Vascular-Targeted Photodynamic Therapy with Padeliporfin (Tookad® Soluble)

Systematic Review

Ludwig Boltzmann Institut
Health Technology Assessment

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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).

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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.

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.

CONTENT INFORMATION

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Content

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List of abbreviations

AdHopHTA .....Adopting Hospital-Based Health Technology Assessment
AE(S).....Adverse event(s) (NW – Nebenwirkung)
AIFA .....Italian Medicines Agency
AS .....Active surveillance
CE.....Conformité Européene
CI.....Confidence interval
CPR.....Price Committee
CRD .....Centre for Reviews and Dissemination
CT.....Computer tomography
DRE .....Digital rectal examination
EAU.....The European Association of Urology
EMA .....European Medicines Agency
FIC .....Fibre insertion catheter
GRADE.....Grading of Recommendations Assessment, Development and Evaluation
HIFU.....High-intensity focused ultrasound
HR.....Hazard ratio
IHE.....International Health Economics
IIEF.....The International Index of Erectile Function Questionnaire
IPSS.....International Prostate Symptom Score
LDI.....Light density index

LITT.....Laser-induced thermotherapy
MCID.....Minimal clinically important difference
MID.....Minimal important difference
MRI.....Magnetic resonance imaging
NCCN.....National Comprehensive Cancer Network
N-RCT.....Non-randomised controlled trial
NSAIDs.....Non-steroidal anti-inflammatory drugs
OS.....Overall survival
Ö.....Österreich (Austria)
PET.....Positron emission tomography
POP.....Planned and Ongoing Projects
PCRD.....Prostate cancer-related death
PSA.....Prostate-specific antigen
PTV.....Planned treatment volume
QoL.....Quality of life
RCT.....Randomised controlled trial
RNA.....Reactive nitrogen species
RoB.....Risk of bias
RR.....Risk ratio
SPECT.....Single photon emission computed tomography
SRD.....Study-related death
SSN.....Servizio Sanitario Nazionale (Italian National Healthcare System)
TNM.....Tumour, Node, Metastasis
TRUS.....Transrectal ultrasound examination
UICC.....Union for International Cancer Control
UK.....United Kingdom
VTP.....Vascular-targeted photodynamic

Executive summary

Introduction

Health problem

Prostate cancer is one of the most common types of cancer in men, with 1.4 million cases in 2016 globally, next to lung and colorectal cancer [1, 2]. According to Statistik Austria, in 2016, 5,245 men were diagnosed with prostate cancer and 1,225 men died from it [3].

prostate cancer one of the most common cancer types in men

The risk of developing prostate cancer is assumed to increase with higher age, African-American origin, a personal and/or family cancer history, diets high in animal fat or low in vegetables, and with cigarette smoking [4].

risk factors are age, ethnicity, genetic and possibly dietary factors

The natural course of prostate cancer is primarily dependent on the tumour aggressiveness. In general, prostate cancer often grows slowly. Thus, most men die of other causes before the disease becomes clinically advanced [5]. This is especially true for low-risk prostate cancer, which has shown not to lead to metastases or death even without treatment [6]. However, if prostate cancer becomes more aggressive, including metastases and related symptoms, curative treatment is usually impossible [7].

often, especially in low-risk prostate cancer no treatment needed, while for advanced stages curative treatments impossible

Description of technology

Until recently, localised low-risk prostate cancer patients were actively monitored without actual treatment. However, this can lead to an additional psychological burden for the patients. Alternatively, also radical therapies such as radical prostatectomy and radiation therapy, associated with severe adverse events have been applied. Vascular-targeted photodynamic (VTP-)therapy with Tookad® Soluble (padeliporfin), a relatively non-invasive procedure, was developed as a new option between radical therapies and active surveillance (AS) [8]. In comparison to radical therapies, it aims to reduce side effects, while achieving similar oncological efficacy and quality of life results. Furthermore, compared to AS, it may help to reduce anxiety [2, 8].

VTP therapy with padeliporfin potentially as effective but safer than radical therapies and associated with less anxiety than with AS

VTP therapy involves the intravenous administration of a vascular-acting photosensitizer, 4 mg/kg Tookad® Soluble (padeliporfin), over ten minutes. Subsequently, the photosensitizer is activated in the prostate by laser light through transperineal interstitial optical fibres [8-10]. Subsequently, a cascade of pathophysiological events has triggered that lead to focal necrosis within a few days [10, 21, 24].

VTP therapy with 4 mg/kg padeliporfin activated in the prostate by laser light

VTP therapy with Tookad® Soluble in patients with localised low-risk prostate cancer has received marketing authorisation by the European Medicines Agency (EMA) and CE mark.

EMA approval and CE mark for localised low-risk prostate cancer

Methods

This systematic review aimed to investigate the use of VTP therapy with Tookad® Soluble in patients with localised low-risk prostate cancer compared to standard therapies (AS or radical therapies). The question was whether VTP therapy with Tookad® Soluble is more effective and safe or equally effective but safer concerning cancer-specific clinical effectiveness outcomes, quality of life and adverse events. The EUnetHTA Core Model® for Rapid Assessment of Relative Effectiveness was the main source for selecting relevant assessment elements.

aim: is VTP therapy with padeliporfin more effective and safer as radical therapies or AS

assessment based on the EUnetHTA Core Model®

a systematic search in 4 databases: 337 hits, after deduplication

search in clinical trial registries for ongoing trials: 22 potential hits; 1 new citation submitted by the manufacturer

The systematic literature search was conducted on the 17th and 18th of December 2019 in four databases (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA]). The search was not limited to a publication year or a specific study design, but articles published in English or German. Overall, 337 citations were included and together with 12 articles identified via hand-search, the overall number of hits was 337, after deduplication. Besides, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on the 31st of January 2020, which yielded 22 potentially relevant hits. The only manufacturer (Steba Biotech) was contacted and submitted one new citation.

RoB and GRADE assessment

The risk of bias (RoB) of the included studies was systematically assessed using the Cochrane RoB tool version 1.0 for randomised controlled trials (RCTs) and the International Health Economics (IHE) checklist for observational studies [11, 12]. Furthermore, data on each selected outcome category was synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [13].

Results

Available evidence

no study available for VTP therapy vs. radical therapies

No evidence could be identified through the systematic literature search comparing VTP therapy with Tookad® Soluble to radical therapies such as radical prostatectomy or radiation therapy.

1 RCT + 4-year follow-up (VTP therapy vs. AS) included for clinical effectiveness analysis: a total of 413 patients

For evaluating clinical effectiveness outcomes, we exclusively considered RCTs and prospective non-randomised controlled trials (N-RCTs). The only studies that met pre-defined inclusion criteria were one RCT and its four-year follow-up study [14, 15] with a total of 413 patients, assessing the clinical effectiveness of VTP therapy with Tookad® Soluble (n=206) compared to AS (n=207).

in addition to the RCT, 1 single-arm study with 68 patients included for safety analysis

For evaluating safety-related outcomes, we considered RCTs, prospective N-RCTs and prospective observational studies with more than 50 included patients. Therefore, in addition to the RCT [14, 15], one prospective single-arm study [16] with a total of 68 patients was considered for the safety analysis.

sponsored by Steba Biotech, follow-up from 24 to 48 months

All included studies were funded by the manufacturer Steba Biotech. Clinical follow-up periods ranged from median 24 to 48 months across the studies.

Clinical effectiveness

no differences in overall survival, prostate cancer-specific survival and quality of life between study groups after 24 months

Concerning the crucial clinical effectiveness outcomes, the prostate cancer-specific survival rate was 100.0% in the VTP treatment group, as well as in the AS group after 24 and 48 months, while the overall survival rate was 98.0% versus 99.0% in the VTP treatment group and the AS group, respectively [14, 15]. Furthermore, there was no statistically significant difference in quality of life between the two study groups after 24 months [14].

statistically significantly fewer patients with disease progression, longer time to progression, fewer negative biopsies & reduced risk of radical therapy conversions in the VTP group;

Concerning the main surrogate outcomes, 28.0% of the patients in the VTP treatment group versus 58.0% in the AS group had disease progression after 24 months (HR 0.34, 95% CI 0.24-0.46, p<0.0001) [14]. The time to progression was longer in the VTP treatment group compared to the AS group (28.3 versus 14.1 months, p<0.0001). Furthermore, 49.0% of the patients in the VTP treatment group compared to 14.0% in the AS group (RR 3.67, 95% CI 2.53-5.33, p<0.0001) had negative biopsy results at month 24, and the intervention reduced the risk of conversion to radical therapy after 24 months (5.8% versus 29.0%, p>0.0001) [14]. In comparison, after 48 months, the rate of con-

version to radical therapy was higher, but still lower in the VTP treatment group (24.0% versus 53.0%, HR 0.31, 95% CI 0.21-0.46, p<0.001) [15]. No statistically significant difference in metastatic-free survival was reported between the study groups after 24 and 48 months [14, 15].

no difference in metastatic-free survival

Safety

The pivotal RCT [14] showed that the exposure to VTP therapy with Tookad® Soluble resulted in an increased frequency of adverse events compared to AS. One in three patients had a severe adverse event with VTP therapy compared to one in ten patients on AS. The most frequently reported severe adverse events in the VTP treatment group were inguinal hernia, rectal haemorrhage, prostatitis and urinary retention, all of which occurred in 1.0-2.0% of the patients. However, most of the reported adverse events were mild to moderate. The RCT [14] also reported that there was no difference in IPSS (urinary symptoms) and IIEF-15 (erectile function) score changes between the study groups from baseline to 24 months.

increased (severe) adverse events through VTP therapy compared to AS after 24 months, no statistically significant differences between study groups in IPSS and IIEF-15 score changes from baseline to 24 months,

No adverse events were reported in the four-year follow-up study [15] of the pivotal RCT [14].

no adverse events reported after 48 months,

The single-arm study [16] reported only mild to moderate adverse events and no severe adverse events during the 42-month follow-up. The most frequently reported mild adverse events were erectile dysfunction (43.8%), lower urinary tract syndrome (18.8%) and perianal pain (14.1%). The two moderate adverse events that occurred were lower urinary tract syndrome (3.1%) and urethral stenosis (1.6%).

single-arm study: no severe adverse events, but 2 moderate and 1 few mild adverse events reported

Upcoming evidence

At this point, there are two ongoing controlled studies: One study (NCT-04017325) represents the extended five-year follow-up of the pivotal RCT [14] and a further RCT (NCT04225299) investigates the efficacy of VTP therapy with Tookad® Soluble versus AS in localised intermediate-risk prostate cancer for a follow-up of 72-months.

ongoing controlled studies: extended 5-year follow-up study & 1 RCT for intermediate-risk prostate cancer

Moreover, there are three ongoing prospective single-arm studies (NCT-03849365, NCT03315754, unknown) with follow-up periods ranging from one to seven years.

3 additional ongoing single-arm studies

Reimbursement

Currently, VTP therapy with Tookad® Soluble (padeliporfin) is not reimbursed in Austria. However, it is fully reimbursed for localised low-risk prostate cancer in Germany and the reimbursement process in Italy is ongoing.

reimbursed in Germany

Discussion

Overall, the quality of evidence was graded as low and moderate for clinical effectiveness and safety, respectively.

overall quality of evidence low-moderate

When interpreting the data, issues with the treatment choice for low-risk prostate cancer patients need to be considered. A significant proportion of low-risk prostate cancer patients would not need any treatment at all, but rather be actively monitored. However, the patient's age and health perception, as well as hope and anxiety also play a substantial role in the final treatment choice [8, 17-19]. So, on the one hand, VTP therapy with Tookad® Soluble may reduce the psychological burden coming along with AS; however, on the other hand, half of the study population still had cancer (positive biopsy results)

challenges with interpreting the data: treatment choice for low-risk prostate cancer include criteria such as risk, age, health status, but also anxiety and hope,

benefit of VTP therapy over AS of reducing anxiety not always clear

24 months after treatment initiation. Therefore, these patients still need to be monitored similarly to patients on AS, thus limiting the potential benefit of VTP therapy with Tookad® Soluble over AS [18].

possible inaccurate risk stratification in the RCTs as pre-treatment MRI was only applied in the VTP group → overestimation of potential benefits of VTP therapy?

Another issue is presented by the possibly inaccurate stratification into low-risk prostate cancer in the included RCT [14, 15]. Only the patients randomised to VTP therapy with Tookad® Soluble had a pre-treatment multi-parametric prostate magnetic resonance imaging (MRI). However, the relatively high proportion of patients in the AS group with a Gleason grade progression within 24 months suggests that the entire study population may not have been low risk [15, 20]. Therefore, integrating MRI into the AS protocols too would have possibly led to a better sampling of the prostate cancer and an enhanced risk stratification, consequently even lowering the potential benefits of VTP therapy with Tookad® Soluble over AS [17-20].

inconsistent number of patients or loss to follow-up

Moreover, in all included studies [14-16], the number of patients or loss to follow-up were reported inconsistently, which further complicated the interpretation of the data.

generalisability to Austrian context

In terms of external validity, the data is considered generalisable to the Austrian context, as the included studies were conducted across ten European countries.

further evidence needed: effect of VTP on subsequent radical therapies, long-term data, different settings

Overall, the evidence found only partially answered our research questions. Further evidence on the effect of how VTP therapy with Tookad® Soluble would impact the feasibility of future radical treatments is needed. Long-term data with a follow-up of at least ten years is additionally recommended, especially concerning crucial outcomes such as overall-survival, prostate cancer-specific survival, quality of life and severe adverse events, as the considered patient population is expected to live at least ten additional years. Finally, future evidence assessing whether different settings, e.g., inpatient or outpatient, result in different effectiveness and safety outcomes, would be worthwhile.

Recommendation

inclusion in the hospital benefit catalogue currently not recommended

The inclusion of VTP therapy with Tookad® Soluble in the Austrian hospital benefit catalogue is currently not recommended.

The currently available evidence is not sufficient to conclude that VTP therapy with Tookad® Soluble (padeliporfin) in localised low-risk prostate cancer patients is more effective and equally safe or equally effective, but safer than AS. There was no evidence, assessing the clinical effectiveness and safety of VTP therapy with Tookad® Soluble in comparison to radical therapies.

re-evaluation only recommended for intermediate-risk prostate cancer as of 2030

New long-term data of at least ten years will potentially influence the effect estimate considerably. For the low-risk prostate cancer patient population currently, no re-evaluation is suggested, due to lacking ongoing RCTs with sufficient long-term follow-up. Nevertheless, a re-evaluation is recommended for intermediate-risk prostate cancer patients in 2030 after the completion of an ongoing RCT (NCT04225299).

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Prostatakrebs eine der häufigsten Krebsarten bei Männern

Mit weltweit 1,4 Millionen Fällen im Jahr 2016 stellt Prostatakrebs neben Lungen- und Darmkrebs eine der häufigsten Krebsarten bei Männern dar [1, 2]. Laut Statistik Austria wurde im Jahr 2016 bei 5.245 Männern Prostatakrebs diagnostiziert und 1.225 Männer starben daran [3].

Risikofaktoren: Alter, Herkunft, Genetik, Ernährung & Rauchen

Es wird angenommen, dass das Risiko, an Prostatakrebs zu erkranken, mit zunehmendem Alter, afroamerikanischer Herkunft, persönlicher und/oder familiärer Krebsanamnese, tierfettreicher oder gemüsearmer Ernährung, sowie durch Rauchen zu nimmt [4].

insbesondere bei Prostatakrebs mit geringem Risiko oft keine Behandlung nötig, bei fortgeschrittenen Stadien kurative Behandlungen oft unmöglich

Der natürliche Verlauf eines Prostatakarzinoms ist in erster Linie von der Aggressivität des Tumors abhängig. In den meisten Fällen wächst der Krebs jedoch so langsam, dass viele Männer an anderen Ursachen als an Prostatakrebs sterben [5]. Dies gilt insbesondere für Niedrig-Risiko-Prostatakrebs, der auch ohne Behandlung oft nicht zu Metastasen oder zum Tod führt [6]. Bei fortgeschrittenen Krebsstadien einschließlich Metastasen und damit einhergehenden Symptomen ist eine kurative Behandlung meist jedoch nicht mehr möglich [7].

Beschreibung der Technologie

VTP-Therapie mit Padeliporfin potenziell genauso wirksam, aber sicherer als radikale Therapien und mit weniger Angst verbunden als mit aktiver Überwachung (AS)

In der Regel wird der Niedrig-Risiko-Prostatakrebs vorerst nicht therapiert, sondern aktiv überwacht, was jedoch eine zusätzliche psychische Belastung für die Patienten bedeuten kann. Als Alternative werden auch radikale Therapien, wie die radikale Prostatektomie oder die Strahlentherapie angewandt, die jedoch mit schwerwiegenden Nebenwirkungen verbunden sind. Die vaskuläre, photodynamische Therapie (engl. vascular-targeted photodynamic [VTP] therapy) mit Padeliporfin (Tookad® Lösung) ist ein weniger invasives Verfahren und soll eine Option zwischen radikalen Therapien und aktiver Überwachung (engl. active surveillance [AS]) darstellen [8]. Im Vergleich zu radikalen Therapien soll die VTP-Therapie mit Padeliporfin mit weniger Nebenwirkungen einhergehen und dabei eine ähnliche onkologische Wirksamkeit, sowie die Erhaltung der Lebensqualität garantieren. Darüber hinaus soll die VTP-Therapie im Vergleich zur aktiven Überwachung den Patienten die damit verbundene zusätzliche psychische Belastung nehmen [2, 8].

bei VTP-Therapie wird Padeliporfin durch Laserlicht in der Prostata aktiviert

Im Zuge der VTP-Therapie wird in einem ersten Schritt der gefäßwirksame Photosensibilisator, 4 mg/kg Padeliporfin (Tookad® Lösung), über zehn Minuten intravenös verabreicht. Anschliessend wird der Photosensibilisator durch Laserlicht über transperianale interstitielle optische Fasern in der Prostata aktiviert [8-10], wodurch eine Kaskade von pathophysiologischen Ereignissen ausgelöst wird, die innerhalb weniger Tage zu einer fokalen Nekrose führen [10, 21, 24].

EMA-Zulassung und CE-Kennzeichnung für lokalisierten Niedrig-Risiko-Prostatakrebs

Die VTP-Therapie mit Padeliporfin wurde durch die Europäische Arzneimittelagentur (engl. European Medicines Agency [EMA]) für die Indikation lokalisiertes Niedrig-Risiko-Prostatakarzinom zugelassen und ist CE zertifiziert.

Methode

Ziel: Ist die VTP-Therapie mit Padeliporfin vs. AS oder radikale Therapien wirksamer und sicherer? Bewertungen basierend auf dem EUnetHTA Core Model®

Ziel der vorliegenden systematischen Übersichtsarbeit war es, die Anwendung der VTP-Therapie mit Padeliporfin bei Patienten mit lokalisiertem Niedrig-Risiko-Prostatakrebs im Vergleich zu Standardtherapien (aktive Überwachung oder radikale Therapien) zu untersuchen. Die Forschungsfrage war, ob die VTP-Therapie mit Padeliporfin wirksamer und gleich sicher bzw. gleich wirksam, aber sicherer hinsichtlich krebsspezifischer klinischer Wirksamkeitsendpunkte, Lebensqualität und Nebenwirkungen ist. Das „EUnetHTA Core Model® for Rapid Assessment of Relative Effectiveness“ war die Hauptquelle für die Auswahl der relevanten Bewertungselemente.

systematische Suche in 4 Datenbanken: insgesamt 337 Treffer nach Deduplizierung, Suche in den Registern für klinische Studien nach laufenden Studien: 22 potenzielle Treffer; + 1 neue Quelle vom Hersteller

Die systematische Literatursuche wurde am 17.-18. Dezember 2019 in den vier Datenbanken (Medline via Ovid, Embase, The Cochrane Library, CRD [DARE, NHS-EED, HTA]) durchgeführt. Die Suche beschränkte sich auf kein Publikationsjahr oder Studiendesign, jedoch auf Artikel, die in englischer oder deutscher Sprache veröffentlicht wurden. Insgesamt wurden 337 Zitate einbezogen. Zusammen mit zwölf Artikeln, die über die Handsuche gefunden wurden, betrug die Gesamtzahl der identifizierten Zitate nach Deduplizierung 337. Darüber hinaus wurde am 31. Januar 2020 eine Suche in drei Registern für laufende klinische Studien (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) durchgeführt, die 22 potenziell relevante Treffer ergab. Der einzige Hersteller (Steba Biotech) wurde kontaktiert und übermittelte eine neue Quelle.

RoB- und GRADE-Bewertung

Das Risiko einer Verzerrung (engl. Risk of Bias [RoB]) der eingeschlossenen Studien wurde systematisch mit Hilfe des Cochrane-Tools RoB Version 1.0 für randomisierte kontrollierte Studien (engl. randomised controlled trials [RCTs]) und der IHE-Checkliste für Beobachtungsstudien bewertet [11, 12]. Darüber hinaus wurden die Daten zu jeder ausgewählten Endpunktkategorie studienübergreifend nach GRADE (Grading of Recommendations Assessment, Development and Evaluation) bewertet [13].

