177Lu-PSMA Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No. 118
ISSN online: 1998-0469

177Lu-PSMA Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, March 2019

Project Team

Project leader: MA, Michal Stanak, AKC

Authors: MA, Michal Stanak, AKC
Mag. Nicole Grössmann
Christoph Strohmaier, Bakk. rer. soc. oec.

Project Support

Systematic literature search: Tarquin Mittermayr, BA

External Review: Prof. Dr. Christian Schwentner, FEBU
Department of Urology, Diakonieklinikum Stuttgart, Stuttgart, Germany

Internal Review: PD. Dr. Claudia Wild

Correspondence

Michal Stanak michal.stanak@hta.lbg.ac.at

This report should be referenced as follows:

Stanak M., Grössmann N., Strohmaier C. 177Lu-PSMA Therapy in Patients with Metastatic Castration-Resistant Prostate Cancer. Decision Support Document No. 118; 2019. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

All authors and the reviewers involved in the production of this report have declared they have no conflicts of interest in relation to the technology assessed according to the Uniform Requirements of Manuscripts Statement of Medical Journal Editors (www.icmje.org).

Disclaimer

The external reviewers did not co-author the scientific report and do not necessarily all agree with its content. Only the LBI-HTA is responsible for errors or omissions that could persist. The final version and the policy recommendations are under the full responsibility of the LBI-HTA.

Commissioned by the Austrian Ministry of Health, this report systematically assessed the intervention described herein as decision support for the inclusion in the catalogue of benefits.

The HTA Core Model®, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. The following version of the Model was used: [HTA Core Model, Version 4.2]. Use of the HTA Core Model does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

CONTENT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Wien
https://hta.lbg.ac.at/page/imprint

Responsible for content:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
https://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at

Decision Support Document No.: 118

ISSN-online: 1998-0469

Content

List of Figures

List of tables

List of abbreviations

AE	adverse event
BFI	Brief Pain Inventory
BSA	body surface area
CI	confidence interval
CT	computed tomography
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EDTMP	ethylenediaminetetra-methylene phosphonic acid
eGFR	(estimated) Glomerular Filtration Rate
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
dL	decilitre
FDG	fluorodeoxyglucose
HBED CC – N,N'	bis(2-hydroxybenzyl) ethylenediamine-N,N'-diacetic acid
L	litre
LHRH	Luteinizing hormone-releasing hormone
IQR	interquartile range
KPS	Karnofsky Performance Status
mCRPC	metastatic castration resistant prostate cancer
mg	Milligramm
min	Minute
mL	Milliliter
mm	millimetre
mo	month
n	number
NA	not available
NaF	sodium fluoride
OS	overall survival
PET	positron emission tomography
PFS	progression free survival
PSMA	prostate specific membrane antigen
PSA PFS	prostate-specific antigen progression free survival
Pts	patients
RECIST	Response Evaluation Criteria in Solid Tumours
QoL	quality of life
VAS (max)	Visual Analogue Scale
SAE	serious adverse event
SD	standard deviation
17F	Fluorine
51Cr	Chromium
68GA	Gallium
177Lu	lutetium
223Ra	Radium

Executive Summary

Introduction

Health Problem

With 1.4 million cases in 2016 globally, prostate cancer (PC) is the most common incident cancer for men [1]. The growth of PC is driven by male sex hormones called androgens and even though 80-90% of patients respond to androgen therapy, nearly all eventually develop metastatic castration-resistant PC (mCRPC) [2]. The exact number of mCRPC patients is unclear as there are no widely accepted criteria for its definition outside of the clinical trial setting [3] – the criteria used include the rise in PSA levels, progression of existing metastases, or the presence of new metastases [4].

prostate cancer (PC) as the most common incident cancer for men; nearly always turns to its metastatic castration-resistant form

The risk for developing PC differs over 50-fold among various world populations with Western countries leading the incidence rate with one in six men [5]. The incidence also increases proportionally with age and is further influenced by genetic factors, diet, cigarette smoking, hormone levels, and obesity [5, 6]. The natural course of PC is primarily dependent on tumour aggressiveness. PC can remain silent throughout a man's life without being detected [7], however, if PC grows to the stage of producing symptoms like bladder neck obstruction, invasion of adjacent organs, or distant metastasis, curative treatment is usually impossible [7].

incidence varies: 1/6 men in Western countries; key risk factors: age, genetics, diet, cigarette smoking, hormone levels, and obesity; PC may remain silent throughout life; if spread, not curative

Description of Technology

177 Lutetium (177Lu) is, to date, the most widely used radioisotope for targeted therapy in PC. Prostate specific membrane antigen (PSMA) is a target for radionuclide therapy of PC and its metastases because in the majority of PC patients (in more than 90%), it is overexpressed up to 1,000 times [8]. The process of labelling of PSMA onto 177Lu can be done in various ways using different PSMA peptides and antibodies [9]. In the studies included in this assessment, the different types of labelling include three ways of chemical conjugation of a peptide, thus three studies used 177Lu-PSMA-DKFZ-617 [10-12], one study used 177Lu-PSMA-I&T [13], and the other 177Lu-PSMA-617 [14].

177Lu-PSMA most widely used radioisotope; PSMA overexpressed up to 1,000 times in PC patients; various forms of labelling used

177Lu-PSMA has neither CE mark, nor FDA approval. The main claimed benefit is that 177Lu-PSMA offers an extra therapeutic option for mCRPC patients in the end stage of cancer. Through its targeted approach, 177Lu-PSMA claims to reduce the level of prostate specific antigen, have potential survival benefits with respect to progression free survival as well as overall survival, and have a safe profile that causes a minimal number of grade 3-4 toxicities [15].

177Lu-PSMA has no CE mark or FDA approval; extra therapeutic option, claims to reduce PSA levels and improve OS and PFS with few side effects

Methods

The aim of this systematic review was to investigate the use of 177Lu-PSMA in mCRPC patients when compared to best supportive care or second line therapy or higher (hormonal therapy, chemotherapy, immunotherapy, radiopharmaceuticals, and steroids). The question was whether 177Lu-PSMA is more effective and safe or equally effective, but safer with respect to the crucial outcomes of overall survival, quality of life, health related quality of life, and side effect (study related death, grade 3-4 toxicities, and discontinuation rate). The EUnetHTA Core Model for Rapid Assessment of Relative Effectiveness was the main source for selecting relevant assessment elements.

aim: is 177Lu-PSMA vs. best supportive care or second line therapy (or higher) more effective and safer

systematic search in 4 databases; 651 hits in total

The systematic literature search was conducted on the 14-17th of December 2018 in the four databases (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA]). The systematic search was not limited to a year of publication or to study design, but to articles published in English or German. After deduplication, overall 643 citations were included and together with eight articles found via hand-search, the overall number of hits was 651.

search in clinical trial registries for ongoing trials, 36 hits, 8 relevant; no new publications from the manufacturers

A search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 18.01.2019 and yielded eight potentially relevant hits (out of 36 hits). Manufacturers of the most common products (Endocyte®, Scintomics GmbH) were contacted and only Scintomics replied submitting six publications of which no new citations were identified.

Results

Available evidence

no study included for the analysis of clinical effectiveness

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the 177Lu-PSMA. RCTs and non-randomised CTs were considered for inclusion, but could not be identified through the systematic literature search.

5 observational before-after studies included for the analysis of safety with 141 patients (116 reported)

For the analysis of safety, prospective observational evidence was also included and hence, we identified five prospective before-after studies that matched our inclusion criteria with the total of 141 patients (yet data were reported on 116 patients) [10-14]. In the absence of data from CTs, no comparisons can be made between the 177Lu-PSMA and the comparators. Only intervention related complications can be considered for the analysis of safety because the effects directly attributable to the intervention can be analysed without a control group.

no study funded by manufacturers; follow-up ranged from mean 13 to median 25 months

None of the studies was explicitly sponsored by the any of the manufacturers, but a member of the authoring team in one study was a shareholder at Scintomics, Germany [13]. One study had no funding [11], another study was funded by Peter MacCallum Foundation and Prostate Cancer Foundation [12], another by University of Innsbruck and Medical University of Innsbruck [14], and the last by Paul Ramsey Foundation [10]. Clinical follow-up was unclear in two studies [10, 14], and ranged from mean 13 to median 25 months in the remaining 3 studies [11-13].

Clinical effectiveness

no evidence found

No evidence was found to answer the question of clinical effectiveness of 177Lu-PSMA.

Safety

SAEs occurring in no studies; no cases of discontinuation; grade 3-4 toxicities: no hepatotoxicity and nephrotoxicity;

Concerning serious adverse events (SAEs), the outcome of study related death was reported in two studies and it did not occur in either [12, 13]. Concerning adverse events (AEs), the outcomes of discontinuation rate was reported in one study where no patients discontinued treatment [12]. With respect to grade 3-4 toxicities, nephrotoxicity was reported in four studies, but did not occur either [11-14]. With respect to hematotoxicity: lymphocytopenia was reported in three studies [12-14] and occurred in one in 37% of patients [12], thrombocytopenia and anaemia were both reported in four studies [10, 12-14] and both occurred in one in 13% of patients [12], neutropenia was reported

in three studies [12-14] and occurred in one in 7% of patients [12], and haemoglobin toxicity was reported in one study in 3.2% of patients [11]. Hepatotoxicity was reported in two studies, but did not occur in either [11, 14], while bone pain flare was reported in one study and occurred in 3% of patients [12].

hematotoxicity and haemoglobin toxicity reported in 3.2-37% of patients in respective studies

As 177Lu-PSMA is a therapy that targets the specific antigen expressed on the surface of PC tumour cells as well as on other cells such as kidneys, liver, spleen, bone marrow, salivary, lacrimal, and parotid glands, the precision of 177Lu-PSMA therapy is important. There is no agreement on which of the above organs is the main dose limiting one and hence which one is most susceptible to harms related dosage of 177Lu-PSMA, which stresses the importance of patient specific dosimetry [15-19].

precision of therapy as an issue with respect to the dose limiting organs

need for patient specific dosimetry

Upcoming evidence

At this point in time, the manufacturer Endocyte® is in the process of applying for an FDA approval with their ongoing RCT comparing 177Lu-PSMA to best standard care (NCT03511664). One further RCT (NCT03392428) comparing 177Lu-PSMA to the chemotherapy cabazitaxel is also in the recruiting phase.

2 ongoing RCTs: one with best standard of care, the other with cabazitaxel

Reimbursement

Up until the end of 2018, 177Lu-PSMA was performed under either clinical trials or under local regulations for unproven interventions for patients who have exhausted all therapeutic options [20]. Since 2019, 177Lu-PSMA is included in the German DRG system [21].

reimbursed in Germany since 2019

Discussion

Overall, the strength of evidence for clinical effectiveness was not assessed due to the lack of controlled studies. Regarding safety of 177Lu-PSMA, the quality of evidence was low (for outcomes of study related death and discontinuation rate) to very low (for the outcome of grade 3-4 toxicities).

quality of the evidence for safety is low to very low

Challenges with interpreting the data arise when we take into consideration the extent to which the patient population was pre-treated before the administration of 177Lu-PSMA, where previous interventions include hormone therapy, luteinizing hormone-releasing hormone (LHRH) agents, external beam radiation, surgical therapy, chemotherapy, antiandrogens, and bone interventions. Hence, in the light of the lack of controlled data, assigning the effects observed to 177Lu-PSMA is questionable. Also, interpreting the data is especially problematic in the light of only one study reporting on the baseline toxicity data [11] and only two studies reporting on the co-interventions that patients continued on during the course of 177Lu-PSMA, which ranged from blood transfusions to bone interventions, palliative radiotherapy, antiandrogens, and LHRH agents [10, 12]. Furthermore, it remains unclear why all reported instances of AEs – except for haemoglobin toxicity [11] – occurred in only one study that acknowledged the co-interventions used, had the best standard of reporting, longest follow-up, and the lowest risk of bias [12].

challenges when interpreting the data: heavily pre-treated population, baseline toxicity, lack of reporting of co-interventions, highest incidence of AEs in the study of best quality and longest follow-up

In terms of external validity, the data is considered generalizable to the Austrian context as the countries of recruitment were Germany, Australia, Austria, and India. At the same time, however, as the Austrian context allows for the administration of 177Lu-PSMA also in the outpatient setting, none of the studies included reported data from this context and hence in this respect, no conclusions can be made.

data generalizable to the Austrian context; studies provide no outpatient data

need for CTs; ambiguity concerning comparators

The evidence found only partially answered our research questions. The prospective observational evidence found can only contribute to the safety assessment, yet still with a low to very low quality of evidence. RCTs or CTs comparing 177Lu-PSMA to alternative treatment options are thus necessary. However, choosing the right comparator presents a challenge. On the one hand, 177Lu-PSMA, as an experimental therapy, is to be used after the exhaustion of all therapeutic options (as it was the case in the studies included in the analysis), yet on the other hand, German AWMF S3 guideline includes 177-Lu-PSMA in the category of second line therapies [22].

Recommendation

currently not recommended; reevaluation recommended in 2021

The inclusion in the catalogue of benefits is currently not recommended.

The current evidence is not sufficient to prove that the assessed technology 177Lu-PSMA is more effective and equally safe or equally effective, but safer than the comparators of best supportive care or the second line therapies: hormonal therapy, chemotherapy, immunotherapy, radiopharmaceuticals, or steroids. New study results will potentially influence the effect estimate considerably. The re-evaluation is recommended in 2021 after the completion of two ongoing RCTs (NCT03392428, NCT03511664).

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Prostatakrebs (PC) ist mit 1,4 Millionen Fällen im Jahr 2016 die häufigste Krebserkrankung unter Männern [1] Beim Wachstum von Prostatakarzinomen spielen die männlichen Sexualhormone, Androgene, eine wichtige Rolle. Obwohl 80-90 % der Patienten auf eine Antiandrogentherapie ansprechen, entwickeln bis auf wenige Ausnahmen ein metastasiertes kastrationsresistentes Prostatakarzinom (mCRPC) [2]. Die genaue Anzahl an mCRPC-erkrankten Patienten ist aufgrund fehlender Kriterien für eine Definition einer mCRPC-Erkrankung außerhalb des klinischen Versuchssettings unklar [3]. Angewendete Kriterien beinhalten den Anstieg des prostataspezifischen Antigens (PSA), Progression von existierenden Metastasen, oder das Vorhandensein neuer Metastasen [4].

Prostatakrebs (PC) ist die häufigste Krebserkrankung für Männer; PC entwickelt sich meist in die metastasierende kastrationsresistente Form

Bezüglich des Auftretens von Prostatakarzinomen weltweit kann es zu Unterschieden kommen, welche in manchen Fällen um das 50-fache variieren. Hinsichtlich der Inzidenz sind westliche Staaten mit Raten von einem in sechs Männern führend. Zusätzlich nimmt die Inzidenz mit steigendem Alter proportional zu. Auch genetische Faktoren, Ernährungsgewohnheiten, Rauchen, der Hormonspiegel und Übergewicht beeinflussen das Auftreten von PC [5, 6]. Der Verlauf eines PC ist hauptsächlich von der Aggressivität des Tumors abhängig. Häufig verläuft das Wachstum von Prostatakrebs langsam und unauffällig, ohne dass er jedoch erkannt wird. Wenn PC allerdings bis zu einem Stadium wächst, in dem Symptome wie Blasenhalsobstruktion, die Ausbreitung der Krebszellen vom Primärtumor zu angrenzenden Organen, oder Fernmetastasen auftreten, dann ist eine kurative Behandlung meistens nicht mehr möglich [7].

Inzidenz variiert: 1/6 Männer in westlichen Staaten; zentrale Risikofaktoren: Alter, Erbanlage, Ernährungsgewohnheiten, Rauchen, Hormonspiegel und Übergewicht;

Beschreibung der Technologie

177Lutetium (177Lu) ist das am häufigsten verwendete Radioisotop für eine zielgerichtete Therapie von PC. Eine Radionuklidtherapie zielt dabei auf eine Reduktion des prostataspezifischen Membranantigens (PSMA) des PC und der Metastasen ab, da in den meisten Patienten (mehr als 90 %) das Antigen um das 1.000-fache erhöht ist [8]. Die Kennzeichnung von PSMA durch 177Lu kann in verschiedenen Varianten mit unterschiedlichen PSMA-Peptiden und -Antikörpern durchgeführt werden [9]. In den eingeschlossen Studien dieses Assessment werden drei Ansätze chemischer Konjugation eingesetzt: 177Lu-PSMA-DKFZ-617 [10-12], 177Lu-PSMA-I&T [13], und 177Lu-PSMA-617 [14].

