

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2019-02-01-D-437 Apalutamid

Stand: November 2017

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

Apalutamid

zur Behandlung des nicht-metastasierten, kastrationsresistenten Prostatakarzinoms

Kriterien gemäß 5. Kapitel § 6 Verfo

Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.

Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“

Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.

- operative Behandlung
- Strahlentherapie

Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen

- Beschluss vom 17. Dezember 2009 über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung in Anlage III (Methoden, deren Bewertung ausgesetzt ist):
Interstitielle Brachytherapie bei lokal begrenzten Prostatakarzinom.
- 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:	
Apalutamid L02BB05 Erleada®	Anwendungsgebiet laut Zulassung: Erleada ist indiziert zur Behandlung erwachsener Männer mit nicht-metastasiertem kastrationsresistentem Prostatakarzinom (nmCRPC), die ein hohes Risiko für die Entwicklung von Metastasen aufweisen.
Antiandrogene	
Bicalutamid L02BB03 Bicalutamid medac®	Bicalutamid medac ist angezeigt entweder als alleinige Therapie oder adjuvant zu radikaler Prostatektomie oder Strahlentherapie bei Patienten mit lokal fortgeschrittenem Prostatakarzinom und hohem Progressionsrisiko.
Flutamid L02BB01 Flutamid-biosyn®	Zur Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine Suppression der Testosteronwirkungen indiziert ist. Initialtherapie in Kombination mit einem LH-RH-Analagon oder in Verbindung mit Orchiektomie (komplette Androgenblockade) sowie bei Patienten, die bereits mit einem LH-RH-Analagon behandelt werden bzw. bei denen bereits eine chirurgische Ablatio testis erfolgt ist. Zur Behandlung von Patienten, die auf andere endokrine Therapieformen nicht ansprechen oder für die eine andere endokrine Therapie nicht verträglich, aber notwendigerweise indiziert ist.
Cyproteron G03HA01 Androcur®-Depot	Androcur®-Depot wird ausschließlich bei Männern angewendet. Anwendungsgebiete sind: <ul style="list-style-type: none"> - palliative Therapie des metastasierenden oder lokal fortgeschrittenen inoperablen Prostatakarzinoms, wenn sich die Behandlung mit LHRH - Analoga oder der operative Eingriff als unzureichend erwiesen haben oder kontraindiziert sind. - initial zur Abmilderung des Flare-Phänomens, das zu Beginn der Behandlung mit LHRH-Agonisten durch den anfänglichen Anstieg des - Serum-Testosterons hervorgerufen werden kann.
Cyproteron G03HA01 Androcur®	<ul style="list-style-type: none"> - zur palliativen Therapie des metastasierenden oder lokal fortgeschrittenen, inoperablen Prostatakarzinoms, wenn sich die Behandlung mit LHRH-Analoga oder der operative Eingriff als unzureichend erwiesen haben, kontraindiziert sind oder der oralen Therapie der Vorzug gegeben wird, - initial zur Verhinderung von unerwünschten Folgeerscheinungen und Komplikationen, die zu Beginn einer Behandlung mit LHRH-Agonisten durch den anfänglichen Anstieg des Serum -Testosteron hervorgerufen werden können, - zur Behandlung von Hitzewallungen, die unter der Behandlung mit LHRH-Agonisten oder nach Hodenentfernung auftreten.

II. Zugelassene Arzneimittel im Anwendungsgebiet

GnRH-Antagonisten

Abarelix L02BX01 Plenaxis® ¹	Plenaxis® ist angezeigt zur Einleitung einer hormonalen Kastration bei fortgeschrittenem oder metastasierendem hormonabhängigem Prostatakarzinom, wenn eine Androgensuppression erforderlich ist.
Degarelix L02BX02 FIRMAGON®	FIRMAGON ist ein Gonadotropin-Releasing-Hormon-(GnRH)-Antagonist zur Behandlung von erwachsenen männlichen Patienten mit fortgeschrittenem hormonabhängigen Prostatakarzinom.

GnRH-Agonisten

Buserelin L02AE01 Profact®	Profact Depot 9,45 mg 3-Monatsimplantat ist angezeigt bei Erwachsenen zur Behandlung des fortgeschrittenen hormonempfindlichen Prostatakarzinoms. Profact Depot 9,45 mg 3-Monatsimplantat ist jedoch nicht angezeigt nach beidseitiger Orchiektomie, da es in diesem Fall zu keiner weiteren Absenkung des Testosteronspiegels kommt.
Goserelin L02AE03 Zoladex®	Behandlung von Patienten mit fortgeschrittenem Prostatakarzinom, bei denen eine endokrine Behandlung angezeigt ist.
Histerelin L02AE05 Vantas®	Palliative Behandlung bei fortgeschrittenem Prostatakrebs.
Leuprorelin L02AE02 ELIGARD®	ELIGARD 22,5 mg ist für die Behandlung des hormonabhängigen, fortgeschrittenen Prostatakarzinoms und in Kombination mit Radiotherapie für die Behandlung von lokalisiertem Hochrisiko- und lokal fortgeschrittenem hormonabhängigem Prostatakarzinom indiziert.
Triptorelin L01AA06 Pamorelin®	Pamorelin LA 3,75 mg ist indiziert zur Behandlung des <ul style="list-style-type: none"> • lokal fortgeschrittenen oder metastasierenden, hormonabhängigen Prostatakarzinoms. • lokal fortgeschrittenen, hormonabhängigen Prostatakarzinoms; begleitend zur und nach der Strahlentherapie.

Zytostatika

Estramustin L01XX11	Palliative Behandlung des fortgeschrittenen hormonrefraktären Prostatakarzinoms
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¹ Außer Vertrieb

II. Zugelassene Arzneimittel im Anwendungsgebiet

Estramustin- Uropharm®	
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Quellen: AMIS-Datenbank, Fachinformationen

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

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Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und evidenzbasierten systematischen Leitlinien zur Indikation kastrationsresistentes Prostatakarzinom durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 26.06.2017 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 670 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 12 Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Indikation:

Behandlung erwachsener Männer mit nicht-metastasiertem, kastrationsresistentem Prostatakarzinom mit hohem Risiko

Abkürzungen:

Akdae	Arzneimittelkommission der deutschen Ärzteschaft
ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CCO	Cancer Care Ontario
CRPC	Kastrationsresistentes Prostatakarzinom
DAHTA	Deutsche Agentur für Health Technology Assessment
DRKS	Deutsches Register Klinischer Studien
ESMO	European Society for Medical Oncology
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
ICTRP	International Clinical Trials Registry Platform
ISRCTN	International Standard Randomised Controlled Trial Number
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
mCRPC	Metastasiertes Kastrationsresistentes Prostatakarzinom
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
PSA	Prostata-spezifisches Antigen
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/G-BA Beschlüsse

<p>G-BA, 2008 [6].</p> <p>Protonentherapie, Indikation: Prostatakarzinom. Abschlussbericht des Unterausschusses „Methodenbewertung“ des Gemeinsamen Bundesausschusses. Beschlussdatum: 19.06.2008 Inkrafttreten: 01.01.2009</p>	<p>Fazit:</p> <p>Unter Berücksichtigung einer Risikostratifizierung nach klinischem Stadium, PSA Spiegel und Gleason-Score lassen die Daten zur Protonentherapie beim Prostatakarzinom sowohl für Patienten mit hohem als auch niedrigem Risiko die Aussage zu, dass die Protonentherapie ebenso wie die konformale Photonentherapie ohne schwere Nebenwirkungen wirksam ist. Berücksichtigt man die erheblich längeren Beobachtungszeiten aus den Protonentherapiestudien, die allerdings aus nur zwei Behandlungszentren stammen, so ist in Bezug auf die langfristigen Nebenwirkungsraten eine höhere Ergebnissicherheit im Vergleich zu den modernen Photonentherapieverfahren gegeben, wenngleich derzeit keine wesentlichen Unterschiede zu erkennen sind. Der Stellenwert der Protonentherapie im direkten Vergleich zur konformalen Photonentherapie kann anhand der vorliegenden Studien jedoch derzeit noch nicht abschließend bestimmt werden. Aus der im Mai 2008 durchgeführten dritten Update-Recherche ergibt sich keine Änderung dieser Bewertung. Angesichts der dargestellten Datenlage und des komplexen Abwägungsprozesses kann zum aktuellen Zeitpunkt keine generelle Präferenz für eine Therapieoption ausgesprochen werden. Für lokal fortgeschrittene (T3 N0 M0) und lokal begrenzte Prostatakarzinome (< T3) mit intermediate oder high risk (T2c und/oder PSA >10 und /oder Gleason Score >6) werden in Kürze 3-armige Studien in Deutschland aufgelegt, so dass hier mittelfristig aussagekräftige Ergebnisse zu erwarten sind. Somit erscheint es gerechtfertigt, das Bewertungsverfahren zunächst auszusetzen.</p>
<p>G-BA, 2010 [5].</p> <p>Interstitielle Brachytherapie beim lokal begrenzten Prostatakarzinom. Abschlussbericht Beratungsverfahren gemäß § 135 Abs. 1 SGB V</p> <p>Siehe auch:</p> <p>IQWiG, 2010 [8]</p> <p>Interstitielle Brachytherapie beim lokal begrenzten Prostatakarzinom – Update. Auftrag N10-01 Version 1.0</p>	<p>Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Richtlinie Methoden vertragsärztliche Versorgung in Anlage III: Interstitielle Brachytherapie beim lokal begrenzten Prostatakarzinom Vom 17. Dezember 2009</p> <p>Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 17.12.2009 beschlossen, die Anlage III der Richtlinie zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung) in der Fassung vom 17. Januar 2006 (BAnz. S. 1523), zuletzt geändert am 29. August 2009 (BAnz. S. 3005) wie folgt zu ändern:</p> <p>I. In der Anlage III „Methoden, deren Bewertung ausgesetzt ist“ wird nach Nummer 2 folgende Nummer 3 neu eingefügt:</p> <p>„Interstitielle Brachytherapie beim lokal begrenzten Prostatakarzinom</p> <p>§ 1 Gegenstand und Zweck des Beschlusses</p> <p>(1) Der Gemeinsame Bundesausschuss setzt im Rahmen der Methodenbewertung zur interstitiellen Brachytherapie mit permanenter Seedimplantation beim lokal begrenzten Prostatakarzinom die</p>