Ergebnisse

Verfügbare Evidenz

keine Studien zu VTP-Therapie vs. radikale Therapien verfügbar

Es konnte keine Evidenz zum Vergleich der VTP-Therapie mit Padeliporfin mit radikalen Therapieoptionen, wie z. B. der radikalen Prostatektomie oder der Strahlentherapie, identifiziert werden.

1 RCT & Follow-up (VTP-Therapie vs. AS) zur Analyse der klinischen Wirksamkeit eingeschlossen: insgesamt 413 Patienten

Für die Bewertung der klinischen Wirksamkeit wurden ausschließlich RCTs und prospektive nicht-randomisierte kontrollierte Studien (N-RCTs) berücksichtigt. Die einzigen Studien, die die vordefinierten Einschlusskriterien erfüllten, waren ein RCT und das 4-Jahres Follow-up des RCTs [14, 15] mit insgesamt 413 Patienten, die die klinische Wirksamkeit der VTP-Therapie mit Padeliporfin (n=206) im Vergleich zu AS (n=207) bewerteten.

für die Sicherheitsanalyse eine einarmige Studie mit 68 Patienten zusätzlich eingeschlossen

Für die Bewertung der sicherheitsbezogenen Endpunkte wurden RCTs, prospektive N-RCTs und prospektive Beobachtungsstudien mit mehr als 50 Patienten berücksichtigt. Demnach wurde zusätzlich zum RCT und der Follow-up Studie [14, 15] eine prospektive einarmige Studie mit insgesamt 68 Patienten [16] für die Sicherheitsanalyse eingeschlossen.

gesponsert von Steba Biotech, Nachbeobachtung von 24 bis 48 Monaten

Alle Studien wurden von dem Hersteller Steba Biotech finanziert. Die klinische Nachbeobachtungszeit reichte von durchschnittlich 24 bis 48 Monaten.

Klinische Wirksamkeit

keine Unterschiede in Bezug auf das Gesamtüberleben, das prostatakrebsspezifische Überleben und die Lebensqualität

Die Ergebnisse zur klinischen Wirksamkeit ergaben eine prostatakrebsspezifische Überlebensrate von 100,0 % in der VTP-Therapiegruppe und in der AS-Gruppe nach 24 und 48 Monaten und eine Gesamtüberlebensrate von 98,0 % in der VTP-Therapiegruppe versus 99,0 % in der AS-Gruppe [14, 15]. Darüber hinaus wurde kein Unterschied in der Lebensqualität zwischen den beiden Studiengruppen nach 24 Monaten berichtet [14].

signifikant weniger Patienten mit Krankheitsprogression, längere Zeit bis zum Fortschreiten der Krankheit, weniger negative Biopsien & reduziertes Risiko für die Notwendigkeit einer radikalen Therapie in der VTP-Gruppe

In Bezug auf die wichtigsten Surrogatparameter hatten 28,0 % der Patienten in der VTP-Therapiegruppe gegenüber 58,0 % in der AS-Gruppe einen fortschreitenden Krankheitsverlauf nach 24 Monaten (HR 0,34, 95 % CI 0,24-0,46, p<0,0001) [14]. Die Zeit bis zur Krankheitsprogression war in der VTP-Therapiegruppe länger als in der AS-Gruppe (28,3 gegenüber 14,1 Monaten, p<0,0001). Des Weiteren hatten 49,0 % der Patienten in der VTP-Therapiegruppe im Vergleich zu 14,0 % in der AS-Gruppe negative Biopsieresultate nach 24 Monaten (RR 3,67, 95 % CI 2,53-5,33, p<0,0001). Darüber hinaus reduzierte die Intervention das Risiko für die Notwendigkeit einer radikalen Therapie nach 24 Monaten (5,8 % versus 29,0 %, p>0,0001) [14]. Nach 48 Monaten, war die Rate an radikalen Therapien in beiden Studiengruppen höher, jedoch immer noch niedriger in der Interventionsgruppe (24.0 % versus 53.0 %, HR 0.31, 95 % CI 0.21-0.46, p<0.001) [15].

Sicherheit

vermehrt (schwer-wiegende) Nebenwirkungen durch VTP-Therapie im Vergleich zur AS und keinen Unterschied in IPSS und IIEF-15-Scores zwischen den Studiengruppen nach 24 Monaten

Das RCT [14] zeigte, dass die Durchführung der VTP-Therapie mit Padeliporfin im Vergleich zur aktiven Überwachung in einer erhöhten Häufigkeit von unerwünschten Nebenwirkungen resultierte. Einer von drei Patienten bekam eine schwerwiegende Nebenwirkung im Zuge der VTP-Therapie, wohingegen in der AS-Gruppe, einer von zehn Patienten eine schwerwiegende Nebenwirkung erlitt. Die am häufigsten berichteten schwerwiegenden Nebenwirkungen in der VTP-Therapiegruppe waren Leistenbruch, rektale Blutung, Prostatitis und Harnverhalt, die alle bei lediglich 1-2% der Patienten auftraten. Die meisten Nebenwirkungen wurden als mild bis moderat eingestuft. Darüber hinaus berichtete das RCT [14] keinen Unterschied in der Veränderung des IPSS-Scores (Harnwegssymptome) und des IIEF-15-Scores (erektile Funktion) nach 24 Monaten zwischen den Studiengruppen.

keine Sicherheitsdaten berichtet in der 4-Jahres Follow-up Studie

Im vier-Jahres Follow-up [15] der Zulassungsstudie [14] wurden keine Sicherheitsdaten berichtet.

einarmigen Studie: keine schwerwiegenden Nebenwirkungen gemeldet, aber 2 moderate & einige milde Nebenwirkungen

Die einarmige Studie [16] berichtete Nebenwirkungen, die auch meist als mild bis moderat eingestuft wurden. Die am häufigsten berichteten milden Nebenwirkungen waren erektile Dysfunktion (43,8 %), Syndrom der unteren Harnwege (18,8 %) und perianale Schmerzen (14,1 %). In der Studie wurden während der 42-monatigen Nachbeobachtungzeit keine schwerewiegenden Nebenwirkungen berichtet, jedoch zwei moderate Nebenwirkungen: das Syndrom der unteren Harnwege (3,1 %) und die Harnröhrenstenose (1,6 %).

Laufende Studien

2 laufende Studien: 5-Jahres Follow-up Studie & RCT für Prostatakrebs mit mittlerem Risiko

Zurzeit gibt es zwei laufende kontrollierte Studien. Eine Studie (NCT04017325) repräsentiert das erweiterte 5-Jahres Follow-up des ursprünglichen RCTs [14]. Die zweite Studie (NCT04225299) repräsentiert ein weiteres RCT zur Wirksamkeit der VTP-Therapie mit Padeliporfin versus AS bei lokalisiertem Prostatakrebs von mittlerem Risiko mit einer Nachbeobachtungszeit von 72 Monaten.

Zusätzlich 3 laufende einarmige Studien

Darüber hinaus wurden drei laufende prospektive einarmige Studien (NCT-03849365, NCT03315754, unbekannt) mit Nachbeobachtungszeiträumen von einem bis sieben Jahren identifiziert.

Kostenerstattung

in Ö aktuell nicht erstattet, jedoch in Deutschland

Zum Zeitpunkt der Berichtverfassung wird die VTP-Therapie mit Padeliporfin in Österreich nicht erstattet. In Deutschland wird die Intervention bei lokalisiertem Prostatakrebs mit niedrigem Risiko vollständig erstattet und in Italien läuft das Verfahren zur Erstattung.

Diskussion

Gesamtqualität der Evidenz gering-moderat

Insgesamt wurde die Qualität der Evidenz hinsichtlich der klinischen Wirksamkeit und Sicherheit als gering bzw. moderat eingestuft.

Interpretation der Daten: Therapiewahl bei Niedrig-Risiko-Prostatakrebs umfasst Risiko, Alter, Gesundheitszustand, aber auch Angst und Hoffnung; Nutzen der VTP-Therapie gegenüber AS zur Verringerung der zusätzlichen psychologischen Belastung nicht eindeutig

Bei der Interpretation der Studienergebnisse müssen die Herausforderungen bei der Therapiewahl bei Niedrig-Risiko-Prostatakrebs berücksichtigt werden. Fakt ist, dass ein erheblicher Anteil der Patienten mit Niedrig-Risiko-Prostatakrebs überhaupt keine Behandlung benötigen würde, sondern viel eher lediglich aktiv überwacht werden sollte. Neben der Risikostratifizierung spielen jedoch auch das Alter und der Gesundheitszustand des Patienten, sowie Hoffnung und Angst eine wichtige Rolle für die endgültige Therapiewahl [8, 17-19]. Ziel der VTP-Therapie mit Padeliporfin ist es, die mit der aktiven Überwachung einhergehende psychische Belastung zu reduzieren. Daten zeigten jedoch, dass mehr als die Hälfte der Studienpopulation positive Biopsieresultate nach 24 Monaten erhielten. Dies bedeutet, dass diese Patienten ähnlich häufig wie Patienten unter AS überwacht werden müssen und dadurch möglicherweise die gleiche Unsicherheit wie unter AS bestehen bleibt [18].

mögliche inakkurate Risikostratifizierung im RCT, da MRT-Untersuchungen nur in der VTP-Gruppe angewendet wurde, wodurch potentieller Nutzen der VTP-Therapie vs. AS überschätzt wurde?

Eine weitere Herausforderung stellt die angenommene inakkurate Risikostratifizierung der Patienten in den eingeschlossenen Studien dar. Im RCT [14, 15] wurden lediglich bei den Patienten, die für die VTP-Therapie mit Padeliporfin randomisiert wurden, eine multiparametrische Prostata-Magnetresonanztomographie (MRT) vor der Behandlung durchgeführt. Der relativ hohe Anteil an Patienten in der AS-Gruppe mit Verschlechterung des Gleason-Grades innerhalb von 24 Monaten deutet darauf hin, dass die gesamte Studienpopulation möglicherweise nicht richtig eingeschätzt wurde und nicht wirklich risikoarm war [15, 20]. Aus diesem Grund hätte eine MRT-Untersuchung in der AS-Gruppe möglicherweise zu einer valideren Diagnose und einer verbesserten Risikostratifizierung geführt, wodurch der potenzielle Nutzen der VTP-Therapie mit Padeliporfin gegenüber der aktiven Überwachung noch weiter verringert hätte werde können [17-20].

inkonsistente Anzahl von Patienten bzw. Loss to Follow-up

Darüber hinaus wurden in allen drei eingeschlossenen Publikationen [14-16] die Anzahl der Patienten bzw. der Loss to Follow-up uneinheitlich präsentiert, was die Interpretation der Daten noch weiter erschwerte.

Verallgemeinerbarkeit auf den österreichischen Kontext gegeben

Hinsichtlich der externen Validität gelten die Daten als auf den österreichischen Kontext übertragbar, da die eingeschlossenen Studien in zehn europäischen Ländern durchgeführt wurden.

Insgesamt beantwortet die vorliegende Evidenz nur teilweise unsere Forschungsfragen. Weitere Erkenntnisse darüber, wie sich die VTP-Therapie mit Padeliporfin auf die Durchführbarkeit künftiger radikaler Therapien auswirkt, sind notwendig. Des Weiteren sind Langzeitdaten mit einer Nachbeobachtungszeit von mindestens zehn Jahren wünschenswert, insbesondere im Hinblick auf das Gesamtüberleben, das prostatakrebsspezifische Überleben, die Lebensqualität und schwerwiegende Nebenwirkungen. Darüber hinaus wird empfohlen, zu untersuchen, ob unterschiedliche Settings, z.B. stationär oder ambulant, zu unterschiedlichen Wirksamkeits- bzw. Sicherheitsergebnissen führen.

weitere Evidenz notwendig: Wirkung von VTP auf nachfolgende radikale Therapien, Langzeitdaten, verschiedene Krankenhaussettings

Empfehlung

Die Aufnahme der VTP-Therapie mit Padeliporfin in den österreichischen Krankenhausleistungskatalog wird derzeit nicht empfohlen.

Aufnahme in den Krankenhausleistungskatalog derzeit nicht empfohlen

Die derzeit verfügbare Evidenz reicht nicht aus, um zu bestätigen, dass die VTP-Therapie mit Padeliporfin bei lokalisiertem Niedrig-Risiko-Prostatakrebs wirksamer und gleich sicher bzw. gleich wirksam, aber sicherer als die aktive Überwachung ist. Es konnte keine Evidenz zur klinischen Wirksamkeit und Sicherheit der VTP-Therapie mit Padeliporfin im Vergleich zu radikalen Therapien identifiziert werden.

Neue Langzeitdaten werden die Ergebnisse zur klinischen Wirksamkeit und Sicherheit maßgeblich beeinflussen. Für die Patientenpopulation mit lokalisiertem Niedrig-Risiko-Prostatakrebs wird aufgrund fehlender laufender RCTs mit langfristiger Nachbeobachtungzeit von mindestens zehn Jahren keine Reevaluierung vorgeschlagen. Eine Reevaluierung wird für die Patientenpopulation mit mittlerem Prostatakrebsrisiko empfohlen, nachdem ein laufendes RCT abgeschlossen ist (NCT04225299, erwartete Fertigstellung im Jahr 2030).

Reevaluierung nur für Prostatakrebs mit mittlerem Risiko ab 2030 empfohlen

1 Scope

1.1 PICO question

PIKO-Frage

Is vascular-targeted photodynamic therapy with padeliporfin (Tookad® Soluble) in comparison to standard therapies, namely active surveillance, radiation therapy or radical prostatectomy, in patients with localised low-risk adenocarcinoma of the prostate more effective and safe or equally effective but safer concerning cancer-specific clinical effectiveness outcomes, quality of life and adverse events?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 1-1: Inclusion criteria [6, 21, 22]

Population	Male patients (≥18 years of age) with localised low-risk adenocarcinoma of the prostate and a life expectancy exceeding ten years. The following criteria indicate low-risk prostate cancer: • Tumour stage T1-T2a • Gleason score ≤6 • PSA ≤10 ng/ml ICD-10 Code: C61 MeSH terms: Prostate, neoplasms, prostatic neoplasms
Intervention	VTP therapy with padeliporfin as first-line monotherapy. Active substance: • Padeliporfin (Tookad® Soluble, WST-11, Steba Biotech) MeSH terms: Focal therapy/treatment, photodynamic therapy, VTP therapy
Control	Standard therapies for patients with a life expectancy of at least ten years: • AS without therapeutic measures • Radiation therapy • Radical prostatectomy MeSH terms: External-beam radiation therapy, brachytherapy, surgical removal of the prostate
Outcomes	

Efficacy	• **Clinical endpoint(s):**
	  • OS
	  • Prostate cancer-specific survival
	  • QoL
	• **Surrogate endpoints:**
	  • Disease progression
	  • Time to progression
	  • Recurrence-free survival
	  • Metastatic-free survival
	  • Radical therapy conversion

Safety	• **Study-related death**
	• **Prostate cancer-related death**
	• **All grade AEs:**
	  • Problems with urinating
	  • Urinary tract infection
	  • Erectile dysfunction
	  • Pain and bleeding around the genital area
	  • Risk of the development of fistulas or abscesses or necrosis around the prostate
	  • Risk of phototoxicity
	  • Mild liver effects
	  • Adverse events related to the general anaesthesia
	• **Discontinuation rate**

Study design	
Efficacy	• Randomised controlled trials (RCTs) • Non-randomised controlled trials (N-RCTs)
Safety	• RCTs • N-RCTs • Prospective observational studies with n>50

Abbreviations: ***AE*** *– Adverse event,* ***AS*** *– Active surveillance,* ***N-RCTs*** *– Non-randomised controlled trials,* ***OS*** *– Overall survival,* ***PSA*** *– Prostate-specific antigen,* ***QoL*** *– Quality of life,* ***RCTs*** *– Randomised controlled trials,* ***VTP*** *– Vascular-targeted photodynamic*

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What are VTP therapy with Tookad® Soluble and the comparator(s)?
A0020	For which indications has VTP therapy with Tookad® Soluble received marketing authorisation or CE marking?
B0002	What is the claimed benefit of VTP therapy with Tookad® Soluble in relation to the comparator(s)?
B0003	What is the phase of development and implementation of VTP therapy with Tookad® Soluble and the comparator(s)?
B0004	Who administers VTP therapy with Tookad® Soluble and in what context and level of care is it provided?
B0008	What kind of special premises are needed to use VTP therapy with Tookad® Soluble?
B0009	What supplies are needed to use VTP therapy with Tookad® Soluble?
A0021	What is the reimbursement status of VTP therapy with Tookad® Soluble?

Health problem and current use	
Element ID	**Research question**
A0001	For which health conditions, and for what purposes is VTP therapy with Tookad® Soluble used?
A0002	What is the disease or health condition in the scope of this assessment?
A0003	What are the known risk factors for localised low-risk prostate cancer?
A0004	What is the natural course of localised low-risk prostate cancer?
A0005	What is the burden of disease for patients with localised low-risk prostate cancer?
A0006	What are the consequences of localised low-risk prostate cancer for society?
A0024	How is localised low-risk prostate cancer currently diagnosed according to published guidelines and in practice?
A0025	How is localised low-risk prostate cancer 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 VTP therapy with Tookad® Soluble utilised?

Clinical effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of VTP therapy with Tookad® Soluble on mortality (part I)?
D0005	How does VTP therapy with Tookad® Soluble affect symptoms and findings (severity, frequency) of localised low-risk prostate cancer?
D0006	How does VTP therapy with Tookad® Soluble affect progression (or recurrence) of localised low-risk prostate cancer?
D0011	What is the effect of VTP therapy with Tookad® Soluble on patients' body functions?
D0016	How does the use of VTP therapy with Tookad® Soluble affect activities of daily living?
D0012	What is the effect of VTP therapy with Tookad® Soluble on generic health-related quality of life?
D0013	What is the effect of VTP therapy with Tookad® Soluble on disease-specific quality of life?
D0017	Was the use of VTP therapy with Tookad® Soluble worthwhile?

Safety	
Element ID	**Research question**
C0008	How safe is VTP therapy with Tookad® Soluble in comparison to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying VTP therapy with Tookad® Soluble?
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 VTP therapy with Tookad® Soluble?
C0007	Are VTP therapy with Tookad® Soluble and comparator(s) associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of VTP therapy with Tookad® Soluble and comparator(s)?
D0001	What is the expected beneficial effect of VTP therapy with Tookad® Soluble on mortality (part II)?
D0003	What is the effect of VTP therapy with Tookad® Soluble on the mortality due to causes other than the target disease?

2.2 Sources

Quellen: Handsuche, sowie Informationen des Herstellers und des einreichenden Krankenhauses

Description of the technology

- Hand-search 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 and the submitting hospital

Health problem and current use

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

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on the 17th and 18th of December 2019 in the following databases:

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

systematische Suche mit 337 Treffern

The systematic search was not limited to a year of publication or specific study design, but articles published in English or German. After deduplication, 337 citations were included overall. The specific search strategy employed can be found in the Appendix.

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 31st of January 2020, resulting in 22 potential relevant hits.

Suche nach laufenden Studien – 22 Treffer

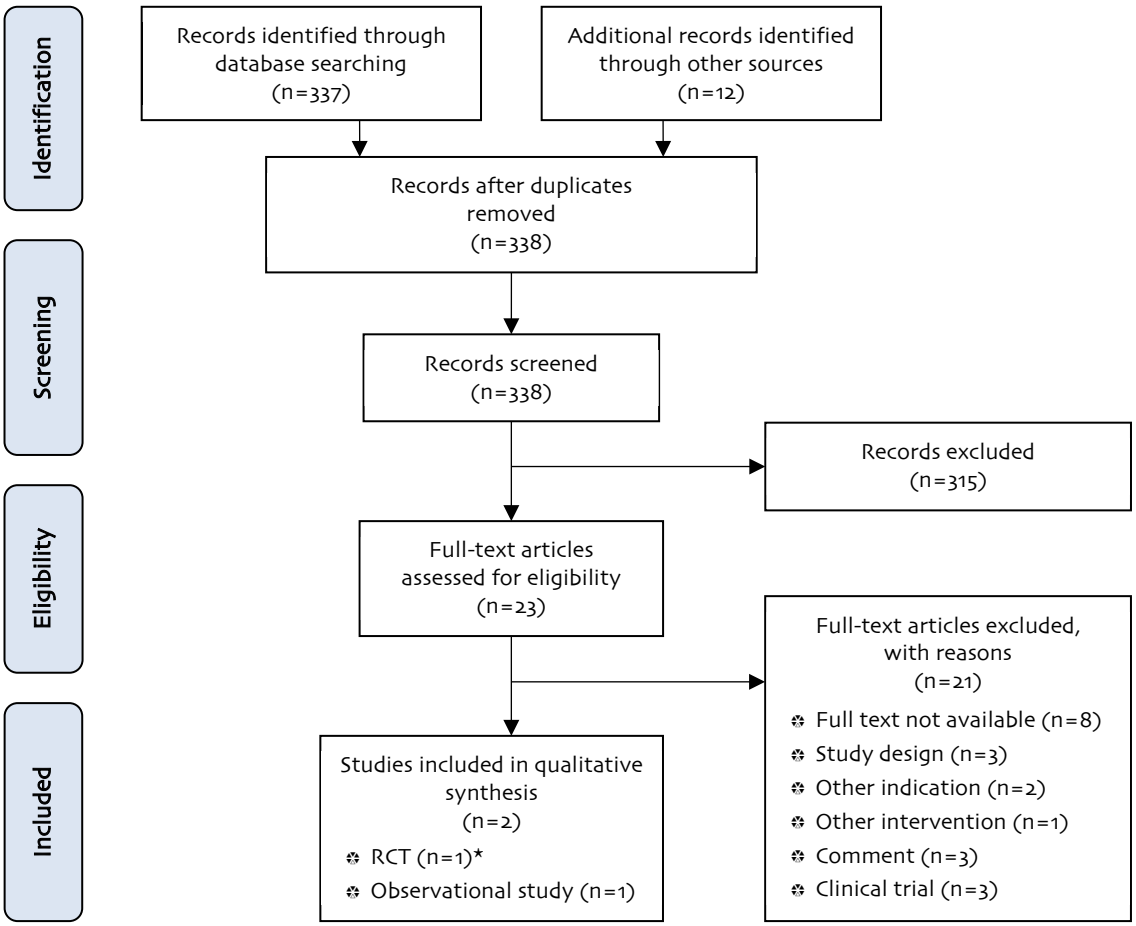
The manufacturer of the available product VTP therapy with Tookad® Soluble, Steba Biotech) submitted six publications, of which one new citation was identified. By hand-search, an additional publication was found, resulting in 338 hits overall after duplicates were removed.

insgesamt 338 Publikationen identifiziert; 1 zusätzliche von Hersteller

2.4 Flow chart of study selection

Overall, 338 hits were identified after deduplication. The references were screened by two independent researchers and in case of disagreement, a third researcher was involved to solve the differences. Three studies were included for the qualitative analysis after applying the predefined criteria (see Table 1-1). The selection process is displayed in Figure 2-1.

