High-intensity focused ultrasound for the treatment of prostate cancer

Rapid assessment of other technologies using the HTA Core Model® for Rapid Relative Effectiveness Assessment

Update 2018

Ludwig Boltzmann Institut
Health Technology Assessment

Decision Support Document No.37/Update 2018
ISSN online: 1998-0469

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Vienna, July 2018

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This report should be referenced as follows:

Erdos J., Fischer S., Mazgele V. High-intensity focused ultrasound for the treatment of prostate cancer. Decision Support Document No. 37/Update 2018 ; 2018. Vienna: Ludwig Boltzmann Institute for Health Technology Assessment.

Conflict of interest

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

Disclaimer

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

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 Application for Rapid REA Assessments (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

Publisher:

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

Responsible for content:

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

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

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

Decision Support Document No.: 37/Update 2018

ISSN-online: 1998-0469

Content

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List of abbreviations

ADT ..... Androgen deprivation therapy
ARI ..... Alpha Reductase Inhibitor
AS ..... Active surveillance
BE ..... Belgium
BMSFI ..... Brief Male Sexual Function Inventory
CAN ..... Canada
CE ..... Conformité Européene
CI ..... Confidence interval
CPG ..... Clinical practice guideline
CRD ..... Centre for Research and Dissemination
CUR ..... Current use of the technology
d ..... day
EAU ..... European Association of Urology
EBRT ..... External beam radiation therapy
EFF ..... Effectiveness
EORTC-QLQ ... European Organisation for Research and Treatment of Cancer-Quality of life questionnaire
EQ-5D ..... EuroQol-5 dimensions
EUnetHTA ..... European Network for Health Technology Assessment
FACIT ..... Functional Assessment of Chronic Illness Therapy

FACT-G ..... Functional Assessment of Cancer Therapy – General
FACT-P ..... Functional Assessment of Cancer Therapy – Prostate
FR..... France
FU ..... Follow-up
GRADE..... Grading of recommendations, assessments, development and evaluation
HADS..... Hospital Anxiety and Depression Scale
HDR..... High dose rate
HIFU..... High-intensity focused ultrasound
HRQoL ..... Health related quality of life
ICD ..... International Classification of Diseases
ICS..... International Continence Society
ICTRP..... International Clinical Trials Registry Platform
IGRT ..... Image-guided radiation therapy
IIEF..... International Index of Erectile Function
IMRT ..... Intensity-modulated radiotherapy
IPSS..... International Prostate Symptom Score
IQR..... Interquartile range
LBI-HTA ..... Ludwig Boltzmann Institute for Health Technology Assessment
LDR ..... Low dose rate
LUTS ..... Lower urinary symptoms
MAX-PC ..... Memorial Anxiety Scale for Prostate Cancer
MeSH ..... Medical Subject Headings
min ..... minute
mpMRI..... Multiparametric magnetic resonance imaging
NA ..... Not applicable
NA..... Not available
NB..... Notified body
NICE ..... National Institute for Health and Care Excellence
PI-RADS ..... Prostate Imaging Reporting and Data System
PORPUS..... Patient Oriented Prostate Utility Scale
PSA ..... Prostate-specific antigen
pts ..... patients
QoL..... Quality of life
RAND-SF..... Research ANd Development Short Form
RCT ..... Randomised Controlled Trial
REA ..... Relative Effectiveness Assessment
ROBIN-S ..... Risk Of Bias In Non-randomized Studies – of Interventions
RP ..... Radical prostatectomy
RT ..... Radiation therapy
SAF ..... Safety
SD ..... Standard deviation
TEC ..... Technical characteristics of the technology
TRUS..... Transrectal ultrasonography
TURP..... Transurethral resection of the prostate
UCLA-EPIC..... University of California, Los Angeles Expanded Prostate Cancer Index Composite
UK..... United Kingdom
US ..... Ultrasound
VASPVT ..... State Health Care Accreditation Agency under the Ministry of Health
WW..... Watchful waiting
ZIN ..... Zorginstituut Netherland

Executive Summary

Introduction

Health Problem

Prostate cancer (PCa) is the most common non-skin cancer in men in Europe [1]. In early stage, prostate cancer is localised and organ-confined [2]. Depending on the risk of progression, the cancerous lesion increases in volume and produces more PSA over time. Localised prostate cancer is often indolent, and has no impact on health; even without treatment. Locally relapsed/recurrent prostate cancer occurs when the cancer is still present or comes back after failed primary therapy [3] (A0002). Incidence rates reported by the International Agency for Research on Cancer (IARC) in 2014 varied between 35 and 132 per 100,000 men in European countries [4] (A0023).

prostate cancer (PCa) one of the most common types of cancer in men

incidence of 35-132 per 100,000 men in European countries

The target population of this assessment is low-risk and intermediate-risk localised and locally recurrent/relapsed PCa patients without any regional lymph nodes (Nx-N0) and without any distant metastases (Mx-M0). Low-risk is defined as prostate-specific antigen (PSA) <10 ng/mL, Gleason Score (GS) <7 and cT1a-T2a. Intermediate-risk is defined as PSA 10-20 ng/mL, or GS 7 or cT2b [1] (A0007).

target population of this assessment: low-risk and intermediate-risk localised and locally recurrent/relapsed PCa

Description of the Technology

High-intensity focused ultrasound (HIFU) uses ultrasound (US) waves to cause tissue damage. The energy of the US waves are absorbed by the target tissue and converted to heat (exceeding 60 °C), causing coagulative necrosis. Inertial cavitation is caused by alternating cycles of compression and rarefaction [1, 5].

HIFU uses ultrasound to destroy tissue

To administer HIFU, a probe is inserted into the rectum (or urethra) while the patient is anaesthetised. This probe enables real-time visualisation of prostatic tissue and also delivers HIFU energy to destroy the desired target parenchyma [5].

probe inserted in rectum under anaesthesia

Two major systems of HIFU exist, based on the type of imaging guidance during the treatment.

two major systems:

1. *HIFU with TRUS imaging guidance* is the traditional approach. TRUS-guided HIFU is used to ablate the whole prostate gland or a relatively large region [6-9].
2. The novel approach is the *HIFU system with MRI guidance*. It is possible to localise the lesions within the prostate with MRI, hence the focal treatment (FT) of the prostate is also possible [6] (B0001).

one with TRUS guidance

one with MRI guidance

Based on the ablation strategy approach we differentiate whole gland ablation and FT. There is no consensus definition of FT, but for the time being any approach to preserve parts of the prostate tissue (hemiablation, hockey stick ablation, and targeted focal ablation) is considered FT [10] (B0001).

differentiation between whole-gland ablation and focal therapy

The CE mark for the HIFU technology has been awarded for the primary treatment of patients with primary localised PCa or for salvage therapy of locally recurrent PCa following failed prior therapy [11] (B0002).

CE mark for primary localised or locally recurrent PCa

claimed that HIFU treatment has lower side-effect

It is claimed that HIFU treatment has significantly lower side-effect profile (erectile and urinary dysfunction) [12], and reduces toxicity compared to other ablation techniques and adjacent blood vessels may be less vulnerable to damage compared with surgical risks [13] (B0002).

comparators:

The comparators

active surveillance (AS) and watchful waiting (WW)

Active surveillance (AS) and watchful waiting (WW) are deferred treatment strategies for men with localised PCa who are not candidates for definitive treatment. These conservative management strategies aim to reduce overtreatment [1] (B0002).

radical prostatectomy (RP)

Radical prostatectomy (RP) is a definitive treatment strategy in which the prostate gland between the urethra and bladder is removed, along with the resection of both seminal vesicles and sufficient surrounding tissue to obtain negative margins. The goal of the procedure is to eradicate the disease, while preserving continence and if possible, potency [1] (B0001).

radiation therapy (RT)

Radiation therapy (RT) is another definitive treatment strategy in which a therapeutic dose of radiation is delivered to the tumour (either as external beam, brachytherapy or a combination of both) while minimizing the radiation to normal tissue [14] (B0001).

Methods

update of existing report from 2010

We updated the LBI-HTA systematic review from 2010 [15], hence the systematic literature search was performed from January 2010 to December 2017 in four databases (Cochrane Library, Centre for Research and Dissemination, Embase, Medline), complemented by handsearch in the reference list of relevant studies. In addition, clinical trials databases were searched to identify ongoing studies on HIFU for prostate cancer treatment.

database search, complemented by handsearch

risk of bias and quality of evidence assed with tools

Risk of bias on study level was assessed with the IHE-20-checklist [16] of the single-arm studies, and with ROBINS-I [17] that of the non-randomised controlled study (non-RCT). The quality of the body of evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [18].

comparative studies for effectiveness, also uncontrolled studies for safety

The inclusion criteria for assessing the clinical effectiveness of HIFU, was exclusively restricted to studies with a comparison group (RCTs, non-RCTs). The inclusion criteria for assessing safety additionally considered prospective studies without a control group (single-arm studies, case series, and registry studies) with at least 50 patients.

Results

Available evidence

Clinical effectiveness

effectiveness: one non-RCT

The systematic literature search identified one controlled study (matched-pair analysis) that met our inclusion criteria. The study compared whole gland primary HIFU with brachytherapy, a type of radiotherapy for the treatment of localised PCa, including 70 patients in each treatment arm [19].

no further evidence identified

We could not identify any controlled trials comparing either primary or salvage HIFU with other treatments, (see comparators above).

Safety

safety: one non-RCT and five single-arm trials

In the systematic literature search we identified four prospective single-arm studies [20-23] in addition to the one non-RCT [19] regarding primary HIFU and one prospective single-arm study regarding salvage HIFU [24], which met our inclusion criteria to assess safety. The single-arm primary HIFU studies applied hemiablation, the matched-pair analysis and the study on salvage HIFU applied whole gland ablation of the prostate.

Clinical effectiveness

Primary HIFU

primary HIFU: no significant difference between HIFU and brachytherapy regarding survival

To assess the effect of HIFU on mortality, overall survival and PCa specific survival were considered. After five years, overall survival and PCa specific survival in the HIFU-group compared to brachytherapy was not significantly different (88 vs. 97.5%, HR 0.24, CI 0.01-1.34 and 89% vs. 92%, HR 0.67, CI 0.32-1.29) [19].

biochemical recurrence-free survival was significantly lower for patients in the HIFU-group

To describe the effect of HIFU on the progression (or recurrence) of localised and locally recurrent PCa biochemical recurrence-free survival (a surrogate outcome and not to be mistaken for "local disease recurrence") was considered. This outcome was significantly lower for patients in the HIFU-group than for patients in the control group: 53.1 vs. 68.5% according to the Phoenix and 51.3 vs. 60.9% according to the Stuttgart definitions (HR 0.41, CI 0.19-0.81 for Phoenix, HR 0.39, CI 0.19-0.74 for Stuttgart, $p<0.05$ for both) [19][1]. Additional outcomes that are suitable to describe the progression of PCa were not reported in the included study (the critical outcome local disease recurrence, or others, like need for salvage/systemic therapy, ablation failure, distant disease recurrence/metastases or disease progression/pathological progression) [19].

Salvage HIFU

salvage HIFU: no evidence

No evidence was found to assess the effectiveness of salvage HIFU in comparison to any of the comparators.

Safety

Primary HIFU

primary HIFU:

To assess the safety of HIFU intervention-specific mortality, functional outcomes (urinary and sexual functions) and adverse events were considered.

no deaths due to HIFU

No intervention-related deaths occurred in any of the studies.

in controlled study no significant difference in urinary incontinence

in one single-arm study significant improvement in IPSS,
in two studies not

Urinary dysfunction was reported in all studies. In the matched-pair analyses, urinary incontinence occurred in 7.2% of patients in the HIFU group and 3.8% in the brachytherapy group ($p=0.44$). De novo urinary incontinence occurred in three single-arm studies: three patients in one study [23](6%) and two patients in each of the other two studies [21, 22] (2% resp. 3.9%) from pre-HIFU continent patients presented persistent incontinence at 12 months follow-up. One study reported that none of the patients had incontinence [20] at 12 months follow-up. Two single-arm studies [20, 21] found no significant change in urinary function based on the mean IPSS score from

[1] Phoenix criteria: PSA nadir +2ng/mL; Stuttgart criteria: PSA nadir +1.2 ng/mL).

baseline to 3 resp. 12 months follow-up, and one study [22] reported a significant improvement in the IPSS score from baseline to 12 months follow-up (95% CI: 1.6; 4.4).

overall negative impact of HIFU on erectile function

Erectile dysfunction was reported as worsening in the IIEF score or as the number of de novo impotent patients. In the matched-pair analysis 5 pre-HIFU potent patients (11.6%) became impotent (no comparison was possible as it was reported only for the HIFU-group). Two studies identified 20-22% de novo erectile dysfunction in pre-intervention potent patients, whereas one study [20] reported that nearly 48% of previously potent patients became impotent post-intervention (none of the studies reported the time point when this was measured). Two single-arm studies [20, 21] showed a significant negative impact on erectile function 3-12 months after HIFU assessed with the IIEF score ($p<0.001$).

most frequent adverse events were grade 1 and 2

more grade 3 complications with HIFU than with brachytherapy

The most frequent adverse events in all studies were grade 1 and 2 events (urinary tract infection, storage and voiding LUTS). When comparing the severity of adverse events in the matched-pair analysis, the rate of grade 3 complications was higher in HIFU patients than in patients treated with brachytherapy (35% vs. 13%). Especially acute urinary retention and stricture occurred more often in the HIFU-cohort than in the brachytherapy-cohort (more than 20% vs. less than 6% each), however, information on statistical significance was not provided [19].Compared to the matched-pair analysis, which applied whole-gland ablation [19], the rate of storage and voiding LUTS [22, 23] (grade 1), acute urinary retention [20, 22, 23] and stricture [21-23] (grade 3 complications) was considerably lower in the single-arm studies, which applied hemiablation. Rectal fistula (grade 3 complication) occurred only in the matched-pair analysis [19]. Grade 4 complications have not occurred in any of the primary HIFU studies.

Salvage HIFU

salvage HIFU: no significant change in incontinence, but in sexual function, 62% of grade 3 complications

The study on salvage HIFU [24] could not show a significant effect on the IPSS score 6 months post-intervention ($p=0.06$), but reported a significant negative effect on the sexual function based on the IIEF-5 scores 6 months post-intervention ($p<0.001$). Grade 3 complications were observed with a rate of 62%. Three grade 4 complications were also observed.

Upcoming evidence

one RCT in planning phase, one non-RCT completed by end of 2019

A search for ongoing studies identified two RCTs and three non-RCTs of which one was terminated due to lack of inclusions, two had unknown status, however according to the registry data completion date was planned for 2008 and 2014, respectively. Results for both trials are still pending. One RCT is currently in the planning phase of recruitment, and one non-RCT is expected to be completed in November 2019.

Discussion

low quality of evidence

lack of comparative studies, small patients numbers, relative short follow-ups

The overall quality of evidence on HIFU as primary treatment for clinically localised low-risk and intermediate-risk prostate cancer as well as on HIFU as salvage treatment for locally recurrent prostate cancer is very low. Studies are lacking sufficiently high patient numbers, comparators and sufficiently long periods (at least ten years) of follow-up. The small case numbers considerably limit the generalizability of the findings. Furthermore, only two studies reported on outcomes with a follow-up of five years. All outcomes estimates on the efficacy of primary HIFU compared to brachytherapy are based

on only one comparative study, which consisted of two matched single-arm studies. The safety outcome estimates of primary HIFU are based on single-arm studies in addition to the comparative study. Regarding salvage HIFU all outcomes estimates are based on one single-arm study. Direct prospective comparison between deferred treatment modalities (AS, WW) and RP or RT for salvage treatment is completely lacking. An additional limitation that hinders the generalizability of the findings is that the matched-pair analysis applied whole gland ablation, whereas the single-arm studies applied hemiablation of the prostate. Whole gland ablation is associated with a worse side-effect profile (more frequent toxicities, incontinence and erectile problems) compared to hemiablation [25, 26].

limitations of present report: lack of stratification, study included with older version of device, no indirect comparison

Limitations of the present assessment are the lack of stratification to different imaging guidance of HIFU, and additional interventions (TURP, ADT) as these information was often lacking. Moreover, we included the comparative study [19], in which in the first period patients were treated with a previous version of device that is not commercially available anymore. It can be expected that the used device, the type of guidance and any concomitant treatments will have a considerable effect on the effectiveness and safety of HIFU. Another limitation is the abstinence of indirect comparisons, which was not feasible within the timeframe of the rapid assessment.

Evidence gaps

no RCTs

To date there are no published RCTs comparing effectiveness and safety outcomes of HIFU (either as whole gland or hemiablation) and any radical treatment modalities or any deferred treatment modalities. MRI-guided HIFU ablation is such a new approach that the first pivotal studies have been completed just lately and their effectiveness and safety is currently being investigated.

Conclusion

no sufficient evidence; reimbursement not recommended

The current evidence is not sufficient to prove that primary HIFU, as well as salvage HIFU is more effective and safe or as effective, but safer than the comparators AS, WW, RP or RT. Thus, the inclusion in the hospital benefit catalogue is currently not recommended.

need for RCTs

There is a need for prospective RCTs with a higher number of patients and longer follow-up in order to be able to determine if HIFU is a suitable alternative to deferred treatment and/or radical therapies.

Zusammenfassung

Einleitung

Indikation und therapeutisches Ziel

Prostatakarzinom eine der häufigsten Krebsarten bei Männern

Prostatakrebs ist eine der häufigsten Krebsarten bei Männern in Europa. Im Frühstadium ist der Krebs noch lokal begrenzt. Lokal begrenzter Prostatakrebs ist meist indolent und hat keinen großen Einfluss auf die Gesundheit. Eine Behandlung ist hier nicht zwingend notwendig. In Abhängigkeit vom Risiko der Progression vergrößert sich der Tumor und mehr prostataspezifischee Antigene (PSA) werden produziert; eine Behandlung kann hier notwendig werden. Rezidivierender Prostatakrebs tritt auf, wenn der Krebs noch vorhanden ist oder nach erfolgloser Primärtherapie wieder auftritt. Die Neuerkrankungsrate von Prostatakrebs in europäischen Ländern liegt zwischen 35 und 132 pro 100.000 Männer.

Inzidenz in Europa 35-132 pro 100.000 Männer

Zielpopulation: Patienten mit lokal begrenztem Karzinom und lokalem Rezidvkarzinom

Der vorliegende Bericht beschränkte sich auf Patienten mit lokal begrenztem Prostatakrebs und geringem oder mittlerem (intermediären) Risiko sowie auf Patienten mit rezidivierendem Prostatakrebs ohne Befall von Lymphknoten (Nx-NO) und ohne Metastasen (Mx-MO). Geringes Risiko ist definiert als: PSA <10 ng/ml, Gleason Score <7 und cT1a-T2a. Intermediäres Risiko ist definiert als: PSA von 10-20 ng/ml oder Gleason Score von 7 oder T2b.

Beschreibung der Technologie

HIFU nutzt Ultraschall, um Gewebe zu zerstören

Hochintensiver fokussierter Ultraschall (HIFU) macht sich die Nutzung von Ultraschallwellen zu Nutze, um Gewebe zu zerstören. Die Energie der Ultraschallwellen wird hierbei vom Gewebe absorbiert und in Hitze umgewandelt (mehr als 60°C), dabei entsteht eine sogenannte Koagulationsnekrose. Die Ultraschallwellen erzeugen immer im Wechsel eine Kompression (Überdruck) und eine Expansion (Unterdruck).

Schallkopf in Rektum, Anästhesie

Bei HIFU wird, unter Anästhesie, der Schallkopf durch das Rektum (oder auch durch die Harnröhre) eingeführt. Somit kann die Bildgebung in Echtzeit erfolgen und gleichzeitig können die Ultraschallwellen das Gewebe zerstören.

zwei Kategorien

HIFU kann technisch in zwei Kategorien unterteilt werden:

mit Ultraschall-Visualisierung

1. *HIFU mit Ultraschall-Visualisierung* ist der "traditionelle" Ansatz. Diese Variante wird für die Ablation der gesamten oder großer Teile der Prostata angewendet.

mit MRT-Visualisierung

2. Der neuere Ansatz ist *HIFU mit Visualisierung über Magnetresonanztomographie* (MRT). Somit können die Läsionen in der Prostata genauer lokalisiert werden. Diese Variante erlaubt auch eine fokale Ablation der Prostata.

Unterscheidung Ablation gesamte Prostata oder Teile

Anhand der beiden Varianten der Ablation wurde im vorliegenden Bericht zwischen einer kompletten und einer teilweisen (fokal) Ablation der Prostata differenziert. Es besteht kein Konsens, was eine fokale Therapie auszeichnet, daher wurden alle Ablationen, die Teile der Prostata erhalten, unter „fokal" gezählt (z.B. Hemiablation).

primärer HIFU und Salvage-HIFU

Die Therapie eines lokal begrenzten Prostatakarzinoms wird als primärer HIFU und die Therapie eines Rezidivkarzinom wird als Salvage-HIFU (d. h. „rettender" HIFU) bezeichnet.

CE-Zertifizierung

Die CE-Zertifizierung von HIFU wurde für die Behandlung von Patienten mit primärem, lokal begrenztem oder rezidivierendem Prostatakrebs nach bereits erfolgter Therapie, erteilt.

propagierter Vorteil: weniger Komplikationen

Der Vorteil von HIFU soll in der signifikant geringeren Anzahl von Komplikationen liegen, aber auch in der Reduktion von Toxizitäten im Vergleich zu anderen Ablationstechniken und geringerer Blutverlust, besonders im Vergleich zu chirurgischen Verfahren.

Die Vergleichsinterventionen

aktive Überwachung und wachsames Abwarten

Aktive Überwachung und wachsames Abwarten sind Behandlungsoptionen für Männer mit lokal begrenztem Prostatakarzinom, die nicht für einen Eingriff geeignet sind. Diese beiden Optionen sollen vor allem eine Überbehandlung reduzieren.

radikale Prostatektomie

Radikale Prostatektomie ist eine Behandlungsmethode, bei der die Prostatadrüse, inklusive der Samenstränge und umliegendem Gewebe, entfernt wird. Bei der Behandlung soll möglichst die Kontinenz und Potenz erhalten bleiben.

Strahlentherapie

Die **Strahlentherapie** ist eine weitere Behandlungsstrategie, bei der das Tumorgewebe bestrahlt wird (entweder perkutan, mittels Brachytherapie oder einer Kombination aus beidem).

Methoden

Update eines existierenden Berichts aus 2010

Der vorliegende Bericht ist ein Update eines Berichts des LBI-HTA aus dem Jahr 2010. Daher wurde die Literatursuche –in vier Datenbanken (Cochrane Library, Centre for Research and Dissemination, Embase, Medline) – auf Publikationen begrenzt, die nach Jänner 2010 publiziert wurden. Die Suche wurde zudem durch eine Handsuche in den Referenzlisten der eingeschlossenen Studien ergänzt. Laufende Studien wurden durch Suchen in Studien-Registern identifiziert.

Suche in Datenbanken, ergänzt durch Handsuche

Bias-Risiko und Qualität der Evidenz mit verschiedenen Tools

Das Bias-Risiko der Studien wurde mittels der IHE-20-Checkliste für Fallserien und mittels ROBINS-I für nicht randomisierte kontrollierte Studien bewertet. Die Qualität bzw. die Stärke der Evidenz wurde mittels GRADE (Grading of Recommendations, Assessment, Development and Evaluation) vorgenommen.

Vergleichsstudien für Wirksamkeit, zusätzlich Fallserien für Sicherheit

Zur Bewertung der klinischen Wirksamkeit von HIFU wurden ausschließlich Studien mit einer Kontrollgruppe eingeschlossen (entweder randomisierte oder nicht randomisierte kontrollierte Studien). Zur Bewertung der Sicherheit wurden zusätzlich auch prospektive Studien ohne Kontrollgruppe, aber mit mindestens 50 Patienten, eingeschlossen (Fallserien, Registerstudien, etc.).

Ergebnisse

Verfügbare Evidenz

Wirksamkeit

Wirksamkeit: eine nicht randomisierte kontrollierte Studie

Die systematische Literatursuche identifizierte eine nicht randomisierte kontrollierte Studie (eine Matched-Pair-Analyse), die den Einschlusskriterien entsprach. In dieser Studie wurde der HIFU (Ablation der gesamten Prostata) mit der Brachytherapie zur Behandlung von lokal begrenztem Prostatakrebs verglichen. In den Studiengruppen waren jeweils 70 Patienten.

keine weiteren Studien

Es konnten keine weiteren kontrollierten Studien identifiziert werden, die primären oder Salvage-HIFU mit anderen Behandlungsmodalitäten (siehe oben) verglichen

Sicherheit

Sicherheit: eine nicht randomisierte kontrollierte Studie und fünf Fallserien

Die Literatursuche konnte, zusätzlich zu o. g. kontrollierter Studie, fünf weitere prospektive Fallserien zur Bewertung der Sicherheit generieren. In vier dieser Fallserien wurde primärer HIFU mittels Hemiablation und in einer Studie wurde eine Salvage-HIFU mittels Ablation der gesamten Drüse angewendet.

Klinische Wirksamkeit

Primärer HIFU

primärer HIFU: keine signifikanten Unterschiede bezüglich Mortalität zwischen HIFU und Brachytherapie

Um den Effekt von HIFU auf die Mortalität zu untersuchen, wurden zwei Endpunkte herangezogen: Gesamtüberleben und krebsspezifisches Überleben. Beide Raten waren mit HIFU etwas geringer als mit Brachytherapie, die Unterschiede waren aber nicht statistisch signifikant (88 vs. 97.5 %, Hazard Ratio 0,24, Konfidenzintervall 0,01-1,34 und 89 % vs. 92 %, Hazard Ratio 0,67, Konfidenzintervall 0,32-1,29).

biochemisches Rezidiv-freies Überleben mit HIFU signifikant niedriger

Um den Effekt von HIFU auf die Progression (oder die Rezidivbildung) bei lokal begrenztem Prostatakrebs zu beschreiben, wurde der Endpunkt „biochemisches Rezidiv-freies Überleben“ herangezogen (ein Surrogat-Parameter und nicht zu verwechseln mit „lokale Rezidive“). Das biochemische Rezidiv-freie Überleben war bei HIFU-Patienten signifikant geringer, als bei Patienten, die mit Brachytherapie behandelt wurden (53,1 vs. 68,5 %, Hazard Ratio 0,41, Konfidenzintervall 0,19-0,81 nach Phoenix, 51,3 vs. 60,9 %, Hazard Ratio 0,39, Konfidenzintervall 0,19-0,74 nach Stuttgart, $p<0,05$ für beide)[2]. Zusätzliche Endpunkte, wie insbesondere der kritische Endpunkt „lokale Rezidive“ wurden nicht berichtet.

