Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2017-B-008-Abirateronacetat

Stand: März 2017

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

Abirateronacetat
[zur Behandlung des hormonsensitiven metastasierten 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 Tabelle II. Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Orchiektomie - Strahlentherapie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse im Anwendungsgebiet: Beschluss vom 19. Juni 2008 über eine Änderung der Richtlinie Methoden Krankenhausbehandlung in Anlage II (Methoden, deren Bewertungsverfahren ausgesetzt sind): Protonentherapie beim Prostatakarzinom.
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:	
Abirateronacetat L02BX03 Zytiga®	Anwendungsgebiet laut Zulassung: 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).
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 LH-RH-Analogon behandelt werden bzw. bei denen bereits eine chirurgische Ablatiotestis 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. (FI Flutamid-CT 250 mg Tabletten, Stand: November 2014)
Bicalutamid L02BB03 Bicalutamid medac	Bicalutamid medac ist angezeigt zur Behandlung des fortgeschrittenen Prostatakarzinoms in Kombination mit einer LHRH-(Luteinisierendes Hormon-Releasing-Hormon)-Analogon-Therapie oder einer operativen Kastration. (FI Bicalutamid medac, Stand: Dezember 2015)
Buserelin L02AE01 Profact®	Profact® Depot 9,45mg 3-Monatsimplantat ist angezeigt zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. Profact® Depot 9,45mg 3-Monatsimplantat ist jedoch nicht angezeigt nach beidseitiger Orchiektomie, da es in diesem Fall zu keiner weiteren Absenkung des Testosteronspiegels kommt. (FI Profact® Depot 9,45 mg, Stand: Juni 2015)
Cyproteron G03HA01 Androcur®	Beim Mann 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. (FI Androcur® 50 mg Tabletten, Stand: September 2014)
Degarelix L02BX02 FIRMAGON	FIRMAGON ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom. (FI FIRMAGON 80 mg, Stand: Oktober 2014)
Goserelin L02AE03 Zoladex®	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist. (FI Zoladex® 3,6 mg, Stand: April 2015)
Leuprorelin	ELIGARD 22,5 mg ist für die Behandlung des hormonabhängigen, fortgeschrittenen Prostatakarzinoms […] indiziert.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L02AE02 ELIGARD	(FI ELIGARD 22,5 mg, Stand April 2015)
Triptorelin L02AE04 Pamorelin LA	Pamorelin LA 3,75mg ist indiziert zur Behandlung des lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. (FI Pamorelin® LA 3,75 mg, Stand: März 2016)

Quellen: AMIS-Datenbank, Fachinformationen, Lauer-Taxe

Gemeinsamer Bundesausschuss

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie (zVT):

Inhalt

Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation Prostatakarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 31.01.2017 abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database), MEDLINE (PubMed), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab 2264 Quellen, die anschließend in einem zweistufigen Screening Verfahren nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Insgesamt ergab dies 17 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Mit Prednison oder Prednisolon in Kombination mit einer Androgenentzugstherapie zur Behandlung von Hochrisiko-Patienten mit neu diagnostiziertem, metastasiertem, hormonnaivem Prostatakarzinom.

Abkürzungen:

ADT	Androgen deprivation therapy
AE	Adverse event
Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CAB	Complete androgen blockade
CAD	Continuous androgen deprivation
CCO	Cancer Care Ontario
CSM	Cancer specific mortality
CSS	Cancer specific survival
CT	Chemotherapy
CVD	Cardiovascular disease
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
EAU	European Association of Urology
EBRT	External beam radiation therapy
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GnRH	Gonadotropin-releasing hormone
IAD	Intermittent androgen deprivation
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
NSAA	Non-steroidal anti-androgen
OS	Overall survival
PC	Prostata carcinom
PFS	Progression free survival
QoL	Quality of life
RCT	Randomised control trial
RT	Radiotherapy
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic review
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

Es sind keine relevanten IQWiG Berichte /G-BA Beschlüsse vorhanden.

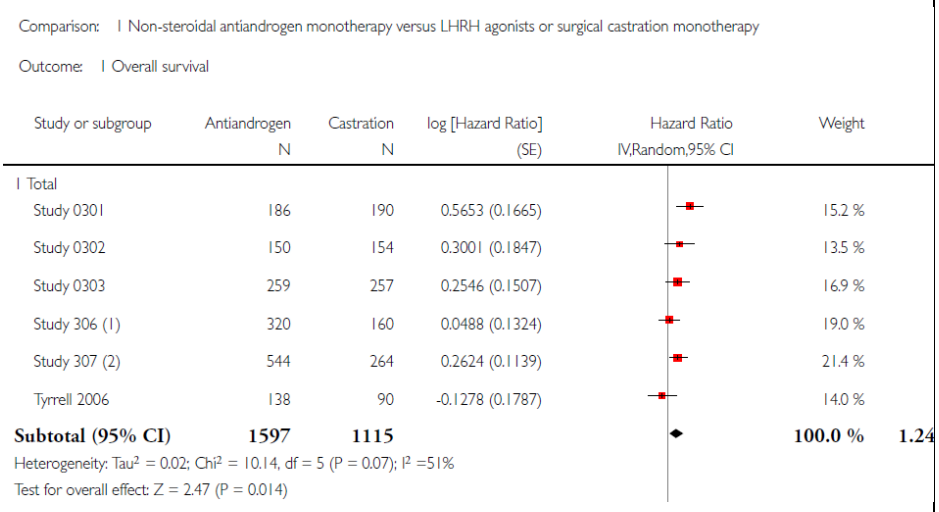
Cochrane Reviews

Kunath F et al., 2014 [8] **Non-steroidal anti-androgen mono-therapy compared with luteinising hormone-releasing hormone agonists or surgical castration mono-therapy for advanced prostate cancer (Review)**	**1. Fragestellung** 1. To assess the effects of non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for treating advanced stages of prostate cancer.

	2. Methodik
	
	• **Population**
	  • men at advanced stages of prostate cancer who had not received prior androgen suppression therapy
	  • prostate cancer that had spread locally outside the prostate gland (locally advanced, T3-4, N0, M0), to regional lymph nodes (local to regionally advanced, T1-4, N1, M0), to the bones or to other areas (advanced, T1-4, N0-1,M1), or those who had recurrent disease after local therapy.
	  • No exclusions were based on age or ethnicity.
	• **Intervention***:* non-steroidal antiandrogen monotherapy
	• **Komparator**: medical or surgical castration monotherapy
	
	We defined medical castration monotherapy as androgen suppression therapy using LHRH agonists (e.g. leuprorelin, goserelin, buserelin, triptorelin).
	
	Bilateral surgical castration included total and subcapsular techniques.
	
	This review did not consider maximal androgen blockade (combination therapy of antiandrogens with medical or surgical castration). However, we did not exclude trials that used antiandrogens as short-term flare protection for up to four weeks after medical castration.
	
	• **Endpunkte**
	
	Primary outcome:
	  • Overall survival
	  • Secondary outcomes
	  • Cancer-specific survival (we assessed data for cancer-specific mortality because data for cancer-specific survival were not available).
	  • Treatment discontinuation due to adverse events
	  • Clinical progression (time from random assignment to progression; determined by an increase in prostatic dimension, appearance of new or increase in existing bone or extraskeletal metastases confirmed by imaging or physical examination).
	  • Biochemical progression (time from random assignment to progression; determined by an increase of more than 25% in

	serum PSA concentration from the nadir value on two determinations). • Treatment failure (determined by death; disease progression, i.e. an increase in prostatic dimensions, appearance of new or increase in existing bone or extraskeletal metastases confirmed by imaging or physical examination; addition of other systemic therapies for prostate cancer; loss to follow-up; refusal to begin or continue with randomly assigned therapy; or discontinuation due to adverse events or for other reasons). • Adverse events, such as breast pain, pelvic pain, bone pain, back pain, headache, abdominal pain, general pain, gynaecomastia, constipation, diarrhoea, vomiting, cardiovascular events, hypertension, loss of sexual interest, asthenia, insomnia, hot flashes, night sweats, anaemia, hepatic enzyme increase, rash, pruritus, dyspnoea, infection, pharyngitis, arthritis, sinusitis, urinary tract infection, dizziness, haemorrhage, haematuria, nocturia, urinary frequency, urinary retention, oedema, anorexia, gastrointestinal disorders, loss of sexual function and lethargy, as well as serious adverse events (defined as adverse events causing death or events that are life threatening, require inpatient hospitalisation, result in persistent or significant disability/ incapacity or require intervention to prevent permanent impairment or damage). • **Suchzeitraum (Aktualität der Recherche):** bis 23. Dezember 2013 • **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 11/ 3060 2. **Qualitätsbewertung der Studien:** followed the domain-based evaluation as described in the Cochrane Handbook for Systematic Reviews of Interventions
	3. Ergebnisdarstellung • Included studies poorly conducted, the quality of evidence was moderate, further research is likely to have an important impact on our confidence in the accuracy of results • no indication of publication bias found by funnel plot asymmetry analysis for primary outcome, risk of publication bias might be low **Overall survival (OS)** • 6 studies (Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) with 2 712 randomly assigned participants measured OS • quality of evidence for this outcome was moderate (Summary of findings for the main comparison) • OS significantly decreased when non-steroidal antiandrogens were used as opposed to castration

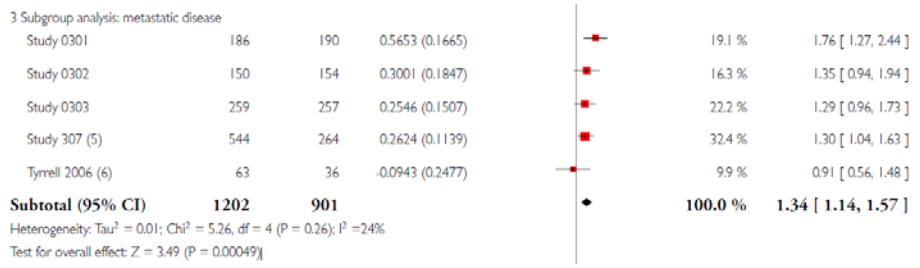
- random-effects model for heterogeneity (I2 = 51%): HR 1.24, 95% CI 1.05 to 1.48



- sensitivity analysis for heterogeneity: after exclusion of the smallest study (Tyrrell 2006), results still showed significant differences with lower heterogeneity (HR 1.31, 95% CI 1.12 to 1.53, I2 = 33%)

Subgroup: disease stage

- 6 studies (Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) showed that OS significantly decreased with non-steroidal antiandrogens in participants with <u>metastatic disease</u> when compared with castration (HR 1.34, 95% CI 1.14 to 1.57, 2103 participants)



<u>Treatment discontinuation due to adverse events (AE)</u>

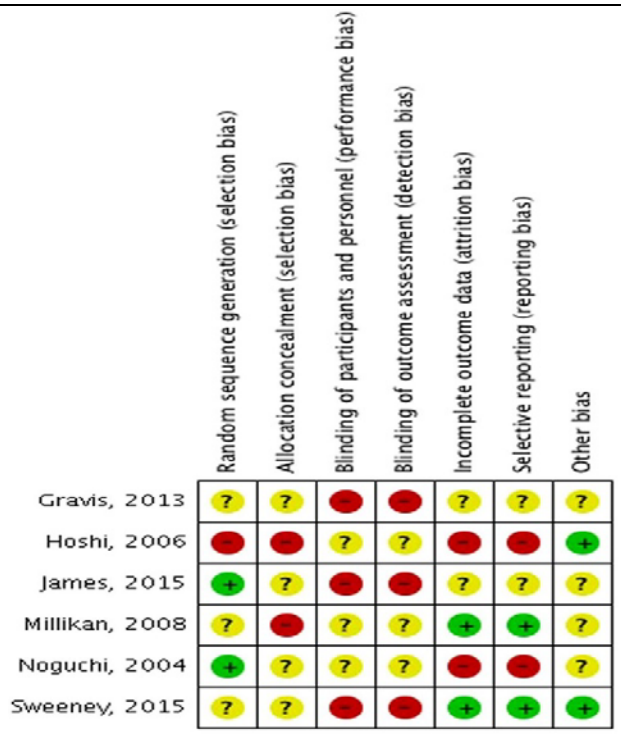
- 8 studies (Boccon-Gibod 1997; Dockery 2009; Sieber 2004; Smith 2004; Study 0301; Study 0302; Study 0303; Tyrrell 2006) with 1 559 randomly assigned participants reported data on treatment discontinuation due to AE
- Non-steroidal antiandrogens significantly increased the rate of withdrawal due to adverse events (RR 1.82, 95% CI 1.13 to 2.94)
- Smith et al 2004: 2 participants in the leuprorelin group discontinued treatment early as the result of adverse events such as hot flashes and fatigue, treatment with bicalutamide

	was interrupted in one participant for three months because of elevated liver enzymes • Sieber et al 2004: 5 of 9 participants who withdrew from the study in the bicalutamide group discontinued treatment as the result of asthenia • Dockery 2009: 2 participants withdrew because of impotence (one in each group for bicalutamide and castration), 2 withdrew because of a skin reaction (both in the bicalutamide group) • Study 0303: 6 participants discontinued treatment (3 with rash and 1 with constipation) • Study 0302: 3 participants withdrew from the study (in the group treated with bicalutamide, one withdrew because of gynaecomastia and back pain; in the group treated with castration, one withdrew because of severe hot flashes) • Boccon-Gibod et al 1997: 4 participants discontinued therapy; 2 were suffering from nausea or vomiting, 1 reported diarrhoea and another showed an increase in hepatic enzymes before discontinuing therapy **clinical progression** • 7 studies (Sciarra 2004a; Study 0301; Study 0302; Study 0303; Study 306; Study 307; Tyrrell 2006) with 2 591 randomly assigned participants included in meta-analyses for clinical progression • non-steroidal antiandrogens significantly increased clinical progression: o one year: risk ratio (RR) 1.25, 95% CI 1.08 to 1.45, 5 studies, 2 067 participants; o 70 weeks: RR 1.26, 95% CI 1.08 to 1.45, 6 studies, 2 373 participants; o two years: RR 1.14, 95% CI 1.04 to 1.25, 3 studies, 1 336 participants • subgroup analyses: nonsteroidal antiandrogens, compared with castration, less favourable for clinical progression in men with metastatic disease **Treatment failure** • 6 studies (Boccon-Gibod 1997; Study 0301; Study 0302; Study 0303; Study 306; Study 307) with 2 411 randomly assigned participants reported data on treatment failure • non-steroidal antiandrogens significantly increased treatment failure: o one year: RR 1.19, 95% CI 1.02 to 1.38, 4 studies, 1 539 participants; o 70 weeks: RR 1.27, 95% CI 1.05 to 1.52, 5 studies, 1 845 participants;

	o two years: RR 1.14, 95% CI 1.05 to 1.24, 2 studies, 808 participants • subgroup analyses: nonsteroidal antiandrogens, compared with castration, less favourable for treatment failure in men with metastatic disease **Adverse events / serious adverse events** • AEs risk decreased when non-steroidal antiandrogens were used o hot flashes (RR 0.23, 95% CI 0.19 to 0.27, 9 studies, 2 774 participants), o haemorrhage (RR 0.07, 95% CI 0.01 to 0.54, 2 studies, 546 participants), o nocturia (RR 0.38, 95% CI 0.20 to 0.69, 1 study, 480 participants), o fatigue (RR 0.52, 95% CI 0.31 to 0.88, 1 study, 51 participants), o loss of sexual interest (RR 0.50, 95% CI 0.30 to 0.83, 1 study, 51 participants), 3. urinary frequency (RR 0.22, 95% CI 0.11 to 0.47, 1 study, 480 participants)
	4. Anmerkungen/Fazit der Autoren Currently available evidence suggests that use of non-steroidal antiandrogen monotherapy compared with medical or surgical castration monotherapy for advanced prostate cancer is less effective in terms of overall survival, clinical progression, treatment failure and treatment discontinuation due to adverse events. Evidence quality was rated as moderate according to GRADE. Further research is likely to have an important impact on results for patients with advanced but non-metastatic prostate cancer treated with non-steroidal antiandrogen monotherapy. However, we believe that research is likely not necessary on non-steroidal antiandrogen monotherapy for men with metastatic prostate cancer. Only high-quality, randomised controlled trials with long-term follow-up should be conducted. If further research is planned to investigate biochemical progression, studies with standardised follow-up schedules using measurements of prostate-specific antigen based on current guidelines should be conducted. ***5. Kommentar zum Review*** *Reviewpopulation umfasst verschiedene Stadien (lokal fortgeschrittenes PC bis hin zu fortgeschrittenes PC mit Fernmetastasen)*

Systematische Reviews

Ramos-Esquivel A.et al., 2016 [15]. **Androgen-deprivation therapy plus chemotherapy in metastatic hormone-sensitive prostate cancer. A systematic review and meta-analysis of randomized clinical trials** Zur Docetaxel-Fragestellung siehe auch: Botrel TE et al., 2016 [3] Tassinari D, et al. 2016 [16] Vale, C.L. et al. 2016 [17]	1. Fragestellung To assess the efficacy and toxicity of androgen-deprivation therapy (ADT) plus chemotherapy in patients with hormone-sensitive metastatic prostate cancer
	2. Methodik **Population:** patients with newly diagnosed metastatic PCa **Intervention** chemotherapy plus ADT **Komparator:** ADT alone **Endpunkt:** OS; biochemical PFS, clinical PFS, AE **Recherche:** in MEDLINE, EMBASE, and The Cochrane Central Register of Controlled Trials; Proceedings of the American Society of Clinical Oncology annual meeting, American Society of Clinical Oncology Genitourinary Symposium meeting and European Society of Medical Oncology annual meeting Suchzeitraum: 01/2000 -10/2015 **Qualitätsbewertung der Studien:** Cochrane Risk of Bias Tool Meta-analyses with random effects model, assessment of heterogeneity using I^2 statistics No funding source had any role in study design, data collection, data analysis, data interpretation, or writing of this article. **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 6 (n=2675); 5 in Meta-Analyse
	3. Ergebnisse *Study characteristics:* <u>ADT used in the studies:</u> • LHRH agonists + flutamide • Endocrine therapy (included LHRH agonist or surgical castration +/- antiandrogen therapy) • LHRH agonist or surgical castration • Orchiectomy or LHRH agonist, alone or combined with nonsteroidal antiandrogens • Medical or surgical castration • LHRH agonist or antagonist, or surgical castration <u>Chemotherapy used in the studies:</u> • 3 studies with docetaxel (GETUG-AFU 15 Trial, CHAARTED Trial, STAMPEDE trial)



- 2 studies with estramustine,
- 1 study with ketoconazole, doxorubicin, vinblastine and estramustine

Because of unequal interventions, we were only able to perform a meta-analysis for 5 trials that compared docetaxel or estramustine-based chemotherapy plus ADT vs. ADT alone.