<p>Und:</p> <p>IQWiG, 2011 [7].</p> <p>Erratum zum Rapid Report Interstitielle Brachytherapie beim lokal begrenzten Prostatakarzinom – Update, Auftrag</p>	<p>Beschlussfassung gemäß Kapitel 2 § 14 Absatz 4 Spiegelstrich 1 der Verfahrensordnung des Gemeinsamen Bundesausschusses für 10 Jahre nach Inkrafttreten dieser Richtlinienänderung aus.</p> <p>(2) Die Aussetzung des Beschlusses erfolgt mit der Maßgabe, dass im Rahmen der vom Gemeinsamen Bundesausschuss festgelegten Anforderungen aussagekräftige wissenschaftliche Unterlagen innerhalb der vom Gemeinsamen Bundesausschuss festgelegten Frist beschafft werden.</p> <p>(3) Der Gemeinsame Bundesausschuss überprüft ein Jahr nach Inkrafttreten, welche Schritte zur Erfüllung der Maßgabe unternommen wurden. Danach informiert der GKVSpitzenverband den Gemeinsamen Bundesausschuss in regelmäßigen Abständen darüber, wie sich die Gewinnung wissenschaftlicher Daten entwickelt.</p> <p>§ 2 Anforderungen an die Anwendung der interstitiellen Brachytherapie im Rahmen des Aussetzungsbeschlusses</p> <p>Für die Anwendung der interstitiellen Brachytherapie beim lokal begrenzten Prostatakarzinom werden folgende Anforderungen festgelegt:</p> <ol style="list-style-type: none"> 1. Ziel ist die Gewinnung wissenschaftlicher Daten zum Nutzen im Hinblick auf patientenrelevante Endpunkte im Rahmen einer Studie. In der Studie sollten der Beginn einer Folgetherapie nach Ersttherapie und Tod als primäre Endpunkte angestrebt werden. Zusätzlich sollte der Surrogat-Endpunkt des PSA-Rezidivs erfasst werden. 2. Die wissenschaftliche Begleitung und die ICH-GCP-konforme (International Conference of Harmonisation - Good Clinical Practice) Durchführung sind durch eine in prospektiven Interventionsstudien erfahrene Institution sicherzustellen. 3. Ein- und Ausschlusskriterien für die Teilnahme an der Studie sind konkret und überprüfbar a priori festzulegen. 4. In der Studie ist ein mehrarmiges randomisiertes Studiendesign vorzusehen, bei dem die Brachytherapie mit der Prostatektomie, mit der perkutanen Strahlentherapie und möglichst mit der Active Surveillance verglichen wird. Patientenpräferenzen sind dabei soweit wie möglich zu berücksichtigen. Für den Fall einer Nicht-Überlegenheitsstudie für den primären Endpunkt muss gleichzeitig die Überlegenheit für einen anderen Endpunkt (z. B. behandlungsbedingte Komplikationen) gezeigt werden. 5. Im Rahmen der Studie ist sowohl eine standardisierte Patienteninformation als auch eine individualisierte Patientenaufklärung vorzusehen. 6. Es ist ein unabhängiges Bewertungsgremium vorzusehen, das das Erreichen des primären Endpunktes prospektiv anhand der Patientenbefunde bewertet und eine Behandlungsempfehlung abgibt. 7. Die Studie ist so zu konzipieren, dass nach einer Nachbeobachtungszeit von fünf Jahren Ergebnisse zu patientenrelevanten Endpunkten für den G-BA vorliegen, die den G-BA zu einer Entscheidung befähigen. 8. Im Rahmen der Studie sind einheitliche Anforderungen an die Struktur-, Prozess- und Ergebnisqualität festzulegen.
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	<p>9. Die Dokumentation des finanziellen und personellen Aufwands der untersuchten Therapieverfahren und eine gesundheitsökonomische Auswertung sind durchzuführen.</p> <p>10. Im Rahmen der Studie, insbesondere bei der Entwicklung der standardisierten Patienteninformation, sind Patientenvertreter zu beteiligen.“</p> <p>II. Die Änderung der Richtlinie tritt am Tag nach Veröffentlichung im Bundesanzeiger in Kraft.</p>
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Cochrane Reviews

Relevante Cochrane Reviews wurden durch die Recherche nicht identifiziert.

Systematische Reviews

Relevante systematische Reviews wurden durch die Recherche nicht identifiziert.

Leitlinien

<p>Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF), 2016 [9].</p> <p>Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms; Langversion 4.0</p>	<p>Fragestellung/Zielsetzung: Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF), AWMF-Register-Nummer 043/022OL</p>							
	<p>Methodik</p> <p><u>Grundlage der Leitlinie:</u></p> <ul style="list-style-type: none"> - Modulare Aktualisierung der LL; 3. Update <p><i>Evidenzbasierung:</i></p> <ul style="list-style-type: none"> - 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) <p><i>Konsensbasierung:</i></p> <ul style="list-style-type: none"> - Interdisziplinäre LL-Entwicklungsgruppe - CoI dargelegt und Umgang beschrieben - Strukturierte Konsensfindung <ul style="list-style-type: none"> - Die Leitlinie ist bis zur nächsten Aktualisierung gültig. Vorgesehen sind weitere modulare Aktualisierungen in einem etwa 2-3 jährlichen Abstand <p><u>LoE nach SIGN</u></p> <table border="1" style="width: 100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr> <th style="width: 10%;"></th> <th>Beschreibung</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">1 ++</td> <td>Qualitativ hochwertige Metaanalysen, systematische Übersichten von RCTs, oder RCTs mit sehr geringem Risiko systematischer Fehler (Bias)</td> </tr> <tr> <td style="text-align: center;">1 +</td> <td>Gut durchgeführte Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit geringem Risiko systematischer Fehler (Bias)</td> </tr> <tr> <td style="text-align: center;">1 -</td> <td>Metaanalysen, Systematische Übersichten von RCTs, oder RCTs mit hohem Risiko systematischer Fehler (Bias)</td> </tr> </tbody> </table>		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 -
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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

(Evidenztabelle 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 ‚Expertenkonsens‘ ersetzt den in den bisherigen Versionen der Leitlinie genutzten Begriff ‚Good Clinical Practice‘ (GCP).	

Freitext/Empfehlungen/Hinweise

6.4 Therapie des androgenunabhängigen oder kastrationsresistenten Prostatakarzinoms

6.24	Empfehlung	modifiziert 2014
Empfehlungsgrad A	Patienten mit kastrationsresistentem Prostatakarzinom sollen über folgende Inhalte aufgeklärt werden: <ul style="list-style-type: none"> • Eine Heilung kann nicht erreicht werden. • Für die weitere Behandlung stehen verschiedene Optionen zur Verfügung. 	
Level of Evidence 4	Expertenkonsens	
Gesamtabstimmung: 91 %		

6.25	Empfehlung	modifiziert 2014
Empfehlungsgrad B	Bei Patienten mit symptomatischer progredienter Erkrankung unter medikamentöser Kastration sollten die therapeutischen Optionen und das therapeutische Vorgehen interdisziplinär beraten und festgelegt werden.	
Level of Evidence 4	Expertenkonsens	
Gesamtabstimmung: 76 %		

6.26	Empfehlung	modifiziert 2011
Empfehlungsgrad A	Folgende für eine Therapieentscheidung ausschlaggebende Faktoren sollen beachtet werden: <ul style="list-style-type: none"> • Symptomatik • Nebenwirkungen der Therapieoptionen • Patientenpräferenz • Komorbidität, Lebenserwartung und Lebensqualität • Progressionsdynamik • Lokalisation von Metastasen und generelle Tumorlast. 	
Level of Evidence 4	Expertenkonsens	
Gesamtabstimmung: 84 %		

Hintergrundinformationen

Zu Empfehlung 6.24, 6.25 und 6.26

Die Behandlung des kastrationsresistenten Prostatakarzinoms ist eine palliative Therapie. Dieser Tatsache ist bei der Indikationsstellung zur Therapie Rechnung zu tragen. Die Patienten sind entsprechend aufzuklären.

6.27	Statement	neu 2014
Level of Evidence 4	Behandlungsfähigkeit für Chemotherapie ist keine eindeutig definierte Variable. Es fehlen daher Grenzwerte, ab denen Behandlungsfähigkeit gegeben bzw. nicht gegeben ist.	
	Expertenkonsens	
	Gesamtabstimmung: 98 %	

6.28	Statement	neu 2014
Level of Evidence 4	Patienten mit erhöhtem ECOG-Performance-Status (ECOG \geq 2) oder erniedrigtem Karnofsky-Index (< 70 %) und Patienten mit Einschränkungen im Geriatrischen Assessment weisen eine eingeschränkte Behandlungsfähigkeit auf.	
	Expertenkonsens	
	Gesamtabstimmung: 91 %	

6.29	Statement	neu 2014
Level of Evidence 4	Ein Geriatrisches Assessment ist zur Entscheidungsfindung vor Einleitung einer tumorspezifischen Therapie bei multimorbiden Patienten über 70 Jahre hilfreich.	
	Expertenkonsens	
	Gesamtabstimmung: 95 %	

6.30	Konsensbasierte Empfehlung	2011
EK	Bei Patienten mit progredienter Erkrankung unter chirurgischer oder medikamentöser Kastrationstherapie soll der Serumtestosteronspiegel kontrolliert werden.	

6.4.1. Erstlinientherapie asymptomatische oder gering symptomatische Patienten

6.31	Empfehlung	modifiziert 2014
Empfehlungsgrad A	Patienten mit kastrationsresistenter, asymptomatischer oder gering symptomatischer, progredienter Erkrankung ohne bildgebenden Nachweis von Metastasen soll ein abwartendes Vorgehen unter Beibehaltung der Androgendeprivation angeboten werden.	
Level of Evidence 4	Expertenkonsens auf der Grundlage von: [760-764].	
	Gesamtabstimmung: 95 %	

Hintergrundinformationen

Zu Empfehlung 6.31

Die Behandlung von Patienten mit ansteigendem PSA-Wert ohne bildgebenden Metastasennachweis war bis zur Aktualisierung 2013 nicht Bestandteil der Leitlinie. In den Studien zur Erstlinientherapie

mit Docetaxel [761; 762], Abirateron [763] und Sipuleucel-T [764] bei Patienten mit asymptomatischer oder gering symptomatischer und progredienter Erkrankung wurden nur Patienten mit metastasierter Erkrankung eingeschlossen. Da es keine Evidenz zur Therapie eines reinen PSA-Rezidivs mit Abirateron, Docetaxel oder Sipuleucel-T gibt, wird ein abwartendes Vorgehen empfohlen.