Literaturauswahl: 3 Studien eingeschlossen



* *Two publications on the RCT were included. One publication presents the pivotal RCT with a follow-up of 24 months and the second publication presents the results of the extended follow-up of 48 months.*

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

2.5 Analysis

Datenextraktion und Bewertung des Bias-Risikos

The data retrieved from the selected studies were systematically extracted into data extraction tables by one author (SW) and controlled by another author (NG) (see Table A-1 and Table A-2). Subsequently, both authors (SW, NG) systematically assessed the risk of bias (RoB) of the included studies using the Cochrane RoB tool version 1.0 and the International Health Economics (IHE) checklist (see Table A-3, Table A-4).

2.6 Synthesis

Beurteilung der Evidenzqualität mittels GRADE

Based on the data extraction tables (see Table A-1 and Table A-2), data on each selected outcome category were synthesised across studies according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) [13]. The questions were then answered in plain text format with reference to GRADE evidence tables (see Table 7-1 and Table A-5).

3 Description and technical characteristics of technology

Features of the technology and comparator(s)

B0001 – What is the technology and the comparator(s)?

The vascular-targeted photodynamic (VTP-)therapy entails the intravenous administration of a vascular-acting photosensitizer consisting of a water-soluble, palladium-substituted bacteriochlorophyll derivative, Tookad® Soluble (padeliporfin) [10]. It is given intravenously at a recommended single dose of 4 mg/kg over ten minutes and subsequently activated in the prostate by laser light (wavelength of 753 nm; radiant power of 15 mW/cm fibre; energy of 200 J/cm) through transperineal interstitial optical fibres [8-10]. Thereby, the laser light is shone along the fibres onto the cancer (light density index [LDI][1] ≥1) for 22 minutes and 15 seconds [21, 23]. The non-thermal light delivered by the laser then triggers a cascade of pathophysiological events that lead to focal necrosis within a few days [10, 21, 24]:

4 mg/kg Padeliporfin: aktiviert durch Laserlicht resultiert in einer fokalen Nekrose des Tumors durch pathophysiologische Ereignisse:

- Firstly, activation in the exposed vascular system of the tumour produces oxygen radicals that cause local hypoxia, which in turn induces the release of nitric oxide radicals. This further leads to a temporary arterial dilatation that triggers the release of the vasoconstrictor endothelin-1.

(1) Sauerstoffradikale → Hypoxie

(2) RNA-Bildung & arterielle Verengung

- Secondly, due to the rapid consumption of NO radicals by oxygen radicals, reactive nitrogen species (RNA, e.g. peroxynitrite) are formed in addition to the arterial constriction.
- Thirdly, it is assumed that the impaired deformability improves the ability of erythrocytes to aggregate from blood clots at the junction between the arterial supply (feeding arteries) and the microcirculation of the tumour, which in turn leads to occlusion of the tumour vessels.

(3) Verschluss der Tumorgefäße durch Bildung von Blutgerinnseln

- Fourthly, this occlusion of the tumour vessels is enhanced by the RNA-induced endothelial cell apoptosis and the initiation of self-spreading necrosis of tumour cells by peroxidation of their membrane.

(4) Nekrose verstärkt durch Peroxidation der Membran der Tumorzellen

The considered comparators are standard therapies for localised low-risk prostate cancer patients with a life expectancy exceeding ten years. According to international guidelines [6, 25, 26], these standard therapy options include two curative treatments (radical prostatectomy and radiation therapy), which result in the ablation of the entire prostate gland, or active survival [9]:

Standardtherapien bei Niedrig-Risiko-Prostatakarzinom als Komparatoren:
- Radikale Therapien
- Aktive Überwachung

- **Radical prostatectomy** includes the surgery to remove the whole prostate gland intended to heal from prostate cancer and is recommended as a treatment option for patients with localised prostate cancer of all risk groups with a life expectancy exceeding ten years.

radikale Prostatektomie empfohlen bei Lebenserwartung von ≥10 Jahren

[1] Light density index (LDI) is determined as the ratio of the total length of used fibres in centimetres to the planned treatment volume (PTV) of targeted prostate tissue in millilitres.

äußere Strahlentherapie (alle Risikogruppen) & Brachytherapie (Strahlung innerhalb der Prostata) empfohlen für lokalisierten Niedrig-Risiko-Prostatakrebs

- **Radiation therapy** can be distinguished between external-beam radiation therapy (EBRT) (recommended as a treatment option for localised prostate cancer of all risk groups), or brachytherapy (recommended as a treatment option for localised low-risk prostate cancer). In general, the goal of radiation therapy is to deliver a therapeutic dose of radiation to the tumour and thereby destroy prostate cancer, while minimising radiation to normal tissue.

aktive Überwachung empfohlen um Nebenwirkungen (NW) von Therapien zu vermeiden

- **Active surveillance** (AS) includes the monitoring of serum PSA concentration and repeat prostate biopsies to select patients for curative therapy. It is recommended as a non-radical treatment option to prevent adverse events of radical treatment options.

A0020 – For which indications has VTP therapy with Tookad® Soluble received marketing authorisation and/or a CE mark?

EMA Marktzulassung für lokalisiertes Niedrig-Risiko-Prostatakarzinom

The European Medicines Agency (EMA) granted a marketing authorisation for Tookad® Soluble(padeliporfin) in combination with VTP therapy for localised low-risk prostate cancer on the 10th of November 2017 [21].

FDA Zulassungsprozess voraussichtlich bis Ende 2020 abgeschlossen

At the time this assessment is being conducted (January 2020), Tookad® Soluble has not received FDA approval. However, the evaluation process for approval is currently taking place and should be finalised by the end of 2020 [information from the manufacturer].

alle Vorrichtungen für VTP-Therapie mit Padeliporfin CE-gekennzeichnet

All devices needed for VTP therapy with Tookad® Soluble (optical fibres and catheters) are CE marked (notified body: 0843; expiry date: March 22, 2023) [information from the manufacturer].

B0002 – What is the claimed benefit of VTP therapy with Tookad® Soluble in relation to the comparator(s)?

VTP-Therapie: Schonung des Normalgewebes

In general, the potential advantages of VTP therapy with Tookad® Soluble in men with localised low-risk prostate cancer include the ability to destroy cancer cells using a relatively non-invasive procedure, as well as sparing normal tissue [23].

weniger NW aber selbe Effektivität als mit radikalen Therapien, ↓ Unsicherheit als mit AS

In comparison to radical therapies such as radical prostatectomy or radiation therapy, VTP therapy with Tookad® Soluble aims to reduce the side-effect profile, to achieve similar oncological efficacy and, subsequently, to maintain quality of life (QoL) [2, 8]. Compared to AS that increases anxiety for some patients, it may help to reduce anxiety.

mögliche Option zwischen radikaler Therapie und AS

Therefore, VTP therapy claims to provide a new option between radical therapy (effective but severe adverse events) and AS (safe but potentially psychologically burdensome) [2, 9, 22].

B0003 – What is the phase of development and implementation of VTP therapy with Tookad® Soluble and the comparator(s)?

aktuell FDA Zulassungsprozess am Laufen, 5-Jahres Follow-up & RCT zu mittlerem Prostatakrebsrisiko laufend

At this point, the manufacturer Steba Biotech has submitted the pivotal randomised controlled trial (RCT) comparing VTP therapy with Tookad® Soluble to AS in localised low-risk prostate cancer patients (NCT01310894) for FDA approval. Furthermore, the five-year follow-up of the initial approval study is deemed to be completed by June 2020 (NCT04017325) Besides, another ongoing RCT is currently investigating the clinical effectiveness and safety of VTP therapy with Tookad® Soluble in intermediate-risk prostate cancer patients (NCT04225299) (see Table A-7).

Administration, investments, personnel and tools required to use the technology

B0004 – Who administers VTP therapy with Tookad® Soluble and in what context and level of care is it provided?

B0008 – What kind of special premises are needed to use VTP therapy with Tookad® Soluble?

B0009 – What supplies are needed to use VTP therapy with Tookad® Soluble?

VTP therapy with Tookad® Soluble is applied by a surgeon, supported by nurses and an anaesthetist [21, 24]. For this reason, Tookad® Soluble can only be used in hospitals by healthcare professionals trained to carry out the intervention [21].

VTP-Therapie im Krankenhaus von Chirurg*innen & Pflegefachkräften durchgeführt

VTP therapy with Tookad® Soluble is a multi-technology solution that involves three inseparable elements [information from the manufacturer]:

benötigt 3 separate Elemente: Medikament, Geräte, Laserausstattung

1. The pharmaceutical drug (Tookad® Soluble, padeliporfin),
2. specific disposable devices (fibre insertion catheters [FICs] with optical fibres with an LDI[2] of ≥1),
3. and laser equipment (e.g., laser machine).

Besides the basic equipment, an operating room including sterile operative areas (e.g., an operating table) is needed for the procedure. Due to the risk of phototoxicity, the integral protection from light exposure within the operating room is thereby crucial [9].

sowie lichtgeschützter Operationsraum

Before the actual procedure, the position of the optical fibres needs to be planned, including the number of optical fibres, the accurate position of the fibres into the prostate, and the length of the light-diffusing of each optical fibre. All three aspects depend on the volume and shape of each prostate and the area of the lesion [9]. For accurate planning, the treatment-planning software (TOOGUIDE, Steba Biotech) can be used [21, 24]. Besides, the preparation of the procedure includes the cleaning of the rectal area [21].

präoperativ: Planung der Positionierung der optischen Fasern mittels Software & Säuberung des Operationsbereichs

For the actual procedure, the patient is placed in a lithotomy position at the edge of the operating table with enough hip flexion, to expose the perineum without being hindered by the pubis. Furthermore, general anaesthesia by an anaesthetist is mandatory, since any movement of the patient can lead to the need for the complete reinstallation of all transperineal FICs [8].

OP unter Vollnarkose, um Bewegungen des Patienten zu vermeiden

The total duration of the procedure lasts between one-and-a-half and two hours, including anaesthesia, fibre placement and illumination. Generally, the duration depends on the volume of the targeted area and the number of optical fibres [8, 24].

Gesamtdauer der OP zwischen 1½ – 2h

After the operation, the patient may be discharged from hospital at the doctor's discretion on the evening of the same day; however, due to the risk of phototoxicity, the patient is deemed to follow certain guidance within 48 hours after the procedure [8, 21, 24]:

postoperativ:

- 0-6 hours after the procedure: The patient should wear goggles and should be medically monitored in a dimmed room.

0-6h: klinische Aufsicht in abgedunkeltem Raum

[2] LDI is determined as the ratio of the total length of used fibres in centimetres to the planned treatment volume (PTV) of targeted prostate tissue in millilitres.

6-12h: Tageslicht vermeiden

- 6-12 hours after the procedure: The patient should stay indoors and should avoid daylight.

12-48h: Vermeidung von Sonnenlicht

- 12-48 hours after the procedure: The patient can go outside in daylight, but only in shady areas or when the sky is cloudy. He should wear dark clothing and be careful when exposing his hands and face to sunlight.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of VTP therapy with Tookad® Soluble?

Padeliporfin in UK, Deutschland & Italien eingeführt:

At the time of conducting this review (January 2020), Tookad® Soluble has been launched in the United Kingdom (UK), Germany and Italy [information from the manufacturer]:

Deutschland: erstattet unter NUB Status 1

- In Germany, Tookad® Soluble VTP-technology is fully reimbursed for localised low-risk prostate cancer under "NUB status 1"[3].

Italien: aktuell laufende Erstattungsprozesse

- In Italy, the SSN (Servizio Sanitario Nazionale) appraisal is currently ongoing: The AIFA (Italian Medicines Agency) technical committee (CTS) has already given its positive opinion for reimbursement, while the price negotiations with the Price Committee (CPR) are ongoing.
- No further information is available for the UK.

in Österreich (Ö) nicht erstattet

Currently, Tookad® Soluble (padeliporfin) is not reimbursed in Austria [information from the manufacturer].

[3] NUBs (new examination and treatment methods, regulated in § 6 para. 2 KHEntgG) are forms of therapies that have been newly introduced into the healthcare market and therefore cannot be properly billed yet via the G-DRG system; *Status 1* indicates that a requested method/performance meets the criteria of the NUB agreement. For this method/service, the agreement of a hospital-specific NUB fee is permissible according to § 1 para. 1 of the NUB agreement.

4 Health problem and current use

Overview of the disease or health condition

A0001 – For which health conditions, and for what purposes is VTP therapy with Tookad® Soluble used?

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

VTP therapy with Tookad® Soluble is approved for the treatment of localised low-risk prostate cancer. At this point, VTP therapy with Tookad® Soluble is not approved for any other indication.

Zielpopulation: lokalisiertes Niedrig-Risiko-Prostatakarzinom

The prostate is an apricot-sized, muscular gland that produces some of the ingredients of semen. It sits just in front of the rectum and below the bladder and has various functions, including [6]:

Prostata = muskulöse Drüse mit unterschiedlichen Funktionen

- Producing the fluid that nourishes and transports sperm.
- PSA, a protein that helps semen retain its liquid state.
- Helping aid urine control.

Prostate cancer originates from the glands of the prostate [6].

Prostatakarzinom unterteilt in unterschiedliche Risikogruppen

Prostate cancer can be staged into different risk groups: very low-risk, low-risk, intermediate-risk, and high-risk.

A0003 – What are the known risk factors for localised low-risk prostate cancer?

Of the several known prostate cancer risk factors, the most important are age, ethnicity, genetic and possibly dietary factors [4]:

Hauptrisikofaktoren:

- **Age**: Prostate cancer has one of the strongest relationships between age and human malignancy. Clinically diagnosed prostate cancer rarely occurs before the age of 40, but the incidence rises rapidly thereafter, peaking between the ages of 65 and 74 [4].

  Alter: steigende Inzidenz ab 40 Jahren
- **Ethnicity**: Prostate cancer is more common in black than white or Hispanic men, perhaps related to a combination of dietary and/or genetic factors. Moreover, the age of onset in African-American men is earlier than for comparative groups [4].

  Ethnizität: afro-amerikansiche Männer häufiger betroffen
- **Genetic factors**: A detailed personal and family cancer history (in first- and second-degree relatives), including the type of cancer, age at diagnosis, and ancestry, may help to identify individuals who may carry BRCA2 or other prostate cancer-associated mutations [4].

  genetische Faktoren
- **Diet**: A diet high in animal fat may be an important factor in the development of prostate cancer. Additionally, a diet low in vegetables may be another risk factor for prostate cancer. There is a clear relationship between obesity and disease aggressiveness, with an increase in both the biochemical recurrence rate following treatment and prostate cancer-specific mortality. Furthermore, cigarette smoking may have an effect on both, the risk of developing prostate cancer and its prognosis, once a diagnosis is established [4].

  Ernährungsweise & Rauchen kann Risiko erhöhen
- **Other factors** that may enhance the development of prostate cancer are infections and chronic inflammations, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) or statins [4].

  andere Faktoren: Infektion & chronische Entzündungen

A0004 What is the natural course of localised low-risk prostate cancer?

natürlicher Verlauf abhängig von Aggressivität des Tumors,

Niedrig-Risiko-Prostatakrebs auch ohne Therapie oft stabil

The natural course of prostate cancer is primarily dependent on the tumour aggressiveness. The clinical behaviour of prostate cancer ranges from a microscopic, well-differentiated tumour that may never be clinically significant to an aggressive, invasive cancer that ultimately results in metastases, morbidity, and death [27]. Without screening, many cases of prostate cancer do not ever become clinically evident. Data suggest that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced [5]. Especially tumours with a low-risk profile have shown to rarely develop metastasis or lead to death even without treatment [6]. However, if prostate cancer grows to the state of producing symptoms like bladder neck obstruction, invasion of adjacent organs, or distant metastasis, curative treatment is usually impossible [7].

relative 5-Jahres-Überlebensrate 100 % bei lokalisiertem Prostatakrebs vs. 31 % bei Metastasierung

Therefore, prostate cancer survival is related to many factors, including the extent of the tumour at the time of diagnosis. The five-year relative survival among men with cancer confined to the prostate (localised) or with regional spread is 100.0%, compared with 31.0% among those diagnosed with distant metastasis.

5-7 Jahre frühere Diagnose durch Screening, aber nicht immer von Vorteil:

Through prostate cancer screening, including PSA test and/or digital rectal examination (DRE) every one to two years, prostate cancer can be detected five to seven years earlier [6]. However, detection at an early stage does not necessarily correlate with a clinically beneficial outcome (e.g., decline in morbidity or prostate cancer-specific mortality) [5]:

Risiken einhergehend mit Therapien

- Increased detection of prostate cancer subjects puts some patients to the risks that are associated with treatments (e.g., morbidity).

klinisch irrelevante Diagnose durch Screening entdeckt

- When screening finds cancer that would never have become clinically significant, patients have still been subjected to the risks of screening, confirmatory diagnostic testing and potential treatments that can result in side effects.

falsch-positive Resultate möglich

- With respect to potential overdiagnosis, some abnormal PSA results are false positives.

mögliche falsch-negative Resultate

- In contrast, even patients with a biopsy result that is negative for prostate cancer may develop anxiety, since a negative result cannot completely rule out prostate cancer due to the false-negative biopsy rate.

keine Daten zum natürlichen Verlauf mit Screening

At present, there is no data available on the natural course of tumours discovered by early detection via prostate cancer screening [6].

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

A0005 – What is the burden of disease for patients with localised low-risk prostate cancer?

lokalisierter Prostatakrebs meist asymptomatisch, vorgeschrittene Stadien mit Symptomen wie Harn-Probleme, etc.

Most prostate cancers are diagnosed in the local stage through prostate cancer screening and are asymptomatic. Uncommonly, low-risk prostate cancer may be present with nonspecific urinary symptoms, haematuria, or hematospermia. In contrast, more advanced stages of prostate cancer are usually accompanied by urinary symptoms (e.g., difficulty passing urine, passing urine more frequently, pain when passing urine, or blood in the urine) like bladder neck obstruction, invasion of adjacent organs, or symptoms related to distant metastasis [7, 10].

As described previously, the burden for patients can also be caused through prostate cancer screening, including the risks of unnecessary treatments due to early prostate cancer detections, or the risk of false-positive/false-negative results.

Belastung der Patienten auch durch Screening möglich

A0006 – What are the consequences of localised low-risk prostate cancer for society?

Prostate cancer is one of the most common types of cancer in men, with 1.4 million cases in 2016 globally [1], next to lung and colorectal cancer [2]. The increasing incidence rates, together with an ageing and growing population, have led to an overall 40.0% increase in prostate cancer cases between 2006 and 2016 [1]. In 2016, prostate cancer was also the leading cause of cancer deaths for men in 48 countries [1]. According to the Global Burden of Disease Study 2015, global estimates of the age-standardised death rate for prostate cancer are 14.24 deaths (95% CI: 11.8-17.95) per 100,000 person-years [28]. While the prostate cancer mortality rate is decreasing in high-income countries, the incidence and burden of disease are steadily increasing globally [28].

Prostatakarzinom: eine der häufigsten Krebserkrankungen bei Männern weltweit

Rückgang der Mortalitätsraten in westlichen Ländern, jedoch Anstieg der Inzidenz weltweit

According to Statistik Austria, in 2016, 5,245 diagnosed prostate cancer patients were living in Austria and 1,225 died from it. The average mortality rates (2014–2016) were highest in the federal states of Carinthia and Styria, and lowest in Vorarlberg. Between 2014 and 2016, on average, 57.4% of all prostate cancer patients were diagnosed with localised disease. At the end of 2016, 63,415 men were alive with a diagnosis of prostate cancer. In 40.0% of all affected men (25,572 men), the diagnosis was made ten or more years ago [3].