Salvage-HIFU

Salvage-HIFU: keine Evidenz

Es konnte keine Evidenz identifiziert werden, die die Wirksamkeit von Salvage-HIFU mit anderen Interventionen verglich.

Sicherheit

Primärer HIFU

Sicherheits-Endpunkte

Zur Bewertung der Sicherheit wurden die Interventions-bedingte Mortalität, Funktionsstörungen (Blase betreffend und sexuell) und unerwünschte Ereignisse als Endpunkte herangezogen.

kein Todesfall mit HIFU

In keiner der identifizierten Studien starben Patienten aufgrund von HIFU.

in kontrollierter Studie keine signifikanten Unterschiede bei Inkontinenz; in zwei Fallserien bei IPSS keine signifikanten Verbesserungen

Blasenfunktionsstörungen wurden in allen Studien erhoben. In der kontrollierten Studie waren nach HIFU 7,2 % und nach Brachytherapie 3,8 % der Patienten inkontinent ($p=0,44$). Die Messung der Inkontinenz anhand des IPSS (International Prostate Symptom Score) wurde in drei Fallserien vorgenommen, wobei in zwei Studien keine signifikanten Änderungen festgestellt wurden und in einer Fallserie eine signifikante Verbesserung berichtet wurde.

[2] Phoenix: tiefster PSA-Wert +2ng/ml; Stuttgart: tiefster PSA-Wert +1.2 ng/ml).

Erektionsstörungen wurden entweder anhand des IIEF (International Index of Erectile Function) oder anhand der Anzahl der impotenten Männer angegeben. In der kontrollierten Studie wurden nach HIFU insgesamt fünf Männer impotent (11,6 %, ein Vergleich war nicht gegeben, da Erektionsstörungen nur bei HIFU-Patienten erhoben wurden). Zwei der Fallserien gaben an, dass 20-22 % der Männer nach HIFU impotent waren. In einer Fallserie war diese Rate 48 % hoch. Zwei Fallserien berichteten über eine signifikante Verschlechterung der Erektion nach HIFU mit dem IIEF-Score ($p<0,001$).

insgesamt negativer Effekt von HIFU auf Potenz

Die häufigsten unterwünschten Ereignisse in den Studien waren Grad 1 und 2 (Infektionen, unerwünschter Harnabgang, etc.). Aus der kontrollierten Studie ging hervor, dass Komplikationen mit Grad 3 bei HIFU häufiger waren, als bei Brachytherapie (35 % vs. 13 %). In den Fallserien, wo eine Hemiablation der Prostata angewendet wurde, war die Komplikationsrate etwas niedriger, als in der kontrollierten Studie, wo die gesamte Prostata einer Ablation unterzogen wurde. Rektale Fisteln traten ausschließlich in der kontrollierten Studie auf. Grad 4 Komplikationen traten in keiner der Studien auf.

Komplikationen vorwiegend Grad 1 und 2

HIFU im Vergleich zu Brachytherapie: etwas mehr schwerwiegendere unerwünschte Ereignisse mit HIFU

Salvage-HIFU

Die Fallserie zu Salvage-HIFU konnte keine signifikanten Effekte bezüglich Inkontinenz feststellen (gemessen mit IPSS; sechs Monate nach HIFU, $p=0,06$). Jedoch lag auch in dieser Studie ein negativer Effekt von HIFU auf die Potenz vor (gemessen mit IIEF-5 Score sechs Monate nach HIFU, $p<0,001$). Grad 3 Komplikationen traten zu 62 % auf und es gab drei Grad 4 Komplikationen.

Salvage-HIFU: keine signifikanten Veränderungen bei Inkontinenz, aber bei Potenz, 62 % Grad 3 Komplikationen

Laufende Studien

Die Suche nach laufenden Studien ergab, dass von zwei randomisierten kontrollierten Studien eine in der Planungsphase ist und eine einen unbekanntem Status hat (die Publikation sollte 2014 erfolgen, es wurde jedoch keine gefunden). Weiters waren drei nicht randomisierte kontrollierte Studien registriert, von der eine im November 2019 beendet werden soll. Von den beiden anderen Studien wurde eine abgebrochen und die andere sollte 2008 publiziert werden, aber eine Publikation konnten nicht gefunden werden.

ein RCT in Planung, ein non-RCT Ende 2019

Diskussion

Die Qualität der Evidenz von HIFU als primäre Behandlung von lokal begrenztem Prostatakrebs mit geringem und mittlerem Risiko sowie als Salvage-Therapie von rezidivierendem Prostatakrebs ist sehr gering. Es fehlen vor allem Studien mit einer entsprechend großen Fallzahl, mit einer Vergleichsgruppe und genügend langen Nachbeobachtungszeiträumen. Somit lassen sich die Studienergebnisse kaum generalisieren. Alle Aussagen bezüglich der Wirksamkeit beruhen auf lediglich einer kontrollierten Studie, die jedoch eine sogenannte Matched-Pair-Analyse war. Die Bewertung der Sicherheit beruht, zusätzlich zu o. g. kontrollierter Studie, auf fünf Fallserien. Somit gibt es keine direkten Vergleiche von HIFU zu anderen Interventionen, wie aktive Überwachung oder auch radikale Prostatektomie. Eine weitere Limitation ist, dass in der Matched-Pair-Analyse die gesamte Prostata mittels HIFU zerstört wurde, in den Fallserien wurde jedoch die Hemiablation angewendet, die mit einer geringeren Komplikationsrate assoziiert ist.

sehr geringe Qualität der Evidenz

Mangel an Vergleichsstudien, geringe Fallzahlen, kurze Nachbeobachtungszeit

Limitationen vorliegender Bericht: fehlende Stratifizierung, Studie mit veraltetem Gerät eingeschlossen, keine indirekten Vergleiche

Die Limitationen des vorliegenden Berichts liegen insbesondere in der fehlenden Stratifizierung nach den zwei Kategorien der Visualisierung (MRT oder Ultraschall) und nach begleitenden Interventionen. Jedoch waren diese Informationen in den Studien zum Teil nicht gegeben. Weiters wurde die kontrollierte Studie eingeschlossen, obwohl in dieser ein Teil der Patienten mit einem veralteten HIFU-Gerät behandelt wurde, welches nicht mehr erworben werden kann. Es kann aber davon ausgegangen werden, dass gerade die Art der Visualisierung, begleitende Interventionen und auch das HIFU-Gerät einen entscheidenden Einfluss auf Studienergebnisse haben. Eine weitere Limitation ist der Verzicht auf indirekte Vergleiche, da dies im Rahmen der relativ kurzen Projektdauer nicht möglich gewesen wäre.

Evidenzlücken

keine randomisierten kontrollierten Studien

Aktuell fehlen randomisierte kontrollierte Studien, die HIFU (sowohl zur Ablation der gesamten als auch Teile der Prostata) mit anderen Therapieoptionen vergleichen. Außerdem ist HIFU unter MRT-Visualisierung noch so neu, dass hier Studien erst kürzlich beendet wurden.

Empfehlung

keine ausreichend robuste Evidenz, Aufnahme derzeit nicht empfohlen

Die derzeitige Evidenz ist nicht ausreichend, um die Effektivität und Sicherheit des primären HIFU als auch des Salvage-HIFU im Vergleich zu aktiver Überwachung, wachsamen Abwarten, radikaler Prostatektomie oder Radiotherapie zu demonstrieren. Daher wird eine Aufnahme in den Leistungskatalog nicht empfohlen.

randomisierte kontrollierte Studien von Nöten

Es besteht der Bedarf an randomisierten kontrollierten Studien mit einer ausreichend großen Patientenzahl und genügend langen Nachbeobachtungszeiträumen.

Summary of the assessment 2010

Update von HTA- Bericht 2010

Commissioned by the Austrian Ministry of Health, the HTA-report "High-intensity focused ultrasound (HIFU) for the treatment of prostate cancer" was prepared by the Ludwig Boltzmann Institute of Health Technology Assessments (LBI-HTA) in March 2010 [15]. This report provides the basis for the current update. The following paragraphs summarize the scope, the results and the recommendation of the 2010 report.

Scope 2010

PIKO -Frage

1. Is HIFU for primary treatment of men with clinically localised or locally advanced prostate cancer an effective and safe alternative to conventional surgical and non-surgical treatment methods, such as radical prostatectomy, radiotherapy (with/without hormone therapy for locally advanced tumour) or active surveillance?
2. Is HIFU for treating men with locally recurrent prostate cancer after failed radical prostatectomy or external beam radiotherapy an effective and safe alternative to radical prostatectomy or radiotherapy (with or without hormone therapy)?

Inclusion criteria for relevant studies are summarised in Table 1.

Table 1: Inclusion criteria

Population	✿ Men with localised (T1-T2, N0-Nx, M0) primary prostate cancer ✿ Men with locally advanced (T3-T4, N0-Nx, M0) primary prostate cancer ✿ Men with locally recurrent prostate cancer after failed radical prostatectomy or external beam radiotherapy
Intervention	High-intensity focused ultrasound (HIFU): ✿ Ablatherm® (Prototypen, Maxis, Integrated Imaging) by EDAP TMS, France ✿ Sonablate® (200, 500) by Focus Surgery, Inc., USA
Control intervention	✿ Radical prostatectomy with or without pelvic lymph node dissection ✿ External radiation therapy (with or without hormone therapy) or interstitial brachytherapy ✿ Active surveillance
Outcomes	Effectiveness: ✿ Clinical (surrogate) endpoints: PSA-kinetics, histology ✿ Patient-relevant: 5 year survival, disease-free survival, overall survival, quality of life Safety: ✿ Morbidity: acute/chronic urinary tract disorder, urinary incontinence, urinary tract infection, stricture/stenosis (bladder neck/urethra), erectile dysfunction, urethrorectal fistula, chronic pain ✿ Mortality
Study design	✿ for Effectiveness: prospective studies with >50 patients ✿ for Safety: prospective studies with > 50 patients

entscheidende Endpunkte

The following outcomes were defined as crucial to derive a recommendation in the report 2010.

Clinical effectiveness:

- Biochemical disease-free survival
- Overall survival
- Negative biopsy rate
- Prostate cancer specific survival

Safety:

- Adverse events urinary tract
- Adverse events potency
- Adverse events rectum
- Pain
- IPSS score
- IPSS-Quality of life

Results

keine Vergleichsstudien vorhanden

No comparative studies to assess the effectiveness and safety of HIFU could be identified. In total 21 studies were included, all of which were case series.

21 Fallserien: 11 Ablatherm® 7 Sonablate®

For assessing HIFU as primary therapy 18 studies were included of which eleven investigated the Ablatherm® and seven investigated the Sonablate® devices. As described in the report, many of the studies reported on the same patient population. For the assessment of salvage HIFU the included three studies investigated the Ablatherm® device.

disease-free survival rate: 66-77% nach 7 Jahren mit Ablatherm®

78% nach 5 Jahren mit Sonablate®

The biochemical disease-free survival rate in clinically localised PCa ranged between 66 and 77% after five years and 69% after seven years in the Ablatherm® studies, whereas it was 78% after five years in the Sonablate® studies. A direct comparison of disease-free survival was not possible on the basis of the available data; an indirect comparison showed that the biochemical disease-free survival of both Ablatherm® and Sonablate® corresponded that of radical prostatectomy, which ranged between 69 and 84% after five years and between 52 and 75% after ten years in clinically localised prostate cancer.

Overall survival: nur von einer Studie berichtet QoL in 14 Studien berichtet

Overall survival or disease-specific survival was reported in only one study. Other patient-relevant outcomes such as quality of life were measured with questionnaires in a total of 14 studies, however, only a few studies presented evaluable data. Adverse events of HIFU therapy mainly affected the urinary tract, the rectum, and the erectile function.

Limitation: PatientInnenselektion

The report highlighted important limitations of the available evidence, namely that most of the case series involved patients with localised prostate cancer with favorable prognostic factors, usually younger than 70 years. Furthermore, the report also pointed out that in addition to radical prostatectomy and radiation therapy, active surveillance would be also an option in this patient population, although would require short-term control (digital rectal examination, PSA measurement, biopsy), but with fewer side effects, and would impair patient quality of life less than HIFU treatment.

Qualität der Evidenz: sehr niedrig

The quality of evidence was rated “very low” due to the uncontrolled study design and that publication bias was suspected in 16 case series.

Recommendation

The available evidence included in the report 2010 was insufficient to prove, that HIFU is an effective and safe alternative to conventional surgical and non-surgical prostate cancer treatments (such as radical prostatectomy, radiotherapy). Therefore the inclusion in the service catalog was not recommended.

keine Empfehlung zur Aufnahme in 2010 aufgrund unzureichender Evidenzlage

1 Scope (2018)

1.1 PICO questions

PIKO-Frage zu primärer HIFU

Is primary HIFU in comparison to AS, WW, RP or RT in patients with low-risk or intermediate-risk clinically localised prostate cancer more effective (or at least as effective) concerning overall survival, prostate cancer specific survival, local disease recurrence, and/or safer (or at least as safe) concerning intervention-specific mortality, serious adverse events and functional outcomes (urinary function and sexual function)?

PIKO-Frage zu Salvage-HIFU

Is salvage HIFU in comparison to AS, WW, salvage RT, or salvage RP in patients with low-risk or intermediate-risk locally relapsed/recurrent prostate cancer after failed RP, RT or HIFU more effective (or at least as effective) concerning overall survival, prostate cancer specific survival, local disease recurrence, and/or safer (or at least as safe) concerning intervention-specific mortality, serious adverse events and functional outcomes (urinary function and sexual function)?

1.2 Inclusion criteria

Einschlusskriterien für relevante Studien

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

Table 1-1: Inclusion criteria

Description	Project scope
Population	✲ Adult men with clinically localised prostate cancer (cT1a-T2, No-Nx, Mo) based on TNM staging, Gleason score (GS), serum PSA ✲ Low-risk: clinical stage cT1a-T2a, GS≤ 6, PSA < 10 ng/mL ✲ Intermediate-risk: clinical stage T2b, GS 7, PSA 10 to 20 ng/mL ✲ Adult men with locally relapsed/recurrent prostate cancer after failed radical prostatectomy (RP), radiation therapy (RT), or high-intensity focused ultrasound (HIFU) (cT1a-T2, No-Nx, Mo) ✲ MeSH: prostatic neoplasms C04.588.945.440.770, C12.294.260.750, C12.294.565.625, C12.758.409.750 ✲ ICD-10: C61 Malignant neoplasm of prostate ✲ Intended use of the technology: *first-line treatment or salvage therapy*. Rationale: population was defined based on the EAU guideline [1], NICE guideline [27], S3 Leitlinie (German oncology guideline program) [28] and the indications of CE mark approvals.
Intervention	✲ Whole gland ablation or focal therapy of the prostate gland using HIFU with trans-rectal ultrasound imaging (TRUS) guidance or with magnetic resonance imaging (MRI) guidance ✲ MeSH: E02.565.280.945.399, E04.014.380 ✲ Products/manufacturers: ✲ Ablatherm® (company: EDAP TMS, France) ✲ Ablatherm® Integrated Imaging and its predecessors (Ablatherm® Maxis and Ablatherm® prototype) ✲ Focal One® ✲ Sonablate® (company: Focus Surgery, Inc., USA) ✲ Sonablate® 500 and its predecessors (Sonablate® 200, Sonablate® 450) ✲ Sonasource® ✲ ExAblate® system (company: Insightec, Israel): focal therapy ✲ TULSA-PRO® (company: Profound Medical, Canada): focal therapy

Comparison	❁ Deferred treatment: ❁ Active surveillance/monitoring (AS) ❁ Watchful waiting (WW) ❁ Radical prostatectomy (RP) with or without pelvic lymphadenectomy including: ❁ Laparoscopic surgery ❁ Robotic surgery ❁ Open surgery ❁ Definitive radiotherapy (RT) including but not restricted to: ❁ External-beam radiation therapy (EBRT) with or without short-term androgen deprivation therapy (ADT) ❁ 3D conformal radiotherapy ❁ Intensity modulated radiotherapy (IMRT) with or without image guided radiotherapy (IGR) ❁ Brachytherapy ❁ Low dose rate (LDR) or ❁ High dose rate (HDR) ❁ Combination of EBRT and brachytherapy Rationale: standard interventions for the target population according to the clinical guidelines (S3 Leitlinie [28], NICE [27], EAU [1]).
Outcomes	**Effectiveness-related:** ❁ **Overall survival/mortality** (e.g. 5 and 10 year survival) (critical) ❁ **Prostate cancer specific survival/mortality** (critical) ❁ **Local disease recurrence** (presence of clinically significant PCa measured by biopsy and/or mpMRI) (critical) ❁ Distant disease recurrence/metastases (important) ❁ Biochemical recurrence/failure (increasing PSA level according to ASTRO or Phoenix definition) (important) ❁ Disease progression/pathological progression (increase in GS or tumour volume evidenced by a larger number of positive biopsies or larger per-core tumour involvement) (important) ❁ Quality of life (QoL): generic and/or disease specific (measured by one of the following: UCLA-EPIC, EORTC-QLQ-30, FACIT (FACT-P and FACT-G), MAX-PC, PORPUS, EQ-5D) (important) ❁ Need for salvage local therapy and need for systemic (hormonal or chemotherapeutic) therapy (important) ❁ Ablation failure (failure of the technique to destroy the tissue in the treated zone, including targeting failure) (important) **Safety-related:** ❁ **Intervention-specific mortality** (peri-operative death) (critical) ❁ **Functional outcomes** (critical) ❁ **Urinary (dys)function**: urinary incontinence (reported as number of patients with urinary leakage or number of patients with new onset of pads required) or worsening of urinary tract symptoms (increase in the IPSS score) ❁ **Sexual (dys)function**: loss of erectile function (reported as number of patients with new onset of importance) or worsening in erectile function (decrease in the IIEF-5, IIEF-15, or BMSFI score) ❁ Clavien-Dindo grade 1-2 procedural complications/adverse events (AEs), including but not restricted to (important) ❁ Urinary tract infection ❁ Storage or voiding lower urinary tract symptoms (LUTS) ❁ Acute/chronic urinary retention ❁ Burn, injuries, bleeding ❁ Proctitis ❁ Pain ❁ Anaesthesia-related complications ❁ Thromboembolic disease (phlebitis) ❁ Clavien-Dindo grade 3-4 procedural complications/serous adverse events (SAEs), including but not restricted to (critical) ❁ Bladder neck/urethral stricture/stenosis ❁ Bladder neck obstruction ❁ Rectal fistula Rationale: we have chosen the outcomes based on the recommended core outcome set for localised prostate cancer [29], Consensus paper on the standardization of definitions on focal therapy of prostate cancer [30], EUnetHTA guidelines on clinical endpoints and safety [31-33], EAU guideline [1].
Study design	**Effectiveness:** randomized controlled trials (RCTs), prospective non-RCTs **Safety:** RCTs, prospective non-RCTs, single arm prospective cohort studies with ≥ 50 patients

2 Methods

2.1 Research questions

Description of the technology	
Element ID	**Research question**
B0001	What is high intensity focused ultrasound (HIFU) ablation with trans-rectal ultrasound (TRUS) imaging guidance or with magnetic resonance imaging (MRI) guidance? What is active surveillance (AS)? What is watchful waiting (WW)? What is radical prostatectomy (RP)? What is definitive radiotherapy (RT)?
A0020	For which indications has HIFU received marketing authorisation or CE marking?
B0002	What is the claimed benefit of HIFU in relation to AS, WW, RP and RT?
B0003	What is the phase of development and implementation of HIFU?
B0004	Who administers HIFU? In what context and level of care is HIFU provided?
B0008	What kind of special premises are needed to use HIFU?
B0009	What supplies are needed to use HIFU?
A0021	What is the reimbursement status of HIFU?

Health problem and Current Use	
Element ID	**Research question**
A0002	What is clinically localised prostate cancer and locally relapsed/recurrent prostate cancer?
A0003	What are the known risk factors for prostate cancer?
A0004	What is the natural course of prostate cancer?
A0005	What is the burden of disease for the prostate cancer patient?
A0006	What are the consequences of prostate cancer for the society?
A0024	How is prostate cancer currently diagnosed according to published guidelines and in practice?
A0025	How is prostate cancer currently managed according to published guidelines and in practice?
A0007	What is clinically localised prostate cancer (cT1a-T2, N0-Nx, M0) and locally relapsed/recurrent prostate cancer (cT1a-T2, N0-Nx, M0)?
A0023	How many people belong to the clinically localised prostate cancer (cT1a-T2, N0-Nx, M0) and locally relapsed/recurrent prostate cancer (cT1a-T2, N0-Nx, M0) patients?
A0011	How much is HIFU utilised?

Clinical Effectiveness	
Element ID	**Research question**
D0001	What is the expected beneficial effect of HIFU on mortality?
D0005	How does HIFU affect symptoms and findings (severity, frequency) of localised and locally recurrent prostate cancer?
D0006	How does HIFU affect progression (or recurrence) of localised and locally recurrent prostate cancer?
D0011	What is the effect of HIFU on patients' body functions?
D0016	How does the use of HIFU affect activities of daily living?
D0012	What is the effect of HIFU on generic health-related quality of life?
D0013	What is the effect of HIFU on disease-specific quality of life?
D0017	Were patients satisfied with the use of HIFU?

Safety	
Element ID	Research question
C0008	How safe is HIFU in comparison to AS, WW, RT, RP?
C0002	Are the harms related to dosage or frequency of applying HIFU?
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 HIFU?
C0007	Is HIFU associated with user-dependent harms?
B0010	What kind of data/records and/or registry is needed to monitor the use of HIFU?

2.2 Sources

Quellen zu Technologie

Description of the technology

- Handsearch in the CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Questionnaire completed by the submitting hospital

Quellen zu Erkrankung und derzeitigem Einsatz

Health problem and Current Use

- Handsearch in the CRD databases for Health Technology Assessments
- Background publications identified in database search: see Section 2.3
- Questionnaire completed by the submitting hospital

2.3 Systematic literature search

systematische Literatursuche in 4 Datenbanken

The systematic literature search was conducted on 01.12.2017 in the following databases:

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

Suche nach neuen Publikationen nach Jänner 2010

Since the present assessment is an update of the systematic review on HIFU from 2010 [15], the time period of the search was limited from January 2010 to December 2017. The search strategy of the 2010 LBI-HTA report was complemented with search for MRI-guided focused ultrasound as this new HIFU approach received CE mark in 2016. Detailed tables on search strategy are included in the Appendix.

Suche Leitlinien in "UptoDate-Datenbank"

Clinical Practice Guidelines (CPGs) were searched in the UptoDate database, through handsearch and consultation with clinical experts comprehensive to the systematic search.

Furthermore, to identify ongoing and unpublished studies, a search in three clinical trial registries (ClinicalTrials.gov; WHO-ICTRP; EU Clinical Trials) was conducted on 29.12.2017 and on 02.01.2018 resulting in 42 potential relevant hits.

Suche nach laufenden Studien

Manufacturers did not submit any publications, or submission files, as well as a cross-reference search did not identify any additional publications.

keine Studien von Herstellern erhalten

2.4 Flow chart of study selection

Overall 1200 hits were identified, after deduplication 884 hits remained for screening. The author and co-author independently screened the titles and abstracts and selected studies according to the pre-defined inclusion as outlined in Table 1-1 for full-text examination. In case of disagreement a third researcher was involved to solve the differences. The selection process is displayed in Figure 2-1.

Literaturauswahl nach Deduplikation 884 Treffer

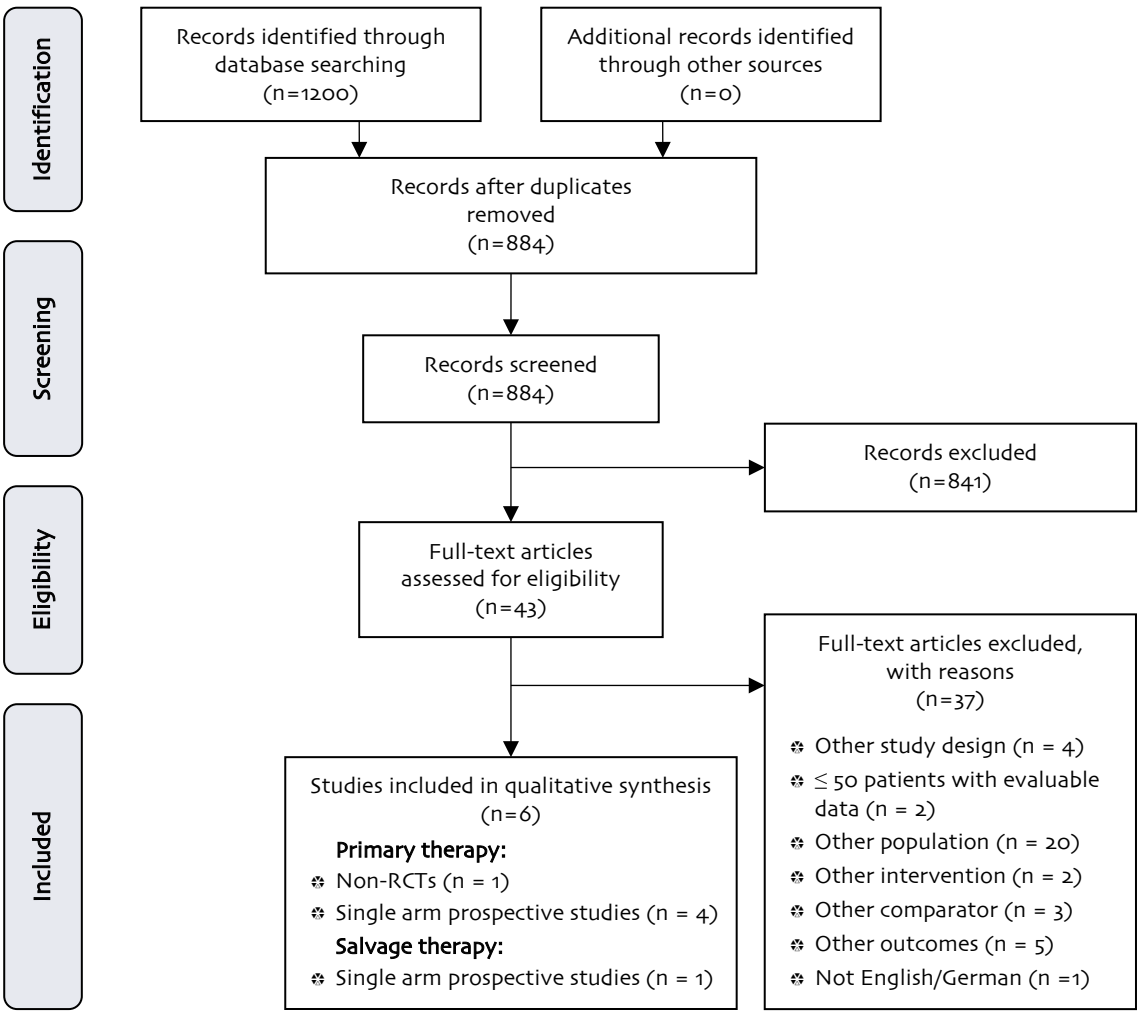

Figure 2-1: Flow chart of study selection (PRISMA Flow Diagram)

43 Studien auf Volltext-Basis, davon 37 ausgeschlossen, letztlich 6 Studien für Datensynthese

43 full-text publications were assessed for eligibility by the author and the co-author independently. 37 publications were excluded according to the pre-defined exclusion criteria: retrospective study design (other study design), less than 50 patients (low-and intermediate-risk) with evaluable data, studies with patients from all risk groups where the number of low-and intermediate risk patients cannot be distinguished (other population), studies in which HIFU is administered as combination therapy (other intervention), comparison of two HIFU modalities (other comparator), none of the study outcomes included in the present assessment (other outcomes), and language other than English or German. Disagreements were resolved by consensus. In the end, a total of six studies were included for data synthesis, of which one was a controlled trial (matched-pair analysis) and five were single arm studies.