Die Datenlage zur Frage, ob eine laufende medikamentöse Androgendeprivation bei Diagnose eines Rezidivs fortgeführt oder abgebrochen werden sollte, ist sowohl qualitativ schwach als auch widersprüchlich (nicht in Evidenztabelle aufgeführt). Bei den publizierten Studien handelt es sich um retrospektive Analysen von kleinen Fallserien mit großem Risiko verzerrter Ergebnisse (Bias) [765-767] und um einen RCT mit wenigen Patienten, die sich von den in diesem Kapitel angesprochenen Patienten stark unterscheiden [768]. Diese Studien wurden in unterschiedlichen Patientenpopulationen mit PSA-Rezidiv durchgeführt. Während laut Taylor [765] die Unterbrechung der Androgendeprivation prognostisch ungünstig erscheint, kann Hussain diesen Zusammenhang nicht herstellen [767]. Bei Fowler [766] und Manni [768] wurden Patienten mit progredienter Erkrankung Androgene verabreicht und ein rascher Progress beobachtet. Die Ergebnisse lassen eine sichere Antwort auf die Frage der Auswirkungen des Absetzens einer bestehenden Androgendeprivation nicht zu. Es ist daher nicht möglich, eine evidenzbasierte Empfehlung zu geben. In der niederländischen Leitlinie von 2007 [158] wurde im Konsens entschieden, dass eine bestehende Androgendeprivation auch bei Rezidiv fortgeführt werden soll, während die EAU-Leitlinie [389] das genaue Gegenteil empfiehlt. Die NICE-Leitlinie [104] äußert sich zum Thema nicht in einer Empfehlung. Zahlreiche Substanzen sind zur sekundären Hormondeprivation des unter primärer Androgendeprivation progredienten Prostatakarzinoms getestet worden (z. B. Kortikosteroide, Ketoconazol, Aminoglutethimid, Östrogene, Progestagen, Tamoxifen, Somatostatin-Inhibitoren, Retinoide, Calcitriol). Nicht alle genannten Substanzen sind für diese Indikation zugelassen. Ketoconazol war in der EU für die Behandlung von Pilzinfektionen zugelassen. Aufgrund der Lebertoxizität wurde die Zulassung 2013 widerrufen. Von den genannten Substanzen zeigte sich lediglich für die Kortikosteroidtherapie eine nachgewiesene Wirksamkeit bezüglich klinisch relevanter Endpunkte [769; 770]. Dies bestätigte sich in der Update-Recherche 2011. Die einzige identifizierte randomisierte kontrollierte Studie zur Gabe von Kortikosteroiden im Vergleich zu einer zusätzlichen Gabe des selektiven Östrogenrezeptor-Modulators (SERM) Diethylstilbestrol ergab keinen statistisch signifikanten Benefit für die zusätzliche Gabe des SERM [771]. Verschiedene weitere Studien zu anderen Wirkstoffen mit

überwiegend kleinen Patientenzahlen sind auf den PSA-Verlauf als Hauptendpunkt beschränkt. Der Einsatz von Kortikosteroiden allein oder in Kombination mit anderen Substanzen kann sowohl Symptome lindern als auch die Lebensqualität vorübergehend bessern [772].

Eine Reihe von Einzelfallberichten und Fallserien zeigen bei einem Teil der Patienten einen Rückgang des PSA-Wertes nach dem Absetzen einer medikamentösen Androgendeprivation [773-777]. Die Experten schätzen diese Evidenz als so schwach ein, dass die Beendigung der Androgendeprivation nicht als gleichwertige Therapieoption zu Beibehaltung bzw. Modifikation der Androgendeprivation angesehen wird. Das Risiko einer Progredienz unter Absetzen der Androgendeprivation wird als so hoch eingeschätzt, dass diese Option nicht empfohlen wird.

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6.4.2. Erstlinientherapie symptomatische Patienten

6.41	Empfehlung	neu 2014
Empfehlungsgrad A	Patienten mit kastrationsresistenter, symptomatischer, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG \geq 2, Karnofsky-Index < 70) soll eine symptombezogene Therapie angeboten werden.	
Level of Evidence 4	Expertenkonsens	
	Gesamtabstimmung: 95 %	
6.42	Empfehlung	neu 2014
Empfehlungsgrad O	Patienten mit kastrationsresistenter, symptomatischer, progredienter Erkrankung und reduziertem Allgemeinzustand (ECOG \geq 2, Karnofsky-Index < 70) kann als Erstlinientherapie zusätzlich eine der folgenden Therapieoptionen angeboten werden: <ul style="list-style-type: none"> • Abirateron • Chemotherapie, wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist • Radium-223 bei ossärer Metastasierung • Steroide (Dexamethason, Prednisolon, Prednison) • Bisphosphonate/Denosumab bei ossärer Metastasierung allein oder in Kombination mit 1.-4., siehe auch Empfehlung 6.53 	
Level of Evidence 4	Expertenkonsens basierend auf [761-763; 786]	
	Gesamtabstimmung: 95 %	

Zu Empfehlung 6.41 und 6.42

	<p>Wie in Statement 6.28 beschrieben, weisen Patienten mit schlechtem Allgemeinzustand (ECOG \geq 2, Karnofsky-Index $<$ 70 %) und Patienten mit Einschränkungen im Geriatriischen Assessment eine eingeschränkte Behandlungsfähigkeit auf. Es gibt keine randomisierten Studien für die Therapie von Patienten mit symptomatischer progredienter Erkrankung und einem reduzierten Allgemeinzustand (ECOG \geq 2). In den Studien zu Abirateron (ECOG: 0-1), Radium-223 (ECOG: 0-2) und Docetaxel (Karnofsky-Index \geq 60 %) waren keine oder nur wenige Patienten mit reduziertem Allgemeinzustand eingeschlossen. Daher wird für diese Patienten eine symptombezogene Therapie empfohlen. Des Weiteren können als Erstlinientherapie zusätzlich verschiedene Therapieoptionen angeboten werden. Hinweise bzw. Einschränkungen bei den Therapieoptionen werden in den Hintergrundtexten zu den Empfehlungen 6.37-6.40 diskutiert.</p> <p>Nur wenn der reduzierte Allgemeinzustand vor allem auf das metastasierte Prostatakarzinom zurückzuführen ist, kann eine Chemotherapie mit Docetaxel, Mitoxantron oder Estramustin angeboten werden.</p>
<p>National Comprehensive Cancer Network (NCCN), 2017 [12].</p> <p>Prostate Cancer</p>	<p>Fragestellung/Zielsetzung: Diagnose, Pathologie, Staging, Therapie des PCA</p> <hr/> <p>Methodik</p> <p>Grundlage der Leitlinie:</p> <p>Allgemeiner NCCN-Methodenreport beschreibt systematische Evidenzaufbereitung mit Konsensusprozessen -</p> <p>Update der LL von 2016.</p> <p>Suchzeitraum: in PubMed zwischen 09/2015 und 09/2016</p> <p>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.</p> <p>The PubMed search resulted in 301 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.</p> <p>GoR, LoE:</p>

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.

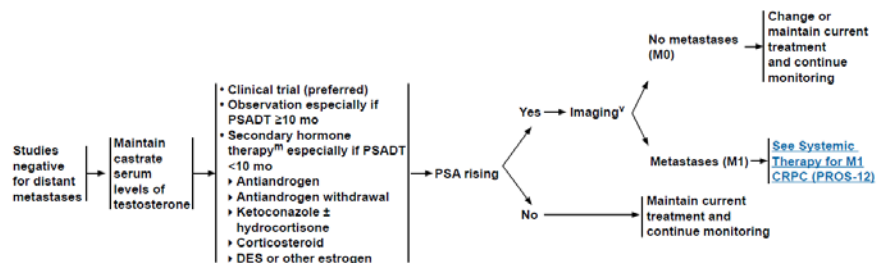
All recommendations are category 2A unless otherwise noted.

Methodische Hinweise

- Repräsentativität der Gremien unklar
- ob formalisierte Konsensusverfahren angewendet werden ist unklar
- industriefinanziert
- Bewertung der Studien unklar

Freitext/Empfehlungen/Hinweise

SYSTEMIC THERAPY FOR M0 CASTRATION-RECURRENT PROSTATE CANCER



^mSee Principles of Androgen Deprivation Therapy (PROS-F).

^vImaging 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).

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.

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Androgen Deprivation Therapy (ADT) for Clinically Localized Disease (PROS-2 through PROS-5), Biochemical Failure Without Metastases OR for Metastatic 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

Secondary Hormone Therapy for M0 or M1 Castration-Recurrent Disease (PROS-11 through PROS-14):

- First-generation antiandrogen
 - › Nilutamide
 - › Flutamide
 - › Bicalutamide
- Second-generation antiandrogen
 - › Enzalutamide
- Ketoconazole
- Ketoconazole plus hydrocortisone
- Corticosteroids (hydrocortisone, prednisone, dexamethasone)
- DES or other estrogen

Systemic Therapy For M1 Castration-Recurrent Disease (PROS-12 through PROS-14):

- Second generation antiandrogen
 - › Enzalutamide (category 1; category 2A if prior therapy with abiraterone)
- Androgen biosynthesis inhibitor
 - › Abiraterone + prednisone (category 1; category 2A for initial treatment of disease with visceral metastases or if prior therapy with enzalutamide)

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.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

ADT for Biochemical Failure Without Metastases

- The timing of ADT for patients whose only evidence of cancer is a rising PSA is influenced by PSA velocity, patient anxiety, the short- and long-term side effects of ADT, and the underlying comorbidities of the patient.
- Most patients will have a good 15-year prognosis, but their prognosis is best approximated by the absolute level of PSA, the rate of change in the PSA level (PSADT), and the initial stage, grade, and PSA level at the time of definitive therapy.
- 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 individualized 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.
- Some patients are candidates for salvage after biochemical failure, which may include radiation after failed operation or RP or cryosurgery after failed radiation.
- Men with prolonged PSADTs (>12 mo) and who are older are candidates for observation.
- Men who choose ADT should consider intermittent ADT. A phase 3 trial that compared intermittent to continuous ADT showed that intermittent ADT was not inferior to continuous ADT with respect to survival, and quality of life was better for the intermittent ADT arm. The 7% increase in prostate cancer deaths in the intermittent ADT arm was balanced by more non-prostate cancer deaths in the continuous ADT arm. An unplanned subset analysis showed that men with Gleason sum 9–10 prostate cancer in the continuous arm had a median overall survival that was 14 mo longer (8 y) than those in the intermittent arm (6.8 y).

