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

**HIGH-INTENSITY FOCUSED ULTRASOUND FOR THE TREATMENT
OF PROSTATE CANCER**

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Disclaimer

The assessment represents a consolidated view of the EUnetHTA assessment team members and is in no case the official opinion of the participating institutions or individuals.

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LIST OF ABBREVIATIONS

ADT	androgen deprivation therapy
ARI	alpha reductase inhibitor
AS	active surveillance
BCR	biochemical recurrence
BCRFS	biochemical recurrence-free survival
BE	Belgium
BMSFI	Brief Male Sexual Function Inventory
CAN	Canada
CE	Conformité Européenne
CI	confidence interval
CPG	clinical practice guideline
CRD	Centre for Research and Dissemination
CT	computed tomography
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
ETH	ethical
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
FT	focal treatment
FU	follow-up
GRADE	Grading of Recommendations, Assessments, Development and Evaluation
HADS	Hospital Anxiety and Depression Scale
HDR	high-dose rate
HDRB	high-dose rate brachytherapy

HIFU	high-intensity focused ultrasound
HR	hazard ratio
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
LDRB	low-dose rate brachytherapy
LEG	legal
LUTS	lower urinary tract 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
ORG	organisational
OS	overall survival
PET	positron emission tomography
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
RIZIV	Rijksinstituut voor ziekte – en invaliditeitsverzekering
ROBINS-I	Risk of Bias in Non-randomised Studies – of Interventions
RP	radical prostatectomy
RT	radiation therapy
s-HIFU	salvage high-intensity focused ultrasound
s-RP	salvage radical prostatectomy
s-RT	salvage radiation therapy
SAF	safety
SD	standard deviation
SOC	social
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 Nederland

SUMMARY OF RELATIVE EFFECTIVENESS OF HIFU FOR THE TREATMENT OF PROSTATE CANCER

Scope

The scope can be found here: [Scope](#).

Introduction

Description of the technology and comparators

The technology

High-intensity focused ultrasound (HIFU) uses ultrasound (US) waves, emitted from a transducer, to cause tissue damage by mechanical and thermal effects as well as by cavitation. The energy of the US waves is 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, 2].

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 [2].

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

1. *HIFU with transrectal ultrasonography (TRUS) imaging guidance* is the traditional approach and has been in use in Europe for many years. Its major limitation is that it is not possible to use current US systems to visualise the focus of the cancer. Therefore, the treatment strategy with TRUS-guided HIFU is to ablate either the whole prostate gland or a relatively large region of it [3-6].
2. The novel approach is the *HIFU system with magnetic resonance imaging (MRI) guidance*. MRI provides high-resolution imaging for patient-specific treatment planning and real-time thermometry for temperature monitoring during treatment. It is possible to localise the lesions within the prostate with MRI and, thus, to optimise the ablation zone. Therefore, focal treatment (FT) of the prostate is also possible [3] (**B0001**).

Based on the ablation strategy approach, we differentiate whole-gland ablation and FT. Although there is no consensus definition of FT, any approach to preserve part of the prostate tissue (hemi-ablation, hockey stick ablation, and targeted focal ablation) is considered here to be FT [7] (**B0001**).

The Conformité Européenne (CE) mark has been awarded to the use of HIFU technology for the treatment of patients with primary localised prostate cancer (PCa) or recurrent localised PCa following previous therapy. HIFU also received the CE mark for various other indications, ranging from hypertension and osteoid osteoma to various cancer types (soft tissue, breast, pancreas, liver, kidney and soft tissue) [8] (**A0020**).

HIFU has the potential to ablate internal tumour tissue with great precision, and the damage to the adjacent or intervening tissues can be minimised with careful image-based treatment planning. Additionally, the tumour can be visualised during treatment. The main advantages of HIFU treatment are claimed to be the lack of induction of apoptosis, thus avoiding late complications of treat-

ment, and the lack of a cumulative effect with the possibility of repeating treatment [4]. It is also claimed that HIFU treatment has a significantly lower adverse effect profile (erectile and urinary dysfunction) [9], and reduces toxicity compared with other ablation techniques; in addition, adjacent blood vessels might be less vulnerable to damage compared with surgical risks [10] (B0002).

The comparators

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] (B0001).

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) 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 minimising the radiation to normal tissue. External beam RT (EBRT) utilises an external source of radiation to treat the prostate gland and a margin of adjacent normal tissue. Brachytherapy directly implants a radioactive source within the prostate, thus providing the highest dose of radiation. Its aim is to maximise irradiation of the tumour while minimising radiation to normal tissue [11] (B0001).

Health problem

PCa is the most common non-skin cancer in men in Europe [1]. Localised PCa is often indolent, and has no impact on health, even without treatment [12-14] (A0002). The incidence of PCa is higher in Northern and Western Europe compared with other areas of Europe, whereas incidence rates in Eastern and Southern Europe have shown a continuous increase since the 1980s' [15]. Incidence rates reported by the International Agency for Research on Cancer (IARC) in 2014 varied between 132 per 100,000 men and 35 per 100,000 men [16] (A0023).

The target population of this assessment is patients with low-risk and intermediate-risk localised and locally recurrent/relapsed PCa 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, GS 7 and cT2b [1] (A0007).

PCa is suspected on the basis of digital rectal examination (DRE) and/or PSA levels; however, a definitive diagnosis is based on histopathological verification in prostate biopsy cores or specimens from transurethral resection of the prostate (TURP). Although there is no general agreement on the benefit of PSA screening and on the cut-off value to perform a biopsy, it is obvious that higher levels indicate a greater likelihood of positive results, but not a definitive sign of PCa. 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] (A0024).

Methods

The selection of assessment elements was based on the HTA Core Model Application for Rapid REA Assessments (4.2). We updated the systematic review authored by LBI-HTA in 2010 [17]. To identify recent primary studies fulfilling the inclusion criteria outlined in the [Scope](#) of the present assessment, a systematic literature search was performed. We limited the time period of the search from January 2010 to December 2017. The search strategy of the 2010 LBI-HTA report was complemented with a search for MRI-guided focused US, because this new HIFU approach received a CE mark in 2016. Detailed tables on the search strategy are included in [Appendix 1](#).