2.5 Analysis

Datenextraktion und Kontrolle

Data was extracted by the author and checked by the co-author. Evidence tables were created based on the pre-defined outcomes set and information about the study.

Definition klinischer Signifikanz aus Studien übernommen

As raw data could not be retrieved, the definition for clinical significance was accepted as used by the single studies. Nevertheless, clinically significant disease has no universally accepted definition. The most frequently used definitions are summarized in the Appendix.

Angabe von Variablen, je nach Verfügbarkeit und Art der Variable

Continuous variables were given using median, interquartile range (IQR), or overall range according to availability. The mean with standard deviation was used when the former was not available. Categorical variables were given using frequencies and percentages. In determining the rate of positive biopsy results only patients who underwent biopsy were part of the denominator. Functional outcomes were determined in relative rates and as continuous values depending on the available outcome measures. To determine incontinence rate in case of physician reported events, only the number of patients for whom this was reported were part of the denominator. In determining the rate of potency in case of physician reported events, only men who were pre-HIFU potent were part of the denominator. When functional outcomes were reported as continuous values, the pre- and post-intervention data were extracted where available, otherwise mean difference and statistical significance was extracted. To calculate the frequency of adverse events, men lost to-follow up with this outcome were excluded from the denominator.

Meta-Analyse und zusammenfügen der Daten nicht möglich

We could not pool data and perform a meta-analysis on specific outcomes because the available evidence comes exclusively from observational studies with heterogeneous outcome measures.

Beschreibung Technologie und Erkrankung ohne Qualitätsbewertung

For Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (CUR) domains, no quality assessment tool was used, but multiple sources were used in order to validate individual, possibly biased, sources. Descriptive analysis of different information sources was performed.

For the Effectiveness (EFF) and the Safety (SAF) domains we applied EUnetHTA guidelines in the selection of quality rating tools. Risk of bias on study level was assessed using the IHE-20-checklist [16] for the single arm studies (case series) and ROBINS-I [17] for the non-RCT. The author and co-authors performed the risk of bias assessment independently. Disagreements were resolved by consensus.

Bewertung Studienqualität und Bias-Risiko zu Wirksamkeit und Sicherheit durch 2 Wissenschaftler, mittels IHE- Checkliste

2.6 Synthesis

Based on the data extraction tables (see Appendix Table A-1, Table A-2, Table A-3), data on each selected outcome were synthesized. The quality of the body of evidence was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluation) [18]. The author performed the GRADE assessment and the co-author checked it. Disagreements were resolved by consensus. The research questions were answered in plain text format. Please note that some research questions were answered together, i.e. these questions are listed below each other and the answer is provided subsequently.

nach Datenextraktion in Tabellen, Bewertung der Evidenzsynthese anhand von GRADE durch zwei AutorInnen

3 Description and technical characteristics of technolgy

Features of the technology and comparators

B0001 –What is HIFU ablation with trans-rectal ultrasound (TRUS) imaging guidance or with magnetic resonance imaging (MRI) guidance?

HIFU nutzt gebündelte Ultraschallwellen, um Gewebe zu zerstören

HIFU is characterised by the use of ultrasound (US) waves, emitted from a transducer, to cause tissue damage by mechanical and thermal effects, as well as by cavitation. It is called high-intensity referring to the power density of the US waves that exceeds 5 W per cm^2. In the clinical setting HIFU uses frequencies within the range of 0.8-3.5 mHz. Cell death occurs through two physiological mechanisms. Firstly, the energy of the US waves are absorbed by the target tissue and converted to heat (exceeding 60 °C), causing coagulative necrosis. Secondly, inertial cavitation is caused by alternating cycles of compression and rarefaction [1, 5].

unter Narkose Einführung Schallkopf durch Rektum, Katheter für Blasenentleerung, Dauer 1,5-4 Stunden

To administer HIFU, a probe is inserted into the rectum (or urethra) while the patient is anaesthetised. This probe or the MRI in the MRI-guided approach enables real-time visualisation of prostatic tissue and also delivers HIFU energy to destroy the desired target parenchyma [5]. A catheter (suprapubic or urethral) is inserted at the end of the treatment to help the bladder to empty comfortably during recovery. It is removed as soon as possible (one to three weeks). The length of the procedure depends on the size of the prostate gland. Larger glands will take longer to treat completely. A way to estimate time is one hour for every 10 grams of tissue to be treated. Most procedures take 1.5 to 4 hours. Depending on equipment and treatment scheme, e.g. half-gland or focal therapy, treatment time can be shorter. Men may return to office-based work the following day. More intense physical activity can be resumed within 3 to 5 days, though no activity should be started that dislodges the catheter or stirs up bleeding from the catheter insertion site [34].

HIFU in zwei Systeme unterteilbar:

Two major systems of HIFU exist based on the type of imaging guidance during the treatment.

1. *HIFU with TRUS imaging guidance* is the traditional approach and has been in use in Europe for many years. Its major limitation is that visualising the focus of the prostate cancer using current ultrasound systems is not possible. Therefore the treatment strategy with TRUS-guided HIFU is to ablate the whole prostate gland or a relatively large region (hemi or partial ablation) where the site of cancer was found using a mapping biopsy and/or mpMRI. There are three commercially available HIFU systems with TRUS imaging guidance: Ablatherm®, Sonablate 500®, and FocalOne®. The baseline technology of the systems is the same, however, there are some technical differences between the devices: the imaging and therapeutic transducers, the position of the patient, the type of software application for treatment planning and safety monitoring [6-9].

   HIFU mit transrektalem Ultraschall

   dazu zählen:

   Ablatherm®, Sonablate 500®, FocalOne®.

   - Ablatherm® integrates both the imaging transducer and the therapeutic transducer in a single endorectal probe focused at 40 mm. The probe is covered by a latex condom filled with liquid to thermally protect the rectal wall. The probe is mounted on a holder that allows movements in three spatial directions. The patient lies in a lateral sitting position during the treatment. There are four treatment protocols: primary care, retreatment, radiation failure and post-brachytherapy.

     Ablatherm® integriert Schallgeber für Visualisierung und Ablation in einer Sonde

Before the treatment the probes are set up to target the thermal lesion within the prostate, and the operator defines the boundaries of the target area. The device has a real-time ultrasound monitoring [7].

Sonablate 500® nutzt doppelseitige Sonde

- Sonablate 500® and its predecessors have a console (portable system with display monitor, motor with three axis, probe holding arm), a fully integrated probe and a module for degassing and circulating chilled water. The probe uses double-sided and dual-mode transducers for imaging and treatment. The transducer has two focal lengths (30-40 mm). The user can switch between these lengths to treat the ventral and the dorsal part of the prostate consecutively. The patient lies in a supine position during the treatment. The treatment is carried out in two or three consecutive layers, depending on the anterior-posterior dimensions of the prostate, starting with the anterior portion and moving to the posterior part by changing the focal length during the procedure. The maximum distance from the transducer that can be treated is 40 mm. The device has a real-time ultrasound monitoring [7].

FocalOne®.nutzt MRT zur präoperativen Visualisierung

- FocalOne® device has integrated software for the image fusion of real-time transrectal ultrasound and pretreatment MRI images. This allows the image-guided HIFU treatment of a defined zone and sparing the rest of the prostate tissue. The transducer's focal length is maximum 60 mm and can be modified during treatment. This dynamic focusing makes it possible to better match the treated area to the morphology of the prostate, keeping the focal point always inside the prostate. This allows the treatment of various sized prostates with various anterior-posterior distances and shortens the duration of treatment [7].

neuerer Ansatz: HIFU unter MRT

dazu zählen:

ExAblate®, TULSA-PRO®

2. The novel approach is the *HIFU system with MRI guidance*. MR imaging provides high resolution imaging for patient-specific treatment planning and real-time thermometry for temperature monitoring throughout the treatment. MRI makes the localisation of lesions within the prostate possible allowing the optimisation of ablation treatment zone; hence the focal treatment (FT) of the prostate is also possible. There are currently two MRI-integrated systems using transrectal or transurethral transmission routes for treatment of the prostate lesions. These systems are fully integrated with the MRI console with temperature feedback control to adjust power, frequency, and rotation rate [6].

ExAblate® auch für Tumore mit weniger als 1 mm Abstand zu angrenzenden Strukturen

- ExAblate®: a movable endorectal focused ultrasound transducer generates an adjustable focus that can ablate cancerous tissue. The sharp margin of the ultrasound beam allows targeting of tumours within less than 1 mm of the sphincters and neurovascular bundles, with no heat applied to these structures. The active rectal cooling system further safeguards the rectal wall. Final assessment with contrast MRI provides immediate verification of complete ablation [35].

TULSA-PRO® hat 10 Ultraschallköpfe auf Sonde

- TULSA-PRO®: the technology is designed for the destruction of the whole prostate gland in a single procedure that lasts about an hour, but can also be used for any targeted or focal ablation of cancerous tissue. After the ultrasound probe is placed in the prostatic urethra near the target, the treatment is performed with MRI real-time planning and guidance. The ten ultrasound transducers along the probe are selectively activated to deliver energy to the whole gland or the targeted part of the prostate only, heating it and in the process killing its tissue. The probe slowly rotates in order to deliver the ablative energy across the entire prostate or at the planned target. During treatment, real-time MRI is used to verify that the planned heating pattern is accu-

rately delivered. Although no energy is delivered transrectally, an endorectal cooling device is used to prevent any unwanted destruction of nearby tissues. Final assessment with contrast MRI provides immediate verification of complete ablation [36].

Übersicht HIFU-Systeme

The characteristics of HIFU systems and the available devices are outlined in Table 3-1.

Table 3-1: Features of HIFU systems

	TRUS-guided HIFU	TRUS-guided HIFU with MRI-image-fusion	TRUS-guided HIFU	MRI-guided HIFU	MRI-guided HIFU
Name	Ablatherm®	FocalOne®	Sonablate®500	ExAblate® system	TULSA-PRO®
Manufacturer	EDAP TMS, France	EDAP TMS, France	SonaCare Medical, LLC, USA	InSightec Ltd., Israel	Profound Medical Inc, Canada
Classification[3]	IIb	IIb	IIb	IIb	IIb
Frequency used (MHz)	7.5 for imaging and 3 for treatment	NA	6.3 for imaging and 4 for treatment	2.3[4]	Low frequency: 4 to 4.8 High frequency: 13.4 to 14.4[5]
Imaging guidance	Real time with ultrasound	Pre-treatment MRI import and fusion with real-time ultrasound	Real time with ultrasound 3 D visualisation	Real time with MRI[6] (1.5 T and 3 T)	Real-time[7] with MRI
Mode of administration	Transrectal	Transrectal[8]	Transrectal	Transrectal	Transurethral
Patient positioning	Right lateral decubitus[9]	Lateral8	Supine or lithotomy[10]	Supine in a knee-bent position[11, 12] or lithotomy[13]	Supine[14] or lithotomy
Therapeutic transducer	2 transducers: 1 for imaging, 1 for treatment	Multielement transducer[15] with 1 treatment and 1 ultrasound imaging probe[16]	4 (2 for imaging, 2 for treatment)[17]	Moveable endorectal probe and focused ultrasound transducer[18]	Array with 10 transducers

Abbreviations: *MHz = megahertz, MRI = magnetic resonance imaging*

Sources*: FDA, Profound Medical, FUS Foundation, USCF, HIFU-planet, European Urology, Radiology Key, Lindner [37], Yuh [26], HIFUprostateservices, Minogue Med, Gelet [38]*

[3] According to MEDDEV 2. 4/1 Rev. 9 of the European Commission

[4] https://radiology.ucsf.edu/mr-guided-focused-ultrasound-mrgfus-research-china-basin

[5] http://www.profoundmedical.com/wp-content/uploads/2015/05/BrochureEmailable_PDF.pdf

[6] https://dev.fusfoundation.org/news/1853-insightec-earns-ce-mark-for-prostate-cancer

[7] https://dev.fusfoundation.org/news/1740-profound-earns-european-approval-for-prostate-device

[8] http://www.specialiste-en-urologie.fr/wp-content/uploads/2015/04/Focal-One_Livret-Patient-148x210-V-FR_20140206.pdf

[9] https://www.accessdata.fda.gov/cdrh_docs/pdf15/k153023.pdf

[10] https://radiologykey.com/high-intensity-focused-ultrasound-for-prostate-cancer/

[11] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4788859/

[12] http://www.europeanurology.com/article/S0302-2838(12)01333-4/fulltext

[13] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529739/

[14] http://www.profoundmedical.com/new-tulsa/

[15] https://books.google.lt/books...

[16] http://www.minogue-med.com/focalone.html

[17] https://www.hifuprostateservices.com/sonablate-vs-ablatherm/

[18] http://www.europeanurology.com/article/S0302-2838(12)01333-4/fulltext

Unterscheidung Ablation gesamte Prostata oder organerhaltende (fokale) HIFU

Based on the ablation strategy approach we differentiate whole gland ablation and focal therapy.

- Because of the often multi focal and multi clonal nature of PCa, whole gland treatment or ablation was considered standard.

fokale Therapie zu gezielter Behandlung Tumor

- Focal therapy is a tissue-preserving strategy to reduce treatment-related toxicity by minimising the damage caused to the prostate and adjacent tissues. Focal or targeted treatment is delivered only to the target, not the whole gland. This can be all tissue identified as cancerous, or that half of the gland, in which the biopsies were positive. However, in cases with multifocal tumours, it is also possible to treat the only the index lesion (the largest lesion with the highest grade), or all lesions with intermediate or high risk cancer and leave low risk cancer lesions untreated [10].

What is active surveillance (AS)? What is watchful waiting (WW)?

konservative Therapieansätze: aktive Überwachung und wachsames Abwarten

Many men with localised PCa will not benefit from definitive treatment and are candidates for deferred treatment. AS and WW are the two strategies for conservative management that aim to reduce over-treatment. AS applies to patients with a life expectancy over ten years, and low-risk of developing PCa, whereas WW applies to patients with all stages, and a life expectancy of less than ten years [1].

bei aktiver Überwachung engmaschige Kontrolle

In AS the patients remain under close surveillance and treatment is started if they reach predefined thresholds that indicate relevant progression or potential for a life threatening disease. Hence the correct timing for a curative treatment is aimed to be achieved [1].

wachsames Abwarten solange Tumor unauffällig

In WW the patients receive the palliative treatment when the disease-related complaints are developed, according to their symptoms, in order to maintain QoL [1].

What is radical prostatectomy (RP)?

bei radikaler Prostataentfernung chirurgisches Entfernen der gesamten Prostata, entweder offen, laparoskopisch oder mit Roboterassistenz

RP means the removal of the prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain negative margins. Often this procedure is accompanied by bilateral pelvis node dissection, or so-called extended lymph node dissection. The goal of the procedure is to eradicate the disease, while preserving continence and if possible, potency. Patients should have at least ten years life expectancy to be offered this treatment [1]. Moreover, RP can be done laparoscopically, in open surgery or laparoscopically under the assistance of a surgical robot.

What is definitive radiotherapy (RT)?

bei Radiotherapie Bestrahlung Tumor

The goal of RT – either external beam RT (EBRT), brachytherapy or a combination of both – in localised prostate cancer is to deliver a therapeutic dose of radiation to the tumour while minimizing the radiation to normal tissue. EBRT utilizes an external source of radiation to treat the prostate gland and a margin of adjacent normal tissue. Brachytherapy directly implants radioactive source within the prostate, thus providing the highest dose of radiation. It is supposed to maximize irradiation of the tumour while minimizing radiation to normal tissue [14]. In low-dose rate brachytherapy radioactive seeds are permanently implanted. It is widely used in combination with EBRT. High-dose rate brachytherapy means the temporary insertion of radioactive sources. It is used mainly in high-risk PCa [8].

A0020 – For which indications has HIFU received marketing authorisation or CE marking?

CE-Zertifizierung für Behandlung primäres oder rezidivierendes Prostatakarzinom

The CE mark has been awarded for the treatment of patients with primary localised PCa or locally recurrent PCa following prior therapy for the HIFU technology. The various HIFU systems and their regulatory status with the verbatim wording of the indications are presented in Table A-12 in the Appendix. Contraindications are also presented in Table A-12, described only for one device, Sonablate® 500. However, they are generalizable to all transrectal HIFU devices.

HIFU aber auch für andere Indikationen zertifiziert

HIFU also received CE mark for various other indications including the treatment of hypertension, thyroid nodules, soft tissue benign tumours, osteoid osteoma, facetogenic back pain, essential tremor, neuropathic pain, parkinsonian tremor, glaucoma, breast fibroadenoma, uterine fibroids, uterine adenomyosis, bone metastasis and various cancer types (soft tissue, breast, pancreas, liver, kidney and soft tissue) [11].

B0002 – What is the claimed benefit of HIFU in relation to AS, WW, RT, or RP?

Hauptvorteile: weniger Komplikationen, keine negative Effekte durch mehrmalige Anwendung

A major claimed benefit of HIFU is the lack of induction of apoptosis avoiding late complications of treatment, a lack of cumulative effect with the possibility of repeating treatment [7]. It is claimed that HIFU treatment has significantly lower side-effect profile (sexual and urinary dysfunction) [12], and reduces toxicity (due to less damage to the adjacent or intervening tissues) compared to other ablation techniques [10, 13].

HIFU kann innenliegendes Tumorgewebe gezielt zerstören

HIFU has the potential to ablate internal tumour tissue with great precision, and during treatment the tumour can be visualized [7]. HIFU is also able to treat only a small focus, hence the ablation of the entire gland can be spared and it is possible to ablate the targeted tissue or the index lesion only. Focal therapy enables the neurovascular bundle to be spared thereby reducing the risk of sexual dysfunction [5].

AS und WW: mögliche psychische Belastung

Although AS and WW are options to avoid overtreatment and hence treatment-related side effects, they may also carry an increased risk of psychological distress (anxiety, depression), which might considerably affect quality of life. Apart from psychological distress, untreated patients may have a higher level of obstructive urinary symptoms compared to patients treated with definitive therapies. Consequently, appropriate patient selection is a crucial issue [1, 5].

B0003 – What is the phase of development and implementation of HIFU?

HIFU bei Prostatakrebs in 1990ern erstmals eigesetzt, kommerziell zu erwerben in den 2000ern

The first description of HIFU about its ability to destroy tissue was made in 1944, but the technology has been approved only recently for clinical indications. The first experiments on the prostate were made in the early 1990s. The first treatments in men were performed in 1992. The results of a pilot study on PCa treatment were first published in 1996. HIFU devices are available commercially since the early 2000s. The first two commercially available HIFU devices (Ablatherm® and Sonablate®) used ultrasound imaging guidance. FocalOne® was the first device to implement MRI/TRUS image fusion to guide transrectal treatment. HIFU performed with real-time magnetic resonance tomography is the newest and most precise imaging to localise and ablate prostate cancer. In addition, this allows real-time temperature monitoring and visualization of treatment effects [7]. To date, there are two MRI-guided HIFU systems which have CE mark, TULSA PRO® and ExAblate®.

aktuelle Evolutionsstufe mit MRT gesteuert

Administration, Investments, personnel and tools required to use the technology and the comparator(s)

B0004 – Who administers HIFU? In what context and level of care is HIFU provided?

für HIFU benötigt es Team aus mehreren Disziplinen, neben Chirurgie auch Radiologie

While a multi-specialist team is required to deliver the whole procedure, the urological surgeon performs the HIFU treatment itself. For image fusion, the radiologist is involved to perform pre-treatment MRI and provide image data required by the software of the HIFU system. If HIFU is performed under MRI guidance, the urological surgeon and the radiologist and their teams are working hand in hand. Internal technical support is needed to set up, teardown, and disinfect the system after the procedure. The manufacturers require that as part of the training of the surgeons a certain number of procedures need to be done with the assistance of a supervisor/specialist. Afterwards the surgeon gets certified HIFU user and is able to use the device without the assistance of the supervisor [39-41].

HIFU auch tagesklinisch, meist aber Aufenthalt von 2-4 Tagen

Although HIFU can be delivered in a day-surgery setting, patients usually spend two to four days in the hospital due to local reimbursement practice and preoperative evaluation – as reported in one of the included studies conducted in Belgium [42], as well as in the topic submission to the Austrian Ministry of Health.

B0008 – What kind of special premises are needed to use HIFU? and

B0009 – What supplies are needed to use HIFU?

für HIFU überall möglich, wo benötigte Ressourcen verfügbar

HIFU treatment can be performed wherever the required resources (anaesthesia, power, internet, nursing, recovery room, etc.) are available [43]. It is usually done in a urological day-case suite with cystoscopy facilities, degassed water (<3 ppm oxygen) and nonsterile sheaths [8]. The required equipment depends on the type of device. The treatment table with the attached probe is part of the Ablatherm® device. The Sonablate® device has a probe holder which can be attached to any operating table; therefore the treatment can be done in any setting where an operating table is available. MRI-guided HIFU devices require MRI [7]. Most devices require few disposables, usually tubing and covers, gels and fluids.

Regulatory & reimbursement status

A0021 – What is the reimbursement status of HIFU?

Details zu Erstattung und Empfehlungen im Anhang

Detailed information on the reimbursement status and recommendations are included in Table A-12 and Table A-13 in the Appendix.

4 Health Problem and Current Use

Overview of the disease or health condition

A0002 – What is clinically localised prostate cancer and locally relapsed/recurrent prostate cancer?

Prostatakarzinom eine der häufigsten Krebsarten bei Männern in Europa

Prostate cancer (PCa) is the most common non-skin cancer in men in Europe [1]. The malignancy usually originates from glandular epithelial cells, often multi focal and multi clonal. Depending on parameters such as tumour grade, tumour volume and PSA concentration at time of diagnosis, risk stratification is possible. Small low grade cancer is a frequent finding, and usually characterized by slow local growth and the lack of metastasis. This type of tumour is named latent or clinically insignificant, because there is a low risk of progression. With increasing tumour grade, in particular, there is an increasing risk of progression. High-risk prostate cancer shows rapid local growth and a high likelihood of metastasis [2, 3, 44].

in Frühstadium Krebs lokal begrenzt

je nach Risiko metastasiert Krebs früh oder spät

In early stage, prostate cancer is localised and organ-confined [2]. Depending on the risk of progression, the cancerous lesion increases in volume and produces more PSA over time. PCa is called locally advanced when the cancer infiltrates the central or transitional zone of the prostate and adjacent tissues and organs, depending on localisation of the initial lesion in the prostate. Depending on the risk of progression, the cancer can metastasize early or late, into regional or distant lymph nodes. Metastatic prostate cancer is also very likely to produce bone metastases with high variation in size and numbers, in any location [1, 45, 46].

bei Hochrisiko Prostatakrebs schnelle Progression und Metastasen

Krebs mit geringem Risiko: Behandlung meist nicht notwendig

High-risk PCa carries a high likelihood of early locally advanced stage and early metastasis. Therefore it is, in general, life-threatening and has a high rate of cancer-specific morbidity, in particular if diagnosed in younger men [47]. In contrast low risk prostate cancer, in particular in elderly men, most often can be left untreated. It might never cause any problems or affect overall survival [27, 44]. Because risk stratification is based on biopsy findings, however, there is a risk of under or overestimation because of sampling error. During follow-up, a shift of grading can also occur [1, 48].

Rezidive lokal oder durch Metastasen

Recurrence of PCA can be local or due to metastasis. Locally relapsed/recurrent PCa occurs when the cancer is still present or comes back after failed primary therapy. After RP, if it was curative, there is no PSA. After RT, or any other procedure which leaves healthy or noncancerous prostatic tissue behind, PSA is still detectable, the lowest value during follow-up being named the nadir. After RT, any PSA above zero is a proof of recurrence or remaining prostate tissue, either locally or metastatic. In most cases, this is a sign the initial tumour was understaged. After RT, the definition of recurrence is more difficult, and is based on increasing PSA in consecutive measures (Phoenix definition). Biochemical recurrence is a term at first used for patients after RP who had a nadir of zero, showed some PSA increase to a low value which stays on a low level during further follow-up, with no detectable lesion. The term biochemical recurrence is also used for recurrence after other therapies, usually with low tumour burden [49-53].