Ö 2016: 1.225 Todesfälle durch Prostatakrebs; 2014-16: 57,4% aller Patienten mit lokalisiertem Prostatakrebs diagnostiziert

The consequences of prostate cancer for the society is not only dependent on the high incidence rates and the associated costs related to the pharmacological treatments, but also on the costs from a societal perspective that are present when prostate cancer impedes on a person's life, particularly on work activity [1].

zusätzliche Kosten auch aus gesellschaftlicher Perspektive: z. B. Arbeitsunfähigkeit

Current clinical management of the disease or health condition

A0024 – How is localised low-risk prostate cancer currently diagnosed according to published guidelines and in practice?

For the diagnosis of localised low-risk prostate cancer, different steps are considered, starting with PSA testing and/or DRE, followed by a biopsy and an associated Gleason score rating, tumour staging and, finally, the stratification into different risk groups.

Diagnostik umfasst 5 nachfolgende Schritte:

1. Prostate cancer screening via PSA testing and/or DRE

As localised low-risk prostate cancer is usually asymptomatic, it is often identified through prostate cancer screening programmes. According to the European Association of Urology (EAU), screening includes PSA testing and DRE, which assesses the size, shape, delimitability, pressure pain, consistency, knots, hardenings and fluctuation of the tumour [6, 29]. Thereby, a higher baseline PSA concentration is associated with an increased risk of identifying a more advanced disease, as well as subsequent disease progression [22, 30]. In addition, a transrectal ultrasound examination (TRUS) can be performed to determine the size, location and extent of the tumour [6].

(1) PSA-Test und digitale rektale Untersuchung innerhalb des Prostatakrebs-Screening-Programms, zusätzlich eine TRUS möglich

2. *Prostate biopsy and subsequent Gleason score classification*

(2) definitive Diagnose mittels Prostatabiopsie, nachfolgend Gleason Grad Klassifizierung → Information über Aggressivität des Tumors

The definitive diagnosis of prostate cancer is based on the histology of tissue obtained on in-office transrectal ultrasound-guided prostate biopsy, during which ten to twelve biopsy cores are taken [6, 31]. A biopsy may show prostate cancer or 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 gives information about the tumour aggressiveness [5, 22, 30]. Five tumour categories based upon the primary and secondary Gleason pattern can be distinguished (see Table 4-1), where a higher histologic grade group indicates a greater likelihood of having a non-organ-confined disease and worse outcomes after treatment of localised disease [6, 27, 30].

in manchen Fällen erneute Biopsien angeordnet

In some cases, a repeat biopsy may be indicated, for instance, in situations where PSA concentration increases further or if findings on DRE or prostate warrant a re-biopsy [5].

3. *Additional diagnostic tools*

(3) zusätzliche diagnostische Instrumente (z. B. MRI) häufig zur Bestätigung einer Niedrig-Risiko-Erkrankung

If lymph node involvement and/or distant metastasis are expected, additional MRI, Computer Tomography (CT) or skeletal scintigraphy are applied. However, imaging for distant disease is not routinely recommended for very low- and low-risk prostate cancer. Nevertheless, an MRI of the prostate is often obtained in men with low- and very low-risk disease to ensure that high-grade disease has not been overlooked [22, 30].

Modelle zur Schätzung des Risikos eines Rezidivs & dem Prostatakrebs-spezifischen Überleben

Models that can be used additionally to predict individualised estimates of biochemical (PSA-only) recurrence and prostate cancer-specific survival are increasingly being developed and validated. One example is the PREDICT Prostate model, an individualised, web-based prognostic tool for men with newly diagnosed non-metastatic prostate cancer that estimates the likelihood of survival at ten and 15 years post-diagnosis [30].

4. *Clinical staging of the tumour*

(4) klinische Stadien (Tumor [T], regionale Lymphknoten [N] und Metastasen [M]) abhängig von Diagnose-untersuchungen

Generally, the clinical staging of the tumour provides the basis for the decisions regarding the extent of evaluation and treatment options. It is based on the results of the DRE, the biopsy findings (including Gleason scores), and imaging studies (if necessary), and involves the staging of the tumour (T), regional lymph nodes (N) and the distant metastasis (M) (see Table 4-1) [6, 27].

Unter/Überschätzung der Tumoraggressivität möglich – Schwankungen in Resultaten berücksichtigen

However, the different evaluations may significantly under- or overestimate the extent and/or aggressiveness of the disease. Therefore, factors that need to be considered when relying upon clinical staging include the variability in the interpretation of findings on DRE, the variability in assessing a Gleason grade on the biopsy, and sampling errors in the prostate biopsy that may lead to missing areas with Gleason 4 or 5 disease [30].

5. *Prostate cancer risk stratification*

(5) TNM-Risiko-stratifizierung anhand von PSA-Level, Gleason Score, TNM-Stadium; Ausmaß der Prostatabeteiligung, & des genomischen Profils Basis für ...

According to the TNM staging system of the American Joint Committee on Cancer (AJCC) (see Table 4-1),

- the baseline PSA concentration,
- the histologic grade groups (Gleason score),
- the TNM stating of the disease,
- the extent of prostate involvement,
- and, in some cases, the molecular characteristics (genomic profile) of the tumour [30]

are used to categorise patients into prognostic stage groups, which are, according to international guidelines, associated with different risk levels, ranging from low- to high-risk prostate cancer (see Table 4-1) [6, 27, 30].

... Unterteilung in Niedrig- bis Hoch-Risiko-Prostatakrebs

Table 4-1: Prostate cancer staging [6, 26, 27, 32, 33]

Clinical stage (cT)		
T category	**T criteria**	
TX	Primary tumour cannot be assessed.	
TO	No evidence of primary tumour	
T1	Clinically inapparent tumour that is not palpable	
T1a	Tumour incidental histologic finding in 5% or less of tissue resected	
T1b	Tumour incidental histologic finding in more than 5% of tissue resected	
T1c	Tumour identified by needle biopsy found in one or both sides, but not palpable	
T2	Tumour is palpable and confined within prostate.	
T2a	Tumour involves one-half of one side or less.	
T2b	Tumour involves more than one-half of one side but not both sides.	
T2c	Tumour involves both sides.	
T3	Extraprostatic tumour that is not fixed or does not invade adjacent structures	
T3a	Extraprostatic extension (unilateral or bilateral)	
T3b	Tumour invades seminal vesicle(s).	
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles such as external sphincter, rectum, bladder, levator muscles, and/or pelvic wall.	
Regional lymph nodes (N)		
N category	**N criteria**	
NX	Regional nodes were not assessed.	
No	No positive regional nodes	
N1	Metastases in regional node(s)	
Distant metastasis (M)		
M category	**M criteria**	
Mo	No distant metastasis	
M1	Distant metastasis	
M1a	Non-regional lymph node(s)	
M1b	Bone(s)	
M1c	Other site(s) with or without bone disease	
PSA		
PSA values		
<10		
≥10 <20		
<20		
≥20		
Histologic grade group		
Grade group	**Gleason score**	**Gleason pattern**
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, or 5+5

Abbreviations: ***PSA*** *– Prostate-specific antigen,* ***TNM*** *– Tumour, Node, Metastasis,* ***UICC*** *– Union for International Cancer Control*

Table 4-2: Prostate cancer risk stratification [6, 26]

Risk	Tumour category		Gleason score		PSA concentration
low	**T1-T2a**	**and**	**≤6**	**and**	**≤10 ng/mL**
intermediate	T2b	or	7	or	>10-20 ng/mL
high	T2c-T4	or	8-10	or	>20 ng/mL

Abbreviations: PSA *– Prostate-specific antigen*

Definition von Niedrig-Risiko-Prostatakrebs

As illustrated in Table 4-2, localised low-risk prostate cancer includes a tumour category between T1-T2a, a Gleason score of maximum 6 and a PSA concentration ≤10 ng/mL.

A0025 – How is localised low-risk prostate cancer currently managed according to published guidelines and in practice?

Kriterien für Therapieauswahl: diagnostische Parameter, Krankheitsgeschichte(n) Lebenserwartung, Komorbiditäten, Präferenzen des Patienten

According to the German AWMF S3 guideline for the diagnosis and treatment of prostate cancer, the actual selection of the treatment depends on the following factors [6]:

- biopsy results and Gleason grading,
- clinical staging (TNM),
- history of cancer of the patient and his family,
- age and life expectancy,
- present comorbidities,
- preferences and expectations of QoL.

kurative radikale vs. nicht-invasive Therapien

In general, a distinction between radical, curative therapies with the aim of healing and non-radical therapies can be made [5]:

Curative radical treatment options

2 radikale Therapien:

Radical prostatectomy

Prostatektomie: vollständige Entfernung der Prostata mit Ziel der Heilung

During a prostatectomy, the prostate gland is completely removed through surgery to heal from cancer. There are three access routes: (1) the perineal prostatectomy via a skin incision at the perineum, (2) the retropubic prostatectomy via an incision in the lower abdomen, and (3) the minimally invasive transabdominal prostatectomy via a small incision in the abdominal wall. Out of the three options, the latter two are the most often performed access routes [6, 22]. However, independent of the access route, radical prostatectomy is associated with severe adverse events, e.g., incontinence, impotence, bleeding requiring treatment, or injury to the rectum [6]. Therefore, it is only in place if the goal is the eradication of prostate cancer, while, whenever possible, preserving continence and potency is important [29]. Therefore, younger and/or healthier men (e.g., with a life expectancy of at least ten years) seem to be more likely to experience cancer control benefits from prostatectomy than older men with comorbidities [22, 31].

Prostatektomie mit schwerwiegenden NW verbunden

Erwägung lediglich bei Patienten mit Lebenserwartung von ≥10 Jahren sinnvoll

Radiation therapy

Another radical treatment possibility with curative intention is radiation therapy. It involves directing high-energy radiation at the tumour tissue. The cell nuclei are damaged, causing the cancer cells to no longer divide and die. There is a distinction between external radiation therapy and brachytherapy. The advantage of external radiation therapy is that no surgery is needed. Similar to radical prostatectomy, radiation therapy can result in acute adverse events such as intestinal and bladder problems, and/or in long-term adverse events like impotence, incontinence, or intestinal problems [6].

Bestrahlung: Zerstörung des Tumorgewebes mit hochenergetischen Strahlen

Bestrahlung mit ähnlichen NW assoziiert wie Prostatektomie

Non-radical or palliative treatment options

Besides radical treatment options, there are non-radical (symptomatic) and palliative treatment options without curative intention, but to prevent significant adverse events of the curative treatments, as well as reducing symptoms and increasing QoL.

nicht-radikale & palliative Therapieoptionen:

Focal therapies

There are non-radical therapies which aim to destroy small tumours inside the prostate while leaving the remaining gland intact and sparing most of its normal tissue (focal therapies). These therapies thereby aspire to be a compromise with curative potential, but with milder side-effects compared to radical options. Examples are high-intensity focused ultrasound (HIFU) therapy, hyperthermia (heating of the tumour cells), cryotherapy (freezing of the tumour cells), and laser-induced thermotherapy (LITT) [6, 22, 23], although some of them are not supported by good evidence [34].

fokale Therapien mit Ziel lediglich Tumorgewebe zu zerstören: HIFU, Hyperthermie, Kryotherapie, LITT

Active surveillance

AS includes a PSA testing, as well as DRE every three months during the first two years. If the PSA concentration is constant, the screening can be expanded to half a year. After the first six months, a biopsy should be additionally performed, following every twelve to eighteen months for the next three years [6]. The aim, thereby, is to withhold definitive treatment unless there is evidence of disease progression or the development of symptoms.

aktive Überwachung mit Ziel radikale Eingriffe hinauszuzögern

This therapy option is generally recommended for patients with (very) low-risk prostate cancer without a very long life expectancy, since these are the only patients who will not miss their chance to be cured and, more importantly, are not endangered to die from prostate cancer (see Table 4-3) [35].

empfohlen bei Niedrig-Risiko-Prostatakrebs

Table 4-3: Disease criteria for active surveillance [6, 22, 30]

Tumour criteria	Value
PSA	≤10 ng/mL
Gleason score	≤6
Tumour category	Up to T2a
Number of affected tissue samples	Maximum of 2 out of 10-12 samples
Proportion of tumour tissue per sample	Maximum of 50%

Abbreviation: PSA *– Prostate-specific antigen*

Watchful Waiting

"beobachtetes Abwarten": symptomatische Behandlung von Symptomen, speziell für komorbide Patienten mit eingeschränkter Lebenserwartung

Watchful waiting includes the administration of systemic or local treatment to palliate symptoms if disease progresses locally or at distant metastatic sites. Therefore, it is based on the premise that men will not benefit from radical treatments because of comorbidities and/or the prolonged natural history of prostate cancer [31]. In comparison to AS, watchful waiting does not require regular testing but involves treating symptoms if they appear [6].

Hormonal traction treatment

palliative Hormontherapie: Reduktion des Testosteronlevels

Another palliative treatment option is the reduction of the testosterone level either by medication or surgery. It slows the growth and division of prostate cancer cells and consequently can prevent the progression of the disease [6].

Follow-up examinations after radical therapy

Follow-up: PSA-Tests spätestens nach 12 Wochen, abnormaler PSA-Wert → digitale rektale Untersuchung, PET Scan oder Biopsieentnahme, etc.

Post-treatment follow-up of prostate cancer survivors is important, starting at a maximum twelve weeks after the last treatment. According to the German AWMF S3 guideline [6], during the first two years after the last treatment, PSA concentration is tested every three months, then every six months during the third and fourth year. As of the fifth year after treatment, PSA testing is recommended yearly. DRE is only recommended if PSA concentration is not constant over time [6]. Besides, the evaluation of a patient with an abnormal PSA may include a nuclear medicine bone scan, a positron emission tomography (PET) scan using prostate-specific tracers, a biopsy of the prostate bed, a PSA kinetic assessment (an indicator of disease aggressiveness), and/or a cross-section imaging. A PSA concentration is defined as abnormal according to the following criteria [6, 31]:

abnormaler PSA-Wert:

Wert von >0.2 ng/mL nach Prostatektomie

- For patients treated by radical prostatectomy, any PSA concentration >0.2 ng/mL is abnormal and raises concern for recurrent or progressive prostate cancer.

steigender Wert >2 ng/mL vom Ausgangswert nach Strahlentherapie

- For patients who underwent radiation therapy and who previously had a low PSA concentration (usually <1.0 ng/mL), a rising PSA concentration, particularly >2 ng/mL from the nadir, indicates disease recurrence.

Target population

A0007 – What is the target population in this assessment?

A0023 – How many people belong to the target population?

Zielpopulation: Patienten mit lokalisiertem Niedrig-Risiko-Prostatakrebs …

The target population of this assessment are localised low-risk prostate cancer patients older than 18 years with the following criteria [6, 21, 30, 36, 37]:

- Prostate cancer stage T1-T2a,
- Gleason score ≤6,
- PSA concentration ≤10 ng/mL,
- three histological positive cancer cores with a maximum length of the tumour centre of 5 mm of each cancer core OR one to two histological positive cancer cores with ≥50.0% evidence of cancer in each cancer core OR a PSA-density of ≥0.15 ng/mL/cm³,
- and life expectancy of ≥10 years.

… machen 57,4% aller Patienten mit Prostatakrebs in Ö aus

In 2016, 5,245 men were diagnosed with prostate cancer in Austria. Between 2014 and 2016, on average, 57.4% were diagnosed with localised prostate cancer [3].

A0011 – How much is VTP therapy with Tookad® Soluble utilised?

At the time of conducting this assessment, VTP therapy with Tookad® Soluble is not reimbursed and therefore not applied in Austria [information from the manufacturer]. However, the submitting hospital estimated eight cases per year being treated with VTP therapy with Tookad® Soluble at the hospital and 30 cases per year across all Austrian hospitals [information from the submitting hospital].

Padeliporfin in Ö aktuell nicht erstattet; geschätzte zukünftige Anzahl pro Jahr: 8 Fälle/ Krankenhaus bzw. 30 Fälle in ganz Ö

5 Clinical effectiveness

5.1 Outcomes

entscheidungsrelevante Endpunkte für die Wirksamkeit

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

- Overall survival (OS)
- Prostate cancer-specific survival
- QoL

Surrogatendpunkte

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

- Disease progression
- Time to progression
- Recurrence-free survival
- Metastatic-free survival
- Radical therapy conversion
- Further oncological results

Endpunkte repräsentieren Ziele der Intervention

The selected outcomes represent the aims of a VTP therapy with Tookad® Soluble for localised low-risk prostate cancer: destroying cancer cells with a relatively non-invasive procedure, thereby maintaining QoL, while achieving similar oncological efficacy as with radical therapy, and preventing from side effects of radical therapy options.

Definitionen der entscheidungs-relevanten Endpunkte: Gesamtüberleben (OS), krebsspezifisches Überleben, Lebensqualität (QoL)

Concerning the *crucial* outcomes, the outcome **OS** refers to the survival rate of patients who did not die from any cause between the start of randomisation and the end of follow-up. Similarly, the outcome **prostate cancer-specific survival** includes the survival rate of patients who did not die due to prostate cancer between the start of randomisation and the end of follow-up. For the outcome **QoL** that measures aspects of an individual's sense of well-being and ability to carry out activities of daily living, two questionnaires were included: the European Quality of Life 5 Dimensions (EQ-5D) and the International Prostate Symptom Score (IPSS), which contains a separate sub-score for QoL.

Definitionen für Surrogatendpunkte: Krankheitsprogression, Progressionszeit, rezidivfreies Überleben, Metastasen-freies Überleben, Rate an radikalen Therapien, weitere onkologische Resultate

With respect to *surrogate* outcomes, the outcome **disease progression** refers to progression from low-risk prostate cancer (*clinical staging T1-T2a & Gleason score ≤6 & PSA concentration ≤10 ng/mL*) to intermediate- or high-risk prostate cancer (see Table 4-2). The outcome **time to progression** presents the median time in months until disease progression. Moreover, the outcome **recurrence-free survival** refers to the proportion of patients with a negative biopsy result at the end of follow-up. The outcome **metastatic-free survival** indicates the absence of any metastases measured by PET, CT, MRI or SPECT at the end of follow-up. Furthermore, the outcome **radical therapy conversion** includes all patients who needed radical therapies after the intervention. The last surrogate outcome, **further oncological results**, includes changes in PSA concentration between baseline and follow-up, as well as the number of patients with positive biopsy results and a Gleason score ≤6.

5.2 Included studies

1 RCT (413 Patienten) inkludiert für Wirksamkeitsanalyse zu VTP-Therapie mit Padeliporfin im Vergleich zur aktiven Beobachtung, Follow-up von 24-48 Monate

For evaluating clinical effectiveness outcomes, we exclusively considered RCTs and prospective non-randomised controlled trials (N-RCTs). The only study that met our inclusion criteria (see Table 1-1) was one RCT [14, 15], with a total of 413 patients, assessing the clinical effectiveness of VTP therapy with Tookad® Soluble (n=206), compared to AS (AS, n=207) and a follow-up of 24 months. Out of the 413 patients, 320 of them had unilateral disease and 93 were diagnosed with bilateral disease. In a second publication [15] the follow-up (48 months) of the pivotal RCT [14] is presented. Overall, 266 out of the 413 patients were followed up four or more years [15].

keine Evidenz mit radikaler Therapie als Kontrollgruppe

No evidence could be identified comparing VTP therapy with Tookad® Soluble to radical therapy options, e.g., radical prostatectomy or radiation therapy.

Study characteristics

1 Hersteller (Steba Biotech) bietet VTP-Therapie Padeliporfin an

Currently, there is one manufacturer on the market (Steba Biotech) offering the intervention under consideration: VTP therapy with 4 mg/kg Tookad® Soluble (active substance: padeliporfin). On average, 13 fibres were used during the procedure. The total fibre length ranged from 155 to 910 mm. 97.0% of the patients undergoing VTP therapy with Tookad® Soluble also received the intervention with an LDI ≥1.

RCT in 10 europäischen Ländern durchgeführt

The RCT [14, 15] was conducted in different clinical centres across ten countries (Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom).

Patient characteristics

Einschlusskriterien: Alter ab 18 Jahre, klinisches Stadium ≤T2a, PSA ≤10 ng/mL, Lebenserwartung ≥10 Jahre, etc.

The patients in the RCT [14, 15] were eligible if they were older than 18 years and had localised low-risk prostate cancer. The identified patients had a clinical stage of up to T2a (pathological or radiological of up to T2c), one positive core with a Gleason score of maximum 3 and a length of minimum 3 mm but maximum 5 mm, or two to three positive cores with a Gleason score of maximum 3, a length of maximum 5 mm, a PSA concentration of ≤10 ng/mL, and a prostate volume of at least 25 cm^3 but not more than 70 cm^3. All patients were expected to live at least ten additional years.

