randomised to ADT alone vs. ADT plus RT to the prostate. This trial confirmed that RT to the primary tumour did not improve OS in unselected patients [1048]. However, following the results from CHAARTED and prior to analysing the data, the original screening investigations were retrieved and patients categorised as low- or high volume. In the low-volume subgroup (n = 819) there was a significant OS benefit by the addition of prostate RT and it must be highlighted that this benefit was obtained without an increased dose. The doses and template used in STAMPEDE should be considered (55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6-weekly fractions of 6 Gy or a biological equivalent total dose of 72 Gy). Therefore RT of the prostate only in patients with low-volume metastatic disease should be considered. Of note, only 18% of these patients had additional docetaxel and no patients had additional abiraterone acetate plus prednisone, so no clear recommendation can be made about triple combinations. In addition, it is not clear if these data can be extrapolated to RP as local treatment as results of ongoing trials are awaited. In a recent systematic review and meta-analysis including the above two RCTs, the authors found that, overall, there was no evidence that the addition of prostate RT to ADT improved survival in unselected patients (HR: 0.92, 95% CI: 0.81‑1.04, p = 0.195) [1080]. However, there was a clear difference in the effect of metastatic burden on survival with an absolute improvement of 7% in 3-year survival in men who had four or fewer bone metastases.

6.4.8 Metastasis-directed therapy in M1-patients

In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. There are two randomised phase II trials testing metastasis-directed therapy (MDT) using surgery +/- SABR vs. surveillance [1081] or SABR vs. surveillance in men with oligo-recurrent PCa [1082]. Oligo-recurrence was defined as < 3 lesions on choline-PET/CT only [1081] or conventional imaging with MRI/CT and/or bone scan [1082]. The sample size was small with 62 and 54 patients, respectively, and a substantial proportion of them had nodal disease only [1081]. Androgen deprivation therapy-free survival was the primary endpoint in one study which was longer with MDT than with surveillance [1081]. The primary endpoint in the ORIOLE trial was progression after 6 months which was significantly lower with SBRT than with surveillance (19% vs. 61%, p = 0.005) [1082]. Currently there is no data to suggest an improvement in OS. Two comprehensive reviews highlighted MDT (SABR) as a promising therapeutic approach that must still be considered as experimental until the results of the ongoing RCT are available [1083, 1084].

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Virgo KS et al., 2021 [24].

ASCO

Initial Management of Noncastrate Advanced, Recurrent, or Metastatic Prostate Cancer: ASCO Guideline Update

Zielsetzung/Fragestellung

Update all preceding ASCO guidelines on initial hormonal management of noncastrate advanced, recurrent, or metastatic prostate cancer.

What are the optimum evidence-based treatment modalities for men with noncastrate advanced, recurrent, or metastatic prostate cancer?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – included a patient representative and an ASCO guidelines staff member with health research methodology expertise.;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert – ist Update.

Recherche/Suchzeitraum:

- The Expert Panel based recommendations on a systematic literature review. Recommendations were approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee.
- The recommendations were developed by using a systematic review of rigorously conducted meta-analyses, phase III randomized clinical trials (RCTs), systematic reviews with or without meta-analyses, other relevant comparative study designs, and clinical experience. The PubMed database was initially searched on August 9, 2018, for evidence published since the previous guideline was completed (January 2007 through to the end of July 2018)

LoE/GoR

ASCO Guidelines Methodology Manual (https://www.asco.org/sites/new-www.asco.org/files/content-files/advocacy-and-policy/documents/Guidelines-Methodology-Manual.pdf)

Table 1. Definitions for Quality of Evidence Grades[7]

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

- *Strength of recommendations.* The Expert Panel provides a rating of the strength of each recommendation. This assessment reflects the extent to which a guideline panel is confident that desirable effects of an intervention outweigh undesirable effects, or vice versa, across the range of patients for whom the recommendation is intended. Recommendations may fall into two categories; strong and weak. Factors determining the strength of a recommendation include balance between benefits and harms, certainty of evidence, confidence in values & preferences, and resource use. Recommendations may be made for or against the use of an intervention.

Sonstige methodische Hinweise

- Update der Leitlinie Morris MJ 2018 Empfehlungen aktualisiert 1.2 (siehe alte Empfehlung) und erweitert um 1.7, 1.8, 1.9 und 1.95

Empfehlungen

CLINICAL QUESTION 1: What are the standard initial treatment options for metastatic noncastrate prostate cancer?

Recommendation 1

Recommendation 1.0. Docetaxel, abiraterone, enzalutamide, or apalutamide, each when administered with androgen deprivation therapy (ADT), represent four separate standards of care (SOCs) for noncastratemetastatic prostate cancer. The use of any of these agents in any particular combination or in any particular series cannot yet be recommended (Type: evidence-based, benefits-harms ratio unknown; Evidence quality: no evidence available; Strength of recommendation: strong).

ADT Plus Docetaxel[3]

Recommendation 1.1. For men with metastatic noncastrate prostate cancer with high-volume disease (HVD) as defined per CHAARTED[7] who are candidates for treatment with chemotherapy, the addition of docetaxel to ADT should be offered (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with HVD).

Recommendation 1.2. For patients with low-volume metastatic disease (LVD) as defined per CHAARTED[7] who are candidates for chemotherapy, docetaxel plus ADT should not be offered (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with LVD).

alte Empfehlung dazu (Morris 2018):

For patients with low-volume disease (LVD) per CHAARTED who are candidates for chemotherapy, docetaxel plus ADT may be offered (Type: evidence based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with LVD as per CHAARTED).

Recommendation 1.3. The recommended regimen of docetaxel for men with metastatic noncastrate prostate cancer is six doses administered at 3-week intervals at 75 mg/m$_2$ either alone (per CHAARTED)[7] or with prednisolone (per Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy [STAMPEDE])[8] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).[3]

Qualifying statements for ADT plus docetaxel

- The strongest evidence of benefit for docetaxel is for those men who were diagnosed with de novo metastatic disease or HVD (defined per CHAARTED[7] as four ormore bonemetastases, one ormore of which is outside of the spine or pelvis, and/ or the presence of any visceral disease). The criteria apply independent of the presence or absence of nodal disease.[3]
- Men with metastatic disease who do not fit into these categories should not be offered docetaxel. The strength of the evidence to support an overall survival (OS) benefit is not compelling for men who do not have de novo metastatic disease and/or who do notmeet the HVD criteria.[3] Long termsurvival data fromCHAARTED[9] and a post hoc aggregated analysis of CHAARTED and GETUG-AFU-15 data only showed an OS benefit for men with HVD and de novo metastases. There was no OS benefit for LVD, irrespective of whether the patients had metastases at diagnosis or after failure of prior local therapy.[9] Clarke et al[10] re-examined OS by disease burden using STAMPEDE data with longer follow-up, but the study was inadequately powered (, 80%) to detect an OS difference by disease burden if in fact one existed.
- As a chemotherapy agent, docetaxel is associated with somewhat greater toxicity than androgen-targeted therapies,such as abiraterone, but the treatment course is relatively short and the costs associated with treatment are generally covered by insurance, hence reducing the financial burden to the patient.

ADT Plus Abiraterone[3]

Recommendation 1.4. For men with high-risk de novo metastatic noncastrate prostate cancer, the addition of abiraterone to ADT should be offered per LATITUDE[11] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong for patients with high-risk disease as defined per LATITUDE).

Recommendation 1.5. For men with low-risk de novo metastatic noncastrate prostate cancer, ADT plus abiraterone may be offered per STAMPEDE12 (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: moderate for patients with low-risk disease per STAMPEDE).

Recommendation 1.6. The recommended regimen for men with metastatic noncastrate prostate cancer is abiraterone 1,000 mg with either prednisolone or prednisone 5 mg once daily until progressive disease is documented (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

ADT Plus Enzalutamide

Recommendation 1.7. ADT plus enzalutamide should be offered to men with metastatic noncastrate prostate cancer including both those with de novo metastatic disease and those who have received prior therapies, such as radical prostatectomy (RP) or radiotherapy (RT) for localized disease. Enzalutamide plus ADT has demonstrated short-term survival benefits (prostatespecific antigen [PSA] progression-free, clinical progression-free, and overall) when compared with ADT alone for men with metastatic noncastrate prostate cancer as a group per ENZAMET[13] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.8. The recommended regimen for men with metastatic noncastrate prostate cancer is enzalutamide (160 mg per day) with ADT (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Qualifying statement for ADT plus enzalutamide

- Among the subgroup of men with metastatic noncastrate prostate cancer previously treated with docetaxel, it is currently unclear whether similar survival benefits accrue long term when compared with treatment with first-generation antiandrogens plus ADT, as the final trial results for ENZAMET[13] and ARCHES[14] are not yet available, although it is anticipated that the long-term results will confirm the early findings. Early results (14.4 months median follow-up) from the ARCHES trial show that the risk of radiographic disease progression (DP) or death was significantly reduced with ADT plus enzalutamide versus ADT plus placebo overall as well as for prespecified subgroups, such as prior docetaxel versus no prior docetaxel and HVD versus LVD. In the ENZAMET trial at 34 months, none of the planned subgroup analyses for heterogeneity, such as among those receiving early docetaxel, were significant after adjusting for multiple comparisons. Enzalutamide was FDA-approved for use in the metastatic noncastrate prostate cancer setting on December 16, 2019. Discussions with patients should include the lack of data regarding long-term benefits and the cost of enzalutamide treatment compared with other options such as abiraterone.

ADT Plus Apalutamide

Recommendation 1.9. ADT plus apalutamide should also be offered to men with metastatic noncastrate prostate cancer, including those with de novo metastatic disease or those who have received prior therapy, such as RP or RT for localized disease per TITAN[15] (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation: strong).

Recommendation 1.95. The recommended regimen for men with metastatic noncastrate prostate cancer is apalutamide (240 mg per day) with ADT (Type: evidence-based, benefits outweigh harms; Evidence quality: high; Strength of recommendation:

strong).

Qualifying statement for ADT plus apalutamide

- Men with metastatic noncastrate prostate cancer previously treated with docetaxel appear to benefit with respect to radiographic progression-free survival (rPFS), but the answer is not yet conclusive. At 22.7 months, ADT plus apalutamide was associated with significantly longer rPFS and OS compared with ADT plus placebo. The effect of ADT plus apalutamide on rPFS was consistently favorable and statistically significant for most subgroups, including disease volume, Gleason score, and metastasis stage (M0/M1) at initial diagnosis, but not previous docetaxel use (favored ADT plus apalutamide but was not statistically significant). It is anticipated that the long-term results will confirm the early findings. Median OS among men previously treated with docetaxel could not yet be estimated. Longer follow-up is needed. Apalutamide was FDA-approved for use in the metastatic noncastrate prostate cancer population as of September 17, 2019. Discussions with patients should include the lack of long-term benefit data for men previously treated with docetaxel and the cost of apalutamide treatment.

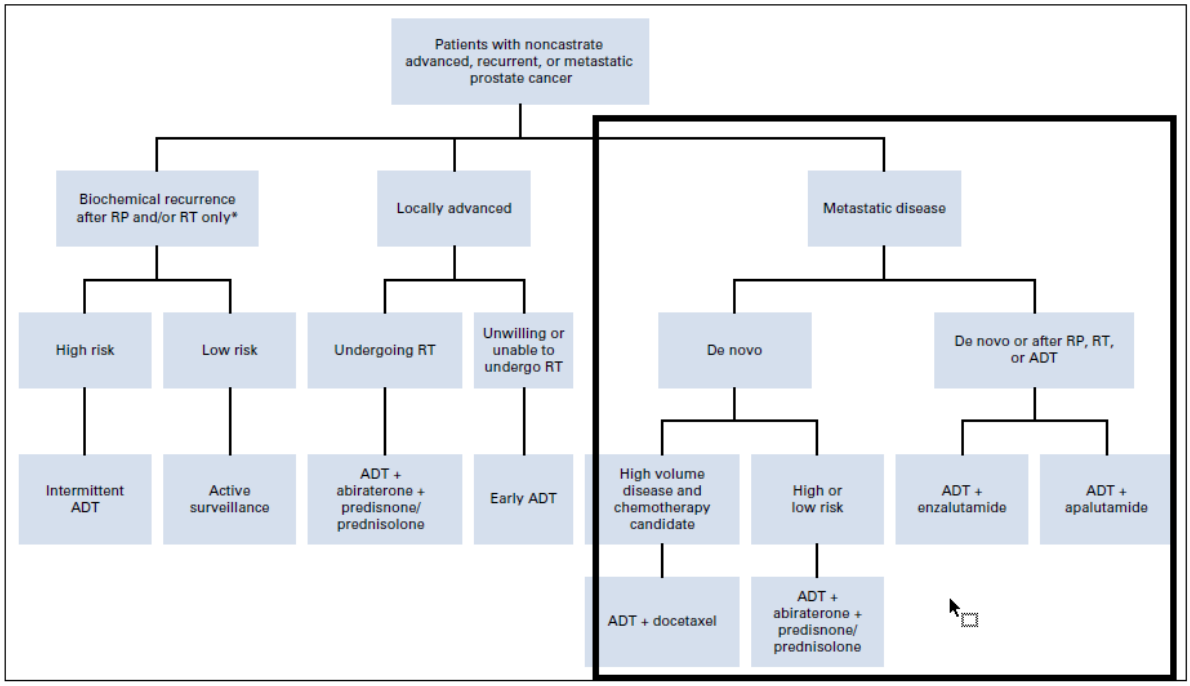

FIG 1. Initial management of noncastrate advanced, recurrent, or metastatic prostate cancer algorithm. ADT, androgen deprivation therapy; RP, radical prostatectomy; RT, radiotherapy. *Consult Lowrance et al[1] and Bekelman et al[2] for further information regarding salvage therapy options after failure of local therapy. [1]Lowrance WT, Breau RH, Chou R, Chapin BF, Crispino T, Dreicer R, Jarrard DF, Kibel AS, Morgan TM, Morgans AK, Oh WK. Advanced prostate cancer: AUA/ASTRO/SUO Guideline PART I. *J Urol.* doi:10.1097/JU.0000000000001375. [2]Bekelman JE, Rumble RB, Chen RC, Pisansky TM, Finelli A, Feifer A, Nguyen PL, Loblaw DA, Tagawa ST, Gillessen S, Morgan TM. Clinically localized prostate cancer: ASCO clinical practice guideline endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology guideline. *J Clin Oncol* 36:3251-3258, 2018.