The following sources of information were used in the search: Cochrane Library, Centre for Research and Dissemination (CRD), Embase, Medline, and manual searches in the reference lists of relevant studies. In addition, the following clinical trials databases were searched to identify ongoing studies on HIFU for PCa treatment: ClinicalTrials.gov, EU Clinical Trials Register and International Clinical Trials Registry Platform (ICTRP). In addition to systematic searches, clinical practice guidelines (CPGs) were searched in the UptoDate database, and through manual searches and consultation with clinical experts.

For the Description and Technical Characteristics of Technology (TEC) and Health Problem and Current Use of the Technology (CUR) domains, no quality assessment tool was used; instead, multiple sources were used to validate individual, possibly biased, sources. A 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 of the single-arm studies (case series) at the study level was assessed using the IHE-20-checklist [18] and of the non-randomised controlled studies (non-RCTs) at the study level using Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) [19].

The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). The author and co-authors performed the risk of bias assessment independently. The author performed the GRADE assessment and the co-authors checked it. Disagreements were resolved by consensus.

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

Results

Available evidence

Clinical effectiveness

The inclusion criteria for assessing the clinical effectiveness of HIFU were 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 PCa, and included 70 patients in each treatment arm [20].

We were unable to identify any controlled trials comparing HIFU with other treatments, such as deferred treatment (AS, WW) or RP (laparoscopic, open or robotic surgery).

Safety

The study inclusion criteria for assessing safety differed from those used for assessing clinical effectiveness. In addition to RCTs and non-RCTs, prospective studies without a control group (single-arm studies, case series and registry studies) with at least 50 patients were considered. In the systematic literature search, we identified four prospective single-arm studies [21-24] in addition to the one matched-pair analysis [20] regarding primary HIFU, and one prospective single-arm study regarding salvage HIFU (s-HIFU) [25], which met our inclusion criteria to assess safety. The single-arm primary HIFU studies applied hemiablation, whereas the matched-pair analysis and the s-HIFU study applied whole-gland ablation of the prostate.

Clinical effectiveness

Primary HIFU

Two outcomes were considered relevant to assess the expected beneficial effect of HIFU on mortality: overall survival (OS) and PCa-specific survival. After 5 years, OS was not significantly different in the brachytherapy cohort compared with the HIFU cohort [88% vs. 97.5%, hazards ratio (HR) 0.24, 95% confidence interval (CI) 0.01–1.34] [20]. Regarding PCa-specific survival, after 5 years, the rate was 89% for patients in the HIFU cohort and 92% for patients in the brachytherapy cohort. Even though the rate was higher for patients treated with brachytherapy, the difference between the study groups was not significant (HR 0.67, 95% CI 0.32–1.29) [20] (**D0001**).

To describe the effect of HIFU on the progression (or recurrence) of localised and locally recurrent PCa, biochemical recurrence-free survival (BCRFS; a surrogate outcome and not to be mistaken for 'local disease recurrence') was considered. This outcome was significantly lower for patients in the HIFU cohort than for patients in the control group: 53.1% versus 68.5% according to the Phoenix definition and 51.3% versus 60.9% according to the Stuttgart definition (HR 0.41, 95% CI 0.19–0.81 for Phoenix, HR 0.39, 95% CI 0.19–0.74 for Stuttgart; $p < 0.05$ for both) [20]³. Additional outcomes that are more suitable for describing the progression of PCa (need for salvage and/or systemic therapy, ablation failure, local disease recurrence, distant disease recurrence and/or metastases or disease progression and/or pathological progression) were not reported in the included study [20] (**D0005**).

Salvage HIFU

No evidence was found to assess the effectiveness of s-HIFU against that of any of the other comparators.

Safety

Primary HIFU

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

No intervention-related deaths occurred in any of the studies (**C0008**).

³ Phoenix criteria: PSA nadir +2ng/mL; Stuttgart criteria: PSA nadir +1.2 ng/mL). See also **A0024**.

Urinary dysfunction was reported in all studies. In the matched-pair analysis, urinary incontinence was higher in patients treated with HIFU compared with patients who received brachytherapy; however, the difference between the two cohorts was not significant (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 [24] (6%) and two patients in each of the other two studies [22, 23] (2% and 3.9%, respectively) who had been continent pre-HIFU continent presented with persistent incontinence at 12 months follow-up. One study reported that none of the patients had incontinence [21] at 12 months follow-up. Two single-arm studies [21, 22] found no significant change in urinary function based on the mean International Prostate Symptom Score (IPSS) score from baseline to 3 and 12 months follow-up, respectively, whereas one study [23] reported a significant change in the IPSS score from baseline to 12 months follow-up (95% CI 1.6–4.4) (C0008).

Erectile dysfunction was reported as a worsening in the International Index of Erectile Function (IIEF) score or as the number of *de novo* impotent patients. In the matched-pair analysis, five patients who had been potent pre-HIFU potent (11.6%) became impotent (no comparison was possible because erectile dysfunction was reported only for the HIFU group). Two studies identified 20%–22% *de novo* erectile dysfunction in patients who had been potent pre-intervention, whereas one study [21] reported that nearly 48% of patients who had been previously potent became impotent post-intervention (none of the studies reported the time point at which this was measured). Two single-arm studies [21, 22] reported a significant negative impact on erectile function 3–12 months after HIFU based on the IIEF score ($p < 0.001$) (C0008).

The most frequent adverse events in all studies were Grade 1 and 2 events [urinary tract infection, storage and voiding lower urinary tract symptoms (LUTS)]. When comparing the severity of adverse events in the matched-pair analysis, the rate of Grade 3 complications was higher in patients treated with HIFU than in patients treated with brachytherapy (35% vs. 13%). In particular, acute urinary retention and stricture occurred more often in the HIFU group than in the brachytherapy group (>20% vs. <6%, respectively); however, information on statistical significance was not provided [20]. Compared with the matched-pair analysis, which applied whole-gland ablation [20], the rate of storage and voiding LUTS [23, 24] (Grade 1), acute urinary retention [21, 23, 24] and stricture [22–24] (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 [20]. Grade 4 complications did not occur in any of the primary HIFU studies. The adverse events are presented in Table 5 categorised by study and severity (C0008).