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

Prostatakrebs wahrscheinlich vorrangig genetisch bedingt

PCa can be divided into three groups: hereditary, familial, and sporadic. Positive family history is a strong epidemiological risk factor for prostate cancer. Gene-environment interactions also play a crucial role in cancer development. Hereditary PCa is demonstrated only in 5% of cases with family history, whereas familial prostate cancer accounts for about 13–25% of cases. Hereditary PCa patients have three or more affected relatives or at least two relatives who have developed early-onset disease, i.e. before the age of 55, and have onset usually six to seven years earlier than spontaneous cases. Epidemiologic studies have shown strong evidence for a genetic predisposition to PCa based on ethnic background too [1, 54].

externe Faktoren z. B. Lebensweise, UV-Strahlung

Exogenous factors may also affect the risk of progression from latent PCa to clinical PCa. These factors such as life-style (diet, sexual behaviour, alcohol consumption), exposure to ultraviolet radiation, chronic inflammation, and occupational exposure are all being considered aetiologically important [1].

A0004 – What is the natural course of prostate cancer?

Verlauf von Prostatakrebs nicht eindeutig, kann jedoch zu Metastasen und zum Tod führen

The natural history of PCa is not totally clarified yet. It might arise from damaged prostate epithelium and progressively develop over many decades, but its heterogeneity and multifocal nature makes it difficult to fully understand its progression. About one-third of men over the age of 50 display histological evidence of PCa. However, the majority of these cases remain clinically insignificant. The likelihood of disease progression is difficult to predict. The progression of the disease is usually slow, nevertheless certain high-grade tumours proceed on a more aggressive course than low-grade, well-differentiated tumours [44]. Nevertheless, PCa can lead to metastases and to death.

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

A0005 – What is the burden of disease for the prostate cancer patient?

Zeichen und Symptome unspezifisch

The signs and symptoms of PCa are unspecific. In the age group affected by PCa, benign prostatic hyperplasia (BPH) and chronic prostatitis are common pre-existing comorbidities causing LUTS. Patients with the primary diagnosis of locally advanced or metastatic disease might suffer from symptoms of these conditions, such as haematuria, incontinence, urinary retention, uni- or bilateral hydronephrosis, urinary tract infection, skeletal pain at various locations. PCa (especially localised disease) is mostly diagnosed as a result of PSA screening, not based on the perceived symptoms. The symptoms of problems in the prostate may be like symptoms of PCA [55].

Diagnose und Behandlung können Lebensqualität negativ beeinflussen

Prostate cancer diagnosis and treatment could have a significant impact on a man's life and cause physical problems such as sexual dysfunction and urinary incontinence, fatigue, pain, hot flashes, body image changes, distant metastasis, lower back pain, weight loss, haematuria, anaemia, inability to walk and force lifestyle changes [56]. Failures to address physical and psychosocial problems can result in suffering for both the patient and their family, and potentially affect the course of the disease [57].

A0006 – What are the consequences of prostate cancer for the society?

häufige Krebsart

PCa is the most common cancer in men in Europe and as life-expectancy increases a subsequent rise in the incidence of PCa is expected along with an increase of the disease's economic burden. There will also be an increased need for resources such as treatment facilities and trained specialists [27].

direkte Kosten Behandlung Prostatakrebs 2.800 bis 5.200 Euro pro Patient

The mean direct costs per patient for initial treatment for PCa were estimated at around EUR 2,800 in the UK, EUR 2,900 in Spain, EUR 3,600 in Germany, EUR 4,650 in Italy, and EUR 5,200 in France. The total estimated costs for all patients in the first year from diagnosis, when the highest proportion of the costs occur, were estimated to be EUR 106 million in the UK, EUR 223 million in Germany, and EUR 352 million in France. This does not include indirect costs, such as time and productivity loss (due to cancer-related illnesses, the impact of the physical and mental suffering of both patients and relatives during diagnosis and follow-up), or end-of-life costs [27]. It is estimated that the total economic costs of PCa in Europe exceeded EUR 8.43 billion in 2009 [1].

Current clinical management of the disease or health condition

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

Verdachtsdiagnose mittels rektaler Untersuchung und/oder PSA

definitive Diagnose über Biopsie

PCa is suspected on the basis of digital rectal examination (DRE) and/or PSA levels; however definitive diagnosis is based on histopathological verification in prostate biopsy cores or specimen from transurethral resection of the prostate (TURP) or prostatectomy for benign prostatic enlargement (BPE). The need for prostate biopsy depends on PSA level and/or suspicious DRE. Although there is no general agreement on the benefit of PSA screening, and no general agreement on the cut-off value to perform a biopsy, it is obvious that higher PSA concentrations indicate a greater likelihood of a positive result, but not definitive sign for PCa [1].

Einteilung Tumorerkrankung über TNM-Klassifikation

Clinical staging is used to stage PCa. It describes the extent of the primary tumour (T stage), the absence or presence of spread to nearby lymph nodes (N stage) and the absence or presence of distant spread, or metastasis (M stage) [1]:

- **T-staging:** the first level of assessment is local tumour stage because the distinction between organ-confined T1/T2 and extraprostatic T3/T4 disease affects treatment decisions. DRE, imaging (transrectal ultrasound (TRUS), multiparametric magnetic resonance imaging (mpMRI)), PSA level and biopsy are tools to predict the final pathological stage of PCa.

T: Stadium Primärtumor

- **N-staging:** it should be performed only when it might directly influence treatment decisions. High PSA values, T2b-T3 stage, poor tumour differentiation and perineural invasion are associated with high risk of nodal metastasis. CT-scan or MRI is used to predict N-stage.

N: Befall Lymphknoten

- **M-staging:** evaluation of bone metastases of PCa using bone scan, PET/CT or MRI.

M: Metastasen

T - Primary tumour		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
T1	Clinically inapparent tumour not palpable or visible by imaging	
	T1a	Tumour incidental histological finding in 5% or less of tissue resected
	T1b	Tumour incidental histological finding in more than 5% of tissue resected
	T1c	Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA) level)
T2	Tumour confined within the prostate[1]	
	T2a	Tumour involves one half of one lobe or less
	T2b	Tumour involves more than half of one lobe, but not both lobes
	T2c	Tumour involves both lobes
T3	Tumour extends through the prostatic capsule[2]	
	T3a	Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
	T3b	Tumour invades seminal vesicle(s)
T4	Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall	
N - Regional lymph nodes[3]		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis[4]	
M - Distant metastasis[5]		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

[1] Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
[2] Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.
[3] The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.
[4] Laterality does not affect the N-classification.
[5] When more than one site of metastasis is present, the most advanced category should be used.

Figure 4-1: TNM classification of prostate cancer
Source: EAU-ESTRO-SIG Guidelines on Prostate cancer, 2016 [1]

Diagnosis of disease recurrence

biochemisches Rezidiv als Zeichen von Rückfall

PSA als Wert

Grenzwert nach Phoenix oder Stuttgart

Biochemical recurrence after curative primary treatment can be a sign of relapse as it universally precedes progression. PSA, although often used as a tumour marker for metastatic disease or subsequent disease progression, is an imprecise marker of risk and PSA rise is not a surrogate for survival endpoints. Treatment failure defined by the PSA level differs between the primary treatment modality the patient received. Following primary RP, there is international consensus that recurrent cancer may be defined by two consecutive PSA values of >0.2 ng/mL and rising. After primary RT, the Phoenix definition of PSA failure is used which defines BCR as any PSA increase >2 ng/mL higher than the PSA nadir value, regardless of the serum concentration of the nadir. To define BCR after primary HIFU the Stuttgart criteria (> PSA nadir + 1.2 ng/mL) was proposed by consensus groups [1].

bei Rückfall wichtig herauszufinden in welchen Regionen

Once a PSA relapse is diagnosed, it is important to determine whether the recurrence developed at local or distant sites [1]. In the diagnosis of this mpMRI is the first step in current clinical practice and it should precede TRUS-guided biopsy, which should follow mpMRI for confirmation. Biopsies should be performed first only at least 24 months after primary therapy. Before considering any local salvage therapy, residual tumour must be demonstrated on histopathology. Once local recurrence is proven, further efforts are needed to rule out metastasis [58].

biochemisches Versagen nach Stuttgart

Biochemical failure was defined according to the Stuttgart definition (a rise of 1.2 ng/ml or more above the nadir PSA) and the Phoenix definition (a rise of 2 ng/ml or more above the nadir PSA).

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

Faktoren mit Einfluss auf Therapiewahl bei lokalisiertem Karzinom

The factors which are considered in the selection of the initial treatment for newly diagnosed localised PCa patients are:

- Anatomic extent of the disease (TNM stage),
- Histologic grade (Gleason score) of the tumour,
- Serum PSA level,
- Estimated outcome with different treatment options,
- Potential complications with each treatment approach,
- The patient's general medical condition, comorbidities,
- The patient's age and life expectancy, as well as
- The individual patient preferences.

Therapieoptionen bei lokalisiertem Karzinom mit geringem Risiko

Standard options for patients with clinically localised low-risk PCa:

- Active surveillance (AS)
- Radiation therapy (RT)
  - External beam (EBRT) or
  - Low-dose rate brachytherapy (LDRB)
- Radical prostatectomy (RP) with optional lymph node dissection
- (Other ablative techniques like cryotherapy and HIFU are not standard)

Therapieoptionen bei lokalisiertem Karzinom mit mittlerem Risiko

Standard options for patients with clinically localised intermediate-risk PCa:

- RT with optional androgen deprivation therapy (ADT)
  - EBRT or
  - High-dose rate brachytherapy (HDRB) or
  - Combination of EBRT and brachytherapy
- RP with pelvic lymph node dissection
- (Other ablative techniques like cryotherapy and HIFU are not standard)
- Watchful waiting (WW) if the life expectancy is limited based upon age and comorbidities [14].

Patientenselektion bei „rettender" Behandlung (Salvage)

There are no standards for patient selection for salvage treatments; however most investigations include patients with biochemical recurrence, local disease and no metastasis and there are some further considerations which help in the treatment decision [49].

- **After failed RT:** patients cannot be treated with additional radiation due to radiation toxicity. They either choose to undergo salvage RP or salvage HIFU. However, these patients often have contraindications for RP (that is the reason they opted for RT), meaning that salvage HIFU remains an option for them.
- **After failed RP:** patients often cannot be treated with salvage RP due to technical constraints (for example in patients with positive margins), as well as imaging limitations which may not be able to identify residual sites of disease. For these reasons salvage RT and salvage HIFU remain options for them.

Therapieoptionen bei lokalisiertem Rezidivkarzinom

Treatment options for locally recurrent prostate cancer are:

- Local salvage therapy:
  - RP
  - RT
  - (Other ablative techniques like cryotherapy and HIFU are not standard).
- **Systemic therapy:** hormonal therapy (ADT) is only recommended to patients who have metastasis, PSA doubling time of <3 months, or have a symptomatic local disease progression [27]. Systemic therapy offer no prospect of cure, patients should fully explore curative salvage options before initiating systemic therapies [49].

HIFU in Leitlinien derzeit als experimentelle Behandlung beschrieben

Considering only HIFU in the guidelines, the EAU guideline [1], along with the unique guidelines from selected European countries (Germany [28], United Kingdom [27]), as well as the American Urologists guideline [59] all recommend the use of HIFU only in the course of clinical trials as it is an experimental treatment (and the same applies for cryotherapy). Available guidelines on HIFU are provided in Table A-11 in the Appendix.

Target population

A0007 – What is clinically localised prostate cancer (cT1a-T2, N0-Nx, M0) and locally relapsed/recurrent prostate cancer (cT1a-T2, N0-Nx, M0)?

Zielpopulation: Patienten mit lokal begrenztem Karzinom und lokalem Rezidvkarzinom mit geringem und mittlerem Risiko

The target population in this assessment is low-risk and intermediate-risk localised and locally recurrent/relapsed prostate cancer patients without any regional lymph nodes (NX-N0) and without any distant metastasis (MX-M0).

- Low-risk is defined as PSA<10 ng/mL, Gleason Score (GS) <7 and cT1a-T2a.
- Intermediate risk is defined as PSA 10-20 ng/mL, or GS 7, or cT2b [1].

The reason for the choice of the target population is outlined in the Scope.

A0023 – How many people belong to the low-intermediate-risk localised and locally relapsed/recurrent prostate cancer patients (cT1a-T2, N0-Nx, M0)?

Inzidenz im Norden und Westen Europas mit mehr als 200 pro 100.000 höher

The incidence of PCa is higher in Northern and Western Europe (>200 per 100,000 men), while rates in Eastern and Southern Europe have shown continues increase [60]. Incidence rates per country reported by the International Agency for Research on Cancer (IARC) in 2014 were as high as 132 per 100,000 men in France, around 100 per 100,000 in Belgium, Finland, Sweden, Switzerland and Lithuania, around 70 per 100,000 in Denmark, the Netherlands, Estonia, Italy, Spain and Portugal, and in Poland and Slovakia around 35 per 100,000 men [4].

Zunahme Neuerkrankungen lokal begrenztes Karzinom in Österreich

A recent study [60] described a rapid increase in the incidence and a pronounced peak in Austria in the last three decades. The annual average localised PCa incidence in Austria is approx. 2,600 cases which is 58% of all PCa cases [61]. During the most recent decade, incidence rates increased the most in Lithuania with an average annual percent change of 19.3% and with the most rapid increase for ages <65 years [60].

Incidence rates of recurrent prostate cancer were not found. However, the proportion of patients who experience recurrence after primary RP and RT has been reported: 20–40% of patients after RP and 30–50% of patients undergoing RT perceive biochemical recurrence within 10 years [3].

keine Daten zu Inzidenz Rezidivkarzinom

A0011 – How much is HIFU utilised?

Data is available for the two biggest manufacturers on approximate number of treated patients. Sonacare Medical's Sonablate® is claimed to be used by over 300 physicians worldwide and over 15,000 procedures had been completed as of 2015 [34].

15.000 Eingriffe mit Sonablate®

EDAP TMS's three generations of commercial devices – Ablatherm® Maxis (from 1993 to 2005), Ablatherm® Integrated Imaging (since 2005) and Focal One® (since 2013) – are claimed to be routinely used for more than 20 years throughout the world with more than 40,000 treatments performed [62].

40.000 Eingriffe mit Ablatherm®

According to the information of the submitting hospital, total utilisation rate in Austria is unclear. In the submitting hospital (1,200 beds; 88,000 inpatients per annum), though, around 30 procedures are delivered annually.

einreichendes Krankenhaus: 30 Eingriffe pro Jahr

5 Clinical effectiveness

5.1 Outcomes

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

entscheidende Endpunkte für Wirksamkeit

- Overall survival
- Prostate cancer specific survival
- Local disease recurrence

The clinical outcomes chosen as *critical* to derive a recommendation are aiming at the avoidance of the natural course of prostate cancer (see A0004).

Auswahl basierend auf Abwendung Verlauf Erkrankung

Overall survival is an outcome to measure how many of the treated patients survived. Ideally, this outcome should be collected after a longer period of time (e.g. after 5 or 10 years after the initial treatment).

Gesamtüberleben, möglichst langfristig erheben

Prostate cancer specific survival is measuring how many patients survive and are not dying due to the prostate cancer (but maybe due to other causes, like age). Again, this outcome should also be collected after a longer period of time (e.g. after 5 or 10 years after the initial treatment).

Prostatakrebs-spezifisches Überleben auch langfristig erheben

Local disease recurrence, though, is a measure of the return of the cancer. It can be measured, for example, by biopsy and/or multiparametric MRI.

lokale Rezidive, z. B. mittels Biopsie

5.2 Included studies

The inclusion criteria for assessing the clinical effectiveness of HIFU, was exclusively restricted to studies with a comparison group, including RCTs and non-RCTs. The systematic literature search identified one non-RCT (matched-pair analysis) that met our inclusion criteria. This study compared whole gland HIFU with brachytherapy, a type of radiotherapy for the treatment of localised prostate cancer, including 70 patients in each treatment arm [19]. Study characteristics and results of included studies are displayed in Table A-1 and in the evidence profile in Table A-6.

für Bewertung Wirksamkeit eine nicht-randomisierte kontrollierte Studie (matched-pair) zu HIFU vs. Brachytherapie

We could not identify any controlled trials comparing HIFU with other treatments, like deferred treatment (AS, WW) or RP (laparoscopic, open or robotic surgery) (see also Scope).

keine Studien mit anderen Vergleichsinterventionen

Patient characteristics

The median age of patients was 74 years in the HIFU-group and 69 years in the brachytherapy-group. Thus, patients in the intervention group were statistically significantly older than patients in the control group ($p<0.01$). Tumour stage was between T1a and T2b for all patients, whereas only 12 vs. 9 patients had an intermediate-risk with stage T2b. The Gleason score was 6 or below 6 in 72.9%, and it was 7 in 27.1% of the included patients in each arm. According to D'Amico, the study included only low and intermediate-risk patients. A total of 19 patients in the HIFU-group and 14 patients in the brachytherapy-group received ADT therapy prior the actual treatment. The

Durchschnittsalter 74 vs. 69 Jahre

Tumorstadium zwischen T1a und T2b

Nachbeobachtung im Mittel 83 vs. 44 Monate

pre-HIFU prostate volume and PSA level were not stated. The median follow-up was 83 months for the HIFU-group and 44 months for the brachytherapy-group (difference was statistically significant, p<0.01).

HIFU procedure and follow-up

HIFU mittels Ablatherm®

HIFU treatment was performed by the use of the Ablatherm® device. However, the first series of patients was treated with Ablatherm® Maxis, which is not commercially available anymore [62]. The second series was treated with Ablatherm® Integrated Imaging. The control group was treated by a permanent transperineal interstitial preloaded-free needles implantation of Iode^{125} using a real-time biplanar ultrasound-guided system [19].

5.3 Results

D0001 – What is the expected beneficial effect of HIFU on mortality?

Gesamtüberleben 88 vs. 97,5 %, Unterschied nicht signifikant

Two outcomes were considered relevant to assess the expected beneficial effect of HIFU on mortality: overall survival and prostate cancer specific survival. After five years, overall survival in the brachytherapy-group compared to HIFU was not significantly different (88 vs. 97.5%, HR 0.24, CI 0.01-1.34) [19].

krebsspezifisches Überleben: 89 vs. 92 %, Unterschied nicht signifikant

Regarding prostate cancer specific survival, after five years, the rate was 89% for patients in the HIFU-group and 92% for patients in the brachytherapy-group. Even though the rate was higher for patients treated with brachytherapy, the difference between the study groups was not significant (HR 0.67, CI 0.32-1.29) [19].

Morbidity

D0005 – How does HIFU affect symptoms and findings (severity, frequency) of clinically localised and locally recurrent prostate cancer? and

D0006 – How does HIFU affect progression (or recurrence) of clinically localised prostate cancer?

biochemisches rezidivfreies Überleben: mittels HIFU signifikant niedriger

Biochemical recurrence-free survival was considered eligible to answer this research question. This outcome (a surrogate and not to be mistaken for "local disease recurrence") was significantly lower for patients in the HIFU-group than for patients in the control group: 53.1 vs. 68.5 % according to the Phoenix and 51.3 vs. 60.9 % according to the Stuttgart definitions (HR 0.41, CI 0.19-0.81 for Phoenix, HR 0.39, CI 0.19-0.74 for Stuttgart, p<0.05 for both) [19][19].

keine Evidenz zu anderen Endpunkten (z. B. zu Bildung von Rezidiven oder Metastasen)

However, the study did not report on additional outcomes that are suitable to answer this research question: need for salvage/systemic therapy, ablation failure, distant disease recurrence/metastases or disease progression/pathological progression or the *critical* outcome "local disease recurrence".

[19] Phoenix criteria: PSA nadir +2ng/mL; Stuttgart criteria: PSA nadir +1.2 ng/mL). See also chapter 4, question A0024

Function

D0011 – What is the effect of HIFU on patients' body functions? and

D0016 – How does the use of HIFU affect activities of daily living?

These two research question will be answered in the next chapter, by presenting the functional outcomes on urinary and sexual (dys)functions (see research question C0008).

Beantwortung im nächsten Kapitel

Health-related quality of life

D0012 – What is the effect of HIFU on generic health-related quality of life? and

D0013 – What is the effect of HIFU on disease-specific quality of life?

No evidence was identified to answer this research question.

keine Evidenz

Patient satisfaction

D0017 – Were patients satisfied with the use of HIFU ?

No evidence was identified to answer this research question.

keine Evidenz

6 Safety

6.1 Outcomes

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

entscheidende Endpunkte für Sicherheit:

- Urinary (dys)function which was defined as the loss of continence (measured with the number of patients with new onset leakage or who started to use pads, or physician reported events), or as worsening of urinary symptoms (measured with the International Prostate Symptom Score (IPSS), which is based on the answers to seven questions concerning urinary symptoms (frequency, emptying, intermittency, urgency, weak stream, straining, nocturnia) and one question concerning quality of life. Each question concerning urinary symptoms allows the patient to choose one out of six answers indicating increasing severity of the particular symptom. The answers are assigned points from 0 to 5. The total score can therefore range from 0 to 35 (asymptomatic to very symptomatic)) [63].

Blasenfunktionsstörungen (z. B. Inkontinenz)

- Sexual (dys)function which was defined as the loss of erectile function (reported as number of patients with new onset of impotence) or worsening of erectile function (decrease in the IIEF-5, IIEF-15, or BMSFI score. IIEF-5 is used to diagnose the presence and severity of erectile dysfunction (ED). The questions are focused on erectile function and intercourse satisfaction. The possible scores for the IIEF-5 range from 5 to 25, and ED was classified into five categories based on the scores: severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25)) [64].

sexuelle Funktionsstörungen (z. B. Erektionsstörungen)

- Serious adverse events/procedural complications: grade 3-4 adverse events according to Clavien-Dindo classification. In Clavien-Dindo risk classification there are four risk categories (Grade 1, 2, 3, 4) where 1 represents any deviation from the normal intraoperative or postoperative course, including need for pharmacologic treatment other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, or physiotherapy; grade 2 represents complications needing only the use of intravenous medications, total intravenous nutrition, or blood transfusion; grade 3 complications are those where surgical, endoscopic or radiologic intervention under local or general anaesthesia is needed; whereas grade 4 complications are life-threatening and require intensive care unit management [24].

schwerwiegende unerwünschte Ereignisse/ eingriffsbezogene Komplikationen

6.2 Included Studies

Primary HIFU

Study characteristics

vier unkontrollierte Studien mit 279 Patienten, 1 kontrollierte Studie mit je 70 Patienten

The single-arm primary HIFU studies [20-23] reported on a total of 279 patients treated with Ablatherm®, originating from France, Germany and Belgium. The matched-pair analysis [19] study reported on 70 patients treated with the Ablatherm® HIFU device and 70 patients treated with brachytherapy in Belgium.

Patient characteristics

in Fallserien: Durchschnittsalter 63-73 Jahre, Tumorstadium T1-T2, Prostatavolumen 31-39 ml

in kontrollierter Studie: Durchschnittsalter 74 vs. 69 Jahre, Tumorstadium zwischen T1a und T2b

Mean patient ages ranged between 63.4 and 73 years in the single arm studies [20-23]. The median patient ages were 74 years in the HIFU group and 69 years in the brachytherapy group in the matched-pair analysis [19]. Tumour stage T1-T2 was reported in two single-arm studies (in one study 16 patients had T1 and 34 T2, in the other study 77 had T1 and 33 had T2) [22, 23] and in the matched-pair analysis [19], two studies did not report the tumour stage [20, 21]. The Gleason score for HIFU-patients was 6 or below 6 in 221 (60%) of the included patients, 7 in 85 patients (23%) and unknown for the rest of the patients (one study [21] stated only the number of patients with Gleason Score 7 and that the median was 6). All four single-arm studies and the matched-pair analysis included only low-and intermediate-risk patients. The single-arm studies did not report on the percentage of patients who received ADT therapy before HIFU, however, one study [21] excluded patients with previous ADT according to the study's exclusion criteria. The matched-pair analysis [19] reported that 27% of HIFU patients received ADT before treatment, whereas 20% of brachytherapy patients received ADT. Mean pre-HIFU PSA level ranged between 6.2 and 6.6 ng/mL (one study [20] reported the median which was 6.1 ng/mL) in the single-arm studies and it was not reported in the matched-pair analysis (only the number of patients below 10 and between 10 and 20 ng/mL). The mean pre-HIFU prostate volume ranged between 31 and 39.3 mL in the single-arm studies and it was not reported in the matched-pair analysis.

HIFU procedure and follow-up

HIFU mittels Ablatherm®, in einer Studie auch FocalOne®

Nachbeobachtung in Fallserien im Mittel 17-39 Monate, in kontrollierter Studie 83 vs. 44 Monate

All studies used the Ablatherm® device in the procedure, except for one [21], which used both Ablatherm® and the newer device from the same manufacturer, FocalOne®. Hemiablation was applied in the single-arm studies [20-23], whereas the matched-pair analysis [19] applied whole gland ablation of the prostate. Only one study [22] reported on TURP performed prior to or in combination with HIFU. This study reported that 60% of patients had TURP prior or in combination with HIFU treatment due to large prostate volume. The duration of the treatment was reported in two studies [20, 21] mean treatment time was 62.2 minutes in one study [21] and an average of 120 minutes in the other study [20]. Catheterisation time was also reported in two studies [21, 23] and ranged between 2.8 and 2.9 days. The mean follow-up ranged between 17.41 and 39 months (one study [20] did not report mean follow-up time, but median which was 12 months) in the single-arm studies. The median follow-up was 83 months in the HIFU group and 44 months in the brachytherapy group in the matched-pair analysis. The number of treatment per patient was reported in two studies [21, 22] and was comparable within the studies, 90% had only one intervention and around 10% had two HIFU treatments.

Study characteristics and results of included studies are displayed in Table A-2 and in the evidence profile in Table 7-1.

Studiencharakteristika und Ergebnisse in Tabellen

Salvage HIFU

Study characteristics

The study on salvage HIFU [24] reported on 84 patients treated with the Sonablate® device in the United Kingdom and Canada. Whole-gland ablation was applied.

eine Studie mit 83 Pateinten

Patient characteristics

The mean age of patients was 68.3 years, the tumour stage and risk categories were not reported, but according to the inclusion criteria it was lower than T3a. A total of 30 patients (36%) received neoadjuvant ADT before the salvage treatment with HIFU. The median Gleason Score was 7, ranging between 6 and 7. All patients failed after EBRT, according to the inclusion criteria. The mean pre-HIFU PSA level was 5.7 ng/mL. Mean pre-HIFU prostate volume was 25.1 mL [24].