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.

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PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Secondary Hormone Therapy

- Androgen receptor activation and autocrine/paracrine androgen synthesis are potential mechanisms of recurrence of prostate cancer during ADT (CRPC). Thus, castrate levels of testosterone should be maintained while additional therapies are applied.
- Once the tumor becomes resistant to initial ADT, there are a variety of options that may afford clinical benefit. The available options are based on whether the patient has evidence of metastases by imaging, M0 CRPC (non-metastatic) vs. M1 CRPC (metastatic), and whether or not the patient is symptomatic.
- In the setting in which patients have no or minimal symptoms, administration of secondary hormonal therapy including addition of, or switching to, a different anti-androgen (flutamide, bicalutamide, nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole with or without hydrocortisone or abiraterone with prednisone), or use of an estrogen, such as DES, can be considered. Ketoconazole ± hydrocortisone should not be used if the disease progressed on abiraterone.
- DES has cardiovascular and thromboembolic side effects at any dose but frequency is dose and agent dependent. DES should be initiated at 1 mg/d and increased, if necessary, to achieve castrate levels of serum testosterone (<50 ng/dL). Other estrogens delivered topically or parenterally may have less frequent side effects but data are limited.
- In a randomized controlled trial in the setting of M1 CRPC prior to docetaxel chemotherapy, abiraterone (1000 mg daily on an empty stomach) and low-dose prednisone (5 mg BID) compared to prednisone alone improved radiographic progression-free survival (rPFS), time to initiation of chemotherapy, time to onset or worsening of pain, and time to deterioration of performance status. An improvement in overall survival was demonstrated. Use of abiraterone and prednisone in this setting is a category 1 recommendation. The side effects of abiraterone that require ongoing monitoring include hypertension, hypokalemia, peripheral edema, atrial fibrillation, congestive heart failure, liver injury, and fatigue, as well as the known side effects of ADT and long-term corticosteroid use.

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.

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ADT for Clinically Localized Disease

- Neoadjuvant ADT for RP is strongly discouraged outside of a clinical trial.
- ADT should not be used as monotherapy in clinically localized prostate cancer.
- Giving ADT before, during, and/or after radiation prolongs survival in selected radiation-managed patients.
- Studies of short-term (4–6 mo) and long-term (2–3 y) neoadjuvant ADT all have used complete androgen blockade. Whether the addition of an antiandrogen is necessary requires further study.
- In the largest randomized trial to date using the antiandrogen bicalutamide alone at high dose (150 mg), there were indications of a delay in recurrence of disease but no improvement in survival. Longer follow-up is needed.
- In one randomized trial, immediate and continuous use of ADT in men with positive nodes following RP resulted in significantly improved overall survival compared to men who received delayed ADT. Therefore, such patients should be considered for immediate ADT.
- Many of the side effects of continuous ADT are cumulative over time on ADT.

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 the 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 to the continuous ADT arm.
- In addition, three meta-analyses of randomized controlled trials failed to show a difference in survival between intermittent and continuous ADT.
- Close monitoring of PSA and testosterone levels and possibly imaging is required when using intermittent ADT, especially during off-treatment periods, and patients may need to switch to continuous ADT upon signs 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 combined with an antiandrogen) provides modest to no benefit over castration 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 for patients with overt metastases who are at risk of developing symptoms associated with the flare in testosterone with initial LHRH agonist alone.
- Antiandrogen monotherapy appears to be less effective than medical or 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 castration can be considered for additional hormonal manipulations (with estrogen, antiandrogens, LHRH antagonists, or steroids), although the clinical benefit remains uncertain. The optimal level of serum testosterone to effect “castration” has yet to be determined.

- A phase 3 study of docetaxel-naïve men showed that enzalutamide (160 mg daily) resulted in significant improvement in rPFS and overall survival. The use of enzalutamide in this setting is category 1. The side effects of enzalutamide that require long-term monitoring include fatigue, diarrhea, hot flashes, headache, and seizures (reported in 0.9% of men on enzalutamide).
- Both randomized trials of abiraterone and enzalutamide in the pre-docetaxel setting were conducted in men who had no or minimal symptoms due to M1 CRPC. How these agents compare to docetaxel for pain palliation in this population of patients is not clear. Both drugs have palliative effects in the post-docetaxel setting. Both abiraterone and enzalutamide are approved in this setting and have category 1 recommendations. Both drugs are suitable options for men who are not good candidates to receive docetaxel.
- In the post-docetaxel CRPC population, enzalutamide and abiraterone plus prednisone have been shown to extend survival in randomized controlled trials. Therefore, each agent has a category 1 recommendation.
- Two randomized clinical trials (STRIVE and TERRAIN) showed that 160 mg/d enzalutamide improved progression-free survival compared with 50 mg/d bicalutamide in men with treatment-naïve CRPC and, therefore, enzalutamide may be the preferred option in this setting. However, bicalutamide can still be considered in some patients, given the different side-effect profiles of the agents and the increased cost of enzalutamide.
- Evidence-based guidance on the sequencing of these agents in either pre- or post-docetaxel remains unavailable.

PRINCIPLES OF ANDROGEN DEPRIVATION THERAPY

Monitor/Surveillance

• ADT has a variety of adverse effects including hot flashes, loss of libido and erectile dysfunction, shrinkage of penis and testicles, loss of muscle mass and strength, fatigue, depression, hair loss, osteoporosis, greater incidence of clinical fractures, obesity, insulin resistance, alterations in lipids, and greater risk for diabetes and cardiovascular disease. Patients and their medical providers should be advised about these risks prior to treatment.

• Screening and treatment for osteoporosis are advised according to guidelines for the general population from the National Osteoporosis Foundation (www.nof.org). The National Osteoporosis Foundation guidelines include recommendations for: 1) supplemental calcium (1200 mg daily) and vitamin D3 (800–1000 IU daily) for all men >50 y of age; and 2) additional treatment for men when the 10-y probability of hip fracture is $\geq 3\%$ or the 10-y probability of a major osteoporosis-related fracture is $\geq 20\%$. Fracture risk can be assessed using FRAX[®], the algorithm recently released by WHO. ADT should be considered “secondary osteoporosis” when using the FRAX[®] algorithm. Treatment options to increase bone density, a surrogate for fracture risk in men without metastases, include denosumab (60 mg SQ every 6 mo), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly).

• A baseline DEXA scan should be obtained before starting therapy in men at increased risk for fracture based on FRAX[®] screening.

A follow-up DEXA scan after 1 year of therapy is recommended by the International Society for Clinical Densitometry, although there is no consensus on the optimal approach to monitoring the effectiveness of drug therapy. Use of biochemical markers of bone turnover to monitor response to therapy is not recommended. The serum level of 25-hydroxy vitamin D and average daily dietary intake of vitamin D will assist the nutritionist in making a patient-specific recommendation for vitamin D supplementation. There are currently no guidelines on how often to monitor vitamin D levels. However, for those who require monitoring with DEXA scans, it makes sense to check the serum vitamin D level at the same time.

• Denosumab (60 mg SQ every 6 mo), zoledronic acid (5 mg IV annually), and alendronate (70 mg PO weekly) increase bone mineral density, a surrogate for fracture risk, during ADT for prostate cancer. Treatment with either denosumab, zoledronic acid, or alendronate sodium is recommended when the absolute fracture risk warrants drug therapy.

• Screening for and intervention to prevent/treat diabetes and cardiovascular disease are recommended in men receiving ADT. These medical conditions are common in older men and it remains uncertain whether strategies for screening, prevention, and treatment of diabetes and cardiovascular disease in men receiving ADT should differ from the general population.

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.

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CRPC without Signs of Metastasis

Clinical trial is the preferred choice for patients with CRPC and no signs of distant metastasis (M0). Observation is another option especially if PSA doubling time is ≥ 10 months since these patients will have a relatively indolent disease history.⁴⁷¹ Secondary hormone therapy is an option mainly for patients with shorter PSA doubling time (<10 months), because the androgen receptor may remain active. Patients whose disease progresses on combined androgen blockade should have the anti-androgen discontinued to exclude an “anti-androgen withdrawal response.”^{472,473} Secondary hormone therapy can be an anti-androgen for patients who initially received medical or surgical castration, anti-androgen withdrawal, ketoconazole (adrenal enzyme inhibitor) with or without hydrocortisone, corticosteroid, diethylstilbestrol (DES), or other estrogen.^{474,475} However, none of these strategies has yet been shown to prolong survival in randomized clinical trials in men who have not yet received docetaxel-based chemotherapy.

471. Smith MR, Kabbavar F, Saad F, et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. *J Clin Oncol* 2005;23:2918-2925. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15860850>.

472. Dupont A, Gomez JL, Cusan L, et al. Response to flutamide withdrawal in advanced prostate cancer in progression under combination therapy. *J Urol* 1993;150:908-913. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7688437>.

473. Sartor AO, Tangen CM, Hussain MH, et al. Antiandrogen withdrawal in castrate-refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9426). *Cancer* 2008;112:2393-2400. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18383517>.