Patienten: Ø 64,2 vs. 62,9 Jahre alt, 86 % vs. 87 % Stadium T1c, Diagnose vor 6,3 vs. 6,0 Monaten getroffen

The mean age of the patients was 64.2 years in the VTP treatment group and 62.9 years in the AS group [14, 15]. The majority of the patients had a clinical stage of T1c (86.0% in the VTP treatment group, 87.0% in the AS group). The mean PSA concentration ranged from 0.1-10.0 in the VTP treatment group and 0.5-10.0 in the AS group. Patients were diagnosed on average 6.3 months previously in the VTP treatment group or 6.0 months in the AS group.

Ausschlusskriterien

In the RCT [14, 15], very low-risk prostate cancer, contraindications to MRI or general anaesthesia were defined as exclusion criteria.

Extraktionstabellen im Anhang

Detailed study and patient characteristics, as well as study results, are displayed in Table A-1 and in the evidence profile in Table A-5.

5.3 Results

Since there was no evidence comparing VTP therapy with Tookad® Soluble to radical therapies, the subsequently presented results are exclusively in comparison to AS.

Wirksamkeit von VTP-Therapie mit Padeliporfin im Vergleich zur aktiven Beobachtung

Mortality

D0001 – What is the expected beneficial effect of VTP therapy with Tookad® Soluble on mortality (part I)?

The basis for this research question was the outcomes "overall survival" and "prostate cancer-specific survival".

The RCT reported prostate cancer-specific survival in 100.0% of the patients in the VTP treatment group and the AS group after 24 and 48 months [14, 15]. An overall survival rate of 98.0% versus 99.0% in the VTP treatment group and the AS group, respectively, was presented after 48 months [15]. For both outcomes, it remained unclear whether the results were statistically significant or not.

Prostatakrebs-spezifisches Überleben 100 % vs. 100 % nach 24 und 48 Monaten
Gesamtüberleben: 98 % vs. 99 % nach 48 Monaten

Morbidity

D0005 – How does VTP therapy with Tookad® Soluble affect symptoms and findings (severity, frequency) of localised low-risk prostate cancer?

Answering this research question was based on the outcome "further oncological results", which includes PSA concentration, the Gleason score and biopsy results.

Beantwortung anhand Endpunkt „weitere onkologische Resultate"

The RCT reported a mean PSA concentration change of -3.08 ng/mL (SD 3.05) in the VTP treatment group and of -0.68 ng/mL (SD 4.10) in the AS group from baseline to month 24 [14]. The study did not mention whether the change was statistically significant between the two groups.

PSA-Veränderung nach 24 Monaten: -3,08 ng/mL vs. -0,68 ng/mL

The follow-up publication [15] stated that 33 patients in the VTP treatment group (16.0%) compared to 84 patients in the AS group (41.0%) (95% CI -33 – -16) obtained a Gleason score of >6 after 24 months – concerning the whole gland. Regarding the "in field"[4] gland, 21 patients (10.0%) versus 70 patients (34.0%) (95% CI -31 – -16) had a Gleason score of >6 at month 24. Both differences in Gleason scores between the study groups – for the whole gland and the "in field" gland – were statistically significant (p<0.001).

Gleason Score >6 nach 24 Monaten: 16 % vs. 41 % (gesamte Prostata); 10 % vs. 34 % („in field" Prostata) → statistisch signifikante Unterschiede

The follow-up publication [15] also stated that 39 patients in the VTP treatment group (19.0%) and 25 patients in the AS group (12.0%) (95% CI 0-14) had a positive biopsy result after 24 months when considering the whole gland. However, this difference was not statistically significant (p=0.054). Considering the "in field" gland, 51 patients in the VTP treatment group (25.0%) compared to 134 patients in the AS group (65.0%) (95% CI -49 – -31) had a positive biopsy result after 24 months. This difference was statistically significant (p<0.001).

positive Biopsien nach 24 Monaten: 25 % vs. 65 % („in field" Prostata) → Unterschied statistisch signifikant

[4] "In field" is defined as in the VTP-treated lobe or, for AS, in the lobe containing the largest index cancer.

D0006 – How does VTP therapy with Tookad® Soluble affect progression (or recurrence) of localised low-risk prostate cancer?

Beantwortung anhand von 5 Endpunkten:

The answer to this research question was based on the outcomes "disease progression", "time to progression", "recurrence-free survival", "metastatic-free survival" and "radical therapy conversion".

Progression nach 24 Monaten: RCT: 28 % vs. 58 % Follow-up: statistisch signifikant niedrigere Progressionsrate in der VTP-Gruppe

The RCT and its follow-up [14, 15] reported disease progression, defined as the progression from low-risk to intermediate- or high-risk prostate cancer. In the RCT [14], the disease of 58 patients (28.0%) in the VTP treatment group had progressed after 24 months, compared to 120 patients (58.0%) in the AS group. This difference was statistically significant (HR 0.34, 95% CI 0.24-0.46, $p<0.0001$). The follow-up publication [15] stated a statistically significant lower progression rate in the VTP treatment group compared to the AS group at month 24, irrespective of whether the whole gland (HR 0.35, 95% CI 0.25-0.48, $p=0.001$) or the "in field" gland (HR 0.21, 95% CI 0.14-0.31, $p<0.001$) was considered.

Zeit bis zur Progression: 28,3 vs. 14,1 Monate → Unterschied statistisch signifikant

The RCT [14] reported on time to progression and stated median time to progression of 28.3 months (95% 26.0-30.6) in the VTP treatment group compared to a median of 14.1 months (95% CI 12.9-23.8) in the AS group. The difference in time to progression was statistically significant between the two study groups ($p<0.0001$).

ohne Rezidiv nach 24 Monaten: 49 %/50 % vs. 14 % → statistisch signifikante Unterschiede

Both RCT publications [14, 15] also reported the number of patients who were free of recurrences – defined as negative biopsy results – after 24 months. In the RCT [14], 101 patients (49.0%) and, in the follow-up publication [15], 104 patients (50.0%) of the VTP treatment group had a negative biopsy result at month 24. In contrast, in the AS group, 28 patients (14.0%) in the RCT [15] and 30 patients (14.0%) in the follow-up publication were recurrence-free. In both publications, the differences in recurrence-free survival were statistically significant between the two study groups ($p<0.0001$ [14], $p<0.001$ [15]).

Metastasen-freies Überleben nach 48 Monaten: 99 % vs. 99 %

Metastatic-free survival was also reported in the two RCT publications [14, 15]. After 24 months [14], 100.0% of the patients in each study group were free from metastasis. After 48 months [15], 99.0% of the patients in both study groups were metastatic-free.

Rate zu radikalen Therapien: 5,8 % vs. 29 % nach 24 Monaten, niedrigere Rate in der Interventionsgruppe nach 24 & 48 Monaten → Unterschied statistisch signifikant

The two RCT publications [14, 15] likewise reported on the outcome "radical therapy conversion". In the RCT [14], 12 patients in the VTP treatment group (5.8%) switched to a radical therapy within 24 months, compared to 60 patients in the AS group (29.0%), making the difference statistically significant ($p<0.0001$). In the follow-up publication [15], the rates of conversion to radical therapy after 24 months and 48 months were lower in the VTP treatment group (7.0% vs. 32.0%; 24.0% vs. 53.0%, HR 0.31, 95% CI 0.21-0.46) compared to the control group. The difference between the two study groups was statistically significant at 48 months ($p<0.001$).

Function

D0011 – What is the effect of VTP therapy with Tookad® Soluble on patients' body functions?

D0016 – How does the use of VTP therapy with Tookad® Soluble affect activities of daily living?

These research questions are answered in the chapter on safety (see Chapter 6.3).

siehe Kapitel 6.3 Sicherheit

Health-related quality of life

D0012 – What is the effect of VTP therapy with Tookad® Soluble on generic health-related quality of life?

D0013 – What is the effect of VTP therapy with Tookad® Soluble on disease-specific quality of life?

The RCT [14] reported on QoL. The effect on QoL was measured using the EQ-5D questionnaire, which resulted in no statistically significant difference between the two study groups after 24 months (p=0.64).

Lebensqualität: kein signifikanter Unterschied nach 24 Monaten

Patient satisfaction

D0017 – Was the use of VTP therapy with Tookad® Soluble worthwhile?

No evidence was available to answer this research question.

keine Evidenz verfügbar

6 Safety

6.1 Outcomes

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

entscheidungsrelevante Endpunkte für die Sicherheit

- Study-related death
- Prostate cancer-related death
- Severe adverse events (grade 3-4 or Clavien IV-V adverse events)

Additional outcomes were *not* considered as *crucial* to derive a recommendation, but were important due to the low-risk cancer profile in the scope of this assessment:

weitere berücksichtigte Sicherheitsendpunkte

- Mild to moderate adverse events (grade 1-2 or Clavien I-III adverse events)
- International Prostate Symptom Score (IPSS)
- The International Index of Erectile Function Questionnaire (IIEF)
- Discontinuation rate

entscheidungs-relevanten Endpunkte: studienbezogener Tod, Prostatakrebs-bezogener Tod, schwerwiegende NW

Concerning the *crucial* outcomes, the outcome **study-related death** refers to all deaths that have occurred due to the treatment of the study (VTP therapy with Tookad® Soluble), while the outcome **prostate cancer-related death** includes all deaths due to prostate cancer. The crucial outcome **severe adverse events** involves severe or medically significant adverse events with hospitalisation indicated, as well as life-threatening or disabling adverse events with an urgent indication.

weitere wichtige Sicherheitsendpunkte: mild bis moderate NW, IPSS Fragebogen, IIEF Fragebogen, Abbruchrate

Concerning the additional important outcomes, the outcome **mild to moderate adverse events** includes mild adverse events with no intervention indicated, as well as moderate adverse events with local or non-invasive intervention indicated. The outcome **IPSS** represents a questionnaire for urinary symptoms such as incomplete emptying, frequency, urgency and weak stream. Lower IPSS-scores indicate a reduction in these symptoms. In a recent study, the minimal important difference (MID) for the IPSS was 5.2 points (95% CI 3.9 to 6.4; SEM 3.6) [38]. The outcome **IIEF** represents a questionnaire for erectile function. Thereby, higher IIEF scores indicate a greater degree of erectile function. Studies showed that the minimal clinically important difference (MCID) for the IIEF was four points [39, 40]. Furthermore, the outcome **discontinuation rate** refers to the rate at which clinicians or patients themselves discontinued the treatment.

6.2 Included studies

RCTs, N-RCTs und Beobachtungsstudien für Sicherheit

For evaluating safety-related outcomes, we considered RCTs, prospective N-RCTs and prospective observational studies with more than 50 included patients (see Table 1-1).

keine Evidenz mit radikaler Therapie als Kontrollgruppe

No evidence could be identified comparing VTP therapy with Tookad® Soluble to radical therapy options such as radical prostatectomy or radiation therapy.

selber RCT wie für Wirksamkeit, follow-up Studie + 1 zusätzliche einarmige Studie für Sicherheitsanalyse eingeschlossen

The only studies meeting the pre-defined inclusion criteria (Table 1-1) were the same two publications on the pivotal RCT already included for efficacy [14, 15], comparing VTP therapy with Tookad® Soluble to AS (study and patient characteristics are already described in Chapter 5.2) and one additional prospective single-arm study [16] involving two-phase II, multicentre, open-label, multiple-arm, single IV dose studies.

einarmige Studie mit 68 Patienten, jedoch 16 Patienten lost-to follow-up nach 42 Monaten

This single-arm study [16] assessed the clinical effectiveness and safety of VTP therapy with Tookad® Soluble in a total of 68 patients. The follow-up of the study ranged from six[5] (=baseline) to 42 months. Over the 42 months, 16 out of the 68 patients were lost to follow-up.

Study characteristics

1 Hersteller (Steba Biotech) vertritt VTP-Therapie Padeliporfin

Currently, there is one manufacturer on the market (Steba Biotech) offering the intervention under consideration: VTP therapy with 4 mg/kg Tookad® Soluble (active substance: padeliporfin). In the single-arm study [16], the procedure was conducted with a mean LDI of 1.45 (SD 0.35).

einarmige Studie in 2 europäischen Ländern durchgeführt

The study [16] was assessed in clinical centres in France and Germany.

Patient characteristics

Einschlusskriterien: klinisches Stadium ≤T2a, Gleason score ≤6, PSA ≤10 ng/mL, etc.

In the single-arm study [16], patients older than 18 years with localised low-risk prostate cancer were included. The identified patients had a clinical stage of up to T2a, a Gleason grade group limited to the Gleason pattern 3 + 3 (Gleason score ≤6), and a maximum PSA concentration of 10 ng/mL.

Patienten: Ø 62,6 Jahre alt, Ø PSA-Level: 5,97 ng/mL

At baseline, the mean age of the patients in the study [16] was 62.6 years (SD 5.6), the majority of the patients had a Gleason score 6, and the mean PSA concentration was 5.97 ng/mL (SD 5.70). Out of the 68 patients, 55 of them (81.0%) had unilateral disease and 13 (19.0%) had bilateral disease. No exclusion criteria were reported in the study.

Extraktionstabellen im Anhang

Study and patient characteristics, as well as results of included studies, are displayed in Table A-2 and in the evidence profile in Table A-5.

[5] The first evaluation period of the presented follow-up study (= baseline) correlates with the endpoints of the clinical phase II studies (PMC201 [NCT00707356], PMC203 [NCT-00975429]) at month six.

6.3 Results

As no evidence could be identified comparing VTP therapy with Tookad® Soluble to radical therapy options, the safety results are only presented for VTP therapy with Tookad® Soluble alone or compared to AS.

Sicherheit von VTP-Therapie mit Padeliporfin verglichen zur aktiven Beobachtung

Patient safety

Cooo8 – How safe is VTP therapy with Tookad® Soluble (in comparison to active surveillance)?

The answer to this research question was based on the following outcomes: "adverse events", "IPSS questionnaire results", "IIEF-15 questionnaire results" and "discontinuation rate".

4 Endpunkte zur Beantwortung der Sicherheit

Adverse events were reported in the pivotal RCT [14] and the single-arm study [16]:

NW:

In the RCT [14], a total of 35 grade 3-4 adverse events[6] (17.8%) occurred in the VTP treatment group compared to 12 (5.8%) in the AS group after 24 months. The most frequently observed grade 3-4 adverse[6] events in the VTP treatment group were inguinal hernia (n=4; 2.0%), rectal haemorrhage (n=4; 2.0%), prostatitis (n=3; 1.5%) and urinary retention (n=3; 1.5%). Besides, 383 (197.4%) grade 1-2 adverse events[6] were reported in the VTP treatment group and 94 (45.4%) in the AS group. The most frequently observed grade 1-2 adverse events[6] in the VTP treatment group were erectile dysfunction (n=72; 37.0%), haematuria (n=55; 28.0%), dysuria (n=51; 26.0%), perianal pain (n=29; 15.0%) and urinary retention (n=29; 15.0%). In the study, urinary retention was managed by the replacement of the urethral catheter and the extension of the period of dependent urinary drainage. In the AS group, erectile dysfunction was also the most frequently observed grade 1-2 adverse event (n=21; 10.0%), followed by urinary incontinence (n=9; 4.0%), prostatitis (n=9; 4.0%) and urinary tract infection (n=7; 3.0%). The study did not report whether the differences in adverse events between the study groups were statistically significant or not. The follow-up publication [15] did not report on adverse events.

RCT:
schwerwiegende NW in 17,8 % vs. 5,8 %, milde – moderate NW in 197,4% vs. 45,4%

häufigste moderate – milde NW in VTP-Gruppe:
- Erektionsstörung,
- Hämaturie
- Dysurie, etc.

Follow-up:
keine NW berichtet

In the single-arm study [16], 84 adverse events were reported overall, 64 of them were study-related events. Out of the 64 study-related adverse events no Clavien IV-V adverse events[7], three Clavien III adverse events[7] (lower urinary tract syndrome: n=2; urethral stenosis: n=1), and 61 Clavien I-II adverse events[7] occurred during the follow-up of 42 months. The most frequently reported Clavien I-II adverse events were erectile dysfunction (n=28), lower urinary tract syndrome (n=12) and perianal pain (n=9).

1 einarmige Studie:
insgesamt 64 studien-bezogene NW,
häufigsten NW:
- Erektionsstörung,
- perianale Schmerzen
- etc.

The RCT [14] also reported on the IPSS and the IIEF-15. For the IPSS questionnaire, there were no statistically significant differences in IPSS score changes from baseline to month 24 between the VTP treatment group and the AS group, meaning that there was no difference in urinary symptoms between the two study groups. Likewise, there were no statistically significant differences in IIEF-15 score changes from baseline to month 24 between the two study groups, indicating no difference in the degree of erectile function between them.

RCT: keine Unterschiede in IPSS und IIEF-15 Scores zwischen den Studiengruppen nach 24 Monaten

[6] Common Terminology Criteria for Adverse Events 4.0.

[7] The Clavien–Dindo classification of surgical complications.

RCT: Abbruchrate: 1% vs. <1%

The outcome "discontinuation rate" was only reported in the RCT [14], which stated that two patients (1.0%) in the VTP treatment group and one patient (<1.0%) in the AS group had discontinued from the study at month 24.

C0002 – Are the harms related to dosage or frequency of applying VTP therapy with Tookad® Soluble?

keine Evidenz verfügbar

No evidence was found to answer this research question.

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

Erektionsstörung häufigste NW unabhängig von der follow-up Zeit

Both the pivotal RCT [14] with a follow-up of 24 months and the single-arm study [16] with a follow-up of 42 months reported on adverse events. In these two studies, the most frequently reported adverse event in the VTP treatment group was erectile dysfunction followed by urinary symptoms such as urinary retention or lower urinary tract symptoms, irrespective of the follow-up period. Therefore, based on this evidence, no changes in the frequency of the adverse events could be observed between a follow-up of 24 or 42 months.

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of VTP therapy with Tookad® Soluble?

keine Evidenz verfügbar

No evidence was found to answer this research question.

B0010 – What kind of data/records and/or registry is needed to monitor the use of VTP therapy with Tookad® Soluble and comparator(s)?

keine direkte Evidenz verfügbar

No evidence was available to answer this research question, but it is addressed in the discussion of this systematic review.

C0007 – Are VTP therapy with Tookad® Soluble and comparator(s) associated with user-dependent harms?

keine Evidenz verfügbar

No evidence was available to answer this research question.

Investments and tools required

Mortality

D0001 – What is the expected beneficial effect of VTP therapy with Tookad® Soluble on mortality (part II)?

Beantwortung anhand von 2 Sicherheitsendpunkten

The answer to this research question was based on the two safety outcomes "study-related death" and "prostate cancer-related death".

keine Evidenz zu studienbezogenem Tod

Neither the RCT and its follow-up [14, 15] nor the single-arm study [16] that were considered for the safety analysis reported on the outcome "study-related death".

RCT: kein Krebs-bezogener Todesfall nach 24 Monaten

Only the pivotal RCT [14] reported on the outcome "prostate cancer-specific death" and stated that no prostate cancer-specific deaths occurred within the 24-month follow-up.

D0003 – What is the effect of VTP therapy with Tookad® Soluble on the mortality due to causes other than the target disease?

keine Evidenz verfügbar

No evidence was available to answer this research question.

7 Quality of evidence

The Risk of Bias (RoB) for RCTs was assessed with the Cochrane Collaboration tool version 1.0 for assessing the risk of bias of randomised controlled studies [12]; the RoB of observational studies was assessed with the International Health Economics (IHE) checklist [11]. The RoB assessments are presented in Table A-3 and Table A-4 in the Appendix.

RoB der RCTs: Cochrane Collaboration Tool, RoB der Beobachtungsstudie: IHE-Checkliste

The pivotal RCT with a follow-up of 24 months [14] was graded with a low RoB, while the four-year follow-up [15] was graded with a high RoB. The main reason for downgrading the follow-up study was selective outcome reporting (QoL and safety data were not reported for the follow-up of 48 months).

RCT: niedriger RoB
Follow-up: hoher RoB

The single-arm study with a follow-up of 42 months [15] was graded with a high RoB. The main reasons for downgrading were that it was unclear whether the patients entered the study at a similar point of time during their disease, outcomes were not measured before and after treatment[8], as well as the unclear reported number of losses to follow-up.

einarmige Studie mit hohem RoB

The strength of evidence was rated according to the GRADE scheme [13] for each endpoint individually. Each study was rated by two independent researchers (SW, NG). In case of any disagreement, a third researcher was involved to solve the difference. A more detailed list of the applied criteria can be found in the recommendations of the GRADE Working Group [13].

Qualität der Evidenz nach GRADE

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.

4 Kategorien für die Bewertung der Evidenzqualität:
- hoch
- moderat
- niedrig
- sehr niedrig

The research question ranking according to the GRADE scheme can be found in the summary of findings table below and in the evidence profile in the Appendix Table A-5.

GRADE Tabelle nächste Seite & Anhang

The outcome "disease progression" was graded separately, as it was reported differently in the two included RCTs. Furthermore, the outcome "radical therapy conversion" was also graded separately, since the outcome was reported for two different follow-up periods (24 months [14] and 48 months [15]).