Durchschnittsalter 68 Jahre, Prostatavolumen 25 ml

HIFU procedure and follow-up

The Sonablate® 500 device was used to deliver the treatment. The mean follow-up was 19.8 months. The treatment duration time was available for 40 patients and it was 158 minutes with a mean of 1.4 days of hospital stay. Over 90% of the patients (78) were treated with one salvage HIFU intervention and 7% (6 patients) had two salvage HIFU treatments [24].

Sonablate® Nachbeobachtung im Mittel 20 Monate

Study characteristics and results of included studies are displayed in Table A-3 and in the evidence profile in Table 7-2.

Studiencharakteristika und Ergebnisse in Tabellen

6.3 Results

Patient safety

C0008 – How safe is HIFU in comparison to AS, WW, RT, RP?

Comparative study

The only available evidence which compared HIFU with any of the comparators was the matched-pair analysis that compared whole-gland HIFU to brachytherapy, as described above [19].

HIFU im Vergleich zu Brachytherapie:

Intervention-related death

No intervention-related deaths occurred in any of the groups.

keine Interventions-bedingte Mortalität

Urinary (dys)function

Urinary dysfunction showed no significant difference in HIFU-patients compared to patients who received brachytherapy (occurred in 7.2% of patients in the HIFU group and 3.8% in the brachytherapy group, p=0.44).

keine signifikanten Unterschiede bei Blasenfunktions-störungen

Sexual (dys)function

Erectile dysfunction was reported only for the HIFU-group (and for patients who were preoperatively potent) and occurred in 5 patients (11.6%).

Adverse events

Harnretention und Harnröhrenstriktur signifikant häufiger bei HIFU

keine Unterschiede bei z. B. Harnwegsinfekten

The most frequent adverse events reported were urinary retention, urinary tract infection, urethral stricture, and storage and voiding LUTS. Urinary retention and urethral stricture (particularly in patients treated with the first generation device) were significantly higher in the HIFU cohort compared to the brachytherapy cohort ($p=0.02$ resp. $p \leq 0.01$). Urinary tract infection and storage and voiding LUTS were the most frequent early and late post-operative complications with no statistically significant difference across the two cohorts ($p=0.07$ resp. $p=1$). Serious adverse events that required surgical or endoscopic treatment occurred in the form of fistulas and haemorrhagic cystitis: one patient per each cohort developed rectourethral fistula, which was managed surgically. One patient in the brachytherapy cohort had haemorrhagic cystitis managed by endoscopic fulguration.

HIFU im Vergleich zu Brachytherapie: etwas mehr schwerwiegendere unerwünschte Ereignisse mit HIFU

When comparing the severity of adverse events, the rate of grade 3 adverse events was higher for HIFU patients than for patients treated by brachytherapy (35% vs. 13%, see also Table 6-1). Especially acute urinary retention and stricture occurred more often in the HIFU-group than in the brachytherapy-group (more than 20% vs. less than 6% each). However, information on statistical significance was not provided [19].

keine weitere vergleichende Evidenz

We found no comparative evidence on HIFU in relation to other treatment options, such as RP, AS, and WW.

Single-arm observational studies

Fallserien

All four single-arm studies on primary HIFU applied hemiablation [20-23]. The study on salvage HIFU [24] applied whole-gland ablation.

Intervention-related mortality

keine Interventions-bedingte Mortalität

No intervention-related deaths occurred in any of the studies.

Urinary (dysfunction)

in drei von 4 Studien keine signifikanten Änderungen bei Symptomen des Harntrakts (gemessen mit IPSS)

Inkontinenz verschieden gemessen, nach HIFU etwas mehr Inkontinenzen

Urinary symptoms with the IPSS score were reported in three studies of which two studies [20, 21] concluded that there was no significant change in urinary function (even without TURP) as there was no change in mean IPSS score from baseline post-HIFU to 3-12 months follow-up visit, and one study [22] concluded that there was a significant improvement in the IPSS score from baseline to 12 months post-intervention (95% CI: 1.6; 4.4). The study on salvage HIFU [24] did not show any significant effect on the IPSS score 6 months post-interventional ($p=0.06$). Urinary incontinence was reported using physician reported events and number of patients who started using pads. One study [23] reported that all patients were continent pre-HIFU and three patients (6%) were incontinent at 12 months follow-up. Three studies measured incontinence with usage of pads [20-22] of which two studies [21, 22] had a follow-up of 12 months and both reported that one patient was incontinent pre-HIFU and three (3% resp. 5.9%) patients had persistent incontinence at 12 month follow-up. One study [20] reported that none of the patients had incontinence at follow-up, but the month of the follow-up was not reported).

Sexual (dys)function

All four single-arm primary HIFU studies reported on erectile dysfunction using the IIEF-5 scale, physician reported rates or both. Three studies [20-22] used the IIEF-5 scale of which two [20, 21] showed a significant negative impact on erectile function 3-12 months after HIFU ($p<0.001$). Two studies using physician reported rates identified 20-22% de novo erectile dysfunction in pre-intervention potent patients, whereas one study [20] reported that nearly 48% of previously potent patients became impotent post-intervention (none of the studies reported the time point when this was measured). The study on salvage HIFU [24] also reported a significant negative effect on the sexual function based on the IIEF-5 scores 6 months after the intervention ($p<0.001$).

alle Fallserien zeigten (zum Teil signifikant) negativen Effekt von HIFU auf Erektionsstörungen

Adverse events

The most frequent adverse events reported in the single-arm studies [20-23] were: urinary tract infection, dysuria, anejaculation, pain and urinary retention. Additionally, in the study on salvage HIFU [24] bladder outlet obstruction and rectal fistula were common adverse events. Compared to the matched-pair analysis [19], the rate of storage or voiding LUTS [22, 23] (grade 1 complication), acute urinary retention [20, 22, 23] and stricture [21-23] (grade 3 complications) was considerably lower in the single-arm studies. Rectal fistula (grade 3 complication) occurred only in the matched-pair analysis [19] and in the study on salvage HIFU [24], which both applied whole-gland ablation. Bladder outlet obstruction, another grade 3 complication, was observed only in the study on salvage HIFU [24] with a rate of 20%. Grade 4 complications did not occur in any of the primary HIFU studies, but three such complications were observed in the study on salvage HIFU [24]. The adverse events are presented in Table 6-1 categorized per study and severity.

häufigste unerwünschte Ereignisse in Fallserien: Harnwegsinfekte, Dysurie, Anejakulation, Schmerzen und Harnretention

C0002 – Are the harms related to dosage or frequency of applying HIFU?

No evidence was found on the relation of the dosage or frequency to the harms associated with both primary and salvage HIFU.

keine Evidenz

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

One single arm study [20] reported that all complications were encountered within the first postoperative month. Another single-arm study [23] and the matched-pair analysis [19] did not report when the complications occurred first, but reported that seven, respectively one patient after HIFU had transient incontinence during follow-up. This transient incontinence was self-resolving in three of the seven patients in the single-arm study and for the one patient in the matched-pair analysis at 12 months postoperatively. These complications were likely to occur shortly after treatment and were only temporary in most of the patients. The matched-pair analysis [19] reported that storage and voiding LUTS developed immediately after the intervention and that these symptoms were generally mild and self-resolving after several months. Three months postoperatively HIFU was more associated with voiding LUTS whereas brachytherapy was more associated with storage LUTS.

Großteil der Komplikationen kurz nach Eingriff

C0005 – What are the susceptible patient groups that are more likely to be harmed through the use of HIFU?

keine ausreichende Evidenz

No evidence was found on the patient groups that are more likely to be harmed through the use of HIFU.

C0007 – Is HIFU associated with user-dependent harms?

nicht explizit in Studien berichtet, jedoch Lerneffekte zu vermuten

The included studies did not report explicitly on user-dependent harms. One study [19] stated that the technical improvements with the introduction of the new Ablatherm® device and the changes in surgical protocol have lowered the high rate of urinary tract infection and bladder outlet obstruction encountered at earlier HIFU interventions. The incidence of rectal fistula has lowered in the last decade which is mainly due to the fact that rectal bleeding has been managed better [19]. This is also underlined by the study on salvage HIFU [24] which reported rectourethral fistula occurred early in the learning curve in the first 20 cases.

Investments and tools required

B0010 – What kind of data/records and/or registry is needed to monitor the use of HIFU?

keine Evidenz

No evidence was found to answer this research question.

Table 6-1: Frequency and severity of adverse events

Clavien-Dindo grade class/ adverse events	Adverse event with HIFU n (%)	Primary HIFU study with control group		Primary HIFU studies without control group				Salvage HIFU study without control group
		Aoun, 2015 [19]		Van Velthoven, 2016 [23]	Rischmann, 2017 [22]	Ganzer, 2017 [21]	Feijoo, 2015 [20]	Uddin Ahmed, 2012 [24]
		HIFU	brachytherapy					
Number of patients with available data on adverse events		**70**	**70**	**50**	**105**	**21**	**67**	**84**
Grade 1	**Primary HIFU: 108/313 (34.5) s-HIFU: 27/84 (32.1)**	**29 (41.4)**	**20 (28.6)**	**79 (32.5)**				**27 (32.1)**
Urge incontinence	4/105 (3.8)	-	-	-	4 (3.8)	-	-	-
Dysuria	18/126 (14.3)	-	-	-	17 (16.2)	1 (4.7)	-	-
Storage or voiding LUTS	42/225 (18.7)	26 (37.1[20])	20 (28.6)[20]	9 (18)	7 (6.7)	-	-	-
Hematospermia	2/105 (1.9)	-	-	-	2 (1.9)	-	-	-
Aspermia	1/21 (4.7)	-	-	-	-	1 (4.7)	-	-
Anejaculation	17/126 (13.6)	-	-	-	16 (15.2)	1 (4.7)	-	-
Anal and perineal pain	15/196 (7.6)	3 (4.3)	0	-	10 (9.5)	2 (9.5)	-	-
Hematuria	4/21 (19)	-	-	-	-	4 (19)	-	-
Urine retention	5/21 (23.8)	-	-	-	-	5 (23.8)	-	-
Grade 2	**Primary HIFU: 106/313 (33.7) s-HIFU: 10/84 (11.9)**	**36 (51.4)**	**24 (34.2)**	**70 (28.8)**				**10 (11.9)**
Thromboembolic disease (phlebitis)	2/105 (1.9)	-	-	-	2 (1.9)	-	-	-
Urge incontinence	2/21 (9.5)	-	-	-	-	2 (9.5)	-	-
Storage or voiding LUTS	21/70 (30)	21 (30)[20]	18 (25.7)[20]	-	-	-	-	-
Urinary tract infection	49/313 (15.6)	15 (21.4)	5 (7.1)	3 (6)	18 (17.1)	9 (42.9)	4 (6)	-
Orchitis	8/105 (7.6)	-	-	-	8 (7.6)	-	-	-
Prostatitis	8/105 (7.6)	-	-	-	8 (7.6)	-	-	-
Hematuria	5/105 (4.7)	-	-	-	5 (4.7)	-	-	-
Chronic urine retention	11/222 (4.9)	-	-	4 (8)	3 (2.8)	-	4 (6)	-
Gastrointestinal toxicities	0/70 (0)	0 (0)	1 (1.4)	-	-	-	-	-

[20] LUTS includes also hematuria.

Clavien-Dindo grade class/ adverse events	Adverse event with HIFU n (%)	Primary HIFU study with control group		Primary HIFU studies without control group				Salvage HIFU study without control group
		Aoun, 2015 [19]		Van Velthoven, 2016 [23]	Rischmann, 2017 [22]	Ganzer, 2017 [21]	Feijoo, 2015 [20]	Uddin Ahmed, 2012 [24]
		HIFU	brachytherapy					
Grade 3	**Primary HIFU: 50/313 (16) s-HIFU: 52/84 (61.9)**	**35 (50)**	**9 (12.9)**	**15 (6.2)**				**52 (61.9)**
Storage or voiding LUTS	0/70 (0)	0 (0)	1 (1.4)[20]	-	-	-	-	-
Acute urinary retention	27/292 (9.2)	16 (22.8)	4 (5.7)	4 (8)	5 (4.7)	-	2 (3)	-
Stricture	21/246 (8.5)	17 (24.3)	2 (2.8)	2 (4)	1 (1)	1 (4.7)	-	-
Rectal fistula	5/154 (3.2)	1 (1.4)	1 (1.4)	-	-	-	-	4 (4.8)
Gastrointestinal toxicities	1/70 (1.4)	1 (1.4)	1 (1.4)	-	-	-	-	-
Bladder outlet obstruction	17/84 (20.2)	-	-	-	-	-	-	17 (20.2)
Grade 4	**Primary HIFU: 0 s-HIFU: 3/84 (3.5)**	**-**	**-**	**0**	**0**	**0**	**0**	**3 (3.5)**
Total adverse events n (%)	**Primary HIFU: 254/313 (81.1) s-HIFU: 92/84 (109)**	**90[21] (128)**	**59[21] (84.3)**	**22 (44)**	**106[21] (109)**	**26[21] (123)**	**10 (15)**	**92 (109)**
Total deaths n (%)	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**

Abbreviations: *LUTS = lower urinary tract symptoms, s-HIFU = salvage high-intensity focused ultrasound*

Sources: [19-24]

Clavien-Dindo risk classification

Grade 1: any deviation from the normal intraoperative or postoperative course, including need for pharmacologic treatment other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, or physiotherapy;

Grade 2: complications needing only the use of intravenous medications, total intravenous nutrition, or blood transfusion;

Grade 3: complications where surgical, endoscopic or radiologic intervention under local or general anaesthesia is needed;

Grade 4: complications that are life-threatening and require intensive care unit management [24]

[21] The study reported a higher number of total adverse events than the total number of patients.

7 Quality of evidence

Bias-Risiko mittels Checklisten

RoB for individual studies was assessed with the IHE-20 checklist and ROBINS-I and is presented in Table A-5, respectively Table A-4 in the Appendix. The overall quality of the studies was very low.

Qualität der Evidenz nach GRADE

The strength of evidence was rated according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) Schema [18] for each endpoint individually. Each study was rated by two independent researchers. In case of disagreement a third researcher was involved to solve the difference. A more detailed list of criteria applied can be found in the recommendations of the GRADE Working Group [18].

GRADE uses four categories to rank the strength of evidence:

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

The ranking according to the GRADE scheme for the research question can be found in the summary of findings table below and in the evidence profile in Appendix Table A-6.

Evidenzstärke sehr gering

Overall the strength of evidence for the effectiveness and safety of primary HIFU in comparison to brachytherapy is very low. The strength of evidence for the safety of primary HIFU, as well as for salvage HIFU is very low.

keine Evidenz zu anderen Vergleichen

No evidence was available for the comparison of primary HIFU and AS, WW or RP, as well as for the comparison of salvage HIFU and AS, WW, salvage RP or salvage RT.

Table 7-1: Summary of findings table of primary HIFU

Outcome	Anticipated absolute effects			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with HIFU	Risk with Radiotherapy	Difference				
EFFICACY							
Overall survival rate Follow up: 5 years	574 per 1,000	971 per 1,000	397 fewer per 1,000 (20 more to 936 fewer)	HR 0.24 (0.01 to 1.34)	140 (1 CT)	⊕⊙⊙⊙ VERY LOW[22,,23]	Overall survival was lower (but not significantly) for HIFU.
Prostate cancer specific survival rate Follow up: 5 years	807 per 1,000	914 per 1,000	397 fewer per 1,000 (20 more to 936 fewer))	HR 0.67 (0.32 to 1.29)	140 (1 CT)	⊕⊙⊙⊙ VERY LOW[22, 23]	Prostate cancer specific survival rate was lower (but not significantly) for HIFU.
Local disease recurrence	-	-	-	-	-	-	Outcome not reported.
SAFETY							
Intervention specific mortality (comparative) Follow up: median 83 vs. 44 months	0 per 1,000	0 per 1,000	0% fewer/more	Not estimable	140 (1 CT)	⊕⊙⊙⊙ VERY LOW[22, 23, 24]	There was no intervention specific mortality.
Intervention specific mortality (single-arm) Follow up: mean 16.3 vs. 44.5 months	See comment.			Not estimable	279 (4 observational studies)	⊕⊙⊙⊙ VERY LOW[25, 26, 27]	There was no intervention specific mortality.
Functional outcomes: urinary (dys)function (comparative) Assessed with: physician reported rate Follow up: median 83 vs. 44 months	72 per 1,000	38 per 1,000[28]	34 more per 1,000 (14 fewer to 359 more)	RR 1.92 (0.39 to 9.51)[28]	122 (1 CT)	⊕⊙⊙⊙ VERY LOW[23, 29]	Urinary dysfunction was higher (but not significantly) for HIFU.

[22] Risk of bias for this endpoint was considered high due to the difference in age between study groups (see also risk of bias assessment of study).

[23] Indirectness was set "serious" for this endpoint, since this study was claimed to be the first to compare patients treated by HIFU and brachytherapy. Furthermore, in this study two generations of Ablatherm devices were used, whereas Ablatherm Maxis is not commercially available anymore. Moreover, there was no information provided on additional treatments and pre-treatment prostate volume.

[24] Imprecision was set "serious" for this particular endpoint, since the probability of intervention-specific mortality is estimated to be low and patient number must be higher to detect differences.

[25] Risk of bias for this particular outcome was set high due to study design (no control group).

[26] Indirectness for this particular outcome was set serious because the studies can only yield indirect evidence regarding the safety of HIFU compared to standard therapies as there was no control arm (safety outcomes could only be compared to historical controls).

[27] Imprecision for this particular outcome was set serious due to the low sample size.

Outcome	Anticipated absolute effects			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with HIFU	Risk with Radiotherapy	Difference				
Functional outcomes: urinary (dys)function (single-arm) Assessed with: IPSS score, usage of pads Follow up: 3-12 months	Mean difference in the IPSS score in 1 study was 3 (95% CI 1.6; 4.4), 2 studies showed no significant difference. 0.7% (0 to 2%) of patients pre-HIFU were incontinent (used pads) and 3.3% (0 to 6%) of patients were incontinent post-HIFU (2.6% (0 to 6%) more patients were incontinent)			-	IPSS: 198 (3 observational studies) Usage of pads: 270 (4 observational studies)	⊕⊙⊙⊙ VERY LOW[25, 26, 27, 30]	There may be little or no difference in the urinary function characterized by the usage of pads or by the IPSS score.
Functional outcomes: sexual (dys)function (comparative) Assessed with: physician reported rate Follow up: median 83 vs. 44 months	116 per 1,000 (11.6%)	NA	-	Not estimable	43 (1 CT)	⊕⊙⊙⊙ VERY LOW[31, 32]	Sexual dysfunction was only reported for HIFU-patients.
Functional outcomes: sexual (dys)function (single-arm) Assessed with: IIEF-5 score, de novo erectile dysfunction Follow up: 3-12 months	Mean difference in the IIEF-5 score in 1 study was 1.2 (95% CI -0.4; 2.7), 2 studies showed significant difference (pre-HIFU score of 17.6 to 17.97 and post-HIFU score of 13.6 to NA, p<0.001) De novo erectile dysfunction ranged from 20% to 47.6% of pre-HIFU potent patients.			-	De novo erectile dysfunction: 122 (3 observational studies) IIEF-5: NA (3 observational studies)	⊕⊙⊙⊙ VERY LOW[25, 26, 27, 33]	HIFU may increase the rate of de novo erectile dysfunction. HIFU may worsen sexual function.
Serious adverse events (SAEs) (comparative) Assessed with : number of events Follow up: mean 12 months	Overall SAEs: 17 vs. 5 (in 70 patients each)			Not estimable	140 (1 CT)	⊕⊙⊙⊙ VERY LOW[23, 34, 35]	In the HIFU group 17 SAEs occurred in 70 patients and in the radiotherapy group 5 SAEs occurred in 70 patients.

[28] Caclulated with MedCalc© (http://www.medcalc.org/calc/relative_risk.php).

[29] Risk of bias for this particular endpoint was set "serious", due to the difference between study groups in age and length of follow-up (see also risk of bias assessment of study). Furthermore, it was not stated how many patients suffered from incontinence before the interventions.

[30] There is inconsistency in the results of IPSS cores as two studies reported no significant change in the score, while one study reported a significant mean decrease (meaning improvement) in the score.

[31] Risk of bias for this particular endpoint was set high, due to the difference between study groups in age and length of follow-up (see also risk of bias assessment of study). Furthermore, maesurement of sexual (dys) function was exclusively done for HIFU-patients.

[32] Indirectness cannot be assessed, because study exclusively reported sexual (dys)function for HIFU-patients.

[33] Inconsistency was set serious as two studies reported around 20% of pre-HIFU potent patients being post-HIFU impotent, while one study reported over 47% of pre-HIFU potent patients being post-HIFU impotent.

Outcome	Anticipated absolute effects			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with HIFU	Risk with Radiotherapy	Difference				
Serious adverse events (SAEs) (comparative) Assessed with : number of events Follow up: median 83 vs. 44 months	Overall SAEs: 18 vs. 4 (in 70 patients each)			Not estimable	140 (1 CT)	⨁⊙⊙⊙ VERY LOW[23, 34, 35]	In the HIFU group 18 SAEs occurred in 70 patients and in the radiotherapy group 4 SAEs occurred in 70 patients.
Serious adverse events (SAEs) (single arm) Assessed with: number of events Follow up: 1-12 months	Overall SAEs: 15 in 273 patients			-	273 (4 observational studies)	⨁⊙⊙⊙ VERY LOW[25, 26, 27, 36]	Overall 15 SEAs occurred in the studies.

***Abbreviations**: CI confidence interval, HIFU high-intensity focused ultrasound, HR hazard ratio, IIEF international index of erectile function, IPSS international prostate symptom score, NA not available*

[34] Risk of bias for this particular endpoint was set "serious", due to the difference between study groups in age (see also risk of bias assessment of study). Furthermore, the study exclusively reported the number of complications and not the number of patients with complications.

[35] Imprecision was set "serious" for this particular endpoint, because the patient number was too low to detect rare adverse events.

[36] There is inconsistency in the percentage of patients presented with an adverse event per study as one study reported in 41% of patients occurred adverse event, another study reported 15%, two studies did not report the percentage of patients in whom adverse event occurred, but the total number of adverse events and these studies did not specify how many patients experienced the adverse event.

Table 7-2: Summary of findings table of salvage HIFU

Outcome	Anticipated absolute effects			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk with s-HIFU	Risk without s-HIFU	Difference				
SAFETY							
Intervention-specific mortality (peri-operative death) Assessed with: number of events Follow up: mean 19.8 months	See comment.			Not estimable	84 (1 observational study)	⊕⊙⊙⊙ VERY LOW[25, 27, 37]	There was no intervention specific mortality.
Functional outcomes: urinary (dys)function Assessed with: IPSS score Follow up: 6 months	No significant difference in IPSS scores (8.3 pre salvage-HIFU and 11.6 post salvage-HIFU).			-	39 (1 observational study)	⊕⊙⊙⊙ VERY LOW[25, 27, 37]	There may be no difference in urinary function characterized by the IPSS score.
Functional outcomes: sexual (dys)function Assessed with: IIEF-5 score Follow up: 6 months	Significant decrease in the IIEF-5 score (8.6 pre salvage-HIFU and 6.2 post salvage-HIFU).			-	43 (1 observational study)	⊕⊙⊙⊙ VERY LOW[25, 27, 37]	Salvage HIFU may increase the risk of sexual dysfunction.
Serious adverse events (SAEs) Assessed with: number of events Follow up: mean 19.8 months	Overall SAEs: 3 in 84 patients			Not estimable	84 (1 observational study)	⊕⊙⊙⊙ VERY LOW[25, 27, 37]	Overall 3 SAEs occurred.

Abbreviations: *CI = confidence interval, IIEF = international index of erectile function, IPSS = international prostate symptom score, s-HIFU = salvage high-intensity focused ultrasound*

[37] Indirectness was set serious because only failed EBRT patients were included (we do not have information on patients failed after other treatment modalities like prostatectomy or HIFU). The studies can only yield indirect evidence on HIFU compared to standard therapies as there was no control group.

8 Discussion

High-intensity focused ultrasound (HIFU) is a technology that uses ultrasound waves to destroy tissue, cancer tissue in particular. The present report focused on the treatment of prostate cancer with HIFU. The ultrasound can be applied for the ablation of the whole gland or in parts, called hemiablation, or focal therapy. Treatment planning can be done under the assistance of ultrasound or MRI, whereas the letter is more appropriate for a focal treatment.

HIFU nutzt gebündelte Ultraschallwellen, um Gewebe zu zerstören

In 2010, the LBI-HTA published a report on HIFU for prostate cancer [15] which concluded that the available evidence was not sufficient to determine any benefit of the intervention. All studies in the previous report were single-arm studies with an overall very low strength of evidence. A re-evaluation was suggested not earlier than two years based on the estimated completion date of the identified ongoing studies. The aim of the present assessment is to update the LBI-HTA report from 2010 to examine the latest, since 2010 published evidence. Nevertheless, the scope of the present assessment has notably changed in two aspects: the population has been limited to low and intermediate risk patients according to the latest guidelines and more patient relevant outcomes formed the basis of the conclusions.

vorliegender Bericht baut auf Bericht aus 2010 auf und sollte neue Evidenz aufzeigen

Interpretation of findings

The present assessment does not alter the general conclusions of the 2010 LBI-HTA report. Overall, we could identify five single-arm studies and one comparative study (a matched-pair analysis) comparing HIFU with brachytherapy (a type of radiotherapy), that met our inclusion criteria. The single-arm studies included 50 to 111 patients and had a mean or median follow-up of 12 to 39 months. The matched-pair analysis included 70 patients in each study arm and had a median follow-up of 83 months in the HIFU and 44 months in the brachytherapy-arm. Therefore, there is still a lack of comparative studies for the most common comparators.

zwar neue Evidenz, aber keine neuen Erkenntnisse von vorliegendem Bericht

The single available comparative study [19] has shown slightly lower prostate cancer specific survival rates after five years, as well as overall survival rates in HIFU-patients, compared to brachytherapy-patients. Even though the differences were not significant, the given confidence intervals, however, indicated considerable harm due to HIFU. However, patients in the HIFU-group were significantly older than patients treated with brachytherapy. This could have had a confounding effect on the survival rates. Local disease recurrence, a critical effectiveness-related outcome, was not reported in the study.

einzige kontrollierte Studie zeigte niedrigere Raten bei Überleben

Although quality of life was not measured in the comparative study included in the present assessment, three single-arm studies (two primary HIFU [21, 22] and one study on salvage HIFU [24]) reported on this outcome. All three studies used various outcome measures. One primary study reported a significant improvement in the quality of life scores 12 months post-treatment [22], the other primary HIFU study and the study on salvage HIFU could not show any significant change in the depression and anxiety scores, as well as in the global quality of life scores at 12 months post-HIFU.