177Lu-PSMA am häufigsten benutztes Radioisotop; PSMA ist um das 1.000-fache in PC-Patienten erhöht

177Lu-PSMA hat weder ein CE-Kennzeichnung, noch eine FDA Zulassung. Der vermeintliche Nutzen von 177Lu-PSMA soll vor allem in der Therapie von PC-Patienten im Endstadium liegen. Dabei soll aufgrund des zielgerichteten Therapieansatzes das prostataspezifische Antigen reduziert und das Überleben, sowohl hinsichtlich des progressionsfreien-Überlebens (PFS) und des Gesamtüberlebens, verlängert werden. Die 177Lu-PSMA Therapie soll weiters ein sicheres Nebenwirkungsprofil und einer geringen Anzahl an Grad 3-4 Nebenwirkungen aufweisen [15].

177Lu-PSMA hat kein CE-Kennzeichnung oder FDA Zulassung;

Methoden

Ziel: Ist 177Lu-PSMA vs. Best Supportive Care als Zweitlinientherapie (oder höher) wirksamer und sicherer?

Das Ziel dieser systematischen Übersichtsarbeit war es, den Einsatz von 177-Lu-PSMA versus Best Supportive Care als Zweitlinientherapie oder höher (Hormontherapie, Chemotherapie, Immunotherapie, radiopharmazeutischen Medikamente und Steroide) zu untersuchen. Folglich sollte festgestellt werden, ob 177Lu-PSMA wirksamer und sicherer oder gleich effektiv ist, insbesondere im Hinblick auf OS, Lebensqualität, gesundheitsbezogene Lebensqualität und Nebenwirkungen (studienbezogene Todesfälle, Grad 3-4 Toxizitäten und Therapieabbruchraten). Das EUnetHTA Core Model für Rapid Assessment of Relative Effectiveness diente als Basis für die Auswahl relevanter Bewertungselemente.

systematische Suche in 4 Datenbanken; 651 Gesamttreffer

Die systematische Literatursuche wurde zwischen dem 14. und 17. Dezember 2018 in vier Datenbanken durchgeführt (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA]). Die Literatursuche beschränkte sich nicht auf ein Publikationsjahr oder Studiendesign, jedoch gab es sprachliche Einschränkungen auf englische und deutsche Artikel. Nach der Deduplikation wurden 643 Zitate zusammen mit acht weiteren Artikeln (Handsuche) in das Assessment eingeschlossen. Somit lag die Gesamtanzahl der Treffer bei 651.

Suche nach laufenden Studien in 3 klinischen Studienregistern

Eine Suche in drei klinischen Studienregistern (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) wurde am 18.01.2019 durchgeführt. Diese Suche ergab acht potentiell relevante Treffer (von 36 Treffern). Die Hersteller der geläufigsten Produkte (Endocyte®, Scintomics GmbH) wurden kontaktiert, von denen nur Scintomics antwortete und sechs Publikation bereitstellte, wobei diese bereits identifiziert wurden.

Ergebnisse

Verfügbare Evidenz

keine Studie für eine Analyse der klinischen Effektivität lag vor

Keine der identifizierten Studien erfüllte die Einschlusskriterien für eine Bewertung der klinischen Wirksamkeit von 177Lu-PSMA. Es hätten randomisierte kontrollierte Studien und nicht-randomisierte kontrollierte Studien berücksichtigt werden sollen, diese konnten jedoch nicht durch die systematische Literaturrecherche ermittelt werden.

5 prospektive Vorher-Nacher-Studien für die Analyse der Sicherheit mit 141 Patienten (116 berichtet) wurden eingeschlossen

Für die Analyse hinsichtlich der Sicherheit wurden prospektive Beobachtungsstudien eingeschlossen. Es konnten fünf prospektive Vorher-Nachher-Studien mit insgesamt 141 Patienten (Daten wurden nur für 116 berichtet) identifiziert werden, welche den Einschlusskriterien entsprachen [10-14]. Ohne kontrollierte Studien kann kein Vergleich zwischen 177Lu-PSMA und den Komparatoren angestellt werden. Ausschließlich Komplikationen, welche die Intervention betreffen, können für die Analyse berücksichtigt werden. Da Auswirkungen, welche direkt auf die Intervention zurückzuführen sind auch ohne Vergleichsgruppe analysiert werden können.

keine Studie wurde durch einen Hersteller finanziert; Follow-Up von 13 (Mittelwert) bis 25 (Median) Monaten

Keine der Studien wurde explizit durch einen Hersteller finanziert. Allerdings war ein Mitglied des Autorenteams einer Studie Aktionär bei Scintomics GmbH, Deutschland [13]. Eine der Studien hatte keine Förderungen [11], eine andere wurde durch die Peter MacCallum Foundation and Prostate Cancer Foundation finanziert [12], eine weitere Studie durch die Universität Innsbruck und durch die Medizinische Universität Innsbruck [14]. Die letzte Studie wurde durch die Paul Ramsey Foundation gefördert [10]. Bei zwei Studien war die Follow-Up Zeit unklar [10, 14]. In den anderen drei Studien reichte die Follow-Up Zeit von 13 (Mittelwert) bis 25 (Median) Monaten [11-13].

Klinische Wirksamkeit

keine Evidenz gefunden

Es konnte keine Evidenz für die klinische Wirksamkeit für 177Lu-PSMA gefunden werden.

Sicherheit

SAEs traten in keiner Studie auf; kein Abbruch der Therapie

Grad 3-4 Toxizitäten: keine Hepatptoxizität und Nephrotoxizität; Hematoxizität und Haemoglobintoxizität wurden in 3,2-37 % der Patienten in den jeweiligen Studien berichtet

In zwei Studien [12, 13] wurden, in Hinsicht auf schwerwiegende unerwünschte Ereignisse (SAE), studienbezogene Todesfälle untersucht, jedoch traten diese nicht auf. In Bezug auf Nebenwirkungen (AEs) untersuchte eine Studie die Abbruchrate von Patienten, wenngleich diese nicht auftrat [12]. Hinsichtlich Grad 3-4 Toxizität wurde Nephrotoxizität in vier Studien untersucht, trat aber in keiner der Studien auf [11-14]. Mit Bezug auf Hematoxizität wurde eine Lymphozytopenie in drei Studien berichtet [12-14] und trat in einer Studie in 37 % der Patienten auf [12]. Thrombozytopenie und Anämie wurden in vier Studien berichtet [10, 12-14] und beide Nebenwirkungen traten in einer Studie in 13 % der Patienten auf [12]. Neutropenie wurde in drei Studien berichtet [12-14] und trat in einer Studie in 7 % der Patienten auf [12]. Eine Studie [11] berichtete eine Haemoglobintoxizität in 3,2 % der Patienten. Zwei Studien berichteten über Hepatoxizität [11-14], welche aber in beiden Fällen nicht auftraten, während aufkommende Knochenschmerzen in einer Studie mit einem Anteil von 3 % der Patienten berichtet wurden [12].

Präzision der Therapie ist mit Blick auf das dosislimitierende Organ von Bedeutung

patientenspezifische Dosimetrie ist von besonderer Bedeutung

PSMA wird an der Oberfläche von PC-Tumorzellen exprimiert und dient als molekulares Target der 177Lu-PSMA-Therapie. Dabei spielt die Präzision der Therapie eine wichtige Rolle, da auch andere Zellen z. B.: der Niere, Leber, Milz, im Knochenmark, der Speicheldrüse, Tränendrüse und Ohrspeicheldrüse, von der Therapie betroffen sein können. Es gibt allerdings keinen Konsens darüber, welches der oben angeführten Organe für eine Dosislimitierung herangezogen werden sollte. Auch herrscht keine klare Einigkeit darüber, welches das empfindlichste Organ für Schäden hinsichtlich der Dosierung darstellt. Folglich ist eine patientenspezifische Dosimetrie von besonderer Bedeutung [15-19].

Laufende Studien

2 laufende RCTs: eine mit bestmöglicher unterstützender Behandlung, die andere mit Cabazitaxel

Zu diesem Zeitpunkt ist der Hersteller Endocyte® im Prozess eine FDA-Zulassung mit ihrer laufenden randomisierten kontrollierten Studie zu beantragen. Diese Studie vergleicht die 177Lu-PSMA Therapie mit dem besten Behandlungsstandard (NCT03511664). Eine weitere randomisierte kontrollierte Studie (NCT03392428) befindet sich in der Rekrutierungsphase und vergleicht die 177Lu-PSMA-Therapie mit der Chemotherapie Cabazitaxel.

Kostenerstattung

in Deutschland seit 2019 erstattungsfähig

Bis zum Ende des Jahres 2018 wurde die 177Lu-PSMA-Therapie entweder in klinischen Studiensettings oder gemäß lokaler Bestimmungen für nicht ausreichend untersuchter Interventionen für Patienten, welche bereits alle therapeutischen Optionen [20] ausgeschöpft haben, eingesetzt. Seit 2019 ist die Therapie mit 177Lu-PSMA im deutschen DRG-System gelistet [21].

Diskussion

Qualität der Evidenz für Sicherheit ist niedrig bis sehr niedrig

Im Allgemeinen wurde die Evidenzstärke für die klinische Wirksamkeit nicht beurteilt, da bis dato keine qualitativ hochwertigen kontrollierten Studien verfügbar sind. In Bezug auf die Sicherheit von 177Lu-PSMA wurde die Qualität der Evidenz als niedrig (studienbezogene Todesfälle und Abbruchraten der Therapie) bis sehr niedrig (Grad 3-4 Toxizitäten) eingestuft.

Herausforderung bei der Interpretation der Daten: stark vorbehandelte Population, Baseline-Toxizität, Mangel an Berichterstattung von Ko-Interventionen

Die Interpretation der Ergebnisse wird durch die jeweilige Vorbehandlung der Patienten, wie bspw. Hormontherapie, luteinisierende Hormon Releasing-Hormon-Wirkstofftherapie (LHRH), externe Bestrahlungstherapie, operative Therapie, Chemotherapie, Antiandrogentherapie und Knocheneingriffe, erschwert. Folglich ist eine direkte Zuordnung der beobachteten Effekte von 177Lu-PSMA ohne kontrollierte Daten nicht möglich. Zusätzlich wird die Interpretation der Daten erschwert, da nur eine Studie Daten zur Baseline-Toxizität [11] und nur zwei Studien über Begleitinterventionen, welche Patienten während der Therapie mit 177Lu-PSMA durchliefen, berichtet. Dazu gehörten Bluttransfusionen bis hin zu Knocheneingriffe, palliative Radiotherapie, Antiandrogentherapie und Therapien mit LHRH-Wirkstoffen [10, 12]. Zusätzlich bleibt unklar, warum alle berichteten Fälle von AEs – außer Haemoglobintoxizität [11] – ausschließlich in einer Studie eintraten. Hinzukommend war diese Studie auch die einzige, welche die angewendeten Ko-Interventionen berücksichtigte, den höchsten Standard hinsichtlich der Berichtsqualität, die längste Follow-Up Periode und das niedrigste Risiko eines Bias aufwies [12].

Daten sind auf den österreichischen Kontext generalisierbar; Studien liefern keine Daten über den Einsatz im niedergelassenen Bereich

Hinsichtlich der externen Validität sind die Daten auf den österreichischen Kontext übertragbar. Die Rekrutierung der Patienten wurde in Deutschland, Australien, Österreich und Indien durchgeführt. Im österreichischen Kontext kann die Anwendung von 177Lu-PSMA auch im niedergelassenen Bereich durchgeführt werden, jedoch lag keine Evidenz zu diesem Kontext vor. Folglich können auch keine Schlussfolgerungen zu diesem Behandlungssetting abgegeben werden.

weitere kontrollierte Studien sind nötig; Mehrdeutigkeit hinsichtlich der Komparatoren und der Therapielinie

Die untersuchte Evidenz erlaubte es uns, unsere Forschungsfrage nur teilweise zu beantworten. Aufgrund der ausschließlichen Evidenz aus prospektiven Beobachtungsstudien, lässt sich nur eine Einschätzung hinsichtlich der Sicherheit abgeben. Diese ist jedoch auch nur auf Grundlage niedriger bis sehr niedriger Qualität hinsichtlich der Evidenz möglich. Aufgrund dessen sind randomisierte kontrollierte oder kontrollierte Studien, welche einen Vergleich von 177Lu-PSMA mit einer alternativen Intervention durchführen, nötig. Allerdings stellt die richtige Wahl des Komparators eine Herausforderung dar. So stellt 177Lu-PSMA einerseits eine experimentelle Therapie dar und wird nach Ausschöpfung aller relevanten therapeutischen Alternativen in Betracht gezogen, andererseits wird die 177Lu-PSMA-Therapie in der deutschen AWMF S3 Leitlinie als Zweitlinientherapie empfohlen [22].

Empfehlung

Aufnahme in den Leistungskatalog derzeit nicht empfohlen

Eine Aufnahme in den Leistungskatalog wird derzeit nicht empfohlen.

Re-Evaluation im Jahr 2021 wird empfohlen

Die momentane Evidenz der 177Lu-PSMA-Technologie ist nicht hinreichend, um zu belegen, dass die Therapie mit 177Lu-PSMA wirksamer und gleichermaßen sicher oder gleichermaßen wirksam, aber sicherer als die zu Verfügung stehenden Komparatoren (Best Supportive Care) oder Zweitlinientherapien (Hormontherapie, Chemotherapie, Immunotherapie, radiopharamzeutische Therapie oder Steroide) ist. Ergebnisse zukünftiger Studien können potentiell den Effektschätzer maßgeblich beeinflussen. Eine Re-Evaluation ist im Jahr 2021 nach der Beendigung von zwei laufenden randomisierten kontrollierten Studien empfohlen (NCT03392428, NCT03511664).

1 Scope

1.1 PICO question

PIKO-Frage

Is Lutetium-177 labelled Prostate-Specific Membrane Antigen (PSMA) inhibitor therapy in comparison to best supportive care or second line therapy (hormonal therapy, chemotherapy, immunotherapy, radiopharmaceuticals, steroids) in patients with castration-resistant metastatic prostate cancer more effective and safe or equally effective, but safer concerning overall survival (OS), quality of life (QoL), and health related quality of life (HRQoL) and side effects?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

Inclusion criteria for relevant studies are summarized in Table 1-1.