Literature Review Update and Analysis

A companion guideline[3] previously addressed the use of abiraterone combined with docetaxel, docetaxel combined with ADT, and abiraterone combined with ADT for men with de novo metastatic noncastrate prostate cancer. The content of the guideline is now outdated and superseded by this guideline.

The current guideline also addresses the use of ADT plus enzalutamide and ADT plus apalutamide for men with de novo metastatic noncastrate prostate cancer, as well as treatment options for patients with metastatic noncastrate prostate cancer who may have had some form of prior treatment, such as docetaxel. The three phase III RCTs that provide data to inform recommendations are the TITAN trial,[15] the ARCHES trial,[14] and the ENZAMET trial.[13]

The multinational ARCHES trial[14] randomly assigned 1,150 men with newly diagnosed or relapsed metastatic noncastrate prostate cancer to ADT plus enzalutamide (160 mg per day) versus ADT plus placebo, stratified by disease volume (low v high) and prior docetaxel administration (none, 1-5 cycles, and 6 cycles). At baseline, approximately 60% of men in each arm had HVD (as defined in the CHAARTED trial,[7] 61.7% and 64.8%, respectively. Slightly ,16%in each arm had prior docetaxel chemotherapy. Most patients had some prior ADT, the majority (72.1% and 68.4%, respectively) for 3 months or less (median 1.6 months). Approximately one-third had prior antiandrogen use (35.8% and 39.9%, respectively). Prior local therapy was balanced between arms (RT 12.7%and 12.5%, respectively; RP 12.5%and 15.5%, respectively). Treatment per the protocol ceased if the patient experienced unacceptable toxicity, radiographic progression, or was started on any new prostate cancer therapy, including investigational therapies. The primary study end point was radiographic progression-free survival (rPFS). The main secondary end points were time to PSA progression, time to initiation of new antineoplastic therapy, PSA undetectable rate, objective response rate, time to urinary symptom deterioration, and OS.

At the planned interim analysis (after 262 events) at a median follow-up of 14.4 months, the risk of radiographic DP or death was significantly reduced with ADT plus enzalutamide versus ADT plus placebo (HR 5 0.39, 95% CI, 0.30 to 0.50, P , .001; rPFS median not reached v 19 months). The results were consistent across prespecified subgroups, such as prior docetaxel (HR 5 0.52, 95% CI, 0.30 to 0.89) versus no prior docetaxel (HR 5 0.37, 95% CI, 0.28 to 0.49) and HVD (HR 5 0.43, 95% CI, 0.33 to 0.57) versus LVD (HR 5 0.25, 95% CI, 0.14 to 0.46). Crossover to enzalutamide was then permitted for those in the placebo arm. Although it was too early to assess OS (planned for assessment at 342 deaths), death within 24 weeks of treatment discontinuation in the absence of radiographic progression was similar (2% in each arm).

Secondary end points also favored ADT plus enzalutamide, including time to first symptomatic skeletal event, time to castration resistance, and time to pain progression. Higher percentages of men achieved an undetectable PSA level and/or an objective response with ADT plus enzalutamide (P , .001). Compared with baseline, higher quality of life (QoL) was maintained over time by patients in both treatment arms. However, additional analyses were planned as part of long-term follow-up. In the preliminary safety analysis, the percentage of men with grade 3 or higher adverse events was similar between the treatment groups (24.3% v 25.6%, respectively) with no unexpected adverse events. Patients were to be followed until the earlier of death or 24 weeks after study drug discontinuation. The planned completion date for the ongoing study is December 2023.

ENZAMET, an open-label multinational phase III RCT,[13] randomly assigned 1,125 men with metastatic noncastrate prostate cancer to ADT plus enzalutamide (160 mg per day) versus ADT plus bicalutamide, nilutamide, or flutamide. After 88 patients had already been accrued, early administration of docetaxel was permitted based on evidence published after the study had begun.[7] Stratification was conducted by disease volume (low v high), planned early docetaxel administration, planned use of bone antiresorptive therapy, Adult Comorbidity Evaluation 27 (ACE- 27) score and trial site. At baseline, slightly more than 50% of men in each arm had HVD (as defined in the CHAARTED trial[7]). Approximately 16% in each arm had prior docetaxel chemotherapy, 75% had prior LHRH agonist or antagonist therapy, and over 50% of patients had prior nonsteroidal antiandrogen therapy within 12 weeks before random assignment. Prior local therapy was 42% in each arm. Bone antiresorptive therapy was 10% in each arm. Early use of docetaxel was planned for approximately 45% of men in each arm. Actual receipt of early docetaxel treatment was 27% among men with LVD and 61% among those with HVD. The primary end point was OS. The secondary end point was PSA progression-free survival (PFS).

At a median follow-up of 34 months, enzalutamide plus ADT was associated with significantly longer PSA progression-free (HR 5 0.39, CI: 0.33 to 0.47, P , .001), clinical progression-free (HR 5 0.40, CI: 0.33 to 0.49, P , .001), and overall (HR 5 0.67, CI: 0.52 to 0.86, P 5 .002) survival. None of the planned subgroup analyses for heterogeneity, such as among those receiving early docetaxel, were significant after adjusting for multiple comparisons. Longer follow-up (beyond 3 years) is needed to ascertain the effects of early docetaxel therapy on OS. The estimated study completion date is September 2020.

The double-blind, multinational TITAN phase III RCT[15] trial conducted at 260 sites in 23 countries randomly assigned 1,052 men with newly diagnosed or relapsed metastatic noncastrate prostate cancer to continuous ADT plus apalutamide (240 mg) or continuous ADT plus placebo, stratified by the Gleason score at diagnosis, geographic region, and previous treatment with docetaxel. At baseline, approximately 67% of men had a Gleason score $ 7 at initial diagnosis and 62% and 64%, respectively, had HVD. Among the 10%-11% previously treated with docetaxel, 47% and 40%, respectively, were node stage N1 at diagnosis. Previous therapy for localized disease was received by 18% and 15% of men, respectively.

At the first planned interim analysis with a median follow-up of 22.7 months, ADT plus apalutamide was associated with significantly longer rPFS (HR 5 0.48, CI: 0.39 to 0.60, P , .001) and OS (HR 5 0.67, CI: 0.51 to 0.89, P 5 .005) compared with placebo plus ADT. The effect of ADT plus apalutamide on rPFS was consistently favorable and statistically significant for most of the subgroups, including disease volume, Gleason score, and metastasis stage (M0/ M1) at initial diagnosis, but not for previous docetaxel use which favored ADT plus apalutamide, but was not statistically significant. Longer follow-up is needed. Median time to subsequent administration of cytotoxic chemotherapy was also significantly longer for apalutamide plus ADT (HR 5 0.39, CI: 0.27 to 0.56, P , .001). The frequency of grade 3 or 4 events was similar between groups. Study crossover was permitted. The estimated study completion date is July 2021.

ADT plus enzalutamide should be offered to men with metastatic noncastrate prostate cancer, including those with de novo metastatic disease and those who have received prior local therapies, such as RP or RT for localized disease. Enzalutamide plus ADT has demonstrated survival benefits (PSA progression-free, clinical progression-free, and overall) when compared with ADT alone for men with metastatic noncastrate prostate cancer as a group per ENZAMET, including among men previously treated with docetaxel. It is currently unclear whether similar survival benefits accrue long term when compared with treatment with first-generation antiandrogens plus ADT as the final trial results for ENZAMET[13] and ARCHES[14] are not yet available. Discussions with patients should include the lack of data regarding long-term benefits and the cost of enzalutamide treatment compared with other second generation antiandrogens, such as abiraterone.

Based on the results of the TITAN trial,[15] apalutamide plus ADT may also be offered to men with metastatic noncastrate prostate cancer, including both those with de novo metastatic disease and those who have received prior therapy, such as RP or RT for localized disease. Men previously treated with docetaxel appear to benefit, but the answer is not yet conclusive. Apalutamide was approved for use in the metastatic noncastrate prostate cancer population as of September 17, 2019. Discussions with patients should include the lack of long-term benefit data for men previously treated with docetaxel and the cost of apalutamide treatment.

Clinical Interpretation

Most trials of men with new or recurrent metastatic noncastrateprostate cancer include patients who have had prior local therapy (RT or RP), prior use of LHRH agonists or antagonists, and/or prior antiandrogens as long as such use has ceased for a prespecified period of time before random assignment. Such trials generally exclude men with any previous chemotherapy use. Per the ongoing ARCHES trial,[14] there are significant benefits (reduced risk of progression or death) associated with the use of enzalutamide with ADT compared with placebo plus ADT, including for men with HVD versus LVD and those previously treated with docetaxel. Per the ENZAMET trial,[13] in comparison to treatment with first-generation antiandrogens (bicalutamide, nilutamide, or flutamide) plus ADT, treatment with enzalutamide plus ADT provided significant benefits in terms of PSA PFS, clinical PFS, and OS. However, longer follow-up is needed to determine whether these benefits apply to the subgroup of men treated with early docetaxel. Similarly, the TITAN trial,[15] which permitted crossover at the first interim analysis, showed both rPFS and OS benefits for apalutamide plus ADT compared with placebo plus ADT for the study population as a whole as well as for most subgroups, although longer follow-up is needed for those previously treated with docetaxel. However, apalutamide is now approved for use in the United States in the metastatic noncastrate prostate cancer population. Furthermore, patients and their partners should understand the potential side effects of docetaxel, abiraterone, enzalutamide, and apalutamide, each when used with ADT. Underlying comorbidities should also be taken into consideration.

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American Urological Association (AUA), American Society for Radiation Oncology (ASTRO), Society of Urologic Oncology (SUO)

Advanced Prostate Cancer: AUA/ASTRO/SUO Guideline

Leitlinienorganisation/Fragestellung

The management of advanced prostate cancer is rapidly evolving. Clinicians are challenged to remain up-to-date and informed with respect to a multitude of treatment options for patients with advanced prostate cancer. To assist in clinical decision-making, evidence-based guideline statements were developed to provide a rational basis for evidence-based treatment. This guideline covers advanced prostate cancer, including disease stages that

range from prostate-specific antigen (PSA) recurrence after exhaustion of local treatment options to widespread metastatic disease.

Methodik

Grundlage der Leitlinie

The systematic review utilized to inform this guideline was conducted by an independent methodological consultant. Determination of the guideline scope and review of the final systematic review to inform guideline statements was conducted in conjunction with the Advanced Prostate Cancer Panel.

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz -angegeben aber kann nicht geprüft werden;
- Formale Konsensusprozesse und externes Begutachtungsverfahren angegeben;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über den Hintergrundtext identifizierbar – Evidenztabellen nicht hinterlegt;
- Regelmäßige Überprüfung der Aktualität gesichert – keine Information.

Recherche/Suchzeitraum:

A research librarian conducted searches in Ovid MEDLINE (1998 to January Week 5 2019), Cochrane Central Register of Controlled Trials (through December 2018), and Cochrane Database of Systematic Reviews (2005 through February 6, 2019). An updated search was conducted prior to publication through January 20, 2020. The methodology team supplemented rearches of electronic databases with the studies included in the prior AUA review and by reviewing reference lists of relevant articles.

LoE & GoR

- Sonstig The AUA categorizes body of evidence strength as Grade A, Grade B, or Grade C.2 The AUA nomenclature system explicitly links statement type to body of evidence strength, level of certainty, magnitude of benefit or risk/burdens, and the Panel's judgment regarding the balance between benefits and risks/burdens (table 2).

Table 2. *AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength*

Evidence Grade	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is substantial -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) appears substantial -Applies to most patients in most circumstances but better evidence is likely to change confidence
Moderate Recommendation (Net benefit or harm moderate)	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances and future research is unlikely to change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) is moderate -Applies to most patients in most circumstances but better evidence could change confidence	-Benefits >Risks/Burdens (or vice versa) -Net benefit (or net harm) appears moderate -Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (Net benefit or harm comparable to other options)	-Benefits = Risks/Burdens -Best action depends on individual patient circumstances -Future Research is unlikely to change confidence	-Benefits = Risks/Burdens -Best action appears to depend on individual patient circumstances -Better evidence could change confidence	-Balance between Benefits & Risks/Burdens unclear -Net benefit (or net harm) comparable to other options -Alternative strategies may be equally reasonable -Better evidence likely to change confidence
Clinical Principle	a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there may or may not be evidence in the medical literature		

e methodische Hinweise

- In der ungekürzten Leitlinie finden sich zusätzliche Informationen zur Bewertung (z. B. RoB, AMSTAR 2) und zum Entscheidungsprozess (www.auanet.org/guidelines).
- Forty-six studies were carried over from the prior AUA review. Dieser ‚prior review' ist leider nicht zitiert worden.

- Formale Konsensusprozesse und externes Begutachtungsverfahren angegeben, können aber nicht überprüft werden

Empfehlungen

Metastatic Hormone-Sensitive Prostate Cancer

Treatment

14. Clinicians should offer ADT with either LHRH agonists or antagonists or surgical castration in patients with mHSPC. (**Strong Recommendation; Evidence Level: Grade B**)

15. In patients with mHSPC, clinicians should offer continued ADT in combination with either androgen pathway directed therapy (abiraterone acetate plus prednisone, apalutamide, enzalutamide) or chemotherapy (docetaxel). (**Strong Recommendation; Evidence Level: Grade A)**

Hintergrund:

The use of primary ADT for the management of mHSPC has been the SOC since its discovery by Huggins and colleagues in the 1940's.[78] Castrate levels of testosterone (<50ng/dL) may be achieved with LHRH analogues, gonadotropin-releasing hormone (GnRH) antagonists or orchiectomy. These treatments are considered equivalent in cancer control, although they have never been compared in large RCTs. GnRH antagonists and orchiectomy as monotherapy have a rapid onset of action and avoid the 'testosterone flare' seen with LHRH analogues alone making them useful in situations needing rapid hormone ablation such as impending spinal cord compression.

mHSPC remains an incurable manifestation of the disease. While ADT, with or without nonsteroidal antiandrogens, has been the backbone of mHSPC treatment for many decades, ADT alone is no longer considered sufficient treatment for mHSPC. In just the past five years, multiple studies have shown that additional therapy significantly extends OS and PFS in mHSPC patients.