Lebensqualität nur in Fallserien berichtet und dort abweichende Ergebnisse

bei Blasenfunktionsstörungen keine signifikanten Unterschiede zwischen HIFU und Brachytherapie, sonst aber durchaus negative Auswirkungen von HIFU bezüglich Komplikationen

Regarding safety-related functional outcomes, the matched-pair analysis has not shown a significant difference in urinary incontinence between HIFU and brachytherapy. In the absence of data on sexual (dys)function for the brachytherapy cohort, no comparative conclusions can be drawn. However, the single-arm primary studies [20-23], as well as the study on salvage HIFU [24] have shown a significant negative impact on sexual function. Concerning complications, in the matched-pair analysis [19] considerably more adverse events have been observed in HIFU-patients than in brachytherapy-patients, especially complications of higher severity occurred more often.

Comparing the matched-pair analysis [19] with the single-arm studies [20-23], storage and voiding LUTS, acute urinary retention and stricture was considerably more frequent in the matched-pair analysis. More severe, grade 3 and 4 complications, like rectal fistula and bladder outlet obstruction did not occur in the primary single-arm studies at all. The applied ablation type might have influence on the severity of adverse events as the matched-pair analysis [13] and the study on salvage HIFU [18] both applied whole-gland ablation, whereas the primary single-arm studies [20-23] applied hemiablation.

Study quality, validity and level of evidence

insgesamt sehr geringe Qualität der Evidenz, da vor allem geringe Studiengrößen, fehlende Vergleichsgruppen und relativ kurze Nachbeobachtungszeiträume

The overall quality of evidence on high-intensity focused ultrasound (HIFU) as primary treatment for clinically localised low-risk and intermediate-risk prostate cancer as well as on HIFU as salvage treatment for locally recurrent prostate cancer is very low. Studies are lacking sufficiently high patient numbers, comparators and sufficiently long periods of follow-up. The small numbers considerably limit the generalizability of the findings and only two studies reported on outcomes with a follow-up of five years, therefore no significant conclusion can be made on disease control. All outcomes estimates on the efficacy of primary HIFU compared to brachytherapy, a type of radiation therapy, are based on only one comparative study. This comparative study, however, consisted of two matched single-arm studies, which cannot accomplish a high evidence level. Moreover, the safety outcome estimates of primary HIFU are based on single-arm studies in addition to the comparative study. Regarding salvage HIFU all outcomes estimates are based on one single-arm study. Direct prospective comparison between deferred treatment modalities (active surveillance, watchful waiting) and radical prostatectomy or radiation for salvage treatment are completely lacking.

nennenswerte Heterogenität der Studien

There was also a considerable heterogeneity in the HIFU studies due to the large variation in follow-up protocols and definitions of outcome measures. Although we considered only the matched-pair analysis in the effectiveness assessment, we noticed that studies had different effectiveness end points (biochemical, variable definitions of PSA end points, and/or biopsy data, and various survival end points: overall, actuarial recurrence-free, biochemical recurrence-free, prostate cancer specific, metastases-free, progression-free, radical treatment-free). Definition of treatment failure was not universal among the studies: some studies defined it as positive biopsy control (indicating local relapse [9]), while others used the need for salvage treatment, initiation of definitive treatment, presence of clinically significant cancer. Biochemical recurrence rates were defined according to Phoenix or Stuttgart criteria, but there is currently no consensus regarding the drop in PSA level which may indicate a treatment success. In addition, Phoenix criteria are not validated for other than radiotherapy, and it tends to generate lower rates of recurrence. It may also be less sensitive in focal ablation because the nadir may have less relevance with the preservation of a large proportion of the pros-

tate tissue [12]. The Stuttgart criteria (> PSA nadir + 1.2 ng/mL) have been proposed to define BCR after HIFU treatment, though is not yet validated.

Heterogenität bei Endpunkten zu Sicherheit z. B. bei Art der Messung von Inkontinenz oder sexuelle Funktionsstörungen

Similarly for the safety end points, there is no standard measurement tool and the studies showed heterogeneity in the outcome measures used for sexual and urinary function and when the outcome was measured. Sexual function was measured with the IIEF-5 score and/or physician reported rates of de novo erectile dysfunction of previously potent patients at 3 months, or at 12 months. Urinary function was measured with the usage of pads and/or with IPSS at 3 months, or at 12 months. A common problem with such measurement tools is that physician reported rates often do not correlate with patient self-assessment questionnaires. In some of the primary HIFU studies there was a lack of data on the IPSS or IIEF-5 score: for instance in one study [22] only the mean difference before and 12 months after treatment was stated or in another study the values after treatment were missing [20].

Limitationen auch bedingt durch Art der Ablation

Additional limitations that hinder the generalizability of the findings include that the matched-pair analysis applied whole-gland ablation, whereas the single-arm studies applied hemiablation of the prostate. Whole-gland ablation is associated with a worse side-effect profile (more frequent toxicities, incontinence and erectile problems) compared to hemiablation [25, 26] (see also applicability table Table A-9).

Meta-Analyse anhand der Studien nicht möglich

Overall, the lack of comparative studies, the lack of standardization, the heterogeneity in the type of ablation and the type of HIFU device used (and device generations), the poor reporting of additional interventions (TURP, ADT), the heterogeneity in follow-up schedule and outcome measures do not allow performing a meta-analysis of the available evidence, nor a stratification to different generations of HIFU (and magnetic resonance imaging guidance), and additional interventions.

Limitations of the present report

Limitationen vorliegender Bericht

keine Unterscheidung nach Produkten

Einschluss Studie mit veraltetem Produkt

Limitations of the present assessment are the lack of stratification to different generations of HIFU (and magnetic resonance imaging guidance), and additional interventions (TURP, ADT) as these information was often lacking. The MRI guidance, for instance, is a relatively new approach and studies evaluation its effectiveness and safety are still ongoing. Moreover, we included the comparative study [19], in which in the first period patients were treated with an older version of device that is not commercially available anymore. However, it can be expected that the used device, the type of guidance and any concomitant treatments will have a considerable effect on the effectiveness and safety of HIFU.

keine indirekten Vergleiche

Another limitation is the abstinence of indirect comparisons (for instance matching and comparing single-arm trials on laparoscopic prostatectomy and HIFU) which was not feasible within the timeframe of the rapid assessment. Regarding the literature search, despite meticulous hand searching, we did not identify any evidence additional to the systematic search. However, it is possible that we did not identify any relevant evidence.

einige Unterschiede im Vergleich zu zugrundeliegendem Bericht

Due to some changes in the project protocol, the present report slightly differs from the original one, especially with regard to patient population and endpoints. Therefore, we also surrendered to merge the findings of the existing report with those of the present one. Nevertheless, it can be concluded that the strength of evidence has not changed, still being on a very low level.

Evidence gaps and ongoing studies

derzeit (noch) keine randomisierten kontrollierten Studien

To date there are no published RCTs comparing oncological and safety outcomes of HIFU (either as whole gland or hemiablation) and any radical treatment modalities or any deferred treatment modalities or even radiation. MRI guided HIFU ablation is such a new approach that the first pivotal studies have been completed lately and their effectiveness and safety is currently being investigated.

derzeit eine randomisierte kontrollierte Studie in Planungsphase

A search for ongoing studies identified two RCTs and three non-randomised controlled trials (non-RCTs) of which one non-RCT was terminated due to lack of inclusions, two had unknown status, however according to the registry data completion was planned for 2008 for one non-RCT and 2014 for an RCT (but no publication was found on the study results). One RCT is currently in the planning phase of recruitment, and one non-RCT is expected to be completed in November 2019 (for further information see Table A-10). It is often claimed that ethical considerations hinder the implementation of randomised controlled trials. To overcome this problem there are some alternative approaches to be considered: cohort embedded multiple RCTs or preference-based randomizations. A pragmatic approach would be to implement other trial designs, such as patient preference trials and parallel prospective cohort studies [12].

9 Recommendation

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

Empfehlungsschema

Table 9-1: Evidence based recommendations

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

Reasoning:

The current evidence is not sufficient to prove that primary HIFU, as well as salvage HIFU is more effective and safe or as effective but safer than the comparators AS, WW, RP or RT.

keine ausreichend robuste Evidenz

On the basis of the limited evidence demonstrating a benefit of HIFU relative to the comparators, the inclusion in the hospital benefit catalogue is currently not recommended.

Aufnahme derzeit nicht empfohlen

The re-evaluation is recommended not earlier than 2020.

Reevaluierung nicht vor 2020

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Appendix

Evidence tables of individual studies included for clinical effectiveness and safety

Table A-1: Primary HIFU versus brachytherapy: Results from non-randomised controlled trials

Author, year, reference number	Aoun, 2015 [19]
Country	BE
Funding	NA
HIFU device	Ablatherm® (Maxis (2001-2006) and Integrated Imaging (2006-2012))
Type of ablation	Whole gland ablation
Comparator	Brachytherapy (permanent implantation of Iode^{125})
Study design	Prospective matched-pair analysis[38]
Study timeframe	2001-2012
Number of patients	70 vs. 70
Inclusion/exclusion criteria	Inclusion: whole gland primary therapy with curative intent for an organ confined prostate cancer, PSA < 20 ng/mL, Gleason score ≤ 7 (3 + 4), T1N0M0-T2N0M0, FU > 12 months Exclusion: patients with incomplete oncologic data or limited FU<12 m
Patient characteristics	
Age of patients Mean (median) [IQR]	NA (74 ± 4.47 vs. 69 ± 6.5) [62-86] vs. [54-79], (p<0.01)
Tumour stage n (% of pts)	T1a : 2 vs. 1 (2.9 vs. 1.4) T1b : 6 vs. 2 (8.6 vs. 2.9) T1c : 31 vs. 38 (44.3 vs. 54.3) T2a :19 vs. 20 (27.1 vs. 28.6) T2b : 12 vs. 9 (17.1 vs. 12.9)
Gleason score n (% of pts)	≤6: 51 vs. 51 (72.9 vs. 72.9) 7: 19 vs. 19 (27.1 vs. 27.1)
Pre-HIFU PSA level (ng/mL) Mean (median) (range)	NA[39]
Risk categories n (% of pts) according to	*D'Amico:* Low: 31 vs. 33 (44.3 vs. 47.1) Intermediate: 39 vs. 37 (55.7 vs. 52.9)
Pre-HIFU prostate volume (mL) Mean (median) (IQR)	NA[40]
Neoadjuvant ADT n (%)	19 vs. 14 (27.1 vs. 20)
HIFU procedure and follow-up	
TURP prior to/combined with HIFU n (% of pts)	NA
Anaesthesia	NA
Number of treatments/patient n (% of pts)	NA
Duration of treatment (min)	NA

[38] Study consisted of two matched single-arm studies. In one study 110 patients received HIFU and in the other study 106 patients received brachytherapy. Of each study, 70 patients were selected for matching. Matching criteria were: Gleason score, PSA, clinical tumour stage, D'Amico risk, and age.

[39] PSA ≤10: 50 vs. 57 patients, PSA>10 ≤20: 20 vs. 13 patients.

[40] Pre-HIFU prostate volume was only given for the 110 patients of the initial HIFU study.

Author, year, reference number	Aoun, 2015 [19]
Hospital stay (d)	NA
Catheterisation time (d)	NA
Follow-up (m) Mean (range)	Median 83 vs. 44 (IQR: 29-98 vs. 21-70) **(p<0.01)**
Loss to follow-up n (%)	NA
Effectiveness-related outcomes	
Overall survival % at X years	*After 5 years:* 62 vs. 68[41] (88 vs. 97.5%), HR 0.24, CI 0.01-1.34, **p=N.S**.
Prostate cancer specific survival n (%) at X years	*After 5 years:* 62 vs. 64[41] (89 vs. 92%), HR 0.67, CI 0.32-1.29, **p=N.S**.
Local disease recurrence n	NA
Distant disease recurrence/metastases n	NA
Biochemical recurrence/failure n (%) at X years according to	*After 5 years*[42]: Phoenix: 37 vs. 48 (53.1 vs. 68.5%), HR 0.41, CI 0.19-0.81, **p<0.05** [low risk: 48 vs. 54[41] (68% vs. 77.5%), HR 0.31, CI 0.09-0.94, **p=0.05**, intermediate risk: 31 vs. 41[41] (44.9 vs. 58.8%), HR 0.47, CI 0.17-1.13, p=0.12] Stuttgart: 36 vs. 43[41] (51.3 vs. 60.9%), HR 0.39, CI 0.19-0.74, **p<0.05** [low risk: 39 vs. 54[41] (56.3 vs. 77.5%), HR 0.31, CI 0.10-0.84, **p=0.03**, intermediate risk: 29 vs. 41[41] (42 vs. 58.8%), HR 0.41, CI 0.15-0.97, **p=0.05**]
Disease progression/pathological progression	NA
QoL measured by (tool)	NA
Need for salvage/systemic therapy (%)	NA
Ablation failure n (%)	NA
Safety-related outcomes	
Intervention-specific mortality	0 vs. 0
Functional outcomes: urinary (dys)function n (%) according to	Physician reported events: Urinary incontinence: 5 vs. 2 (7.2 vs. 3.8%), p=0.44
Functional outcomes: sexual (dys)function n (%) according to	*Events*[43]: Erectile dysfunction: 5[44] vs. NA (11.6 vs. NA), p=NA
Complications/adverse events (AEs) (grade 1-2) n at x months Urinary tract infection Storing or voiding lower urinary tract symptoms (LUTS) Acute/chronic urinary retention Burn, injuries, bleeding Proctitis Pain Anaesthesia-related complications Thromboembolic disease (phlebitis) Other AEs	**43 vs. 31**[45], p=NA within 1 year post-intervention; **22 vs. 13**, p=NA after more than 1 year post-intervention Urinary tract infection: 15 vs. 5 (21.4 vs. 8.5%), p=0.07 within 1 year post-intervention LUTS: 28 vs. 25 (40 vs. 42.4%), p=0.93 within 1 year post-intervention; 19 vs. 13 (27.5 vs. 24.5%), p=NA[46] after 1 year post-intervention Burn, injuries, bleeding: NA Proctitis: NA Pain[47]: 3 vs. 0 (4.3 vs. 0), p=0.34 after 1 year post-intervention Anesthesia-related complications: NA Thromboembolic disease (phlebitis): NA Gastrointestinal toxicity[48]: 0 vs. 1 (0 vs.1.7%) within 1 year post-intervention

41 Own calculations.

42 Study reported biochemical recurrence-free survival.

43 Method to document erectile dysfunction was not stated.

44 Measured in 43 patients

45 These numbers were reported for early and long-term postoperative complications (events that occurred within one year after intervention or more than one year after the intervention). Furthermore, these are the numbers of complications and not the number of patients with complications.

46 Study did not report p values separately for grade 1-2 and grade 3-4 events after 1 year post-intervention.

47 Study reported chronic pelvic pain

48 Study reported gastrointestinal toxicity. The p value (p=0.59) was reported for all events (grade 1-3).

Author, year, reference number	Aoun, 2015 [19]
Serious adverse events (SAEs) (grade 3-4) n at x months Bladder neck/urethral stricture/stenosis Bladder neck obstruction Rectal fistula Other SAEs	**17 vs. 5,** p=NA within 1 year post-intervention; **18 vs. 4,** p=NA after 1 year post-intervention Stricture: 17 vs. 2 (24.6 vs. 3.8%), **p<0.01**[49] after 1 year post-intervention Bladder neck obstruction: NA Rectal fistula: 1 vs. 1 (1.4 vs. 1.9%), p=1[50] after 1 year post-intervention Acute urinary retention: 16 vs. 4 (22.9 vs. 6.8%), p=0.02 within 1 year post-intervention LUTS/hematuria: 0 vs. 1 (1.9%), p=NA after 1 year post-intervention Gastrointestinal toxicity: 1 vs. 1 (1.4 vs. 1.7%), p=NA within 1 year post-intervention

***Abbreviations**: ADT = androgen deprivation therapy. AE = adverse event, BE = Belgium, d = day, FU = follow-up, HIFU = high-intensity focused ultrasound, IQR = interquartile range, LUTS = lower urinary tract symptoms, n number, min = minute, NA = not available, pts patients, PSA = prostate-specific antigen, QoL = quality of life, TURP = transurethral resection of the prostate*

[49] Study reported urethral stricture.

[50] Study reported rectourethral fistula.

Table A-2: Primary HIFU: *Results from single-arm observational studies*

Author, year, reference number	Van Velthoven, 2016 [23]	Rischmann, 2017 [22]	Ganzer, 2017 [21]	Feijoo, 2015 [20]
Country	BE	FR	D	FR
Funding	NA	None	NA	None
HIFU device	Ablatherm®	Ablatherm®	Ablatherm®, FocalOne®	Ablatherm®
Type of ablation	Hemiablation	Hemiablation	Hemiablation	Hemiablation
Study design	Prospective single-centre single-arm phase 2a study	Prospective multicentre single-arm phase 2b study	Prospective multicentre single-arm phase 2 study	Prospective single-centre single-arm study
Study timeframe	2007	2009-2014	2013-2016	2009-2013
Number of patients	50	111	51	67
Inclusion/exclusion criteria	Inclusion: ≤T2, PSA<15 ng/ml, ≥5 y life expectancy, prostate volume <40 cm^3. Exclusion: extraprostatic extension disease on mpMRI, suspected regional lymph nodes, or distant metastases, previous HIFU or RT.	Inclusion: treatment naïve, T1/T2, unilateral cancer, Gleason score ≤7. Exclusion: biopsy confirmed mpMRI lesion located <6 mm from the apex or <5 mm from the sagittal midline.	Inclusion: age≥18, T1c-T2a, Gleason score ≤7, max cancer core length 5 mm, PSA≤10 ng/ml, height of the peripheral zone ≤30 and ≤ 40 mm on TRUS. Exclusion: significant cancer on the contralateral side on mpMRI (PI-RADS v.1 or 2 ≥4), in case of previous prostatic/urethral surgery and/or intake of 5-ARIs ≤6 m and/or previous ADT.	Inclusion: unilateral cancer, T1c-T2a, max positive biopsies <33%, Gleason score≤7, PSA<15 ng/ml, >10 y life expectancy. Exclusion: previous PCa related treatment, extraprostatic extension disease on mpMRI.
Patient characteristics				
Age of patients Mean ± SD (median) [IQR]	73 (74) [70-77]	64.8 ± 6.2 (64.9) [61-69]	63.4 ± 8.3	70.2 ± 6.8
Tumour stage n (% of pts)	T1c : 16 (32) T2 : 34 (68)	T1 : 77 (69) T2 : 33 (30) Unknown : 1 (1)	NA	NA
Gleason score n (% of pts)	3+3: 30 (60) 3+4: 14 (28) 4+3: 6 (12)	≤6: 82 (74) =7: 29 (26)	3+4: 8 (15.7) Median 6	3+3: 58 (86.6) 3+4: 9 (13.4)
Pre-HIFU PSA level (ng/mL) Mean ± SD (median) [range]	6.6 (6.3) [3.9-8.3]	6.2 ± 2.5 (5.6) [4.7-7.6]	6.2 ± 2.1	(6.1) [IQR: 1.6-15.5]
Risk categories n (% of pts) according to	*D'Amico:* low 24 (48) intermediate 26 (52)	*NA:* low 75 (68) intermediate 36 (32)	*NA:* low NA intermediate NA	*NA:* low: 67 (100)

Author, year, reference number	Van Velthoven, 2016 [23]	Rischmann, 2017 [22]	Ganzer, 2017 [21]	Feijoo, 2015 [20]
Pre-HIFU prostate volume (mL) Mean ± SD (median) [IQR]	31 (27) [20-38]	31.6 ±12.3 (28.3) [23-39]	34.1 ± 15.0	39.3 ± 13.7
Neoadjuvant ADT n (%)	NA	NA	NA	NA
HIFU procedure and follow-up				
TURP prior to/combined with HIFU n (% of pts)	NA	67 (60)	NA	NA
Anaesthesia	Spinal, general[51]	Spinal, general	General	NA
Number of treatments/patient n (% of pts)	NA	NA	NA	NA
Duration of treatment (min) ± SD	NA	NA	62.2 ± 20.3	Ø 120
Hospital stay (d)	4[52]	NA	NA	NA
Catheterisation time (d)	2.8[53]	NA	2.9 ± 4.3	NA
Follow-up (m) Mean ± SD (median) [range]	39 (34) [IQR: 13-58][54]	30.4 ±14.1	17.41 ± 4.5 [12-24]	(12) [IQR: 6-50]
Loss to follow-up n (%)	39 (78) over 5 y	10 (10)[55] 32 (29) over 2 y	0	15 (22.4) over 16 m
Effectiveness-related outcomes				
Overall survival n (%) at X years	46[56] (87)/5 y	109 (98.2)[57]/1 y	51 (100)/1 y	NA
Prostate cancer specific survival % at X years	100/5 y	NA	100/1 y	NA

[51] Procedure described in Van Velthoven, 2014

[52] Procedure described in Van Velthoven, 2014

[53] Procedure described in Van Velthoven, 2014

[54] The data is presented in a table and described in the text, however they slightly differ. We applied data from the table. In the results section 40 (35), in the summary section (39.5) is stated.

[55] In study it is stated that no patient was lost but control biopsy was performed in 101 patients, 10 patients refused or had contraindication, or died from other cause.

[56] Three patients with severe comorbidities died from unrelated confirmed cause, and one patient died from a heart attack. Study authors reported 87% overall survival rate which is lower than the rate if we calculate with the 4 deaths.

[57] Two patients died from other causes: pancreatic and ethmoidal bone cancers.

Author, year, reference number	Van Velthoven, 2016 [23]	Rischmann, 2017 [22]	Ganzer, 2017 [21]	Feijoo, 2015 [20]
Local disease recurrence n	*Positive biopsy*: 6/8/NA of which 3 (50%) were significant on the contralateral side	*Positive biopsy*: 8/12/NA of which 5 (63%) were significant	*Positive biopsy*: 13/49/1 y in the treated lobe of which 4 (8.2%) were significant; 17/49/1 y on the contralateral side of which 1 (2%) was significant	*Positive biopsy*: 17/67/NA of which 11 (64.7%) were significant
Distant disease recurrence/metastasis n	NA	NA	NA	NA
Biochemical recurrence/failure n (%) at X years according to	*Phoenix*: 14 (28)/NA *Stuttgart*: 18 (36)/NA	NA	NA	*Phoenix*: 6 (9.7)/NA
Disease/pathological progression	NA	NA	NA	NA
QoL measured by (tool)	NA	*EORTC QLQ-C28 at 0 m/12 m FU (n=76):* mean increase 0.4 (95% CI: −1.0; 1.7)	*Global health status/quality of life score (± SD) at 0 m/12 m FU:* 74.6±17.8/73.9±22.0, p=0.39 *HADS-D depression score (± SD) at 0 m/12 m FU:* 8.8±4.7/10.1±3.2, p=0.276 *HADS-D anxiety score (± SD) at 0 m/12 m FU:* 6.5±3.8/6.8±2.6, p=0.804	NA
Need for salvage therapy n (%)	s-HIFU:3 (6) s-RT: 3 (6) AS: 2 (4)	AS: 16 (15.8) s-RP: 6 (5.9) s-EBRT: 3 (3.0) s-HIFU: 9 (8.9) 4 pts needed 3rd line therapy	s-RT: 4 (7.8) s-HIFU: 5 (9.8) s-RP: 1 (1.9) = 10 (19.6) AS: 8 (15.7)	NA
Ablation failure n (%)	NA	NA	NA	NA
Safety-related outcomes				
Intervention-specific mortality	0	0	0	0
Functional outcomes: urinary (dys)function according to	*Physician reported rate: incontinent pre-HIFU/12 m post-HIFU, n (%) (n=50):* 0 (0)/3 (6) (transient incontinence before 12 m post-HIFU: 7 (14))	*Usage of pads pre-HIFU/12 m post-HIFU, n (%) (n=102):* 1 (1)/3 (3) *IPSS pre-HIFU/12 m post-HIFU (n=80):* improvement with a mean decrease of 3 (95% CI: 1.6; 4.4)	*Usage of pads pre-HIFU/12 m post-HIFU, n (%) (n=51)*: 1 (2)/3 (5.9) *IPSS pre-HIFU/12 m post-HIFU:* No significant change	*Usage of pads pre-HIFU/x m post-HIFU, n (%) (n=67):* 0 (0)/0 (0) *IPSS (range) pre-HIFU/3 m post-HIFU:* 6.24 (0-26)/NA, p=0.217 *ICS (range) pre-HIFU/3 m post-HIFU:* 0.42 (0-8)/NA, p=0.840