Table 1-1: Inclusion criteria

Population	Fourth line therapy (third line in case that patients are ineligible for chemotherapy) after exhaustion of all therapeutic options for male patients (≥18 years old) with castration-resistant/ recurrent metastatic prostate cancer (CRPC or CRMPC). CRPC can also be called hormone-resistant prostate cancer (HRPC) or androgen-insensitive/independent prostate cancer (AIPC). ICD-10 Code: C61 MeSH-terms:Prostate, Neoplasms, Prostatic Neoplasms, Neoplasm Metastasis, Castration, Castration-Resistant
Intervention	Lutetium (Lu)-177-labelled Prostate-Specific Membrane Antigen (PSMA) Inhibitor Therapy administered intravenously. PSMA can be also called folate hydrolase I or glutamate carboxypeptidase II. Available agents: • ^{177}LU-PSMA-617 (Endocyte®, Indiana, USA) • ^{177}LU-PSMA-I&T (Scintomics GmbH, Fürstenfeldbruck, Germany) • alternatively, own agents made by radiopharmacists MeSH-terms: Lutetium, Prostate, Antigens, Therapeutics, Lutetium-177, Ligands, Radioisotopes, radiopharmaceuticals Keine MeSH: radioligand therapy

Control	Best supportive/best standard of care (incl. registered treatments at physician's choice as well as palliative care such as mitigation of pain, fatigue, loss of weight, fear, depression ...)
	Second line therapy or higher (≥2nd-line)
	• Hormonal therapy
	  • Abiraterone (Zytiga) alone or in combination with prednisone
	  • Enzalutamide (Xtandi)
	• Chemotherapy
	  • Docetaxel (Docefrez/Taxotere) + prednisone
	  • Cabazitaxel (Jevtana)
	  • Mitoxantrone (Novantrone)
	  • Estramustine (Emcyt)
	• Immunotherapy
	  • Sipuleucel-T (Provenge)

Control *(continuation)*	❁ Radiopharmaceuticals ❁ Radium 223 (Xofigo) ❁ Steroids ❁ Dexamethasone ❁ Prednisolone ❁ Prednisone MeSH-terms: Pharmaceutical Preparations, Immunotherapy, Drug Therapy, Antigens, Prostatic Neoplasms, Bone and Bones, Palliative Care
Outcomes	
Efficacy	***Clinical endpoints:*** ❁ **Overall survival (OS)** *(time from randomization until death from any cause)* ❁ **Quality of Life (QoL) –** *measures aspects of an individual's sense of well-being and ability to carry out activities of daily living)* ❁ **The European Organisation for Research and Treatment of Cancer (EORTC-Q30)** ❁ **Eastern Cooperative Oncology Group (ECOG)** ❁ **Karnofsky Performance Status (KPS)** ❁ **Pain scores** *(a scale for rating pain)* ❁ Brief Pain Inventory Short-Form (BPI-SF) ❁ Visual Analogue Scale (VAS) ❁ **Health Related Quality of Life (HRQoL)** *(measures aspects of an individual's sense of well-being with respect to physical and mental health)* ❁ Functional Assessment of Cancer Therapy – Prostate cancer (FACT-P) ***Surrogate endpoints*:** ❁ **Progression free survival (PFS)** (radiographically/otherwised confirmed progression free survival-(FDG)PET/CT/MRI/SPECT) ❁ **Response evaluation criteria in solid tumors (RECIST) response** *(a method measuring patients' response to treatment: when tumors improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment)* ❁ **Prostate Specific Antigen (PSA) PFS** *(progresson free survival as measured by the prostate specific membrane antigen levels)*
Safety	Serious adverse events (SAEs): ❁ **Study related death** Adverse events (AEs): ❁ **All grade 3-4 toxicities related to the treatment i.e. nephrotoxicity, hematotoxicity, hepatotoxicity bone pain flare etc.** (*as measured by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0)* ❁ **Discontinuation rates**
Study design	
Efficacy	Randomised controlled trials Prospective non-randomised controlled trials
Safety	Randomised controlled trials Prospective non-randomised controlled trials Prospective case-series (single arm studies, registries ... etc.) (No minimum number of patients requird, but individual case report excluded)

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is 177Lu-PSMA and the comparators?
A0020	For which indications has 177Lu-PSMA received marketing authorisation or CE marking?
B0002	What is the claimed benefit of 177Lu-PSMA in relation to the comparators?
B0003	What is the phase of development and implementation of 177Lu-PSMA and the comparators?
B0004	Who administers 177Lu-PSMA and the comparators and in what context and level of care are they provided?
B0008	What kind of special premises are needed to use 177Lu-PSMA and the comparators?
B0009	What supplies are needed to use 177Lu-PSMA and the comparators?
A0021	What is the reimbursement status of 177Lu-PSMA?

Health problem and Current Use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is 177Lu-PSMA used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for mCRPC?
A0004	What is the natural course of mCRPC?
A0005	What is the burden of disease for the patients with mCRPC?
A0006	What are the consequences of mCRPC for the society?
A0024	How is mCRPC currently diagnosed according to published guidelines and in practice?
A0025	How is mCRPC currently managed according to published guidelines and in practice?
A0007	What is the target population in this assessment?
A0023	How many people belong to the target population?
A0011	How much is 177Lu-PSMA utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of 177Lu-PSMA on mortality?
D0003	What is the effect of 177Lu-PSMA on the mortality due to causes other than mCRPC?
D0005	How does 177Lu-PSMA affect symptoms and findings (severity, frequency) of mCRPC?
D0006	How does 177Lu-PSMA affect progression (or recurrence) of mCRPC?
D0011	What is the effect of 177Lu-PSMA on patients' body functions?
D0016	How does the use of 177Lu-PSMA affect activities of daily living?
D0012	What is the effect of 177Lu-PSMA on generic health-related quality of life?
D0013	What is the effect of 177Lu-PSMA on disease-specific quality of life?
D0017	Was the use of 177Lu-PSMA worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is 177Lu-PSMA in comparison to the comparators?
C0002	Are the harms related to dosage or frequency of applying 177Lu-PSMA?
C0004	How does the frequency or severity of harms change over time or in different settings?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of 177Lu-PSMA?
C0007	Are 177Lu-PSMA and comparators associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of 177Lu-PSMA and the comparator?

2.2 Sources

Quellen: systematische Suche, Handsuche sowie Informationen des einreichenden Krankenhauses

Description of the technology

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospital

Health problem and Current Use

- Handsearch in the POP, AdHopHTA and CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Documentation provided by the manufacturers
- Questionnaire completed by the submitting hospital

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 14-17th of December 2018 in the following databases:

- Medline via Ovid
- Embase
- The Cochrane Library
- CRD (DARE, NHS-EED, HTA)

The systematic search was not limited to a year of publication or to study design, but to articles published in English or German. After deduplication, overall 643 citations were included. The specific search strategy employed can be found in the Appendix.

Suche nach laufenden Studien

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trials registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 18.01.2019 resulting in eight potentially relevant hits.

insgesamt wurden 651 Publikationen identifiziert

Manufacturers of the most common products (Endocyte®, Scintomics GmbH) were contacted and only Scintomics replied submitting six publications of which no new citations were identified.

By hand-search an additional eight were found, resulting in overall 651 hits.

2.4 Flow chart of study selection

Literaturauswahl

Overall 643 hits were identified. The references were screened by two independent researchers and in case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

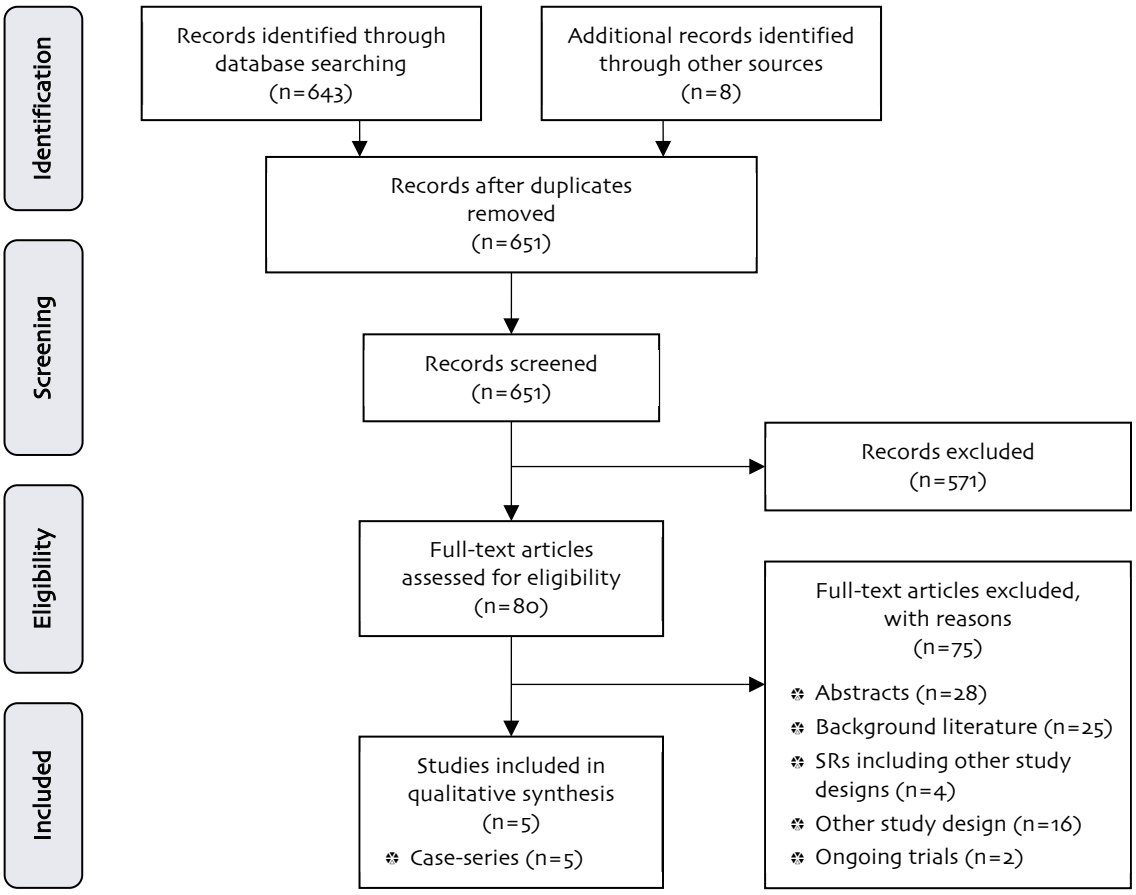

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

2.5 Analysis

Datenextraktion und Bewertung des Bias-Risikos laut IHE Checkliste

The data retrieved from the selected studies were systematically extracted into a data-extraction-table (see Table A-1). No further data processing (e.g. indirect comparison) was applied. Three independent researchers (MS, NG, CS) systematically assessed the quality of evidence (see Table 7-1) and the risk of bias (RoB) using the checklists presented in the Table A-2.

2.6 Synthesis

Evidenzsynthese mittels GRADE

Based on the data-extraction-table (see Table A-1), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [23]. The research questions were answered in plain text format with reference to GRADE evidence tables (see Table 7-1).

3 Description and technical characteristics of technology

Features of the technology and comparators

B0001 – What is 177Lu-PSMA and the comparators?

177Lu-PSMA and labelling

177 Lutetium (177Lu) is, to date, the most widely used radioisotope for targeted therapy in prostate cancer (PC). In terms of its properties, it is a medium energy β-emitter (490 KeV) with a maximum energy of 0.5 MeV and a maximal tissue penetration of <2 mm [9]. 177Lu is a reactor produced radiometal that emits low-energy γ-rays at 208 and 113 keV with 10 and 6% abundance, respectively [9]. It has a relatively long physical half-life of 6.73 days, which, together with the properties above, makes it a favourable theranostic agent [9]. Administration of a single dose ranges from 3-9.3GBq [9].

177LU ist das am häufigsten verwendetste Radioisotop im Bereich der zielgerichteten Therapie von Prostatakarzinomen

Prostate specific membrane antigen (PSMA) is a target for radionuclide therapy of PC and its metastases [24]. PSMA, known also as Glutamate Carboxypeptidase II (GCPII, EC 3.4.17.21), N-acetyl-┘-linked acidic dipeptidase I (NAALADase), or folate hydrolase, is a 750 amino acid type II transmembrane glycoprotein that is thought to have a number of functions with relation to nutrient uptake, cell migration, cell survival, and cell proliferation [25]. Under normal conditions, PSMA is expressed at low levels in prostate epithelium, but in the majority of PC patients (in more than 90%), it is overexpressed up to 1,000 times [8]. PSMA, however, is not only prostate specific, but it is also expressed in other cells found, for instance, on kidneys, liver, spleen, bone marrow, salivary, lacrimal, and parotid glands [9]. Because of the correlation between PSMA expression and the Gleason score (used for staging of PC) [18], PSMA is considered to be a valid prognostic and diagnostic biomarker [19].

PSMA = molekulares Target für die Radionuklidtherapie

Labelling of cells can be done in various ways using different PSMA peptides and antibodies [9]. Because the PSMA receptor has an internalization process allowing endocytosis of bound proteins on the cell surface into an endosomal compartment, PSMA labelled radioisotopes like 177Lu can be concentrated within the cell [26]. In the studies included in this assessment, the different types of labelling include three ways of chemical conjugation of a peptide, thus three studies used 177Lu-PSMA-DKFZ-617 [10-12], one study used 177Lu-PSMA-I&T [13], and the other 177Lu-PSMA-617 [14].

kennzeichnen von Zellen mittels verschiedener PSMA Peptide und Antikörper

Comparators

The role of 177Lu-PSMA in the care pathways of PC patients is partly unclear. While all the studies included in the analysis use 177Lu-PSMA as an experimental intervention after the exhaustion of all therapeutic options (see the Table A-1), the German AWMF S3 guideline includes 177Lu-PSMA in the category of second line therapies for metastatic castration-resistant prostate cancer (mCRPC) [22].

unklare Einordnung in den Therapiealgorithmus des Prostatakarzinoms

If 177Lu-PSMA is understood as a second line therapy, **hormonal therapies** with abiraterone (alone or in combination with prednisone) or enzalutamide are considered as alternatives. Both of these hormonal therapy interventions are indicated after progression of PC despite the first line androgen deprivation therapy [3]. Abiraterone inhibits the products of CYP17 gene and in do-

als Zweitlinientherapie wäre 177Lu-PSMA eine mögliche Alternative zur Hormontherapie (Abiraterone, Enzalutamide)

ing so, it blocks the synthesis of androgens in the tumour as well as in the testis and adrenal glands [3]. Enzalutamide acts in multiple sites in the androgen receptor signalling pathway and unlike in abiraterone, concurrent treatment with steroids is not required [3].

alternative Chemotherapien: Docetaxel, Cabazitaxel, Mitoxantrone, Estramustine

An alternative to the above hormonal therapy, **chemotherapy** options include docetaxel (with prednisone), cabazitaxel, mitoxantrone, and estramustine. While estramustine is an estrogen and cytostatic antineoplastic agent combined, the former three agents all belong to the class of anticancer agents called taxanes that bind to and stabilize microtubules causing cell-cycle arrest and apoptosis [3].

weitere Komparatoren umfassen: Immuntherapeutika (Sipuleucel-T), Radiopharmazeutika, Steroide (Dexamethason, Prednisolon, Prednison)

Further comparators to 177Lu-PSMA are **immunotherapy** options including sipuleucel-T that is a dendritic cell vaccine prepared from peripheral blood mononuclear cells obtained by leukapheresis where the activated cells are infused back into the patients ca three days after harvesting [3]. Sipuleucel-T is, however, not accessible in Europe. **Radiopharmaceuticals** like Radium 223 are also an alternative as they allow for deposition of high-energy radiation over a shorter distance than it is the case with beta-emitting radioisotopes, thus minimizing toxicity [3]. **Steroids** like dexamethasone, prednisolone, prednisone represent the last set of alternatives that can be prescribed alone, or in combination with the set of therapy options outlined above mainly for the sake of symptom and side-effect management [22].

A0020 – For which indications has 177Lu-PSMA received marketing authorisation or CE marking?

177Lu-PSMA ist nicht zugelassen durch die FDA und besitzt keine CE-Zertifizierung

As indicated by the manufacturer Scintomics, 177Lu-PSMA has neither CE mark, nor FDA approval. The therapy is currently performed either under clinical trials or under local regulations for unproven interventions for patients who have exhausted all therapeutic options [20]. Since 2019, 177Lu-PSMA is part of the German DRG system [21].

B0002 – What is the claimed benefit of 177Lu-PSMA in relation to the comparators?

177Lu-PSMA bietet eine weitere Therapiemöglichkeit für mCRPC Patienten im Endstadium

The main claimed benefit is that 177Lu-PSMA offers an extra therapeutic option for mCRPC patients in the end stage of cancer. Through its targeted approach, 177Lu-PSMA claims to reduce the level of prostate specific antigen (PSA), have potential survival benefits with respect to progression free survival as well as overall survival, and have a safe profile that causes a minimal number of grade 3-4 toxicities [15].

B0003 – What is the phase of development and implementation of 177Lu-PSMA and the comparators?

5 prospektive Studien aus 2018 und 2 laufende RCTs (NCT03511664 und NCT03392428)

At this point in time, the manufacturer Endocyte® is in the process of applying for an FDA approval with their ongoing randomized controlled trial (RCT) comparing 177Lu-PSMA to best standard care (NCT03511664). So far, there were five prospective trials published by 2018 and no controlled trials published on 177Lu-PSMA for mCRPC. One further RCT (NCT03392428) comparing 177Lu-PSMA to the chemotherapy cabazitaxel is also in the recruiting phase. Moreover, the question of individual patient dosimetry is still a matter research [19].

Administration, Investments, personnel and tools required to use 177Lu-PSMA and the comparators

B0004 – Who administers 177Lu-PSMA and the comparators and in what context and level of care are they provided?

B0008 – What kind of special premises are needed to use 177Lu-PSMA and the comparators?

177Lu-PSMA kann nach österreichischen Strahlenschutz-Richtlinien sowohl ambulant als auch stationär angewendet werden

According to the questionnaire from the submitting hospital, 24 hour clinical observation and gamma camera imaging is preferable with patient's maximum stay of two days. The studies included for the analysis were conducted in the inpatient setting where 2-4 days of post-intervention observation was reported in one study [13]. Depending on the context, the Australian regulation allows for 177Lu-PSMA to be administered in the outpatient setting, the German regulation requires a minimum three day hospital admission [9], and the Austrian Radiation-protection guideline (Strahlenschutz-Richtlinien) allows for 177Lu-PSMA to be performed both in outpatient as well as inpatient context.