Salvage HIFU

The s-HIFU study [25] could not show a significant effect on the IPSS score 6 months post-intervention ($p = 0.06$), but reported a significant negative effect on 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 (C0008).

Upcoming evidence

A search for ongoing studies identified two RCTs and three non-RCTs, of which one non-RCT was terminated because of poor recruitment and two were of an unknown status; however, according to the registry, the study completion dates were planned for 2008 and 2014, respectively. Thus, 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.

Table 1: Summary of findings table for primary HIFU

Outcome	Anticipated absolute effects			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk associated with HIFU	Risk associated with radiotherapy	Difference				
Efficacy							
Overall survival rate Follow-up: 5 years	574 per 1000	971 per 1000	397 fewer per 1000 (20 more to 936 fewer)	HR 0.24 (0.01–1.34)	140 (1)	⊕⊕⊕⊕ VERY LOW ^{4,5}	Overall survival was lower (but not significantly) for HIFU.
Prostate cancer-specific survival rate Follow-up: 5 years	807 per 1000	914 per 1000	397 fewer per 1000 (20 more to 936 fewer)	HR 0.67 (0.32–1.29)	140 (1)	⊕⊕⊕⊕ VERY LOW ^{4,5}	Prostate cancer-specific survival rate was lower (but not significantly) for HIFU.
Local disease recurrence	—	—	—	—	—	—	Outcome not reported.
Safety							
Intervention-specific mortality Follow-up: median 83 vs. 44 months	0 per 1000	0 per 1000	0% fewer/more	Not estimable	140 (1)	⊕⊕⊕⊕ VERY LOW ^{4,5,6}	There was no intervention-specific mortality.
Intervention-specific mortality (single-arm) Follow-up: mean 16.3 vs. 44.5 months	See 'Comments'.			Not estimable	279 (4)	⊕⊕⊕⊕ VERY LOW ^{7,8,9}	There was no intervention-specific mortality.

⁴ Risk of bias for this particular endpoint was set high because of the difference between study groups in age (see also risk of bias assessment of study).

⁵ Indirectness was set 'serious' for this particular endpoint, because this study was claimed to be the first to compare patients treated with HIFU versus those treated with brachytherapy. Furthermore, in this study, two generations of Ablatherm devices were used, whereas Ablatherm Maxis is no longer commercially available. Moreover, there was no information provided on additional treatments and pretreatment prostate volume.

⁶ Imprecision was set 'serious' for this particular endpoint, because the probability of intervention-specific mortality was estimated to be low and patient number needed to be higher to detect differences.

⁷ Risk of bias for this particular outcome was set high because of the study design (no control group).

⁸ Indirectness for this particular outcome was set as 'serious' because the studies could only yield indirect evidence regarding the safety of HIFU compared with standard therapies because there was no control arm (safety outcomes could only be compared with historical controls).

⁹ Imprecision for this particular outcome was set to 'serious' because of the low sample size.

Outcome	Anticipated absolute effects			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk associated with HIFU	Risk associated with radiotherapy	Difference				
Functional outcomes: urinary dysfunction (comparative) Assessed with: physician-reported rate Follow-up: median 83 vs. 44 months	72 per 1000	38 per 1000 ¹⁰	34 more per 1000 (14 fewer to 359 more)	RR 1.92 (0.39–9.51) ¹⁰	122 (1)	⊕○○○ VERY LOW ^{5,11}	Urinary dysfunction was higher (but not significantly) for HIFU.
Functional outcomes: urinary dysfunction (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%–2%) of patients pre-HIFU were incontinent (used pads) and 3.3% (0%–6%) of patients were incontinent post-HIFU [2.6% (0–6%) more patients were incontinent].			—	IPSS: 198 (3) Usage of pads: 270 (4)	⊕○○○ VERY LOW ^{7,8,9,12}	There might be little or no difference to baseline in the urinary function characterised by usage of pads or by IPSS score.
Functional outcomes: sexual dysfunction (comparative) Assessed with: physician-reported rate Follow-up: median 83 vs. 44 months	116 per 1000 (11.6%)	NA	—	Not estimable	43 (1)	⊕○○○ VERY LOW ^{13,14}	Sexual dysfunction was only reported for patients treated with HIFU.
Functional outcomes: sexual dysfunction (single-arm) Assessed with: IIEF-5 score, <i>de novo</i> erectile dysfunction Follow-up: 3–12 months	Mean difference in the IIEF-5 score in one study was 1.2 (95% CI –0.4 to +2.7), two studies showed significant difference (pre-HIFU score of 17.6–17.97 and post-HIFU score of 13.6 to NA, p<0.001) <i>De novo</i> erectile dysfunction ranged from 20% to 47.6% of patients who were potent pre-HIFU.			—	<i>De novo</i> erectile dysfunction: 122 (3) IIEF-5: NA (3)	⊕○○○ VERY LOW ^{7,8,9,15}	HIFU might increase rate of <i>de novo</i> erectile dysfunction and might worsen sexual function.

¹⁰ Calculated with MedCalc® (www.medcalc.org/calc/relative_risk.php).

¹¹ Risk of bias for this particular endpoint was set as ‘serious’, because of 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 were incontinent before the interventions.

¹² There is inconsistency in the results of IPSS cores because two studies reported no significant change in the score, whereas one study reported a significant mean decrease (meaning improvement) in the score.

¹³ Risk of bias for this particular endpoint was set high, because of the difference between study groups in age and length of follow-up (see also risk of bias assessment of study). Furthermore, measurement of sexual (dys)function was exclusively done for patients treated with HIFU.

¹⁴ Indirectness cannot be assessed, because study exclusively reported sexual (dys)function for patients treated with HIFU.