2 Endpunkte separat pro Studie gegraded

According to the GRADE scheme, only the outcomes defined as critical (see Table 9-1) were considered for the overall strength of evidence. In addition, the overall strength of evidence is generally based on the outcome with the lowest level of evidence. Therefore, the overall strength of evidence for the effectiveness and safety of VTP therapy with Tookad® Soluble in comparison to AS is *low* and *moderate*, respectively.

niedrige Evidenzstärke für Wirksamkeit & moderat für Sicherheit

[8] The first evaluation period of the presented follow-up study correlates with the endpoints of the clinical phase II studies (PMC201 [NCT00707356], PMC203 [NCT00975429]) at month six.

wichtige Endpunkte zusätzlich gegraded

Moreover, the outcomes considered as important (see Table 9-1) were also graded; however, according to the GRADE scheme, these assessments were not taken into account for the overall strengths of evidence.

keine Evidenz zu VTP-Therapie vs. radikaler Therapie

For the comparison of VTP therapy with Tookad® Soluble to radical therapy options such as radical prostatectomy or radiation therapy, no evidence was available.

Table 7-1: Summary of findings table of vascular-targeted photodynamic therapy with Tookad® Soluble in localised low-risk prostate cancer [13]

Outcome	Anticipated absolute effects* (95% CI)			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments	Importance
	Risk with AS	Risk with VTP therapy with Tookad® Soluble	Difference					
Efficacy								
OS assessed with: number of patients with event (%) follow-up: median 48 months	144/147 (98.0%) vs. 118/119 (99.0%)				266 (FU) [a]	⊕⊕⊕◯ **MODERATE** [b, c]	-	**Critical**
Prostate cancer-specific survival assessed with: number of patients with event (%) follow-up: range 24-48 months	At month 24: 206/206 (100.0%) vs. 207/207 (100.0%) At month 48: 147/147 (100.0%) vs. 119/119 (100.0%)				413 (RCT & FU) [d]	⊕⊕⊕◯ **MODERATE** [b, e]	-	**Critical**
QoL assessed with: EQ-5D questionnaire follow-up: median 24 months	There was no difference in EQ-5D scores between VTP therapy vs. AS at month 24 (p=0.64).				413 (RCT) [f]	⊕⊕◯◯ **LOW** [b, c, e, g]	-	**Critical**
Disease progression assessed with: number of patients with event (%) follow-up: median 24 months	58 per 100	20 per 100 (14 to 27)	-	HR 0.34 (0.24 to 0.46)	413 (RCT) [f]	⊕⊕⊕⊕ HIGH [b, c, e, h]	Progression defined as switch from low-risk to intermediate- or high-risk prostate cancer	Important
Disease progression follow-up: median 24 months	Lower whole gland progression rate in the VTP treatment group vs. the AS group: HR 0.35, 95% CI 0.25-0.48, p=0.001. Lower in field progression rate in the treatment group (VTP therapy) vs. control group (AS): HR 0.21, 95% CI 0.14-0.31, p<0.001.				266 (FU) [a]	⊕⊕⊕⊕ HIGH [b, c, h]	Progression defined as switch from low-risk to intermediate or high-risk prostate cancer	Important
Recurrence-free survival assessed with: number of patients with event (%) follow-up: median 24 months	14 per 100	51 per 100 (35 to 75)	-	RR 3.67 (2.53 to 5.33)	413 (RCT) [f, i]	⊕⊕◯◯ LOW [b ,c, e, j]	Negative biopsy results.	Important
Radical therapy conversion assessed with: number of patients with event (%) follow-up: median 24 months	12/206 (5.8%) vs. 60/207 (29.0%) (p<0.0001)				413 (RCT) [f]	⊕⊕⊕◯ MODERATE [b, c, e]	-	Important
Radical therapy conversion assessed with: cumulative % of patients with event at follow-up: median 48 months	24.0% vs. 53.0% (HR 0.31, 95% CI 0.21-0.46, p<0.001)				204 (FU) [a]	⊕⊕⊕◯ MODERATE [b, c]	-	Important

Outcome	Anticipated absolute effects* (95% CI)			Relative effect	Number of	Quality	Comments	Importanc
Safety								
Study-related death **follow-up median 24-48 months**	-	-	-	-	-	-	Not reported	**Critical**
Prostate cancer-related death assessed with: number of patients with event (%) **follow-up: median 24 months**	0/206 (0.0%) vs. 0/207 (0.0%)				413 (RCT) [f]	⨁⨁⨁◯ **MODERATE** [b,c,e]	-	**Critical**
Severe adverse events (grade 3-4) assessed with: number of patients with event (%); **follow-up: median 24 months**	35/197 (17.8%) vs. 12/207 (5.8%)				404 (RCT) [f]	⨁⨁⨁◯ **MODERATE** [b,c,e]	Adverse events that occurred in >1 patient are reported.	**Critical**
Number of Clavien I-III: number of reported adverse events follow-up: range 6-42 months	In total, 64 adverse events related to the study drug, device or procedure (VTP therapy with Tookad® Soluble) were reported over the follow-up period, among which three were of Clavien III and 61 of Clavien I-II.				68 (1 observational study)	⨁◯◯◯ VERY LOW [c, m, n]	-	Important

Abbreviations: ***AS*** *– Active surveillance,* ***CI*** *– Confidence interval,* ***FU*** *– Follow-up,* ***HR*** *– Hazard ratio,* ***OS*** *– Overall survival,* ***QoL*** *– Quality of life,* ***RR*** *– Risk ratio*

* *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

Explanations

[a] *Follow-up study PCM301 FU4.*

[b] *Funded by the manufacturer.*

[c] *Only one study reported this outcome.*

[d] *RCT PCM301 and follow-up study PCM301 FU4.*

[e] *Missing data were not imputed in the study PCM301.*

[f] *RCT PCM301.*

[g] *No significant difference.*

[h] *HR <0.5.*

[i] *Study PCM301 FU4 also reports the same outcome for 24 months; however, with slightly different results.*

[j] *Wide confidence intervals.*

[m] *Relevant outcome measures were not made before and after the intervention.*

[n] *The reported number of loss to follow-up was not comprehensible.*

8 Discussion

To our knowledge, this is the first systematic review analysing VTP therapy with Tookad® Soluble for localised low-risk prostate cancer patients. No other systematic review could be identified in our systematic literature search.

erste Übersichtsarbeit zur VTP-Therapie mit Padeliporfin

For patients with low-risk prostate cancer, in whom the risk of treatment likely outweighs the risks of the disease itself, AS had emerged as a management strategy. However, because AS includes no actual treatment, it can be a cause of anxiety for a patient. VTP therapy with Tookad® Soluble, a tissue-preserving therapy approach, claims to reduce this anxiety [23, 41]. Moreover, it could defer or even avoid radical treatment and, thereby, potentially reduce side-effects while achieving similar oncological efficacy and QoL results as with radical therapies [2, 8]. Therefore, VTP therapy with Tookad® Soluble is deemed to provide a new treatment option between radical therapy (effective but severe adverse events) and AS (safe but potentially psychologically burdensome) [2, 9, 22].

VTP-Therapie als neue Option zwischen radikalen Therapien (mit schwerwiegenden NW) und AS (möglicherweise zusätzlich psychisch belastend)?

Against this background, the present systematic review aimed to investigate whether VTP therapy with Tookad® Soluble in patients with localised low-risk prostate cancer is more effective and safe or equally effective but safer in comparison to standard therapies namely AS, radiation therapy or radical prostatectomy.

Ziel: Bewertung der Wirksamkeit und Sicherheit der VTP-Therapie mit Padeliporfin

Summary and interpretation of the main results

No evidence comparing VTP therapy with Tookad® Soluble to radical therapies (radiation therapy or radical prostatectomy) could be identified.

keine Evidenz mit radikalen Therapien als Komparatoren

After applying the inclusion criteria (see Table 1-1), one RCT comparing the clinical effectiveness and safety of VTP therapy with Tookad® Soluble to AS in localised low-risk prostate cancer patients and a follow-up study [14, 15], as well as one prospective single-arm study assessing the effectiveness and safety of VTP therapy with Tookad® Soluble in the same patient population [16], were included. However, the single-arm study was only considered for safety analysis.

RCT für Wirksamkeits- & Sicherheitsanalyse, einarmige Studie für Sicherheitsanalyse

The RCT [14, 15] was conducted in ten European countries in 47 university centres and community hospitals with a total of 413 patients who were followed-up for 24 months [14]. The four-year follow-up study [15] presents the data from 266 men. The mean age of the patients was 64.2 years.

RCT mit 413 Patienten und Follow-up zw. 24-48 Monaten
Ø Alter: 64,2 Jahre

The single-arm study was conducted in France and Germany, and included a total of 68 patients with a mean age of 62.6 years. The patients were followed-up for 42 months.

einarmige Studie mit 68 Patienten und 42 Monate Follow-up

All three studies were funded by the manufacturer Steba Biotech.

Sponsor = Hersteller

Concerning crucial clinical effectiveness outcomes, the prostate cancer-specific survival rate was 100.0% in the VTP treatment group, as well as in the AS group after 24 and 48 months, while the OS rate was 98.0% versus 99.0% in the VTP treatment group and the AS group, respectively [14, 15].

kein Unterschied: krebsspezifisches Überleben:
100 % vs. 100 %,
Gesamtüberleben:
98 % vs. 99 %

Furthermore, there was no difference in QoL between the two study groups.

kein Lebensqualitäts-unterschied

Krankheitsprogression: 28 % vs. 58 %, längere Progressionszeit in VTP-Gruppe, rezidivfreies Überleben: 49 % vs. 14 %, radikale Therapien in 5,8 % vs. 29 %

Concerning the main surrogate outcomes, 28.0% of the patients in the VTP treatment group versus 58.0% in the AS group had disease progression after 24 months (HR 0.34, 95% CI 0.24-0.46, p<0.0001). The time to progression was longer in the VTP treatment group compared to the AS group (28.3 versus 14.1 months, p<0.0001). Furthermore, 49.0% in the VTP treatment group compared to 14.0% in the AS group (RR 3.67, 95% CI 2.53-5.33, p<0.0001) had a negative biopsy result at month 24, and the intervention reduced the risk of conversion to radical therapy after 24 months (5.8% versus 29.0%, p>0.0001) [14].

relativer Zusatznutzen der VTP-Therapie gegenüber AS, jedoch absoluter Nutzen der VTP-Therapie marginal: z. B. 51% der Patienten mit positiven Biopsien nach 24 Monaten

The reduced disease progression, increased rates of negative biopsies and reduced rates of conversion to radical therapy after 24 months indicate a benefit of the VTP therapy with Tookad® Soluble in comparison to AS for the population of low-risk prostate cancer patients. However, VTP therapy with Tookad® Soluble shows some deficits, as more than half of the patients still have residual cancer (positive biopsies in 51.0%) and nearly one-third of the men (28.0%) progressed within the two-year follow-up [19, 20].

mehr NW durch VTP: die meisten NW als mild eingestuft (z. B. Dysurie, Hämaturie, Erektionsstörung), jedoch auch mehr schwerwiegende NW durch VTP

Concerning the safety analysis, the pivotal RCT [14] showed that the exposure to VTP therapy with Tookad® Soluble resulted in an increased frequency of adverse events. Nearly 80.0% of the patients reported a procedure-related adverse event. However, most of the adverse events were mild (grade 1-2). For example, more than a quarter of men in the VTP treatment group had mild dysuria or haematuria (26.0% and 28.0%, respectively) and 37.0% had mild erectile dysfunction compared to 10.0% in the AS group. Nevertheless, one in three patients had a serious adverse event with VTP therapy compared to one in ten patients in the AS group. The most frequently observed grade 3-4 adverse events in the VTP treatment group were inguinal hernia (2.0%), rectal haemorrhage (2.0%), prostatitis (1.5%) and urinary retention (1.5%). In the follow-up study [15], no safety data were reported.

Follow-up keine NW berichtet

keine Unterschiede in Symptomen im Harnbereich bzw. der Erektionsfunktion

The RCT [14] also reported that there was no difference in urinary symptoms and/or erectile function between VTP therapy with Tookad® Soluble and AS after 24 months (no differences in IPSS/IIEF-15 score change from baseline to 24 months between study groups).

ähnliche Ergebnisse in der einarmigen Studie: rezidivfreies Überleben: 63,2 % (nach 6 Monaten) vs. 49 % (nach 24 Monaten) radikalen Therapien in 11,8 % vs. 5,8 %, ähnliche NW in einarmiger Studie berichtet

The presented effectiveness and safety results of the RCT are supported by the results of the prospective single-arm study [16]. In this study, 63.2% of the patients had negative biopsy results six months after the intervention, presenting a slightly higher rate compared to the 49.0% after 24 months in the RCT [14]. In contrast, a few more patients needed radical therapy in the single-arm study compared to the RCT (11.8% versus 5.8%). Similar to the RCT [14], most of the reported adverse events were of a low grade (Clavien I-II), including erectile dysfunction (43.8%), lower urinary tract syndrome (18.8%) and perianal pain (14.1%) as the most frequently reported events. The study did not report any Clavien IV-V adverse events during the 42-month follow-up.

Internal and external validity

Gesamtqualität der Evidenz als niedrig bis moderat eingestuft

Overall, taking into account the outcomes defined as crucial for recommendations, the strength of evidence for clinical effectiveness and safety was low and moderate, respectively. The pivotal RCT [14] was graded with a low RoB, while the follow-up study [15] was graded with a high RoB. The main reason was the selective outcome reporting in the study. The prospective single-arm study was graded with a high RoB since the outcome before and after treatment was not assessed and the reporting of the number of loss to follow-up was unclear.

Therapieauswahl bei Niedrig-Risiko-Prostatakrebs nicht immer eindeutig:

häufig aus klinischer Sicht keine Therapie notwendig

Auswahl jedoch abhängig von mehreren Faktoren, z. B. Angst

VTP-Therapie als Alternative zu AS für Patienten mit Angst, jedoch potentieller Zusatznutzen nicht eindeutig bestätigt

One issue that needs to be addressed concerning the presented results refers to the difficulties with the treatment choice for low-risk prostate cancer patients, namely the decision between AS versus treatments that are accompanied by adverse events affecting the patient's daily life. On the one hand, data suggests that prostate cancer often grows so slowly that most men die of other causes before the disease becomes clinically advanced [14]. Especially low-risk prostate cancer patients often do not develop metastases or die due to prostate cancer without any treatment [8]. For example, in Austria, in 40.0% of all affected men (n=25,572; status 2016), the diagnosis was made ten or more years previously [3]. This means that a significant proportion of patients would not need any treatment at all (from a clinical perspective) and that treating these low-risk patients, e.g., with VTP therapy with Tookad® Soluble, would expose them to unnecessary harm [17-19]. Furthermore, it has been shown that different criteria, including the patient's age and health perception, as well as hope and anxiety, generally determine the final choice of therapy [8]. In some patients, solely the term cancer invokes a fear of death, which is instinctively avoided. These patients therefore often opt for treatment, even if the risk is low. For these patients, VTP therapy with Tookad® Soluble was deemed to provide an alternative to AS. However, as shown in the two RCTs [14, 15], more than half of the study populations still had cancer (positive biopsy results) 24 months after treatment initiation. This means that these patients still need to be monitored similarly to patients on AS. Thus, the potential benefit of VTP therapy with Tookad® Soluble over AS is limited [18].

Stratifizierung in „echte" Niedrig-Risiko-Patienten problematisch, moderne Technologien (z. B. MRI) können Risikostratifizierung verbessern → verbesserte Patienten-selektion in den Studien → Effekt von VTP-Therapie vs. AS mglw. niedriger

Another concern arises concerning the risk stratification of prostate cancer. In the RCT and its extended follow-up [14, 15], all patients randomised to VTP therapy with Tookad® Soluble had a pre-treatment multi-parametric prostate MRI; however, the patients in the AS group did not. As a consequence, the relatively high proportion of patients in the AS group who had Gleason grade progression within 24 months (41.0%) [15] suggests that the entire study population may not have truly been low-risk patients [20]. Therefore, integrating MRI into the AS protocols as well would have possibly led to better sampling of the prostate and an enhanced risk stratification [18]. In other words, modern imaging (e.g., MRI), but also genomic testing or imaging-based biopsies may help to improve the risk stratification of low-risk patients who either will need aggressive treatment or should be monitored (AS). Thereby, the risk of progression in patients on AS can be reduced, which may consequently lower the potential benefits of VTP therapy with Tookad® Soluble [17, 19, 20].

Patientenanzahl bzw. Anzahl der Loss to follow-up in den inkludierten Studien teilweise inkonsistent bzw. nicht nachvollziehbar

Moreover, the number of patients or losses to follow-up were reported inconsistently in the included studies. No losses to follow-up were reported in the extended follow-up study [15], even if only 266 out of 413 patients remained therein for the follow-up period beyond 24 months. In the single-arm study [16], patients of two clinical trials (NCT00707356 and NCT00975429) were included. Due to the heterogeneity in the follow-up period across the clinical trials, the number of losses to follow-up in the single-arm study was not comprehensible.

Endpunkte teilweise unvollständig

Furthermore, some outcomes were also reported incompletely in the studies:

studienbezogener Tod nicht berichtet

1. Firstly, the outcome "study-related death," defined as crucial, was not reported in any study.

Lebensqualität nur nach 24 Monaten berichtet

2. Secondly, the crucial outcome "QoL" was only reported for the two-year follow-up [14]. This is particularly problematic concerning the low-risk cancer profile, as the majority of the patients do not have symptoms and, consequently, additional treatments such as VTP therapy with Tookad® Soluble might worsen the QoL of patients due to an increase in adverse events [7].

Studien in insgesamt 10 europäischen Ländern durchgeführt → Übertragbarkeit der Resultate auf Ö

In terms of external validity, the RCT [14, 15] and the single-arm study [16] were conducted across ten European countries, including Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the United Kingdom. Therefore, the generalisability of the study results to the Austrian context can be assumed (see Applicability table in the Appendix).

in Ö wird Padeliporfin aktuell nicht erstattet

However, currently (status January 2020), VTP therapy with Tookad® Soluble is not reimbursed and therefore not applied in Austrian hospitals yet (information from the manufacturer).

Limitations of evidence

keine Evidenz zu VTP-Therapie in Vergleich zu radikalen Therapien, da Biopsie-basierte Endpunkte bei radikalen Therapien nicht möglich

Overall, no evidence was available for assessing the clinical effectiveness and safety of VTP therapy with Tookad® Soluble compared to radical therapies such as radiation therapy or radical prostatectomy. The main reasons for choosing AS as a comparator instead of radical therapy in the available RCT was that radical prostatectomy, for example, would not be suitable for a biopsy-based outcome because there is no prostate after the procedure from which to take a biopsy [14]. However, what remains interesting for future research is how the effect on VTP therapy with Tookad® Soluble would impact the feasibility of future radical treatments, as the possibility is given that previous gland ablation (e.g., through VTP therapy) can negatively impact functional outcomes of future therapies [8, 42]. This is of special interest since the evidence has shown that a substantial number of patients will still require radical therapy, as 49.0% of the patients still had prostate cancer 24 months after VTP therapy with Tookad® Soluble [14].

Evidenz zum Effekt einer VTP-Therapie auf zukünftige radikale Therapien zu untersuchen

Evidenz spezifisch für mittleres Prostatakrebsrisiko notwendig

Besides, due to the aforementioned issues of accurate risk stratification, further evidence is needed to investigate the clinical effectiveness and safety of VTP therapy with Tookad® Soluble for intermediate-risk prostate cancer patients dissociated from the low-risk patient group [42].

Langzeitdaten von ≥10 Jahren empfohlen

Moreover, long-term data with a follow-up of at least ten years is recommended, especially concerning crucial outcomes, OS, prostate cancer-specific survival, QoL and severe adverse events, as the considered patient population is expected to live at least ten additional years.

weitere Evidenz zu unterschiedlichen Settings zukünftig interessant

With respect to the different settings of applying VTP therapy with Tookad® Soluble, for example, inpatient or day-care setting, future evidence assessing whether different settings result in different clinical effectiveness and safety outcomes would be worthwhile.

Evidenz zur Kosteneffektivität empfohlen

Finally, further evidence on the cost-effectiveness of VTP therapy with Tookad® Soluble in prostate cancer treatment is recommended [9].

Upcoming evidence

2 laufende RCTs & 3 laufende einarmige Studien:

The clinical trial search resulted in two ongoing RCTs and two ongoing prospective single-arm studies. In addition, the manufacturer submitted information on another ongoing single-arm study.

5-Jahres Follow-up für Niedrig-Risiko-Prostatakrebs, RCT für mittleres Prostatakrebsrisiko

One study (NCT04017325) represents the extended five-year follow-up of the pivotal RCT [14] with an estimated completion date in June 2020. The second study presents a further ongoing RCT (NCT04225299) with a follow-up of 72 months, investigating the clinical effectiveness of VTP therapy with Tookad® Soluble versus AS in localised intermediate-risk prostate cancer (expected completion date in January 2030).