177Lu-PSMA ist Teil der Sekundär- und Tertiärversorgung der jeweiligen Radiologie Abteilung im stationären Bereich

177Lu-PSMA is administered in secondary and tertiary levels of care in the hospital's radiology department either as a slow injection by hand, or via an infusion pump [20]. According to the submitting hospital, experts in nuclear medicine, radiology technology, and medical physics are necessary. Furthermore, the intervention is to be performed in 3-4 cycles at intervals of 6-8 weeks that may be interrupted according to pre-defined criteria such as PSA increase after two cycles.

alternative Zweitlinien Therapien werden entweder im stationären oder ambulanten Bereich verabreicht

The inpatient or outpatient administration of the alternative second line treatment depends on the specific intervention. While hormonal therapy and steroids can be administered in an oral form in the outpatient or home context, immunotherapy, radiotherapy, and chemotherapy are predominantly administered in the inpatient setting.

keine speziellen infrastrukturellen Voraussetzungen für die Anwendung von 177Lu-PSMA notwendig

No special premises are required for the administration of 177Lu-PSMA as well as the alternative treatment options. According to the submitting hospital, the only premises and equipment required for the administration of 177-Lu-PSMA are warm room, C lab equipment, and gamma camera.

B0009 – What supplies are needed to use 177Lu-PSMA and the comparators?

177Lu-PSMA kann entweder bei den Herstellern erworben werden oder von Radiopharmazeuten hergestellt werden

177Lu-PSMA can be either purchased from the manufacturers listed (Endocyte®, Scintomics GmbH, Telix Pharmaceuticals Limited), or prepared by individual radiopharmacists. On top of the intervention itself, a single day kidney protection protocol may be followed, which includes a cocktail of lysine and arginine diluted in two litres of normal saline infused over four hours, starting 30–60 min before the 177Lu-PSMA infusion [11].

abhängig vom Gesundheitszustand der Patienten sollten zusätzliche Therapien verabreicht werden

Furthermore, depending on the patient's health state before the intervention, application of the following agents may be considered: diuretics in cases of urinary flow disorders; laxatives in cases of constipation to support rapid clearance of unbound 177Lu-PSMA; icepacks for the salivary glands to potentially reduce blood flow and 177Lu-PSMA uptake during the blood pool phase until approximately four hours after the start of radio ligand therapy; prophylactic antiemetic therapy such as ondansetron; and corticosteroids in cases of cerebral, spinal, or other metastases with risk of swelling and mechanical obstruction [20].

Behandlung von Komorbiditäten

Concerning supplies for the comparators of hormonal therapies, chemotherapy, immunotherapy, radiopharmaceuticals, and steroids, what is needed are the specific substances together with potential interventions for the treatment of comorbidities.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of 177Lu-PSMA?

seit 2019 in das deutsche DRG-System aufgenommen

Up until the end of 2018, 177Lu-PSMA was performed under either clinical trials or under local regulations for unproven interventions for patients who have exhausted all therapeutic options [20]. Since 2019, 177Lu-PSMA is included in the German DRG system [21].

4 Health Problem and Current Use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is 177Lu-PSMA used?

A0002 – What is the disease or health condition in the scope of this assessment?

177Lu-PMSA wird als letzte Therapiemöglichkeit für die Behandlung von mCRPC eingesetzt

177Lu-PMSA is used as the last line of treatment of metastatic castration-resistant prostate cancer (mCRPC). The growth of PC is driven by male sex hormones called androgens. Hence, the common first line treatment option is to lower their level in the man's body androgen deprivation therapy (ADT) [27]. Even though 80-90% of patients respond to androgen therapy, nearly all eventually develop progressive CRPC [2], which can be measured by the rise in PSA levels, progression of existing metastases, or the presence of new metastases [4]. The exact number of mCRPC patients is unclear as there are no widely accepted criteria for its definition outside of the clinical trial setting [3]. Once the only evidence is the rise of PSA levels, whether it is the instance of CRPC is particularly unclear because the decision requires judgment on the part of the treating physician. While some define CRPC by a serum PSA rising over one month to more than two ng/mL, others define it by PSA twofold rise [3]. Gleason Score is the tool used for determining the aggressiveness of prostate cancer [28].

A0003 – What are the known risk factors for mCRPC?

1,4 Millionen PC Fälle weltweit

With 1.4 million cases in 2016 globally, PC is the most common incident cancer for men [1]. The risk of prostate cancer in the US men is one in six [29], but the rates differ over 50-fold among various world populations with Western countries leading the incidence rate [5]. One of the factors is ethnicity as PC is more common in black than white and Hispanic men, and least common in Asian [5, 6].

steigende Inzidenz mit höherem Alter

The incidence also increases proportionally with age as in the Western countries, the incidence is ~12% in the 60-69 year old men, whereas it is ~48% in 80-89 year old [6]. Furthermore, genetic factors, diet, cigarette smoking, hormone levels, and obesity also play a role [5].

A0004 What is the natural course of mCRPC?

der natürliche Verlauf von PC ist abhängig von der Tumoraggressivität

The natural course of PC is primarily dependent on tumour aggressiveness. PC can remain silent throughout a man's life without being detected [7], especially in the context of the proportional increase in the incidence of PC with age [6]. However, if PC grows to the stage of producing symptoms like bladder neck obstruction, invasion of adjacent organs, or distant metastasis, curative treatment is usually impossible [7]. For that reason, PSA blood tests have been used for screening of PC, but amidst controversies about their survival benefit and the question of overdiagnosis, PSA screening is currently not recommended, for instance by USPSTF or by Public Health England [30].

90 % der mCRPC Patienten weisen Knochenmetastasen auf

Because nearly all patients who initially respond to ADT eventually develop mCRPC, the natural course of mCRPC is death [2]. Bone metastases occur in 90% of men with mCRPC and can produce significant morbidity such as pain, pathologic fractures, spinal cord compression, and bone marrow failure. Paraneoplastic effects are also common, including anaemia, weight loss, fatigue, hypercoagulability, and increased susceptibility to infection [31].

Effects of the disease or health condition on the individual and society

A0005 – What is the burden of disease for patients with mCRPC?

altersstandardisierte Krebsmortalitätsrate 14,24 Todesfälle/ 100.000 Personen/Jahr (Global Burden of Disease 2015)

According to Global Burden of Disease 2015, global estimates of the age standardized death rate for PC are 14.24 deaths (95% CI: 11.8-17.95) per 100,000 person-years [32]. While the prostate cancer mortality rate is decreasing in high income countries, the incidence and burden of disease is steadily increasing globally [32]. In 2016, PC was the cancer with the highest incidence for men in 92 countries, and the leading cause of cancer deaths for men in 48 countries [1]. The increasing incidence rates, together with an ageing and growing population, have led to a 40% increase in prostate cancer cases between 2006 and 2016 [1].

Statistik Austria: 1.225 Sterbefälle/Jahr (2016)

According to Statistik Austria, the mortality from PC in 2016 was 1,225 with the highest mortality in the states with highest incidence rates of Lower Austria, Upper Austria, and Vienna [33].

A0006 – What are the consequences of mCRPC for the society?

PC verursachte weltweit im Jahr 2016 6,1 Millionen DALYs

The consequences of PC for the society lie not only in the costs related to the pharmacological treatment, but also in the costs from a societal perspective that are present when PC impedes on a person's life, particularly on work activity. Globally in 2016, PC caused 6.1 million (95% UI, 5.0-6.6 million) disability-adjusted life years (DALYs) with 91% coming from years of life lost and 9% from years lived with disability [1].

Current clinical management of the disease or health condition

A0024 – How is mCRPC currently diagnosed according to published guidelines and in practice?

PC Erstdiagnose entweder durch PSA Screening oder aufgrund von auftretenden Symptomen

PC is either found via screening for PSA or via the occurrence of symptoms in more advanced cancers. PC screening, as mentioned in A0004, however, is one of the most controversial topics in current urology as three large prospective RCTs result in conflicting positions [34].

DRU und PSA Level können als Prädiktoren für PC dienen

According to the European Association of Urology (EAU), PC is usually suspected on the basis of digital rectal exam (DRE) and/or PSA levels [34]. In ~18% of cases, PC is detected by suspect DRE alone, irrespective of PSA levels [34]. Yet, as an independent variable, PSA is a better predictor of cancer than DRE [34]. Definitive diagnosis, however, depends on histopathological verification of adenocarcinoma in prostate biopsy cores or specimens from transurethral resection of the prostate (TURP) or prostatectomy for benign prostatic enlargement (BPE).

ultraschallgeführte Biopsie wird derzeit als Standard Diagnosehilfsmittel für PC angesehen

Ultrasound-guided biopsy is the current standard of care with prostate biopsy being performed by either the transrectal or transperineal approach [34]. Biopsy may then show prostate cancer, precancerous, or benign findings. If the biopsy indicates prostate cancer, architectural features of the cells in the biopsy tissue are used to generate a Gleason grade that correlates closely with clinical behaviour [35]. The Gleason grade is key to determining treatment approaches [35]. Repeated biopsy may be indicated, for instance, in situations when PSA level increases further or if findings on digital rectal examination or prostate imaging warrant rebiopsy [35].

In situation when PC initially presents after becoming metastatic to bone, pain is the most common manifestation [36]. The choice of imaging procedure is guided by the clinical setting and includes: radionuclide bone scan, plain radiographs, and magnetic resonance imaging [36].

Knochenmetastasen können sich häufig durch Schmerzen äußern

A0025 – How mCRPC currently managed according to published guidelines and in practice?

In localized PC, a life expectancy of at least 10 years is considered mandatory for any benefit from local treatment [34]. Comorbidity is more important than age in predicting life expectancy in men with PC [34]. However, for those men with a short life expectancy, watchful waiting with symptom-guided treatment is appropriate in order to maintain quality of life [34]. Radical prostatectomy is in place only if the goal is eradication of PC, while, whenever possible, preserving continence and potency is important [34].

lokalisiertes Prostatakarzinom: ≥10 Jahre Lebenserwartung

Concerning mCRPC patients, ADT is the first line therapy and it can be accomplished either with bilateral orchiectomy (surgical castration) or medical orchiectomy [3]. Currently, multiple agents are given in conjunction with continued ADT or as a second line therapy, which, according to the German AWMF S3 guideline, include (the selection of comparators listed in B0001) [22]:

ADT wird als Erstlinientherapie bei mCRPC angewendet

- Interference with androgenic stimulation of prostate cancer growth through abiraterone or enzalutamide.
- Taxane chemotherapy using docetaxel, cabazitaxel, mitoxantrone, or estramustine. Docetaxel (with prednisone) is the standard therapy regimen and cebazitaxel is the option of choice for patients who progress despite using docetaxel, yet at the same time for those who show that it prolonged their survival. Mitoxantrone is an added therapeutic option as both of the taxanes above have shown superiority to mitoxantrone [3].
- Immunotherapy via the use of sipuleucel-T.
- The bone-targeted radiopharmaceutical therapy with Radium-223.
- Steroids such as dexamethasone, prednisolone, and prednisone.

Therapieoptionen laut AWMF S3 Leitlinien

The above approaches have in general not been compared with each other in a large RCT. The proper sequencing of these approaches requires consideration of multiple factors, in particular, the sites and extent of disease involvement and the rate of disease progression. Both hormonal as well as chemotherapy treatment options, however, are effective only temporarily and patients can develop resistance [15].

es liegen keine vergleichenden RCT Studien zu den genannten Therapieoptionen vor

Target population

A0007 – What is the target population in this assessment?

A0023 – How many people belong to the target population?

The target population of this assessment are mCRPC patients of more than 18 years of age who have exhausted all therapeutic options and have an expression of PSMA as conventionally measured by 68Ga-PSMA- PET CT.

erwachsene mCRPC Patienten, welchen keine weiteren Therapieoptionen zur Verfügung stehen

According to Statistik Austria, the annual number of disseminated PC (most presumably an equivalent to mCRPC) is 242.3 patients [33]. Furthermore, the annual PC incidence rate in 2016 in Austria was 5,245 with the highest incident rate in Lower Austria, Upper Austria, and Vienna [33]. For the comparison, the age-standardized incidence rate from the European Standard Population in 2016 was 138.3 per 100,000 men per year [33].

Neuerkrankungen in Österreich im Jahr 2016: 5.245

A0011 – How much is 177Lu-PSMA utilised?

es liegen keine Informationen zur Häufigkeit der Leistungserbringung vor

The previous administrations of 177Lu-PSMA in mCRPC patients have been within the scope of clinical trials or under local regulations for unproven interventions for patients who have exhausted all therapeutic options [20]. The German University Clinics offer radio ligand therapies since 2013 on a compassionate use basis and they developed a consensus recommendation on the use of 177Lu-PSMA [37, 38]. Because neither the manufacturers, nor the submitting hospital have answered the question on the volume of utilization, an estimate on the number of current and potential/expected utilisation of 177Lu-PMSA is not yet available for Austria.

5 Clinical effectiveness

5.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

entscheidungsrelevante Endpunkte für die Wirksamkeit

- Overall survival (OS)
- Quality of Life (QoL)
- Health Related Quality of Life (HRQoL)

The following outcomes were defined as *surrogate* to derive a recommendation:

Surrogatendpunkte

- Progression free survival (PFS)
- Response evaluation criteria in solid tumours (RECIST)
- Prostate Specific Antigen (PSA) PFS

Concerning *crucial* outcomes, the outcome **OS** (reported in the form of a median) refers to the amount of time after which 50% of the patients have died and 50% have survived. For the outcome of **QoL** that measures aspects of an individual's sense of well-being and ability to carry out activities of daily living, Eastern Cooperative Oncology Group (ECOG), Karnofsky Performance Status (KPS), and European Organisation for Research and Treatment of Cancer (EORTC-Q30) were included. Furthermore, the following pain scores were included as a sub-outcome of QoL: Visual Analogue scale (VAS) and Brief Pain Inventory Short-Form (BPI-SF). Also, the outcome **HRQoL** that measures aspects of an individual's sense of well-being with respect to physical and mental health in connection to prostate cancer that was included was Functional Assessment of Cancer Therapy – Prostate cancer (FACT-P).

Definition der entscheidungsrelevante Endpunkte: Gesamtüberleben (OS), Lebensqualität (QoL), gesundheitsbezogene Lebensqualität (HRQoL)

Concerning *surrogate* outcomes, **PFS** refers to progression free survival confirmed radiographically (PET/CT/MRI/SPECT scans) or otherwise. The outcome **RECIST response** refers to a method measuring patients' response to treatment: when tumours improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment. And, **PSA PFS** refers to PFS as measured by the PSA levels.

Surrogatendpunkte: progressionsfreies Überleben (PFS), prostataspezifisches Antigen PFS, Response Evaluation Criteria in Solid Tumoren (RECIST)

5.2 Included studies

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table 7-1.

No study fulfilled the study inclusion criteria for assessing clinical effectiveness of the 177Lu-PSMA. RCTs and non-randomised CTs were considered for inclusion, but could not be identified through the systematic literature search (see Figure 2-1).

es konnten weder RCTs noch nicht-randomisierte CTs für die Beurteilung der Wirksamkeit identifiziert werden

Observational evidence consisting of five prospective before-after studies was included [10-14] and is described in the results on safety.

5.3 Results

keine Evidenz für die Beurteilung der Wirksamkeit

Mortality

D0001 – What is the expected beneficial effect of 177Lu-PSMA on mortality?

No evidence was found to answer the research question.

D0003 – What is the effect of 177Lu-PSMA on the mortality due to causes other than mCRPC?

No evidence was found to answer the research question.

Morbidity

D0005 – How does 177Lu-PSMA affect symptoms and findings (severity, frequency) of mCRPC?

No evidence was found to answer the research question.

D0006 – How does 177Lu-PSMA affect progression (or recurrence) of mCRPC?

No evidence was found to answer the research question.

Function

D0011 – What is the effect of 177Lu-PSMA on patients' body functions?

No evidence was found to answer the research question.

D0016 – How does the use of 177Lu-PSMA affect activities of daily living?

No evidence was found to answer the research question.

Health-related quality of life

D0012 – What is the effect of 177Lu-PSMA on generic health-related quality of life?

No evidence was found to answer the research question.

D0013 – What is the effect of 177Lu-PSMA on disease-specific quality of life?

No evidence was found to answer the research question.

Patient satisfaction

D0017 – Was the use of 177Lu-PSMA worthwhile?

No evidence was found to answer the research question.