Outcome	Anticipated absolute effects			Relative effect (95% CI)	Number of participants (studies)	Quality	Comments
	Risk associated with HIFU	Risk associated with radiotherapy	Difference				
Serious adverse events (comparative) Assessed with: number of events Follow-up: mean 12 months	Overall SAEs: 17 vs. 5 (in 70 patients each)			Not estimable	140 (1)	⊕⊕⊕⊕ VERY LOW ^{5,16,17}	In the HIFU group, 17 SAEs occurred in 70 patients and, in the radiotherapy group, 5 SAEs occurred in 70 patients.
Serious adverse events (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)	⊕⊕⊕⊕ VERY LOW ^{5,16,17}	In the HIFU group, 18 SAEs occurred in 70 patients and, in the radiotherapy group, 4 SAEs occurred in 70 patients.
Serious adverse events (single-arm) Assessed with: number of events Follow-up: 1–12 months	Overall SAEs: 15 in 273 patients			—	273 (4)	⊕⊕⊕⊕ VERY LOW ^{7,8,9,18}	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; SAE=serious adverse event.

- ¹⁵ Inconsistency was set as 'serious' because two studies reported approximately 20% of patients who were potent pre-HIFU as being impotent post-HIFU, whereas one study reported >47% of patients who were potent pre-HIFU as being impotent post-HIFU.
- ¹⁶ Risk of bias for this particular endpoint was set as 'serious', because of the difference between the 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.
- ¹⁷ Imprecision was set as 'serious' for this particular endpoint, because the patient number was too low to detect rare adverse events.
- ¹⁸ There was inconsistency in the percentage of patients presenting with an adverse event per study because one study reported adverse events occurring in 41% of patients, another study reported that they occurred in 15% of patients; two studies did not report the percentage of patients in whom the adverse event occurred but only the total number of adverse events and did not specify how many patients experienced the adverse event.

Table 2: Summary of findings table for 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 (perioperative death) Assessed with: number of events Follow-up: mean 19.8 months	See 'Comments'.			Not estimable	84 (1)	⊕⊕⊕⊕ VERY LOW ^{7,9,19}	There was no intervention specific mortality.
Functional outcomes: urinary dysfunction Assessed with: IPSS score Follow-up: 6 months	No significant difference in IPSS scores (8.3 pre-s-HIFU and 11.6 post-s-HIFU).			—	39 (1)	⊕⊕⊕⊕ VERY LOW ^{7,9,19}	There might be no difference in urinary function characterised by IPSS score.
Functional outcomes: sexual dysfunction Assessed with: IIEF-5 score Follow-up: 6 months	Significant decrease in IIEF-5 score (8.6 pre-s-HIFU and 6.2 post-s-HIFU).			—	43 (1)	⊕⊕⊕⊕ VERY LOW ^{7,9,19}	Salvage HIFU might increase 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)	⊕⊕⊕⊕ VERY LOW ^{7,9,19}	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; SAE=serious adverse event.

Table 1 and Table 2 present the summary of findings for HIFU and s-HIFU, respectively, detailing the main findings and providing key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) and defined as high, moderate or low, based on the following definitions: 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 might be substantially different from the estimate of the effect.

¹⁹ Indirectness was set as 'serious' because only patients whose PCa had failed to respond to external beam radiation therapy (EBRT) were included (we do not have information on patients whose PCa failed to respond to other treatment modalities, such as prostatectomy or HIFU). The studies can only yield indirect evidence on HIFU compared with standard therapies because there was no control group.

Discussion

The overall quality of evidence for HIFU as a primary treatment for clinically localised low-risk and intermediate-risk prostate cancer as well as for HIFU as a salvage treatment for locally recurrent prostate cancer is very low. The available studies lack sufficiently high patient numbers, comparators and sufficiently long periods of follow-up. The small numbers considerably limit the generalisability of the findings and only two studies reported on outcomes with a follow-up of 5 years; therefore, no significant conclusion can be reached on disease control. All outcome estimates on the efficacy of primary HIFU compared with brachytherapy, a type of RT, are based on only one comparative study. However, this comparative study comprised two matched single-arm studies, which do not provide a high level of evidence. Moreover, the safety outcome estimates of primary HIFU are based on single-arm studies in addition to the comparative study. Regarding s-HIFU, all outcome estimates are based on one single-arm study. Direct prospective comparisons between deferred treatment modalities (AS and WW) and radical prostatectomy or radiation for salvage treatment are completely lacking.

There was considerable heterogeneity in the follow-up protocols and definitions of outcome measures across the included studies. Although we considered only the matched-pair analysis in the effectiveness assessment, we noticed that studies had different effectiveness endpoints (BCR, variable definitions of PSA endpoints, and/or biopsy data, and various survival endpoints). Definition of treatment failure was not universal among the studies: it varied from positive biopsy control (indicating local relapse [6]) to need for salvage treatment, initiation of definitive treatment, and presence of clinically significant cancer. There are no validated criteria and definition of BCR after HIFU (the Stuttgart criteria was proposed). Similarly for the safety endpoints, there is no standard measurement tool and the studies showed heterogeneity in the outcome measures used for sexual and urinary function and in time point of measurement. In some of the primary HIFU studies, there was a lack of data on the IPSS or IIEF-5 scores.

Additional limitations that hinder the generalisability of the findings include the variation across studies in the number of HIFU treatments per patient and that the retreatments were often not included in the analysis (they were short-term after initial HIFU and were considered as part of the primary therapy). Furthermore, 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 adverse effect profile (more frequent toxicities, incontinence and erectile problems) compared with hemiablation and there is no consensus or standard about how to use HIFU with regard to treated volumes [26, 27].

Limitations of the present assessment are the lack of stratification to different generations of HIFU (and MRI guidance), and additional interventions [TURP and androgen deprivation therapy (ADT)] because this information was often lacking. The MRI guidance, for instance, is a relatively new approach and studies evaluating its effectiveness and safety are ongoing. Moreover, we included a comparative study [20], in which patients were treated during the first period of treatment with an older version of a device that is no longer commercially available. However, it could be expected that the device used, the type of guidance and any concomitant treatments could have a considerable effect on the effectiveness and safety of HIFU. Another limitation is the absence of indirect comparisons (e.g., matching and comparing single-arm trials on laparoscopic prostatectomy and HIFU), which was not feasible within the timeframe of this rapid assessment.