Author, year, reference number	Van Velthoven, 2016 [23]	Rischmann, 2017 [22]	Ganzer, 2017 [21]	Feijoo, 2015 [20]
Functional outcomes: sexual (dys)function according to	*Physician reported rate pre-HIFU potent/NA m post-HIFU potent (n=50):* 30/24 De novo erectile dysfunction n (% of previously potent): 6 (20)	*IIEF-5 pre-HIFU/12 m post-HIFU:* mean difference 1.2 (95% CI: −0.4; 2.7) *Physician reported rate pre-HIFU potent/NA m post-HIFU potent (n=51):* 51/40 De novo erectile dysfunction n (% of previously potent): 11 (21.6)	*IIEF-5 score (± SD) pre-HIFU/12 m post-HIFU*: 17.6±6.1/13.6±8.6, p<0.001 *ICS-male score at 0 m/12 m FU*: 0.9±2.3/1.4±3.0, p=0.131	*IIEF-5 score (range) pre-HIFU/3 m post-HIFU:* 17.97 (0-25)/NA, p<0.001 *Physician reported rate pre-HIFU potent/NA m post-HIFU potent (n=21):* 21/11 De novo impotence n (% of previously potent): 10 (47.6)
Complications/adverse events (AEs) (grade 1-2) n at x months Urinary tract infection Storage or voiding lower urinary tract symptoms (LUTS) Acute/chronic urinary retention Burn, injuries, bleeding Proctitis Pain Anesthesia-related complications Thromboembolic disease (phlebitis) Other AEs	**16/NA m (n=50)** Urinary tract infection: 3 LUTS: 9 Chronic urinary retention: 4	**100/12 m (n=105)** Urinary tract infection: 18 LUTS: 7 Urge incontinence: 4 Gross hematuria: 5 Transient dysuria: 17 Chronic urinary retention: 3 Hematospermia: 2 Anejaculation: 16 Orchitis: 8 Proctitis: 8 Transient anal and perineal pain: 10 Deep phlebitis: 1 Superficial phlebitis: 1	**25/NA m (n=21)** Urinary tract infection: 9 Transient hematuria: 4 Urge incontinence: 2 Dysuria: 1 Chronic urinary retention: 5 Anejaculation: 1 Pelvic pain: 2 Aspermia: 1	**8 within 1 m (n=67)** Urinary tract infection: 4 Urinary retention: 4
Serious adverse events (SAEs) (grade 3-4) n at x months (n pts) Bladder neck/urethral stricture/stenosis Bladder neck obstruction Rectal fistula Other SAEs	**6/NA m (n=50)** Stricture: 2 Bladder neck obstruction: NA Rectal fistula: NA Acute urinary retention: 4	**6/12 m (n=105)** Stricture: 1 Bladder neck obstruction: NA Rectal fistula: NA Acute urinary retention: 5	**1/NA m (n=21)** Stenosis: 1 Bladder neck obstruction: NA Rectal fistula: NA	**2 within 1 m (n=67)** Urinary retention: 2

***Abbreviations**: ADT = androgen deprivation therapy, AE = adverse event, ARI = Alpha reductase inhibitor, AS = active surveillance, BE = Belgium, d = day, EBRT= external beam radiation therapy, EORTC-QLQ = European Organisation for Research and Treatment of Cancer-Quality of Life Questionnaire, D = Germany, FR = France, FU = follow-up, HADS = hospital anxiety and depression scale, HIFU = high-intensity focused ultrasound, ICS = International Continence Society score, IIEF = international index of erectile function, IPSS = international prostate symptom score, IQR = interquartile range, LUTS = lower urinary tract symptoms, n = number, min = minute, mpMRI = multiparametric magnetic resonance imaging, NA = not available, pts = patients, PCa = prostate cancer, PI-RADS = prostate imaging reporting and data system, PSA = prostate-specific antigen, QoL = quality of life, RP = radical prostatectomy, RT = radiation therapy, SD = standard deviation, TURP = transurethral resection of the prostate*

Table A-3: Salvage HIFU: Results from single-arm observational studies

Author, year, reference number	Uddin Ahmed, 2012 [24]
Country	UK, CAN
Funding	Med. Research Council, Pelican Cancer Foundation, Prostate Action, St Peters Trust, Prostate Cancer Research Centre
HIFU device	Sonablate® 500
Type of ablation	Salvage-whole gland ablation
Study design	Prospective registry after a multicentre single-arm phase 2 feasibility study
Study timeframe	2004-2009
Number of patients	84
Inclusion/exclusion criteria	Inclusion: biochemical failure after EBRT, localised PCa < T3aNoMo
Patient characteristics	
Age of patients Mean (median) [IQR]	68.3 [65-72]
Tumour stage n (% of pts)	NA
Gleason score n (% of pts)	Median 7 (range 6-7)
Pre-HIFU PSA level (ng/mL) Mean (median) [range]	5.7 (3.8) [1.5-7.7]
Risk categories n (% of pts) according to	NA
Pre-HIFU prostate volume (mL) Mean (median) [IQR]	25.1 (24) [19-30]
Neoadjuvant ADT n (%)	30 (36)
HIFU procedure and follow-up	
TURP prior to/combined with HIFU n (% of pts)	NA
Anaesthesia	NA
Number of treatments/patient n (% of pts)	1: 78 (92.9) 2: 6 (7.1)
Duration of treatment (min)	158[58]
Hospital stay (d)	Mean 1.4
Catheterisation time (d)	NA
Follow-up (m) Mean (median) [range]	19.8 [3.0-35.1]
Loss to follow-up n (%)	0
Effectiveness-related outcomes	
Overall survival % at X years	NA
Prostate cancer specific survival % at X years	NA
Local disease recurrence n	Positive biopsy: 21/49/NA of which NA were significant
Distant disease recurrence/metastasis n	NA
Biochemical recurrence/failure n (%) at X years according to	NA
Disease/pathological progression	NA
QoL measured by (tool)	*RAND-SF36 at 0m/6 m (n=39):* 102.7 (103)/100.4 (100), p=0.03
Need for salvage therapy n (%)	WW or ADT: 21 (25)
Ablation failure n (%)	6 patients needed redo-s-HIFU

[58] Data available only on 40 patients

Author, year, reference number	Uddin Ahmed, 2012 [24]
Safety-related outcomes	
Intervention-specific mortality	0
Functional outcomes: **urinary (dys)function according to**	*IPSS pre-salvage-HIFU/6 m post-salvage-HIFU (n=39):* 8.3 (7)/11.6 (9.5), p=0.06
Functional outcomes: **sexual (dys)function according to**	*IIEF-5 pre-salvage-HIFU/6 m post-salvage-HIFU (n=43):* 8.6 (6)/6.2 (3), p<0.001
Complications/adverse events (AEs) **(grade 1-2) n at x months (n pts)** Urinary tract infection Lower urinary tract symptoms (LUTS) Acute/chronic urinary retention Burn, injuries, bleeding Proctitis Pain Anesthesia-related complications Thromboembolic disease (phlebitis) Other AEs	**37/NA m (n=84)** Grade 1: 27 Grade 2: 10
Serious adverse events (SAEs) **(grade 3-4) n at x months (n pts)** Bladder neck/urethral stricture/stenosis Bladder neck obstruction Rectal fistula Other SAEs	**55/NA m (n=84)** Grade 3: 52 Grade 4: 3 (Bladder outlet obstruction: 17 Rectal fistula: 4 (2 after 1 treatment, 2 after redo-s-HIFU))

***Abbreviations**: ADT = androgen deprivation therapy. AE = adverse event, d = day, CAN = Canada, EBRT = external beam radiation therapy, FU = follow-up, HIFU = high-intensity focused ultrasound, IIEF = international index of erectile function, IPSS = international prostate symptom score, IQR = interquartile range, LUTS = lower urinary tract symptoms, n = number, min = minute, NA = not available, pts = patients, PCa = prostate cancer, PSA = prostate-specific antigen, QoL = quality of life, RAND-SF = Research ANd = Development Short Form, SD = standard deviation, TURP = transurethral resection of the prostate, UK = United Kingdom, WW = watchful waiting*

Risk of bias tables and GRADE evidence profile

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-4: Outcome – specific risk of bias of non – randomised studies comparing primary HIFU versus brachytherapy [19]

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias.
Where questions relate only to sign posts to other questions, no formatting is used.

Risk of bias assessment applies for all critical outcomes together (prostate cancer specific survival, local disease recurrence, functional outcomes and complication), since judgement is similar for all outcomes (any additional considerations were added in the GRADE assessment).

Signalling questions	Description	Response options
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study?	Based on the information given, confounding cannot be excluded. Main potential confounders are the difference in age (age was a matching criteria) and difference in follow-up time between study groups (see also 1.4). Both might have an influence on treatment effects. Another important confounder is the fact that HIFU was performed by one surgeon and brachytherapy by two different surgeons.	Y
If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:		
1.2. Was the analysis based on splitting participants' follow up time according to intervention received? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, go to question 1.3.	It is not clear how it was decided that patients receive HIFU or brachytherapy. Thus, it is not clear if patients could switch between study groups.	PY
1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? **If N/PN**, answer questions relating to baseline confounding (1.4 to 1.6) **If Y/PY**, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)		N
Questions relating to baseline confounding only		
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Wilcoxon's rank-sum or χ^2 tests were used to asses absence of clinical and pathological differences. However, no sufficient infor-mation was provided if other confounders were controlled for (e.g., age).	PN
1.5. **If Y/PY to 1.4**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	-	-
1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	No sufficient information given in study.	NI

Signalling questions	Description	Response options
Questions relating to baseline and time-varying confounding		
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	-	-
1.8. **If Y/PY to 1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	-	-
Risk of bias judgement	Due to the lack of information and the potential risk of confounding, risk of bias was considered as "serious".	Serious
Optional: What is the predicted direction of bias due to confounding?	In HIFU-group patients were older and the follow-up period was longer, which lead in a potential favouritism of brachytherapy (even though there are no other studies for confirmation).	Favours comparator (brachytherapy)
Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? **If N/PN to 2.1:** go to 2.4	Study is a matched-pair analysis of two single-arm studies. Thus, selection of the participants for matched-pair analysis was done after the start of both interventions (matching was based on Gleason score, PSA, clinical tumour stage, D'Amico risk, and age). Furthermore, the study says: "Patients […] were matched 1:1 […]. The matching procedure was blinded to the outcome […]." The blinding process, though, was not properly described. Thus, study personnel could have been aware of characteristics and outcomes. Plus, patients in the interventions group were older than in control group (p<0.01).	PY
2.2. **If Y/PY to 2.1**: Were the post-intervention variables that influenced selection likely to be associated with intervention?		N
2.3 **If Y/PY to 2.2**: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	-	-
2.4. Do start of follow-up and start of intervention coincide for most participants?	-	-
2.5. **If Y/PY to 2.2 and 2.3, or N/PN to 2.4**: Were adjustment techniques used that are likely to correct for the presence of selection biases?	-	-
Risk of bias judgement		Moderate
Optional: What is the predicted direction of bias due to selection of participants into the study?		Unpredictable
Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	Interventions were not very well defined. Not clear how many patients had earlier HIFU version applied, and how many the new one. Criteria for considering individuals to have received each intervention was not mentioned (e.g. type, setting, dose, intensity, and timing of intervention).	PN
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Explicit information about interventions received was not given. It is not clear how many patients received ADT, how many patients had earlier HIFU version applied. Patients of intervention group were collected from a bigger intervention group after initial intervention.	N

Signalling questions	Description	Response options
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Study says: "The matching procedure was blinded to the outcomes in order to avoid selection bias." But blinding procedure was not described in detail.	PY
Risk of bias judgement		Serious
Optional: What is the predicted direction of bias due to classification of interventions?		Unpredictable
Bias due to deviations from intended interventions		
If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	It seems that there were no deviations.	N
4.2. **If Y/PY to 4.1**: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	-	-
If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6		
4.3. Were important co-interventions balanced across intervention groups?	Study says: "Patients with prostates exceeding this threshold are offered neoadjuvant cytoreductive androgen deprivation therapy (ADT). Hormonal treatment is always discontinued at the time of surgery." Thus, it is not clear how many patients received ADT (see also 3.2).	N
4.4. Was the intervention implemented successfully for most participants?		Y
4.5. Did study participants adhere to the assigned intervention regimen?		Y
4.6. **If N/PN to 4.3, 4.4 or 4.5**: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?		-
Risk of bias judgement		Serious
Optional: What is the predicted direction of bias due to deviations from the intended interventions?		Unpredictable
Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?		Y
5.2 Were participants excluded due to missing data on intervention status?	Patients were a-priori excluded when outcome data of 12 months or more was not available. However, patients were not excluded from study, when matched-pair analysis was done.	N
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Patients with missing oncological data were excluded.	PY
5.4 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Are the proportion of participants and reasons for missing data similar across interventions?	It is not clear how many patients, who received control intervention, were excluded for final analysis.	NI
5.5 **If PN/N to 5.1, or Y/PY to 5.2 or 5.3**: Is there evidence that results were robust to the presence of missing data?		NI

Signalling questions	Description	Response options
Risk of bias judgement		Serious
Optional: What is the predicted direction of bias due to missing data?		Unpredictable
Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Study mainly measured "soft" outcomes.	Y
6.2 Were outcome assessors aware of the intervention received by study participants?	Study is a matched-pair analysis of two single-arm studies. Therefore, it was assumed that assessors were aware of intervention.	Y
6.3 Were the methods of outcome assessment comparable across intervention groups?	The same outcome detection methods and thresholds, same definition, and same measurements were used. However, it is not clear, if outcome assessment was done at same time point for all patients.	PY
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Same classification systems were used.	N
Risk of bias judgement		Serious
Optional: What is the predicted direction of bias due to measurement of outcomes?		Unpredictable
Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from ...		
7.1. ... multiple outcome *measurements* within the outcome domain?		N
7.2 ... multiple *analyses* of the intervention-outcome relationship?		N
7.3 ... different *subgroups*?		N
Risk of bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		Towards null
Overall bias		
Risk of bias judgement		Serious
Optional: What is the overall predicted direction of bias for this outcome?		Unpredictable

Table A-5: Risk of bias – study level (case series), (IHE-20-Criteria checklist)

Y/N/Partial/Unclear	Van Velthoven, 2016 [23]	Ganzer, 2017[21]	Rischmann, 2017 [22]	Feijoo, 2015 [20]	Ahmed, 2012 [24]
Study objective					
1 Was the hypothesis/aim/objective of the study clearly stated?	Yes	Partial	Yes	Yes	Partial
Study design					
2 Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Unclear
3 Were the cases collected in more than one centre?	No	Yes	No	Yes	Yes
4 Were patients recruited consecutively?	Unclear	Yes	Unclear	Unclear	Yes
Study population					
5 Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes
6 Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes	Yes	Partial
7 Did patients enter the study at a similar point in the disease?	Yes	Yes	Yes	Yes	Yes
Intervention and co-intervention					
8 Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Partial
9 Were additional interventions (co-interventions) clearly described?	Yes	Partial	Yes	Yes	Partial
Outcome measure					
10 Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes
11 Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No
12 Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes
13 Were the relevant outcome measures made before and after the intervention?	Partial	Yes	Yes	Yes	Yes
Statistical analysis					
14 Were the statistical tests used to assess the relevant outcomes appropriate?	No	Yes	Yes	Yes	Yes
Results and conclusions					
15 Was follow-up long enough for important events and outcomes to occur?	Partial	Partial	Partial	Partial	Partial
16 Were losses to follow-up reported?	Yes	Yes	Yes	Yes	Yes
17 Did the study provided estimates of random variability in the data analysis of relevant outcomes?	No	Yes	Yes	Yes	Yes
18 Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes
19 Were the conclusions of the study supported by results?	Unclear	Yes	Yes	Yes	Yes
Competing interests and sources of support					
20 Were both competing interests and sources of support for the study reported?	Partial	No	Yes	Yes	Yes

Table A-6: Evidence profile: efficacy and safety of primary HIFU versus brachytherapy

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIFU	brachytherapy	Relative (95% CI)	Absolute (95% CI)		
Overall survival rate (follow up: 5 years)												
1	Observational study (matched-pair analysis)	Serious[61]	NA (only 1 trial)	Serious[61]	Serious[59]	Plausible confounding (would suggest spurious effect)	62/70 (89%)	68/70 (97%)	HR 0.24 (0.01 to 1.34)	397 fewer per 1,000 (from 20 more to 936 fewer)	Very low	Critical
Prostate cancer specific survival rate (follow up: 5 years)												
1	Observational study (matched-pair analysis)	Serious[60]	NA (only 1 trial)	Serious[61]	Serious[62]	Plausible confounding (would suggest spurious effect)	62/70 (89%)	64/70 (92%)	HR 0.67 (0.32 to 1.29)	107 fewer per 1,000 (from 44 more to 370 fewer)	Very low	Critical
Local diseases recurrence (follow up: 5 years): NA												
Intervention-specific mortality (follow up: median 83 vs. 44 months)												
1	Observational study (matched-pair analysis)	Serious[60]	NA (only 1 trial)	Serious[61]	Serious[63]	None	0/70 (0%)	0/70 (0%)	Not estimable	NA	Very low	Critical
Functional outcomes: urinary (dys)function (physician reported events) (follow up: median 83 vs. 44 months)												
1	Observational study (matched-pair analysis)	Serious[64]	NA (only 1 trial)	Serious[61]	Serious[65]	All plausible re-sidual confounding would reduce the demonstrated effect	5/69 (7.2%)	2/53 (3.8%)	RR 1.92 (0.39 to 9.51)[66]	34 more per 1,000 (14 fewer to 359 more)	Very low	Critical

[59] Imprecision was set "serious" for this particular endpoint, since the confidence interval (0.01 to 1.34) indicates considerable harm due to HIFU.

[60] Risk of bias for this particular endpoint was set "serious" due to risk of bias assessment of study and particularly due to difference between study groups in age.

[61] Indirectness was set "serious" for this particular endpoint, since this study was claimed to be the first to compare patients treated by HIFU and brachytherapy. Furthermore, in this study two generations of Ablatherm® devices were used, whereas Ablatherm® Maxis is not commercially available anymore. Moreover, there was no information provided on additional treatments and pre-treatment prostate volume.

[62] Imprecision was set "serious" for this particular endpoint, since the confidence interval (0.32 to 1.29/0.39 to) indicates considerable harm due to HIFU.

[63] Imprecision was set "serious" for this particular endpoint, since the probability of intervention-specific mortality is estimated to be low and patient number must be higher to detect differences.

[64] Risk of bias for this particular endpoint was set "serious", due to risk of bias assessment of study particularly the difference between study groups in age and length of follow up. Furthermore, it was not stated how many patients suffered from incontinence before the interventions.

[65] Imprecision was set "serious" for this particular endpoint, since the confidence interval (0.39 to 9.51) indicates considerable harm due to HIFU.

[66] Caclulated with MedCalc© (http://www.medcalc.org/calc/relative_risk.php).

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	HIFU	brachytherapy	Relative (95% CI)	Absolute (95% CI)		
Functional outcomes: sexual (dys)function (events) (follow up: median 83 vs. 44 months)												
1	Observational study (matched-pair analysis)	Serious[67]	NA (only 1 trial)	Not serious[68]	Serious[62]	None	5/43 (11.6%)	NA	Not estimable	NA	Very low	Critical
Serious adverse events (follow up: mean 12 months)												
1	Observational study (matched-pair analysis)	Serious[69]	NA (only 1 trial)	Serious[61]	Serious[70]	All plausible residual confounding would reduce the demonstrated effect	17/70 (24.3%)	5/70 (7.1%)	Not estimable	NA	Very low	Critical
Serious adverse events (follow up: median 83 vs. 44 months)												
1	Observational study (matched-pair analysis)	Serious[69]	NA (only 1 trial)	Serious[61]	Serious[70]	All plausible residual confounding would reduce the demonstrated effect	18/70 (25.7%)	4/70 (5.7%)	Not estimable	NA	Very low	Critical

***Abbreviations**: CI = confidence interval, HIFU = high-intensity focused ultrasound, IPSS = international prostate symptom score, IIEF-5 = international index of erectile function, NA = not applicable*

***Sources:** [19]*

[67] Risk of bias for this particular endpoint was set "serious", due to risk of bias assessment of study, particularly the difference between study groups in age and length of follow-up. Furthermore, measurement of sexual (dys)function was exclusively done for HIFU-patients.

[68] Indirectness cannot be assessed, because study exclusively reported sexual (dys)function for HIFU-patients.

[69] Risk of bias for this particular endpoint was set "serious", due to the difference between study groups in age (see also risk of bias assessment of study). Furthermore, the study exclusively reported the number of complications and not the number of patients with complications.

[70] Imprecision was set "serious" for this particular endpoint, because the patient number was too low to detect rare adverse events.

Table A-7: Evidence profile: safety of primary HIFU (single-arm studies)

Quality assessment							Summary of findings					
							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-HIFU	Post-HIFU	Relative (95% CI)	Absolute (95% CI)		
Intervention-specific mortality (follow up: range mean 16.3 months to mean 44.5 months; assessed with number of events)												
4	Observational study	Serious[71]	Not serious	Serious[72]	Serious[73]	None	0/279 (0.0%)	0/279 (0.0%)	Not estimable	NA	Very low	Critical
Functional outcomes: urinary (dys)function (follow up: 12 months; assessed with usage of pads)												
4	Observational study	Serious[71]	Not serious	Serious[72]	Serious[73]	None	2/270 (0.7%)	9/270 (3.3%)	Not estimable	NA	Very low	Critical
Functional outcomes: urinary (dys)function (follow up: range 3 months to 12; assessed with IPSS, Scale from 0 to 26 worse)												
3	Observational study	Serious[71]	Serious[74]	Serious[72]	serious[73]	None	198[75]	198	Not pooled	NA	Very low	Critical
Functional outcome: sexual (dys)function (follow up: range 3 months to 12; assessed with IIEF-5, Scale from: 0 to 25 worse)												
3	Observational study	Serious[71]	Not serious	Serious[72]	Serious[73]	None	NA[76]	NA	Not pooled[77]	NA	Very low	Critical
Functional outcomes: sexual (dys)function (follow up: 3 months; assessed with physician reported rates of de novo erectile dysfunction)												
3	Observational study	Serious[71]	Serious[78]	Serious[72]	Serious[73]	None	0/122 (0.0%)	27/122 (22.1%)	Not estimable	NA	Very low	Critical
Serious adverse events (follow up: range 1 to 12 months; assessed with number of events)												
4	Observational study	Serious[71]	Serious[79]	Serious[72]	Serious[73]	None	0/273 (0.0%)	15/273[80] (5.5%)	Not estimable	NA	Very low	Critical

Abbreviations: *CI = confidence interval, HIFU = high-intensity focused ultrasound, IPSS = international prostate symptom score, IIEF-5 = international index of erectile function, NA = not applicable*

Sources: *[20-23]*

71 No control group.

72 The studies can only yield indirect evidence regarding the safety of HIFU compared to standard therapies as there was no control arm (safety outcomes could only be compared to historical controls).

73 Low sample size.

74 There is inconsistency in the results as two studies reported no significant change in the score, while one study reported a significant mean decrease (meaning improvement) in the score.

75 The number of patients answering the questionnaire pre- and post-treatment.

76 The number of patients answering the questionnaire was not available.

77 The range of effect: 1.2 to 4

78 There is inconsistency as two studies reported around 20% of pre-HIFU potent patients being post-HIFU impotent, while one study reported over 47% of pre-HIFU potent patients being post-HIFU impotent.

79 There is inconsistency in the percentage of patients presented with an adverse event per study as one study reported in 41% of patients occurred adverse event, another study reported 15%, two studies did not report the percentage of patients in whom adverse event occurred, but the total number of adverse events and these studies did not specify how many patients experienced the adverse event.

80 Number of events in the total number of patients.

Table A-8: Evidence profile: safety of salvage HIFU

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pre-salvage-HIFU	Post-salvage-HIFU	Relative (95% CI)	Absolute (95% CI)		
Intervention-specific mortality (follow up: mean 19.8 months)												
1	Observational study	Serious[81]	NA (only 1 study)	Serious[83]	Very serious[84]	None	0/84 (0.0%)	0/84 (0.0%)	not estimable	NA	Very low	Critical
Functional outcomes: urinary (dys)function (follow up: 6 months; assessed with IPSS)												
1	Observational study	Serious[82]	NA (only 1 study)	Serious[83]	Very serious[84]	None	39[85]	39	NA	NA	Very low	Critical
Functional outcomes: sexual (dys)function (follow up: 6 months; assessed with IIEF-5)												
1	Observational study	Serious[86]	NA (only 1 study)	Serious[83]	Very serious[84]	None	43[85]	43	NA	NA	Very low	Critical
Complications/adverse events (follow up: mean 19.8 months; assessed with number of events)												
1	Observational study	Serious[81]	NA (only 1 study)	Serious[83]	Very serious[84]	None	0/84 (0.0%)	55/84[80] (65.5%)	Not estimable	NA	Very low	Critical

***Abbreviations**: CI = confidence interval, HIFU = high-intensity focused ultrasound, IPSS = international prostate symptom score, IIEF-5 = international index of erectile function, NA = not applicable*

***Sources:** [24]*

[81] No control group.

[82] No control group, follow-up data available only for 39 patients (46%).

[83] Only failed EBRT patients were included (we do not have information on patients failed after other treatment modalities like prostatectomy or HIFU). The studies can only yield indirect evidence on HIFU compared to standard therapies as there was no control group.

[84] Very low sample size.

[85] Number of patients answering the questionnaire pre-and post-treatment.

[86] No control group, follow-up data available only for 43 patients (51%).

Applicability table

Table A-9: Summary table characterizing the applicability of a body of studies

Domain	Description of applicability of evidence
Population	The enrolled populations in the studies do not differ substantially from the target population; therefore the findings are generalizable to the target population.
Intervention	Only the Ablatherm® device was used in all of the primary HIFU studies and only the Sonablate® device in the study on salvage HIFU. This does not reflect clinical practice, as both devices can be used in both primary and salvage setting. The matched-pair analysis study used in the beginning of the study period the Ablatherm® Maxis device which is the predecessor of the current Ablatherm® device and the applied device generation might negatively affect occurrence of adverse events. Patients in the matched-pair analysis treated with the Maxis Ablatherm® (not commercially available anymore) had a higher number of complications than patients treated with the newer device (Ablatherm® Integrated Imaging) [19]. Nevertheless, the study did neither report on how many patients were treated with which HIFU-device, nor on the percentage of patients per sub-group with complications. Thus, a definitive conclusion cannot be drawn. Also, only one primary HIFU study described concomitant TURP which might not reflect how the intervention is done routinely and might affect the harms associated with the intervention.
Comparators	The only one comparative study compared HIFU with brachytherapy, which is only one of the standard treatment modalities. There were no other comparative studies. For salvage HIFU there was no comparative study available.
Outcomes	Most frequently reported outcomes were overall survival rate, urinary function, sexual function and complications/adverse events. The oncologic outcomes were reported on very different time spans. Overall survival rate was reported either at 1 year or at 5 years. Sexual function (IIEF-5 score) was reported at 12 months post-operatively and urinary function (IPSS score and usage of pads) was reported either at 12 months or at 3 months post-operatively. It was often not stated over what time period complications/adverse events were reported. The follow-up period for these outcomes is very short. Overall survival would require at least 5 year follow-up, but 10 year would be desirable. Functional outcomes would also need to be followed-up on a longer time period.
Setting	The studies represent a geographic spread across Western European countries. Clinical settings were not described in any of the studies. It was stated in some of the studies that experienced surgeon conducted the intervention which might have a relevance in the harms associated with the intervention, but as the prerequisite for the surgeon of receiving a certificate from the manufacturer is to complete a training and a certain number of treatments with a supervisor from the manufacturer, this is unlikely that unexperienced surgeons will perform the intervention.