<u>Previous treatment:</u>

- Not allowed in 2 studies
- 1 study: Prior hormone therapy was allowed as adjuvant after definitive local therapy and it was given for ≤ 6mo; treatment must be completed ≤12 mo before initiating therapy for metastatic disease.
- 1 study: prior CT for metastatic diesas not allowed; prior CT or ADT were allowed in neoadjuvant or adjuvant setting, but must be discontinued ≤12 mo before inclusion
- 1study: Prior docetaxel not allowed; adjuvant ADT alllowed if duration was ≤24 mo, but must be completed ≤12 mo before inclusion
- 1 study: CT and longterm ADT not allowed, Antiandrogen allowed to cover tumor flare; Adjuvant treatmetn allowed but must be completed ≤ 12mo before inclusion

<u>Risk of bias:</u>

- there were some concerns about the blinding of participants and investigators
- some doubts about the allocation concealment process in all the included trials

Results

Overall survival

- docetaxel plus ADT vs ADT (n=3, 2261 pts.): HR 0,75 [95%KI 0,61; 0,91]; I^2= 51%→ superiority of combination
- Estramustine-based chemotherapy plus ADT vs ADT(n=2, 106 pts.): HR 0,64 [95%KI 0,22; 1,89]; I^2=58% → n.s.
- ketoconazole, doxorubicin, vinblastine and estramustine plus ADT vs ADT (n=1, 306 pts.): Median OS: 6.1 y (experimental) vs. 5.4 y (control); HR 1,14 [95% KI 0,83; 1,56]→ n.s.

Toxicity

- Estramustine-based chemotherapy plus ADT vs ADT alone: similar incidences of AE Grade 3 or higher,
- ketoconazole, doxorubicin, vinblastine and estramustine plus ADT vs ADT alone: 51% of patients in the CT-arm experiencing any ADR grade 3 or higher, especially thromboembolic events and infections vs. 9% of ADR in the control arm
- docetaxel plus ADT vs. ADT alone: a higher rate of neutropenia and febrile neutropenia in the combination arm

Referenzen

[13] GravisG, FizaziK, JolyF, et al. Androgen-deprivation therapy alone or with docetaxelinnon-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149– 58;

[14] Sweeney C J, Chen Y H, Carducci M, et al. Chemohormonaltherapy in metastatic hormone-sensitive prostate cancer. NEnglJMed2015; 373:737–46.

[15] JamesND, SydesMR, ClarkeNW, et al. Addition of docetaxel, zoledronic acid, orbothto first-line long-termhormonetherapyin prostate cancer(STAMPEDE):survival results from an adaptive, multiarm, multistage, platform randomized controlled trial. Lancet 2015. http://dx.doi.org/10.1016/S0140-6736(15)01037-5:pii: S0140- 6736(15)01037-5;

[19] Noguchi M, NodaS,YoshidaM,UedaS,ShiraishiT,ItohK. Chemohormonal therapy as primary treatment for metastatic prostate cancer: a randomized study of estramustine phosphate plus luteinizing hormone-releasing hormone agonist versus flutamide plus luteinizing hormone-releasing hormone agonist. Int J Urol 2004;11:103–9.

[20] Hoshi S,Yamaguchi O,FujiokaT,etal. A randomized comparative study of endocrine monotherapy and a combination of estramustine phosphate with the endocrine therapy in patients with untreated stage D prostate cancer. Int J Clin Oncol 2006;11:303–8.

[21] Millikan RE, Wen S, Pagliaro L C, et al. Phase III trial of androgen ablation with or without three cycles of systemic chemotherapy for advanced prostate cancer. J Clin Oncol 2008;26: 5936–42.

4. Anmerkungen/Fazit der Autoren

Our analysis shows an OS benefit of combining docetaxel-based chemotherapy with ADT in patients with newly diagnosed metastatic prostate cancer. This benefit was not detected with other cytotoxic agents. A longer follow-up of the current trials would clarify which patients benefit the most from this approach.

	5. Kommentare zum Review • *Anwendung der Chemotherapien bei hormonnaiven Patienten entspricht nicht dem Zulassungsstatus* • *Studien zu Estramustin (n=2) jeweils mit < 60 Patienten*
Kunath F et al., 2015 [7]. **Gonadotropin-releasing hormone antagonists versus standard androgen suppression therapy for advanced prostate cancer A systematic review with meta-analysis.** Zu Degarelix-Fragestellung siehe auch Hosseini SA et al., 2016 [6].	1. Fragestellung To evaluate efficacy and safety of gonadotropin-releasing hormone (GnRH) antagonists compared to standard androgen suppression therapy for advanced prostate cancer
	2. Methodik predefined methodology and outcomes of the SR (registration in the prospective registry 'International Prospective Register of Systematic Reviews') **Population:** patients with advanced prostate cancer (= locally advanced (T3-4, N0, M0), local to regionally advanced (T1-4, N1, M0), disseminated disease (T1-4, N0-1, M1) or PSA relapse after local therapy) **Intervention**: GnRH antagonists (abarelix and degarelix) **Komparator**: standard androgen suppression therapy (monotherapy with surgical or medical castration, antiandrogen monotherapy or maximal androgen blockade (combination of either surgical or medical castration with antiandrogens)) **Endpunkt:** OS, cancer specific survival, clinical or PSA progression, treatment failure and quality of life, AE **Recherche:** in CENTRAL, MEDLINE, Web of Science, EMBASE, trial registries and conference books for 12igh quali controlled trials (RCT) for effectiveness data analysis, and 12igh quali or 12igh quality12 controlled studies (non-RCT) for safety data analysis Suchzeitraum: March 2015 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 13 (10 RCT, 3 non-RCT) **Qualitätsbewertung der Studien**: Cochrane Risk of bias Tool for RCT; checklist recommended by Reeves et al for non-RCT; GRADE for assessment of overall quality of evidence
	3. Ergebnisse *Study characteristics* • 6 studies on abarelix vs. leuprolipde or goserelin • 7 studies on degarelix vs. leuprolipde or goserelin *Efficacy* <u>GnRH antagonists vs GnRH agonist</u> • 0 study reported cancer-specific survival or clinical progression.

	• There were no differences in
	  o overall mortality (3 studies on abarelix with 697 pts., 6 studies on degarelix with 2323 pts.; RR 1.35, 95% CI 0.63 to 2.93, I^2=55%)
	  o treatment failure (2 studies on abarelix with 1110pts., 5 studies on degarelix with 1090 pts; RR 0.91, 95% CI 0.70 to 1.17; [but significant difference based on abarelix studies alone: RR 0.66, 95% CI 0.45 to 0.98])
	  o prostate-specific antigen progression (1 studiy on abarelix with 176 pts., 6 studies on degarelix with 2313 pts: RR 0.83, 95% CI 0.64 to 1.06)
	  o quality of life related to urinary symptoms (3 studies on degarelix with 461 pts.])
	• ,improved quality of life regarding prostate symptoms, measured with the International Prostate Symptom Score (IPSS), with the use of GnRH antagonists (degarelix) compared with the use of standard androgen suppression therapy (mean score difference −0.40, 95% CI −0.94 to 0.14, and −1.84, 95% CI −3.00 to −0.69, respectively) was found (n=3, 461 pts).
	• Quality of evidence for all assessed outcomes was rated low according to GRADE.
	Safety
	• no statistically significant differences regarding SAE (RR 0.82, 95% CI 0.62 to 1.08, 7 studies with 2179 patients included), severe/ life-threatening AE (RR 0.76, 95% CI 0.58 to 1.00, 5 studies with 2064 patients included), or discontinuations due to AE (RR 0.86, 95% CI 0.57 to 1.31, 8 studies with 2290 patients included).
	• No statistically significant differences for the predefined adverse events fatigue, hot flushes, infections, loss of sexual interest, sexual dysfunction, asthenia, urinary retention, diarrhoe, or constipation
	• No significant difference in urinary tract infection was observed between the different therapy groups. However, subgroup analysi showed a significant positive effect for degarelix 240/80 or 240/160 mg compared with standard androgen therapy (RR 0.57; 95% CI 0.39 to 0.83, 6 studies with 2328 patients included
	• The risk of injection site pain (RR 7.9 (5.7 to 11.0) or reaction RR 79.6 (11.2 to 564.5), significantly increased with GnRH antagonists compared with standard therapy
	• cardiovascular events may occur less often by using GnRH antagonist (degarelix 240/80 and 240/160 mg) than with standard therapy (RR 0.60, 95% CI 0.38 to 0.94, 6 studies with 2328 patients included)

	4. Anmerkungen/Fazit der Autoren Evidence is hampered by risk of bias, selective reporting, and limited follow-up. Quality of evidence for all assessed outcomes was rated low according to GRADE. There is currently insufficient evidence to make firm conclusive statements on the efficacy of GnRH antagonist compared to standard androgen suppression therapy for advanced prostate cancer. The risk for injection-site events was increased, but cardiovascular events may occur less often using GnRH antagonist. Further 14igh quality research on GnRH antagonists with long-term follow-up is required. *5. Kommentare zum Review* • *Heterogeneity in review population: patients with localized, locally advanced or metastatic disease included* • *Abarelix nicht mehr auf dem Markt* • *Ergebnisse konsistent mit dem SR von Hosseini SA et al., 2016 [6], in dem ebenfalls Degarelix untersucht wurden (4 Studien eingeschlossen)*
Hosseini SA et al., 2016 [6]. **Degarelix for the treatment of advanced prostate cancer compared with GnRh-Agonists: a systematic review and meta-analysis**	1. Fragestellung To compare safety, efficacy and effectiveness of degarelix, a new gonadotropin-releasing hormone (GnRH) antagonist (blocker), versus gonadotropin-releasing hormone (GnRH) agonists.
	2. Methodik **Population:** Patients with advanced prostate cancer **Intervention*:*** ADT using degarelix **Komparator:** ADT using GnRH agonists (including goserelin, leuprolin and triptorelin) with or without anti-androgen therapy; **Endpunkt**: reducing prostate volume, health related quality of life, IPSS score, general survival, reducing testosterone level, reducing PSA level, drug induced side effects; **Recherche** in Ovid MEDLINE (R), Scopus (by Elsevier), Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) and also Google Scholar and related websites; Suchzeitraum: up to 2014 **Anzahl eingeschlossene Studien/Patienten** (Gesamt): 4 (n=1090) **Qualitätsbewertung der Studien**: Cochrane Risk of Bias Tool random effect model for meta-analysis. Heterogeneity was deemed substantial if the I^2 analysis suggested more than 50 % of the variability in an analysis was due to differences between trials. In such outcome measures we did qualitative analysis

3. Ergebnisdarstellung

4 RCT:

- 3 studies compared degarelix with goserelin, Follow up: 3 months
- 1 study compared degarelix with leuprolide, Follow up: 12 months (Klotz 2008, Ivarsen 2011, Tombal 2010)

Hinweis: Iversen 2011 und Tombal 2010 stellen weitere Publikationen der Studie von Klotz dar

Risk of bias

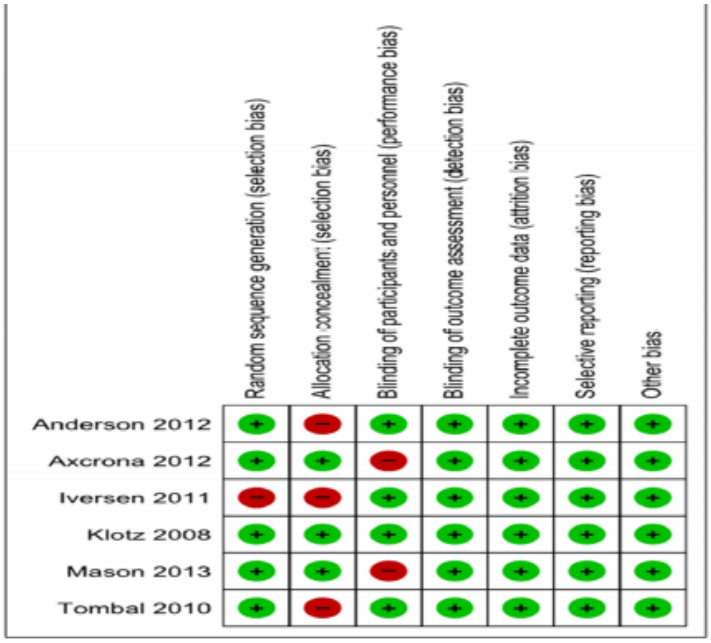


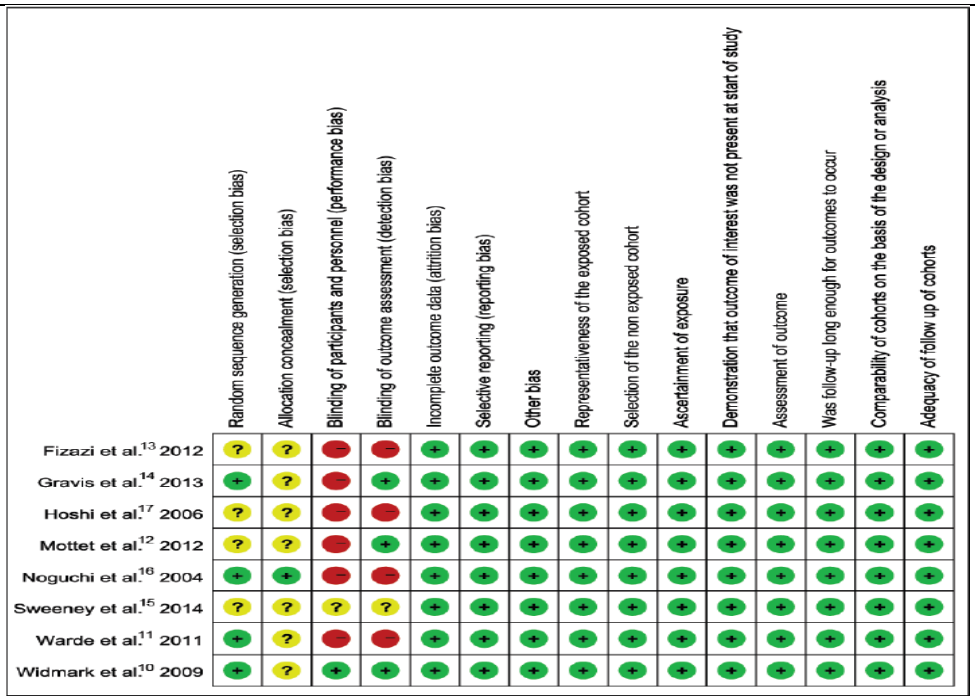
Fig. 2. Included studies risk of bias based on results of critical appraisal

Results

- International Prostate Symptom Score (IPSS) reduction at week 12, (MD=-1.85, 95% CI: -2.97 to - 0.72, p=0.001) was statistically higher in degarelix-treated group.
- Testosterone reduction between day 1-28, (OR=11.58, 95% CI: 5.77 to 23.22, p<0.001) was higher in degarelix-treated group, but no difference was seen after day 28
- No significant difference in prostate volume reduction after day 28
- QoL: In two studies more patients in degarelix treated groups reported improvement in QOL score but this difference was not statistically significant. Anderson study (18) showed that significantly more degarelix patients had improved quality of life at week 12 (85 vs. 46%; p = 0.01).
- general mortality rate was lower in degarelix-treated group (OR= 2.06, 95% CI: 1.08 to 3.93, p=0.03);
- AEs:
    - Hot flushes as an important treatment induced side effect: deagrelix and GnRHagonists are similar in this outcome (OR=1.04, 95% CI: 0.75 to 1.44, p= 0.83). (I_2= 13%).

	• mortality due to the drug side effects was not different. • the only statistically significant difference in safety between the degarelix treated group and GnRH agonists treated group was complication in the injection site which was higher in degarelix-treated group (OR= 46.34, 95% CI: 15.79 to 136, p<0.001). Referenzen 11. Tombal B, Miller K, Boccon-Gibod L, Schroder F, Jensen JK, Olesen TK, et al. Degarelix vs leuprolide treatment in patients with advanced prostate cancer: PSA failures during a randomised, phase 3 trial (CS21). European Urology Supplements 2009; 8(4):130. 12. Iversen P- Karup C, van der Meulen E, Tanko LB, Huhtaniemi I. Hot flushes in prostatic cancer patients during androgen-deprivation therapy with monthly dose of degarelix or leuprolide. Prostate Cancer and Prostatic Diseases 2011; 14(2):184-90. 13. Klotz L, Boccon Gibod L, Shore ND, Andreou C, Persson B-E, Cantor P, et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU International 2008; 102(11):1531-8. 14. Anderson J, Al-Ali G, Wirth M, Gual JB, Gomez Veiga F, Colli E, et al. Degarelix versus goserelin (+ anti-androgen flare protection) in the relief of lower urinary tract symptoms secondary to prostate cancer: results from a phase IIIb study (NCT00831233). Urol Int 2013; 90(3):321-8. 15. Mason M, Maldonado Pijoan X, Steidle C, Guerif S, Wiegel T, van der Meulen E, et al. Neoadjuvant Androgen Deprivation Therapy for Prostate Volume Reduction, Lower Urinary Tract Symptom Relief and Quality of Life Improvement in Men with Intermediate- to High-risk Prostate Cancer: A Randomised Non-inferiority Trial of Degarelix versus Goserelin plus Bicalutamide. Clinical Oncology 2013; 25(3):190-6. 16. Axcrona K - Aaltomaa S, da Silva CM, Ozen H, Damber J-E, Tanko LB, Colli E, et al. Androgen deprivation therapy for volume reduction, lower urinary tract symptom relief and quality of life improvement in patients with prostate cancer: degarelix vs goserelin plus bicalutamide. BJU International 2012; 110(11):1721-8.
	4. Anmerkungen/Fazit der Autoren This systematic review provides some evidence that, for patients with locally advanced and metastatic prostate cancer, the only statistically significant treatment effect in degarelix treated groups (compared with GnRH agonists group), which lasts beyond first month of treatment is improvement in LUTS. *5. Kommentare zum Review* • *Heterogeneity in population: patients with localized, locally advanced or metastatic disease included* • *3 out of 4 RCTs with short follow up* • *Results on general survival presented in abstract only, no further information*
Lei JH et al., 2015 [9] **Androgen-deprivation therapy alone**	1. Fragestellung In this paper, we reviewed the long-term survival outcomes, safety, and quality-of-life of androgen-deprivation therapy (ADT) alone versus combined with radiation therapy (RT) or chemotherapy for locally advanced and metastatic prostate cancer (PCa).
	2. Methodik

versus combined with radiation therapy or chemotherapy for nonlocalized prostate cancer: a systematic review and meta-analysis	**Population**: • locally advanced (T3/4 N0/X M0 disease or clinical T2 tumors with either PSA >40 ng ml−1 , or T2 and PSA >20 ng ml−1 with a Gleason score >8) and • metastatic prostate cancer **Intervention:** androgen-deprivation therapy alone **Komparator**: combined with radiation therapy or chemotherapy **Endpunkt**: overall survival (OS), progression-free survival (PFS), cancer-specific mortality (CSM), cancer-specific survival (CSS) **Suchzeitraum**: until August 2014 **Anzahl eingeschlossene Studien/Patienten (Gesamt):** 8/k.A. **Qualitätsbewertung der Studien:** according to the recommendations of the Cochrane collaboration **Heterogenitätsanalysen**: random effects model to estimate the effect when I2 >75%; otherwise, a fixed effect model
	3. Ergebnisse • 3 studies compared ADT versus ADT plus RT (n = 2 344) • 1 compared ADT versus ADT plus docetaxel-estramustine (n = 413) in locally advanced PCa • 2 compared ADT versus ADT plus docetaxel (n = 1 175) • 2 compared ADT versus ADT plus estramustine (n = 114) in patients with metastatic PCa • regardless of unclear selection bias and no-use of blinding, all studies considered to be of a satisfactory quality • meta-analysis available for OS in studies with locally advanced PCa comparing ADT and ADT plus docetaxel



<u>Studies included metastatic prostate cancer (n=4)</u>

Androgen-deprivation therapy versus androgen-deprivation therapy plus docetaxel (n = 2)

Gravis et al.: 385 patients with metastatic noncastrate PCa, randomized to ADT alone (n = 193) or ADT plus docetaxel (n = 192)

- 72 serious adverse events reported for combined group: most frequent neutropenia (40 [21%]), febrile neutropenia (6 [3%]), abnormal liver function tests (3 [2%]), 4 treatment-related deaths occurred in combined group

Sweeney et al.: patients with metastatic noncastrate PCa; 393 in ADT arm and 397 in combined group

- all toxic reactions occurred in combined group: 2% for Grade (G) 3/4 Neutropenic fever, 2% for G3 neuropathy, 1 case for treat-related death.