Evidence gaps and ongoing studies

To date, there are no published RCTs comparing the effectiveness and safety outcomes of HIFU (either as whole gland or hemiablation) with any radical treatment modalities or any deferred treatment modalities. MRI-guided HIFU ablation is such a new approach that the first pivotal studies were completed only relatively recently and their effectiveness and safety are currently being investigated. Further research, preferably in the form of RCTs, is required into the safety, effectiveness and cost-effectiveness of HIFU. This research should include endpoint survival with at least a 10 year follow-up, local recurrence, toxicity and quality of life outcomes. The comparators should include deferred treatment, RP, other forms of RT and their combinations.

Conclusion

There is insufficient evidence to determine whether primary HIFU is more effective than (or at least as effective as) and/or has a better (or at least similar) safety profile compared with AS, WW, and RP or RT for the treatment of PCa.

There is insufficient evidence to determine whether s-HIFU is more effective than (or at least as effective as) and/or has a better (or at least similar) safety profile than AS, WW, salvage RP or salvage RT (s-RT) for the treatment of PCa.

Therefore, there is a need for prospective RCTs with a higher number of patients and longer follow-up to be able to determine whether HIFU is a suitable alternative to deferred treatment and/or standard radical therapies for the treatment of PCa.

1 SCOPE

Description	Project scope
Population	<ul style="list-style-type: none"> • Adult men with clinically localised prostate cancer (PCa) (cT1a-T2, N0-Nx, M0) based on TNM staging, Gleason score/GRADE group, and serum prostate-specific antigen (PSA) <ul style="list-style-type: none"> ○ Low risk: clinical stage cT1a-T2a, Gleason score ≤6, PSA<10 ng/mL ○ Intermediate risk: clinical stage T2b, Gleason score 7, PSA 10–20 ng/mL • Adult men with locally relapsed/recurrent PCa after failed radical prostatectomy (RP), radiation therapy (RT), or high-intensity focused ultrasound (HIFU) (cT1a-T2, N0-Nx, M0) • 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: <i>first-line treatment or salvage therapy</i> <p>Rationale: population was defined based on the EAU guideline [1], NICE clinical guideline [12], S3 Leitlinie (German oncology guideline program) [28] and the indications of Conformité Européenne (CE) mark approvals.</p>
Intervention	<ul style="list-style-type: none"> • Whole-gland ablation or focal therapy of the prostate gland using HIFU with either transrectal ultrasonography (TRUS) or magnetic resonance imaging (MRI) guidance • MeSH: E02.565.280.945.399, E04.014.380 • Products/manufacturers: <ul style="list-style-type: none"> ○ Ablatherm[®] (company: EDAP TMS, France) <ul style="list-style-type: none"> - Ablatherm[®] Integrated Imaging and its predecessors (Ablatherm[®] Maxis and Ablatherm[®] prototype) - Focal One[®] ○ Sonablate[®] (company: SonaCare Medical, USA) <ul style="list-style-type: none"> - 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	<ul style="list-style-type: none"> • Deferred treatment: <ul style="list-style-type: none"> ○ Active surveillance/monitoring (AS) ○ Watchful waiting (WW) • RP with or without pelvic lymphadenectomy, including: <ul style="list-style-type: none"> ○ Laparoscopic surgery ○ Robotic surgery ○ Open surgery • RT including, but not restricted to: <ul style="list-style-type: none"> ○ External-beam RT (EBRT) with or without short-term ADT <ul style="list-style-type: none"> - 3D conformal radiotherapy - Intensity-modulated radiotherapy (IMRT) with or without image-guided RT (IGRT)

Description	Project scope
	<ul style="list-style-type: none"> ○ Brachytherapy <ul style="list-style-type: none"> - Low-dose rate (LDR) or - High-dose rate (HDR) ○ Combination of EBRT and brachytherapy <p>Rationale: standard interventions for the target population according to the clinical guidelines (S3 Leitlinie [28], NICE [12], EAU [1]).</p>
Outcomes	<p>Effectiveness-related:</p> <ul style="list-style-type: none"> ● Overall survival/mortality (e.g., 5- and 10-year survival) (critical) ● PCa-specific survival/mortality (critical) ● Local disease recurrence (presence of clinically significant PCa²⁰ measured by biopsy and/or multiparametric MRI) (critical) ● Distant disease recurrence/metastases (important) ● Biochemical recurrence (BCR)/failure (increasing PSA level according to ASTRO or Phoenix definition) (important) ● Disease progression/pathological progression (increase in Gleason score or tumour volume evidenced by a larger number of positive biopsies or larger per-core tumour involvement) (important) ● Quality of life (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-5D²¹(important) ● Need for salvage local therapy and 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) <p>Safety-related:</p> <ul style="list-style-type: none"> ● Intervention-specific mortality (perioperative death) (critical) ● Adverse events (AEs) (Clavien-Dindo Grade 1–2) (important) including, but not restricted to: <ul style="list-style-type: none"> ○ 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) ● Serious adverse events (SAEs) (Clavien-Dindo Grade 3–4) (critical) including, but not restricted to: <ul style="list-style-type: none"> ○ Bladder neck/urethral stricture/stenosis ○ Rectal fistula ○ Bladder neck obstruction

²⁰ Respective definitions of the studies were used as there is no standard definition of clinical significance. A list of commonly used definitions of clinically significant disease is available [Appendix 4](#).

²¹ Definitions are detailed in [Chapter 6.2](#).

Description	Project scope
	<ul style="list-style-type: none"> • Functional outcomes (critical) <ul style="list-style-type: none"> ○ 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 International Prostate Symptom Score) ○ Sexual (dys)function: loss of erectile function (reported as number of patients with new onset of impotence) or worsening of erectile function [decrease in the International Index of Erectile Function (IIEF)-5, IIEF-15, or Brief Male Sexual Function Inventory (BMSFI) score] <p>Rationale: we have chosen the outcomes based on the recommended core outcome set for localised PCa [29], Consensus paper on the standardisation of definitions on focal therapy of prostate cancer [30], EUnetHTA guidelines on clinical endpoints and safety [31-33], and EAU guideline [1].</p>
Study design	<p>Effectiveness: randomised controlled trials (RCTs), prospective non-randomised controlled trials (non-RCTs)</p> <p>Safety: RCTs, prospective non-RCTs, single-arm prospective cohort studies with at least 50 patients</p>

2 METHODS AND EVIDENCE INCLUDED

2.1 *Assessment team*

Description of the distribution of responsibilities and the workload between authors and co-authors:

LBI-HTA (author):

- Develop first draft of EUnetHTA project plan, amend the project plan following co-author's, dedicated reviewers', as well as external experts' comments.
- Perform the literature search, screening, and selection, data extraction and risk of bias assessment of the selected references, perform the quality of the body of evidence assessment, check the discrepancies with the co-author and reach consensus.
- Answer assessment elements; fill in the checklist regarding potential ethical (ETH), organisational (ORG), social (SOC) and legal (LEG) aspects of the HTA Core Model® for Rapid Relative Effectiveness (REA).
- Send draft versions to reviewers, compile feedback from reviewers and perform changes according to reviewers' comments.
- Prepare the final assessment and write the executive summary of the assessment.