3 einarmige Studien mit Follow-up zwischen 1-7 Jahren

What's more, one twelve-month follow-up phase IV single-arm study (NCT-03849365) assesses the occurrence and dynamics of the time with toxicities with an estimated completion date in January 2021. Another prospective single-arm study (NCT03315754) investigates the clinical effectiveness, safety and QoL of VTP therapy with Tookad® Soluble in intermediate-risk prostate cancer patients (expected completion date at the end of 2024). The additional ongoing single-arm study presented by the manufacturer is focusing on the clinical effectiveness and safety of VTP therapy with Tookad® Soluble in localised low-risk prostate cancer for a follow-up of seven years and is expected to be completed by the end of 2025.

keine laufende Studie mit Follow-up von ≥10 Jahren, jedoch Studien zu mittlerem Prostata-krebsrisiko

The identified ongoing studies will not fill the gap of long-term evidence. Nevertheless, two ongoing studies (1 RCT, 1 single-arm study) will provide evidence for intermediate-risk prostate cancer patients.

Detailinformationen zu laufenden Studien im Appendix

Detailed information about the currently ongoing studies is given in Table A-7 in the Appendix.

Limitations to this report

prospektive Studien nur mit >50 Patienten eingeschlossen

First of all, retrospective studies were generally excluded and only prospective observational studies with more than 50 patients were included in the present systematic review. Additional evidence – though of lower quality of evidence – on VTP therapy with Tookad® Soluble could thereby have been missed.

häufig narrative Analyse mittels GRADE aufgrund fehlender Daten

Furthermore, for the majority of the extracted outcomes, estimates of random variability (e.g., standard error, standard deviation or confidence intervals) were rarely provided. Therefore, for some outcomes only narrative analyses could be performed within the GRADE scheme.

Conclusions

niedrige bis moderate Qualität der Evidenz

Overall, the quality of evidence was graded as low and moderate for clinical effectiveness and safety, respectively.

VTP-Therapie nicht effektiver in Bezug auf Gesamtüberleben, etc. und weniger sicher

In terms of OS, prostate cancer-specific survival and QoL, the evidence is not sufficient to prove that VTP therapy with Tookad® Soluble is more effective compared to AS after 24 months. In addition, the evidence indicates that the intervention is less safe than the comparator at least after 24 months.

möglicher Nutzen von VTP-Therapie, jedoch immer noch zahlreiche Krebsfälle nach 24 Monaten überschätzter Effekt durch inakkurate Risikostratifizierung?

Furthermore, although the evidence shows a potential benefit of the intervention compared to AS concerning disease progression, time to progression, recurrence-free survival and conversion to radical therapies, the intervention shows some deficits with respect to the remaining high number of positive biopsies after 24 months (51.0%) and the high proportion of patients who progressed within the two-year follow-up (28.0%). This and the potentially overestimated benefit of VTP therapy with Tookad® Soluble over AS might be due to the inaccurate risk stratification in the included studies.

keine zuverlässige Aussage zu Wirksamkeit und Sicherheit möglich

On these grounds and because the included studies showed partly poor quality of evidence and high RoB, it is not possible to draw any reliable conclusion on the clinical effectiveness and safety of the intervention.

weitere Studien mit Langzeitdaten und zu Patienten mit mittlerem Prostatakrebsrisiko erwünscht

Future RCTs investigating the effect of VTP therapy with Tookad® Soluble on subsequent radical therapies are crucial, due to the high number of patients who still had prostate cancer after 24 months and who will probably need further treatment. Moreover, studies with a long-term follow-up of at least ten years are also important, because of the insufficient evidence currently available for OS, prostate cancer-specific survival, QoL and severe adverse events. Finally, additional RCTs investigating the effectiveness and safety of VTP therapy with Tookad® Soluble in intermediate-risk prostate cancer patients are desirable.

9 Recommendation

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

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:

There was no evidence available assessing the clinical effectiveness and safety of VTP therapy with Tookad® Soluble in comparison to radical therapies.

keine Evidenz im Vergleich zu radikalen Therapien

The currently available evidence is not sufficient to conclude that VTP therapy with Tookad® Soluble (padeliporfin) in localised low-risk prostate cancer patients is more effective and as safe or equally effective and safer than AS. Current evidence solely indicates that VTP therapy with Tookad® Soluble is more effective concerning disease progression, recurrence-free survival and conversion to radical therapy, but no statistically significant differences between the study groups were reported for OS, prostate cancer-specific survival and QoL after 24 to 48 months. Moreover, the evidence proves that the technology is less safe than AS after 24 months.

unklar ob VTP-Therapie wirksamer ist in Bezug auf Gesamtüberleben, krebsspezifisches Überleben & Lebensqualität; eindeutig weniger sicher als AS nach 24 Monaten

Recommendation:

Due to the poor to modest quality of evidence, the questionable benefit of VTP therapy compared to AS and the worse safety profile of VTP therapy, it is not possible to draw any reliable conclusion on the clinical effectiveness and safety of the intervention. As a result, VTP therapy with Tookad® Soluble is currently not recommended for inclusion in the hospital benefit catalogue.

unzureichende Evidenz → verlässliche Empfehlung nicht möglich

New long-term data of at least ten years will potentially influence the effect estimate considerably for this low-risk prostate cancer patient population. In addition, new results of studies investigating the effect of VTP therapy with Tookad® Soluble in intermediate-risk prostate cancer patients will bring additional evidence for another patient population.

neue Studien mit längerem Follow-up und zu Patienten mit mittlerem Prostatakrebsrisiko notwendig

As long as there is no RCT with a follow-up of at least ten years, no re-evaluation of VTP therapy with Tookad® Soluble in localised low-risk cancer patients is currently recommended. Nevertheless, since there is one ongoing RCT for the intermediate-risk prostate cancer patient population (see Table A-7), a re-evaluation of VTP therapy with Tookad® Soluble in prostate cancer patients with intermediate-risk is recommended, but not before 2030.

Re-evaluation für Niedrig-Risiko-Patienten nicht empfohlen, für Patienten mit mittlerem Risiko ab 2030 empfohlen

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Vascular-targeted photodynamic therapy with Tookad® Soluble: Results from randomised controlled trials

Author, year Trial name [Reference]	Azzouzi et al. 2016, PCM301 [14] Gill et al. 2018, PCM301 FU4 [15]
Country (of participated centres)	Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, Switzerland, and the UK
Sponsor	Steba Biotech [14] National Institutes of Health, National Cancer Institute, the Sidney Kimmel Center for Prostate and Urologic Cancers, the Thompson Family Foundation, United Kingdom National Institute of Health Research, University College London Hospital and University College London NIHR Biomedical Research Centre, and Steba Biotech [15]
Study design	Randomised controlled trial
Study period	03/2011-04/2013 [14] 03/2011-08/2017 [15]
Indication	Untreated localised low-risk prostate cancer
Diagnostic tool	Transrectal ultrasound-guided biopsy
Intervention	First-line VTP therapy with Tookad® Soluble (4 mg/kg padeliporfin)
Comparator	AS
Number of patients, n (%)	413 (206[9] vs. 207) [14] • Unilateral disease: 157 (76.0) vs. 163 (79.0) • Bilateral disease: 49 (24.0) vs. 44 (21.0) 266[10] (147 vs. 119) [15]
Inclusion criteria	• Age of ≥18 years • 1 positive core with a Gleason score of ≤3 and a length of ≥3 mm but ≤5 mm • 2 or 3 positive cores with a Gleason score of ≤3 and a length of ≤5 mm • Clinical stage of up to T2a (pathological or radiological up to T2c) • PSA concentration ≤10 ng/mL • Prostate volume ≥25 cm³ but ≤70 cm³ • The predicted life expectancy of ≥10 years
Exclusion criteria	• Very low-risk prostate cancer • Contraindications to undergoing MRI (e.g., cardiac pacemaker) • Factors excluding accurate reading of pelvic MRI (e.g., bilateral hip replacement) • Contraindications to general anaesthesia • Any disorder or history of illness or surgery that might pose an additional risk to men undergoing VTP therapy
Age of patients, mean years (SD, range)	64.2 (6.7, 45-85) vs. 62.9 (6.7, 44-79)
Time since diagnosis, mean months (SD, range)	6.3 (8.5, 0.2-54.2) vs. 6.0 (7.9, 0.2-47.4)
PSA, mean ng/mL (SD, range)	6.2 (2.1, 0.1-10.0) vs. 5.9 (2.0, 0.5-10.0)
TNM staging: T1a, n (%) T1c, n (%) T2a, n (%)	 1 (<1.0) vs. 0 (0.0) 177 (86.0) vs. 180 (87.0) 28 (14.0) vs. 27 (13.0)

[9] Out of the 206 patients in the treatment arm, 196 of them received initial VTP therapy.

[10] Out of the 413 patients included in the original study (PMC301), a total of 266 of them were followed up four or more years.

Author, year Trial name [Reference]	Azzouzi et al. 2016, PCM301 [14] Gill et al. 2018, PCM301 FU4 [15]
Gleason score, mean (SD)	NR
Total fibre length, mean mm (SD, range)	389.7 (124.84, 155-910)[11]
Number of fibres used, mean (SD, range)	12.9 (2.44, 6-20)[11]
LDI: <1, n (%) ≥1, n (%)	 6 (3.1)[11] 190 (96.9)[11]
Follow-up, median months	24 (24 vs. 25) [14] 48[12] [15]
Loss to follow-up, n[13] (%)	10 (4.9) vs. 18 (8.7) [14] NR [15]
Outcomes	
Efficacy	
OS, n (%)	At month 24 [14]: NR At month 48 [15]: 144 (98.0) vs. 118 (99.0)
Prostate cancer-specific survival, n (%)	At month 24 [14]: 206 (100.0) vs. 207 (100.0) At month 48 [15]: 147 (100.0) vs. 119 (100.0)
QoL ☘ EQ-5D questionnaire ☘ IPSS QoL subscore (higher scores indicate greater unhappiness with urinary symptoms)	☘ No significant difference in EQ-5D scores between the two study groups at month 24 (p=0.64) [14]. ☘ IPSS QoL subscore at month 24: NR [14] ☘ IPSS QoL subscore at month 48: NR [15]
Disease progression, n (%) *Progression from low-risk to moderate- or high-risk prostate cancer*	At month 24 [14]: 58 (28.0) vs. 120 (58.0), HR 0.34, 95% CI 0.24-0.46, p<0.0001 At month 24[14] [15]: ☘ Lower progression rate in the VTP group (whole gland progression): HR 0.35, 95% CI 0.25-0.48, p=0.001 ☘ Lower progression rate in the VTP group (in field progression[15]): HR 0.21, 95% CI 0.14-0.31, p<0.001
Time to progression, median months (95% CI)	28.3 (26.0-30.6) vs. 14.1 (12.9-23.8), p<0.0001 [14] NR [15]
Recurrence-free survival, n (%) *Negative biopsy results*	At month 24 [14]: 101 (49.0) vs. 28 (14.0), RR 3.67, 95% CI 2.53-5.33, p<0.0001 At month 24[14] [15]: 104 (50.0) vs. 30 (14.0), Risk difference 36%, 95% CI 28-44, p<0.001
Metastatic-free survival, n (%)	At month 24 [14]: 206 (100.0) vs. 207 (100.0) At month 48 [15]: 146 (99.0) vs. 118 (99.0)
Radical therapy conversion[16]	At month 24, n (%) [14]: 12 (5.8) vs. 60 (29.0), p<0.0001 At month 24, cumulative % at the end [15]: 7.0 vs. 32.0[17] At month 48, cumulative % at the end[18] [15]: 24.0 vs. 53.0[19], HR 0.31, 95% CI 0.21-0.46, p<0.001

11 Mean number of the 196 patients who received initial VTP therapy.

12 Not clear whether mean or median was presented.

13 Including patients who withdrew consent before study completion.

14 Biopsy results are reported at month 24 since annual biopsies were not mandated in all participants beyond that point.

15 In field is defined as in the VTP-treated lobe or for AS in the lobe containing the largest index cancer.

16 Triggers for conversion to radical therapy: a grade increase to Gleason grade group ≥2, an increase in cancer volume without a grade change, PSA failure and patient choice.

17 Patient number at risk at start (month 24): 195 vs. 189.

18 The types of radical therapy included radical prostatectomy (80.0%), radiation therapy (14.0%), whole gland cryotherapy or HIFU (5.0%) and unknown (1.0%).

19 Patient number at risk at start (month 48): 127 vs. 77.

Author, year Trial name [Reference]	Azzouzi et al. 2016, PCM301 [14] Gill et al. 2018, PCM301 FU4 [15]
Further oncological results	PSA concentration change from baseline to month 24, mean ng/mL (SD) [14]: -3.08 (3.05) vs. -0.68 (4.10) At month 24 [15][14]: ☘ Out of field positive biopsy result, n (%): 39 (19.0) vs. 25 (12.0), risk difference 7%, 95% CI 0-14, p=0.054 ☘ "In field" positive biopsy result, n (%): 51 (25.0) vs. 134 (65.0), risk difference -40%, 95% CI -49- -31, p<0.001 ☘ Overall Gleason grade group >1[20], n (%): 33 (16.0) vs. 84 (41.0), risk difference -25%, 95% CI -33- -16, p<0.001 ☘ "In field" Gleason grade group >1[20], n (%): 21 (10.0) vs. 70 (34.0), risk difference -24%, 95% CI -31- -16, p<0.001
Safety	
Study-related death (SRD), n (%) **Prostate cancer-related death (PCRD), n (%)**	At month 24 [14]: SRD NR, PCRD 0 (0.0) vs. 0 (0.0) At month 48 [15]: SRD: NR, PCRD: NR
Grade 3-4 AEs[21] that occurred in >1 patient, n (%) *sorted by incidence in the VTP group*	At month 24 [14][22]: Total of: 35 (17.8) vs. 12 (5.8) ☘ Inguinal hernia: 4 (2.0) vs. 0 (0.0) ☘ Rectal heamorrhage: 4 (2.0) vs. 0 (0.0) ☘ Prostatitis: 3 (2.0) vs. 1 (<1.0) ☘ Urinary retention: 3 (2.0) vs. 1 (<1.0) ☘ Urinary tract infection: 2 (1.0) vs. 2 (<1.0) ☘ Urinary incontinence: 2 (1.0) vs. 1 (<1.0) ☘ Erectile dysfunction: 2 (1.0) vs. 3 (1.0) ☘ Ejaculation failure: 2 (1.0) vs. 0 (0.0) ☘ Osteoarthritis: 2 (1.0) vs. 1 (<1.0) ☘ Arthralgia: 2 (1.0) vs. 0 (0.0) ☘ Cataract: 2 (1.0) vs. 0 (0.0) ☘ Drug hypersensitivity: 2 (1.0) vs. 0 (0.0) ☘ Fibrin D-dimer increased: 2 (1.0) vs. 0 (0.0) ☘ Cerebrovascular accident: 2 (1.0) vs. 0 (0.0) ☘ Myocardial infarction: 1 (<1.0) vs. 3 (1.0) At month 48 [15]: NR
Grade 1-2 AEs[23] that occurred in >1 patient, n (%) *sorted by incidence in the VTP group*	At month 24 [14][22]: Total of: 383 (197.4) vs. 94 (45.4) ☘ Erectile dysfunction: 72 (37.0) vs. 21 (10.0) ☘ Haematuria: 55 (28.0) vs. 6 (3.0) ☘ Dysuria: 51 (26.0) vs. 5 (2.0) ☘ Perianeal pain: 29 (15.0) vs. 1 (<1.0) ☘ Urinary retention: 29 (15.0) vs. 1 (<1.0) ☘ Micturition urgency: 21 (11.0) vs. 2 (<1.0) ☘ Pollakiuria: 20 (10.0) vs. 6 (3.0) ☘ Urinary tract infection: 19 (10.0) vs. 7 (3.0) ☘ Urinary incontinence: 17 (9.0) vs. 9 (4.0) ☘ Ejaculation failure: 14 (7.0) vs. 1 (<1.0) ☘ Prostatitis: 7 (4.0) vs. 9 (4.0) ☘ Orchitis: 6 (3.0) vs. 0 (0.0)

[20] Gleason grade group 1 includes Gleason scores ≤6 and Gleason patterns ≤3+3.

[21] Grade 3-4 adverse events include severe or medically significant adverse events with (prolongation of) hospitalisation indicated (grade 3) and life-threatening or disabling adverse events with urgent indication indicated (grade 4) [Common Terminology Criteria for Adverse Events version 4.0].

[22] Nine patients were lost to follow-up for the safety analysis in the VTP treatment group (n=197).

[23] Grade 1-2 adverse events include mild adverse events with no intervention indicated (grade 1) and moderate adverse events with local or non-invasive intervention indicated (grade 2) [Common Terminology Criteria for Adverse Events version 4.0].

Author, year Trial name [Reference]	Azzouzi et al. 2016, PCM301 [14] Gill et al. 2018, PCM301 FU4 [15]
Grade 1-2 AEs that occurred in >1 patient, n (%) *(continuation)*	✿ Prostatic pain: 5 (3.0) vs. 0 (0.0) ✿ Pyrexia: 4 (2.0) vs. 2 (<1.0) ✿ Abdominal pain: 4 (2.0) vs. 1 (<1.0) ✿ Depression: 4 (2.0) vs. 1 (<1.0) ✿ Epididymitis: 4 (2.0) vs. 0 (0.0) ✿ Inguinal hernia: 4 (2.0) vs. 1 (<1.0) ✿ Rectal haemorrhage: 4 (2.0) vs. 0 (0.0) ✿ Arthralgia: 3 (2.0) vs. 4 (2.0) ✿ Headache: 3 (2.0) vs. 2 (<1.0) ✿ Osteoarthritis: 2 (1.0) vs. 3 (1.0) ✿ Cataract operation: 2 (1.0) vs. 2 (<1.0) ✿ Procedural pain: 2 (1.0) vs. 2 (<1.0) ✿ Fibrin D-dimer increased: 2 (1.0) vs. 0 (0.0) ✿ Phlebitis: 0 (0.0) vs. 2 (<1.0) At month 48 [15]: NR
IPSS questionnaire (score range from -35 to 35) *Lower scores indicate a reduction in urinary symptoms*	Changes in IPSS scores from baseline to month 24 [14]: No difference between the two study groups.
IIEF-15 questionnaire (score range from -29 to +29) *Higher scores indicate a greater degree of erectile function*	Changes in IIEF-15 scores from baseline to month 24 [14]: No difference between the two study groups.
Discontinuation rate, n (%)	At month 24 [14]: 2 (1.0) vs. 1 (<1.0) At month 48 [15]: NR

Abbreviations: ***AE*** *– Adverse events,* ***AS*** *– Active surveillance,* ***CI*** *– Confidence interval,* ***HR*** *– Hazard ratio,* ***IIEF*** *– The International Index of Erectile Function Questionnaire,* ***IPSS*** *– International Prostate Symptom Score,* ***LDI*** *– Light density index,* ***MRI*** *– Magnetic resonance imaging,* ***n*** *– Number,* ***NR*** *– Not reported,* ***OS*** *– Overall survival,* ***PSA*** *– Prostate-specific antigen,* ***RR*** *– Relative risk,* ***QoL*** *– Quality of life,* ***SAE*** *– Severe adverse events,* ***SD*** *– Standard deviation,* ***VTP*** *– Vascular-targeted photodynamic*

Table A-2: Vascular-targeted photodynamic therapy with Tookad® Soluble: Results from observational studies

Author, year [Reference]	Noweski et al., 2018 [16]
Country (of participated centres)	France, Germany
Sponsor	Steba Biotech
Study design	A prospective follow-up study of two-phase II, multicentre, open-label, multiple-arm, single IV dose studies[24]
Study period	2009-2014
Indication	Localised, low-risk prostate cancer
Diagnostic tool	Systematic transrectal ultrasound-guided biopsies
Intervention	VTP therapy with Tookad® Soluble (4 mg/kg padeliporfin)
Comparator	-
Number of patients, n (%)	68 ❁ Unilateral disease: 55 (81.0) ❁ Bilateral disease: 13 (19.0)
Inclusion criteria	❁ Clinical stage up to T2a ❁ Gleason grade group limited to Gleason pattern 3+3 (= Gleason score 6) ❁ PSA concentration of ≤10 ng/mL
Exclusion criteria	NR
Age of patients, mean years (SD)	62.6 (5.6)
Time since diagnosis, months (range)	NR
PSA, mean ng/mL (median)	5.97 (5.70)
TNM staging: T1a, n (%) T1c, n (%) T2a, n (%)	NR
Gleason pattern, n	❁ Gleason pattern 3+3: 21 ❁ Gleason pattern 3+4: 3
Total fibre length, mean mm (SD, range)	NR
Number of fibres used, mean (SD, range)	NR
LDI, mean (SD)	1.45 (0.35)
Follow-up, range of months	6-42
The loss to follow-up, n (%)	16[25]
Outcomes	
Efficacy	
OS, n (%)	NR
Prostate cancer-specific survival, n (%)	NR
QoL ❁ EQ-5D questionnaire ❁ IPPS QoL subscore (higher scores indicate greater unhappiness with urinary symptoms)	 NR NR
Disease progression, n (%) *Progression from low-risk to moderate- or high-risk prostate cancer*	NR
Time to progression, median months (95% CI)	NR

[24] Two phase two studies: PMC201 (NCT00707356), PMC203 (NCT00975429).