The pooled OR of OS for the two trials was 1.29 (95%CI 1.01-1.65) with a moderate heterogeneity (I2 = 63%) when compared ADT plus RT with ADT (P = 0.04).

Androgen-deprivation therapy versus androgen-deprivation therapy plus estramustine (n = 2)

Noguchi et al.: randomly divided 57 patients with newly diagnosed metastatic PCa into two groups, receiving ADT alone and ADT plus estramustine

	• ADT plus estramustine showed longer clinical CSS than ADT alone (p = 0.03), no difference in the OS and response rate of tumor (p = 0.796 and P > 0.05) • serious side effects: 2 in combination group, 1 in ADT alone group (cardiovascular disorders), 1 in ADT alone group (diarrhea) Hoshi et al.: similar study, • OS significantly prolonged in combination group (p = 0.0394) • response rate of tumor: no differences between groups (p = 0.6723) • both treatment groups tolerated treatment well: side effects were 7/26 (26.9%) in ADT and 14/31 (45.2%) in combination group, with no significant difference (p = 0.2517) *serious side effects (≥grade 3):* 1 in each group (cardiovasc. disorders), 2 in combination group (GI toxicity) Referenzen: 14 Gravis G, Fizazi K, Joly F, Oudard S, Priou F, et al. Androgen deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013; 14: 149–58. 15 Sweeney C, Chen YH, Carducci MA, Liu G, Jarrard DF, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial. J Clin Oncol 2014; 32: 5s. [Suppl; Abstract LBA2]. 16 Noguchi M, Noda S, Yoshida M, Ueda S, Shiraishi T, et al. Chemohormonal therapy as primary treatment for metastatic prostate cancer: a randomized study of estramustine phosphate plus luteinizing hormone-releasing hormone agonist versus flutamide plus luteinizing hormone-releasing hormone agonist. Int J Urol 2004; 11: 103–9. 17 Hoshi S, Yamaguchi O, Fujioka T, Arai Y, Tomita Y, et al. A randomized comparative study of endocrine monotherapy and a combination of estramustine phosphate with the endocrine therapy in patients with untreated stage D prostate cancer. Int J Clin Oncol 2006; 11: 303–8.
	4. Anmerkungen/Fazit der Autoren In summary, for locally advanced PCa, the addition of RT to long-term ADT can improve the outcomes of survival and tumor control with fully acceptable adverse effects and QoL than ADT alone; however, added DE to ADT lacks data related to the long-term outcomes on relapse and survival. For newly diagnosed metastatic hormonally sensitive PCa, particularly for cases with visceral metastases and/or 4 or more bone metastases, the concurrent use of docetaxel plus ADT was necessary. It is too soon to say that ADT plus estramustine is better than ADT alone for metastatic PCa. *5. Kommentare zum Review* • *All authors declare no competing financial interests.* • *This research was funded by the National Natural Science Foundation of China (grant No. 81200551; 81370855; 81270841; 30901484; 81300627).*
	1. Fragestellung

Meng F. et a. 2016 [10]

Stroke related to androgen deprivation therapy for prostate cancer: a meta-analysis and systematic review

Ähnlicher SR: Bosco C, 2015 [2]

[…] we performed a meta-analysis and systematic review to investigate whether ADT is associated with stroke in patients with PCa.

2. Methodik

Population: Patients diagnosed with PCa only

Intervention: ADT (either monotherapy or combination therapy)

Komparator: non-ADT (e.g. radical prostatectomy, radiotherapy, active surveillance.)

Endpunkt: stroke (ischemic, hemorrhagic or TIA)
Suchzeitraum: September, 2014. No language restrictions.

Anzahl eingeschlossene Studien/Patienten (Gesamt): 6 studies (160485 patients)

Qualitätsbewertung der Studien: Jadad score, Newcastle-Ottawa quality assessment scale (NOS), classifications of Phillips for level of evidence (Phillips B. GRADE: levels of evidence and grades of recommendation. Arch Dis Child. 2004;89(5):489).
Heterogenitätsanalysen: I2 statistic, Cochrane's Q

3. Ergebnisdarstellung

Studiencharakteristika

- […] we finally identified five cohort studies [14, 21–24] and one nested case–control study [13] that met the inclusion criteria. All articles included were published in English.
- All of these observational studies were of high LOE (2a)
- According to the assessment of NOS for observational studies, all eligible studies were high-quality with scores more than seven stars.
- Funnel plots showed balance in our assessment of publication bias. Begg's and Egger's tests also indicated that no significant publication bias existed

Table S2. Newcastle-Ottawa Scale Quality Assessment of Included Studies

	Selection				Comparability	Outcome			
study	Representativ-eness of exposed cohort	Selection of non-expos-ed cohort	Ascertainment of exposure	outcome of interest was not present at start of study	Comparability on the basis of the design or analysis[a]	Assessment of outcome	follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Scores
Jespersen et al, [28] 2013	☆	☆	☆	☆	☆	☆	☆	☆	8
Hemelrijck et al, [30] 2010	☆	☆	☆	☆	☆	☆	☆	☆	8
Alibhai et al, [10] 2009	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Keating et al, [29] 2010	-	☆	☆	☆	☆	☆	☆	☆	7
Azoulay et al, [9] 2011	☆	☆	☆	☆	☆☆	-	☆	☆	8
Huang et al,[31] 2014	☆	☆	☆	☆	☆	-	☆	☆	7

[a] A maximum of 2 stars can be allotted in this category, one for the most important factors (Age) the other for second important factors (gender, race, etc.).

Ergebnisse

Fatal or non-fatal stroke morbidity

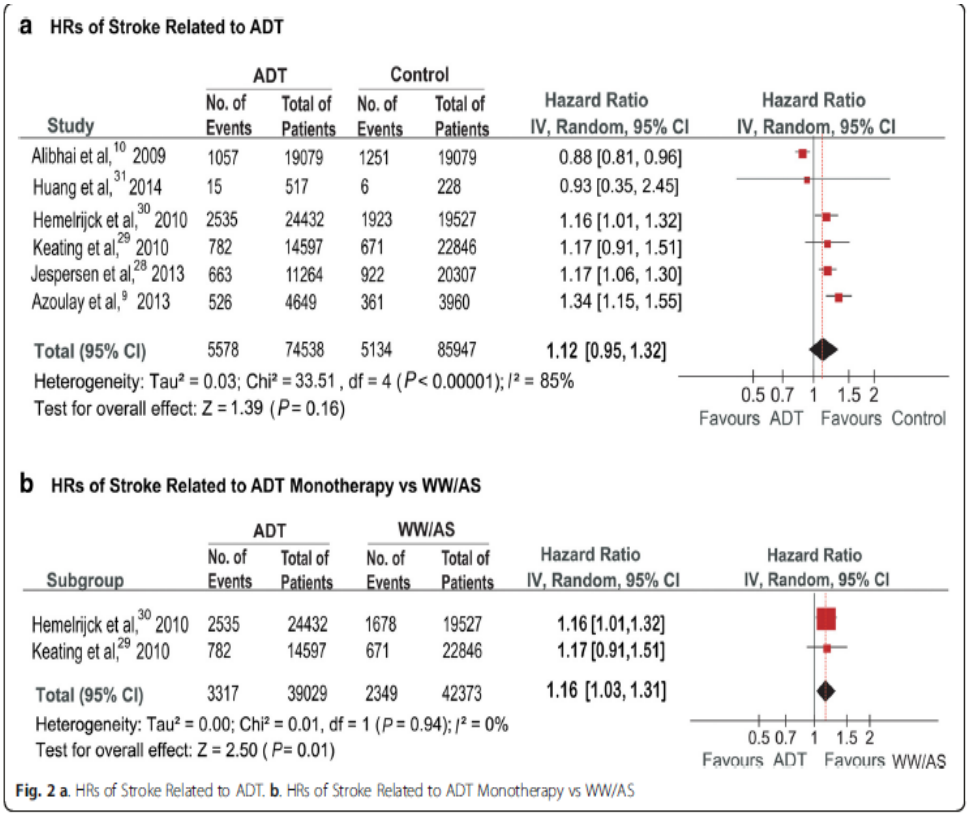


Fig. 2 a. HRs of Stroke Related to ADT. b. HRs of Stroke Related to ADT Monotherapy vs WW/AS

<u>Subgroup analysis: Stroke events</u>

Different types of ADT, four studies [13, 23–25] were identified:

- three studies [13, 23, 24] respectively compared AA alone, GnRH alone and GnRH plus AA with control groups,
- four studies [13, 23–25] were available for the subgroup-analyses of orchiectomy vs non-ADT.

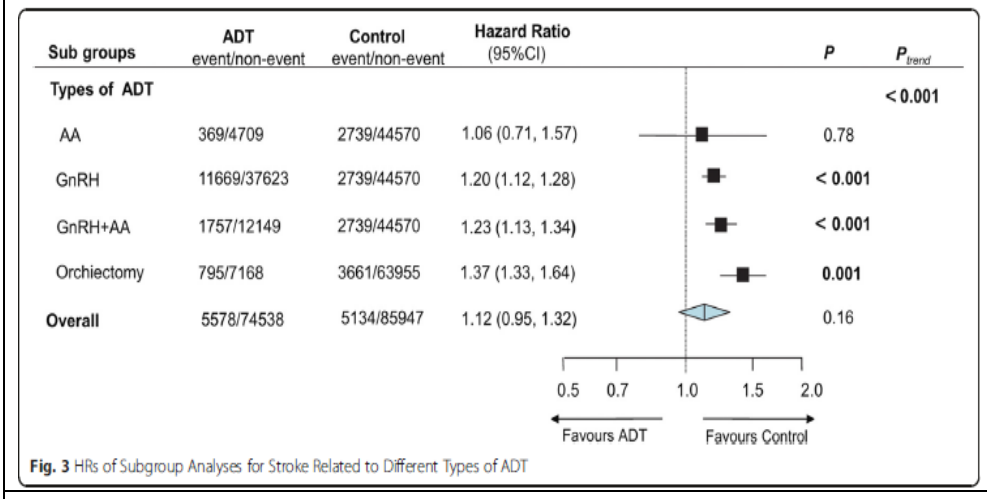


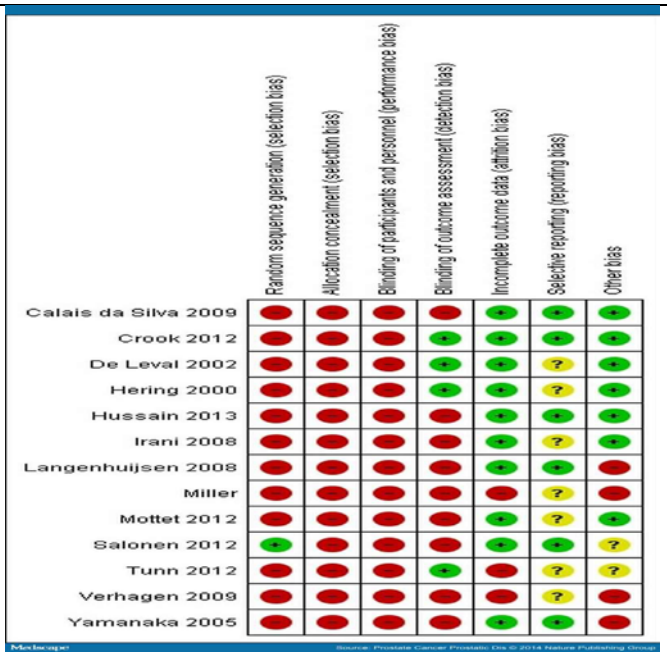
Fig. 3 HRs of Subgroup Analyses for Stroke Related to Different Types of ADT

Referenzen

14. Alibhai SM, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. J Clin Oncol. 2009;27(21):3452–8.

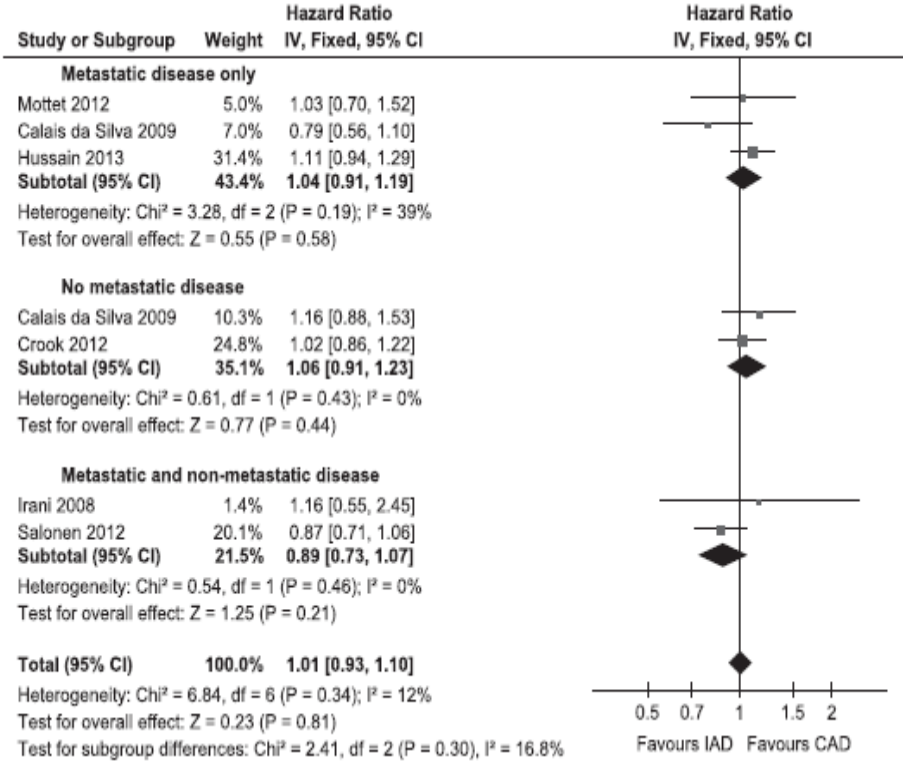
	21. Huang G, Yeung CY, Lee KK, Liu J, Ho KL, Yiu MK, et al. Androgen deprivation therapy and cardiovascular risk in chinese patients with nonmetastatic carcinoma of prostate. J Oncol. 2014;2014:529468. 22. Jespersen CG, Norgaard M, Borre M. Reply to C. Mary Schooling, Grace Sembajwe and Ilir Agalliu's letter to the editor Re: Christina G. Jespersen, Mette Norgaard, Michael Borre. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Eur Urol. 2013;64(3):e61. 23. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010;102(1):39–46. 24. Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelson A, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. J Clin Oncol. 2010;28(21):3448–56. 25. Jespersen CG, Norgaard M, Borre M. Androgen-deprivation therapy in treatment of prostate cancer and risk of myocardial infarction and stroke: a nationwide Danish population-based cohort study. Euro Urol. 2014:65(4): 704–9. 4. Anmerkungen/Fazit der Autoren In conclusion, there is a tendency that ADT could increase the risk of stroke. Significant association of ADT monotherapy with stroke was observed after removing patients with prostatectomy and radiotherapy. Additionally, GnRH, GnRH plus AA, and orchiectomy can significantly result in stroke. These findings may help clinicians be aware of the potential risks of ADT and ensure clinical management when prescribing this treatment. Additional studies should also focus on the different definitions of stroke since they require different approaches to treatment. *5. Kommentare zum Review* • *Unklar, ob Patienten bereits vortherapiert wurden* • *Patienten mit metastasiertem als auch nicht-metastasiertem Prostatakarzinom eingeschlossen* • *Keine RCTs*
Brungs D et al., 2014 [4]. **Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a**	1. Fragestellung We aimed to evaluate the relative harms and benefits of IAD compared with CAD for the treatment of prostate cancer, and sought to extend current evidence by assessing the effect of IAD versus CAD on the overall survival (OS) of patients with metastatic disease
	2. Methodik Population: patients diagnosed **with any stage of prostate cancer**. Intervention + Komparator: IAD and CAD Endpunkt: OS, disease-specific survival and/or progression to castrate-resistant disease, mortality unrelated to prostate cancer, QOL and toxicity outcome. Suchzeitraum (Aktualität der Recherche) bis 2014. Searches were restricted to English language publications.