VASPVT (co-author):

- Review and comment on the draft EUnetHTA project plan.
- Check and approve all steps (e.g., literature screening and selection, data extraction, risk of bias assessment, quality of the body of evidence assessment).
- Produce the overview of available devices and their regulatory status.
- Review the draft assessment, propose amendments where necessary (perform additional manual search of literature if needed) and provide written feedback.

2.2 *Source of assessment elements*

The selection of assessment elements is based on the HTA Core Model Application for Rapid REA Assessments (4.2). The selected issues (generic questions) were translated into actual research questions (answerable questions).

Please note that some research questions were answered together; that is, these questions can be listed below each other and the answer can then be provided subsequently.

2.3 Search

We updated the systematic review authored by LBI-HTA in 2010 [17]. To identify recent primary studies fulfilling the inclusion criteria outlined in the [Scope](#) of the present assessment, a systematic literature search was performed. We limited the time period of the search to January 2010 to December 2017. The search strategy of the 2010 LBI-HTA report was complemented with a search for MRI-guided focused US because this new HIFU approach received a CE mark in 2016.

Detailed tables on search strategy are included in [Appendix 1](#).

The following sources of information were used in the search:

- Cochrane Library
- Centre for Research and Dissemination (CRD)
- Embase
- Medline
- Manual search (in reference list of relevant studies).

In addition, the following clinical trial databases were searched to identify ongoing studies on HIFU for PCa treatment:

- ClinicalTrials.gov
- EU Clinical Trials Register
- International Clinical Trials Registry Platform (ICTRP).

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

2.4 Study selection

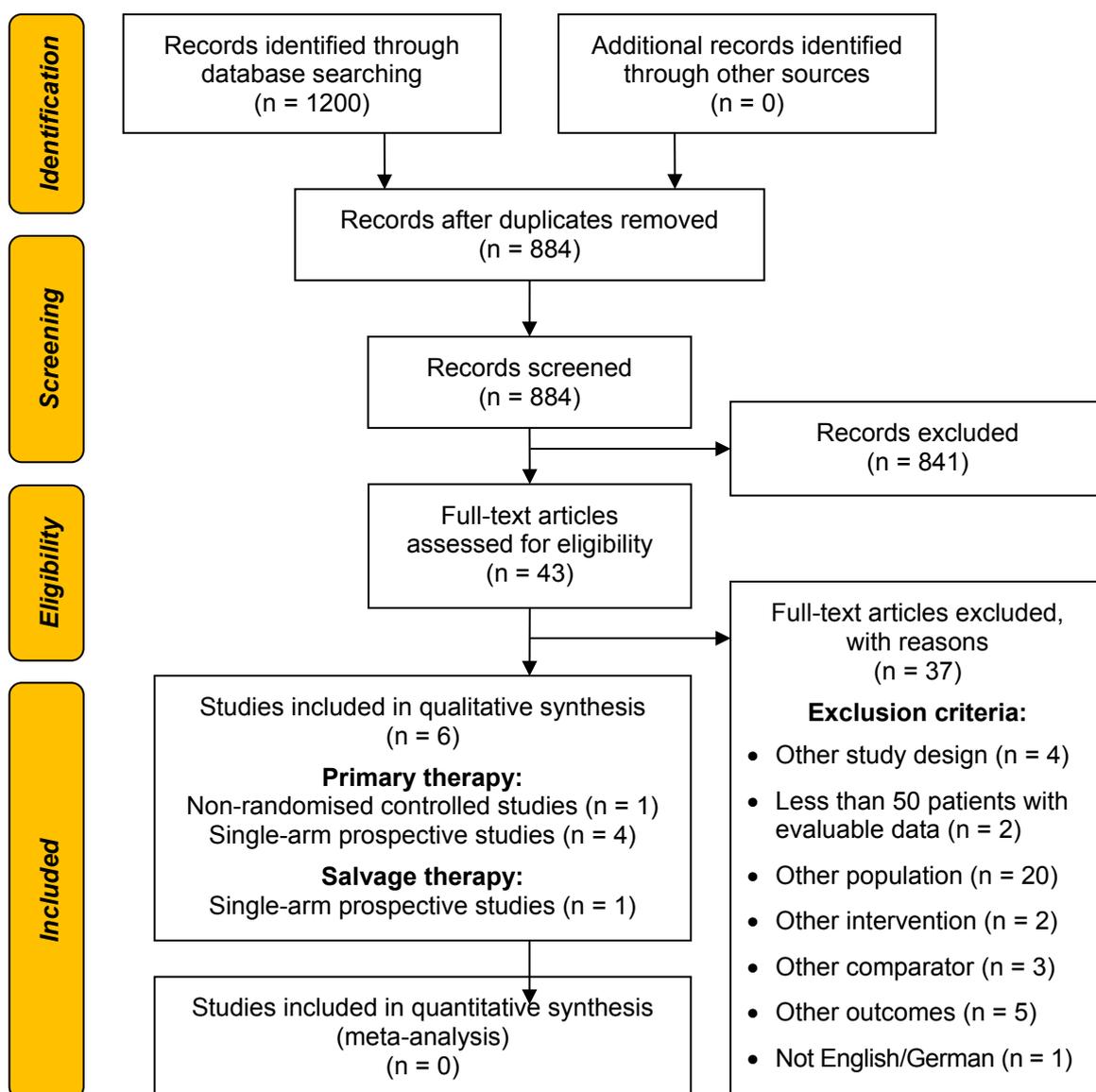


Figure 1: Flow chart

The search yielded 1200 records; after deduplication, 884 records remained for screening. The author and co-author independently screened the titles and abstracts and selected studies according to the predefined inclusion as outlined in the [Scope](#) and that were published after 1st January, 2010 for full-text examination; 841 records were excluded.