474. Small EJ, Halabi S, Dawson NA, et al. Antiandrogen withdrawal alone or in combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583). *J Clin Oncol*

	<p>2004;22:1025-1033. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15020604.</p> <p>475. Oh WK, Kantoff PW, Weinberg V, et al. Prospective, multicenter, randomized phase II trial of the herbal supplement, PC-SPE5, and diethylstilbestrol in patients with androgen-independent prostate cancer. J Clin Oncol 2004;22:3705-3712. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15289492.</p>														
<p>Mottet N et al., 2016 [10].</p> <p>EAU - ESTRO - SIOG Guidelines on Prostate Cancer</p>	<p>Fragestellung/Zielsetzung: The European Association of Urology (EAU) Prostate Cancer Guidelines Panel have prepared this guidelines document to assist medical professionals assess the evidence-based management of prostate cancer (PCa).</p> <hr/> <p>Methodik</p> <p>Grundlage der Leitlinie</p> <ul style="list-style-type: none"> • The Prostate Cancer Guidelines Panel consists of an international multidisciplinary group of urologists, radiation oncologists, medical oncologists, a radiologist, a pathologist and a patient representative. • New and relevant evidence has been identified, collated and appraised through a structured assessment of the literature and incorporated in all chapters of the 2016 EAU PCa Guidelines. • 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 <i>von 2014</i> • Suchzeitraum: bis April 24th 2015 <p>LoE und GoR</p> <p>A classification system modified from the Oxford Centre for Evidence-Based Medicine Levels of Evidence</p> <p>Table 1: Level of evidence*</p> <table border="1" data-bbox="534 1568 1380 1892"> <thead> <tr> <th>Level</th> <th>Type of evidence</th> </tr> </thead> <tbody> <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> </tbody> </table> <p><i>*Modified from Sackett, et al. (1).</i></p>	Level	Type of evidence	1a	Evidence obtained from meta-analysis of randomised trials	1b	Evidence obtained from at least one randomised trial	2a	Evidence obtained from one well-designed controlled study without randomisation	2b	Evidence obtained from at least one other type of well-designed quasi-experimental study	3	Evidence obtained from well-designed non-experimental studies, such as comparative studies, correlation studies and case reports	4	Evidence obtained from expert committee reports or opinions or clinical experience of respected authorities
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Table 2: Grade of recommendation*

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

*Modified from Sackett, et al. (1).

Sonstige methodische Hinweise

Studiencharakteristika sowie Qualitätsbeurteilung nicht gelistet.

Freitext/Empfehlungen/Hinweise

6.11 Treatment: Castration-resistant PCa (CRPC)

6.11.2 Definition of progressing PCa after castration

Frequent post-treatment PSA surveillance has resulted in earlier detection of progression. Although approximately one-third of men with a rising PSA will develop bone metastases within 2 years [825], there are no available studies suggesting a benefit for immediate treatment.

In men with CRPC and no detectable clinical metastases, baseline PSA level, PSA velocity and PSA doubling time have been associated with time to first bone metastasis, bone metastasis-free and OS [825, 826]. These factors may be used when deciding which patients should be evaluated for metastatic disease. A consensus statement by the PCa Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group [827] suggested a bone scan when the PSA reached 2 ng/mL and if this was negative it should be repeated when the PSA reached 5 ng/mL and again after every doubling of the PSA based on PSA-testing every 3 months for asymptomatic men. Symptomatic patients should undergo relevant investigation regardless of PSA level.

The rest of this Section focuses on management of men with proven metastatic CRPC (mCRPC).

6.11.10 Summary of evidence and guidelines for life-prolonging treatments of castrate-resistant PCa

Summary of evidence	LE
No definitive strategy regarding treatment choice (which drug/drug family first) can be devised	4
No clear-cut recommendation can be made for the most effective drug for secondary treatment (i.e. hormone therapy or chemotherapy) as no clear predictive factors exist.	3

Recommendation	LE	GR
Ensure that testosterone levels are confirmed to be < 50 ng/mL, before diagnosing CRPC.	4	A
Do not treat patients for <u>non-metastatic</u> CRPC outside of a clinical trial.	3	A

	<table border="1" data-bbox="523 192 1398 293"> <tr> <td data-bbox="523 192 1278 293">In men treated with maximal androgen blockade, stop anti-androgen therapy once PSA progression is documented. <i>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</i></td> <td data-bbox="1278 192 1337 293">2a</td> <td data-bbox="1337 192 1398 293">A</td> </tr> </table> <p data-bbox="523 376 1398 405">6.11.11 Guidelines for cytotoxic treatment in castrate-resistant PCa</p> <table border="1" data-bbox="523 423 1398 479"> <thead> <tr> <th data-bbox="523 423 1278 452">Recommendation</th> <th data-bbox="1278 423 1337 452">LE</th> <th data-bbox="1337 423 1398 452">GR</th> </tr> </thead> <tbody> <tr> <td data-bbox="523 452 1278 479">In non-metastatic CRPC, offer cytotoxic therapy only in a clinical trial setting.</td> <td data-bbox="1278 452 1337 479">3</td> <td data-bbox="1337 452 1398 479">B</td> </tr> </tbody> </table> <p data-bbox="523 551 1398 786"> 825. Smith, M.R., et al. Natural history of rising serum prostate-specific antigen in men with castrate nonmetastatic prostate cancer. J Clin Oncol, 2005. 23: 2918. http://www.ncbi.nlm.nih.gov/pubmed/15860850 826. Smith, M.R., et al. Disease and host characteristics as predictors of time to first bone metastasis and death in men with progressive castration-resistant nonmetastatic prostate cancer. Cancer, 2011. 117: 2077. http://www.ncbi.nlm.nih.gov/pubmed/21523719 827. Crawford, E.D., et al. Challenges and recommendations for early identification of metastatic disease in prostate cancer. Urology, 2014. 83: 664. http://www.ncbi.nlm.nih.gov/pubmed/24411213 </p>	In men treated with maximal androgen blockade, stop anti-androgen therapy once PSA progression is documented. <i>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</i>	2a	A	Recommendation	LE	GR	In non-metastatic CRPC, offer cytotoxic therapy only in a clinical trial setting.	3	B
In men treated with maximal androgen blockade, stop anti-androgen therapy once PSA progression is documented. <i>Comment: Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect will be apparent.</i>	2a	A								
Recommendation	LE	GR								
In non-metastatic CRPC, offer cytotoxic therapy only in a clinical trial setting.	3	B								
<p data-bbox="199 801 485 954">Alberta Provincial Genitourinary Tumour Team, 2015 [1].</p> <p data-bbox="199 987 411 1016">Prostate cancer</p>	<p data-bbox="523 813 1299 920">Fragestellung/Zielsetzung: The purpose of this guideline is to describe the appropriate management and follow up strategies for prostate cancer.</p> <p data-bbox="523 949 1398 1480"> Methodik Grundlage der Leitlinie: Repräsentatives Gremium, konsentiert klinische Fragestellungen, nach systematischer Literatursuche, -bewertung und –aufbereitung in Evidenztabelle 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 </p> <p data-bbox="523 1514 1369 1890"> Freitext/Empfehlungen/Hinweise Stage M+ Castrate Resistant Disease ... With regards to systemic therapy, it is important to note that chemotherapy is not indicated in patients without evidence of metastatic disease on imaging whose only have manifestation of hormone insensitive disease is a rising PSA. ... </p>									
<p data-bbox="199 1915 467 1989">Cookson MS et al., 2013 [3].</p>	<p data-bbox="523 1921 1374 2029">Fragestellung/Zielsetzung: The goal of this Guideline is to provide evidence based recommendations for the treatment of CRPC. Given that this is a</p>									

<p>American Urological Association</p> <p>Castration-resistant prostate cancer: AUA Guideline</p> <p>Sowie:</p> <p>Cookson MS et al., 2015 [2].</p>	<p>rapidly evolving field, this guideline should be used in conjunction with recent systematic literature reviews and an understanding of the individual patient's treatment goals. In all cases, the patient's preferences and personal goals should be considered when choosing therapy. Although we are discussing castration-resistant disease, we support the standard of care to maintain castrate testosterone levels even in the face of castration-resistant disease.</p> <p>Index patient 1: Asymptomatic non-metastatic CRPC</p>
<p>American Urological Association</p> <p>Castration-resistant prostate cancer: AUA guideline amendment</p>	<p>Methodik</p> <p>Grundlage der Leitlinie:</p> <p>Leitlinienpanel aus Mitgliedern der American Urological Association Education and Research, Inc. (AUA); systematische Literatursuche, -bewertung und –aufbereitung, Konsensusverfahren nicht näher beschrieben, Peer-Review-Verfahren, Interessenkonflikte offengelegt</p> <p>Suchzeitraum: The search strategy was developed and executed by reference librarians and methodologists and spanned across multiple databases including Ovid Medline In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Database of Systematic Reviews, Ovid Cochrane Central Register of Controlled Trials and Scopus. The evidence report was limited to English-language, peer-reviewed literature published between January 1996 and February 2013. Comprehensive searches of several databases from February 2013 to February 2014 (2014 amendment) and February 2014 to February 2015 (2015 amendment).</p> <p>LoE / GoR:</p> <p>AUA Nomenclature: Linking Statement Type to Evidence Strength.</p> <p>The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgment regarding the balance between benefits and risks/burdens (see Table 1).The framework of rating the quality of evidence is an adaptation and modification of the GRADE framework (Grading of Recommendations, Assessment, Development and Evaluation). In this adaptation, the AUA rates the quality of evidence as high, moderate or low (A, B or C).</p>

**Table 1: AUA Nomenclature
Linking Statement Type to Evidence
Strength**

Standard: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade A or B evidence

Recommendation: Directive statement that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be taken based on Grade C evidence

Option: Non-directive statement that leaves the decision regarding an action up to the individual clinician and patient because the balance between benefits and risks/burdens appears equal or appears uncertain based on Grade A, B, or C evidence

Clinical Principle: a statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature

Expert Opinion: a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence

Freitext/Empfehlungen/Hinweise

Index Patient 1: Asymptomatic non-metastatic CRPC

Guideline Statement 1.

Clinicians should recommend observation with continued androgen deprivation to patients with non-metastatic CRPC.
(Recommendation; Evidence Level Grade C)

Discussion:

In men with non-metastatic CRPC, no treatment has been shown to prolong OS. Since all agents have potential side effects and no treatment has been shown to extend survival, we must first do no harm. As such, it is the panel judgment that no treatment (i.e. observation) other than continued androgen deprivation therapy (ADT) be the recommended treatment based upon the lack of any data to refute this recommendation. Given the lack of data showing that any treatment in this disease setting meaningfully impacts clinical outcome, there is a strong panel judgment that patients should be encouraged to enter clinical trials, when available.