systematic review and meta-analysis	Anzahl eingeschlossene Studien/Patienten (Gesamt): 13 RCTs (n=5767 Patienten) Qualitätsbewertung der Studien: Cochrane Collaboration tool
	3. Ergebnisdarstellung Studiencharakteristika • Thirteen studies (5767 patients) fulfilled the criteria for inclusion in the systematic review.9–11,22–32 Five studies (1099 patients) included in the systematic review did not have published data suitable for inclusion in the pooled analysis.26,28–31 […] • The range of median follow-up was 29–118 months. Study sample size ranged from 31 to 1535 patients. Most studies used a drug combination of gonadotrophin agonists (e.g., goserelin, leuprolide) and oral antiandrogens (e.g., bicalutamide). • **The study populations were heterogeneous with respect to prostate cancer stage:** six studies10,22,24,25,28,29 included locally advanced prostate cancer with and without metastatic disease; two studies23,27 included patients with rising PSA after local therapy; four studies 9,11,30,31 included only patients with radiologically confirmed metastatic disease, while one study25 included any stage of prostate cancer. Bias risk […] all of the analysed studies contained sources of bias: these included allocation bias, with no study reporting concealment of allocation and only one study (Salonen et al.22) reporting method of allocation generation; performance bias, with no patient or physician blinded to treatment allocation; and detection bias, with no studies reporting blinded assessment of outcomes, which may have a significant impact in those studies whose definition of progressive disease included subjective outcomes.9,10,22,25,26,29

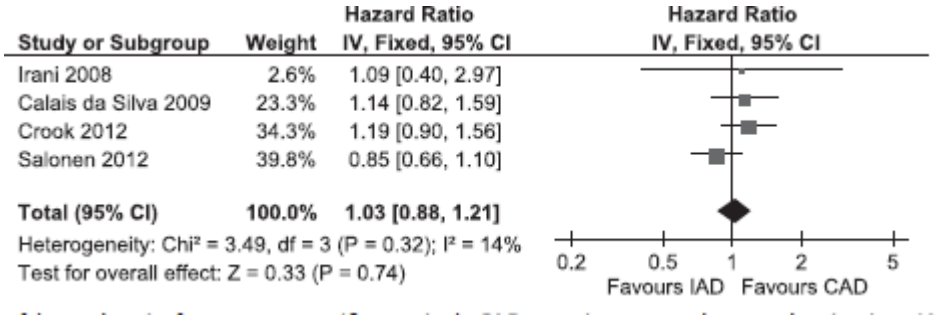


Ergebnisse

<u>Overall survival (OS)</u>



Cancer specific survival

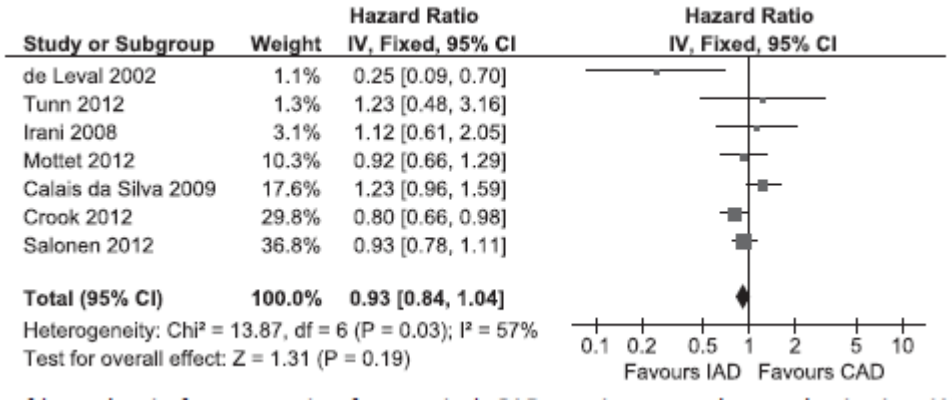


Prostate cancer-specific survival

No difference in prostate cancer mortality between IAD and CAD (4 studies, 2695 participants, HR 1.03, 95% CI 0.88-1.21, P=0.74)

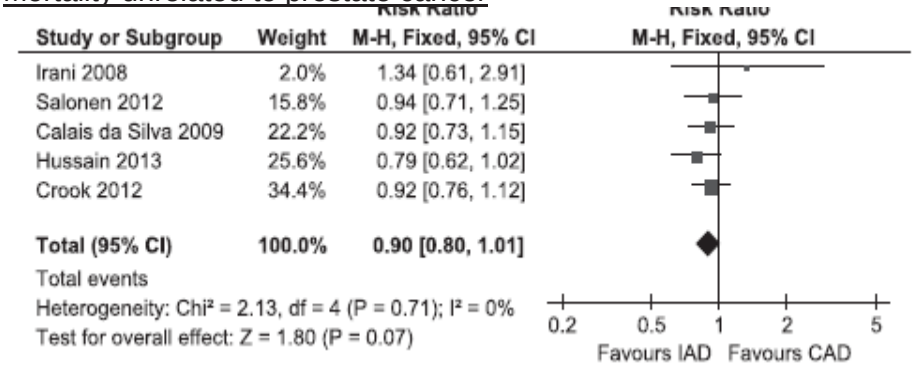
Progression free survival

The criteria used to define progression varied between studies. All studies included PSA in criteria for progression, although cutoffs varied between studies. Other criteria included performance status,[10,28] metastatic progression,[10,22,25,28,30] pain,[10,25] and weight loss due to cancer.[28] Two studes did not report the criteria used for progression.[26,29]



Kommentar: Patienten mit und ohne Metastasen abgebildet bei cancer specific survival, progression-free survival.

Mortality unrelated to prostate cancer



By calculating pooled estimates for OS, PFS and prostate cancer mortality, we have also demonstrated equivalent OS in subgroups of patients with and without metastatic disease for the first time.

QOL and toxicity

We were unable to perform a quantitative analysis of QOL and toxicity as the methods used to measure and report these outcomes varied between studies. Most studies found that IAD reduced adverse effects or improved QOL compared with CAD. However, there was no placebo blinding of treatment in any included study, so patients' knowledge of treatment allocation is likely to bias these results in favour of IAD. There were insufficient published data to confirm an increased risk of cardiovascular death with CAD.

Anmerkungen des Autors bezüglich Einschränkungen der Meta-Analyse

- First, there was significant heterogeneity in the characteristics of included studies, with differences in patient populations, PSA cutoffs and criteria for progressive disease.
- Second, there was a variety of hormone treatments used in the included studies, which reflects uncertainty in the optimal androgen deprivation therapy regimen. Despite this, results were consistent across studies with little heterogeneity in the largest pool of data (OS meta-analysis, I2=12%).
- Third, each trial used different criteria to assess prostate cancer progression, as reflected in the high heterogeneity of the pooled HR for progression (I2=57%).
- Fourth, there was an intrinsic delay in diagnosis of progressive disease in the IAD arm, as patients demonstrate progression after restarting hormone therapy, biasing results in favour of IAD.

[…]

Referenzen

9 Hussain M, Tangen CM, Berry DL, Higano CS, Crawford ED, Liu G et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013; 368: 1314–1325.

10 Calais da Silva FE, Bono AV, Whelan P, Brausi M, Marques Queimadelos A, Martin JA et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol 2009; 55: 1269–1277.

11 Mottet N, Van Damme J, Loulidi S, Russel C, Leitenberger A, Wolff JM et al. Intermittent hormonal therapy in the treatment of metastatic prostate cancer: a randomized trial. BJU Int 2012; 110: 1262–1269.

22 Salonen AJ, Taari K, Ala-Opas M, Viitanen J, Lundstedt S, Tammela TLJ. The FinnProstate Study VII: intermittent versus continuous androgen deprivation in patients with advanced prostate cancer. J Urol 2012; 187: 2074–2081.

23 Crook JM, O'Callaghan CJ, Duncan G, Dearnaley DP, Higano CS, Horwitz EM et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012; 367: 895–903.

24 de Leval J, Boca P, Yousef E, Nicolas H, Jeukenne M, Seidel L et al. Intermittent versus continuous total androgen blockade in the treatment of patients with advanced hormone naı¨ve prostate cancer: results of a prospective randomized. Clin Prostate Cancer 2002; 1: 163–171.

25 Irani J, Celhay O, Hubert J, Bladou F, Ragni E, Trape G et al. Continuous versus six months a year maximal androgen blockade in the management of prostate cancer: a randomised study. Eur Urol 2008; 54: 382–391.

26 Langenhuijsen JF, Schasfoort EMC, Heathcote P, Lock MTWT, Zerbib M, Dijkema HE et al. Intermittent androgen suppression in patients with advanced prostate cancer: an update of the TULP survival data. Eur Urol 2008; 7: 205.

27 Tunn UW, Canepa G, Kochanowsky A, Kienle E. Testosterone recovery in the offtreatment time in prostate cancer patients undergoing intermittent androgen deprivation therapy. Prostate Cancer Prostatic Dis 2012; 15: 296–302.

28 Yamanaka H, Ito K, Naito S, Usami M, Fujimoto H, Matsuoka N et al. Effectiveness of adjuvant intermittent endocrine therapy following neoadjuvant endocrine therapy and external beam radiation therapy in men with locally advanced prostate cancer. Prostate 2005; 63: 56–64.

29 Miller K, Steiner U, Lingnau A. Randomised prospective study of intermittent versus continuous androgen suppression in advanced prostate cancer (abstract #5015). J Clin Oncol 2007; 25(Suppl): 5015.

30 Hering F, Rodrigues PRT, Aurelio Lipay M, Nesrallah L, Srougi M. Metastatic adenocarcinoma of the prostate: comparison between continuous and intermittent hormonal treatment. Braz J Urol 2000; 26: 276–282.

31 Verhagen PC, Wissenburg MF, Wildhagen WA, Bolle AM, Verkerk FH, Schro¨ der CH et al. Quality of life effects of intermittent and continuous hormonal therapy by cyproterone acetate (CPA) for metastatic prostate cancer. Eur Urol Supp 2008; 7: 206.

32 Salonen AJ, Ala-Opas KTM, Viitanen J, Lundstedt S, Tammela TLJ. Advanced Prostate Cancer Treated with Intermittent or Continuous Androgen Deprivation in the Randomised FinnProstate Study VII: Quality of Life and Adverse Effects. Eur Urol 2013; 63: 111–120.

4. Anmerkungen/Fazit der Autoren

We conclude that IAD confers similar efficacy outcomes to CA across a range of stages of prostate cancer. The results of this meta-analysis strongly suggest that IAD, in preference to CAD, should be considered as a new standard of care for initial management of progressive prostate cancer.

Leitlinien

National Comprehensive Cancer Network (NCCN), 2016 [14]. Prostate Cancer (Vers. 12.2016)	**Fragestellung** Diagnose, Pathologie, Staging, Therapie des PCA
	Methodik Grundlage der Leitlinie: Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen - Update der LL von 2014. Suchzeitraum: in PubMed zwischen 09/2014 und 04/2015 The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The PubMed search resulted in 97 citations and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed relevant to these guidelines and discussed by the panel have been included in this updated Discussion section. Recommendations for which high-level evidence was lacking were based on panel review of lower-level evidence and expert opinion. GoR, LoE: **NCCN Categories of Evidence and Consensus** **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. **All recommendations are category 2A unless otherwise noted.** **Methodische Hinweise** • Repräsentativität der Gremien unklar • ob formalisierte Konsensusverfahren angewendet werden ist unklar • -industriefinanziert • Bewertung der Studien unklar

- Diskussion wird aktualisiert

Empfehlungen (Algorithmen siehe Anhang)

RISK GROUP [f]

Clinically Localized:

Very low:
- T1c
- Gleason score ≤6/grade group I
- PSA <10 ng/mL
- Fewer than 3 prostate biopsy cores positive, ≤50% cancer in each core
- PSA density <0.15 ng/mL/g

Low:
- T1-T2a
- Gleason score ≤6/grade group I
- PSA <10 ng/mL

Intermediate:[f]
- T2b-T2c or
- Gleason score 3+4=7/ grade group II or
- Gleason score 4+3=7/ grade group III or
- PSA 10–20 ng/mL

High:[f]
- T3a or
- Gleason score 8/grade group IV or
- Gleason score 9–10/grade group V
- PSA >20 ng/mL

Locally Advanced:

Very high:
- T3b-T4 or
- Primary Gleason pattern 5/ grade group V or
- >4 cores with Gleason score 8–10/grade group IV or V

Metastatic:

Any T, N1 or

Any T, Any N, M1

Androgen Deprivation Therapy (ADT) for Clinically Localized Disease (through PROS-6), Biochemical Failure Without Metastases OR for Met Castration-Naïve Disease (PROS-8 through PROS-10):
- LHRH agonist alone
  - Goserelin
  - Histrelin
  - Leuprolide
  - Triptorelin
- LHRH agonist (as above) plus first-generation antiandrogen
  - LHRH agonist plus nilutamide
  - LHRH agonist plus flutamide
  - LHRH agonist plus bicalutamide
- LHRH agonist (as above) plus second-generation antiandrogen
  - LHRH agonist plus enzalutamide
- LHRH antagonist
  - Degarelix

ADT for Metastatic Disease

- **ADT is the gold standard for men with metastatic prostate cancer.**
- **A phase 3 trial compared continuous ADT to intermittent ADT, but t study could not demonstrate non-inferiority for survival. However, quality-of-life measures for erectile function and mental health were better in the intermittent ADT arm after 3 months of ADT compared continuous ADT arm.**
- **In addition, three meta-analyses of randomized controlled trials fail show a difference in survival between intermittent and continuous**
- **Close monitoring of PSA and testosterone levels and possibly imag is required when using intermittent ADT, especially during off-treat periods, and patients may need to switch to continuous ADT upon of disease progression.**

Optimal ADT

- **LHRH agonist or antagonist (medical castration) and bilateral orchiectomy (surgical castration) are equally effective.**
- **Combined androgen blockade (medical or surgical castration comb with an antiandrogen) provides modest to no benefit over castratio alone in patients with metastatic disease.**
- **Antiandrogen therapy should precede or be co-administered with LHRH agonist and be continued in combination for at least 7 days f patients with overt metastases who are at risk of developing sympt associated with the flare in testosterone with initial LHRH agonist a**
- **Antiandrogen monotherapy appears to be less effective than medic surgical castration and is not recommended.**
- **No clinical data support the use of finasteride or dutasteride with combined androgen blockade.**
- **Patients who do not achieve adequate suppression of serum testosterone (less than 50 ng/dL) with medical or surgical castratio be considered for additional hormonal manipulations (with estroge antiandrogens, LHRH antagonists, or steroids), although the clinica benefit remains uncertain. The optimal level of serum testosterone effect "castration" has yet to be determined.**

High Risk

Men with prostate cancer that is clinical stage T3a, Gleason score 8 to 10, or PSA level greater than 20 ng/mL are categorized by the panel as high risk. Patients with multiple adverse factors may be shifted to the very high-risk category. The preferred treatment is EBRT in conjunction with 2 to 3 years of neoadjuvant/concurrent/adjuvant ADT (category 1); ADT alone is insufficient. In particular, patients with low-volume, high-grade tumor warrant aggressive local radiation combined with typically 2 or 3 years of neoadjuvant/concurrent/adjuvant ADT. Fit men in the high-risk group can consider 6 cycles of docetaxel without prednisone after

	EBRT is completed and while continuing ADT. The combination of EBRT and brachytherapy, with or without neoadjuvant/concurrent/adjuvant ADT, is another primary treatment option. However, the optimal duration of ADT in this setting remains unclear. Radical prostatectomy with PLND remains an option because a subset of younger and healthier men in the high-risk group may benefit from operation. **Very High Risk** Patients at very high risk (locally advanced) are defined by the NCCN Guidelines as men with clinical stage T3b to T4, primary Gleason pattern 5, or more than 4 biopsy cores with Gleason score 8 to 10.[344] The options for this group include: 1) EBRT and long-term ADT (category 1); 2) EBRT plus brachytherapy with or without long-term ADT; 3) EBRT plus ADT and docetaxel; 4) radical prostatectomy plus PLND in selected patients with no fixation to adjacent organs; or 5) ADT for patients not eligible for definitive therapy. **Nodal and Metastatic Disease** ADT or EBRT of the primary tumor plus 2 or 3 years neoadjuvant/concurrent/adjuvant ADT are options for patients diagnosed with N1 disease on presentation. Positive nodal disease identified during radical prostatectomy is addressed under *Adjuvant or Salvage Therapy after Radical Prostatectomy*. ADT is recommended for patients with M1 cancer.
National Cancer Control Programme (NCCP), 2015 [12] **Department of Health (Ireland)** Diagnosis, staging and treatment of patients with prostate cancer.	**Fragestellung(en):** 2.7.2: Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer? 2.9.1: When should palliative care be introduced for patients with cancer?
	Methodik Grundlage der Leitlinie: Step 1: Develop clinical questions, Step 2: Search for the evidence, Step 3: Appraise the literature for validity & applicability, Step 4: Formulation and grading of recommendations, National Stakeholder Review, International Expert Review, CoI-Erklärungen der Mitglieder standardisiert erfasst und diskutiert, Suchzeitraum: September 2014 LoE:

National Clinical Guideline No. 8.

Table 3 Levels of evidence for interventional studies (SIGN grading system 1999-2012)

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3	Non-analytic studies (e.g. case reports, case series).
4	Expert opinion.

GoR:

Table 4 Grades of recommendations for interventional studies (SIGN grading system 1999-2012)

A	At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results.
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+.
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Note: the grade of recommendation does not necessarily reflect the clinical importance of the recommendation.

Freitext/Empfehlungen/Hinweise

Evidence statement
The current EAU guideline (Mottet et al., 2014) and a retrospective cohort study (D'Amico et a 1998) addressed this question.

Prostate Specific Antigen (PSA), Gleason score and tumour stage are predictive of canc outcome (D'Amico et al., 1998).

Low-risk: cT1-T2a and Gleason score ≤6 and PSA <10µg/L (Mottet et al., 2014).
Intermediate-risk: cT2b-T2c or Gleason score = 7 or PSA 10-20µg/L (Mottet et al., 2014).
High-risk: cT3a Gleason score 8-10 or PSA >20µg/L (Mottet et al., 2014).
Very-high-risk: cT3b-T4 N0 or any T, N1 (Mottet et al., 2014).

Other disease classification systems are emerging, e.g. CAPRA. However, the D'Ami classification system is currently the gold standard. This will remain under review as new eviden emerges.

Clinical question 2.7.1

In men with prostate cancer who have biochemical/clinical relapse following definitive treatment, when should you commence hormonal therapy?