6 Safety

6.1 Outcomes

The following outcomes were defined as *crucial* to derive a recommendation:

- Serious adverse event (SAEs)

Additional outcomes considered were Adverse event (AEs):

- All grade 3-4 toxicities
- Discontinuation rate

entscheidungsrelevanter Endpunkt für die Sicherheit: schwerwiegende unerwünschte Ereignisse (SAEs)

Concerning *crucial* outcomes, **SAEs** included were study related death.

Additional outcomes considered were **all grade 3-4 toxicities** related to treatment such as nephrotoxicity, hematotoxicity, hepatotoxicity, and bone pain flare, as measured by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. **Discontinuation rate**, referring to the rate at which clinicians or patients themselves discontinued the treatment, was also considered.

weitere berücksichtigte Endpunkte: Grad 3-4 AEs, Abbruchrate, Präzision der Therapie

6.2 Included Studies

The study inclusion criteria for assessing safety differed from the ones for assessing clinical effectiveness. In addition to RCTs and non-randomised CTs, prospective studies without a control group were considered for the assessment of safety. The systematic literature search (see Figure 2-1) identified five prospective before-after studies that matched our inclusion criteria [10-14].

für die Beurteilung der Sicherheit konnten 5 Beobachtungsstudien identifiziert werden

Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table 7-1.

Study characteristics

Four studies were explicitly conducted in one centre [11-14], but it was unclear in the fifth [10]. Countries of recruitment were Germany [13], Australia [10, 12], Austria [14], and India [11]. Study recruitment times were either not stated [10, 14], or in the rest of the studies, they were between 05/2013 – 12/2016 [11-13]. Clinical follow-up was unclear in two studies [10, 14], and ranged from mean 13 to median 25 months in the remaining 3 studies [11-13]. Loss to follow-up was 35.7% in one study [10], and it was unclear or unreported in the remaining studies [11-14]. None of the studies was explicitly sponsored by the any of the manufacturers, but a member of the authoring team in one study was a shareholder at Scintomics, Germany [13]. One study had no funding [11], another study was funded by Peter MacCallum Foundation and Prostate Cancer Foundation [12], another by University of Innsbruck and Medical University of Innsbruck [14], and the last by Paul Ramsey Foundation [10].

4 Studien wurden in einem Zentrum durchgeführt für eine Studie lagen keine Informationen dazu vor

keine Studie wurde von einem Hersteller gesponsert

Peptide:
3 x 177Lu-PSMA-DKFZ-617
1 x 177Lu-PSMA-I&T
1 x 177Lu-PSMA-617

In terms of the chemical conjugation of the labelled peptide, three studies used 177Lu-PSMA-DKFZ-617 [10-12], one study used 177Lu-PSMA-I&T [13], and the other 177Lu-PSMA-617 [14]. The mean strength of radiation ranged in all studies from 5.07 (SD±1.85) to 7.5 (range 4.4-8.7) and the average number of cycles per patient ranged from 2.2 to 3.2 [10-14]. In terms of imaging procedures, all studies used PET/CT with 68Ga-PSMA for selection of patients and therapy monitoring [10-14]. Two studies also used 18F-FDG PET/CT, bone scan, and CT of the chest, abdomen, and pelvis [10, 12].

Patient characteristics

Von 141 Pts, nur Charakteristika von 116 beschrieben
Einschlusskriterien: PSMA Expression und letzte Therapiemöglichkeit

Overall, out of the total of 141 patients included in the five studies, basic characteristics were reported on 116 patients. In terms of inclusion criteria, PSMA expression and exhaustion of all therapeutic options were the conditions in all studies [10-14], whereas two studies also specified that patients should have had ECOG less or equal to two, life expectancy of more than 12 weeks, and confirmed disease progression [10, 12]. One of them also required specific baseline blood counts [10].

Exklusionskriterien lagen in 2 Studien nicht vor

In terms of exclusion, two studies did not state their exclusion criteria [13, 14], two studies further excluded patient with clinically significant impaired bone marrow [10, 12], two studies excluded patients with specific poor baseline blood counts [11, 12], of which one also excluded patients with clinically significant impaired kidney and liver function, and patients who used concomitant nephrotoxic drugs, who had radiotherapy within six weeks, or who had uncontrolled intercurrent illness [12].

unterschiedliche Co-Interventionen wurden in den Studien angewendet

Concerning the use of co-interventions, two studies allowed the concomitant use of denosumab or biphosphorate [10, 12], whereas one of them also allowed the use of blood transfusions, palliative radiotherapy, and 2nd generation anti-androgens [12] and the other allowed the use of luteinising hormone-releasing hormone (LHRH) agents [10]. One other study also applied the use of a kidney protection cocktail of lysine and arginine diluted in two litres of normal saline before the application of 177Lu-PSMA [11].

vorausgehende Behandlungen: Chemotherapie, Hormontherapie, LHRH, Bestrahlung, chirurgische Eingriffe, antiandrogene und Knocheninterventionen

With regards to prior treatments, hormone therapy was used in two studies [11, 13], LHRH therapy in three [10, 13, 14], external beam radiation as well as surgical therapy in three [11, 13, 14], chemotherapy was used in all studies [10-14], and antiandrogens and bone interventions in four [10, 12-14].

das mediane Alter in 4 von 5 Studien reichte von 67-72 Jahren, in der fünften Studie lag das Durchschnittsalter bei 65,9 Jahren

Concerning further baseline criteria, the median age in four studies ranged from 67 (range 56-82) to 72 (range 50-88) [10, 12-14], with one stated as a mean of 65.9 (range 38-81) [11]. Baseline median Gleason score ranged from eight to nine in three studies [10, 12, 13], it was more or equal to eight without stating the statistical measure in one study [14], and unclearly reported in another [11]. Baseline ECOG performance status was not reported in two studies [13, 14], it was reported as a mean of 2.54 in one study [11], and it was reported in categories 0/1/2 in two studies with 37/47/17% of patients in one of them [12], and 35.7/64.3/0.0% of patients in each category in the other [10]. Tumour stage was explicitly reported in one study with tumour stages 1/2/3/4 in 13/23.2/62.5/12.5% of patients, respectively [13]. Baseline toxicity was reported in one study with 32.3% of patients having grade 1 haemoglobin toxicity [11].

6.3 Results

Patient safety

C0008 – How safe is 177Lu-PSMA in comparison to the comparators?

es liegen keine komparativen Studien vor

In the absence of data from CTs, no comparisons can made between the 177-Lu-PSMA and the comparators. Only intervention related complications can be considered for the analysis of safety because the effects directly attributable to the intervention can be analysed without a control group.

SAEs traten in keiner Studie auf

Concerning SAEs, the outcome of study related death was reported in two studies and it did not occur in either [12, 13].

eine Studie berichtete von einer Abbruchrate

Grad 3-4 Toxizitäten wurden in 4 Studien untersucht traten jedoch nicht auf

Concerning AEs, the outcomes of discontinuation rate was reported in one study where no patients discontinued treatment [12]. With respect to grade 3-4 toxicities, nephrotoxicity was reported in four studies, but did not occur either [11-14]. With respect to hematotoxicity: lymphocytopenia was reported in three studies [12-14] and occurred in one in 37% of patients [12], thrombocytopenia and anaemia were both reported in four studies [10, 12-14] and both occurred in one in 13% of patients [12], neutropenia was reported in three studies [12-14] and occurred in one in 7% of patients [12], and haemoglobin toxicity was reported in one study in 3.2% of patients [11]. Hepatotoxicity was reported in two studies, but did not occur in either [11, 14], while bone pain flare was reported in one study and occurred in 3% of patients [12].

C0002 – Are the harms related to dosage or frequency of applying 177Lu-PSMA?

Unklarheiten, welches Organ primär Dosis-limitierend wirkt

As 177Lu-PSMA is a therapy that targets the specific antigen expressed on the surface of PC tumour cells as well as on other cells such as kidneys, liver, spleen, bone marrow, salivary, lacrimal, and parotid glands, the precision of 177Lu-PSMA therapy is important. There is no agreement on which of the above organs is the main dose limiting one and hence which one is most susceptible to harms related dosage of 177Lu-PSMA [15-19]. Furthermore, it was observed that treatment outcome is worse in patients with organ metastases and elevated lactate dehydrogenase in blood tests [39]. For these reasons, individual patient specific dosimetry presents key challenges as on the one hand, the goal is to apply maximal justifiable dose of 177Lu-PSMA that does not cause serious toxicity in order to get the antitumor effect and on the other hand, if radiation gets to be absorbed by bone marrow, fatal damage is possible [40]. In this respect, a possible harm was reported in one study where a significant bone pain during the administration of 177Lu-PSMA occurred in 7.1% of patients (n=1/14) [10]. Furthermore, there are harms related to the frequent use of computed tomography (CT) scans as those have an impact on mCRPC patients' morbidity [41].

individuelle patientenspezifische Dosimetrie erforderlich

C0004 – How does the frequency or severity of harms change over time or in different settings?

die Datenlage zu Änderungen der Häufigkeiten oder Schwere der Schäden im Laufe der Zeit ist nicht aussagekräftig

As 177Lu-PSMA is the last intervention used after the exhaustion of all therapeutic options, the patient population at stake has received a list of previous interventions beforehand, which makes it hard to directly attribute any effect to 177Lu-PSMA. Also, there is no data with longer term follow-up than median 25 months (IQR 12.7-25.2) from one study [12] where the highest number of AEs are reported. However, it remains unclear at what time-point the safety data were reported and hence no conclusions can be made about the change in frequency or severity of harms over time.

alle Daten wurden im stationären Bereich erhoben

Also, there is no data concerning the delivery of 177Lu-PSMA in other than inpatient setting and hence, even though 177Lu-PSMA could in theory be also used in the outpatient context in Austria (according to the questionnaire from the submitting hospital), there is no data comparing the safety profile of the 177Lu-PSMA use in the two settings.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of 177Lu-PSMA?

geringe Lebensqualität und Komorbiditäten

The most susceptible patient groups are patients with low baseline QoL and patients with comorbidities – especially those with comorbidities related to the dose limiting organs of kidneys, liver, spleen, bone marrow, salivary, lacrimal, and parotid glands [15-18].

C0007 – Are 177Lu-PSMA and comparators associated with user-dependent harms?

keine Evidenz

No information was found to answer this research question.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of 177Lu-PSMA and the comparators?

Wirksamkeitsdaten aus RCTs notwendig

RCT data are needed to establish the efficacy of 177Lu-PSMA and prospective registry data to monitor its use for the sake of providing a longer-term safety and efficacy follow-up data.

7 Quality of evidence

RoB bewertet mittels IHE Checkliste

The risk of bias (RoB) for individual studies was assessed with the Institute of Health Economics (IHE) checklist for single-arm studies (CITE) and it is presented in Table A-2 in the Appendix [42]. The overall RoB ranged from low to high, with two studies being ranked as high [13, 14], two studies as medium [10, 11], and one as low [12]. The main reasons for downgrading were lack of clarity concerning consecutiveness of recruitment, eligibility criteria, and patients' stage of disease when entering the study. Also, studies were downgraded due to no reporting of co-interventions, length and loss to follow up, and due to no blinding.

niedriger bis hoher RoB in den eingeschlossenen Studien

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [23] for each endpoint individually. Each study was rated by three independent researchers. All disagreements were resolved among the researchers. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [23].

GRADE uses four categories to rank the strength of evidence:

- **High** = We are very confident that the true effect lies close to that of the estimate of the effect;
- **Moderate** = We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
- **Low** = Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect;
- **Very low** = Evidence either is unavailable or does not permit a conclusion.

The ranking according to the GRADE scheme for the research question can be found in the evidence profile table below (see Table 7-1).

Gesamtstärke der Evidenz konnte aufgrund fehlender kontrollierter Studien nicht untersucht werden

Overall, the strength of evidence for clinical effectiveness was not assessed due to the lack of controlled studies as no evidence was available comparing 177Lu-PSMA and any second line therapy (or higher line therapy) or best supportive care. Regarding safety of 177Lu-PSMA, the quality of evidence was low (for outcomes of SAEs and discontinuation rate) – due to the study design, and very low (for the outcome of grade 3-4 toxicities) – due to RoB and inconsistency in reporting on the outcome of grade 3-4 toxicities.

Table 7-1: Evidence profile: efficacy and safety of 177Lu-PSMA in mCRPC patients

Certainty assessment							Estimate of effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Efficacy									
Due to the lack of a controlled group, no data on efficacy can be reported.									
Safety									
Serious adverse events									
2 (55 pts)	prospective before-after studies	not serious	not serious	not serious	not serious	none	SAEs occurred in 0/55 pts and were not reported in the remaining 55 pts	⊕⊕◯◯ LOW	CRITICAL
Adverse events									
Grade 3-4 toxicities									
5 (116 pts)	prospective before-after studies	serious [a]	serious [b]	not serious	not serious	none	nephrotoxicity occurred in 0/96 pts, hematotoxicity occurred in 11/65 pts, thrombocytopenia and anemia occurred in 4/79 pts, neutropenia occurred in 2/65 pts, hemoglobin toxicity occurred in 1/31 pts, hepatotoxicity occurred in 0/41 pts, bone pain flare occurred in 1/30 pts	⊕◯◯◯ VERY LOW	CRITICAL
Discontinuation rate									
1 (30 pts)	prospective before-after study	not serious	not serious	not serious	not serious	none	no discontinuation rate was reported in 80 pts and 0/30 pts discontinued therapy in Hofman et al.	⊕⊕◯◯ LOW	IMPORTANT

Abbreviations: *IHE = Institute of Health Economics, RoB = risk of bias, pts = patients*

Explanations

[a] *Using the IHE RoB checklist, 2 studies were evaluated to have high, 2 medium, and 2 low risk of bias.*

[b] *The study with the lowest risk of bias reports grade 3-4 toxicities occurring in up to 37% of patients while the remaining studies report no toxicities.*

8 Discussion

prospektive Evidenz zu 177Lu-PSMA bei mCRPC

To our knowledge, this is the first systematic review (SR) of 177Lu-PSMA for mCRPC patients that is based on prospective evidence only. In our systematic search, there were three SRs found that all included both prospective as well as retrospective studies and were published in 2017 and 2018. All three SRs conclude a positive efficacy as well as safety profile of 177Lu-PSMA based on the outcome of PSA decline and SAEs/AEs [43-45].

Summary of evidence from prospective clinical studies

keine kontrollierten Studien lagen vor

We found no controlled trials for the analysis of clinical effectiveness. For the analysis of safety, we found five prospective before-after studies including 141 patients receiving 177Lu-PSMA.

Beobachtungsstudien deuten auf keine SAEs und Grad 3-4 Toxizitäten hin

Intervention related complications based on the prospective observational studies without a control group suggest that 177Lu-PSMA was not related to any SAEs in the form of study related death. Furthermore, with respect to AEs of grade 3-4 toxicities, 177Lu-PSMA was not related to any nephrotoxicity and hepatotoxicity, but it was related to bone pain flare and a list of hematotoxicities reported in one study [12]: lymphocytopenia in 37% of patients, thrombocytopenia and anaemia in 13% of patients, neutropenia in 7% of patients, and haemoglobin toxicity reported in another study in 3.2% of patients [11]. Regarding the AE of discontinuation rate, it was reported in one study where no patients discontinued treatment [12].

Internal and external validity

keine Evaluierung der Gesamtstärke der Evidenz möglich

Overall, the strength of evidence for clinical effectiveness was not assessed due to the lack of controlled studies. Regarding safety of 177Lu-PSMA, the quality of evidence was low (for outcomes of SAEs and discontinuation rate) to very low (for the outcome of grade 3-4 toxicities).

Unterschiede in der Vorbehandlung von Patienten in den 5 Beobachtungsstudien

Challenges with interpreting the data arise when we take into consideration the extent to which the patient population was pre-treated before the administration of 177Lu-PSMA, where previous interventions include hormone therapy, LHRH agents, external beam radiation, surgical therapy, chemotherapy, antiandrogens, and bone interventions. Hence, in the light of the lack of controlled data, assigning the effects observed to 177Lu-PSMA is questionable.