Docetaxel

In the phase III CHAARTED study,[67] 790 patients with mHSPC were equally randomly assigned to receive either ADT in combination with docetaxel for up to 6 cycles or ADT alone. At a median follow-up of 53.7 months, the median OS was 57.6 months for the chemohormonal therapy arm versus 47.2 months for ADT alone (HR=0.72; 95%CI 0.59 to 0.89; P=0.0018.

Similarly, in the STAMPEDE trial,[10] ADT plus docetaxel significantly improved median OS compared with ADT alone. The study randomly assigned 2,962 men 2:1:1:1 to receive SOC defined as hormone therapy for at least 2 years, SOC plus zoledronic acid, SOC plus docetaxel, or SOC with zoledronic acid and docetaxel. Docetaxel was given for six 3-week cycles with prednisolone (10mg) daily. Patients were followed up 6-weekly to 6 months, 12-weekly to 2 years, 6-monthly to 5 years, then annually. At a median follow up of 43 months, median OS was 71 months for SOC compared to 81 months for SOC plus docetaxel (HR=0.78; 95%CI 0.66 to 0.93; p=0.006).

Abiraterone Acetate

In the double-blind, placebo-controlled, phase 3 LATITUDE trial,[28] 1,199 patients were randomly assigned to receive either ADT plus abiraterone acetate plus or ADT plus placebo. The median follow-up was 40 months. There were 184 deaths in the abiraterone acetate group compared with 262 in the ADT group (HR=0.63; 95% CI 0.52-0.76; p <0.001).

In the STAMPEDE trial,[80] 1,917 patients were randomized in a 1:1 ratio to receive ADT alone or ADT plus abiraterone acetate and prednisolone. The median follow-up was 40 months. There were 184 deaths in the abiraterone acetate group compared with 262 in the ADT

group (HR= 0.63; 95%CI 0.52 to 0.76; P<0.001); the HR was 0.61 in those with metastatic disease.

Apalutamide

In the double-blind, phase 3 TITAN study,[82] 525 patients were assigned to receive apalutamide (240mg daily) with ADT compared to 527 patients receiving placebo plus ADT. At a median of 22.7 months follow up, the percentage of patients with radiographic PFS at 24 months was 68.2% in the apalutamide group compared to 47.5% in the placebo group (HR= 0.48; 95%CI 0.39 to 0.60; P<0.001). OS at 24 months was greater with apalutamide compared to placebo (82.4% versus 73.5%; HR= 0.67; 95%CI 0.51 to 0.89; P=0.005).

Enzalutamide

In the open-label, randomized, phase 3 ENZAMET trial,[84] 1,125 men were randomized to receive testosterone suppression plus either open-label enzalutamide or a standard nonsteroidal antiandrogen therapy (bicalutamide, nilutamide, or flutamide—standard care). With a median follow up of 34 months, there were 102 deaths in the enzalutamide group compared to 143 deaths in the standard care group (HR= 0.67; 95%CI 0.52 to 0.86; P= 0.002). Kaplan-Meier estimates of OS at 3 years were 80% in the enzalutamide group an 72% in the standard care group.

In the double-blind, phase III ARCHES trial, Armstrong et al. randomly assigned 1,150 men with mHSPC in a 1:1 ratio to receive either enzalutamide or placebo. As of October 2018, the risk of radiographic PFS or death was significantly reduced with enzalutamide plus ADT versus placebo plus ADT (median not reached versus 19.0 months; HR= 0.39; 95%CI 0.30 to 0.50; P<.001.

In terms of intermittent ADT, SWOG 9346 [85] evaluated intermittent ADT compared with continuous ADT and did not demonstrate non-inferiority in mHSPC. In fact, there was a non-significant benefit in OS with continuous ADT. Given all of the recent data suggesting that additional therapy (chemotherapy or androgen receptor-targeted therapy [ART]) added to continuous ADT significantly improves OS, the Panel generally advises against intermittent ADT in otherwise healthy patients with mHSPC.

16. In selected mHSPC patients with low-volume metastatic disease, clinicians may offer primary radiotherapy to the prostate in combination with ADT. **(Conditional Recommendation; Evidence Level: Grade C)**

Hintergrund:

Two recent Phase III randomized trials examining ADT and prostate radiotherapy versus ADT alone in men with metastatic prostate cancer demonstrated no difference in OS. However, the subgroup analysis for the low-volume group in STAMPEDE Arm H revealed a survival benefit in patients with low-volume metastatic cancer.[64] Given this was a secondary analysis, and that few of the patients had received optimized systemic therapy, the Panel provides a conditional recommendation for ADT plus radiation as an option for patients with minimal metastatic disease willing to undergo the risks associated with local therapy.

The HORRAD trial reported on 432 patients randomized either to ADT alone or ADT with EBRT to the prostate.86 Median PSA was 142ng/mL, and 67% of patients had more than 5 osseous metastases by conventional imaging. OS was not different (HR= 0.9; 95%; CI 0.7 to 1.14; p=0.4). In the STAMPEDE trial, 2,061 men with metastatic HSPC were randomized to ADT alone versus ADT plus prostate radiation given at moderate doses and with unconventional fractionation [64] Radiotherapy improved failure-free survival (HR=0.76; 95%CI 0.68 to 0.84; p<0.0001), but not OS (HR=0.92; 95%CI 0.80 to 1.06; p=0.266) similar to HORRAD. An additional pre-specified analysis utilizing the CHAARTED definition of low-

volume cancer encompassing 40% of the population was performed. Low-volume metastatic disease demonstrated a benefit to ADT plus radiation (HR= 0.68; 95% CI 0.52 to 0.90; p= 0,007).

Physicians have suggested these results point to the benefits of local therapy raising the question whether radical prostatectomy might have the same results. These trials are ongoing, and at present the use of surgery should be considered investigational and only conducted within the context of a trial. In the STAMPEDE trial,64 no patients had concurrent abiraterone acetate, and only 18% had early docetaxel so no clear recommendation can be made about other drug combinations combined with prostate radiation in the metastatic setting.

17. Clinicians should not offer first generation antiandrogens (bicalutamide, flutamide, nilutamide) in combination with LHRH agonists in patients with mHSPC, except to block testosterone flare. (**Strong Recommendation; Evidence Level: Grade A**)

Hintergrund:

With compelling level A evidence supporting the use of docetaxel, abiraterone acetate plus prednisone, apalutamide, or enzalutamide in combination with ADT in men with newly diagnosed mHSPC, the Panel believes that long-term use of first generation antiandrogens bicalutamide, flutamide, nilutamide in lieu of the above noted agents cannot be supported.

In the first week after LHRH agonists are administered, there is typically a surge in luteinizing hormone resulting in an increase in circulating testosterone. This may cause clinical “flares,” which may be associated with worsening of disease symptoms (e.g., bone pain, urinary tract obstruction) in approximately 10% of patients. This surge can be “blocked” by short term (i.e., 4 weeks or less) of a first-generation antiandrogen, although there is limited evidence of significant clinical utility.[87]

18. Clinicians should not offer oral androgen pathway directed therapy (e.g., abiraterone acetate plus prednisone, apalutamide, bicalutamide, darolutomide, enzalutamide, flutamide, nilutamide) without ADT for patients with mHSPC. **(Expert Opinion**)

Hintergrund:

Non-steroidal antiandrogen therapy without ADT in advanced prostate cancer is not recommended. Evidence based on 11 studies encompassing 3,060 patients suggests that use of non-steroidal antiandrogens without ADT compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of OS, clinical progression, treatment failure, and treatment discontinuation due to adverse events.[88]

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So AI et al., 2020 [20].

Canadian Urological Association (CUA)

Canadian Urological Association-Canadian Urologic Oncology Group guideline on metastatic castration-naive and castration-sensitive prostate cancer

Zielsetzung/Fragestellung

The Canadian Urologic Oncology Group (CUOG), in collaboration with the Canadian Urological Association (CUA) sought to provide management guidelines to optimize the treatment of mCNPC/mCSPC patients.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: expert panel comprised of urologists, medical oncologists, and radiation oncologists with significant experience managing mCNPC/mCSPC;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;

- Systematische Suche beschrieben, Auswahl und Bewertung der Evidenz nicht dargelegt, nur genannt;
- Formale Konsensusprozesse und externes Begutachtungsverfahren nicht dargelegt, nur genannt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist über den Hintergrundtext dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert - unklar;

Recherche/Suchzeitraum:

- EmBASE and Medline databases
- between January 2000 and August 2019

LoE/ GoR

- WHO modified Oxford Center for Evidence-Based Medicine grading system.

Sonstige methodische Hinweise

- Diese Leitlinie entspricht überwiegend, aber nicht vollständig den Grundanforderungen für eine methodisch hochwertige Leitlinie.

Empfehlungen

Local therapy: Treatment of the primary cancer in mCNPC

- Patients with low-volume metastatic disease burden should be considered for external beam radiation to the prostate (Level of evidence 2, Strong recommendation).

  Hintergrundinformationen:

  Treatment of the primary PC has theoretical benefits, including reducing local side effects that may occur due to disease progression during mCRPC, as well as removing the cancer that could be source of cytokines and growth factors that may induce disease progression. Two recent, randomized trials assessed the impact of external beam radiation therapy (EBRT) in mCNPC.

  The HORRAD trial randomized 432 men with mCNPC and PSA >20 ng/mL to receive EBRT of the prostate with ADT or ADT alone. The median PSA was 142 ng/ml and 67% of patients had more than five bone metastases. No significant difference was found in OS (hazard ratio [HR], 0.90; 95% confidence interval [CI] 0.70–1.14; p=0.4), but there was a benefit to median time to PSA progression in the radiotherapy group (15 vs. 12 m, crude HR 0.78; 95% CI 0.63–0.97; p=0.02). Subgroup analysis showed that mCNPC with <5 metastases (HR 0.90; 95% CI 0.70-–1.14; p=NS) and no bony pain (HR 0.83; 95% CI 0.69–1.14; p=NS) appeared to have the most impact of EBRT.

  The STAMPEDE trial, also known as MRC PR08, is a multi-arm, multi-stage (MAMS), randomized trial recruiting in the U.K. and Switzerland. It aims to evaluate multiple therapeutic strategies in the management of high-risk, locally advanced and mCNPC compared to standard of care (androgen deprivation only). In the EBRT component of the study, the trial randomized 2061 men with mCNPC to either EBRT and ADT or ADT alone.[15] The median PSA was 97 ng/ mL; 819 (40%) men had low metastatic burden based on CHAARTED criteria and 1664 (81%) had no pain.[8,15] Subgroup analyses were prespecified for baseline metastatic burden (low vs. high).

Similar to the HORRAD trial, EBRT improved failure-free survival (FFS) (HR 0.76; 95% CI 0.68–0.84; p<0.0001) but not OS (HR 0.92; 95% CI 0.80–1.06; p=0.266). Subgroup analysis by metastatic burden showed FFS was improved in both low and high metastatic burden (low metastatic burden HR 0.59; 95% CI 0.49–0.72; p<0·0001and metastatic burden, interaction p=0.002; high metastatic burden HR 0.88; 95% CI 0·77–1.01; p=0·059). OS was improved in patients with low metastatic burden at baseline who were allocated EBRT (HR 0.68; 95% CI 0.52–0.90; p=0.007), whereas in patients with a high metastatic burden, there was no impact on OS (HR 1.07; 95% CI 0.90–1.28; p=0.420). Although both trials showed negative impact of EBRT in unselected men in mCNPC, both HORRAD and STAMPEDE reveal the benefits of local therapy in those with low-burden disease. A recent STOPCAP meta-analysis combining data from the trials confirm the benefits of EBRT in men with fewer than five bone metastases.[16] This meta-analysis showed that there was 7% improvement in three-year survival in men with fewer than four bone metastases.

- Radical prostatectomy in mCNPC should only be performed in a clinical trial setting (**Expert opinion, Strong recommendation**).

  Hintergrundinformationen:

  Currently, there is limited evidence showing the benefit of radical prostatectomy in mCNPC. However, the results from HORRAD and STAMPEDE imply that there may also be certain men with mCNPC that may benefit from surgical extirpation. There are many clinical trials currently assessing this question, including TRoMBONE (Testing radical prostatectomy in men with PC and oligometastases to the bone: a randomized, controlled, feasibility trial),[17] SWOG1802 (Standard systemic therapy with or without definitive treatment in treating participants with metastatic PC; https://www.swog.org/clinical-trials/s1802), and G-RAMPP/AUO–AP-75/13 (Impact of radical prostatectomy as primary treatment in patients with PC with limited bone metastases).18 Until the results of these trials clarify the impact of radical prostatectomy in mCNPC and, more importantly, which patients would benefit the most, surgery of the primary is not recommended in patients with metastatic PC.

Systemic therapies: Chemotherapy, abiraterone acetate, enzalutamide, and apalutamide

- Docetaxel (75 mg/m2 every three weeks for six cycles) plus ADT is an option for men with mCNPC/mCSPC with good performance status and high-volume metastatic disease, defined as: presence of visceral metastases, or four or more bone lesions with at least one beyond the vertebral bodies and pelvis (Level 1, Strong recommendation).
- Docetaxel plus ADT may also be an option in patients with mCNPC/mCSPC with good performance status with low-volume disease (Level 2, Weak recommendation).
- "High risk" mCNPC/mCSPC patients (defined as at least two of: Gleason score of 8–10, visceral metastases, and three or more bone metastases) with good performance status can also be considered for docetaxel chemotherapy (Level 1, Strong recommendation).