	Recommendation 2.7.1.1 The evidence that favours immediate hormone therapy over delayed therapy is not convincing. Therefore, this choice should be made on an individual basis for each patient. Relevant factors include patient preference, the presence of symptoms (i.e. pain), the extent of metastases, PSADT, age, comorbidity, and the effect of treatment on quality of life. **GRADE C** Evidence statement Guidelines from the NCCN (2014) and Oncoline (2007) addressed this question. The question whether hormone therapy should be started *immediately after a diagnosis of metastatic prostate cancer or delayed until subjective, biochemical, or objective progression occurs has been a point of discussion for years* (Newling, 2001). The number of studies addressing this topic is limited, and the available studies have reported conflicting results and have methodological flaws (Nesbit and Baum, 1950, Byar and Corle, 1988). (Oncoline, 2007) The timing of androgen deprivation therapy (ADT) for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, and the short and long-term effects of ADT. (NCCN, 2014) […] Earlier ADT may be better than delayed ADT, although the definitions of early and late (what level of PSA) are controversial. Since the benefit of early ADT is not clear, treatment should be individualised until definitive studies are done. Patients with a shorter PSADT (or a rapid PSA velocity) and an otherwise long life expectancy should be encouraged to consider ADT earlier. (NCCN, 2014) **Clinical question 2.7.2** Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer? Recommendation 2.7.2.1 For patients with biochemical relapse or metastatic recurrence continuous androgen deprivation therapy is the standard option. **Grade B** Recommendation 2.7.2.2 Intermittent androgen deprivation therapy can be considered an acceptable alternative option to be discussed with patients. **Grade B** Evidence statement *Overall survival* Moderate quality evidence from six randomised trials shows no significant difference in overall survival between men treated with intermittent hormone therapy and those treated with continuous hormone therapy (*P*=0.17; only five included in meta-analysis). However, the most recent randomised study (Hussain et al., 2013)

	suggested an inferior overall survival outcome for the intermittent ADT approach (5.8 vs. 5.1 years). (NICE, 2014) *Progression-free survival (not biochemical)* Low quality evidence from two randomised trials found no significant difference in progression free survival between intermittent and continuous therapy. However, both trials included both clinical and biochemical progression in their definition of disease progression. Three studies also provided very low quality evidence of no significant difference in progression-free survival between intermittent and continuous treatment groups for clinical progression. (NICE, 2014) *Adverse events* One moderate quality study found the incidence of treatment-emergent adverse events to be borderline significantly higher in the continuous treatment group (P = 0.042) (Mottet et al., 2009, Mottet et al., 2012). However, two further studies provided low quality evidence of no significant difference in the rates of adverse events between groups but provided no figures. Crook et al., (2012, 2011) and Duncan et al., (2011) also reported no significant difference between treatment arms in the rate of cardiovascular events or osteoporotic fractures (but did not provide figures). Hering et al., (2000) observed fewer mild adverse events (gastrointestinal, gynaecomastia and fatigue) and severe adverse events (severe nausea/vomiting and oedema of the lower limb) with intermittent than with continuous therapy (relative risk (RR) 0.29 and 0.15, respectively) (NICE, 2014) Low quality evidence from two randomised trials suggests that hot flushes are significantly less likely with intermittent than with continuous hormone therapy. While both studies reported fewer hot flushes with intermittent therapy (RR 0.66 and 0.97, respectively) there is uncertainty about the size of the effect due to heterogeneity. (NICE, 2014) Moderate quality evidence from one randomised trial (Calais da Silva et al., 2011, 2009, 2003) shows gynaecomastia is less likely in men treated with intermittent than with continuous hormone therapy (RR 0.64, 95% CI 0.43-0.93). […] Crook et al., (2012, 2011) and Duncan et al., (2011) also reported patients receiving intermittent therapy had significantly less gynaecomastia than those receiving continuous therapy but no effect size was reported (P<0.001). (NICE, 2014) Low quality evidence from one randomised trial (Calais da Silva et al., 2011, 2009, 2003) suggests sexual activity within the previous month was more likely during intermittent therapy than during continuous therapy (RR 2.90, 95% CI 1.52-5.53). […] Low quality evidence from another randomised trial (Hering et al., 2000) found impotence was much less likely in men receiving intermittent than in those on continuous therapy (RR 0.06, 95% CI 0.01-0.28). […] **Clinical question 2.8.2** Is external beam radiation therapy (EBRT) and/or brachytherapy a treatment option for the following categories of prostate cancer: […] • High-risk prostate cancer • Very-high-risk prostate cancer

	Recommendation 2.8.2.4 High-risk Radiotherapy treatment options for patients with high-risk prostate cancer are EBRT in combination with hormonal therapy; EBRT and brachytherapy combinations; EBRT in combination with brachytherapy and hormonal therapy. **GRADE B** Recommendation 2.8.2.5 Very-high-risk A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. **GRADE A** Recommendation 2.8.2.6 Very-high-risk A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients. **GRADE C** Evidence statement *High-risk* Randomised trials have shown a benefit for active treatment in this group of patients (Warde et al., 2011, Widmark et al., 2009). Combination treatment (EBRT and hormonal therapy) has a survival advantage over either modality alone (Warde et al., 2011, Widmark et al., 2009, Bolla et al., 2002, Lawton et al., 2005). Retrospective results have shown good long-term results with a combination of EBRT, hormonal therapy and brachytherapy (Grimm et al., 2012). There are no randomised data to suggest that radiotherapy and hormonal therapy is superior to surgery (with or without ART/SRT) for high-risk patients. Dose escalation has been shown to improve outcomes for intermediate- and high-risk prostate cancer (Kuban et al., 2011, Dearnaley et al., 2007, Zelefsky at al., 2008, Eade et al., 2007, Alicikus et al., 2011, Schulz and Kagan, 2011). *Very-high-risk* Two large randomised controlled trials have demonstrated a survival benefit for the combination of radiotherapy and hormonal therapy compared to hormonal therapy alone (Warde et al., 2011, Widmark et al., 2009). **Clinical question 2.8.5** Which patients with prostate cancer will benefit from neoadjuvant or adjuvant hormone therapy in conjunction with radiotherapy? Recommendation 2.8.5.3 High-risk A combination of radiation therapy and consideration for long term hormone androgen deprivation therapy. **GRADE A** Recommendation 2.8.5.4 EBRT plus brachytherapy with or without androgen deprivation therapy. **GRADE C** Recommendation 2.8.5.5 Very-high-risk A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node negative patients. **GRADE A**

	Recommendation 2.8.5.6 A combination of EBRT and long-term androgen deprivation therapy is recommended in lymph node positive patients. **GRADE C** Evidence statement The options for patients with high-risk prostate cancer include a combination of radiation therapy and consideration for long term hormone androgen deprivation therapy (Bolla et al., 2002, Hanks et al., 2003, Bolla et al., 2009, Lawton et al., 2005) or EBRT plus brachytherapy with or without ADT. A combination of EBRT and long-term androgen deprivation therapy is recommended for patients with very high-risk disease (Bolla et al., 2002, Hanks et al., 2003, Bolla et al., 2009, Lawton et al., 2005).
Deutsche Gesellschaft für Urologie (DGU), 2016 [5] Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms. Version 4.0 Aktualisierte Version	Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), AWMF-Register-Nummer 043/022OL **Fragestellung(en)** in der Indikation rezidiviertes oder metastasiertes Prostatakarzinom u.a: • Frühe Hormonchemotherapie (3. Aktualisierung 2016) • Behandlung des metastasierten PCa: Therapie der symptomatischen/ asymptomatischen Knochenmetastasen (Erstversion/ 1. Aktualisierung 2011) • Behandlung des metastasierten PCa: Supportivtherapie: Maßnahmen bei belastenden Symptomen (Tumor-/Therapie-bedingt). (Erstversion/ 1. Aktualisierung 2011) • Wann ist die maximale Androgendeprivation der einfachen Androgendeprivation (Orchiektomie, LHRH-Analoga) überlegen? • Stellenwert der intermittierenden Androgenblockade
	Methodik: Grundlage der Leitlinie: - Modulare Aktualisierung der LL; 3. Update *Evidenzbasierung:* - Syst. Recherche nach evidenzbasierten Leitlinien in 2006, 2009 für die erste LL-Version; keine weitere LL-Recherche für im Aktualisierungsprozess (aber Berücksichtigung von LL-Updates) - Syst. Recherche nach RCTs (für vereinzelte Fragestellungen auch inkl. Fallserien) oder Quellen aggregierter Evidenz (HTA-Berichte, systematische Reviews und Metaanalysen) in Medline und den Datenbanken der Cochrane Library zu ausgewählten Fragestellungen - Für 3. Update wurden 4 Themen priorisiert, die systematisch in Medline und Datenbanken der Cochrane Library recherchiert wurden, u. a zum Thema Therapie des metastasierten PCa mittels früher kombinierter Hormon-Chemotherapie (Recherchedatum: 04/2016)

Konsensbasierung:

- Interdisziplinäre LL-Entwickungsgruppe
- CoI dargelegt und Umgang beschrieben
- Strukturierte Konsensfindung

- Die Leitlinie ist bis zur nächsten Aktualisierung gültig. Vorgesehen sind weitere modulare Aktualisierungen in einem etwa 2-3 jährlichen Abstand

LoE nach SIGN

	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

(Evidenztabellen verfügbar)

GoR

Empfehlungsgrad	**Beschreibung**	**Syntax**
A	Starke Empfehlung	Soll
B	Empfehlung	Sollte
O	Empfehlung offen	Kann
Statements	Als Statements werden Darlegungen oder Erläuterungen von spezifischen Sachverhalten oder Fragestellungen ohne unmittelbare	

	Handlungsaufforderung bezeichnet. Sie werden entsprechend der Vorgehensweise bei den Empfehlungen im Rahmen eines formalen Konsensusverfahrens verabschiedet u. können entweder auf Studienergebnissen oder auf Expertenmeinungen beruhen.	
Expertenkonsens (EK)	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. Der Begriff ‚Expertenkonses' ersetzt den in den bisherigen Versionen der Leitlinie genutzten Begriff ‚Good Clinical Practice' (GCP).	

Empfehlungen (nur für das AWG relevante Empfehlungen dargestellt)

6.3 Therapie des hormonsensitiven, metastasierten Prostatakarzinoms

6.17 Statement (neu 2016)

Die Möglichkeit der kombinierten Hormon-Chemotherapie hat die Erstlinienbehandlung des metastasierten (M1), hormonsensitiven Prostatakarzinoms bei Erstdiagnose grundlegend verändert. (LoE 1+, Literatur: [734-736])

734. Gravis G et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14(2):149-58.

735. Sweeney CJ et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. The New England journal of medicine 2015;373(8):737-46.

736. James ND et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387(10024):1163-77

Hintergrund:

Zwei neue Studien, CHAARTED [735] und STAMPEDE [736], zeigten einen bedeutsamen Überlebensvorteil bei früher Chemotherapie ab Beginn der Androgendeprivation bei Patienten mit metastasiertem, hormonsensitivem Prostatakrebs. Diese Ergebnisse legen nahe, die Indikation zur Chemotherapie bei Männern in gutem Allgemeinzustand (ECOG 0-1), anders als bislang Standard, bereits in der hormonsensitiven Situation begleitend zur Androgendeprivation zu stellen.

6.18 Empfehlung (modifiziert 2016)

Bestandteil der Aufklärung über eine Androgendeprivation oder Hormon-Chemotherapie sollen insbesondere folgende Punkte sein:

- der palliative Charakter der Therapie;
- Einfluss auf die Lebensqualität;
- die unerwünschten Wirkungen.

(A, LoE 4; Expertenkonsens auf Grundlage von [685-687; 690; 691]

685. Iversen P et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scand J Urol Nephrol 2006;40(6):441-52.

686. Studer UE et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24(12):1868-76.

687. The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. Br J Urol 1997;79(2):235-46

690. Boustead G, Edwards SJ. Systematic review of early vs deferred hormonal treatment of locally advanced prostate cancer: a meta-analysis of randomized controlled trials. BJU Int 2007;99(6):1383-9.

691. Wilt TJ, air B, MacDonald R, Rutks I. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev 2001;(4):CD003506

6.19 Empfehlung (neu 2016)

Patienten in gutem Allgemeinzustand (ECOG 0-1) mit metastasiertem (M1), hormonsensitiven Prostatakarzinom sollte zusätzlich zur Androgendeprivation eine Chemotherapie mit Docetaxel empfohlen werden. (B; LoE 1+; Literatur: [734-736])

734. Gravis G et al.Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14(2):149-58.

735. Sweeney CJ et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. The New England journal of medicine 2015;373(8):737-46.

736. James ND et al.. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet 2016;387(10024):1163-77

Hintergrund

In zwei von drei RCT, die eine Kombinationstherapie von Docetaxel mit gleichzeitiger Androgendeprivation untersuchten, zeigte sich eine signifikante Verlängerung des Gesamtüberlebens um 15 bzw. 13,6 Monate (60 vs. 45 bzw. 57,6 vs. 44 Monate; 2.962 bzw. 790 Patienten) [735; 736], die Unterschiede die Ergebnisse einer dritten Studie (62,1 vs. 48,6 Monate; 385 Patienten) waren statistisch nicht signifikant [734]. Das progressionsfreie Überleben bzw. 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 vor und kommt dennoch zu einem signifikanten Ergebnis für die Gesamtgruppe. Die Leitliniengruppe adressiert diese Subgruppe in der Empfehlung daher nicht explizit, spricht aber eine abgeschwächte Empfehlung (sollte) aus. 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.

6.20 Empfehlung (neu 2016)

Entscheidet sich der Patient 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/m^2 gegeben werden. (A, LoE 1+; Literatur: [37; 685; 686; 691]

37. Loblaw DA et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2007;25(12):1596-605.

685. Iversen P et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scand J Urol Nephrol 2006;40(6):441-52.

686. Studer UE et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24(12):1868-76.

691. Wilt TJ, air B, MacDonald R, Rutks I. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev 2001;(4):CD003506

6.21 Empfehlung (modifiziert u. ergänzt 2016)

a. Patienten, die nicht für eine Kombinationsbehandlung in Frage kommen, soll eine Androgendeprivation empfohlen werden. (A, LoE 1++, Literatur: [685-687; 690; 691])

685. Iversen P et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scand J Urol Nephrol 2006;40(6):441-52.

686. Studer UE et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24(12):1868-76.

687. The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. Br J Urol 1997;79(2):235-46

690. Boustead G, Edwards SJ. Systematic review of early vs deferred hormonal treatment of locally advanced prostate cancer: a meta-analysis of randomized controlled trials. BJU Int 2007;99(6):1383-9.

691. Wilt TJ, air B, MacDonald R, Rutks I. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev 2001;(4):CD003506

b. Die Androgendeprivation kann medikamentös oder operativ erfolgen. (0, LoE 1++, Literatur: [37; 685; 686; 691])

37. Loblaw DA et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2007;25(12):1596-605.

685. Iversen P et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scand J Urol Nephrol 2006;40(6):441-52.

686. Studer UE et al. Immediate or deferred androgen deprivation for patients with prostate cancer not suitable for local treatment with curative intent: European Organisation for Research and Treatment of Cancer (EORTC) Trial 30891. J Clin Oncol 2006;24(12):1868-76.

691. Wilt TJ, air B, MacDonald R, Rutks I. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev 2001;(4):CD003506

c. Die medikamentöse Androgendeprivation kann als Monotherapie oder als maximale Androgenblockade erfolgen. (0, LoE 1++, Literatur: [99; 104; 158; 694])

99. Heidenreich A et al. European Association of Urology (EAU). EAU guidelines on prostate cancer. Arnhem: EAU; 2007.

104. National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence (NICE). Prostate Cancer: diagnosis and treatment. 2008 [cited: 2011 Jan 27].

158. Dutch Urological Association. Prostate Cancer. Nation-wide guideline. Version 1.0. Maastricht: Dutch Urological Association; 2007

694. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet 2000;355(9214):1491-8

d. Die Androgendeprivation sollte kontinuierlich durchgeführt werden, wenn der PSA-Wert nach spätestens 7 Monaten nicht unter 4 ng/mL abfällt. (B, LoE 1(+), Literatur: [737-739])

737. Magnan S et al. Intermittent vs Continuous Androgen Deprivation Therapy for Prostate Cancer: A Systematic Review and Meta-analysis. JAMA Oncol 2015;1(9):1261-9.

738. Niraula S, Le LW, Tannock IF. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2013;31(16):2029-36.

739. Hussain M et al. Intermittent versus continuous androgen deprivation in prostate cancer. The New England journal of medicine 2013;368(14):1314-25.

e. Bei Abfall des PSA-Wertes unter 4 ng/mL kann nach ausführlicher Aufklärung alternativ eine intermittierende Hormontherapie angeboten werden. (0, LoE 1(+), Literatur: [737-739])

Hintergrund

a) Eine sofortige hormonablative Therapie ist mit einer Verlängerung des progressionsfreien Überlebens verbunden [691]. Die Ergebnisse sind 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 meta-stasierten Stadium wird jedoch eine starke Empfehlung zur sofortigen hormonabla-tiven Therapie ausgesprochen. Die kausale Therapie ist einer symptomatischen Behandlung eindeutig vorzuziehen. Neben einer Verlängerung des progressions-freien Überlebens gibt es Hinweise darauf, dass eine frühzeitig eingeleitete Androgendeprivation Komplikationen infolge einer Progression der Grunderkran-kung (z. B. durch eine pathologische Fraktur) reduziert [693].

Sowohl bezüglich der Indikationsstellung als auch bezüglich anderer Aspekte der Androgendeprivation (AD) lässt sich auf dem Boden der publizierten Analysen die Situation von Patienten mit lokalisiertem PCa nicht sicher von der bei Patienten mit metastasiertem PCa differenzieren. Außerdem existiert kein Nachweis dafür, dass sich hormonnaive Patienten in lokalisierten Tumorstadien bezüglich des Anspre-chens auf eine AD anders verhalten als solche mit metastasiertem PCa. Demzufol-ge wurden sowohl in der methodisch guten Metaanalyse von Wilt 2001[691] als auch in den ASCO-Leitlinien von 2004 bzw. 2007 [37; 693] sowie in der vorliegen-den Leitlinie Studienergebnisse von Patienten mit lokalisierten und fortgeschritte-nen Stadien für die Empfehlungen herangezogen.