Berichterstattung der AE unklar, da alle AE nur in 1 Studie (der besten) berichtet wurden

Also, interpreting the data is especially problematic in the light of only one study reporting on the baseline toxicity data [11] and only two studies reporting on the co-interventions that patients continued on during the course of 177Lu-PSMA, which ranged from blood transfusions to bone interventions, palliative radiotherapy, anti-androgens, and LHRH agents [10, 12]. Furthermore, it remains unclear why all reported instances of AEs – except for haemoglobin toxicity [11] – occurred in only one study that acknowledged the co-interventions used, had the best standard of reporting, longest follow-up, and the lowest RoB [12].

generalisierbare Daten für den österreichischen Kontext, jedoch keine Ergebnisse aus dem ambulanten Bereich

In terms of external validity, the data is considered generalizable to the Austrian context as the countries of recruitment were Germany, Australia, Austria, and India. At the same time, however, as the Austrian context allows for the administration of 177Lu-PSMA also in the outpatient setting, none of the studies included reported data from this context and hence in this respect, no conclusions can be made.

Effectiveness data from observational studies

With respect to crucial outcomes, the data from the five observational studies with 141 patients suggest the following. Median OS was not reached in one study at 15.5 months follow-up [13], in another study, it was 13.5 months (95% CI: 10.4-22.7) [12], in another 16 months [11], and reported as a mean, it was 12.5 months (SD ± 33 weeks) in the last study [10].

nur zwei der eingeschlossenen Studien weisen Daten zu QoL auf

QoL was reported using the EORTC-QLQ-C30 score in one study, where the mean difference in score after three months post last 177Lu-PSMA cycle compared to baseline was 0 points [12]. QoL was also reported in another study using KPS and ECOG scores that were reported as mean score three months after the last 177Lu-PSMA cycle compared to baseline. KPS scores were 50.32 (SD±11.6) compared to 65.42 (SD±13.6) with the p-value of 0.0001 and ECOG scores were 2.54 (SD±0.85) compared to 1.78 (SD±0.92) with p-value of 0.0001 [11]. HRQoL was not reported in any of the studies. The fact that only two studies reported on QoL and no studies on HRQoL is particularly problematic with respect to mCRPC because QoL is of particular importance for end stage PC patients where palliation is a therapeutic aim. Patients with mCRPC report significantly worse QoL than other PC patients, owing to pain, fatigue, and decreased physical activity [46].

QoL Daten sind notwendig vor allem da es sich um ein palliatives Setting handelt

2 Studien untersuchten Schmerz Scores mittels VAS Scale

Pain scores reported on the VAS scale (11 point scale that goes from 0 no pain to 10 maximum pain) were addressed in two studies [11, 13]. In one study, VAS was reported on six patients only, where 33.3% of patients improved, 66.6% remained the same, and no patients deteriorated [13]. Another study reported the VAS score as mean score between baseline and three months after the last 177Lu-PSMA cycle follow-up scoring 7.5 (SD±1) compared to 3 (SD±0.9) with p-value of 0.0001 [11]. Concerning the minimum clinically important difference (MCID) on the VAS, a systematic review concludes that the threshold lies between 0.8 and 4 points (cm of improvement measured on the VAS scale) and hence the difference of 4.5 points from above lies near the upper limit of the threshold [47]. Concerning the BPI-SF pain score, it improved in pain severity at three months post last treatment cycle compared to baseline by 1.1 points (95% CI: 1.9 to 0.4) and in pain interference by 1.0 points (95% CI: 1.9 to 0.1) [11]. The improvements reached however, do not seem to reach the MCID as in patients with bone metastases, MCID in BPI-SF ranges depending on the response to treatment. An improvement of 1.9 to 4.0 units could indicate minimal clinical significance in patients with complete or partial response, whereas the minimal change ranged from 1.7 to 3.8 units for patients with indeterminate response [48].

Veränderungen der klinischen Relevanz inkonsistent

medianes progressionsfreies Überleben wurde in 2 Studien berichtet: 13,4 Monate und 12 Monate

With respect to surrogate outcomes, median PFS was reported in two studies where it was 13.4 months [13] and 12 months [11]. RECIST score was reported in four studies in the form of respond/stabilize/progress [10, 12-14]. The category of respond ranged from 20-60% of patients, stabilize from 0-52%, and progress from 27-30%. One study used the PERCIST tool instead and reported it on six patients where 33% had complete remission, 50% had partial remission, and 16.6% had stable disease [11]. PSA PFS was reported only in one study and it was median 7.6 months (95% CI: 6.3-9) [12].

Limitation of evidence

The evidence found only partially answered our research questions. The prospective observational evidence found can only contribute to the safety assessment, yet still with a low to very low quality of evidence. RCTs or CTs comparing 177Lu-PSMA to alternative treatment options are thus necessary. However, choosing the right comparator presents a challenge. On the one hand, 177Lu-PSMA, as an experimental therapy, is to be used after the exhaustion of all therapeutic options (as it was the case in the studies included in the analysis), yet on the other hand, German AWMF S3 guideline includes 177Lu-PSMA in the category of second line therapies [22]. Currently, there are two ongoing RCTs where one is comparing 177Lu-PSMA to the second line chemotherapy of cabazitaxel (NCT03392428) and the other to best supporting care (NCT03511664). Both studies have its primary completion date in 2020 (see Table A-4). Furthermore, there are six more ongoing prospective studies on 177Lu-PSMA and a number of studies examining the use of 177Lu-PSMA when combined with immunotherapy such as J591 antibody or pembrolizumab.

RCTs sind notwendig, um 177Lu-PSMA mit anderen Therapiemöglichkeiten zu vergleichen und Aussagen zur Wirksamkeit treffen zu können

9 Recommendation

In Table 9-1 the scheme for recommendations is displayed and the according choice is highlighted.

Empfehlungsschema

Table 9-1: Evidence based recommendations

	The **inclusion** in the catalogue of benefits is **recommended**.
	The **inclusion** in the catalogue of benefits is **recommended with restrictions**.
X	The inclusion in the catalogue of benefits is ***currently*** **not recommended.**
	The **inclusion in** the catalogue of benefits is **not recommended.**

Reasoning:

The current evidence is not sufficient to prove that the assessed technology 177Lu-PSMA is more effective and equally safe or equally effective, but safer than the comparators of best supportive care or the second line therapies: hormonal therapy, chemotherapy, immunotherapy, radiopharmaceuticals, or steroids. New study results will potentially influence the effect estimate considerably.

Evidenz unzureichend → 177Lu-PSMA derzeit nicht empfohlen

The re-evaluation is recommended in 2021 after the completion of two ongoing RCTs (NCT03392428, NCT03511664).

Re-Evaluierung nach 2021 empfohlen, wenn die derzeit laufende RCTs abgeschlossen sind

10 References

[1] Collaboration GBoDC. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease StudyGlobal Burden of Cancer, 1990 to 2016Global Burden of Cancer, 1990 to 2016. JAMA Oncology. 2018;4(11):1553-68.

[2] Dawson NA, Ryan CJ. Castration-resistant prostate cancer: Treatments targeting the androgen pathway. In: Vogelzang N, Richie JP, Lee R, Savarese DMF, editors. UpToDate: UpToDate; 2019.

[3] Dawson NA. Overview of the treatment of castration-resistant prostate cancer (CRPC). In: Vogelzang N, Lee R, Richie JP, Savarese DMF, editors. UpToDate. Waltham MA: UpToDate; 2018.

[4] Moghadam MJF, Taheri S, Peiravian F. A Systematic Review of Clinical Practice Guidelines for Castration-Resistant Prostate Cancer. Iran J Pharm Res. 2018;17:17-37.

[5] Sartor AO. Risk factors for prostate cancer. In: Vogelzang N, Lee R, Richie JP, Savarese DMF, editors.: UpToDate; 2019.

[6] Chakravarty R, Siamof CM, Dash A, Cai W. Targeted alpha-therapy of prostate cancer using radiolabeled PSMA inhibitors: a game changer in nuclear medicine. Am J Nucl Med Mol Imaging. 2018;8(4):247-67.

[7] Estebanez J, Teyrouz A, Gutierrez MA, Linazasoro I, Belloso J, Cano C, et al. Natural history of prostate cancer. Arch Esp Urol. 2014;67(5):383-7.

[8] Wright GLJ, Haley C, Beckett ML, Schellhammer PF. Expression of prostate-specific membrane antigen in normal, benign, and malignant prostate tissues. Urol. 1995;1(1):18-28.

[9] Emmett L, Willowson K, Violet J, Shin J, Blanksby A, Lee J. Lutetium (177) PSMA radionuclide therapy for men with prostate cancer: a review of the current literature and discussion of practical aspects of therapy. J Med Radiat Sci. 2017;64(1):52-60. Epub 2017/03/18.

[10] Emmett L, Crumbaker M, Ho B, Willowson K, Eu P, Ratnayake L, et al. Results of a Prospective Phase 2 Pilot Trial of (177)Lu-PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. Clin Genitourin Cancer [Internet]. 2018 Sep 27 [cited 27.12.2018]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30425003.

[11] Yadav MP, Ballal S, Tripathi M, Damle NA, Sahoo RK, Seth A, et al. (177)Lu-DKFZ-PSMA-617 therapy in metastatic castration resistant prostate cancer: safety, efficacy, and quality of life assessment. Eur J Nucl Med Mol Imaging. 2017;44(1):81-91. Epub 2016/08/11.

[12] Hofman MS, Violet J, Hicks RJ, Ferdinandus J, Thang SP, Akhurst T, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. Lancet Oncol. 2018;19(6):825-33. Epub 2018/05/13.

[13] Baum RP, Kulkarni HR, Schuchardt C, Singh A, Wirtz M, Wiessalla S, et al. 177Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. J Nucl Med. 2016;57(7):1006-13.

[14] Scarpa L, Buxbaum S, Kendler D, Fink K, Bektic J, Gruber L, et al. The (68)Ga/(177)Lu theragnostic concept in PSMA targeting of castration-resistant prostate cancer: correlation of SUVmax values and absorbed dose estimates. Eur J Nucl Med Mol Imaging. 2017;44(5):788-800. Epub 2017/01/14.

[15] Awang ZH, Essler M, Ahmadzadehfar H. Radioligand therapy of metastatic castration-resistant prostate cancer: current approaches. Radiat. 2018;13(1):98.

[16] Delker A, Fendler WP, Kratochwil C, Brunegraf A, Gosewisch A, Gildehaus FJ, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2016;43(1):42-51.

[17] Hohberg M, Eschner W, Schmidt M, Dietlein M, Kobe C, Fischer T, et al. Lacrimal Glands May Represent Organs at Risk for Radionuclide Therapy of Prostate Cancer with [(177)Lu]DKFZ-PSMA-617. Mol Imaging Biol. 2016;18(3):437-45.

[18] Kabasakal L, Toklu T, Yeyin N, Demirci E, Abuqbeitah M, Ocak M, et al. Lu-177-PSMA-617 Prostate-Specific Membrane Antigen Inhibitor Therapy in Patients with Castration-Resistant Prostate Cancer: Stability, Bio-distribution and Dosimetry. Mol Imaging Radionucl Ther. 2017;26(2):62-8. Kastrasyona Direncli Prostat Kanseri Hastalarinda Lu-177-PSMA-617 ile Prostat Spesifik Membran Antijen Inhibitor Tedavisi: Kararlilik, Biyodagilim ve Dozimetri.

[19] Pfestroff A, Luster M, Jilg CA, Olbert PJ, Ohlmann CH, Lassmann M, et al. Current status and future perspectives of PSMA-targeted therapy in Europe: opportunity knocks. Eur J Nucl Med Mol Imaging. 2015;42(13):1971-5.

[20] Fendler WP, Rahbar K, Herrmann K, Kratochwil C, Eiber M. (177)Lu-PSMA Radioligand Therapy for Prostate Cancer. J Nucl Med. 2017;58(8):1196-200. Epub 2017/07/01.

[21] Institut für das Entgeltsystem im Krankenhaus (InEK). Aufstellung von NUB-Leistungen mit Status 1 in 2018. 2018 [cited 06.02.2019]; Available from: https://www.g-drg.de/G-DRG-System_2019/Neue_Untersuchungs-_und_Behandlungsmethoden_NUB/Aufstellung_von_NUB-Leistungen_mit_Status_1_in_2018.

[22] Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft DK, AWMF):. Interdisziplinäre Leitlinie der Qualität S3 zur Früherkennung, Diagnose und Therapie der verschiedenen Stadien des Prostatakarzinoms, Langversion 5.0. 2018 Contract No.: AWMF Registernummer: 043/022OL.

[23] Guyatt G, Oxman A, Akl E, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64:383-94.

[24] Rahbar K, Afshar-Oromieh A, Jadvar H, Ahmadzadehfar H. PSMA Theranostics: Current Status and Future Directions. Mol Imaging. 2018;17:1536012118776068. Epub 2018/06/07.

[25] Rajaskeran AK, Anilkumar G, Christiansen JJ. Is prostate specific membrane antigen a multifunctional protein? American journal of cell physiology 2005;288:C975-81.

[26] Liu H, Rajasekaran AK, Moy P, Xia Y, Kim S, Navarro V, et al. Constitutive and antibody-induced internalization of prostate-specific membrane antigen. Cancer Res. 1998;58(18):4055-60.

[27] American Society of Clinical Oncology A. Treatment of Metastatic Castration-Resistant Prostate Cancer. 2014 [cited 07.02.2019]; Available from: https://www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer.

[28] Prostate Conditions Education Council P. Gleason Score: Prostate Cancer Grading & Prognostic Scoring,. 2019 [cited 07.02.2019]; Available from: https://www.prostateconditions.org/about-prostate-conditions/prostate-cancer/newly-diagnosed/gleason-score.

[29] Siegel RL, Miller KD, Jemal A, . Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.

[30] O'Sullivan J. Controversies in PSA screening. BMJ EMB Spotlight; 2017 [updated 19.10.2017; cited 08.02.2019]; Available from: https://blogs.bmj.com/bmjebmspotlight/2017/10/19/controversies-in-psa-screening/.

[31] Saad F, Hotte SJ. Guidelines for the management of castrate-resistant prostate cancer. Can Urol Assoc J 2010;4(6):380-4.

[32] Pishgarab F, Ebrahimia H, Moghaddamac SS, Fitzmauricede C, Aminib E. Global, Regional and National Burden of Prostate Cancer, 1990 to 2015: Results from the Global Burden of Disease Study 2015. The Journal of Urology. 2018;199(5):1224-32.

[33] Statistik Austria. Prostata. 2016 [cited 08.02.2019]; Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/prostata/index.html.

[34] Mottet N, van den Bergh RCN, Briers E, Bourke L, Cornford P, De Santis M, et al. EAU – ESTRO – ESUR – SIOG Guidelines on Prostate Cancer 2018. European Association of Urology Guidelines 2018 Edition. Arnhem, The Netherlands: European Association of Urology Guidelines Office; 2018.

[35] Kantoff PW, Taplin ME, Smith JA. Clinical presentation and diagnosis of prostate cancer. In: Vogelzang N, Lee R, Richie JP, Melin JA, editors. UpToDate2018.

[36] Sartor AO, DiBiase SJ. Bone metastases in advanced prostate cancer: Clinical manifestations and diagnosis. In: Vogelzang N, Lee R, Richie JP, Savarese DMF, editors. UpToDate2018.

[37] Ahmadzadehfar H, Albers P, Bockisch A, Boegemann M, Bohme C, Burchert W, et al. [Lutetium-177-PSMA radioligand therapy : Consensus within the framework of GKV-funded care between the university hospitals in Aachen, Bonn, Dusseldorf, Essen, and Cologne and the MDK Nordrhein]. Urologe A. 2018;57(6):709-13. Lutetium-177-PSMA-Radioligandentherapie : Konsensus im Rahmen der GKV-finanzierten Versorgung zwischen den Hochschulkliniken in Aachen, Bonn, Dusseldorf, Essen und Köln und dem MDK Nordrhein.

[38] Fendler WP, Kratochwil C, Ahmadzadehfar H, Rahbar K, Baum RP, Schmidt M, et al. [177Lu-PSMA-617 therapy, dosimetry and follow-up in patients with metastatic castration-resistant prostate cancer]. Nucl Med (Stuttg). 2016;55(3):123-8. Therapie mit 177Lu-PSMA-617, Dosimetrie und Nachsorge beim metastasierten kastrationsresistenten Prostatakarzinom.

[39] Heck MM, Tauber R, Schwaiger S, Retz M, D'Alessandria C, Maurer T, et al. Treatment Outcome, Toxicity, and Predictive Factors for Radioligand Therapy with (177)Lu-PSMA-I&T in Metastatic Castration-resistant Prostate Cancer. Eur Urol [Internet]. 2018 Nov 22 [cited 27.12.2018]; Available from: http://www.ncbi.nlm.nih.gov/pubmed/30473431.