  Hintergrundinformationen

  […] Three different, large, randomized trials assessed the impact of introducing docetaxel in mCNPC/mCSPC: CHAARTED, STAMPEDE, and GETUG-AFU 15.[8,20,21] The CHAARTED trial randomized 790 with mCNPC/mCSPC patients to ADT plus docetaxel (75 mg/m2 every three weeks for six cycles) or ADT alone.[8] Within this trial, 35% (277 patients) had low-volume metastases and 65% (513 patients) had high-volume metastases (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). Overall, the median OS was 13.6 months longer with ADT plus docetaxel than with ADT alone (57.6 vs. 44.0 months; HR 0.61; 95% CI 0.47–0.80; p<0.001). Subgroup analysis showed that OS benefits of combination were maintained in the high-volume mCNPC/mCSPC (n=513; HR 0.63; 95% CI 0.50–0.79; p<0.001), whereas survival benefits were lost in low-volume disease (n=277; HR 1.04; 95% CI 0.70–1.55; p=0.86).[22] The GETUG-AFU15 trial randomized 385 mCNPC/ mCSPC patients to receive ADT plus docetaxel or ADT alone.[21] Although the dosage of docetaxel was the same as in CHAARTED, patients were allowed to receive up to nine cycles compared to the six cycles in CHAARTED. There was no survival difference between the groups (58.9 months in the combined group vs. 54.2 months in the ADT alone group; HR 1.01; 95% CI 0.75–1.36). The differences in the outcomes of the two studies is likely due to the differences in the burden of disease in the two studies. Although 65% of patients in CHAARTED had high-volume metastases, less than 25% of the patients had low-volume disease. An unplanned posthoc analysis of the high-volume cohort of GETUG-AFU [15] showed a non-significant trend toward improved OS in this cohort (39.8 vs. 35.1 months; HR 0.78; 95% CI 0.56–1.09).[23] A recent pooled analysis of both studies confirm the benefit of combined docetaxel and ADT in high-volume disease and lack of benefit on low-volume metastatic burden.[24] The third trial to assess the impact of docetaxel in mCNPC/ mCSPC was the docetaxel component of the STAMPEDE trial.[20] Unlike the CHAARTED and GETUG-AFU[15] trials, patients with high-risk, non-metastatic PC were included. Eligible patients included: newly diagnosed metastatic, node-positive, or high-risk locally advanced (with high-risk features defined as at least two of: T3/4, Gleason score of 8–10, and PSA ≥40 ng/mL); or previously treated with radical surgery and/or radiotherapy with high-risk features. Of the 2962 patients randomized, 1817 (61%) men had bony metastases and 592 patients received only ADT and six cycles of docetaxel (75 mg/m2 every three weeks for six cycles). The combination of ADT and docetaxel had a survival advantage compared to ADT alone (HR 0.78; 95% CI 0.66–0.93; p=0.006). Although patients were not classified having high- or low-volume metastases, only patients with metastatic disease had evidence of benefit with ADT and docetaxel (HR 0.76; 95% CI 0.62–0.92; p=0.005).

A recent post-hoc, non-prespecified analysis of STAMPEDE was published.[25] Metastatic burden was assessable in only 76% of patients for the analysis (830 of 1086 patients) and 362 (44%) had low and 468 (56%) high metastatic burden. Although OS was neither statistically significant in low-burden nor in high-burden disease (HR 0.76; 95% CI 0.54–1.07; p=0.107 vs. HR 0.81; 95% CI 0.64–1.02; p=0.064), the authors found no evidence of heterogeneity of docetaxel effect between metastatic burden subgroups (interaction p=0.827). The authors concluded that upfront docetaxel is considered for mCNPC/mCSPC patients regardless of metastatic burden. This retrospective analysis contradicts the results of CHAARTED, but the authors point out that this may be due to the larger number of de novo mCNPC/mCSPC (n=362) in the low-burden group compared to the low-burden group in the CHAARTED trial (n<160). A recent meta-analysis of CHAARTED, GETUG-AFU[15], and STAMPEDE confirms the benefit of addition of docetaxel to ADT in mCNPC/mCSPC (HR 0.77; 95% CI 0.68–0.87; p<0.0001). The authors of the meta-analysis show that this translates to an absolute improvement in four-year survival of 9%.

- Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT is an option for mCNPC patients with at least two of the three: Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis (Level of evidence 1, Strong recommendation).

- Abiraterone acetate (1000 mg daily) with prednisone (5 mg daily) plus ADT may be considered for patients with low volume mCNPC (Level of evidence 3, Weak recommendation).

  Hintergrundinformationen

  Abiraterone acetate is a prodrug of abiraterone, which is a CYP17A1 inhibitor; CYP17A1 is expressed in and is required for androgen biosynthesis. Abiraterone acetate, when combined with prednisone, was initially shown to improve survival in mCRPC, both prior to and after docetaxel treatment.[26,27] Two trials, LATITUDE and STAMPEDE, assessed the impact of abiraterone in mCNPC/mCSPC.[9,28,29] In the LATITUDE trial, 1199 patients were randomly assigned to either the abiraterone acetate (1000 mg) plus prednisone (5 mg) once daily orally. Eligible patients included mCNPC with at least two of three high-risk features (Gleason score of ≥8, presence of three or more lesions on bone scan, or presence of measurable visceral metastasis except lymph node metastasis). Updated OS data with median follow-up of 51.8 months showed that OS was significantly longer in the abiraterone acetate plus prednisone group (median 53.3 months [95% CI 48.2–not reached]) than in the placebo group (median 36.5 months [95% CI 33.5–40.0]), with a HR of 0.66 (95% CI 0.56−0.78; p<0·0001). A post-hoc, exploratory analysis of the impact of disease burden showed that OS was improved only in high-volume disease (n=487 in the abiraterone acetate plus prednisone and ADT, and 468 in the ADT only group; HR 0.62; 95% CI 0.52−0.74; p<0·0001); however, only few patients had low-volume disease in this study (n=110 in the abiraterone acetate plus prednisone and ADT, and n=133 in the ADT only group; HR 0.72; 95% CI 0.47−1.10; p=0.1242). In the abiraterone component of the STAMPEDE trial, the efficacy of abiraterone acetate and prednisolone was assessed in men with mCNPC.[28] In this study, 1917 mCNPC patients were enrolled with: newly diagnosed and metastatic, node-positive, or high-risk, locally advanced (with at least two of following: cT3 or cT4, a Gleason score of 8–10, or PSA level ≥40 ng/mL), or disease that was previously treated with radical surgery or radiotherapy and was now relapsing with high-risk features (PSA >4 ng/mL with a doubling time of <6 months, a PSA level >20 ng/mL, nodal or metastatic relapse). Men were randomized to receive abiraterone acetate (1000 mg daily) plus prednisolone (5 mg) plus ADT or ADT alone; 52% of the patients had metastatic disease, 20% had node-positive or node-indeterminate non-metastatic disease, and 28% had node-negative, nonmetastatic disease; 95% had newly diagnosed disease. In a subgroup analysis, the OS benefit was seen in PC patients with metastatic disease (HR 0.61; 95% CI 0.49–0.75) but not those with non-metastatic, high-risk patients (HR 0.75; 95% CI 0.48–1.18).[28] The impact of volume tumor burden was not reported.

  In a recent, unplanned, post-hoc analysis of 759 evaluable patients with bone metastases in the above STAMPEDE trial, patients were reclassified using CHAARTED “high- or low-volume” criterion or LATITUDE “high- or low-risk” criterion.[30] Men with mCNPC had OS benefit with the addition of abiraterone acetate and prednisone to ADT irrespective of risk stratification for “risk” or “volume.” Using CHAARTED criteria, low-volume HR was 0.66 (95% CI 0.44–0.98) and high-volume HR was 0.54 (95% CI 0.41–0.70); using the LATITUDE criteria, low-risk HR was 0.64 (95% CI 0.42–0.97) and high-risk HR was 0.60 (95% CI 0.46–0.78). Although these results are intriguing, the retrospective nature of the reclassification of risk and tumor volume is a significant limitation and, thus, the results can only be considered hypothesis-generating.
- Enzalutamide (160 mg/day) is a treatment option for mCNPC/mCSPC regardless of volume of disease (Level of evidence 1, Strong recommendation).
- Enzalutamide should not be used in combination (concurrent use) with docetaxel to treat mCNPC/mCSPC (Level of evidence 2, Strong recommendation).

- Enzalutamide may be considered in mCSPC patients previously treated with docetaxel chemotherapy (sequential use) (Level of evidence 1, Weak recommendation).

  Hintergrundinformationen

  Enzalutamide binds to the androgen receptor (AR) and inhibits the AR nuclear translocation and interaction with DNA. Suppression of the AR with enzalutamide was initially shown to improve survival in docetaxel-naive or treated mCRPC.[31,32] Two recent studies assessed the role of enzalutamide in mCNPC: ARCHES and ENZAMET.[33,34] The ARCHES trial randomized 1150 mCNPC/mCSPC patients to either enzalutamide (160 mg/day) plus ADT or placebo plus ADT. The primary endpoint was radiological progression-free survival (rPFS), defined as the time from randomization to the first objective evidence of radiographic disease progression or death. The combination of enzalutamide plus ADT improved rPFS compared to placebo-ADT (HR 0.39; 95% CI 0.30–0.50; p= 0.001; median not reached vs. 19.0 months). Due to the immaturity of the study and the median duration of OS, median OS was not reached in either arm and no survival differences were observed between the two arms. Prior docetaxel of up to six cycles was allowed, and 18% (205) men received at least one dose of docetaxel prior to randomization; subgroup analysis showed that rPFS benefit was seen in both chemotherapy-treated and chemotherapy-naive patients. As well, although 35% (405 patients) of men were low-volume based on CHAARTED criteria, benefit in rPFS with enzalutamide-treated patients was seen regardless of volume of disease.

  ENZAMET was an open-label clinical trial that randomized 1125 men with mCNPC/mCSPC to receive ADT and enzalutamide daily (160 mg) or a non-steroidal antiandrogen (NSAA: bicalutamide, nilutamide, or flutamide), with a primary endpoint of OS. There was an OS benefit in the enzalutamide plus ADT arm compared to NSAA (HR 0.67; 95% CI 0.52–0.86; p=0.002). Kaplan-Meier estimates of OS at three years were 80% in the enzalutamide group and 72% in the NSAA arm. Unlike ARCHES, concurrent use of docetaxel was allowed and the decision to treat with chemotherapy was at the discretion of the investigator. Use of chemotherapy was well-balanced between the two arms (45% of those receiving enzalutamide and 44% of those receiving a NSAA planned for early docetaxel use). In a subgroup analysis, the benefits of enzalutamide on OS appeared only in the group without planned early docetaxel use (concurrent docetaxel: HR 0.9; 95% CI 0.62–1.31; no concurrent docetaxel: HR 0.8; 95% CI 0.59–1.07). Although the authors state that the study is underpowered and data is too immature to specifically answer whether combination docetaxel and enzalutamide is beneficial in mCNPC/mCSPC, these results demonstrate that this combination should not be used until further evidence is shown for its benefits.

- Apalutamide (240 mg) is a treatment option for men with mCNPC/mCSPC regardless of volume of disease (Level ofevidence 1, Strong recommendation).

  Hintergrundinformationen

  Apalutamide inhibits the AR by preventing its nuclear translocation and DNA binding. The first large, randomized clinical trial assessing apalutamide in mCNPC/mCSPC was the TITAN trial, which randomized 1052 men with mCNPC/ mCSPC (any) to receive apalutamide (240 mg once daily) plus ADT or ADT alone. As well, 10.7% received previous docetaxel therapy and 37.3% had low-volume disease. With a median of 22.7 months of followup, rPFS at 24 months was 68.2% in the apalutamide group and 47.5% in the placebo group (HR 0.48; 95% CI 0.39–0.60; p<0.001). Benefit with apalutamide in rPFS was seen regardless of prior chemotherapy use or disease burden. OS at 24 months was also greater with apalutamide than with placebo (82.4% in the apalutamide group vs. 73.5% in the placebo group; HR 0.67; 95% CI 0.51–0.89; p=0.005).35 Benefit with apalutamide in OS was seen regardless of disease burden.

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National Institute for Health and Care Excellence (NICE), 2019 [16].

NICE

Prostate cancer: diagnosis and management.

[B] Evidence review for docetaxel in people with hormone sensitive prostate cancer.

NICE guideline NG131. Evidence review

Zielsetzung/Fragestellung

- What is the most clinically- and cost-effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive locally-advanced prostate cancer?
- What is the most clinically- and cost-effective scheduling of docetaxel added to standard treatment for the treatment of hormone-sensitive metastatic prostate cancer?

Methodik

Grundlage der Leitlinie

- transparentes Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Regelmäßige Überprüfung der Aktualität gesichert. Last updated 15 December 2021

Recherche/Suchzeitraum:

- Source searched for this review question: Cochrane Database of Systematic Reviews – CDSR (Wiley), Cochrane Central Register of Controlled Trials – CENTRAL (Wiley), Database of Abstracts of Reviews of Effects – DARE (Wiley), Health Technology Assessment Database – HTA (Wiley), EMBASE (Ovid), MEDLINE (Ovid), MEDLINE In-Process (Ovid), PubMed (NLM)
- The clinical searches were conducted in October 2017

LoE/ GoR

- Keine Angaben
- *Anmerkung FBMed:* NICE verzichtet in der Regel auf die Auszeichnung der Stärke der Empfehlung, sondern realisiert das über die Formulierung (Wording):
  - must/must not
  - should/should not
  - could/could not
  - For reccomendations on interventions that should be used (strong) use direct instructions rather than using the word „should“. Use verbs such as „offer“, „refer“, „advise“, and „discuss“

Sonstige methodische Hinweise

- This review was conducted as part of a larger update of the NICE Prostate Cancer guideline (CG175).
- Quality assessment: RoB und CASP
- GRADE was used to assess the quality of evidence for the selected outcomes as specified in ‘Developing NICE guidelines: the manual (2014)’.
- Die nachfolgend dargestellten Empfehlungen zur Behandlung der metastasierten Prostatakarzinoms entstammen der Online-Publikation der NICE-Leitlinie. Die Hintergrundinformationen (Review) adressieren ausschließlich das metastatisierte hormonsensitive Prostatakarzinom und gehören zur Empfehlung 1.5.6.