693. Loblaw DA et al. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol 2004;22(14):2927-41

b) Eine ähnliche Empfehlung findet sich im Kapitel Watchful Waiting und alleinige hormonablative Therapie beim nichtmetastasierten PCa. Die Empfehlung zitiert die Substanzen, die in randomisierten kontrollierten Studien wirksam zur AD einge-setzt wurden. Der systematische Review von Wilt 2001 [691] beinhaltet Studien zu Orchiektomie und LHRH-Agonisten. Zusätzlich sind in den Studien der VACURG [696] noch Östrogene bzw. DES eingesetzt worden. Iversen 2006 [685] setzt Bicalutamid ein, Studer 2006 [686] ebenfalls LHRH-Agonisten oder Orchiektomie. Der Einsatz von GnRH-Blockern wird aus der ebenso guten Ab-senkung des Testosteronspiegels wie durch LHRH-Agonisten abgeleitet. Von den GnRH-Antagonisten sind die Substanzen Abarelix seit 2005 und Degarelix seit Feb-ruar 2007 für die Indikation der hormonablativen Therapie des fortgeschrittenen PCa zugelassen. 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) Die PCTCG-Metaanalyse [694] mit überwiegend metastasierten Patienten weist ei-nen nicht signifikanten etwa zweiprozentigen Vorteil im Fünf-Jahres-Überleben für Patienten mit maximaler Androgenblockade nach. Eine Subgruppenanalyse der maximalen Androgenblockade mit Nilutamid oder Flutamid ergibt einen signifikanten Fünf-Jahres-Überlebensvorteil zu Gunsten der maximalen Blockade von 3 %. Demgegenüber ist die kombinierte Gabe mit Cyproteronacetat signifikant schlech-ter als die einfache AD. Insgesamt fiel ein nichtsignifikanter Trend zu mehr Ne-benwirkungen in der Gruppe der maximalen AD auf. Aufgrund des geringen Über-lebensvorteils durch die kombinierte AD bei gleichzeitigen Hinweisen auf eine ge-steigerte Toxizität und erheblichen Mehrkosten kommen alle drei Quell-Leitlinien [99; 104; 158] zu dem Schluss, dass die maximale AD nicht als Therapie erster Wahl eingesetzt werden soll. Die ASCO-Leitlinie [37] empfiehlt dagegen eine Be-rücksichtigung der kombinierten AD (‚should be considered') und begründet dies durch einen methodisch von den Autoren dieser Leitlinie als kritisch zu betrach-tenden indirekten Analogieschluss aus mehreren Studien [744]. Weiter verweisen die ASCO-Autoren zur Begründung auf eine methodisch schwache Studie von Akaza 2004 (Update in [745]). Die zusätzliche Toxizität von Bicalutamid in der Kombinationstherapie

wird von den ASCO-Autoren als minimal bzw. vernachläs-sigbar klein eingeschätzt. Daraus resultiert die von den übrigen o. g. Leitlinien ab-weichende Formulierung.

744. Klotz L, Schellhammer P, Carroll K. A re-assessment of the role of combined androgen blockade for advanced prostate cancer. BJU Int 2004;93(9):1177-82 http://www.ncbi.nlm.nih.gov/pubmed/15180600.

745. Usami M. Bicalutamide 80 mg combined with a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A monotherapy in advanced prostate cancer: findings from a phase III randomized, double-blind, multicenter trial in Japanese patients. Prostate Cancer Prostatic Dis 2007;10(2):194-201

d) Grundlage dieser Empfehlung sind zwei Metaanalysen [737; 738], die jeweils Primärstudien zum Vergleich von kontinuierlicher und intermittierender Androgendeprivation zusammenfassen. Die Mehrheit der eingeschlossenen Studi-en, inklusive der größten Studie mit mehr als eintausend Patienten [739], 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 Wer-ten nach der ADT-Induktionsphase liegen nach Ansicht der Leitliniengruppe unge-nügende Daten zur Wirksamkeit und Sicherheit einer IADT vor, sodass sie für diese Indikation nicht empfohlen wird.

e) 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 Krebsspezifischem Überleben sowie der Zeitdauer bis zum Fort-schreiten der Krankheit belegen. Allerdings zeigt die Hussain-Studie einen nicht signifikanten Überlebensvorteil von median 5,8 vs. 5,1 Jahren für die kontinuierli-che ADT 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. Die 2016 aktualisierte EAU-Leitlinie [746] spricht ebenfalls eine kann-Empfehlung zur intermittierenden Therapie nach entsprechender Induktionsphase bei metastasierten Patienten aus.

746. European Association of Urology (EAU), Mottet N, Bellmunt J, Briers E, Bolla M, Cornford P, De Santis M, Henry A, Joniau S, Lam T, Mason MD, Matveev V, van der Poel H, van der Kwast TH, Rouvière O, Wiegel T. EAU guidelines on prostate cancer: 6. Disease Management. Arnhem: EAU; 2016 [cited: 2016 Sep 19].

6.22 Empfehlung (2009)

Die kombinierte, maximale Androgenblockade kann als Primärtherapie zum Einsatz kommen. (0; LoE 1+, Literatur: [99; 104; 158; 694]

99. Heidenreich A et al. European Association of Urology (EAU). EAU guidelines on prostate cancer. Arnhem: EAU; 2007.

104. National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence (NICE). Prostate Cancer: diagnosis and treatment. 2008 [cited: 2011 Jan 27].

158. Dutch Urological Association. Prostate Cancer. Nation-wide guideline. Version 1.0. Maastricht: Dutch Urological Association; 2007

694. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Lancet 2000;355(9214):1491-8

6.23 Empfehlung (2009)

Nach vorheriger Aufklärung über die noch fehlenden Langzeitdaten kann die intermittierende Androgendeprivation eingesetzt werden. (0, LoE 1+; Literatur: [104; 389; 740-742]

104. National Collaborating Centre for Cancer, National Institute for Health and Clinical Excellence (NICE). Prostate Cancer: diagnosis and treatment. 2008 [cited: 2011 Jan 27].

389. Heidenreich A et al. European Association of Urology (EAU). EAU guidelines on prostate cancer. Arnhem: EAU; 2011.

740. Miller K et al. Therapeutic options for hormone-refractory prostate cancer. Der Urologe Ausg A 2006;45(5):580, 582-5.

741. Conti PD et al. Intermittent versus continuous androgen suppression for prostatic cancer. Cochrane Database Syst Rev 2007;(4):CD005009 http://www.ncbi.nlm.nih.gov/pubmed/17943832.

742. Hering F et al. Metastatic adenocarcinoma of the prostate: comparation between continous and intermittent hormonal treatment. Braz J Urol 2000;26:276-82.

	Kommentar zur Leitlinie Aktualisierte Empfehlungen zu Docetaxel berücksichtigen nicht die Zulassung
NICE, 2014 [13] Prostate Cancer: diagnosis and treatment	**Fragestellung(en)** In men with metastatic prostate cancer, which type of initial hormone therapy is the most clinically effective? Is intermittent hormone therapy as effective as continuous hormone therapy in men receiving long-term hormonal therapy for prostate cancer?
	Methodik Grundlage der Leitlinie • development of this guideline was based upon methods outlined in the „NICE guidelines manual", Modified Delphi consensus methodology • update of CG58: Recommendations are marked **[2008]**, **[2014]** or **[new 2014]** to indicate the year of the last evidence review: - [2008] indicates that the evidence has not been updated and reviewed since 2008 - [2014] indicates that the evidence has been updated and reviewed but no changes to the 2008 recommendation has been made - [new 2014] indicates that the evidence has been reviewed and a new recommendation has been made. Suchzeitraum: o For topics that were updated from the 2008 guideline, searches were set to only identify evidence published after June 2007 o No date limits to searches carried on new topics o Search up to 14 May 2013 LoE: GRADE (Grading of Recommendations, Assessment, Development and Evaluation): evidence profiles for each outcome with an overall assessment of both the quality of the evidence as a whole (very low, low, moderate or high) as well as an estimate of the size of effect. • (zu detaillierten Angaben der jeweiligen quality of evidence siehe GL fullversion) GoR: • „Offer" – for the vast majority of patients, an intervention will do more good than harm • „Do not offer" – the intervention will not be of benefit for most patients „Consider" – the benefit is less certain, and an intervention will do more good than harm for most patients. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend

on the patient‟s values and preferences than for an „offer‟ recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Freitext/Empfehlungen/Hinweise

Table 1 Risk stratification for men with localised prostate cancer

Level of risk	PSA		Gleason score		Clinical stage
Low risk	<10 ng/ml	and	≤6	and	T1–T2a
Intermediate risk	10–20 ng/ml	or	7	or	T2b
High risk[1]	>20 ng/ml	or	8–10	or	≥T2c

[1] High-risk localised prostate cancer is also included in the definition of locally advanced prostate cancer.

8 Metastatic prostate cancer

Recommendation	**Offer bilateral orchidectomy to all men with metastatic prostate cancer as an alternative to continuous luteinising hormone-releasing hormone agonist therapy. [2008]**
Qualifying statement	There are randomised studies which show comparable survival benefit and side effects for bilateral orchidectomy. There is good evidence that bilateral orchidectomy is more cost effective, but the GDG recognised the importance of patient preference in this issue.

Clinical evidence (2008)

Evidence came from a systematic review of 13 randomised trials of hormonal monotherapy in prostate cancer. Meta-analysis suggested comparable overall survival benefit between orchidectomy and LHRHa‟s. The evidence about adverse effects was less reliable due to reporting inconsistencies between trials, although adverse event rates appeared similar in orchidectomy and LHRHa treatment groups.

Seidenfeld, J., et al. (2001) Relative effectiveness and cost-effectiveness of methods of androgen suppression in the treatment of advanced prostate cancer. [Review] [330 refs]. Evidence Report: Technology Assessment (Summary), i-x.

Seidenfeld, J., et al. (2000) Single-therapy androgen suppression in men with advanced prostate cancer: A systematic review and meta-analysis. Ann Intern.Med, 132: 566–577.

Recommendation	**Do not offer combined androgen blockade as a first-line treatment for men with metastatic prostate cancer. [2008]**
Qualifying statement	Evidence shows only a modest survival benefit for combined androgen blockade and high costs.

Clinical evidence (2008)

Evidence from 27 randomised trials, summarised in two systematic reviews, shows a small survival advantage with combined androgen blockade using non-steroidal anti-androgens. The estimate of five year overall survival from meta-analysis was 28% for men treated with combined androgen blockade compared with 25% for those treated with androgen deprivation alone. Using the rate of treatment deprivation as a index of treatment toxicity, Samson, Seidenfeld and co-workers reported that men treated with LHRHa alone withdrew from therapy at a rate of 4% or less compared with a rate of 8% or more in men receiving CAB.

Prostate Cancer Trialists (2000) Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet, 355: 1491–1498.

Seidenfeld et al. 2001: siehe oben

Samson, D. J., et al. (2002) Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. Cancer, 95: 361–376.

Recommendation	**For men with metastatic prostate cancer who are willing to accept the adverse impact on overall survival and gynaecomastia in the hope of retaining sexual function, offer anti-androgen monotherapy with bicalutamide[ee] (150 mg). [2008]**
Qualifying statement	Evidence from randomised trials confirms the relative protection from loss of sexual function.
Recommendation	**Begin androgen deprivation therapy and stop bicalutamide treatment in men with metastatic prostate cancer who are taking bicalutamide monotherapy and who do not maintain satisfactory sexual function. [2008]**
Qualifying statement	This recommendation is based on GDG consensus alone.

Clinical evidence (2008)

Meta-analysis of 13 randomised trials of hormonal monotherapy showed a trend towards poorer overall survival with anti-androgen monotherapy than with castration. The two therapies had different toxicity profiles. Gynaecomastia was more likely with non-steroidal anti-androgens, whereas hot flushes and reduced sexual function were more likely with androgen deprivation. The proportion withdrawing from anti-androgen monotherapy and LHRHa treatment was similar, however, suggesting comparable tolerability.

Seidenfeld, J., et al. (2001): sieh oben

Seidenfeld, J., et al. (2000): siehe oben

The European Association of Urology (EAU) Prostate Cancer Guidelines Panel have prepared this guidelines document to assist

<table>
<tr><td>Mottet N et al., 2015 [11].

EAU

Guidelines on Prostate Cancer

Update von 2014</td><td>medical professionals assess the evidence-based management of prostate cancer (PCa).

Methodik

Grundlage der Leitlinie

• The Prostate Cancer Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, a radiologist, a pathologist and a patient stakeholder organisation representative.
• For the 2016 PCa Guidelines, new and relevant evidence has been identified, collated and appraised through a structured assessment of the literature.
• Specific sections of the text have been updated based on a systematic review questions prioritised by the Guidelines Panel. These reviews were performed using standard Cochrane systematic review methodology
• Update von 2014
• Suchzeitraum: bis April 24th 2015

LoE und GoR

A classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence

Table 1: Level of evidence*
<table><tr><th>Level</th><th>Type of evidence</th></tr><tr><td>1a</td><td>Evidence obtained from meta-analysis of randomised trials</td></tr><tr><td>1b</td><td>Evidence obtained from at least one randomised trial</td></tr><tr><td>2a</td><td>Evidence obtained from one well-designed controlled study without randomisation</td></tr><tr><td>2b</td><td>Evidence obtained from at least one other type of well-designed quasi-experimental study</td></tr><tr><td>3</td><td>Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports</td></tr><tr><td>4</td><td>Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities</td></tr></table>*Modified from Sackett, et al. (1).

Table 2: Grade of recommendation*
<table><tr><th>Grade</th><th>Nature of recommendations</th></tr><tr><td>A</td><td>Based on clinical studies of good quality and consistency addressing the specific recommendatio and including at least one randomised trial</td></tr><tr><td>B</td><td>Based on well-conducted clinical studies, but without randomised clinical trials</td></tr><tr><td>C</td><td>Made despite the absence of directly applicable clinical studies of good quality</td></tr></table>*Modified from Sackett, et al. (1).

Sonstige methodische Hinweise</td></tr>
</table>

- Studiencharakteristika sowie Qualitätsbeurteilung nicht gelistet.

Freitext/Empfehlungen/Hinweise

Table 4.2.2: EAU risk groups for biochemical recurrence of localised and locally advanced prostate cancer

	Low-risk	Intermediate-risk	High-risk	
Definition	PSA < 10 ng / mL and GS < 7 and cT1-2a	PSA 10-20 ng /mL or GS 7 or cT2b	PSA > 20 ng / mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			**Locally advanced**

PSA=prostate-specific antigen.

Empfehlung

6.6.8. ***Guidelines for the first-line treatment of metastatic prostate cancer***

Treatment type	Modality	Recommendation	LE	GR
Castration combined with chemotherapy	Docetaxel combined with castration	Offer castration combined with chemotherapy to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.	1a	A
Castration alone	Surgical, LHRH agonist, OR LHRH antagonist	Offer castration alone with or without an anti-androgen to patients unfit for, or unwilling to consider, castration combined with chemotherapy.	1b	A
		Do not prescribe abiraterone acetate or enzalutamide outside of a clinical trial.	3	A
Castration combined with any local treatment	Radiotherapy/Surgery	Use castration combined with local treatment in an investigational setting only.	3	A

6.6.9. ***Guidelines for hormonal treatment of metastatic prostate cancer***

Recommendation		LE
In M1 symptomatic patients, offer immediate castration to palliate symptoms and reduce the risk for potentially catastrophic sequelae of advanced disease (spinal cord compression, pathological fractures, ureteral obstruction, extra-skeletal metastasis).		1b
In M1 asymptomatic patients, offer immediate castration to defer progression to a symptomatic stage and prevent serious disease progression-related complications.		1b
In newly diagnosed M1 patients, offer castration combined with docetaxel, provided patients are fit enough to receive chemotherapy.		1a
In M1 asymptomatic patients, discuss deferred castration with a well-informed patient since it lowers the treatment side-effects, provided the patient is closely monitored.		2b
Anti-androgens		
In M1 patients treated with an LHRH agonist, offer short-term administration of anti-androgens to reduce the risk of the 'flare-up' phenomenon.		2a
Start anti-androgens used for 'flare-up' prevention on the same day as an LHRH analogue is started or for up to 7 days before the first LHRH analogue injection if patient has symptoms). Treat for four weeks.		3
Do not offer anti-androgen monotherapy in M1 patients.		1a
Intermittent treatment		
Population	In asymptomatic M1 patients, offer intermittent treatment to highly motivated men, with a major PSA response after the induction period.	1b
Threshold to start and stop ADT	• In M1 patients follow the schedules used in published clinical trials on timing of intermittent treatment. Stop treatment when the PSA level is < 4 ng/mL after 6 to 7 months of treatment. • Resume treatment when the PSA level is > 10-20 ng/mL (or to the initial level if < 20 ng/mL).	4
Drugs	In M1 patients, offer combined treatment with LHRH agonists and NSAA.	1b
	Offer LHRH antagonists, especially in patients with an impending spinal cord compression or bladder outlet obstruction.	2

ADT=androgen deprivation therapy; LHRH=luteinising hormone-releasing hormone; NSAA=non-anti-androgen; PSA=prostate specific antigen.

6.5.2. Testosterone-lowering therapy (castration)

6.5.2.1. Castration level

Surgical castration is still considered the primary treatment modality for ADT. It leads to a considerable decline in testosterone levels: the 'castration level' […]

521.Oefelein, M.G., et al. Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. Urology, 2000. 56: 1021. http://www.ncbi.nlm.nih.gov/pubmed/11113751

522.Morote, J., et al. Individual variations of serum testosterone in patients with prostate cancer receiving androgen deprivation therapy. BJU Int, 2009. 103: 332. http://www.ncbi.nlm.nih.gov/pubmed/19007366

523.Pickles, T., et al. Incomplete testosterone suppression with luteinizing hormone-releasing hormone agonists: does it happen and does it matter? BJU Int, 2012. 110: E500. http://www.ncbi.nlm.nih.gov/pubmed/22564197

524.Klotz, L., et al. MP74-01 Nadir Testosterone on ADT predicts for time to castrate resistant progression: A secondary analysis of the PR-7 intermittent vs continuous ADT trial. J Urol. 191: e855. http://www.jurology.com/article/S0022-5347(14)02593-2/abstract

6.5.2.2. Bilateral orchiectomy

Bilateral orchiectomy, or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia [525] and it is the quickest way to achieve a castration level which is usually reached within less than 12 hours. It is irreversible and does not allow for intermittent treatment.

525.Desmond, A.D., et al. Subcapsular orchiectomy under local anaesthesia. Technique, results and implications. Br J Urol, 1988. 61: 143. http://www.ncbi.nlm.nih.gov/pubmed/3349279

[…]

6.5.4.1. Achievement of castration levels

Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH and FSH secretion and therefore testosterone production. A castration level is usually obtained within 2-4 weeks [529]. Although there is no formal direct comparison between the various compounds, they are considered to be equally effective [530] and comparable to orchiectomy [531] [530].