Guideline Statement 2.

Clinicians may offer treatment with first- generation anti-androgens (flutamide, bicalutamide and nilutamide) or first generation androgen synthesis inhibitors (ketoconazole+steroid) to select patients with non-metastatic CRPC who are unwilling to accept observation. (Option; Evidence Level Grade C)

Discussion:

While it is the panel's judgment that observation is the most appropriate treatment for this patient population, some patients in this setting may be uncomfortable with treatment with systematic ADT alone and may wish to initiate additional treatment despite the lack of good evidence with regards to their benefits and harms in this setting.

Anti-androgens: Though anti-androgens (flutamide, bicalutamide and nilutamide) are commonly used, these agents can be associated with side effects including gastrointestinal upset and liver toxicity. Though some small single-arm non-randomized studies suggest a PSA benefit,¹⁷⁻²² the actual PSA benefit appears modest with PSA declines >50% occurring typically in 20-40% of men with a median duration measured in several months. In addition, anti-androgen withdrawal has been used as an option in this setting. There are no randomized studies of either anti-androgens or anti-androgen withdrawal compared to observation, and as such there is a lack of data suggesting any meaningful clinical benefit, such as delayed disease progression, improved QOL or OS compared to the recommended treatment of observation. As such, the data associated with this statement rated a C-level. There are no published reports of the newest generation of oral anti-androgens in this patient population. Though the mechanism of action appears similar to previously-studied anti-androgens, given the lack of data, the efficacy and side effect profile of this newer generation of anti-androgens in this population is unknown.

Androgen synthesis inhibitors (ketoconazole): The oral androgen synthesis inhibitor ketoconazole is often used for men with non-metastatic CRPC. Ketoconazole is a weak inhibitor of CYP11A and CYP17A and suppresses the synthesis of adrenal and tumor tissue androgens. Ketoconazole can be associated with nausea and hepatotoxicity and must be given with replacement steroids. There are numerous single-arm studies²³⁻²⁹ that show PSA response rates (>50% decline in PSA) of 30-60% with typical responses around 50%. Only one published report³⁰ of abiraterone + prednisone included men with non- metastatic CRPC. Since only four men with non-metastatic CRPC were included in this study, it prevents any meaningful conclusions for the use of such a treatment in this

patient population. Additional androgen synthesis inhibitors are available or in development, but there is currently no data to support their use in this patient population.

17. Fujii Y, Kawakami S, Masuda H et al: Deferred combined androgen blockade therapy using bicalutamide in patients with hormone-refractory prostate cancer during androgen deprivation monotherapy. *BJU Int* 2006; 97: 1184.
18. Fujikawa K, Matsui Y, Fukuzawa S et al: Prostate-specific antigen levels and clinical response to flutamide as the second hormone therapy for hormone-refractory prostate cancer. *Eur Urol* 2000; 37: 218.
19. Kojima S, Suzuki H, Akakura K et al: Alternative antiandrogens to treat prostate cancer relapse after initial hormone therapy. *J Urol* 171: 679.
20. Miyake H, Hara I and Eto H: Clinical outcome of maximum androgen blockade using flutamide as second-line hormonal therapy for hormone-refractory prostate cancer. *BJU Int* 2005; 96: 791.
21. Nakabayashi M, Regan MM, Lifsey D et al: Efficacy of nilutamide as secondary hormonal therapy in androgen-independent prostate cancer (AIPC). *J Clin Oncol* 2005; 23: 4683.
22. Nishimura K, Arichi N, Tokugawa S et al: Effects of flutamide as a second-line agent for maximum androgen blockade of hormone refractory prostate cancer. *Int J Urol* 2007; 14: 264.
23. Harris KA, Weinberg V, Bok RA et al: Low dose ketoconazole with replacement doses of hydrocortisone in patients with progressive androgen independent prostate cancer. *J Urol* 2002; 168: 542.
24. Nakabayashi M, Xie W, Regan MM et al: Response to low-dose ketoconazole and subsequent dose escalation to high-dose ketoconazole in patients with androgen-independent prostate cancer. *Cancer* 2006; 107: 975.
25. Ngo LS, Yeo A, Wong AS et al: Efficacy of low-dose ketoconazole in hormone refractory prostate cancer patients at the National Cancer Centre and The Cancer Institute, Singapore. *Ann Acad Med Singapore* 2007; 36: 811.
26. Scholtz M, Jennrich R, Strum S et al: Long-term outcome in men with androgen independent prostate cancer treated with ketoconazole and hydrocortisone. *J Urol* 2005; 173: 1947.
27. Small EJ, Baron A and Bok R: Simultaneous antiandrogen withdrawal and treatment with ketoconazole and hydrocortisone in patients with advanced prostate carcinoma. *Cancer* 1997; 80: 1755.
28. Taplin ME, Regan MM, Ko YJ et al: Phase II study of androgen synthesis inhibition with ketoconazole, hydrocortisone, and dutasteride in asymptomatic castration-resistant prostate cancer. *Clin Cancer Res* 2009; 15: 7099.
29. Wilkinson S and Chodak G: An evaluation of intermediate-dose ketoconazole in hormone refractory prostate cancer. *Eur Urol* 2004; 45: 581.
30. Attard G, Reid AHM, A'Hern R et al: Selective inhibition of CYP17 with abiraterone acetate is highly active in the treatment of castration-resistant prostate cancer. *J Clin Oncol* 2009; 27: 3742.

Guideline Statement 3.

Clinicians should not offer systemic chemotherapy or immunotherapy to patients with non-metastatic CRPC outside the context of a clinical trial. (Recommendation; Evidence Level Grade C)

Discussion:

The past few years have seen a plethora of new treatments for men with mCRPC. Indeed, multiple agents have been shown to prolong survival for men with mCRPC. However, there is no data to support their use in this non-metastatic CRPC patient population. Thus, the panel strongly recommends against this practice due to a lack of outcome data in the non-metastatic disease setting.

Of the classes of agents recommended against, only denosumab

	<p>has been systematically studied in this non-metastatic state. Denosumab 120 mg subcutaneously monthly, which in a placebo-controlled randomized trial,¹¹ was shown to modestly delay the development of radiographically detected bone metastases, but it did not impact QOL or OS. This agent showed only a modest delay in bone metastases of three months and was specifically denied approval by the FDA for this indication. It was associated with significant side-effects, including osteonecrosis of the jaw. Thus, monthly denosumab is not indicated for non-metastatic CRPC.</p> <p>Thus, the primary reason the panel recommends against the routine use of these agents in this patient population is concerns about toxicity. All of the agents not recommended have the potential for significant toxicity. While this toxicity may be greater for some classes (i.e. chemotherapy) than others, all of these agents have the potential to harm patients. Thus, the combination of no known benefit with known and potentially serious harms results in a recommendation not to use these agents.</p> <p>11. Smith MR, Saad F, Coleman R et al: Denosumab and bone-metastasis-free survival in men with castration-resistant prostate cancer: results of a phase 3, randomized, placebo-controlled trial. Lancet 2012; 379: 39.</p>
<p>Department of Health (Ireland), 2015 [4].</p> <p>National Cancer Control Programme (NCCP)</p> <p>Diagnosis, staging and treatment of patients with prostate cancer.</p> <p>National Clinical Guideline No. 8.</p>	<p>Fragestellung/Zielsetzung:</p> <p>Clinical question 2.7.3 Should androgen deprivation therapy be continued in patients who develop castration resistant prostate cancer?</p> <p>Clinical question 2.7.4 Is secondary hormone therapy beneficial in patients with castration resistant prostate cancer?</p> <p>Clinical question 2.7.5 Which treatment options are beneficial for patients with castration resistant prostate cancer?</p> <hr/> <p>Methodik</p> <p>Grundlage der Leitlinie:</p> <p>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, Col-Erklärungen der Mitglieder standardisiert erfasst und diskutiert,</p> <p>Suchzeitraum: September 2014</p> <p>(5. LoE:</p>

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.

(6.

(7. 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.

(8.

Freitext/Empfehlungen/Hinweise

Clinical question 2.7.3

Should androgen deprivation therapy be continued in patients who develop castration resistant prostate cancer?

Recommendation 2.7.3.1	Grade
Androgen deprivation therapy should be continued indefinitely in these patients.	D

Good practice point
When men with prostate cancer develop biochemical evidence of castration resistant prostate cancer, their treatment options should be discussed by the urological cancer multidisciplinary team with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate.

Evidence statement

The current EAU guideline (Mottet et al., 2014) addressed this question.

Eventually men with prostate cancer show evidence of disease progression despite castration. In this situation continued testicular androgen suppression in castration resistant prostate cancer (CRPC) is debatable, as suggested by Manni et al., (1988). (Mottet et al., 2014)

These data have been challenged by two trials that showed only a

marginal survival benefit for patients remaining on luteinising hormone-releasing hormone (LHRH) analogues during second-and third-line therapies (Taylor et al., 1993, Hussain et al., 1994). However, in the absence of prospective data, the modest potential benefits of a continuing castration outweigh the minimal risk of treatment. In addition nearly all subsequent treatments have been studied in men with ongoing androgen suppression and therefore it should be continued indefinitely in these patients. (Mottet et al., 2014)

HUSSAIN, M., WOLF, M., MARSHALL, E., CRAWFORD, E. D. & EISENBERGER, M. 1994. Effects of continued androgendeprivation therapy and other prognostic factors on response and survival in phase II chemotherapy trials for hormone-refractory prostate cancer: a Southwest Oncology Group report. J Clin Oncol, 12, 1868-75.

MANNI, A., BARTHOLOMEW, M., CAPLAN, R., BOUCHER, A., SANTEN, R., LIPTON, A., HARVEY, H., SIMMONDS, M., WHITEHERSHEY, D. & GORDON, R. 1988. Androgen priming and chemotherapy in advanced prostate cancer: evaluation of determinants of clinical outcome. J Clin Oncol, 6, 1456-66.