- Die Informationen zur Methdodik beziehen sich ausschließlich auf das Review zum metastatisierten hormonsensitiven Prostatakarzinom.

Empfehlungen

1.5 Metastatic prostate cancer

Treatment

1.5.6 Offer docetaxel chemotherapy to people with newly diagnosed metastatic prostate cancer[1] who do not have significant comorbidities as follows:

• start treatment within 12 weeks of starting androgen deprivation therapy and

• use six 3-weekly cycles at a dose of 75 mg/m2 (with or without daily prednisolone). [2019]

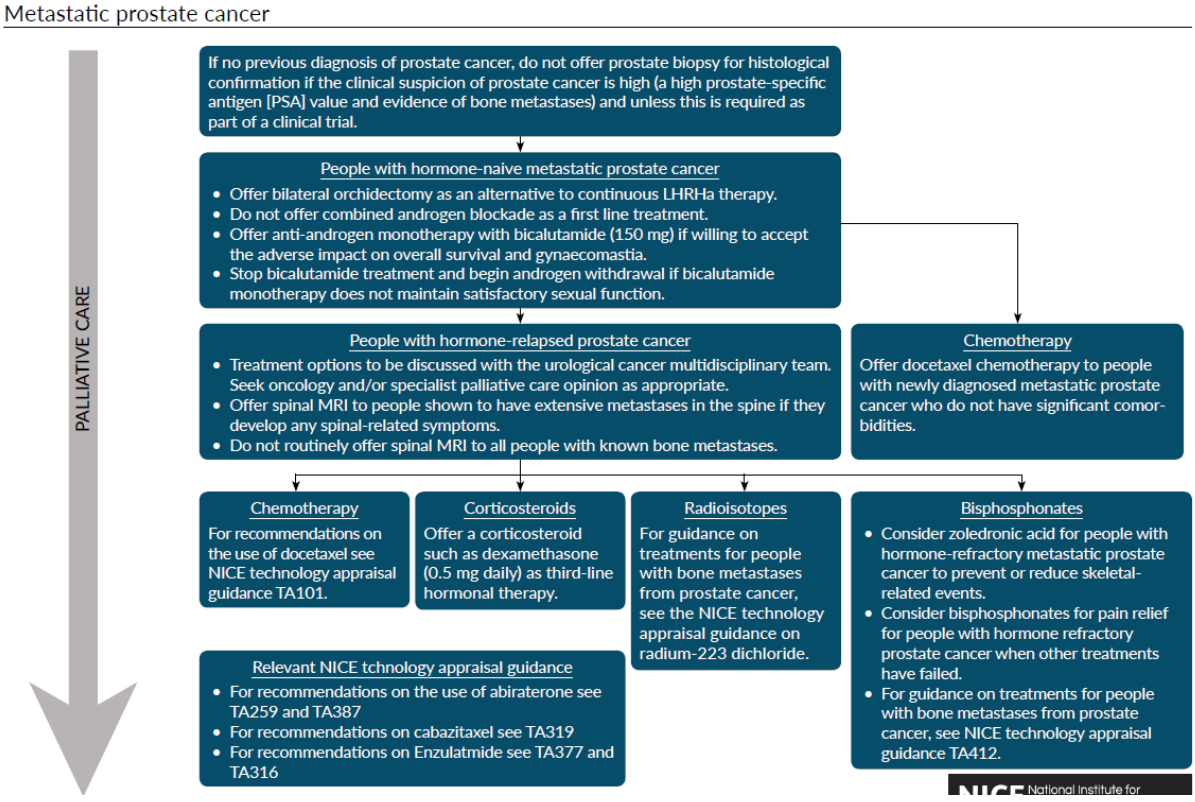
To find out why the committee made the 2019 recommendation on docetaxel chemotherapy and how they might affect practice, see rationale and impact.

1.5.7 Offer bilateral orchidectomy to all people with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy. [2008]

1.5.8 Do not offer combined androgen blockade as a first-line treatment for people with metastatic prostate cancer. [2008]

1.5.9 For people with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia with the aim of retaining sexual function, offer anti-androgen monotherapy with bicalutamide[6] (150 mg). [2008]

1.5.10 Begin androgen deprivation therapy and stop bicalutamide treatment in people with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function. [2008]



Hintergrundinformation:

Hormone-sensitive metastatic prostate cancer

Three randomised controlled trials where included in this review. All three unique studies where directly applicable as they adhered to the protocol.

Table 3: Docetaxel doses used in the studies

Study (location)	Study arms (total sample size)	Doses
STAMPEDE James 2016 (United Kingdom)	ADT (plus radiotherapy) versus ADT plus docetaxel	75mg/m2 every 3 weeks for 6 cycles with 10mg of prednisolone daily and standard premedication before each injection
STAMPEDE James 2016 (United Kingdom)	ADT plus zoledronic acid versus ADT plus zoledronic acid plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles with 10mg of prednisolone daily and standard premedication before each injection 4mg of zoledronic acid every 3-4 weeks for 2 years
GETUG-15 Gravis 2013 (France)	ADT alone versus ADT plus docetaxel	75mg/m^2 of intravenous docetaxel in a 250cm^3 5% glucose solution in the course of 1h on the first of each 21 day cycle for up to 9 cycles. Premedication with corticosteroid (8mg dexamethasone or equivalent) given orally in the evening before the infusion of docetaxel on the day of docetaxel infusion and on the next day.
CHAARTED Sweeney 2015 (USA)	ADT (luteinizing hormone-releasing hormone agonist or luteinizing hormone-releasing hormone antagonist or surgical castration) versus ADT plus docetaxel	75mg/m2 of docetaxel every 3 weeks for 6 cycles, with 8mg of oral dexamethasone at 12 hours, 3 hours and 1 hour before docetaxel infusion. Daily prednisolone was not required.

Outcomes and sample sizes

The reported outcomes where data was extractable were

- Overall survival
- Clinical progression-free survival defined as failure-free survival expressed as time from randomisation to first evidence of at least one of-: biochemical failure (defined as a rise of 50% above the within-24-week nadir and above 4ng/ml confirmed by rest or treatment), progression either locally, in lymph nodes, or in distant metastases or death from cancer (STAMPEDE James et al. 2016)
- Biochemical progression free survival.
- Prostate cancer-specific survival
- Quality of life

The sample sizes ranged from 385 to 1,776 participants across the studies

Adverse outcomes were only reported for the treatment arm, therefore analysis could not be carried out. An adverse outcome table is included in appendix E.

Appendix E – Clinical evidence tables

Hormone-sensitive metastatic prostate cancer

Short Title	Title	New column	New column
Gravis (2013)	Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial	**Study type** Randomised controlled trial **Associated studies** Gravis G, Boher J M, Joly F, Soulie M, Albiges L, Priou F, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Theodore C, Deplanque G, Ferrero J M, Culine S, Mourey L, Beuzeboc P, Habibian M, Oudard S, and Fizazi K (2016) 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. European Urology 70(2), 256-262 **Study details** Study location 29 Centres in France and 1 centre in Belgium Study setting Hospital Study dates	**Random sequence generation** Low risk of bias Randomisation was done by a clinical research organisation and was centralised nationally. **Allocation concealment** High risk of bias Patients, physicians, and data analysts were not masked to treatment allocation **Blinding of participants and personnel** High risk of bias Open label study **Blinding of outcome assessment** High risk of bias Open label study **Incomplete outcome data** Low risk of bias

Short Title	Title	New column	New column
		Oct 18, 2004, and Dec 31, 2008 Duration of follow-up Median follow-up 6 years, 11 months **Sources of funding** French Health Ministry and Institut National du Cancer (PHRC), Sanofi -Aventis, AstraZeneca, and Amgen **Inclusion criteria** Aged more than 18 years Histologically confirmed adenocarcinoma and radiologically proved metastases Karnofsky score of at least 70%; A life expectancy of at least 3 months Adequate hepatic, haematological and renal function **Exclusion criteria** Previous chemotherapy for metastatic disease severe cardiac disease Had surgical castration before metastatic disease occurred had peripheral neuropathy (at least grade 2) A history of another cancer in the past 5 years **Sample characteristics** Sample size 385 patients Split between study groups %female all male - prostate cancer Mean age (SD) ADT plus docetaxel - 63(57-68) ADT alone - 64(58-70) **Interventions** ADT and Docetaxel patients received 75 mg/m² intravenous docetaxel in a 250 cm³ 5% glucose solution in the course of 1 h on the	none identified **Selective reporting** Low risk of bias none identified **Overall risk of bias** Moderate Patients, physicians, and data analysts were not masked to treatment allocation. the study was an open label study, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable

Short Title	Title	New column	New column
		first day of each 21-day cycle. Treatment with docetaxel continued for up to nine cycles on the basis of the median exposure reported in the TAX 327 trial, ADT alone **Outcome measure(s)** Overall survival Clinical progression-free survival; cPFS biochemical progression-free survival; bPFS	
James (2016)	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	**Study type** Randomised controlled trial **Study details** Study setting Hospital **Study dates** October 2005 and March 2013 Duration of follow-up 6 weekly to 6 months, 12 weekly to 2 years, 6 monthly to 5 years then annually (Median follow up – 3 years, 6 months) **Sources of funding** Cancer Research Uk, MedicalResearch Council, Novartis, Sanofi-Aventis, Pfizer, Janssen, Astellas, NIHR Clinical Research Network, Swiss Group for Clinical Cancer Research **Inclusion criteria** Newly diagnosed with prostate cancer- as metastatic, node positive or high-risk locally advanced (with at least two of T3/4, Gleason score of 8-10, and prostate-specific >/= 40ng/ml) Or previously treated with radical surgery, radiotherapy or both and relapsing with high-risk features	**Random sequence generation** Low risk of bias Patients were randomised centrally using a computerised algorithm, developed and maintained by the trials unit. **Allocation concealment** High risk of bias Authors state "..Masking to treatment allocation was considered impracticable and of limited value given the primary outcome measure" **Blinding of participants and personnel** High risk of bias As above **Blinding of outcome assessment** Low risk of bias Authors state "Cause of death was determined by masked central review..." **Incomplete outcome data** Low risk of bias None identified

Short Title	Title	New column	New column
		No age restrictions **Exclusion criteria** severe cardiac disease **Sample characteristics** Sample size 1776 patients Split between study groups Mean age (SD) Median age (range) = 65 years (40-84) **Interventions** Docetaxel and standard of care 75mg/m2 was given for six 3-weekly cycles with 10mg of prednisolone daily and standard premedication before each injection. Standard of care Hormone therapy for at least 2 years with gonadotropin-releasing hormone agonists or antagonists or only between 2006 and 2011 for patients with non-metastatic disease, oral anti-androgens alone. Radiotherapy was encouraged for patients with N0M0 disease until November 2011. Outcome measure(s) Overall survival Failure-free survival Time from randomisation to 1st evidence of at least one of the following - biochemical failure, progression either locally, in lymph nodes or in distant metastases or death from prostate cancer	**Selective reporting** Low risk of bias None identified **Other sources of bias** Unclear risk of bias the exclusion criteria mentioned that participants had to be newly diagnosed with prostate cancer, 6% of participants had recurrent Prostate cancer **Overall risk of bias** Moderate No details were provided on sequence generation and blinding, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable
Sweeney (2015)	Chemohormonal therapy in metastatic	**Study type** Randomised controlled trial	**Random sequence generation** High risk of bias The study was randomised however no details

Short Title	Title	New column	New column
	hormone-sensitive prostate cancer	**Study details** Study location Study setting Hospitals **Study dates** July, 2006– November, 2012 Duration of follow up Median follow-up 2 years, 5 months Sources of funding National cancer institut, National Institutes of Health, Department of Health and Human Services and by grants from the Public health services, Sanofi provided the docetaxel and grant to ECOG-ACRIN **Inclusion criteria** Pathological disease of prostate cancer or dora clinical scenario consistent with prostate cancer elevated PSA Radiologic evidence of metastatic disease ECOG performance score of 0, 1, 2 Planned use of combined androgen blockade for more than 30 days or agents approved for prevention of skeletal related events in castration disease (zoledronic acid or denosumab) **Exclusion criteria** None reported **Sample characteristics** Sample size 790 patients Split between study groups Mean age (SD) Not provided - median (range) =64years (36-91)	provided on random sequence generation **Allocation concealment** Unclear risk of bias no details provided **Blinding of participants and personnel** Unclear risk of bias No details provided **Blinding of outcome assessment** Unclear risk of bias no details provided **Incomplete outcome data** Low risk of bias none identified **Selective reporting** Low risk of bias none identified **Other sources of bias** Low risk of bias none identified **Overall risk of bias** Moderate No details were provided on sequence generation and blinding, however as the primary outcomes are subjective the study was rated as moderate risk of bias **Directness** Directly applicable

Short Title	Title	New column	New column
		Interventions ADT and Docetaxel 75mg/m2 every 3 weeks for 6 cycles ADT alone **Outcome measure(s)** Overall survival Clinical progression-free survival; cPFS Time to castration-resistant prostate cancer	

Table 9: Adverse events - Metastatic prostate cancer

Study	Authors description of adverse events	Number (%)
CHAARTED Sweeney 2016	Only docetaxel group was reported - 1 patient had a grade 5 adverse event. 111 patients had grade 3-4 adverse events. The most frequent adverse events were neutropenia (12.1%), febrile neutropenia (6.1%) and fatigue 4.1%	111/390 (28%)
GETUG-15 Gravis 2013	2 patients had grade 5 adverse events. It is unclear how many patients had at least one grade 3-4 adverse event. The most frequent adverse events at grade 3-5 were neutropenia (32%, febrile neutropenia (7%), erectile dysfunction (8%) and decreased lobido (6%)	
STAMPEDE James 2016 (also applies to the locally advanced prostate cancer)	5 patients had grade 5 adverse events and 298 patients had grade 3-5 adverse events in the group that received docetaxel treatment. The most frequent adverse events were endocrine disorder (10% of the intervention group), febrenile neutropenia (15% of the intervention group) and neutropenia (12% of the intervention group)	