The remaining 43 full-text publications were assessed for eligibility by the author and the co-author independently; of these, 37 publications were excluded according to the predefined 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.

2.5 Data extraction and analyses

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

Given that raw data could not be retrieved, the definition for clinical significance was accepted as used by each study. However, there is no universally accepted definition of clinically significant PCa. The most frequently used definitions are summarised in [Appendix 4](#).

Continuous variables were given using median, interquartile range (IQR), or overall range according to availability. The mean with standard deviation (SD) 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 the incontinence rate in cases 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 cases of physician-reported events, only men who were potent pre-HIFU 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 were extracted. To calculate the frequency of AEs, men lost to follow-up with this outcome were excluded from the denominator.

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

Quality rating

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 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 to the selection of quality-rating tools. Risk of bias at the study level was assessed using the IHE-20-checklist [18] for the single-arm studies (case series) and Risk Of Bias In Non-randomised Studies – of Interventions (ROBINS-I) [19] for the non-RCTs.

The quality of the body of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE). The author and co-authors performed the risk of bias assessment independently. The author performed the GRADE assessment and the co-author checked it. Disagreements were resolved by consensus.

2.6 Description of the evidence used

The main characteristics of the included studies are presented in [Table 3](#). Detailed information about the studies can be found in [Appendix 1 Table A1](#), [Table A3](#), and [Table A4](#).

Table 3: Main characteristics of studies included

Author and year or study name	Study type	Number of patients	Intervention	Main endpoints	Included in clinical effectiveness and/or safety domain
Aoun 2015 [20]	Non-RCT study (matched-pair analysis)	140 (HIFU = 70, brachytherapy = 70)	Whole-gland HIFU, brachytherapy	BCRFS (Stuttgart, Phoenix), OS, MFS, PCa-specific survival, AEs	Effectiveness and safety
Feijoo 2015 [21]	Prospective single-centre single-arm study	71	Hemiablation HIFU	Positive biopsy in treated lobe or need for salvage therapy at 12 m (treatment failure), urinary function, erectile function, AEs	Safety
Ganzer 2017[22]	Prospective multicentre single-arm Phase 2 study	51	Hemiablation HIFU	No initiation of definitive treatment within study period, no evidence of tumour on control biopsy at 12 m, OS, PCa-specific survival, QoL, urinary function, erectile function, AEs	Safety
Rischmann 2017 [23]	Prospective multicentre single-arm Phase 2b study	111	Hemiablation HIFU	Absence of clinically significant cancer (GS ≥ 7 or cancer core length >3 mm or >2 positive cores), presence of any cancer on biopsy, biochemical response, radical treatment-free survival, urinary function, erectile function, AEs, QoL	Safety
Van Velthoven 2016 [24]	Prospective single-centre single-arm Phase 2a study	50	Hemiablation HIFU	BCR (Stuttgart, Phoenix), positive biopsy result of treated area (treatment failure), 5-year actuarial recurrence-free survival, 5-year actuarial PCa survival, MFS, OS, urinary function, erectile function, AEs	Safety
Uddin Ahmed 2012 [25]	Prospective registry of a multicentre single-arm Phase 2 feasibility study	84	Hemiablation s-HIFU	Actuarial 1- and 2-year PFS (Phoenix or biopsy or onset of hormone therapy), urinary function, erectile function, QoL	Safety

Abbreviations: AE=adverse event; BCR=biochemical recurrence; BCRFS=biochemical recurrence-free survival; GS=Gleason Score; HIFU=high-intensity focused ultrasound; m=months; MFS=metastasis-free survival; non-RCT=non-randomised controlled trial; OS=overall survival; PCa=prostate cancer; PFS=progression-free survival; QoL=quality of life; s-HIFU=salvage high-intensity focused ultrasound.

Sources: [20-25].

2.7 Deviations from project plan

Positive surgical margin as an endpoint was removed because it is not relevant for HIFU. One major characteristic of HIFU is the non-surgical eradication of the tissue; thus, this endpoint is applicable solely for prostatectomy. Given that we found no evidence for HIFU compared with prostatectomy, this endpoint became futile. Furthermore, a positive surgical margin is a surrogate endpoint of BCR, which was an endpoint in the present assessment.

Bowel dysfunction as an endpoint was removed based on the clinical expert's feedback. This endpoint is not relevant for HIFU, because it can occur only in RT and proctitis is covered by this category, which is already listed under AEs/complications.

The safety-related endpoint AEs/complications was separated according to Clavien-Dindo grading and two major categories were formed: AEs (Clavien-Dindo Grade 1–2) and SAEs (Clavien-Dindo Grade 3–4). The latter was considered a critical outcome and, hence, only this was presented in the GRADE and summary of findings tables ([Table 1](#) and [Table 2](#)).

3 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF TECHNOLOGY (TEC)

3.1 Research questions

Element ID	Research question
B0001	What is high-intensity focused ultrasound (HIFU) ablation [with transrectal either ultrasonography (TRUS) imaging guidance or 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)?
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 equipment and supplies are needed to use HIFU?
A0020	For which indications has HIFU received marketing authorisation or CE marking?
A0021	What is the reimbursement status of HIFU?

3.2 Results

Features of the technology and comparators

[B0001] – What is high-intensity focused ultrasound (HIFU) ablation [with either transrectal ultrasonography (TRUS) imaging guidance or magnetic resonance imaging (MRI) guidance]?

HIFU is characterised by the use of 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’ because of the power density of the US waves, which exceeds 5 W per cm². In the clinical setting, HIFU uses frequencies within the range of 0.8–3.5 MHz. Cell death occurs through two physiological mechanisms. First, the energy of the US waves is absorbed by the target tissue and converted to heat (exceeding 60°C), causing coagulative necrosis. Second, inertial cavitation is caused by alternating cycles of compression and rarefaction [1, 2].