MOTTET, N., BASTIAN, P.J., BELLMUNT, J., VAN DEN BERGH, R.C.N, BOLLA, M., VAN CASTEREN, N.J., CORNFORD, P., JONIAU, S., MASON, M.D., MATVEEV, V., VAN DER KWAST, T.H., VAN DER POEL, H., ROUVIÈRE, O., WIEGEL, T., MEMBERS OF THE EUROPEAN ASSOCIATION OF UROLOGY (EAU) GUIDELINES OFFICE. 2014. Guidelines on Prostate Cancer. In: EAU Guidelines, edition presented at the 25th EAU Annual Congress, Barcelona 2010. ISBN 978-90-79754-70-0.

TAYLOR, C. D., ELSON, P. & TRUMP, D. L. 1993. Importance of continued testicular suppression in hormone-refractory prostate cancer. J Clin Oncol, 11, 2167-72.

Clinical question 2.7.4

Is secondary hormone therapy beneficial in patients with castration resistant prostate cancer?

Recommendation 2.7.4.1	Grade	Resource Implications
For men with castration resistant prostate cancer, second line hormone therapy should be considered.	A	-

Recommendation 2.7.4.2	Grade	Resource Implications
For men with castration resistant prostate cancer in whom chemotherapy is not yet clinically indicated, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide.	A	Enzalutamide is licensed for this indication in the ROI and is currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH with the pharmaceutical industry.

Recommendation 2.7.4.3	Grade	Resource Implications
For men with castration resistant prostate cancer, whose disease has progressed on or after a docetaxel-based chemotherapy regimen, there is strong clinical data supporting the efficacy of abiraterone (+ prednisone) or enzalutamide.	A	-

Anmerkung: In allen im "Evidence statement" genannten RCTs wurden Patienten mit metastasiertem Prostatakarzinom untersucht.

Evidence statement

The current NCCN (2014) guideline and four RCTs (Beer et al., 2014, Logothetis et al., 2012, Ryan et al., 2013, Scher et al., 2012) addressed this question.

In the setting in which patients are docetaxel naïve and have no or minimal symptoms, administration of secondary hormonal

manipulations including the addition of, or switching to, a different antiandrogen (flutamide, bicalutamide, nilutamide, enzalutamide), addition of adrenal/paracrine androgen synthesis inhibitors (ketoconazole or abiraterone (+ prednisone)), or use of an oestrogen, such as diethylstilbestrol (DES), can be considered. (NCCN, 2014)

Ryan et al., (2013) found that abiraterone improved radiographic progression-free survival (16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone; hazard ratio for abiraterone-prednisone vs. prednisone alone, 0.53; 95% confidence interval [CI], 0.45 to 0.62; $P < 0.001$), showed a trend toward improved overall survival (25% decrease in the risk of death in the abiraterone-prednisone group, median not reached, vs. 27.2 months for prednisone alone; hazard ratio, 0.75; 95% CI, 0.61 to 0.93; $P = 0.01$), and significantly delayed clinical decline (time to decline, 12.3 vs. 10.9 months; hazard ratio for decline, 0.82; 95% CI, 0.71 to 0.94; $P = 0.005$) and initiation of chemotherapy in patients with metastatic CRPC (mCRPC) (median time to the initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone-prednisone group vs. 16.8 months in the prednisone-alone group; hazard ratio, 0.58; 95% CI, 0.49 to 0.69; $P < 0.001$).

In a double-blind, phase 3 study, Beer et al. (2014) randomly assigned 1717 patients to receive either enzalutamide (at a dose of 160 mg) or placebo once daily. The co-primary end points were radiographic progression-free survival and overall survival.

The study was stopped after a planned interim analysis showed a benefit of the active treatment. The rate of radiographic progression-free survival at 12 months was 65% among patients treated with enzalutamide, as compared with 14% among patients receiving placebo (81% risk reduction; hazard ratio in the enzalutamide group, 0.19; 95% CI, 0.15 to 0.23; $P < 0.001$). A total of 626 patients (72%) in the enzalutamide group, as compared with 532 patients (63%) in the placebo group, were alive at the data-cutoff date (29% reduction in the risk of death; hazard ratio, 0.71; 95% CI, 0.60 to 0.84; $P < 0.001$). The benefit of enzalutamide was shown with respect to all secondary end points, including time to initiation of cytotoxic chemotherapy (hazard ratio, 0.35), time to first skeletal-related event (hazard ratio, 0.72), a complete or partial soft-tissue response (59% vs. 5%), time to PSA progression (hazard ratio, 0.17), and a rate of decline of at least 50% in PSA (78% vs. 3%) ($P < 0.001$ for all comparisons). Fatigue and hypertension were the most common clinically relevant adverse events associated with enzalutamide treatment. These results showed enzalutamide significantly decreased the risk of radiographic progression and death and delayed the initiation of

chemotherapy in men with metastatic prostate cancer.

Scher et al. (2012) concluded that enzalutamide significantly prolonged the survival of men with mCRPC after chemotherapy (18.4 months (95% confidence interval [CI], 17.3 to not yet reached) in the enzalutamide group versus 13.6 months (95% CI, 11.3 to 15.8) in the placebo group (hazard ratio for death in the enzalutamide group, 0.63; 95% CI, 0.53 to 0.75; P<0.001).

In patients with mCRPC previously treated with docetaxel, Logothetis et al. (2012) found abiraterone (+ prednisone) offer significant benefits compared with prednisone alone in terms of pain relief (157 of 349 [45%] patients vs. 47 of 163 [29%] respectively; P=0.0005), delayed pain progression, and prevention of skeletal-related events (time to first skeletal related event: 25.0 months [95% CI 25.0-not estimable] vs. 20.3 months [16.9-not estimable] respectively; P=0.0001).

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NATIONAL COMPREHENSIVE CANCER NETWORK (NCCN). 2014. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Prostate Cancer V.2.2014. ©National Comprehensive Cancer Network, Inc 2014. All rights reserved. Accessed [September 01, 2014]. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®P, NCCNP®P, NCCN GUIDELINES®P, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

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Clinical question 2.7.5

Which treatment options are beneficial for patients with castration resistant prostate cancer?

Recommendation 2.7.5.1	Grade	Resource Implications
Clinicians should offer treatment with abiraterone (+ prednisone), cabazitaxel or enzalutamide to patients with metastatic castration resistant prostate cancer with good performance status who have received prior docetaxel chemotherapy.	A	-
Recommendation 2.7.5.2	Grade	Resource Implications
Abiraterone (+ prednisone) or enzalutamide may also be considered in patients who have not received docetaxel.	A	Enzalutamide is licensed for this indication in the ROI and is currently being reviewed by the HSE under the pricing and reimbursement framework agreed by the DOH and the HSE with the pharmaceutical industry.
Recommendation 2.7.5.3	Grade	Resource Implications
Patients with metastatic castration resistant prostate cancer who have predominantly bone metastases may benefit from radium-223.	A	-

Anmerkung: In allen im "Evidence statement" genannten RCTs wurden Patienten mit metastasiertem Prostatakarzinom untersucht.

Evidence statement

Six high quality phase III RCTs on the treatment for CRPC, with many therapeutic options in this setting (Beer et al., 2014, De Bono et al., 2011, Logothetis et al., 2012, Parker et al., 2013, Ryan et al., 2013, Scher et al., 2012) addressed this question.

Where there is no evidence of metastases, second-line hormonal options would be preferred to chemotherapy.

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	<p>SCHER, H. I., FIZAZI, K., SAAD, F., TAPLIN, M. E., STERNBERG, C. N., MILLER, K., DE WIT, R., MULDER, P., CHI, K. N., SHORE, N. D., ARMSTRONG, A. J., FLAIG, T. W., FLECHON, A., MAINWARING, P., FLEMING, M., HAINSWORTH, J. D., HIRMAND, M., SELBY, B., SEELY, L. & DE BONO, J. S. 2012. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med, 367, 1187-97.</p>
<p>National Collaborating Centre for Cancer, 2014 [11].</p> <p>NICE</p> <p>Prostate cancer: diagnosis and treatment</p>	<p>Fragestellung/Zielsetzung: This guidance updates and replaces NICE clinical guideline 58 (published February 2008).</p> <p>New and updated recommendations have been included on the diagnosis and treatment of men with prostate cancer.</p> <hr/> <p>Methodik</p> <p>Grundlage der Leitlinie</p> <p>development of this guideline was based upon methods outlined in the „NICE guidelines manual“, Modified Delphi consensus methodology</p> <p>update of CG58: Recommendations are marked [2008], [2014] or [new 2014] to indicate the year of the last evidence review:</p> <ul style="list-style-type: none"> - [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. <p>Suchzeitraum:</p> <ul style="list-style-type: none"> 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 <p>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.</p> <ul style="list-style-type: none"> • (zu detaillierten Angaben der jeweiligen quality of evidence siehe GL fullversion) <p>GoR:</p> <ul style="list-style-type: none"> • „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 <p>„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</p>

	more time considering and discussing the options with the patient.
	Freitext/Empfehlungen/Hinweise Algorithmus siehe Anhang

Ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren

Relevante ergänzende Dokumente anderer Organisationen zu möglichen Komparatoren wurden durch die Recherche nicht identifiziert.