Quality assessment of clinical studies included in the evidence review

Appendix G – GRADE tables

Hormone-sensitive metastatic prostate cancer

Docetaxel (combined with ADT) versus Standard of Care (hormone therapy or ADT)

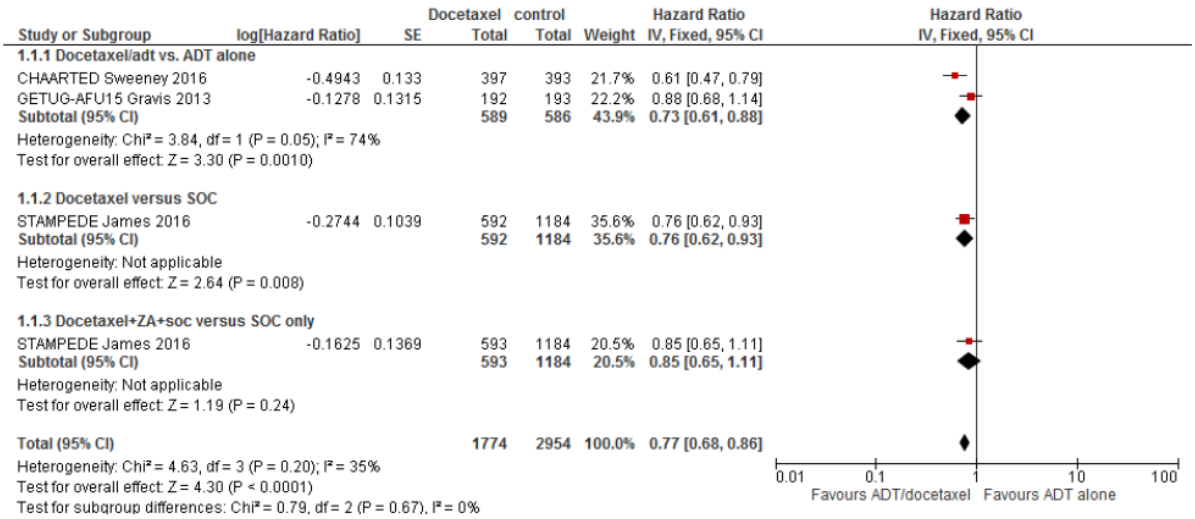
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Overall survival – HR <1 favours docetaxel group										
3 studies GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015, STAMPEDE James 2016	RCTs	2617	HR 0.77 (0.68, 0.86)	-	-	Not serious	Not Serious	Not serious	Not serious	High
Subgroup Analysis - • **Overall survival by dose 75mg/m2 of Docetaxel delivered every 3 weeks for 6 cycles– HR <1 favours docetaxel group**										
2 Studies STAMPEDE James 2016, CHAARTED Sweeney 2015	RCTs	2233	HR 0.74 (0.64, 0.84)	-	-	Not serious	Not serious	Not serious	Not serious	High
• **Overall survival by dose 75mg/m2 of Docetaxel delivered every 3 weeks for 9 cycles – HR <1 favours docetaxel group**										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	HR 0.88 (0.68, 1.14)	-	-	Not serious	N/A	Not serious	Serious[1]	Moderate
• **Overall survival – high volume disease - HR <1 favours docetaxel group**										
2 Studies	RCTs	183	HR 0.67 (0.54, 0.83)	-	-	Not serious	Not serious	Not serious	Not serious	High

No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015										
Overall survival – low volume disease - HR <1 favours docetaxel group										
2 Studies GETUG-AFU15 Gravis 2013, CHAARTED Sweeney 2015	RCTs	202	HR 0.87 (0.61, 1.23)	-	-	Not serious	Not serious	Not serious	Not serious	High
Clinical progression-free survival/ Failure-free survival/Relapse-free survival– HR <1 favours docetaxel group										
3 Studies GETUG-AFU15 Gravis 2013, STAMPEDE James 2016, CHAARTED Sweeney 2015,	RCTs	2617	HR 0.62 (0.57, 0.77)	-	-	Not serious	Not serious	Not serious	Not serious	High
Biochemical progression free survival – HR <1 favours docetaxel group										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	HR 0.67 (0.54, 0.83)	-	-	Not Serious	N/A	Not serious	Not serious	High
Prostate cancer specific survival – HR <1 favours docetaxel group										

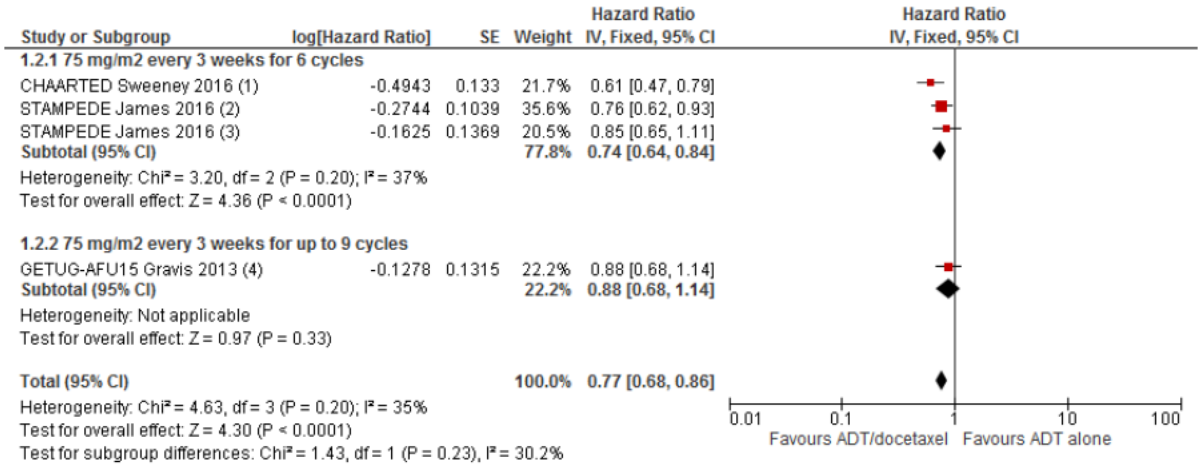
No. of studies	Study design	Sample size	Effect size (95% CI)	Absolute risk: control	Absolute risk: intervention (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
1 study STAMPEDE James 2016	RCT	1442	HR 0.81 (0.66, 0.98)	-	-	Not serious	N/A	Not serious	Not serious	High
Quality of life scores during treatment phase (@ 6months) – EORTC – MD >1 favours docetaxel group										
1 Study GETUG-AFU15 Gravis 2013	RCT	385	MD -9.08 (-12.79, -5.37)	-	-	Serious[2]	N/A	Not serious	Not serious	Moderate

1. 95% confidence intervals crosses the line of no effect – downgraded once
2. Moderate risk of bias – due to self-completed questionnaires , downgraded once

Overall survival



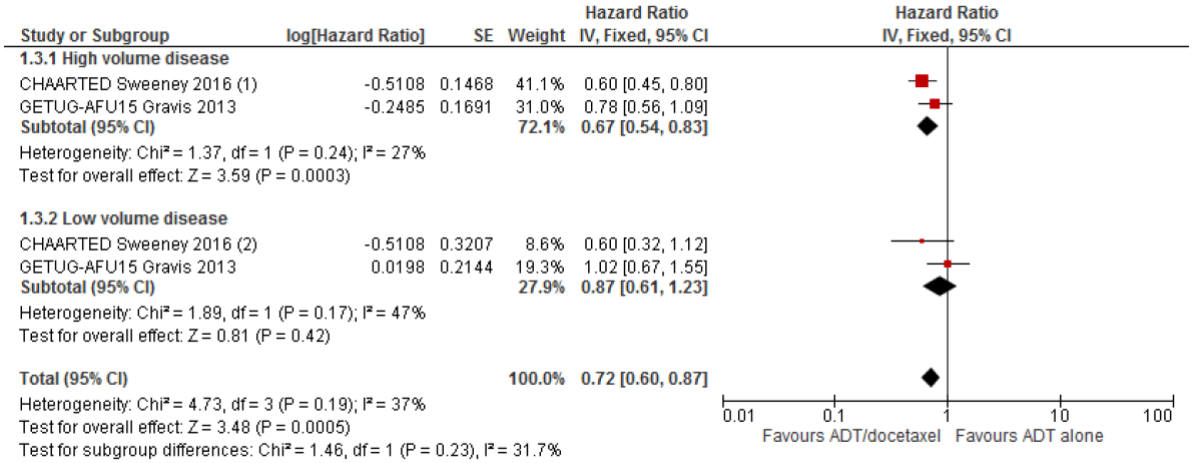
Overall survival stratified by dose



Footnotes

(1) ADT and Docetaxel vs ADT alone
(2) Docetacel alone vs SOC
(3) Doxetacel and Zoledronic Acid and SOC
(4) ADT and Docetaxel vs ADT alone

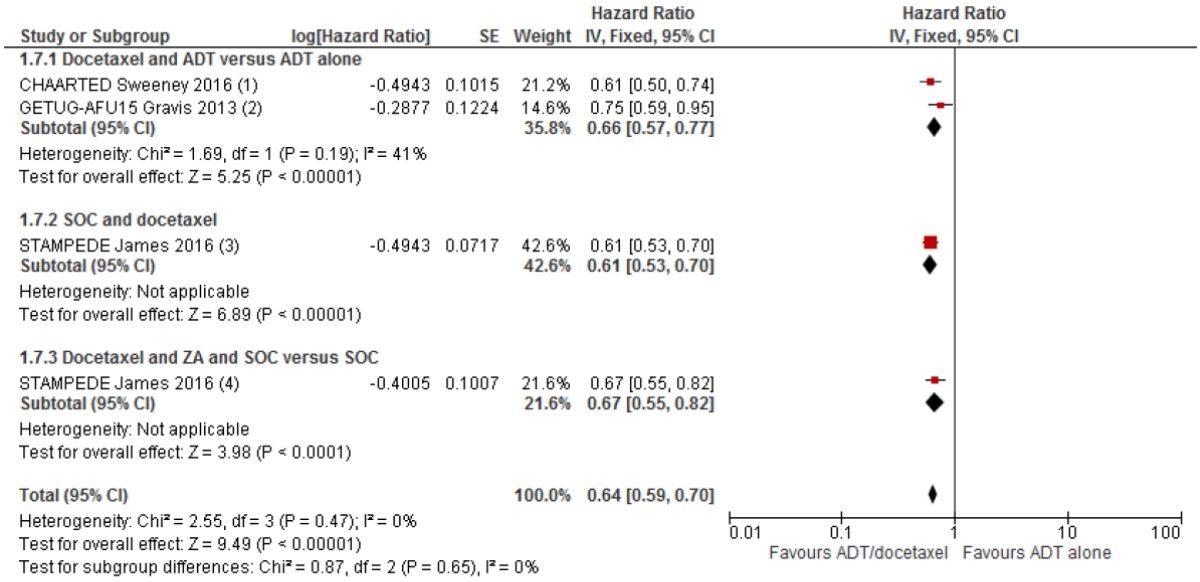
Overall survival by high volume or low volume disease



Footnotes

(1) high volume disease defined as the presence of visceral metastases or at least 4 bone lesions
(2) not meeting the HVD criteria

Clinical progression free survival



High-quality evidence from up to 2 RCTs reporting data on up to 1,442 people with hormone-sensitive metastatic prostate cancer found that quality of life scores during the treatment phase worsened in those receiving docetaxel compared to those receiving standard care alone (defined as either hormone therapy or androgen deprivation therapy).

Moderate-quality to high-quality evidence from up to 3 RCTs reporting data on up to 2,617 people with hormone-sensitive metastatic prostate cancer found overall survival, prostate cancer-specific survival, clinical progression-free survival and biochemical progression-free survival was prolonged in those receiving docetaxel compared to those receiving standard care alone (defined as androgen deprivation therapy). Subgroup analysis of the evidence showed there was improved overall survival in those receiving a dose of 75mg/m2 of docetaxel delivered every 3 weeks for up to 6 cycles and those with high volume disease and could not differentiate overall survival in those receiving the same dose of docetaxel delivered every 3 weeks for up to 9 cycles and those with low volume disease.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that the critical outcomes were overall survival, clinical progression-free survival and adverse events as these had the most impact on the patients. The committee noted that the definition of clinical progression-free survival differed across the studies; however all the studies included biochemical progression (as measured by an increase in prostate-specific antigen [PSA]). The committee raised concerns that this was a laboratory marker, but agreed this was a sufficient marker as an increase in PSA has an impact on the treatment of the patient in practice.

The quality of the evidence

All 6 included studies were at moderate or high risk of bias owing to the lack of blinding of participants and investigators as the studies were open label. The largest study was from the United Kingdom (STAMPEDE (James et al. 2016)). The committee agreed that the evidence presented was representative of current practice and acknowledged that the

evidence (especially for high-risk non-metastatic prostate cancer) was likely to become more definitive as more study data becomes available.

The committee was interested in reviewing the evidence for populations with high-risk non-metastatic prostate cancer and those with metastatic prostate cancer. The review question specified high-risk prostate cancer as locally advanced; the committee felt that there was no universal definition of locally advanced or localised prostate cancer. As a result they referred to non-metastatic cancer as just high-risk prostate cancer. The committee agreed to apply the inclusion criteria from studies in non-metastatic disease as the working definition of high-risk prostate cancer for this evidence review.

Three studies (STAMPEDE (James et al. 2016), GETUG-15 (Gravis et al. 2013) and CHAARTED (Sweeney et al.2015)) contributed evidence for the metastatic prostate cancer population group and 3 studies contributed evidence for the high-risk prostate cancer population group (STAMPEDE (James et al. 2016), TAX 3501 (Schweizer et al. 2014) and Getug-12 (Fizazi et al. 2015). The STAMPEDE trial contributed evidence to both populations.

Despite the relatively small number of studies, the committee appreciated that the studies had large sample sizes ranging from 228 to 1,776 participants.