[25] Two of the 68 optimally-treated patients were not evaluable during the follow-up period and were excluded. Furthermore, 14 patients underwent interventional treatment for prostate cancer (radical surgery [n=8], brachytherapy [n=5], and HIFU [n=5]) and could, therefore, not be monitored for treatment effect or study-related toxicity.

Author, year [Reference]	Noweski et al., 2018 [16]
Recurrence-free survival, n (%) *Negative biopsy results*	At month 6: 43 (63.2) At month 42: 1 (1.9)[26]
Metastatic-free survival, n (%)	NR
Radical therapy conversion, n (%)	At month NR 8 (11.8)
Further oncological results	PSA concentration change from baseline to month 6, mean ng/mL (median): -2.64 (-2.80) ✿ Gleason score change defined as upgrading by 1 Gleason point after 30 months after VTP therapy: n=8
Safety	
Study-related death, n (%) **Prostate cancer-related death, n (%)**	NR NR
Clavien IV-V AEs[28], n(%)	No Clavien IV or V AEs occurred during the follow-up of 42 months.
Clavien III AEs[28], n (%)[27]	Total of: 3 (4.7*) ✿ Lower urinary tract syndrome: 2 (3.1*) ✿ Urethral stenosis: 1 (1.6*)
Clavien I-II AEs[28], n (%)[27]	Total of: 61 (95.3*) ✿ Erectile dysfunction[29]: 28 (43.8*) ✿ Lower urinary tract syndrome: 12 (18.8*) ✿ Perianal pain: 9 (14.1*) ✿ Ejaculation sequelae: 5 (7.8*) ✿ Decreased libido: 4 (6.3*) ✿ Urinary infection: 2 (3.1*) ✿ Macroscopic haematuria: 1 (1.6*)
IPSS questionnaire **(score range from -35 to 35)** *Lower scores indicate a reduction in urinary symptoms*	NR
IIEF-15 questionnaire **(score range from -29 to +29)** *Higher scores indicate a greater degree of erectile function*	NR
Discontinuation rate, n (%)	NR

Abbreviations: ***AE*** *– Adverse event,* ***CI*** *– Confidence interval,* ***IIEF*** *– The International Index of Erectile Function Questionnaire,* ***IPPS*** *– International Prostate Symptom Score,* ***LDI*** *– Light density index,* ***n*** *– Number,* ***NR*** *– Not reported,* ***OS*** *– Overall survival,* ***PSA*** *– Prostate-specific antigen,* ***QoL*** *– Quality of life,* ***SD*** *– Standard deviation,* ***VTP*** *– Vascular-targeted photodynamic*

[26] After 42 months, 16 patients were lost to follow-up (n=52).

[27] It total, 84 adverse events were reported, of which 20 were not related to the study drug, device or procedure. Therefore, 64 of the 84 adverse events were study-related ones and taken as the base case for the percent calculation (*=self-calculated).

[28] The number of adverse events reported according to the Clavien–Dindo classification of surgical complications.

[29] Erectile dysfunction was reported by 11 pts. after 6 months; by 9 pts. after 12 months; by 3 pts. after 18 months; by 3 pts. after 24 months; by 1 pt. after 30 months; by no pt. after 36 months; and by 1 pt. after 42 months.

Risk of bias tables and GRADE evidence profile

The internal validity of the included studies was judged by two independent researchers. In case of disagreement, a third researcher was involved to solve the differences. A more detailed description of the criteria used to assess the internal validity of the individual study designs can be found in the Internal Manual of the LBI-HTA [2] and in the Guidelines of EUnetHTA [3].

Table A-3: Risk of bias – study level (randomised studies), see [12]

Trial	Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding		Incomplete outcome data	Selective outcome reporting unlikely	No other aspects which increase the risk of bias	Risk of bias – study level
			Patient	Treating Physician				
PCM301, [14]	Yes	Yes	Yes[30]	Yes[30]	No[31]	Yes	No[32]	**Low**
PCM301 FU4, [15]	Yes	Yes	Yes[30]	Yes[30]	Unclear	No[33]	No[32]	**High**

Table A-4: Risk of bias – study level (observational studies), see [11]

Study reference/ID	Noweski et al. (2018) [16]
Study objective	
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes
Study design	
2. Was the study conducted prospectively?	Yes
3. Were the cases collected in more than one centre?	Yes
4. Were patients recruited consecutively?	Unclear
Study population	
5. Were the characteristics of the patients included in the study described?	Partial
6. Were the eligibility criteria (i.e., inclusion and exclusion criteria) for entry into the study clearly stated?	Partial
7. Did patients enter the study at a similar point in the disease?	Unclear

[30] Patients and investigational site staff were not masked to study treatment, but investigators assessing primary efficacy outcomes were masked to treatment allocation.

[31] Missing data were not imputed.

[32] The study was funded by the manufacturer.

[33] The four-year follow-up of the original PMC301 study fails to include results for outcomes that would be expected to have been reported for such a study: QoL and safety.

Study reference/ID	Noweski et al. (2018) [16]
Intervention and co-intervention	
8. Was the intervention of interest clearly described?	Yes
9. Were additional interventions (co-interventions) clearly described?	NR
Outcome measures	
10. Were relevant outcome measures established a priori?	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Unclear
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes
13. Were the relevant outcome measures made before and after the intervention?	No[34]
Statistical analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear
Results and conclusions	
15. Was follow-up long enough for important events and outcomes to occur?	Yes
16. Were losses to follow-up reported?	Unclear[35]
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Partial
18. Were the adverse events reported?	Yes
19. Were the conclusions of the study supported by results?	Yes
Competing interests and sources of support	
20. Were both competing interests and sources of support for the study reported?	Yes
The overall risk of bias	**High**

***Abbreviation: NR** – not relevant*

[34] The first evaluation period of the presented follow-up study correlates with the endpoints of the clinical phase II studies (PMC201 [NCT00707356], PMC203 [NCT00975429]) at month six.

[35] Losses to follow-up were reported, but the reported number of loss to follow-up was not comprehensible.

Table A-5: Evidence profile: efficacy and safety of vascular-targeted photodynamic therapy with Tookad® Soluble [13]

Certainty assessment							N of patients		Effect		Certainty	Importance
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VTP therapy	AS	Relative (95% CI)	Absolute (95% CI)		
Efficacy												
OS (follow-up: median 48 months; assessed with: number of patients with event (%))												
1 [a]	Follow-up study	serious [b]	not serious [c]	not serious	not serious	none	144/147 (98.0%) vs. 118/119 (99.0%)				⊕⊕⊕◯ **MODERATE**	**Critical**
Prostate cancer-specific survival (follow-up: range 24-48 months; assessed with: number of patients with event (%))												
2 [d]	Randomised trial & follow-up study	serious [b, e]	not serious	not serious	not serious	none	At month 24: 206/206 (100.0%) vs. 207/207 (100.0%) At month 48: 144/144 (100.0%) vs. 119/119 (100.0%)				⊕⊕⊕◯ **MODERATE**	**Critical**
QoL (follow-up: median 24 months; assessed with: EQ-5D questionnaire)												
1 [f]	Randomised trial	serious [b, e]	not serious [c]	not serious	serious [g]	none	There was no difference in EQ-5D scores between VTP therapy vs. AS at month 24 (p=0.64).				⊕⊕◯◯ **LOW**	**Critical**
Disease progression: progression from low-risk to intermediate or high-risk prostate cancer (follow-up: median 24 months; assessed with: number of patients with event [%])												
1 [f]	Randomised trial	serious [b, e]	not serious [c]	not serious	not serious	strong association [h]	58/206 (28.2%)	120/207 (58.0%)	HR 0.34 (0.24 to 0.46)	38 fewer per 100 (from 44 fewer to 31 fewer)	⊕⊕⊕⊕ HIGH	Important
Disease progression: progression from low-risk to intermediate- or high-risk prostate cancer (follow-up: median 24 months)												
1 [a]	Follow-up study	serious [b]	not serious [c]	not serious	not serious	strong association [h]	Lower whole gland progression rate in the VTP treatment group vs. the AS group: HR 0.35, 95% CI 0.25-0.48, p=0.001. Lower in field progression rate in the VTP treatment group vs. the AS group: HR 0.21, 95% CI 0.14-0.31, p<0.001.				⊕⊕⊕⊕ HIGH	Important
Recurrence-free survival: negative biopsy results (follow-up: median 24 months; assessed with: number of patients with event (%))												
1 [f, i]	Randomised trial	serious [b, e]	not serious [c]	not serious	serious [j]	none	101/206 (49.0%)	29/207 (14.0%)	RR 3.67 (2.53 to 5.33)	37 more per 100 (from 21 to 61 more)	⊕⊕◯◯ LOW	Important
Radical therapy conversion (follow-up: median 24 months; assessed with: number of patients with event (%))												
1 [f]	Randomised trial	serious [b, e]	not serious [c]	not serious	not serious	none	12/206 (5.8%) vs. 60/207 (29.0%) (p<0.0001)				⊕⊕⊕◯ MODERATE	Important
Radical therapy conversion (follow-up: median 48 months; assessed with: cumulative % of patients with event at the end of follow-up)												
1 [a]	Follow-up study	serious [b]	not serious [c]	not serious	not serious	none	24.0% vs. 53.0% (HR 0.31, 95% CI 0.21-0.46, p<0.001)				⊕⊕⊕◯ MODERATE	Important

Certainty assessment							N of patients		Effect		Certainty	Importance
N of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	VTP therapy	AS	Relative (95% CI)	Absolute (95% CI)		
Safety												
Study-related death (follow-up median 24-48 months) – not reported												
-	-	-	-	-	-	-					-	**Critical**
Prostate cancer-related death (follow-up: median 24 months; assessed with: number of patients with event [%])												
1 [f]	Randomised trial	serious [b, e]	not serious [c]	not serious	not serious	none	0/206 (0.0%)	vs. 0/207 (0.0%)			⨁⨁⨁◯ MODERATE	**Critical**
Severe adverse events (grade 3-4) that occurred in >1 patient (follow-up: median 24 months; assessed with: number of patients with event (%))												
1 [f]	Randomised trial	serious [b, e]	not serious [c]	not serious	not serious	none	35/197 (17.8%)	vs. 12/207 (5.8%)			⨁⨁⨁◯ MODERATE	**Critical**
Number of Clavien I-III adverse events (follow-up: range 6 months to 42 months; assessed with: number of reported adverse events)												
1	Observational study	serious [l, m]	not serious [c]	not serious	not serious	none	In total, 64 adverse events related to the study drug, device or procedure (VTP therapy with Tookad® Soluble) were reported over the follow-up period, among which three were of Clavien III and 61 of Clavien I-II.				⨁◯◯◯ VERY LOW	Important

Abbreviations: ***AS*** *– Active Surveillance,* ***CI*** *– Confidence interval,* ***HR*** *– Hazard ratio,* ***MD*** *– Mean difference,* ***OS*** *– Overall survival,* ***QoL*** *– Quality of life,* ***RR*** *– Risk ratio*

GRADE Working Group grades of evidence

High certainty: *We are very confident that the true effect lies close to that of the estimate of the effect.*

Moderate certainty: *We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.*

Low certainty: *Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.*

Very low certainty: *We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.*

Explanations

[a] *Follow-up study PCM301 FU4.*

[b] *Funded by the manufacturer.*

[c] *Only one study reported this outcome.*

[d] *RCT PCM301 & follow-up study PCM301 FU4.*

[e] *Missing data were not imputed in the study PCM301.*

[f] *RCT PCM301.*

[g] *No significant difference.*

[h] *HR <0.5.*

[i] *PCM301 FU4 also reports the same outcome for 24 months; however, with slightly different results.*

[j] *Wide confidence intervals.*

[l] *Relevant outcome measures were not made before and after the intervention.*

[m] *The reported number of loss to follow-up was not comprehensible.*

Applicability table

Table A-6: Summary table characterising the applicability of a body of studies

Domain	Description of applicability of evidence
Population	All studies included patients with localised low-risk prostate cancer defined as clinical stage T1-T2a, Gleason scores ≤6 and a PSA concentration of ≤10 ng/mL. Across the three included studies, the mean age of the patients was 63.4 years. The studies included a total of 481 patients. The inclusion criteria and the population in the included studies seem to be in accordance with the intended patient population for the technology; however, in practice difficulties exist concerning the risk stratification, this means that identifying the truly low-risk prostate cancer patients might be challenging in practice.
Intervention	In all included studies the same intervention was used: 4 mg/kg Tookad® Soluble (padeliporfin) was given intravenously for ten minutes following VTP therapy. The whole procedure lasted around two hours and was conducted under general anaesthesia.
Comparators	Possible comparators include AS or radical therapies, as suggested by the German AWMF S3 guideline: In the two included RCTs, the control groups followed AS, which only includes monitoring but no actual treatment. To date, there are no published studies in which VTP therapy with Tookad® Soluble has been compared with radical therapies such as radiation therapy or radical prostatectomy.
Outcomes	Clinical effectiveness outcomes considered crucial for the recommendation in this assessment are OS, prostate cancer-specific survival and QoL. However, taking into account the low-risk profile of prostate cancer, surrogate outcomes such as disease progression, time to progression, recurrence-free survival, metastasis-free survival and conversion to radical therapy were additionally considered to derive a recommendation. Concerning safety, study-related death, prostate cancer-related death and serious adverse events (grade 3-4 or Clavien IV-V) were considered as outcomes crucial for the recommendation. However, due to the low-risk cancer profile mild to moderate adverse events (grade 1-2 or Clavien I-III) were also taken into account, as for these low-risk prostate cancer patients mild to moderate adverse events also play an important role.
Setting	Overall, the three studies were carried out across ten European countries. No applicability issues are expected from the geographical setting. Patients were recruited and the interventions were performed in an inpatient or day-care setting. Therefore, the settings of the studies reflect the clinical practice in which the technology is intended to be used appropriately. In Austria, padeliporfin (Tookad® Soluble) is currently not approved. Therefore, the intervention has not been applied yet in Austria. Consequently, the setting in which VTP therapy with Tookad® Soluble will be used (inpatient/day-care/ outpatient) is not yet known for Austria. In fact, before the actual implementation of the technology, the centres are trained by the manufacturer on how to perform the intervention. Without this training, centres are not allowed to apply the technology (information from the manufacturer).

***Abbreviations: AS** – Active surveillance, **VTP** – Vascular-targeted photodynamic, **OS** – Overall survival, **QoL** – Quality of life*

List of ongoing studies

Table A-7: List of ongoing studies of vascular-targeted photodynamic therapy with Tookad® Soluble

Identifier/ Trial name	Patient population	Intervention	Comparison	Primary Outcome	Estimated completion date	Sponsor
Randomised controlled trials						
NCT04017325 (PCM301-FU5)	Low-risk prostate cancer initially randomised to PCM301 (n around 374)	VTP therapy with Tookad® Soluble	AS	Disease progression over 5 yrs, Conversion to other therapies after 5 yrs, Prostate cancer-related death after 5 yrs	June 2020	Steba Biotech
NCT04225299 (PCM306)	Localised intermediate-risk prostate cancer (n around 400)	VTP therapy with Tookad® Soluble	AS	Rate of objective progression over 30 months	January 2030	Steba Biotech
Prospective single-arm studies						
NCT03315754 (PCM204)	Localised intermediate-risk prostate cancer (n around 50)	VTP therapy with Tookad® Soluble	X	Absence of biopsy detectable grade 4/5 Gleason prostate cancer tumours after 12-months (post-treatment)	End of 2024	Steba Biotech
NCT03849365 (PCM404)	Low-risk prostate cancer (n around 200)	VTP therapy with Tookad® Soluble	X	Adverse events profile (erectile dysfunction, urinary incontinence) and QoL after 12 months (post-treatment)	January 2021	Steba Biotech
CLIN1501 (PCM401)	Localised low-risk prostate cancer	VTP therapy with Tookad® Soluble	X	Long-term safety and efficacy (7 years) of VTP with Tookad® Soluble in real life	End of 2025	Steba Biotech (Information from the manufacturer)

Abbreviations: ***AS*** *– Active surveillance,* ***QoL*** *– Quality of life,* ***VTP*** *– Vascular-targeted photodynamic*

Literature search strategies

Search strategy for Cochrane

Search Name: VTP-Therapy with Padeliporfin in Prostate Cancer	
Last saved: 18/12/2019 17:16:53	
Comment: MEL2010 SW/NG 181219	
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 neoplasm*)) (Word variations have been searched)
#3	#1 OR #2 (Word variations have been searched)
#4	(padeliporfin*) (Word variations have been searched)
#5	(stakel*) (Word variations have been searched)
#6	(Tookad® Soluble ® Soluble*) (Word variations have been searched)
#7	(wst 11) (Word variations have been searched)
#8	(wst11) (Word variations have been searched)
#9	MeSH descriptor: [Photochemotherapy] explode all trees
#10	(vascular) (Word variations have been searched)
#11	(VTP):ti,ab,kw (Word variations have been searched)
#12	#10 OR #11 (Word variations have been searched)
#13	#9 AND #12 (Word variations have been searched)
#14	(vascular NEAR (photodynamic* OR photo-dynamic* OR photochem* OR photo-chem*)) (Word variations have been searched)
#15	(vascular-target*) (Word variations have been searched)
#16	(bacteriopheophorbide*) (Word variations have been searched)
#17	(WST09) (Word variations have been searched)
#18	(WST 09) (Word variations have been searched)
#19	#4 OR #5 OR #6 OR #7 OR #8 OR #11 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 (Word variations have been searched)
#20	#3 AND #19 (Word variations have been searched)
Total: 15 Hits	

Search strategy for CDR

Search Name: VTP-Therapy with Padeliporfin in Prostate Cancer	
Comment: MEL2010 SW/NG 181219	
ID	Search
1	(padeliporfin*)
2	(stakel*)
3	(Tookad® Soluble ® Soluble*)
4	(wst 11)
5	(wst11)
6	MeSH DESCRIPTOR Photochemotherapy EXPLODE ALL TREES
7	(vascular)
8	(VTP)
9	#7 OR #8

10	#6 AND #9
11	(vascular NEAR (photodynamic* OR photo-dynamic* OR photochem* OR photo-chem*))
12	(vascular-target*)
13	(bacteriopheophorbide*)
14	(WST09)
15	(WST 09)
16	#1 OR #2 OR #3 OR #4 OR #5 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES
18	(prostat*)
19	#17 OR #18
20	#16 AND #19
Total: 1 Hit	

Search strategy for Embase

Search Name: VTP-Therapy with Padeliporfin in Prostate Cancer		
Comment: MEL2010 SW/NG 181219		
No.	Query Results	Results
#22	#3 AND #21	322
#21	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #13 OR #14 OR #16 OR #17 OR #18 OR #19 OR #20	4,581
#20	'wst 09':ti,ab,de,kw	6
#19	wst09:ti,ab,de,kw	20
#18	bacteriopheophorbide*:ti,ab,de,kw	132
#17	(vascular NEAR/4 (photodynamic* OR 'photo dynamic*' OR photochem* OR 'photo chem*')):ti,ab,de,kw	477
#16	#11 AND #15	1,885
#15	#12 OR #13 OR #14	1,072,246
#14	vtp:ti,ab	316
#13	'vascular target*':ti,ab,de,kw	2,403
#12	vascular:ti,ab,de,kw	1,072,025
#11	'photodynamic therapy'/exp	24,409
#10	'vascular targeted photodynamic therapy'/exp	29
#9	'wst11':ti,ab,de,kw,tn	64
#8	'wst 11':ti,ab,de,kw,tn	57
#7	Tookad® Soluble *:ti,ab,de,kw,tn	118
#6	stakel*:ti,ab,de,kw,tn	15
#5	padeliporfin*:ti,ab,de,kw,tn	96
#4	'padeliporfin'/exp	94
#3	#1 OR #2	270,421
#2	(prostat* NEAR/4 (cancer* OR tumor* OR tumour* OR carcinom* OR adenom* OR adenoc* OR 'adeno c*' OR neoplasm*)):ti,ab,de,kw	270,305
#1	'prostate cancer'/exp	210,045

Search strategy for Medline

Search Name: VTP-Therapy with Padeliporfin in Prostate Cancer		
Comment: MEL2010 SW/NG 171219		
ID	Search	Results
1	exp Prostatic Neoplasms/	147,169
2	(prostat* adj5 (cancer* or tumo?r* or carcinom* or adenom* or adeno?c* or neoplasm*)).mp.	194,724
3	1 or 2	194,724
4	padeliporfin*.mp.	43
5	stakel*.mp.	10
6	Tookad® Soluble *.mp.	60
7	wst 11.mp.	11
8	wst11.mp.	42
9	exp Photochemotherapy/	23,481
10	vascular.mp.	851,770
11	VTP.ti,ab.	214
12	10 or 11	851,924
13	9 and 12	1,621
14	(vascular adj5 (photodynamic* or photo-dynamic* or photochem* or photo-chem*)).mp.	394
15	vascular-target*.mp.	1,261
16	bacteriopheophorbide*.mp.	86
17	WST09.mp.	19
18	"WST 09".mp.	5
19	4 or 5 or 6 or 7 or 8 or 11 or 13 or 14 or 15 or 16 or 17 or 18	3,078
20	3 and 19	141
21	remove duplicates from 20	117

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