Detaillierte Darstellung der Recherchestrategie

Cochrane Library (Cochrane Database of Systematic Reviews, Health Technology Assessment Database) am 21.06.2017

#	Suchfrage
1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
2	MeSH descriptor: [Prostatic Neoplasms, Castration-Resistant] explode all trees
3	(prostate or prostatic):ti,ab,kw (Word variations have been searched)
4	(cancer* or tumor* or tumour* or carcinoma* or neoplasm* or adenocarcinoma*):ti,ab,kw (Word variations have been searched)
5	#3 and #4
6	(independent or independence or insensitive or resistant or resistance or refractory):ti,ab,kw and (hormone or androgen or castrate or castration):ti,ab,kw
7	#1 or #5
8	#7 and #6
9	#2 or #8
10	#9 Publication Year from 2012 to 2017, in Cochrane Reviews (Reviews only) and Technology Assessments

SR, HTAs in Medline (PubMed) am 21.06.2017

#	Suchfrage
1	Prostatic Neoplasms[MeSH Terms]
2	Prostatic Neoplasms, Castration-Resistant[MeSH Terms]
3	(prostate[Title/Abstract]) OR prostatic[Title/Abstract]
4	(((((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]
5	#3 AND #4
6	(((((independent[Title/Abstract]) OR independence[Title/Abstract]) OR insensitive[Title/Abstract]) OR resistant[Title/Abstract]) OR resistance[Title/Abstract]) OR refractory[Title/Abstract]
7	((((hormone[Title/Abstract]) OR androgen[Title/Abstract]) OR castrate[Title/Abstract]) OR castration[Title/Abstract]
8	#6 AND #7
9	#1 OR #5
10	#9 AND #8
11	#10 OR #2
12	((#11) AND ((Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp]) OR (((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR (((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract]))

	OR meta-analy*[Title/Abstract] OR (meta[Title/Abstract] AND analyz*[Title/Abstract]) OR (meta[Title/Abstract] AND analys*[Title/Abstract]) OR (meta[Title/Abstract] AND analyt*[Title/Abstract])) OR (((review*[Title/Abstract] OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract] AND based[Title/Abstract]))))
13	(#12) AND ("2012/06/01"[PDAT] : "2017/06/21"[PDAT])

Leitlinien in Medline (PubMed) am 21.06.2017

#	Suchfrage
1	"Prostatic Neoplasms"[Mesh]
2	(prostate[Title] OR prostatic[Title])
3	(((((tumor[Title] OR tumors[Title] OR tumour*[Title] OR carcinoma*[Title] OR adenocarcinoma*[Title] OR neoplasm*[Title] OR cancer*[Title])
4	#2 AND #3
5	#1 OR #4
6	(Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[Title])
7	#5 AND #6
8	(#7) AND ("2012/06/01"[PDAT] : "2017/06/21"[PDAT])

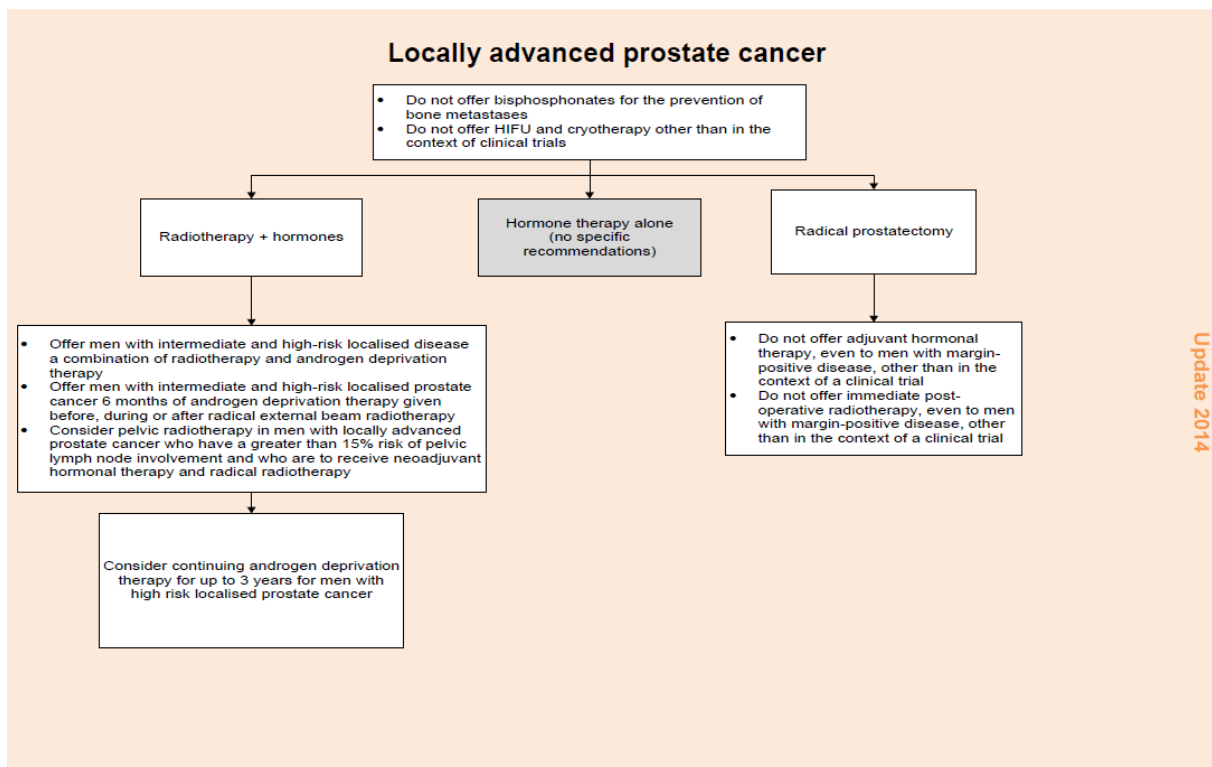
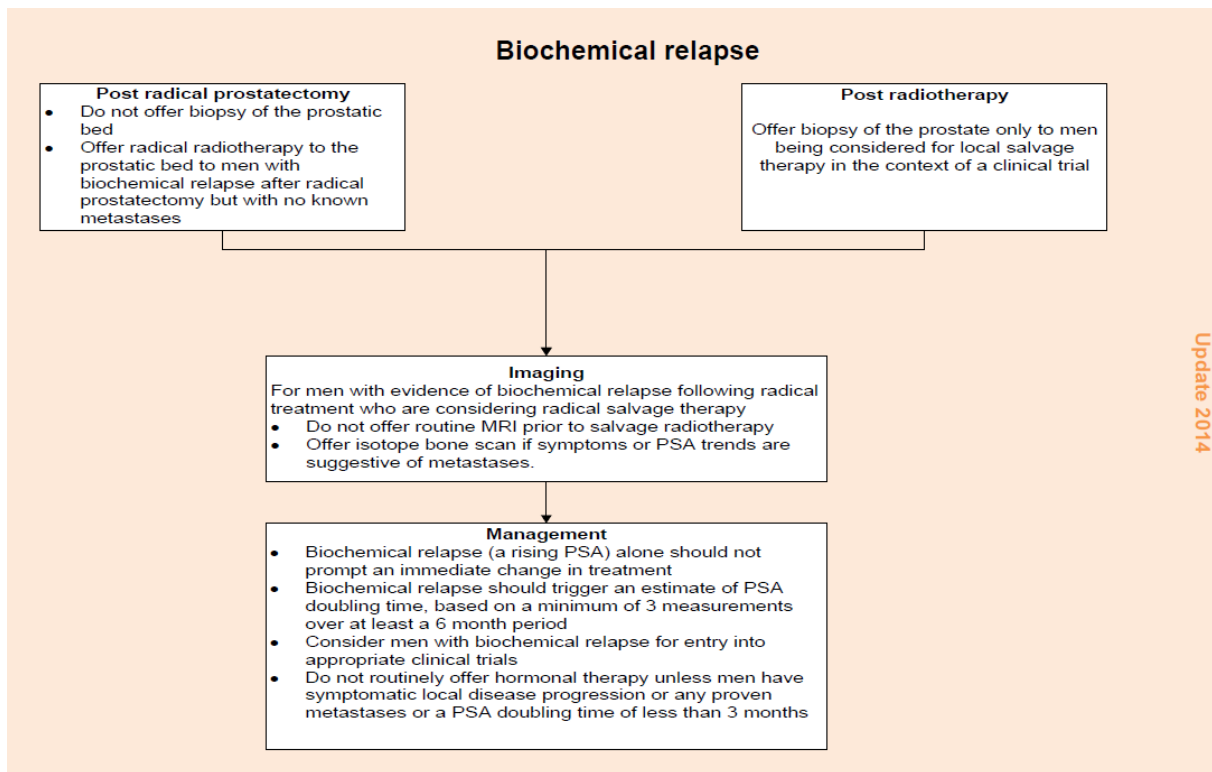
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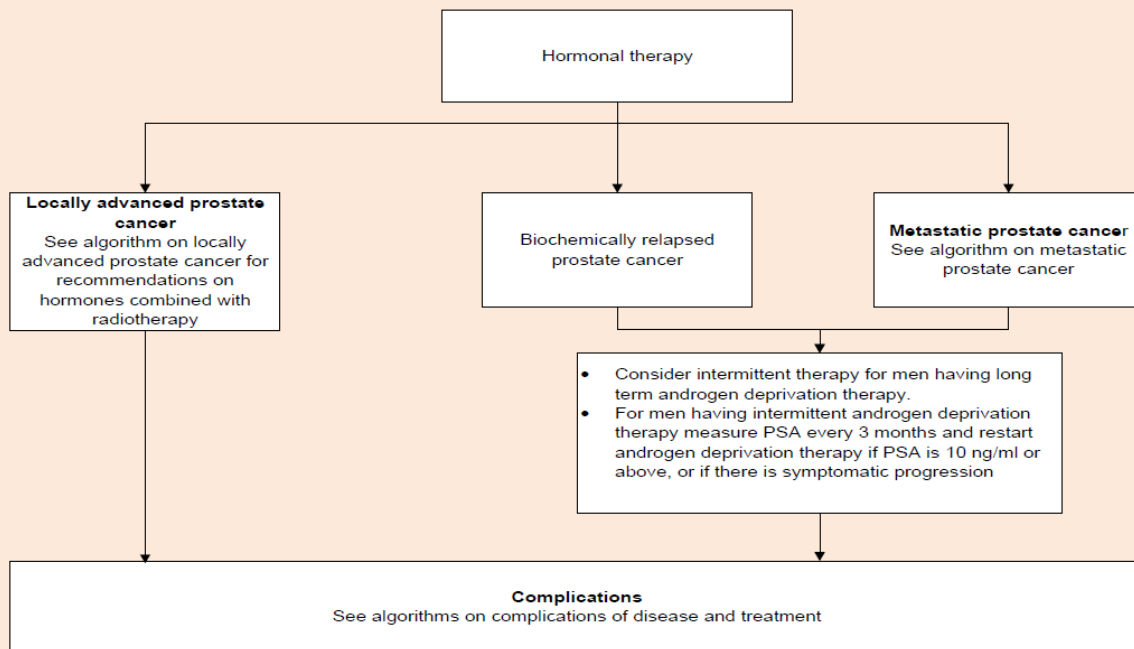
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Anhang

Algorithmus aus National Collaborating Centre for Cancer, 2014 [11].



Hormonal therapy for prostate cancer



Update 2014