The GETUG-15 study included the estramustine in the same arm as docetaxel. The committee agreed to not downgrade or exclude this study because it that docetaxel given with estramustine was equivalent to docetaxel given with prednisolone in the other studies. This is reflected by the fact that the results from GETUG study was consistent with the results from the other studies in the meta-analysis.

The committee was also interested in the dose and frequency of docetaxel and whether or not daily prednisolone was used in conjunction with docetaxel. Two of the 3 studies (GETUG-12 (Fizazi et al. 2015) and STAMPEDE (James et al, 2016)) whose population had high-risk prostate cancer included prednisolone as part of their treatment. Only one (STAMPEDE (James et al. 2016)) of the metastatic prostate cancer studies included it.

The doses of docetaxel were similar at 75 mg/m2 in all 3 metastatic prostate cancer studies. However the GETUG-AFU15 (Gravis et al. 2013) study delivered docetaxel for up to 9 cycles every week unlike the STAMPEDE (James et al. 2016) and CHAARTED (Sweeney et al. 2016) studies which delivered for up to 6 cycles.

The committee acknowledged that, though the studies termed clinical progression-free survival as either failure-free survival (STAMPEDE (James et al. 2016)), relapse-free survival (GETUG-12 (Fizazi 2015)), progression-free survival (TAX 3501 (Schweizer et al. 2013)) and clinical progression (CHAARTED (Sweeney et al. 2016) and GETUG-AFU15 (Gravis et al. 2013)), they all included change in prostate-specific antigen in their definitions, among other elements such as death from cancer, distant metastases and proven local relapse.

Overall, when the evidence was assessed using GRADE, the majority of the of it was of moderate to high quality, this was due to precise 95% confidence intervals mean that the studies were not downgraded for imprecision and the objective nature of the outcomes meant that potential sources of bias such as the open-label status of the studies were unlikely to have an impact on the results.

Benefits and harms

Based on the evidence, the benefit of docetaxel for hormone-sensitive metastatic cancer outweighs the harms. The evidence shows that docetaxel can prolong overall survival and clinical progression-free survival in people with newly diagnosed metastatic prostate cancer who are starting long-term hormone therapy (GETUG AFU15 (Gravis et al. 2013), CHAARTED (Sweeney et al. 2016) and STAMPEDE (James et al.2016)). All 3 studies included androgen deprivation therapy and participants were either hormone naïve or hormone

sensitive. The committee interpreted this to mean participants were newly diagnosed with metastatic prostate cancer.

The STAMPEDE (James et al. 2016) trial reported that docetaxel chemotherapy is associated with a number of adverse events including infections, febrile neutropenia, gastrointestinal and respiratory symptoms in people with either metastatic or high risk prostate cancer. Because the evidence showed survival benefit in those with hormone-sensitive metastatic cancer, the committee agreed that the benefits of docetaxel chemotherapy outweighed the harm. As a result the committee made a strong recommendation for clinicians to offer docetaxel to those people with hormone-sensitive metastatic prostate cancer.

In addition, the committee was able to specify dose and frequency of treatment because the evidence showed an improvement in survival in studies which considered 75mg/m2 of docetaxel every 3 weeks for 6 cycles (CHAARTED (Sweeney et al. 2016) and STAMPEDE (James et al. 2016)). One study (GETUG-AFU15) which considered a dose of 75mg/m2 of docetaxel delivered every 3 weeks for 9 cycles could not detect a difference in survival between the intervention and control group. The committee explained that docetaxel is a highly toxic chemotherapy treatment therefore it is not unexpected that prolonged use is not beneficial.

The committee considered the definition of 'high-risk' non-metastatic prostate cancer and agreed that (based on the inclusion criteria of the Stampede and GETUG-12 studies) for the purposes of these recommendations, high-risk disease meant one or more of the following:

- Stage T3/T4 or
- Gleason score 8-–10 or
- PSA greater than 40ng/ml

The committee also noted that this definition will be different from the one mentioned in the table on risk stratification for people with localised prostate cancer where high risk localised prostate cancer is defined as

- clinical stage ≥T2c or
- PSA >20ng/ml or
- Gleason score 8-10

This is because, the recommendation made here reflects the exact population included in the studies

When considering docetaxel in people with newly diagnosed high-risk non-metastatic prostate cancer, the benefits were not as clear as in those diagnosed with metastatic cancer. The evidence could not detect a difference in overall survival and prostate-specific survival between the intervention and control group. However, the evidence showed that clinical progression-free survival improved in those who received docetaxel compared with those who were on hormone therapy alone. As a result, the committee made a recommendation for clinicians to discuss the benefits and harms of docetaxel chemotherapy with those people who have been diagnosed with high-risk prostate cancer to arrive at a shared decision about docetaxel chemotherapy. The committee emphasised that this should be a joint decision taking into account the person's values and preferences.

Based on the evidence from 2 out of the 3 studies (STAMPEDE (James 2016), and TAX 3501 (Schweizer 2014)), the committee recommended that clinicians should use six 3-weekly cycles at a dose of 75mg/m2. This dose was shown to prolong clinical progression free-survival in men with high-risk non-metastatic prostate cancer. Similar to the regimen in those with hormone-sensitive metastatic cancer this can be with or without daily prednisolone. Only 1 out of the 3 studies (STAMPEDE (James 2016) used daily prednisolone.

Docetaxel chemotherapy was shown to be effective in improving clinical progression-free survival with or without daily prednisolone use.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2022) am 03.01.2022

#	Suchfrage
1	[mh "Prostatic Neoplasms"]
2	(prostate OR prostatic):ti,ab,kw
3	(cancer* OR tum*r* OR carcinoma* OR neoplas* OR adenocarcinoma* OR sarcoma* OR lesions* OR malignan*):ti,ab,kw
4	#1 OR (#2 AND #3)
5	#4 with Cochrane Library publication date from Jan 2017 to present

Systematic Reviews in Medline (PubMed) am 03.01.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	prostatic neoplasms[mh] AND neoplasm metastasis[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	(#2 AND #3) AND (advanced[tiab] OR metastat*[tiab] OR metastas*[tiab] OR recurren*[tiab] OR oligometastatic[tiab])
5	#1 OR #4
6	(#5) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR

#	Suchfrage
	review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
7	((#6) AND ("2017/01/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
8	(#7) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 03.01.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	*Suchfrage*
1	prostatic neoplasms[mh]
2	prostate[tiab] OR prostatic[tiab]
3	(((((((((tumor[tiab]) OR tumors[tiab]) OR tumour*[tiab]) OR carcinoma*[tiab]) OR adenocarcinoma*[tiab]) OR neoplas*[tiab]) OR sarcoma*[tiab]) OR cancer*[tiab]) OR lesion*[tiab]) OR malignan*[tiab]
4	#1 OR (#2 AND #3)
5	(#4) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
6	(((#5) AND ("2017/01/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))
7	(#6) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 03.01.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- *Alberta Health Service (AHS)*
- *European Society for Medical Oncology (ESMO)*
- *National Comprehensive Cancer Network (NCCN)*
- *National Cancer Institute (NCI)*

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2022-B-145-z

Kontaktdaten

Bundesärztekammer, Bereich Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 10.05.2022

Indikation gemäß Beratungsantrag

Behandlung des Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinoms bei Erwachsenen

Was ist der Behandlungsstandard in o. g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zunächst ist anzumerken, dass die Definition „Hochrisiko-metastasiertes, hormonsensitives Prostatakarzinom“ unscharf und nicht allgemein gültig akzeptiert ist. Kriterien hierfür sind Höhe des PSA-Wertes, Gleason-Score des Prostatakarzinoms und Anzahl und Lokalisation der Metastasen. In Studien zu Abirateron wurden beispielsweise folgende Kriterien angewendet: Gleason-Score 8 oder höher, mindestens drei Knochenmetastasen und nachweisbare viszerale Metastasen (1).

In Abgrenzung und als Gegensatz zum „Hochrisiko-metastasierten Prostatakarzinom“ wird auch der Begriff „oligometastasiertes Prostatakarzinom“ verwendet, wofür jedoch ebenfalls unterschiedliche Kriterien bestehen; mehr als fünf Metastasen sind laut einer Übersichtsarbeit jedoch nicht gemeint (2).

Aktuell besteht nun eine gute Datenlage darüber, dass die „neuen“ Antiandrogene (Abirateron, Enzalutamid, Apalutamid und Darolutamid) in Kombination mit der konventionellen Hormonentzugstherapie die Prognose beim fortgeschrittenen Prostatakarzinom signifikant verbessern. Die Hormonentzugstherapie (in der Regel mit LHRH-Analoga) wird dabei kontinuierlich fortgeführt und das Antiandrogen zusätzlich oral gegeben. Die Entscheidung über die zusätzliche Gabe eines Antiandrogens hängt dann von der Einschätzung des Behandlers ab, in welcher Situation ein „Hochrisiko-metastasiertes“ Prostatakarzinom diagnostiziert wird. Alle genannten Antiandrogene weisen eine gute Verträglichkeit auf, sodass allgemein die Bereitschaft zum Einsatz dieser Substanzen als eher hoch einzustufen ist.

Ergänzend ist bei Knochenmetastasen die Gabe eines Bisphosphonats indiziert.

Als erste Option wird häufig Abirateron/Prednison eingesetzt. Der Grund dafür mag sein, dass diese Kombination als erste die entsprechende Zulassung erhielt und entsprechend ausreichende Erfahrungen im Umgang damit bestehen.

Alternativ dazu (oder off-label in Sequenz) kommen zahlenmäßig Enzalutamid und Apalutamid etwa gleich häufig zum Einsatz.

Es gibt derzeit keinen Hinweis dafür, dass eines der genannten Antiandrogene überlegen ist und damit als primäre Option eingesetzt werden sollte.

Die Option einer Chemotherapie mit Docetaxel wird aufgrund der schlechteren Verträglichkeit und des höheren Aufwands deutlich weniger häufig gewählt. Unabhängig von der Zulassung hängt dies besonders damit zusammen, dass die meisten Prostatakarzinome durch Urologen diagnostiziert und behandelt werden. Im Gegensatz zu Onkologen haben nur die Minderheit der niedergelassenen Urologen die Zulassung und Möglichkeit für die

Kontaktdaten

Bundesärztekammer, Bereich Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 10.05.2022

Indikation gemäß Beratungsantrag

Behandlung des Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinoms bei Erwachsenen

Durchführung einer Chemotherapie, sodass die Verschreibung eines oral verfügbaren Medikamentes mit guter Verträglichkeit wesentlich attraktiver ist.

Neu hinzugekommen ist die Therapie mit PARP-Inhibitoren (Olaparib, Niraparib, Talazoparib, Rucaparib). Olaparib ist zugelassen beim metastasierten, **kastrationsresistenten** Prostatakarzinom und nachgewiesener BRCA-Mutation. Die Gabe beim hormonsensitiven Prostatakarzinom zusätzlich zu Abirateron wird derzeit in einer Studie evaluiert.

Checkpoint-Inhibitoren (z. B. Pembrolizumab) spielen besonders beim hormonsensitiven Prostatakarzinom derzeit eine untergeordnete Rolle.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des „*Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinoms bei Erwachsenen***“, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Zusammenfassend ist die häufigste Therapieoption beim Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinom die Hormonentzugstherapie in Kombination mit einem Antiandrogen. Die Wahl des Antiandrogens bleibt aufgrund der Datenlage dem Behandler überlassen. Eindeutige Empfehlungen für die Bevorzugung einer Substanz ergaben sich aus der derzeitigen Datenlage nicht.

Eine Chemotherapie wird aufgrund der schlechteren Verträglichkeit und des höheren Aufwands sehr viel seltener in dieser Indikation durchgeführt.

Olaparib und andere zielgerichtete Therapieformen kommen derzeit nur ausnahmsweise und außerhalb der Zulassung (off-label) oder in Studien zur Anwendung.

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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs.

2022-B-145-Z

Kontaktdaten

Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
Deutsche Gesellschaft für Urologie (DGU)

Indikation gemäß Beratungsantrag

Behandlung des Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinoms bei Erwachsenen

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

In der Nachfrage wurde die Fragestellung folgendermaßen spezifiziert:

Es geht um Patienten, die bisher keine systemische Therapie für das metastasierte Stadium erhalten haben. Der pU macht allerdings folgende Ausnahmen, unter der Voraussetzung, dass es unter Therapie nicht zum Progress kam:

- *ADT (medizinische oder chirurgische Intervention zur Senkung des Testosteron-Spiegels) für bis zu 3 Monate vor der Zuweisung zum Behandlungsarm,*
- *bis zu 6 Zyklen Chemotherapie mit Docetaxel in Kombination mit ADT (und kein radiographischer oder PSA-Progress vor der Randomisierung).*

Hochrisiko definiert der pU folgendermaßen:

- *≥ 4 Knochenmetastasen*
- *≥ 1 viszerale Metastasen (z.B. Leber, Lunge und Nebenniere) im CT oder MRT. Lokale Invasion (z.B. Blase) oder Lymphknoten qualifizieren sich nicht als viszerale Metastasen. Eine zuvor bestrahlte viszerale Läsion als einziger Ort der Krankheit ist erlaubt, vorausgesetzt es hat nachfolgend ein Progress stattgefunden.*

Zusammenfassung

Die Therapie des metastasierten, hormonsensitiven Prostatakarzinoms (mHSPC) hat sich in den letzten Jahren grundlegend geändert. Eine umfassende Darstellung der aktuellen Empfehlungen und des Hintergrunds findet sich in der S3 Leitlinie vom Juli 2021 [1]. Die Androgendeprivationstherapie (ADT) wurde durch unterschiedliche Kombinationen erweitert. Empfohlen werden:

metastasiert (M1), ECOG 0-1, hohe Tumorlast	ADT + Docetaxel
metastasiert, ECOG 0-1, Hochrisiko	ADT + Abirateron (+ Prednison/Prednisolon)
metastasiert, ECOG 0-1, ohne weitere Spezifikation	ADT + Apalutamid

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metastasiert, ECOG 0-1, ohne weitere Spezifikation	ADT + Enzalutamid
metastasiert, nicht für Kombinationstherapie geeignet	ADT

Die jeweils neuen Arzneimittel wurden gegen ADT verglichen. Daten zum direkten Vergleich der neuen Kombinationen untereinander liegen bisher nicht vor.