[40] Kabasakal L, AbuQbeitah M, Aygun A, Yeyin N, Ocak M, Demirci E, et al. Pre-therapeutic dosimetry of normal organs and tissues of (177)Lu-PSMA-617 prostate-specific membrane antigen (PSMA) inhibitor in patients with castration-resistant prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(13):1976-83.

[41] Hunink MGM, Gazelle GS. CT screening: a trade-off of risks, benefits, and costs. The Journal of clinical investigation. 2003;111(11):1612-9.

[42] Institute of Health Economics (IHE). Quality Appraisal of Case Series Studies Checklist.: Edmonton (AB): Institute of Health Economics; 2014 [cited 01.10.2018]; Available from: http://www.ihe.ca/research-programs/rmd/cssqac/cssqac-about.

[43] Calopedos RJS, Chalasani V, Asher R, Emmett L, Woo HH. Lutetium-177-labelled anti-prostate-specific membrane antigen antibody and ligands for the treatment of metastatic castrate-resistant prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2017;20(3):352-60. Epub 2017/04/26.

[44] Kim YJ, Kim YI. Therapeutic Responses and Survival Effects of 177Lu-PSMA-617 Radioligand Therapy in Metastatic Castrate-Resistant Prostate Cancer: A Meta-analysis. Clin Nucl Med. 2018;43(10):728-34.

[45] von Eyben FE, Roviello G, Kiljunen T, Uprimny C, Virgolini I, Kairemo K, et al. Third-line treatment and (177)Lu-PSMA radioligand therapy of metastatic castration-resistant prostate cancer: a systematic review. Eur J Nucl Med Mol Imaging. 2018;45(3):496-508. Epub 2017/12/17.

[46] Fallowfield L, Payne H, Jenkins V. Patient-reported outcomes in metastatic castration-resistant prostate cancer. Nature Reviews Clinical Oncology. 2016;13(10):643-50.

[47] Olsen MF, Bjerre E, Damkjaer Hanse M, Hilden J, Landler NE, Tendal B, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain BMC Med. 2017;15(35).

[48] Wong K, Zeng L, Zhang L, Bedard G, Wong E, Tsao M, et al. Minimal clinically important differences in the brief pain inventory in patients with bone metastases. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2013;21(7):1893-9. Epub 2013/02/16.

Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: 177Lu-PSMA: Results from observational studies

Author, year	Baum et al. [13] (2016)	Hofman et al. [12] (2018)	Scarpa et al. [14] (2017)	Yadav et al. [11] (2016)	Emmet et al. [10] (2018)
Country	Germany	Australia	Austria	India	Australia
Sponsor	unclear[1]	Peter MacCallum Foundation, Prostate Cancer Foundation[2]	University of Innsbruck and Medical University of Innsbruck[3]	none	Paul Ramsey Foundation
Study design	Prospective single centre before-after study	Prospective single centre before-after study	Prospective single centre before-after study	Prospective single centre before-after study	Prospective before-after study
Conducted in	05/2013 – 06/2015	08/2015-12/2016	NA	2014-2016	NA
Indication	mCRPC	mCRPC	mCRPC	mCRPC	mCRPC
Intervention	Intravenous 177Lu-PSMA-I&T	Intravenous 177Lu-PSMA-DKFZ-617	Intravenous 177Lu-PSMA-617	Intravenous 177Lu-PSMA- DKFZ-617	Intravenous 177Lu-PSMA-DKFZ-617
☘ Strength of radiation, GBq (range)	median 5.76 (3.6-8.7)	mean 7.5 (4.4-8.7)[4]	mean 6.1 (5.4-6.5)	mean 5.07 (SD±1.85)	mean 7 (6-8)[5]
☘ Total number of cycles	125[6]	96	29	66	42
☘ Average number of cycles per patient, n	2.2	3.2	2.9	2.1	3
Comparator	none	none	none	none	none
Number of pts	56[7]	30[8]	10	31[9]	14[10]

[1] Member of the authoring team is a shareholder at Scintomics, Germany.

[2] Study supported by the Peter MacCallum Foundation and Prostate Cancer Foundation. Two members of the authoring team have conflicts of interest. One has received fees from the 177Lu PSMA manufacturer Endocyte®.

[3] Funding the open access of the manuscript.

[4] Adjusted according to tumor burden, patient weight, and renal function.

[5] Adjusted according to a combination of eGFR, pt weight, and the number of sites of metastatic disease.

[6] Discrepancy in the total number of cycles as the indicated total is 125, yet the sum of all the listed cycles is 131 (see: 1 cycle in 16 pts, 2 cycles in 15 pts, 3 cycles in 17 pts, 4 cycles in 6 pts, 5 cycles in 2 pts).

[7] At the time of analysis, data on 25 pts.

[8] 43 pts screened, 30 eligible for treatment.

[9] 36 pts screened, 31 eligible for treatment.

[10] 18 pts screened, 14 eligible for treatment.

Author, year	Baum et al. [13] (2016)	Hofman et al. [12] (2018)	Scarpa et al. [14] (2017)	Yadav et al. [11] (2016)	Emmet et al. [10] (2018)
Imaging procedure used	68Ga-PSMA PET/CT	68Ga-PSMA-11 PET CT, 18F-FDG PET/CT, 51Cr-EDTA GFR, radionuclide bone scan, CT of the chest/abdomen/pelvis	68Ga-PSMA-HBED-CC, 17F-NaF PET/CT	68Ga-PSMA-HBED-CCPET/CT	68Ga-HBEDD-PSMA-11 PET CT, 18F-FDG PET/CT, bone scan, CT of the chest/abdomen/pelvis
Inclusion criteria	PSMA expression, exhaustion of all therapeutic options	PSMA expression, exhaustion of most therapeutic options, life expectancy <12 weeks, ECOG ≤2, pathologically confirmed mCRPC, PSMA PET/CT demonstrating uptake intensity significantly greater than liver at sites of disease, PC progression within last 12 months as defined by RECIST or new metastases on a bone scan or new pain in an area of radiographically evident disease[11]	PSMA expression, exhaustion of all therapeutic options	PSMA expression, exhaustion of all therapeutic options	PSMA expression, exhaustion of all therapeutic options, confirmed disease progression (new sites on CT and bone scan or rising PSA on 3 occasions), life expectancy >12 weeks, ECOG score ≤ 2, platelet count ≥ 75,000 x 109/L, haemoglobin ≥ 9.0 g/dL, albumin ≥ 25, neutrophil count ≥ 1.5 x109 and an eGFR ≥ 40 ml/min.
Exclusion criteria	NA	Clinically significant impaired bone marrow, kidney (estimated GFR < 40 ml/min, hydronephrosis), liver function (albumin <= 25), poor blood counts (platelet count < 75,000 x10^9/L, neutrophil count < 1.5 x 10^9/L, or Hb < 9.0 g/dL), the use of concomitant nephrotoxic drugs, radiotherapy within 6 wks, uncontrolled intercurrent illness[11]	NA	Pts with Hb < 10 gp, platelet count < 60,000/mm^3, TLC<4,000/mm^3, serum creatinine>1.3 mg%, serum bilirubin >1.2 mg%, and GFR <60 mL/min/1.73 m^2 BSA, KPS<30	Inadequate marrow function
Co-interventions[12]	NA	Blood transfusions, bisphosphonates, palliative radiotherapy, 2nd generation anti-androgens	NA	kidney protection cocktail of lysine and arginine diluted in 2 L of normal saline	14 (100%) pts on LHRH agent and 6 (43%) pts on denosumab/bisphosphonate treatments
Age, yrs (range)	median 72 (50-88)	median 71 (IQR 67-75)	median 67 (56-82)	mean 65.9 (38-81)	median 69.5 (56-81)
Gleason score, n	median 8	median 8 (IQR 7-9)	≥8[13]	unclear[14]	median 9 (range 8-9)
ECOG performance status (0/1/2), n (%)	NA	11(37)/14(47)/5(17)	NA	mean 2.54[15]	5(35.7)/9(64.3)/0

[11] Added from the registry website: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=368970.

[12] Imaging was not understood as a co-intervention due to the low dose of radioisotopes administered.

[13] Not specified in statistical terms.

[14] Gleason score values cannot be understood from the table. It is assumed that 7 pts had a score of 6-7 and 24 pts a score pf 8-10.

[15] Reported as a mean and not in the ECOG categories of 0/1/2.

Author, year	Baum et al. [13] (2016)	Hofman et al. [12] (2018)	Scarpa et al. [14] (2017)	Yadav et al. [11] (2016)	Emmet et al. [10] (2018)
Tumor stage (pT1/pT2/pT3/pT4), n (%)	1(1.8)/13(23.2)/35(62.5)/ 7(12.5)	unclear[16]	NA	NA	unclear[17]
Previous interventions, n (%)					
❁ Hormone therapy	56 (100)	NA	NA	12 (38.7)[19]	NA
❁ Luteinizing hormone-releasing hormone analogs	56 (100)	NA	10 (100)[18]	NA	14 (100)
❁ Surgical therapy					
❁ Prostatectomy	40 (71.4)	NA	7 (70)	7 (22.6)[20]	NA
❁ Orchiectomy (bilateral)	NA	NA	NA	25 (80.6)	NA
❁ External beam radiation	47 (83.9)	NA	4 (40)	1 (3.2)	8 (57)
❁ Chemotherapy	25 (44.6)	26 (87)[21]	3 (30)[22]	30 (96.7)[23]	10 (71)[24]
❁ Antiandrogens					
❁ Cyproterone	17 (30.4)	NA	0	NA	NA
❁ Bicalutamide	26 (46.4)	NA	3 (30)	NA	10 (71)
❁ Abiraterone	21 (37.5)	25 (83)[25]	2 (20)	NA	14 (100)[26]
❁ Enzalutamide	11 (19.6)	see above	4 (40)	NA	14 (100)
❁ Detasteride	NA	NA	NA	NA	NA
❁ Bone interventions					
❁ 223Ra-chloride	1 (1.8)	NA	3 (30)	NA	NA
❁ Bisphosphonate or denosumab	NA	22 (73)	5 (50)	NA	7 (50)
❁ Toxicity at baseline, n (%)	NA	NA	NA	10 (32.3)[27]	NA

16 ≤20 metastases in 2 pts (7%), and >20 metastases in 28 pts (93%).

17 Extent at diagnosis: localized in 8 (57%) pts and de novo metastatic in 6 (43%) pts.

18 Hormone therapy used: degarelix in 3 (30%) pts, leuprorelin in 6 (60%) pts, goserelin in 1 (10%) pts, tamoxifene in 1 (10%) pts, and pamorelin in 2 (20%) pts.

19 9 pts on hormonal therapy and chemotherapy and 3 pts on hormonal therapy, chemotherapy and 177Lu-EDTMP.

20 5 pts with prostatectomy and 2 pts with prostatectomy and nodal dissection.

21 Docetaxel in 24 (80%) and cebazitaxel in 14 (47%) pts. Also, 12 pts (40%) on 1 chemotherapy regimen, 12 (40%) on 2 chemotherapy regimens, 2 pts (7%) on ≥3 chemotherapy regimens.

22 Docetaxel in 1 (10%) and taxotere in 2 (20%) pts.

23 10 pts with chemotherapy alone, 8 pts with chemotherapy combined with radiotherapy, 9 pts with chemotherapy combined with hormonal therapy, and 3 pts with chemotherapy combined with hormonal therapy and 177Lu-EDTMP

24 Docetaxel in 9 (64%) pts and cebazitaxel in 6 (43%) pts.

25 Reported as abiraterone or enzalutamide or both.

26 Only the use of abiraterone or enzalutamide are reported. Also, 7 pts (50%) received both interventions.

27 Grade 1 hemoglobin toxicity.

Author, year	Baum et al. [13] (2016)	Hofman et al. [12] (2018)	Scarpa et al. [14] (2017)	Yadav et al. [11] (2016)	Emmet et al. [10] (2018)
Follow-up time, mo	median 15 (range 6-28)	median 25 (IQR 12.7-25.2)	unclear[28]	mean 13 (range 12-35)	unclear
Loss to follow-up, n (%)	unclear[29]	unclear	NA	NA	5 (35.7)[30]
Efficacy					
OS, in mo	not reached at 15.5 follow-up	median 13.5 (95% CI: 10.4-22.7)	NA	median 16	mean 12.5 (± 33 weeks)[31]
QoL • EORTC-QLQ-C30, mean difference in score 3 mo after last cycle vs baseline	NA	mean 0 (95% CI: −9 to 8)	NA	NA	NA
• KPS, mean n ±SD, mean score, 3 mo after last cycle vs baseline	NA	NA	NA	50.32±11.6 vs 65.42±13.6 (p=0.0001)	NA
• ECOG, mean n ±SD, mean score, 3 mo after last cycle vs baseline	NA	NA	NA	2.54±0.85 vs 1.78±0.92 (p=0.0001)	NA
HRQoL	NA	NA	NA	NA	NA
Pain score • VAS, %(improved/remained/worsened)	33.3/66.6/0[32]	NA	NA	7.5±1 vs 3±0.9[33] (p<0.0001) (mean score baseline vs 3 mo after last cycle±SD)	NA
• BPI-SF (improvement 3 mo vs baseline)					
◦ Pain severity	NA	1.1 (95% CI: 1.9 to 0.4)	NA	NA	NA
◦ Pain interference	NA	1.0 (95% CI: 1.9 to 0.1)	NA	NA	NA
PFS, median mo	13.7[34]	NA	NA	12	NA

[28] It is reported that follow-up was until death, while the time point at which death occurred is not reported.

[29] Analysis done of 25/56 pts at 15 mo follow-up, yet 12 pts died before 28 mo follow-up.

[30] 5/14 pts did not complete follow-up due to poor clinical condition and travel distance to facility.

[31] 56 ± 38 in responders vs. 36 ± 8 non-responders

[32] Reported on 6/56 pts.

[33] VASmax scale used, yet the description of VAS and VASmax read identical.

[34] Unclear if PFS was measured radiographically as figure 7 refers to radiographic PFS, while the text only mentions PFS.

Author, year	Baum et al. [13] (2016)	Hofman et al. [12] (2018)	Scarpa et al. [14] (2017)	Yadav et al. [11] (2016)	Emmet et al. [10] (2018)
RECIST[35], n (%) (respond/stabilize/progress)	5(20)/13(52)/7(28)	12(40)/0/8(27)[36]	6(60)/1(10)/3(30)[37]	NA[38]	7(50)/NA/NA
PSMA PFS, median (95% CI) in mo	NA	7.6 (6.3-9)	NA	NA	NA
Safety					
SAEs, n (%)					
❁ Study related death	0	0[39]	NA	NA[40]	NA
AEs, n (%)					
❁ Grade 3 and 4 toxicities					
❁ Nephrotoxicity	0	0	0	0	NA
❁ Hematotoxicity					
❁ Lymphocytopenia	0	11 (37)	0	NA	NA
❁ Thrombocytopenia	0	4 (13)[41]	0	NA	0
❁ Anaemia	0	4 (13)	0	NA	0
❁ Neutropenia	0	2 (7)	0	NA	NA
❁ Haemoglobin	NA	NA	NA	1 (3.2)	NA
❁ Hepatotoxicity	NA	NA	0	0	NA
❁ Bone pain flare	NA	1 (3)	NA	NA	NA
❁ Discontinuation rate	NA	0	NA	NA	NA

Abbreviations: *AE – adverse event, BFI – Brief Pain Inventory, BSA – body surface area, CI – confidence interval, CT – computed tomography, ECOG – Eastern Cooperative Oncology Group, EDTA – ethylenediaminetetraacetic acid, EDTMP – ethylenediaminetetramethylene phosphonic acid, eGFR – (estimated) Glomerular Filtration Rate, EORTC-QLQ-C30 – European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, dL – decilitre, FDG – fluorodeoxyglucose, HBED CC – N,N'-bis (2-droxybenzyl) ethylenediamine-N,N'-diacetic acid, L – litre, LHRH – Luteinizing hormone-releasing hormone, IQR – interquartile range, KPS – Karnofsky Performance Status, mCRPC – metastatic castration resistant prostate cancer, mg – milligram, min – minute, mL – millilitre, mm – millimetre, mo – month, n – number, NA – not available, NaF – sodium fluoride, OS – overall survival, PET – positron emission tomography, PFS – progression free survival, PSMA – prostate specific membrane antigen, PSA PFS – prostate-specific antigen progression free survival, pts – patients, RECIST – Response Evaluation Criteria in Solid Tumours, QoL – quality of life, VAS (max) – Visual Analogue Scale, SAE – serious adverse event, SD – standard deviation, 68GA – Gallium, 17F –Fluorine, 51Cr – Chromium, 223Ra – Radium, 177Lu – lutetium*

[35] PET/CT measured.