List of ongoing controlled trials

Table A-10: List of ongoing controlled trials of HIFU

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT00295802	September 2014 (status unknown, no publication found)	RCT (non-inferiority)	141	HIFU (device not stated)	Cryotherapy	✲ Diagnosis of prostate cancer confirmed by PSA and prostate biopsy, ✲ Male, aged ≥ 50 years, ✲ Organ-confined PCa, clinical stage T1a, b, or c or T2a, ✲ ≥ 1 positive biopsy within the previous 6 months, ✲ PSA ≤ 10 ng/ml, ✲ Gleason score ≤ 6, ✲ Histological grading of 3+3, 3+2, 2+3, 2+4, or 2+2 based upon baseline TRUS-guided 10 core biopsy, ✲ Prostate volume ≤ 40 cc, ✲ Prostate anteroposterior diameter ≤ 25 mm, ✲ Normal rectal anatomy and rectal mucosa, ✲ < 6mm rectal wall measurement , ✲ The subject is willing and able to read, understand, and sign the study specific informed consent form, ✲ The subject agrees to comply with study protocol requirements, including HIFU or cryotherapy treatment and all follow up visit requirements through 24 months of follow up.	*Primary:* ✲ Attainment achievement of PSA nadir < 0.5 ng/ml and stability of PSA according to ASTRO criteria through 24 month follow up without a positive biopsy (timeframe: 24 month). *Secondary:* ✲ Achievement of a nadir PSA within 6 months < 0.5 ng/ml (timeframe: 6 months), ✲ Overall survival, defined as time to death due to any cause (timeframe: from date of treatment until the date of death due to any cause), ✲ Disease specific survival, defined as the time to death due to the underlying disease (timeframe: from date of treatment until the date of death due to the underlying cause), ✲ Change from baseline in the UCLA QOL (timeframe: 1 month, 6 months, 12 months, 24 months), ✲ Change from baseline in the IPSS (timeframe: 1 month, 6 months, 12 months, 24 months).
NCT00770822	December 2017 (terminated due to lack of inclusions)[87]	Non-randomized concurrently controlled study	466	HIFU (Sonablate)	Brachytherapy	✲ T1c or T2a carcinoma of the prostate confirmed by biopsy, ✲ Life expectancy ≥ 5 years, ✲ Prostate biopsy with ≥ 10 core biopsies, ✲ Gleason score ≤ 6, ✲ Serum PSA ≤ 10 ng/ml, ✲ Prostate volume ≤ 40cc, ✲ Distance from the anterior capsule surface to the posterior capsule surface (AP Diameter) ≤ 40 cm, ✲ Informed consent for the treatment study through 24 months post-treatment follow-up.	*Primary:* ✲ Absence of biochemical failure (timeframe: 24 months)

[87] See: http://www.eu-focus.europeanurology.com/article/S2405-4569(15)00031-0/pdf

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
NCT03348722	November 2019	Non-randomised controlled study (cohort study)	3,000	Active surveillance	Radical prostatectomy, radiotherapy, Other radical treatments (HIFU, cryotherapy, others)	✿ Newly diagnosed low risk PCa patients, defined according to the presence of all the following criteria: ✿ Diagnosis of adenocarcinoma of the prostate, ✿ PCa clinical stage T1c o T2a, ✿ PSA ≤10ng/ml at diagnosis, ✿ Adequate biopsy sampling according to prostate volume, ✿ ≤ 2 positive cores for random sampling and ≤ 2 lesions for target biopsies (even if the number of positive samples if >2) ✿ Gleason grade 3+3 (in patients age>70 Gleason 3+4) ✿ Residence in Piemonte or Valle D'Aosta regions, ✿ Patients suitable for radical treatment (surgery or radiotherapy), ✿ Age at diagnosis ≤ 75 years or >75 years if fragility assessment (measured with the G8 score) ≥14, ✿ Patients suitability for expressing a valid consent to participate in the study.	*Primary:* ✿ Treatment-Free Survival Secondary: ✿ Quality of life
NCT00777452	October 2008 (recruiting completed, no publication found)	Non-randomised controlled study (cohort study)	93	Active surveillance	Radical prostatectomy, radiotherapy, HIFU	Patients diagnosed with clinically localised PCa.	*Primary:* ✿ HRQoL changes over time *Secondary:* ✿ Urinary symptom score and erectile function over time
DRKS00005179	NA (recruiting planned)	RCT	60	HIFU (Ablatherm®)	No intervention	✿ Male, ✿ 18 – 80 years, ✿ High risk patients (PSA<20 ng/ml, Gleason Score ≥8) ✿ Life expectancy ≥10 years.	*Primary:* ✿ Biochemical disease free survival *Secondary:* ✿ Recurrence ✿ Necessity of additional therapy ✿ QoL

Abbreviations: *ASTRO = American Society for Radiation Oncology, BCR = biochemical recurrence, BCRFS = biochemical recurrence free survival, HIFU = high-intensity focused ultrasound, HRQoL = health-related quality of life, IPSS = International Prostate Symptom Score, NA = not available, PCa = prostate cancer, PSA = prostate specific antigen, TRUS = trans-rectal ultrasound imaging, UCLA-QOL = University of California, Los Angeles Quality of Life, QoL = quality of life*

Sources: *ClinicalTrials.gov; WHO ICTRP; EU Clinical Trail (EudraCT) Register*

Table A-11: Overview of guidelines on HIFU

Name of society/ organisation issuing guidance	Date of issue	Country/ies to which applicable	Summary of recommendation	Level of evidence (A,B,C)/class of recommendation (I, IIa, IIb, III)
EAU-ESTRO-SIOG	2016	Europe	Only offer HIFU within a clinical trial setting. The lack of long-term efficacy compared to standard modality has to be discussed with patients. Do not offer focal treatment outside clinical trials. Offer/discuss salvage HIFU to/with patients without evidence of metastasis and with histologically proven local recurrence. Inform them about the experimental nature of it.	C A B/III
NICE	2014	UK	Do not offer HIFU to men with localised prostate cancer other than in the context of controlled clinical trials comparing its use with established interventions.	"strong" recommendation
S3 Leitlinie	2016	Germany	HIFU is an experimental treatment and should be offered only in prospective studies.	A/III
AUA-ASTRO-SUO	2017	USA	Clinicians should inform those localised prostate cancer patients considering focal therapy or HIFU that ❁ these treatment options lack robust evidence of efficacy. ❁ even though HIFU is approved by the FDA for the destruction of prostate tissue, it is not approved explicitly for the treatment of prostate cancer. ❁ tumour location may influence oncologic outcome. Limiting apical treatment to minimize morbidity increases the risk of cancer persistence. ❁ focal therapy may not be curative and that further treatment for prostate cancer may be necessary. (As prostate cancer is often multifocal).	 Expert opinion Expert opinion C/moderate recommendation Expert opinion

Literature search strategies

Search strategy for Cochrane

Search Date: 01/12/2017	
ID	Search
#1	MeSH descriptor: [Prostatic Neoplasms] explode all trees
#2	(prostat* near (cancer* or neoplasm* or carcinoma* or tumo*r* or adenoma*)) (Word variations have been searched)
#3	#1 or #2
#4	MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] explode all trees
#5	MeSH descriptor: [Ultrasound, High-Intensity Focused, Transrectal] explode all trees
#6	high-intens* focus*ed ultra*sound* (Word variations have been searched)
#7	high-intens* focal* ultra*sound* (Word variations have been searched)
#8	HIFU:ti,ab,kw (Word variations have been searched)
#9	Magnetic resonance-guided focus*ed ultra*sound* (Word variations have been searched)
#10	MR*-guided focus*ed ultra*sound* (Word variations have been searched)
#11	Ablatherm:ti,ab,kw (Word variations have been searched)
#12	EDAP:ti,ab,kw (Word variations have been searched)
#13	Sonablate (Word variations have been searched)
#14	Focus Surgery:ti,ab,kw (Word variations have been searched)
#15	ExAblate:ti,ab,kw (Word variations have been searched)
#16	Insightec:ti,ab,kw (Word variations have been searched)
#17	#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18	#3 and #17 Publication Year from 2010 to 2017
Total: **106 Hits**	

Search strategy for CRD

Search Date: 01/12/2017	
ID	Search
1	MeSH DESCRIPTOR Prostatic Neoplasms EXPLODE ALL TREES
2	MeSH DESCRIPTOR Prostatic Neoplasms, Castration-Resistant EXPLODE ALL TREES
3	(prostat* NEAR (cancer* OR neoplasm* OR carcinoma* OR tumo*r* OR adenoma*))
4	#1 OR #2 OR #3
5	MeSH DESCRIPTOR High-Intensity Focused Ultrasound Ablation EXPLODE ALL TREES
6	MeSH DESCRIPTOR Ultrasound, High-Intensity Focused, Transrectal EXPLODE ALL TREES
7	(high-intens* focus*ed ultra*sound*)
8	(high-intens* focal ultra*sound*)
9	(HIFU)
10	(Magnetic resonance-guided focus*ed ultra*sound*)
11	(MR*-guided focus*ed ultra*sound*)
12	(Ablatherm)
13	(EDAP)
14	(Sonablate)
15	(Focus Surgery)

16	(ExAblate)
17	(Insightec)
18	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17
19	#4 AND #18
20	*WHERE LPD FROM 29/01/2010 TO 01/12/2017
21	#19 AND #20
Total: **13 Hits**	

Search strategy for Embase

Search Date: 01/12/2017		Results
#27	#25 AND 'human'/de AND ([english]/lim OR [german]/lim)	580
#26	#25 AND 'human'/de	601
#25	#3 AND #23 AND [29-1-2010]/sd NOT [1-12-2017]/sd	711
#24	#3 AND #23	972
#23	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22	5,097
#22	insightec:df	142
#21	exablate:dn	134
#20	'focus surgery':df	48
#19	sonablate:dn	80
#18	edap:df	110
#17	ablatherm:dn	88
#16	'magnetic resonance-guided focus*ed	343
#15	insightec/df	139
#14	exablate/dn	31
#13	'focus surgery'/df	47
#12	sonablate/dn	33
#11	edap/df	100
#10	ablatherm/dn	71
#9	'mr*-guided focus*ed ultra*sound*':ti,ab	845
#8	'mr-guided focused ultrasound device'/exp	10
#7	'mr-guided focused ultrasound'/exp	54
#6	hifu:ti,ab	3,045
#5	'high-intens* focus*ed ultra*sound*':ti,ab	3,398
#4	'high intensity focused ultrasound'/mj/exp	2,593
#3	#1 OR #2	137,630
#2	((recurrent OR relapsed OR 'locally advanced' OR 'clinically localised' OR 'clinically localized') NEAR/1 prostat* NEAR/1 (cancer* OR neoplasm* OR carcinoma* OR tumor* OR tumour* OR adenoma*)):ti,ab	6,380
#1	'prostate tumor'/mj/exp	136,717

Search strategy for Ovid MEDLINE(R)

Search Date: 01/12/2017		
ID	Search	Results
1	exp Prostatic Neoplasms/	123,427
2	(prostat* adj2 (cancer* or neoplasm* or carcinoma* or tumo?r* or adenoma*)).mp.	155,384
3	1 or 2	1553,84
4	exp High-Intensity Focused Ultrasound Ablation/	1,788
5	exp Ultrasound, High-Intensity Focused, Transrectal/	486
6	high-intens* focus?ed ultra?sound*.mp.	3,138
7	high-intens* focal ultra?sound*.mp.	8
8	HIFU.ti,ab.	2,072
9	Magnetic resonance-guided focus*ed ultra*sound*.mp.	257
10	MR?-guided focus?ed ultra?sound*.mp.	298
11	Ablatherm.ti,ab.	58
12	EDAP.ti,ab.	196
13	Sonablate.ti,ab.	44
14	Focus Surgery.ti,ab.	19
15	ExAblate.ti,ab.	48
16	Insightec.ti,ab.	45
17	4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	4,054
18	3 and 17	860
19	limit 18 to ed=20100129-20171201	513
20	("17034499" or "16831068" or "16834675" or "18704441" or "19021611" or "19268572" or "19513068" or "16287436" or "16829268" or "16011815" or "18651999" or "19084862" or "16971038" or "18718643" or "17921730" or "18409659" or "12756085" or "10671777" or "18025853" or "18025852" or "19388986" or "18313119" or "17997026" or "18829078" or "16850340" or "14972475" or "15161124" or "19337912" or "17339141" or "18508189" or "18852702" or "19220245" or "17006697" or "11062372" or "11394458" or "12756090" or "16474762" or "10795622" or "19455298" or "19334790" or "18491529" or "16237234" or "16467581" or "19098966" or "16285451" or "18164806" or "18949746" or "18476973" or "15452554" or "14977222" or "11885680" or "16286025" or "19856677" or "18508190" or "16225512" or "18544989" or "17432561" or "19163505" or "15675669" or "15000627" or "18094311" or "19764975" or "17573894" or "17699732" or "17218948" or "17997016" or "19997112" or "17936815" or "17125477" or "17997014" or "19091354" or "17662520" or "16425987" or "10954310" or "11528187" or "15072864" or "16430617" or "16536790" or "19084860" or "17482933" or "19406315" or "15933426" or "19499752" or "16861120" or "17356831" or "15963124" or "17956536" or "17382151" or "12909212" or "19357510" or "16278168" or "11212878" or "18507002" or "15245946" or "17578342" or "17280536" or "17125476" or "17960490" or "18521101" or "15162826" or "18533805" or "11221062" or "18025857" or "18430829" or "18561684" or "18223121" or "17936800" or "16107241" or "16362603" or "17434108" or "14716736" or "16894640" or "12796636" or "16847468" or "19412512" or "17495490" or "19298406" or "18831671" or "16197615" or "15592029" or "19391448" or "19326161" or "17430694" or "19047195" or "19260381" or "19095127" or "17414518" or "17437427" or "16813071" or "19081465" or "16344253" or "12827258" or "18581118" or "18024094" or "18419995" or "17615530" or "18508188" or "18281309" or "17155972" or "18502487" or "15963152" or "16225515" or "17225800" or "16430625" or "18258351" or "15877941" or "16857310" or "18382236" or "12600425" or "19084847" or "17378856" or "12096077" or "12096076" or "16053358" or "18325057" or "17121439" or "12532172" or "16144674" or "17459269" or "16013714" or "15264239" or "11684842" or "16439055" or "12243656" or "15182413" or "17414071" or "10765094" or "16281097" or "17880293" or "17557565" or "17482931" or "18070196" or "17549907" or "17682946" or "19451896" or "19098969" or "12878247" or "17482937" or "17688922" or "17919699" or "16145391" or "18355899" or "11425148" or "18070694" or "11337740" or "11062373" or "11405127" or "17593339" or "14622488" or "15816628" or "18211209" or "19386137" or "16285617" or "16879448" or "16925749" or "16336329" or "16643614" or "11880077" or "18242358" or "15126799" or "10889823" or "17958041" or "19220260" or "15027239" or "17659632" or "17365674" or "18699899" or "17499292" or "18564135").ui.	229
21	18 not 20	661
22	19 or 21	661
23	exp animals/not humans.sh.	4,743,197
24	22 not 23	648
25	limit 24 to (english or german)	577
26	remove duplicates from 25	501
Total: **501 Hits**		

Clinical trials registry search

ClinicalTrials.gov

Date: 29/12/2017

(Advanced Search): (prostate OR prostatic OR prostat*) [DISEASE] AND (High-Intensity Focused Ultrasound OR Magnetic resonance-guided focused ultrasound OR HIFU OR MRgFUS) [TREATMENT]

33 Hits

WHO-ICTRP

Date: 02/01/2017

Basic Search mode: focused ultrasound AND prostat*

32 (9 new) Hits

EU Clinical Trials (EUdraCT) Register

Date: 02/01/2017

focused ultrasound

4 (0 new) Hits

Regulatory and reimbursement status

Table A-12: Regulatory status of HIFU devices

	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch
Sonablate®500 Sonatherm®	Europe	CE mark (NB 0843)	Yes	**Sonablate®:** transrectal treatment of prostate cancer[88] **Sonablate® 500**: for treatment of primary and focal prostate cancer.[89] **Sonatherm®:** laparoscopic or intraoperative ablation of soft tissue from the ultrasound focal zone back to the surface of the targeted ablation area in general surgery.[90]	**Sonablate®:** >10mm fluid-filled cavities, large reflective surfaces observed in the ablation zone. Metal implants or stents in the urethra. Brachytherapy seeds adjacent to the posterior prostate capsule, the Denon-villiers' fascia, or the rectal wall. Pre-existing inflammatory disease of the colon or rectum. Prior significant rectal surgery. Inability to insert or tolerate a transrectal ultrasound probe. Active urinary tract infection. Urethral stricture. Latex allergy.[91] **Sonatherm®** is not to be used to spare intervening tissue.	Sonablate® 500: 2001[92] Sonatherm®: March, 2015[93]	Yes

[88] http://sonacaremedical.com/index.php?option=com_content&view=article&id=38&Itemid=36

[89] https://www.fusfoundation.org/news/728-sonacares-devices-treat-prostate-cancer-other-urological-conditions

[90] http://sonacaremedical.com/index.php/surgeons/peer-reviewed-library

[91] http://sonacaremedical.com/index.php/surgeons/starting-my-hifu-practice

[92] http://drstevensukinurology.com/blog/hifu-high-intensity-focused-ultrasound-for-prostate-cancer/

[93] EC CERTIFICATE sent via email

	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch
Sonablate®500 Sonatherm®	USA	FDA	Sonablate® 500: yes Sonatherm®: is 510(k) cleared.[94]	Sonablate® 500: transrectal high intensity focused ultrasound (HIFU) ablation of prostatic tissue[95, 96]	-	Sonablate®: Oct, 2015	yes
Ablatherm®	Europe	CE mark	Yes	Localised prostate cancer (T1, T2) as first choice therapy for non-candidates to surgery and as salvage therapy for local recurrence after radiotherapy, brachytherapy, radical prostatectomy and HIFU[97].	-	Ablatherm® Maxis: 2000[98, 99] Ablatherm® Integrated Imaging: 2005[100]	yes
Ablatherm®	USA	FDA	Yes	Ablation of the prostate tissue[101]	-	Oct, 2015[102]	Yes
Focal One®	Europe	CE mark	Yes	Focal therapy of prostate cancer[103], non-invasive treatment of prostate cancer[104]		June, 2013[105]	Yes
Focal One®	USA	FDA	No[106]	-	-	-	EDAP filed for new 510(k) application[107]

94 http://sonacaremedical.com/index.php/blog/press-releases/62-us-hifu-announces-name-change-to-sonacare-medical

95 http://sonacaremedical.com/index.php/surgeons/our-products/sonablate-ablation-tool

96 https://www.accessdata.fda.gov/cdrh_docs/pdf16/K160942.pdf

97 http://www.fusfoundation.org/images/pdf/Prostate_System_Comparison_Chart_Jan2016.pdf

98 https://www.edap-tms.com/en/about-edap-tms/a-tradition-of-innovation

99 http://www.fusfoundation.org/images/pdf/Prostate_System_Comparison_Chart_Jan2016.pdf

100 http://www.fusfoundation.org/images/pdf/Prostate_System_Comparison_Chart_Jan2016.pdf

101 https://www.accessdata.fda.gov/cdrh_docs/pdf15/k153023.pdf

102 https://www.accessdata.fda.gov/cdrh_docs/pdf15/k153023.pdf

103 https://globenewswire.com/news-release/2017/12/18/1263273/0/en/EDAP-s-Focal-One-Robotic-HIFU-Treatments-Performed-at-Acibadem-Hospital-Istanbul-Turkey.html

104 https://www.medgadget.com/2013/06/focal%E2%80%A2one-robotic-high-intensity-focused-ultrasound-for-prostate-cancer-gets-green-light-in-eu.html

105 https://www.edap-tms.com/en/about-edap-tms/a-tradition-of-innovation

106 https://www.edap-tms.com/news/40/71/First-Focal-One-HIFU-Device-in-North-America-First-Focal-One-HIFU-Device-in-North-America

107 https://www.edap-tms.com/news/98/151/EDAP-Announces-Filing-of-New-510K

	Country	Institution issuing approval	Authorisation status yes/no/ ongoing	Verbatim wording of the (anticipated) indication(s)	Specified contra-indications	Date of approval (include expiry date for country of assessment)	Launched yes/no If no include date of launch
ExAblate® system	Europe	CE mark	Yes	Treating locally-confined prostate cancer[108]	-	December, 2016[109]	Yes
ExAblate® system	USA	FDA	No	-	-	-	No
TULSA-PRO®	Europe	CE mark	Yes[110]	Ablation of prostate tissue[111]	-	April, 2016[112]	Yes
TULSA-PRO®	USA	FDA	No[113]	-	-	-	No: TACT trial is expected to support Profound's FDA application.[114]

***Abbreviations**: CE Conformité Européenne, FDA food and drug administration, NB notified body*

108 https://www.massdevice.com/insightecs-exablate-wins-ce-mark-approval-prostate-treatment-japanese-approval-essential-tremor/

109 https://www.insightec.com/news-events/press-releases/2016/insightec-receives-ce-mark-for-the-exablate-prostate-for-treating-locally-confined-prostate-cancer

110 http://www.profoundmedical.com/new-tulsa/

111 https://globenewswire.com/news-release/2017/06/30/1035465/0/en/Profound-Medical-Corp-Announces-Definitive-Agreement-with-Royal-Philips-to-Expand-Collaboration-and-Acquire-Sonalleve-MR-HIFU-Business.html

112 https://globenewswire.com/news-release/2016/05/19/841557/0/en/FDA-Grants-Profound-Medical-Corp-IDE-Approval-for-TULSA-PRO.html

113 http://www.profoundmedical.com/new-tulsa/

114 http://www.biotuesdays.com/features/2017/3/23/profound-medicals-tulsa-pro-pilot-ous-launch-paving-the-way-for-global-growth

Table A-13: Summary of (reimbursement) recommendations in European countries for HIFU

Country and issuing organisation e.g. G-BA, NICE	Summary of (reimbursement) recommendations and restrictions	Source
NICE, England	Do not offer HIFU and cryotherapy to men with localised prostate cancer other than in the context of controlled clinical trials comparing their use with established interventions. 311 inpatient episodes in England where the main procedure was 'High intensity focused ultrasound of prostate'	https://www.nice.org.uk/guidance/cg175/chapter/1-Recommendations#localised-and-locally-advanced-prostate-cancer-2
ZIN, Netherlands	No reimbursement due to insufficient evidence. There has been no request to re-evaluate since 2013.	https://www.zorginstituutnederland.nl/publicaties/standpunten/2013/04/22/high-intensity-focused-ultrasound-hifu-bij-prostaatcarcinoom
VASPVT, Lithuania	Not reimbursed. When evidence will be available to support the use of the HIFU technology, VASPVT will recommend defining strategies to gather all the related costs to calculate proper HIFU specific reimbursement fees.	http://www.vaspvt.gov.lt/files/SPTV/HIFU%20pilnas%20vertinimas%202015.pdf
Romania	HIFU is used for the treatment of prostate cancer in few private clinics and the treatment is not reimbursed by health insurance.	-
Germany	In line with the principle of "permission with the reservation of prohibition" HIFU is reimbursed within the inpatient sector. In the base case scenario, DRG reimbursement (M09-B) amounts to 3,467 €, which includes between 2 and 11 days of hospital stay. The exact number of procedures performed in Germany is not publicly available. According to a list prepared by a German patients' association, about 50 hospitals currently offer HIFU in this indication.	https://www.prostatakrebs-bps.de/medizinisches/spezialkliniken-und-aerzte/159-kliniken-fuer-hifu-therapie
RER, Italy	Do not offer HIFU (in the Regione Emilia-Romagna region).	-
LBI-HTA, Austria	No reimbursement due to insufficient evidence to support the benefit of the technology.	http://eprints.hta.lbg.ac.at/887/

Abbreviations: *HIFU = high-intensity focused ultrasound, LBI-HTA = Ludwig Boltzmann Institute for Health Technology Assessment, NICE = National Institute for Health and Care Excellence, RER = Regione Emilia-Romagna, VASPVT = State Health Care Accreditation Agency under the Ministry of Health, ZIN = Zorginstituut Netherland*

Definition of clinically significant disease

Study (year)	Clinically significant disease
[25] (2014) [a]	UCL1 / UCL2 / Gleason 3 + 4 or higher / Gleason 4 + 3 or higher / CCL_{max} ≥6 mm / CCL_{max} ≥4 mm
[26] (2014)	Epstein criteria / Epstein criteria or ADC <850 $\mu m^2/s$
[27] (2013)	Epstein criteria / UCL1 / UCL2 / Gleason score ≥7 / Gleason score ≥8
[28] (2014) [a]	UCL2
[22] (2013) [a]	UCL1 / UCL2
[29] (2013) [a]	UCL2
[30] (2012)	PSA >10 ng/ml, PSA density >0.15, clinical stage ≥T2b, Gleason 4 or 5, total CCL ≥10 mm
[31] (2013)	Gleason ≥7 / Gleason ≥8
[32] (2011) [a]	CCLI ≥3 mm and/or Gleason ≥7 / CCLI ≥5 mm and/or Gleason ≥7
[33] (2014)*	Gleason 7 with >5% Gleason 4 + either ≥30% of cores positive or Or Gleason 6–7 with ≤5% Gleason 4 + either ≥30% of cores positive or CCL_{max} >8 mm
[34] (2014)	Gleason ≥7
[35] (2014)	Epstein criteria

ADC = apparent diffusion coefficient; CCL = cancer core length; CCL_{max} = maximum CCL; Epstein criteria = Gleason score > 6, PSA >10 ng/ml, >3 biopsy cores positive, or at least one biopsy core with >50% involvement; UCL1 = University College London definition 1: Gleason ≥4 + 3 and/or CCL_{max} ≥6 mm and/or total CCL ≥6 mm; UCL2 = UCL definition 2: Gleason ≥3 + 4 and/or CCL_{max} ≥4 mm and/or total CCL ≥6 mm.

* Definition 4 was used.

[a] Publications from the same centre.

Source: Fütterer [65]

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