Aktuelle Daten zur Triple-Therapie mit ADT + Abirateron + Docetaxel deuten auf eine weitere Verlängerung der Gesamtüberlebenszeit hin, sind aber noch nicht als Standard eingeführt.

Standard bei Patienten, bei denen eine Heilung durch lokale Intervention mit kurativer Intention (z. B. Prostatektomie oder Bestrahlung) unwahrscheinlich ist, ist die Androgenprivationstherapie (ADT). Diese Patienten waren in die Zulassungsstudien für die oben aufgeführten Kombinationstherapien zum mHSPC nicht eingeschlossen.

Fragestellung

Die Empfehlungen haben sich seit unserer letzten Stellungnahme zu diesem Thema (2022-B-024) vom März 2022) nicht grundlegend geändert, ergänzt sind die Daten zur Triple-Therapie.

Stand des Wissens

Das Prostatakarzinom ist der mit Abstand häufigste maligne Tumor des Mannes [1]. Die Zahl der Neuerkrankungen in Deutschland wird für das Jahr 2020 auf etwa 61.200 geschätzt. Das Prostatakarzinom macht etwa ein Viertel aller Krebserkrankungen bei Männern mit einem mittleren Erkrankungsalter von 72 Jahren aus. Die Inzidenz stieg seit 1980 kontinuierlich aufgrund der Einführung der PSA-gestützten Früherkennung und zuletzt vor allem wegen der demographischen Entwicklung an. Die altersstandardisierte Erkrankungsrate ist seit etwa 10 Jahren konstant. Die Zahl der Todesfälle nach einer Prostatakrebsdiagnose hingegen steigt – trotz sinkender bzw. seit 2007 konstanter Sterberate – jährlich um durchschnittlich 2,3% an. Dafür ist neben steigenden Überlebensraten (relative 5-Jahres-Überlebensrate 2003: 85,9%, 2012: 93,3%) auch eine Zunahme von Personen im höheren Alter verantwortlich.

Das Prostatakarzinom ist primär hormonempfindlich. Die antihormonelle oder hormonablative Therapie kann mit dem Effekt einer Kastration (Orchiektomie, LHRH-Analoga, GnRH-Blocker) durchgeführt werden.

Prostatakarzinomzellen exprimieren Androgenrezeptoren und sind regelhaft hormonempfindlich. Standard bei Fernmetastasen ist die ADT [1, 3]. Sie wird als systemische Therapie durchgeführt. Grundsätzlich ist bei

Kontaktdaten

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Patienten mit lokal fortgeschrittenem, hormonsensitivem Prostatakarzinom auch der Nutzen einer Lokaltherapie (Operation, Strahlentherapie) zu prüfen. Dies betrifft auch die oligometastatische Situation.

In den letzten Jahren hat sich die Überlebenszeit der Patienten durch die Möglichkeiten der kombinierten, hormonablativen Erstlinientherapie mit Docetaxel oder mit Abirateron (plus Prednison / Prednisolon) deutlich verbessert. Die Empfehlungen der aktuellen S3 Leitlinie sind [1]:

7.20	Evidenzbasierte Empfehlung	neu 2021
Empfehlungsgrad **A**	Bei Patienten mit metastasiertem, hormonsensitiven Prostatakarzinom (mHSPC) soll eine Einteilung nach high- und low-volume sowie high- und low-risk erfolgen.	
Level of Evidence **1+ bis 1-**	Literatur: [787–789]	
	Gesamtabstimmung: 98 %	

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Behandlung des Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinoms bei Erwachsenen

7.22	Evidenzbasierte Empfehlung	modifiziert 2021
Empfehlungsgrad **A**	a. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven, Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Apalutamid angeboten werden.	
Empfehlungsgrad **A**	b. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Enzalutamid angeboten werden.	
Empfehlungsgrad **A**	c. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit neu-diagnostiziertem (de novo), metastasierten (M1), hormonsensitiven, high-risk Prostatakarzinom (mHSPC) soll zusätzlich zur Androgendeprivation eine Hormontherapie mit Abirateron (plus Prednison / Prednisolon) angeboten werden.	
Empfehlungsgrad **A**	d. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven, high-volume Prostatakarzinom (mHSPC) soll unter Aufklärung über die im Vergleich zu neuen Hormonsubstanzen höhere Toxizität zusätzlich zur Androgendeprivation eine Chemotherapie mit Docetaxel angeboten werden.	
Empfehlungsgrad **0**	e. Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven, low-volume Prostatakarzinom (mHSPC) kann zusätzlich zur Androgendeprivation eine Chemotherapie mit Docetaxel angeboten werden.	
Level of Evidence **1+ bis 1-**	Literatur: a. [791,792] b. [793] c. [788,789] d. und e. [787,794,795]	
	Gesamtabstimmung: a. 98 %, b. 92 %, c. 86 %, d. 93 %, e. 95 %	

Die diesen Empfehlungen zugrundeliegenden Daten zur ADT und zur Kombinationstherapie können folgendermaßen zusammengefasst werden:

- Die frühe Einleitung einer hormonablativen Therapie führt gegenüber einer verzögerten Therapie in

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einer Metaanalyse von 10 randomisierten Studien wahrscheinlich zu einer Verlängerung der krankheitsspezifischen und der Gesamtüberlebenszeit [4]. Sie reduziert das Risiko von ossären Metastasen.

- Medikamente der ersten Wahl sind GnRH Agonisten oder GnRH-Antagonisten. Die Kombination mit oralen, nicht-steroidalen Antiandrogenen als maximale Androgenblockade führt gegenüber der hormonablativen Therapie zu einer statistisch nicht signifikanten Erhöhung der 5-Jahres-Überlebensrate um 2% [5] und wird nicht mehr empfohlen.
- Bei Patienten in gutem Allgemeinzustand und mit hoher Tumorlast führt die Kombination der ADT mit Docetaxel gegenüber ADT in der Metaanalyse der randomisierten Studien zur Verlängerung des progressionsfreien Überlebens (HR 0,64; Reduktion der Versagensrate nach 4 Jahre um 16%) und zu einer Verlängerung der Gesamtüberlebenszeit (HR 0,77; Überlebensrate nach 4 Jahren + 9%) [6 - 9]. Die Therapie soll innerhalb von 4 Monaten nach Beginn der hormonablativen Therapie beginnen. Dosierung sind 75 mg/m^2 über 6 Zyklen.
    - Von der Therapie mit Docetaxel profitierten in den ersten Studienauswertungen vor allem Patienten mit hoher Tumorlast. Diese war in den prospektiven Studien und den Post-Hoc-Analysen definiert als:
    - viszerale Metastasen <u>oder</u>
    - <u>≥</u>4 Knochenmetastasen mit <u>≥</u>1 Knochenmetastase außerhalb von Becken und Wirbelsäule.
- Die Daten zu den Patienten mit niedriger Tumorlast sind uneinheitlich. Während diese Gruppe in der CHAARTED- und GETUG-AFU15-Studie keinen signifikanten Lebensvorteil erfährt, besteht in der schweizerisch-britischen STAMPEDE-Studie keine Heterogenität zwischen den Behandlungsgruppen mit unterschiedlichem Tumorvolumen (Interaktions-p-Wert: 0,827), d.h. die Chemotherapie ist unabhängig von der Tumorlast von Vorteil [10].
- Eine signifikante Verbesserung des Gesamtüberlebens (HR 0,62) und des progressionsfreien Überlebens (HR 0,43 – 0,47) konnte auch für die Kombination der hormonablativen Therapie mit Abirateron/Prednison bzw. Prednisolon gegenüber einer alleinigen hormonablativen Therapie gezeigt werden [11, 12]. Während in der LATITUDE-Studie nur Patienten mit primär metastasiertem Prostatakarzinom und einem Hochrisiko-Profil (s.u.) eingeschlossen werden konnten, war in der STAMPEDE-Studie eine Behandlung unabhängig von einer lokalen Vortherapie und der Ausdehnung der Metastasierung möglich. Exploratorische Datenanalysen der STAMPEDE-Daten zeigten einen Vorteil für Abirateron / Prednison bzw. Prednisolon unabhängig von der Risikokonstellation und dem Tumorvolumen [13]. Die Zulassung von Abirateron/ Prednison bzw.

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Prednisolon erfolgte allerdings nur für die Patienten mit einer Hochrisikokonstellation. Die Therapie soll innerhalb von 3 Monaten nach Beginn der hormonablativen Therapie beginnen und bis zum Progress fortgeführt werden. Hochrisiko ist in definiert als Vorliegen von mindestens zwei der folgenden drei Risikofaktoren:

  - Gleason-Score von ≥ 8;
  - ossäre Metastasen
  - Vorliegen von messbaren viszeralen Metastasen (ausgeschlossen Lymphknotenbefall)

- Auch die Kombination von Androgenrezeptor-Antagonisten mit ADT ist beim metastasierten, hormonsensitiven Prostatakarzinom wirksam. Die Kombination aus Apalutamid in Ergänzung zu einer AD wurde in TITAN, einer randomisierten, doppelt-verblindeten, placebo-kontrollierten Phase 3 Studie mit insgesamt 1.052 Patienten untersucht [14]. Eingeschlossen wurden Patienten mit dokumentiertem metastasiertem, Hormon-sensitiven Prostatakarzinom (mHSPC) mit einem ECOG Performance Status von 0 oder 1, die eine vorherige AD von bis zu 3 Monaten oder bis zu sechs Zyklen Docetaxel mit AD von bis zu 6 Monaten erhalten haben konnten. Insgesamt zeigt sich ein signifikanter Vorteil zugunsten der Kombination mit Apalutamid beim radiographischen progressionsfreien Überleben (rPFS) sowie in der Gesamtüberlebenszeit (OS). Die Gesamtzahl der unerwünschten Ereignisse (AEs) sowie die Grad 3-5 AEs unterschieden sich nur gering zwischen Interventions- und Kontrollgruppe. Hautausschläge wurden mit Apalutamid deutlich häufiger beobachtet, die Lebensqualität wurde nicht beeinträchtigt [15].
- Die Kombination aus Enzalutamid in Ergänzung zu einer ADT gegenüber einer alleinigen ADT wurde in ARCHES, einer randomisierten, doppelt-verblindeten, placebo-kontrollierten Phase 3 Studie mit insgesamt 1.150 Patienten mit pathologisch bestätigtem metastasiertem, hormon-sensitiven Prostatakarzinom (mHSPC) untersucht [16]. Eingeschlossen wurden erwachsene Patienten mit einem ECOG Performance Status von 0 oder 1, die eine vorherige AD von bis zu 3 Monaten oder bis zu sechs Zyklen Docetaxel mit AD von bis zu 6 Monaten in der Vorbehandlung erhalten haben konnten. In den aktuellen Auswertungen zeigte sich ein signifikanter Vorteil für die Kombination aus Enzalutamid + ADT für den primären Studienendpunkt rPFS. Eine signifikante Verlängerung der Gesamtüberlebenszeit konnte gezeigt werden. Die Gesamtzahl der unerwünschten Ereignisse (AEs) sowie die Grad 3-5 AEs unterschieden sich nur gering zwischen Interventions- und Kontrollgruppe. Die Verschlechterung der Lebensqualität wurde durch Enzalutamid verzögert [17].

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Eine neue Entwicklung ist die sog. Triple-Therapie, bei der ADT, Docetaxel und ein „New Hormonal Agent" kombiniert werden (PEACE-1: Abirateron, ARASENS: Darolutamid). In der PEACE-1-Studie, einer akademischen Studie des europäischen Prostatakarzinomkonsortiums, für Patienten mit de novo metastasiertem Prostatakarzinom führte die Hinzunahme von Abirateron + Prednison zur Hormonchemotherapie zu einer signifikanten Verlängerung des radiologischen, progressionsfreien Überlebens (0,50; 99,9% KI 0,34–0,71; p<0·0001) und einer 25%igen Reduktion des Risikos zu versterben (0,75; 95,1% KI 0,59–0,95; p=0,017) [18]. Besonders ausgeprägt war dieser Vorteil bei Patienten mit hoher Tumorlast mit einem Überlebensvorteil der Triple-Therapie von 1,5 Jahren im Vergleich zur alleinigen Hormon-Chemotherapie (HR 0,72; 95% KI 0,55-0,95; p=0,019). Unklar ist die Bedeutung derzeit noch bei Patienten mit niedrigem Tumorvolumen (0,83; 95%KI 0,50-1,38; p=0,66).

In der ARASENS-Studie erfolgte die Intensivierung der Hormonchemotherapie mit Darolutamid. Auch diese Studie erreichte ihren primären Endpunkt mit einer Absenkung des Risikos zu versterben um 32,5% (HR 0,68; 95% KI, 0,57-0,80; p<0,001). Dabei war der Überlebensvorteil durch die Hinzunahme von Darolutamid über alle Untergruppen hinweg konsistent. Ein Vorteil der Triple-Therapie zeigte sich auch in klinisch relevanten, sekundären Endpunkten wie beispielsweise der Zeit bis zum Übergang in die Kastrationsresistenz, zur Verschlechterung der Schmerzsymptomatik oder dem Auftreten skelettaler Ereignisse. Ähnlich wie in der PEACE-1 Studie wiesen viele Patienten bei Studieneinschluss eine Hochrisikokonstellation auf, obwohl ein Studieneinschluss unabhängig von der Behandlung des Primärtumors und des Gleason-Scores möglich war. Eine Auswertung zur Bedeutung der Tumorlast liegt aktuell nicht vor.

Kritikpunkt an beiden Studien ist der fehlende Vergleichsarm mit einer Kombination aus dem jeweiligen NHA und der ADT. Diese Behandlungsoption war zum Zeitpunkt der Konzeption der Studien noch kein Standard und wurde daher nicht berücksichtigt.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung des „*Hochrisiko-metastasierten, hormonsensitiven Prostatakarzinoms bei Erwachsenen***" die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?**

Ja, diese sind im obigen Text dargestellt.

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