529.Klotz, L., et al. The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int, 2008. 102: 1531.http://www.ncbi.nlm.nih.gov/pubmed/19035858

530.Seidenfeld, J., et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. Ann Intern Med, 2000. 132: 566.http://www.ncbi.nlm.nih.gov/pubmed/10744594

531.Hedlund, P.O., et al. Parenteral estrogen versus combined androgen deprivation in the treatment of metastatic prostatic cancer: part 2. Final evaluation of the Scandinavian Prostatic Cancer Group (SPCG) Study No. 5. Scand J Urol Nephrol, 2008. 42: 220.http://www.ncbi.nlm.nih.gov/pubmed/18432528

6.5.4.2.‘Flare-up’ phenomenon

The ‘flare-up’ phenomenon might lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status [532].

Patients at risk are usually those with high-volume, symptomatic, bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely remove the risk.

532.Bubley, G.J. Is the flare phenomenon clinically significant? Urology, 2001. 58: 5. http://www.ncbi.nlm.nih.gov/pubmed/11502435

6.5.5.Luteinising-hormone-releasing hormone antagonists

Luteinizing-hormone releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with only monthly formulations being available.

[…]

6.5.5.2.Degarelix

Degarelix is an LHRH antagonist with a monthly subcutaneous formulation. The standard dosage is 240 mg in the first month, followed by monthly injections of 80 mg. Most patients achieve a castrate level at day 3 [535]. An extended follow-up has been published, suggesting a better PFS compared to monthly leuprorelin [535]. Its definitive superiority over the LHRH analogues remains to be proven.

535.Crawford, E.D., et al. A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. J Urol, 2011. 186: 889. http://www.ncbi.nlm.nih.gov/pubmed/21788033

6.5.6.1.Steroidal anti-androgens

These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side-effects are secondary to castration (gynaecomastia is quite rare) whilst the non-pharmacological side effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

6.5.6.1.1.Cyproterone acetate (CPA)

[…] In one randomised trial [536] CPA showed a poorer OS when compared with LHRH analogues. An underpowered RCT comparing CPA monotherapy with flutamide in M1b PCa did not show any difference in disease specific- and OS at a median follow-up of 8.6 years [537]. Other CPA monotherapy studies suffer from methodological limitations preventing firm conclusions.

536.Moffat, L.E. Comparison of Zoladex, diethylstilbestrol and cyproterone acetate treatment in advanced prostate cancer. Eur Urol, 1990. 18 Suppl 3: 26. http://www.ncbi.nlm.nih.gov/pubmed/2151272

537.Schroder, F.H., et al. Metastatic prostate cancer treated by flutamide versus cyproterone acetate. Final analysis of the “European Organization for Research and Treatment of Cancer” (EORTC) Protocol 30892. Eur Urol, 2004. 45: 457. http://www.ncbi.nlm.nih.gov/pubmed/15041109

[…]

6.5.6.2.Non-steroidal anti-androgens

Non-steroidal anti-androgen monotherapy has been promoted on the basis of improved QoL compared to castration. Anti-androgens do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved [538]. Non-androgen pharmacological side-effects differ between agents, with bicalutamide showing a more favourable safety and tolerability profile than flutamide and nilutamide [539]. All three

	agents share a common potential liver toxicity (occasionally fatal) therefore, patients' liver enzymes must be monitored regularly. 538.Smith, M.R., et al. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol, 2004. 22: 2546. http://www.ncbi.nlm.nih.gov/pubmed/15226323 539.Iversen, P. Antiandrogen monotherapy: indications and results. Urology, 2002. 60: 64. http://www.ncbi.nlm.nih.gov/pubmed/12231053 […] 6.5.6.2.3.Bicalutamide The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists [538,540]. 538.Smith, M.R., et al. Bicalutamide monotherapy versus leuprolide monotherapy for prostate cancer: effects on bone mineral density and body composition. J Clin Oncol, 2004. 22: 2546. http://www.ncbi.nlm.nih.gov/pubmed/15226323 540.Wadhwa, V.K., et al. Long-term changes in bone mineral density and predicted fracture risk in patients receiving androgen-deprivation therapy for prostate cancer, with stratification of treatment based on presenting values. BJU Int, 2009. 104: 800. http://www.ncbi.nlm.nih.gov/pubmed/19338564 6.6.Treatment: Metastatic prostate cancer […] 6.6.3.First-line hormonal treatment Primary ADT has been the standard of care for the past decades [520]. There is no level 1 evidence for, or against, a specific type of ADT, whether orchiectomy, an LHRH analogue or antagonist, except in patients with impending spinal cord compression for whom either a bilateral orchidectomy, or an LHRH antagonist are the preferred options. 520.Pagliarulo, V., et al. Contemporary role of androgen deprivation therapy for prostate cancer. Eur Urol, 2012. 61: 11. http://www.ncbi.nlm.nih.gov/pubmed/21871711 […] 6.6.4.Combination therapies 6.6.4.1.Complete androgen blockade (CAB) There are conflicting results from several studies comparing CAB with monotherapy. The largest RCT in 1,286 M1b patients found no difference between surgical castration with or without flutamide [550]. Systematic reviews have shown that CAB using a non-steroidal anti-androgen (NSAA) appears to provide a small survival advantage (< 5%) vs. monotherapy (surgical castration or LHRH agonists) [551,552] beyond 5 years of survival [553] 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. 550.Eisenberger, M.A., et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med, 1998. 339: 1036. http://www.ncbi.nlm.nih.gov/pubmed/9761805

551.Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. Prostate Cancer Trialists' Collaborative Group. Lancet, 2000. 355: 1491. http://www.ncbi.nlm.nih.gov/pubmed/10801170

552.Schmitt, B., et al. Maximal androgen blockade for advanced prostate cancer. Cochrane Database Syst Rev, 2000: Cd001526. http://www.ncbi.nlm.nih.gov/pubmed/10796804

553.Akaza, H., et al. Combined androgen blockade with bicalutamide for advanced prostate cancer: long-term follow-up of a phase 3, double-blind, randomized study for survival. Cancer, 2009. 115: 3437. http://www.ncbi.nlm.nih.gov/pubmed/19536889

6.6.4.2.Non-steroidal anti-androgen (NSAA) monotherapy

Based on a Cochrane systematic review [554] comparing 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. The evidence quality of the studies included in this review was rated as moderate.

554.Kunath, F., et al. Non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database Syst Rev, 2014. 6: CD009266. http://www.ncbi.nlm.nih.gov/pubmed/24979481

6.6.4.3.Intermittent versus continuous androgen deprivation therapy (IAD)

[….] So far, the SWOG 9346 [559] is the largest trial conducted in M1b patients. Out of 3,040 selected patients, only 1,535 were randomised based on the inclusion criteria set. This highlights that at best only 50% of M1b patients might be candidates for IAD, i.e. the best PSA responders. This was a non-inferiority trial leading to inconclusive results: (HR: 1.1; CI: 0.99-1.23), with the upper limit being above the pre-specified 90% upper limit of 1.2. The pre-specified non-inferiority limit was not achieved, and the results did not show a significant inferiority for any treatment arm. However, inferior survival with IAD cannot be completely ruled out based on this study.

Other trials did not show any survival difference with a HR for OS of 1.04 (0.91-1.19). […] there was no difference in OS or CSS between IAD and continuous androgen deprivation. A recent review of the available phase III trials highlighted the limitations of most trials and suggests a cautious interpretation of the non-inferiority results. There is a trend favouring IAD in terms of QoL, especially regarding treatment-related side effects, such as hot flushes. In some cohorts the negative impact on sexual function was less pronounced with IAD. Two very recently published prospective trials came to the same conclusions [560,561].

Other possible long-term benefits of IAD include bone protection [562] and a protective effect against metabolic syndrome. This possible protective effect has been challenged recently [563] and deserves more studies. Testosterone recovery was observed in most studies [564] leading to intermittent castration. […] IAD is feasible and accepted by the patients [564].

	The PSA threshold at which ADT must be stopped or resumed still needs to be defined in prospective studies [556,564]. Nevertheless, there is consensus amongst authors on some statements:
	• IAD is based on intermittent castration. Therefore, only drugs leading to castration are suitable.
	• Most data has been published on CAB (rather than IAD).
	• LHRH antagonist might be a valid alternative to an agonist.
	• The induction cycle cannot be longer than 9 months, otherwise testosterone recovery is unlikely.
	• ADT should be stopped only if patients have fulfilled all of the following criteria:
	  • well-informed and compliant patient;
	  • no clinical progression;
	  • clear PSA response, empirically defined as a PSA < 4 ng/mL in metastatic disease.[…]
	• The group of patients who will benefit most from IAD still has to be defined but the most important factor seems to be the patient's response to the first cycle of IAD, e.g. the PSA level response [556].
	IAD might be an option in patients with metastatic disease after a standardised induction period.
	555.Niraula, S., et al. Treatment of prostate cancer with intermittent versus continuous androgen deprivation: a systematic review of randomized trials. J Clin Oncol, 2013. 31: 2029. http://www.ncbi.nlm.nih.gov/pubmed/23630216
	556.Sciarra, A., et al. A novel therapeutic option for castration-resistant prostate cancer: after or before chemotherapy? Eur Urol, 2014. 65: 905. http://www.ncbi.nlm.nih.gov/pubmed/23838638
	557.Botrel, T.E., et al. Intermittent versus continuous androgen deprivation for locally advanced, recurrent or metastatic prostate cancer: a systematic review and meta-analysis. BMC Urol, 2014. 14: 9. http://www.ncbi.nlm.nih.gov/pubmed/24460605
	558.Brungs, D., et al. Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a systematic review and meta-analysis. Prostate Cancer Prostatic Dis, 2014. 17: 105. http://www.ncbi.nlm.nih.gov/pubmed/24686773
	559.Hussain, M., et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med, 2013. 368: 1314. http://www.ncbi.nlm.nih.gov/pubmed/23550669
	560.Verhagen, P.C., et al. Intermittent versus continuous cyproterone acetate in bone metastatic prostate cancer: results of a randomized trial. World J Urol, 2014. 32: 1287. http://www.ncbi.nlm.nih.gov/pubmed/24258313
	561.Calais da Silva, F., et al. Locally advanced and metastatic prostate cancer treated with intermittent androgen monotherapy or maximal androgen blockade: results from a randomised phase 3 study by the South European Uroncological Group. Eur Urol, 2014. 66: 232. http://www.ncbi.nlm.nih.gov/pubmed/19249153
	562.Higano, C., et al. Bone mineral density in patients with prostate cancer without bone metastases treated with intermittent androgen suppression. Urology, 2004. 64: 1182. http://www.ncbi.nlm.nih.gov/pubmed/15596194
	563.Hershman, D.L., et al. Adverse Health Events Following Intermittent and Continuous Androgen Deprivation in Patients With Metastatic Prostate Cancer. JAMA Oncol, 2015: 1.

564.Abrahamsson, P.A. Potential benefits of intermittent androgen suppression therapy in the treatment of prostate cancer: a systematic review of the literature. Eur Urol, 2010. 57: 49.

565.Nair, B., et al. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev, 2002: Cd003506. http://www.ncbi.nlm.nih.gov/pubmed/11869665

6.6.4.4.Immediate versus deferred androgen deprivation therapy

In symptomatic patients, immediate treatment is mandatory. However, controversy still exists for asymptomatic metastatic patients due to the lack of quality studies. Current insights are mainly based on flawed, underpowered RCTs, with mixed patient populations (i.e. locally advanced, M1a, M1b status), and a variety of ADT treatments and follow-up schedules. […]

A Cochrane review extracted four good-quality RCTs: the VACURG I and II trials, the MRC trial, and the ECOG 7887 study [554]. All of these studies were conducted in the pre-PSA era and included patients with advanced PCa, who had received early vs. deferred ADT, either as primary therapy or adjuvant after RP [565]. No improvement in OS was observed in the M1a/b population, although early ADT significantly reduced disease progression and associated complications. […]

554.Kunath, F., et al. Non-steroidal antiandrogen monotherapy compared with luteinising hormone-releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database Syst Rev, 2014. 6: CD009266. http://www.ncbi.nlm.nih.gov/pubmed/24979481

565.Nair, B., et al. Early versus deferred androgen suppression in the treatment of advanced prostatic cancer. Cochrane Database Syst Rev, 2002: Cd003506. http://www.ncbi.nlm.nih.gov/pubmed/11869665

6.6.5.Hormonal treatment combined with chemotherapy

[…] upfront docetaxel combined with ADT should be considered as a new standard in men presenting with metastases at first presentation, provided they are fit enough to receive the drug [572]. Docetaxel is used at the standard regimen of 75mg/sqm combined with steroids premedication, but without prolonged corticotherapy.

544.Glass, T.R., et al. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol, 2003. 169: 164. http://www.ncbi.nlm.nih.gov/pubmed/12478127

546.Sweeney, C.J., et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med, 2015. 373: 737. http://www.ncbi.nlm.nih.gov/pubmed/26244877

568.Gravis, G., et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol, 2013. 14: 149. http://www.ncbi.nlm.nih.gov/pubmed/23306100

569.James N.D., et al. Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: First overall survival results from STAMPEDE (NCT00268476). J Clin Oncol 33, 2015 (suppl; abstr 5001), 2015. http://www.ncbi.nlm.nih.gov/pubmed/26719232

571.James, N.D., et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an

	adaptive, multiarm, multistage, platform randomised controlled trial. Lancet, 2015. http://www.ncbi.nlm.nih.gov/pubmed/26719232 572.Vale, C.L., et al. Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol, 2015. http://www.ncbi.nlm.nih.gov/pubmed/26718929 573.Smith, T.J., et al. Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol, 2015. 33: 3199. http://www.ncbi.nlm.nih.gov/pubmed/26169616 6.6.6.Prostate targeted therapy in newly diagnosed metastatic disease Data from the retrospective SEER data-base [574] and the Munich cancer registry [575] suggest an OS and CSS benefit when RP or brachytherapy are added to ADT in newly diagnosed M1 patients. A small prospective experimental cohort of well selected patients responding to 6 months ADT and with < 3 bone spots confirmed the feasibility and after a median 34 months follow up, suggested a better CSS [576]. However, these results must be considered as experimental and deserve prospective trials (already underway) before being adopted in daily practice. 574.Culp, S.H., et al. Might men diagnosed with metastatic prostate cancer benefit from definitive treatment of the primary tumor? A SEER-based study. Eur Urol, 2014. 65: 1058.http://www.ncbi.nlm.nih.gov/pubmed/24290503 575.Gratzke, C., et al. Role of radical prostatectomy in metastatic prostate cancer: data from the Munich Cancer Registry. Eur Urol, 2014. 66: 602. http://www.ncbi.nlm.nih.gov/pubmed/24821581 576.Heidenreich, A., et al. Cytoreductive radical prostatectomy in patients with prostate cancer and low volume skeletal metastases: results of a feasibility and case-control study. J Urol, 2015. 193: 832. http://www.ncbi.nlm.nih.gov/pubmed/25254935 6.6.7.Metastasis-directed therapy In patients relapsing after a local treatment, a metastases-targeting therapy has been proposed, with the aim to delay systemic treatment. A recent systematic review clearly highlighted that at this time this approach must, as yet, be considered as experimental [577]. 577.Ost, P., et al. Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. Eur Urol, 2015. 67: 852. http://www.ncbi.nlm.nih.gov/pubmed/25240974
Alberta Provincial Genitourinary Tumour Team, 2012 [1]	**Fragestellung** The purpose of this guideline is to describe the appropriate management and follow up strategies for prostate cancer.
	Methodik Grundlage der Leitlinie: Repräsentatives Gremuium, konsentiert klinische Fragestellungen, nach systematischer Literatursuche, -bewertung und –aufbereitung in

Prostate cancer. Clinical practice guideline Vers. 6	Evidenztabellen von „Knowledge Management Specialists“, informale Konsensusprozesse, kein Graduierungssystem Update: originally developed in January, 2005; revised in January 2009, January 2011, September 2013, and October 2014 and March 2015 Suchzeitraum: for the 2015 update, no formal literature review conducted; for the 2014 update, the Pubmed searched from 2010 to 2014; only phase III trials evaluated for inclusion
	Freitext/Empfehlungen/Hinweise <u>Definition of risk categories for clinical staging (10-12)</u> • Low- must have all of the following: T1- T2a and Gleason score ≤6 and PSA <10 ng/mL. • Intermediate- tumors not meeting criteria for low- or high-risk: T2b-T2c or Gleason 7 or PSA 10-20 ng/mL. • High- must have any one of the following: T3a or higher; Gleason score ≥ 8; or PSA >20 ng/mL. ADVANCED DISEASE <u>Stage T1-4, N1-3, M+ Hormone Sensitive Disease (</u>Indications include symptomatic disease or asymptomatic disease.) *Management* • Surgical castration • Medical castration • Treatment with an LHRH analogue (agonist or antagonist) o 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 LHRH for 2 weeks to 1 month in order to block the potential initial testosterone flare. o The non-steroidal antiandrogen should be administered concurrently with the first LHRH analogue injection and continue for a minimum of 14 days afterward. o Medical and surgical castration are equally effective and the risks, benefits, and economic implications should be discussed with the patient. • Treatment with gonadotropin-releasing hormone (GnRH) o The GnRH antagonist Degarelix is as effective at suppressing testosterone and may achieve testosterone suppression faster (49) than GnRH Agonists. Treatment with a GnRH antagonist (Degarelix) avoids the risk of

	testosterone ‘flare” that occurs with GnRH agonists (50). Treatment with a GnRH antagonist eliminates the need for concomitant administration of a peripheral anti androgen. o PSA reduction occurred significantly faster with Degarelix when compared to GnRH agonists without increases in treatment related side effects (49). o No survival benefit has been demonstrated with Degarelix compared to traditional LHRH agonists and injections are administered monthly. o Degarelix is not presently funded in Alberta. • Single agent antiandrogens o Nonsteroidal antiandrogens can be administered to those patients wishing to maintain potency. This may result in a reduction in disease-free survival. To date there is insufficient data to recommend biclutamide at the 150 mg/day dose and it is not approved by Health Canada. o Biclutamide 50 mg orally once a day. o Flutamide 250 mg orally three times daily. o Nilutamide 300 mg orally once a day for one month, then decrease to 150 mg daily. • Use of intermittent hormone therapy is controversial. Recent data suggests that intermittent is not non-inferior to continuous, which does not necessarily mean intermittent is inferior to continuous. • 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. NOTE: Ongoing total androgen blockade (e.g. castration with LHRH agonist/antagonist plus a nonsteroidal antiandrogen) is not recommended. • Docetaxel chemotherapy for castrate sensitive disease o Data from the CHAARTED trial demonstrated significant overall survival benefit of 13 months when administered to patients with castrate sensitive metastatic prostate cancer who are about to or just recently (within 4 months) started hormonal therapy. The greatest benefit was seen in patients with high volume disease. (53) Sweeney C, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPRCA): An ECOG-led phase III randomized trial. J Clin Oncol 2014;32(5s):suppl; abstr LBA2. o Patients with high volume disease castrate sensitive metastatic prostate cancer who are about to or just recently started hormonal therapy should be offered 6 cycles of docetaxel chemotherapy at 75 mg/m2 every 3 weeks (given

without prednisone). Hormone therapy as above is carried throughout and after docetaxel completion.