[36] Assessed at 3 mo and not performed in 10 pts (33%) (due to clinical progression or death).

[37] Mixed response (disappearance and/or decrease of uptake of some lesions next to appearance of new lesions) in 3 pts.

[38] Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) tool used instead of RECIST in 6 pts: 2 pts with complete remission, 3 pts with partial remission, and 1 pt with stable disease.

[39] No death was judged to be study related, yet 22 (73%) of pts were deceased at the time of data cut-off.

[40] 5 pts (16.1%) died from due to disease.

[41] In 8 pts in total, but 4 in pts with unequivocal marrow progression.

Risk of bias table

Table A-2: Risk of bias – study level (case series), see [4]

Study reference/ID	Baum et al., 2016, [13]	Hofman et al., 2018, [12]	Scarpa et al., 2017, [14]	Yadav et al., 2017, [11]	Emmet et al. 2018, [10]
Study objective					
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes
Study design					
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	No	No	No	No	Unclear
4. Were patients recruited consecutively?	Unclear	Unclear	Yes	Unclear	Unclear
Study population					
5. Were the characteristics of the participants included in the study described?	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (inclusion and exclusion criteria) for entry into the study clearly stated?	Partial[42]	Yes	Partial[43]	Partial[44]	Yes
7. Did participants enter the study at similar point in the disease?	Unclear[45]	Unclear[45]	Unclear[45]	Unclear[45]	Unclear[45]
Intervention and co-intervention					
8. Was the intervention clearly described?	Yes	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	No	Yes	No	Partial	Yes
Outcome measure					
10. Were relevant outcome measures established a priori?	Yes	Yes	Partial[46]	Yes	Partial[47]
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Partial[48]	Yes	Partial[48]

[42] Only the inclusion criteria were broadly stated in the study.

[43] Inclusion criteria were stated without the necessary detail and exclusion criteria were not state at all.

[44] Lack of detail in inclusion criteria.

[45] Not enough information about participants provided to make a judgment.

[46] Outcome measures with respect to QoL and OS were not stated.

[47] Outcome measures with respect to QoL were not stated.

[48] As some crucial outcomes were not measured at all, they could not be measured in appropriate ways.

Study reference/ID	Baum et al., 2016, [13]	Hofman et al., 2018, [12]	Scarpa et al., 2017, [14]	Yadav et al., 2017, [11]	Emmet et al. 2018, [10]
13. Were the relevant outcomes measured before and after intervention?	Yes	Yes	No[49]	Yes	Yes[50]
Statistical Analysis					
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Partial[51]
Results and Conclusions					
15. Was follow-up long enough for important events and outcomes to occur?	No	Yes	Unclear[52]	Yes	Unclear[52]
16. Was the loss to follow-up reported?	Unclear[53]	No	No	No	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No	Yes	No	Partial[54]	Yes
18. Were adverse events reported?	Yes	Yes	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	No[55]	No[56]	Yes	No[55]	Yes
Competing interest and source of support					
20. Were both competing interest and source of support for the study reported?	Partial[57]	Yes	Partial[57]	Yes	Partial[58]
Overall Risk of bias	**High**	**Low**	**High**	**Medium**	**Medium**

[49] No crucial efficacy outcome was measured in the study and hence not measured before and after the intervention.

[50] QoL was not measured in the study and hence not measured before and after the intervention.

[51] OS reported as a mean instead of the common reporting in median.

[52] The length of follow-up was not clearly reported.

[53] There was a discrepancy between the total number of patients and the patients included in the analysis.

[54] CI for PFS and OS are missing.

[55] The study design cannot meet the conclusions about effectiveness.

[56] The study design cannot meet the conclusions about effectiveness and the conclusions are only made on the basis of a subgroup of patients from the results.

[57] Source of support was not clearly reported.

[58] Conflict of interests was not clearly reported.

Applicability table

Table A-3: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The population enrolled in the studies is similar to the target population of the intervention in that metastatic castration-resistant prostate cancer patients with overexpressed prostate specific membrane antigen (PSMA) are included. In all studies, 177Lutetium (Lu)-PSMA was applied after the exhaustion of all therapeutic options. However, in clinical practice, it is unclear whether 177Lu-PSMA is supposed to be second, third, or fourth line therapy option.
Intervention	Lu-177-labelled PSMA inhibitor therapy administered intravenously is the intervention at stake. PSMA can be also called folate hydrolase I or glutamate carboxypeptidase II. In the studies included in this assessment, the different types of radioligand therapy labelling include three ways of chemical conjugation of a peptide: 177Lu-PSMA-DKFZ-617, 177Lu-PSMA-I&T, and 177Lu-PSMA-617. In clinical practice, own radioligand agents can also be prepared by hospital radiologists.
Comparators	The comparators include best supportive care on the one hand and, as suggested by the German AWMF S3 guidelines, second line therapy options on the other hand: hormonal therapy options with abiraterone or enzalutamide; chemotherapy options of docetaxel + prednisone, cabazitaxel, mitoxantrone, and estramustine; immunotherapy options of sipuleucel-T; radiopharmaceutical option of radium 223; and steroids such as dexamethasone, prednisolone, prednisone.
Outcomes	Clinical effectiveness outcomes considered crucial in this assessment were: overall survival; health related quality of life (HRQoL) reported through Functional Assessment of Cancer Therapy – Prostate cancer score; quality of life (QoL) reported through the scoring charts of the European Organisation for Research and Treatment of Cancer, Eastern Cooperative Oncology Group, Karnofsky Performance Status; and pain scores reported through Brief Pain Inventory Short-Form and the Visual Analogue Scale. Of these, the most frequently reported was overall survival, while no HRQoL score was reported, and QoL was reported in two studies. Concerning surrogate outcomes used for the assessment of clinical effectiveness, progression free survival (PFS), Response Evaluation Criteria in Solid Tumors (RECIST) response, and Prostate Specific Antigen (PSA) PFS were used. Most frequently repoted was RECIST response. Safety outcomes considered were serious adverse event of study related death, adverse events of grade 3-4 toxicities, and discontinuation rates. Grade 3-4 toxicities were most frequently reported.
Setting	All the studies included were conducted in the inpatient setting in the countries of Germany, Australia, Austria, and India. The settting is thus similar to the Austrian one, however, 177Lu-PSMA may be also used in the outpatient setting in Austria, yet no data were reported from this contet.

List of ongoing randomised controlled trials

Table A-4: List of ongoing randomised controlled trials of 177Lu-PSMA

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Primary completion date	Sponsor
NCT03454750	210 mCRPC pts	177Lu PSMA 617	NA	Disease control rate; Incidence of treatment-emergent AEs	April 2020	Istituto Scientifico Romagnolo per lo Studio e la cura dei Tumori
NCT03780075	30 mCRPC pts	177Lu-EB-PSMA617	NA	Change of the PSA; Standardized uptake value of 68Ga-PSMA before and after the treatment	December 2019	Peking Union Medical College Hospital|National Institute for Biomedical Imaging and Bioengineering (NIBIB)
NCT03403595	30 mCRPC pts	177Lu-EB-PSMA617	NA	Standardized uptake value of 177Lu-EB-PSMA617 in normal organs	December 2018	Peking Union Medical College Hospital|National Institute for Biomedical Imaging and Bioengineering (NIBIB)
NCT03392428 ACTRN12617001590358	200 mCRPC pts	177Lu-PSMA617	Cabazitaxel	Prostate Specific Antigen response rate	December 2020	Australian and New Zealand Urogenital and Prostate Cancer Trials Group|Australian Nuclear Science and Technology Organisation (ANSTO)|Endocyte®|Prostate Cancer Foundation of Australia (PCFA)|Australasian
NCT03511664 EUCTR2018-000459-41-DK EUCTR2018-000459-41-FR EUCTR2018-000459-41-SE	750 mCRPC pts	177Lu-PSMA-617	Best supportive care	Overall Survival	August 2020	Endocyte®
NCT03042312	72 mCRPC pts	177Lu-PSMA-617	NA	Decline in tumor marker level (PSA) ≥50% at 12 weeks	February 2019	Endocyte®
IRCT20180113038331N1	20 mCRPC pts	177Lu-PSMA	NA	Change the number of metastases after 3 cycles of therapy	NA	Mashhad University of Medical Sciences
DRKS00013665	40 mCRPC pts	177Lu-PSMA	NA	Evaluation of serologic and imaging response to Lutetium-177-PSMA	NA	Universitätsklinikum Freiburg

Literature search strategies

Search strategy for Cochrane

Search Name: Lutetium for Prostate Cancer (MS/NG)	
Last Saved: 14/12/2018 20:44:07	
Comment: prelim MEL (2019) search 141218	
ID	Search
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	(prostat* NEAR (cancer* or tumor* or tumour* or carcinom* or adenom* or adenoc* or adeno-c* or neoplasm*)):ti,ab,kw (Word variations have been searched)
#3	#1 OR #2 (Word variations have been searched)
#4	MeSH descriptor: [Lutetium] explode all trees
#5	(lutetium) (Word variations have been searched)
#6	(Lu* NEAR (177 OR 617 OR I&T OR PSMA)) (Word variations have been searched)
#7	(PSMA NEAR (Lu* OR 177 OR 617 OR I&T)) (Word variations have been searched)
#8	(J591) (Word variations have been searched)
#9	MeSH descriptor: [Prostate-Specific Antigen] explode all trees and with qualifier(s): [therapeutic use - TU]
#10	(radioligand*) (Word variations have been searched)
#11	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 (Word variations have been searched)
#12	#3 AND #11 (Word variations have been searched)
Total: 42 Hits	

Search strategy for CDR

Search Name: Lutetium for Prostate Cancer (MEL 2019)	
Search Date: 17.12.2018	
ID	Search
#1	MeSH DESCRIPTOR Lutetium EXPLODE ALL TREES
#2	(Lutetium)
#3	(Lu* NEAR (177 OR 617 OR I&T OR PSMA))
#4	#1 OR #2 OR #3
Total:1 Hit	

Search strategy for Medline

Search Name: Lutetium for Prostate Cancer (MEL 2019)	
Search Date: 17.12.2018	
ID	Search
#1	exp Prostatic Neoplasms/ (117325)
#2	(prostat* adj5 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*)).mp. (157312)
#3	1 or 2 (157312)
#4	exp Neoplasm Metastasis/ (190047)
#5	metasta*.mp. (519720)
#6	((castrat* or hormon*) adj resist*).mp. (8959)
#7	androgen* insensitiv*.mp. (3221)
#8	4 or 5 or 6 or 7 (534695)
#9	3 and 8 (36462)
#10	exp Prostatic Neoplasms, Castration-Resistant/ (2662)
#11	((((castrat* or hormon*) adj resist*) or (metasta* or androgen* insensitiv*)) adj5 (prostat* adj5 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*))).mp. (19876)
#12	CRPC.ti,ab. (2459)
#13	CRPRC.ti,ab. (5)
#14	HRPC.ti,ab. (671)
#15	AIPC.ti,ab. (207)
#16	9 or 10 or 11 or 12 or 13 or 14 or 15 (37089)
#17	exp Lutetium/ (788)
#18	lutetium*.mp. (1446)
#19	(Lu* adj5 "177").mp. (1162)
#20	17 or 18 or 19 (2067)
#21	exp Prostate-Specific Antigen/ (23661)
#21	(Prostat* adj5 Anti?gen*).mp. (36945)
#22	PSMA*.mp. (3164)
#23	folate hydrolas*.mp. (80)
#24	exp Glutamate Carboxypeptidase II/ (1151)
#25	glutamat* carboxypeptidas*.mp. (1250)
#26	21 or 22 or 23 or 24 or 25 or 26 (38922)
#27	20 and 27 (110)
#28	(Lu* adj5 ("177" or "617" or I&T or PSMA)).mp. (21646)
#29	(PSMA adj5 (Lu* or "177" or "617" or I&T)).mp. (278)
#30	J?591.mp. (96)
#31	exp *Prostate-Specific Antigen/tu [Therapeutic Use] (11)
#32	radio?ligand*.mp. (28764)
#33	"Therapeutic Use".fs. (2098775)
#34	33 and 34 (948)
#35	radioligand therap*.mp. (100)
#36	28 or 29 or 30 or 31 or 32 or 35 or 36 (22833)
#37	16 and 37 (289)
#38	remove duplicates from 38 (288)
#39	exp Prostatic Neoplasms/ (117325)
Total: 228 hits	

Search strategy for Embase

Search Name: Lutetium for Prostate Cancer (MEL 2019)	
Search Date: 17 Dec 2018	
ID	Search
#1	'metastatic prostate cancer'/mj
#2	'castration resistant prostate cancer'/mj
#3	'hormone resistant prostate cancer'/mj
#4	'androgen independent prostate cancer'/mj
#5	crpc:ti,ab
#6	crprc:ti,ab
#7	hrpc:ti,ab
#8	aipc:ti,ab
#9	'prostate cancer'/exp
#10	(prostat* NEAR/5 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm*)):ti,ab,de
#11	#9 OR #10
#12	'castration resistant':ti,ab,de
#13	'hormone resistant':ti,ab,de
#14	metasta*:ti,ab,de
#15	'androgen* insensitiv*':ti,ab,de
#16	#12 OR #13 OR #14 OR #15
#17	#11 AND #16
#18	(('castration resistant' OR 'hormon* resistant' OR metasta* OR 'androgen insensitiv*') NEAR/5 ('prostat* cancer*' OR 'prostat* tumor*' OR 'prostat* tumour*' OR 'prostat* carcinom*' OR 'prostat* adenom*' OR 'prostat* adenoc*' OR 'prostat* adeno-c*' OR 'prostat* neoplasm*')):ti,ab,de
#19	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #17 OR #18
#20	'lutetium 177'/exp
#21	(lutetium* NEAR/1 177):ti,ab,de
#22	lu177:ti,ab,de
#23	'lu 177':ti,ab,de
#24	177lu:ti,ab,de
#25	'177 lu':ti,ab,de
#26	#20 OR #21 OR #22 OR #23 OR #24 OR #25
#27	'prostate specific antigen'/exp
#28	(prostat* NEAR/2 antigen):ti,ab,de
#29	psma*:ti,ab
#20	'folate hydrolase 1'/exp
#31	'folate hydrolas*':ti,ab,de
#32	'glutamate carboxypeptidase ii'/exp
#33	'glutamate carboxypeptidas*':ti,ab,de
#34	#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33
#35	#26 AND #34
#36	'lutetium prostate specific membrane antigen 617 lu 177'/exp
#37	(lu* NEAR/5 ('177' OR '617' OR i&t OR psma)):ti,ab,de
#38	(psma NEAR/5 (lu* OR '177' OR '617' OR i&t)):ti,ab,de
#39	'monoclonal antibody j591'/exp
#40	j591:ti,ab,de
#41	'prostate specific antigen'/exp/dd_dt

#42	'radioligand'/exp/dd_dt
#43	((radioligand* OR 'radio ligand*') NEAR/5 (therap* OR treat* OR regimen* OR program*)):ti,ab,de
#44	#35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
#45	#19 AND #44
#46	#19 AND #44 AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim)
#47	'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#48	#45 AND #47
#49	'clinicaltrials gov'
#50	#45 AND #49
#51	#46 OR #48 OR #50
Total: 378 hits	

Search strategy for ClinicaTrials.gov

Date: 18/01/2019

(Prostate Cancer OR Prostate Carcinoma OR Prostate Tumor OR Prostate Tumour OR Prostate Neoplasm OR Prostate Adenocarcinoma OR prostate OR prostatic) [DISEASE] AND (lutetium OR Lu177 OR lu 177 OR radioligand OR LuPSMA OR Lu-PSMA) [TREATMENT]

Total: 21 hits

Search strategy for WHO-ICTRP

Date: 18/01/2019

Condition: Condition: Prostate Cancer OR Prostate Carcinoma OR Prostate Tumor OR Prostate Tumour* OR Prostate Neoplasm OR Prostate Adenocarcinoma OR prostate OR prostatic

AND

Intervention: lutetium OR Lu177 OR lu-177 OR radioligand OR LuPSMA OR Lu-PSMA

Total: 23 (14 further) hits

Search strategy for EU Clinical Trials (EUdraCT)

Date: 18/01/2019

prostat* AND (lutetium OR Lu177 OR lu-177 OR radioligand OR LuPSMA OR Lu-PSMA)

Total: 3 (1 further/relevant)hits

Ludwig Boltzmann Institut
Health Technology Assessment