Discussion

ADVANCED DISEASE

Stage T1-4, N1-3, M+ Hormone Sensitive Disease

Options for management include surgical castration or medical castration. Medical castration can include treatment with an LHRH analogue. 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 LHRH for 2 weeks to 1 month in order to block the potential initial testosterone flare. The non-steroidal antiandrogen should be administered concurrently with the first LHRH analogue injection and continue for a minimum of 14 days afterward. Another option is single agent antiandrogens. Nonsteroidal antiandrogens can be administered to those patients wishing to maintain potency. This may result in a reduction in disease-free survival. To date there is insufficient data to recommend biclutamide at the 150 mg/day dose and it is not approved by Health Canada. These treatments are equally effective and the risks, benefits, and economic implications should be discussed with the patient. Ongoing total androgen blockade (e.g. castration with LHRH agonist plus a nonsteroidal antiandrogen) is not recommended. Use of intermittent hormone therapy is controversial. Recent data suggests that intermittent is not non-inferior to continuous, which does not necessarily mean intermittent is inferior to continuous.

(46) Calais da Silva FE, et al. Intermittent androgen deprivation for locally advanced and metastatic prostate cancer: results from a randomised phase 3 study of the South European Uroncological Group. Eur Urol 2009 Jun;55(6):1269-1277.

(51) Crook JM, et al. Intermittent androgen suppression for rising PSA level after radiotherapy. N Engl J Med 2012 Sep 6;367(10):895-903.

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.

(52) Segal RJ, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol 2003 May 1;21(9):1653-1659.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 31.01.2017

#	Suchfrage
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	MeSH descriptor: [Prostatic Neoplasms] explode all trees and with qualifier(s): [Therapy - TH]
#3	prostate or prostatic:ti,ab,kw (Word variations have been searched)
#4	tumor* or tumour* or carcinoma* or adenocarcinoma* or neoplasm* or cancer*:ti,ab,kw (Word variations have been searched)
#5	#3 and #4
#6	#2 or #5
#7	#6 Publication Year from 2012 to 2017
#8	#6 Publication Year from 2012 to 2017, in Technology Assessments
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	MeSH descriptor: [Prostatic Neoplasms] explode all trees and with qualifier(s): [Therapy - TH]
#3	prostate or prostatic:ti,ab,kw (Word variations have been searched)

SR, HTAs in Medline (PubMed) am 31.01.2017

#
#1
#2
#3
#4
#5
#6
#7
#8
#9
#10
#11
#12
#13
#14

Leitlinien in Medline (PubMed) am 31.01.2017

#	Suchfrage
#1	Prostatic Neoplasms [Mesh]
#2	Search ((prostate[Title/Abstract]) OR prostatic[Title/Abstract])
#3	Search (((((((tumor[Title/Abstract]) OR tumors[Title/Abstract]) OR tumour*[Title/Abstract]) OR carcinoma*[Title/Abstract]) OR adenocarcinoma*[Title/Abstract]) OR neoplasm*[Title/Abstract]) OR cancer*[Title/Abstract]))
#4	Search (#3 AND #2)
#5	#1 OR #4
#6	Search (((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR ((guideline*[Title] OR recommendation*[Title]) NOT medline[sb]))
#7	Search (#4 AND #6)
#8	Search (#7) Sort by: PublicationDate Filters: Publication date from 2012/01/01 to 2017/12/31
#9	(#8) NOT ((comment[Publication Type]) OR letter[Publication Type])
#10	(#9) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp]))

Literatur:

1. **Alberta Provincial Genitourinary Tumour Team.** Prostate cancer. Version 6 [online]. Edmonton (USA): CancerControl Alberta; 03.2015. [Zugriff: 02.02.2017]. (Clinical practice guideline; Band GU-004.). URL: http://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-gu004-prostate.pdf.

2. **Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M.** Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol 2015;68(3):386-396.

3. **Botrel TE, Clark O, Lima Pompeo AC, Horta Bretas FF, Sadi MV, Ferreira U, et al.** Efficacy and Safety of Combined Androgen Deprivation Therapy (ADT) and Docetaxel Compared with ADT Alone for Metastatic Hormone-Naive Prostate Cancer: A Systematic Review and Meta-Analysis. PLoS One 2016;11(6):e0157660.

4. **Brungs D, Chen J, Masson P, Epstein RJ.** Intermittent androgen deprivation is a rational standard-of-care treatment for all stages of progressive prostate cancer: results from a systematic review and meta-analysis. Prostate Cancer Prostatic Dis 2014;17(2):105-111.

5. **Deutsche Gesellschaft für Urologie (DGU).** Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms [online]. Registernummer 043 - 022OL. 22.12.2016. Düsseldorf (GER): Arbeitsgemeinschaft der Wissenschaftlich Medizinischer Fachgesellschaften (AWMF); 2016. [Zugriff: 01.02.2017]. URL: http://www.awmf.org/uploads/tx_szleitlinien/043-022OLl_S3_Prostatakarzinom_2016-12.pdf.

6. **Hosseini SA, Rajabi F, Akbari Sari A, Ayati M, Heidari S, Ghamary F.** Degarelix for the treatment of advanced prostate cancer compared with GnRh-Agonists: a systematic review and meta-analysis. Med J Islam Repub Iran 2016;30:317.

7. **Kunath F, Borgmann H, Blumle A, Keck B, Wullich B, Schmucker C, et al.** Gonadotropin-releasing hormone antagonists versus standard androgen suppression therapy for advanced prostate cancer A systematic review with meta-analysis. BMJ Open 2015;5(11):e008217.

8. **Kunath F, Grobe HR, Rücker G, Motschall E, Antes G, Dahm P, et al.** Non-steroidal antiandrogen monotherapy compared with luteinising hormone?releasing hormone agonists or surgical castration monotherapy for advanced prostate cancer. Cochrane Database of Systematic Reviews [online]. 2014(6):Cd009266. URL: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD009266.pub2/abstract.

9. **Lei JH, Liu LR, Wei Q, Song TR, Yang L, Meng Y, et al.** Androgen-deprivation therapy alone versus combined with radiation therapy or chemotherapy for nonlocalized prostate cancer: a systematic review and meta-analysis. Asian J Androl 2016;18(1):102-107.

10. **Meng F, Zhu S, Zhao J, Vados L, Wang L, Zhao Y, et al.** Stroke related to androgen deprivation therapy for prostate cancer: a meta-analysis and systematic review. BMC Cancer 2016;16:180.

11. **Mottet N, J. Bellmunt EBP, Representative) RCNvdBGA, M. Bolla NJvCGA, P. Cornford, , S. Culine SJ, T. Lam, M.D. Mason, V. Matveev, , H. van der Poel THvdK, O. Rouvière, , et al.** Prostate Cancer [online]. März 2015European Association of Urology (EAU); 2015. [Zugriff: 02.02.2017]. URL: http://uroweb.org/wp-content/uploads/EAU-Guidelines-Prostate-Cancer-2015-v2.pdf.

12. **National Cancer Control Programme (NCCP), National Clinical Effectiveness Committee (NCEC).** Diagnosis, staging and treatment of patients with prostate cancer. [online]. 06.2015. Dublin (IRL): Department of Health (DH); 2015. [Zugriff: 02.02.2017]. (National Clinical Guideline; Band 8). URL: http://www.hse.ie/eng/services/list/5/cancer/profinfo/guidelines/prostate/Summary%20Guideline_Prostate%20Cancer.pdf.

13. **National Collaborating Centre for Cancer.** Prostate cancer: diagnosis and treatment [online]. Januar 2014. London (GBR): National Institute for Health and Care Excellence (NICE); 2014. [Zugriff: 02.02.2017]. (Clinical guideline; Band 175). URL: https://www.nice.org.uk/guidance/CG175.

14. **National Comprehensive Cancer Network (NCCN).** Prostate Cancer. [online]. Version 1.2017 Fort Washington (USA): NCCN; 12.2016. [Zugriff: 02.02.2017]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf.

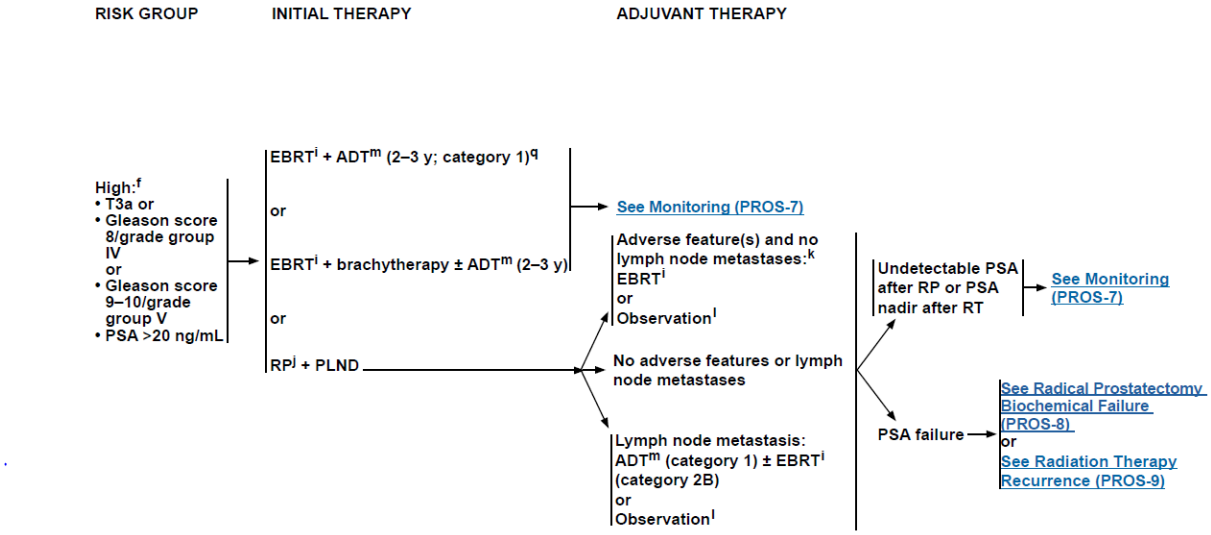
15. **Ramos-Esquivel A, Fernandez C, Zeledon Z.** Androgen-deprivation therapy plus chemotherapy in metastatic hormone-sensitive prostate cancer. A systematic review and meta-analysis of randomized clinical trials. Urol Oncol 2016;34(8):335 e339-335 e319.

16. **Tassinari D, Tamburini E, Gianni L, Drudi F, Fantini M, Santelmo C, et al.** Early Docetaxel and Androgen Deprivation in the Treatment of Metastatic, Hormone-sensitive Prostate Cancer. Rev Recent Clin Trials 2016;11(4):317-323.

17. **Vale CL, Burdett S, Rydzewska LH, Albiges L, Clarke NW, Fisher D, et al.** Addition of docetaxel or bisphosphonates to standard of care in men with localised or metastatic, hormone-sensitive prostate cancer: a systematic review and meta-analyses of aggregate data. Lancet Oncol 2016;17(2):243-256.

Anhang

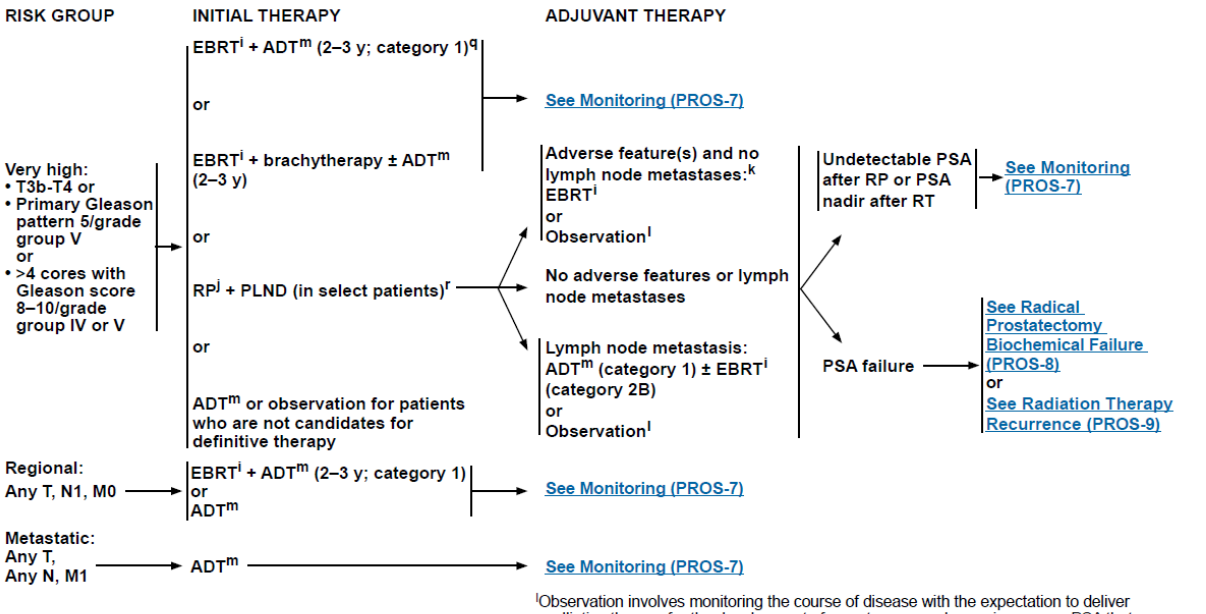
NCCN Guideline: Prostate Cancer V1.21017 [14]



[f]Patients with multiple adverse factors may be shifted into the next highest risk group.
[i]See Principles of Radiation Therapy (PROS-D).
[j]See Principles of Surgery (PROS-E).
[k]Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.
[l]Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[q]Six cycles of docetaxel every 3 weeks without prednisone may be administered after completion of radiation in selected patients who are fit for chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PROS-5

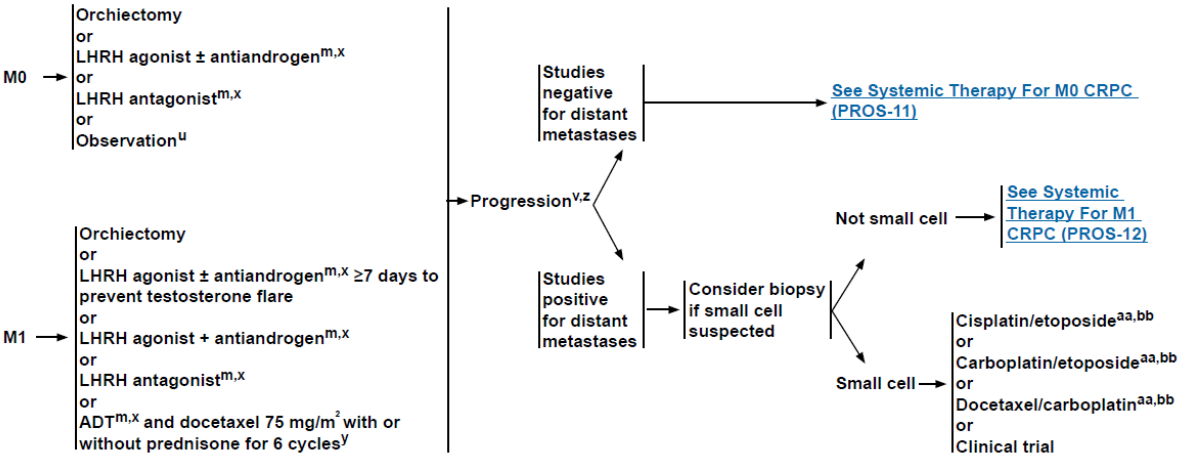


[i]See Principles of Radiation Therapy (PROS-D).
[j]See Principles of Surgery (PROS-E).
[k]Adverse laboratory/pathologic features include: positive margin(s), seminal vesicle invasion, extracapsular extension, or detectable PSA.
[l]Observation involves monitoring the course of disease with the expectation to deliver palliative therapy for the development of symptoms or a change in exam or PSA that suggests symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[m]See Principles of Androgen Deprivation Therapy (PROS-F).
[q]Six cycles of docetaxel every 3 weeks without prednisone may be administered after completion of radiation in selected patients who are fit for chemotherapy.
[r]RP + PLND can be considered in younger, healthier patients without tumor fixation to the pelvic side-wall.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PROS-6

SYSTEMIC THERAPY FOR PROGRESSIVE CASTRATION-NAIVE DISEASE[w]



[m] See Principles of Androgen Deprivation Therapy (PROS-F).
[u] Observation involves monitoring the course of disease with the expectation to begin ADT when symptoms develop or PSA changes to suggest symptoms are imminent. See Principles of Active Surveillance and Observation (PROS-C).
[v] Imaging should include chest x-ray, bone scan, and abdominal/pelvic CT or MRI with and without contrast. Consider C-11 choline PET/CT. See Principles of Imaging (PROS-B).
[w] The term "castration-naive" is used to define patients who are not on ADT at the time of progression. The NCCN Prostate Cancer Panel uses the term "castration-naive" even when patients have had neoadjuvant, concurrent, or adjuvant ADT as part of radiation therapy provided they have recovered testicular function.
[x] Intermittent ADT can be considered for men with M0 or M1 disease to reduce toxicity. See Principles of Androgen Deprivation Therapy (PROS-F)
[y] High-volume disease is differentiated from low-volume disease by visceral metastases and/or 4 or more bone metastases, with at least one metastasis beyond the pelvis vertebral column. Patients with low-volume disease have less certain benefit from early treatment with docetaxel combined with ADT.
[z] Assure castrate level of testosterone.
[aa] See Principles of Immunotherapy and Chemotherapy (PROS-G).
[bb] See NCCN Guidelines for Small Cell Lung Cancer.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.