To administer HIFU, a probe is inserted into the rectum (or urethra) while the patient is anaesthetised. This probe or MRI in an MRI-guided approach enables real-time visualisation of prostatic tissue and also delivers HIFU energy to destroy the desired target parenchyma [2]. 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 (1–3 weeks). The length of the procedure depends on the size of the prostate gland. Larger glands will take longer to treat completely. One way to estimate the time of treatment is 1 h for every 10 g of tissue to be treated. Most procedures take 1.5–4 h. Depending on equipment and treatment scheme, for example, half-gland or focal therapy, treatment time can be shorter. The patient can return to office-based work the following day. More intense physical activity can resume in 3–5 days, although no activity should be started that dislodges the catheter or stirs up bleeding from the catheter insertion site [34].

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 PCa using current US 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 multiparametric (mp)MRI. There are three commercially available HIFU systems with TRUS imaging guidance: Ablatherm[®], Sonablate 500[®] and FocalOne[®]. Although the baseline technology of the systems is the same, there are some technical differences between the devices: imaging and therapeutic transducers; position of the patient; and type of software application for treatment planning and safety monitoring [3-6].
 - 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. 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 real-time US monitoring [4].
 - Sonablate 500[®] and its predecessors have a console (portable system with display monitor, motor with three axes, and a 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 mm and 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 real-time US monitoring [4].
 - In FocalOne[®], image fusion of real-time transrectal US and pretreatment MRI images is achieved by integrated software. This allows image-guided HIFU treatment of a defined zone, sparing the rest of prostate tissue. The focal length of the transducer is a maximum of 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 a range of anterior–posterior distances and shortens the duration of treatment [4].
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 optimisation of the ablation treatment zone; hence, 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 [3].

- ExAblate[®]: this is a movable endorectal focused US transducer that generates an adjustable focus that can ablate cancerous tissue. The sharp margin of the US 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[®]: this technology is designed for the destruction of the whole prostate gland in a single procedure that lasts approximately 1 h, but can also be used for any targeted or focal ablation of cancerous tissue. After the US probe is placed in the prostatic urethra near the target, the treatment is performed with MRI real-time planning and guidance. The ten US 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 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 accurately 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].

The characteristics of the HIFU systems and the available devices are outlined in [Table 4](#).

Table 4: Features of HIFU systems

Feature	Type of HIFU system				
	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 ²²	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 ²³	Low frequency: 4–4.8 High frequency: 13.4–14.4 ²⁴
Imaging guidance	Real-time US	Pre-treatment MRI import and fusion with real-time US	Real-time US and 3D visualisation	Real-time MRI (1.5 T and 3 T) ²⁵	Real-time MRI ²⁶
Mode of administration	Trans rectal	Trans rectal ²⁷	Trans rectal	Trans rectal	Trans urethral

²² According to MEDDEV 2. 4/1 Rev. 9 of the European Commission.

²³ <https://radiology.ucsf.edu/mr-guided-focused-ultrasound-mrgfus-research-china-basin>

²⁴ www.profoundmedical.com/wp-content/uploads/2015/05/BrochureEmailable_PDF.pdf

²⁵ <https://dev.fusfoundation.org/news/1853-insightec-earns-ce-mark-for-prostate-cancer>

²⁶ <https://dev.fusfoundation.org/news/1740-profound-earns-european-approval-for-prostate-device>

²⁷ http://www.specialiste-en-urologie.fr/wp-content/uploads/2015/04/Focal-One_Livret-Patient-148x210-V-FR_20140206.pdf

Patient positioning	Right lateral decubitus ²⁸	Lateral ²⁷	Supine or lithotomy ²⁹	Supine in a knee-bent position ³⁰ , supine ³¹ or lithotomy ³²	Supine ³³ or lithotomy
Therapeutic transducer	Two transducers: 1 for imaging, 1 for treatment	Multi-element transducer ³⁴ with one treatment and one US imaging probe ³⁵	4 (2 for imaging, 2 for therapy) ³⁶	Moveable endorectal probe and focused US transducer ³¹	Array with ten transducers

Abbreviations: MHz=megahertz; MRI=magnetic resonance imaging; NA=not available; T=tesla; US=ultrasound.

Sources: FDA, Profound Medical, FUS Foundation, USCF, HIFU-planet, European Urology, Radiology Key, Lindner [37], Yuh [27], HIFU Prostate Services, Minogue Med, Gelet [38]

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

- Given the often multifocal and multiclonal nature of PCa, whole-gland treatment or ablation was considered standard.
- 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 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 [7].

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

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 overtreatment. AS applies to patients with a life expectancy over 10 years and a low risk of developing PCa, whereas WW applies to patients with all stages of PCa and a life expectancy of less than 10 years [1].

In AS, the patients remain under close surveillance (including rebiopsies after 2 years) and treatment is started if they reach predefined thresholds that indicate relevant progression or potential for a life-threatening disease. Thus, the aim is to achieve the correct timing for curative treatment [1].

In WW, the patients receive palliative treatment when disease-related complaints develop, with the aim of maintaining the patients' QoL [1].

²⁸ https://www.accessdata.fda.gov/cdrh_docs/pdf15/k153023.pdf

²⁹ <https://radiologykey.com/high-intensity-focused-ultrasound-for-prostate-cancer/>

³⁰ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4788859/>

³¹ [http://www.europeanurology.com/article/S0302-2838\(12\)01333-4/fulltext](http://www.europeanurology.com/article/S0302-2838(12)01333-4/fulltext)

³² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3529739/>

³³ <http://www.profoundmedical.com/new-tulsa/>

³⁴ <https://books.google.it/books?id=...=onepage&q=ablatherm%20hifu%20lateral&f=false>

³⁵ <http://www.minogue-med.com/focalone.html>

³⁶ <https://www.hifuprostateservices.com/sonablate-vs-ablatherm/>

What is radical prostatectomy (RP)?

RP refers to 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. This procedure is often 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 10 years' life expectancy to be offered this treatment [1]. Moreover, RP can be done laparoscopically, openly or laparoscopically under the assistance of a surgical robot.

What is definitive radiotherapy (RT)?

The goal of RT, either EBRT, brachytherapy or a combination of both, in localised PCa is to deliver a therapeutic dose of radiation to the tumour while minimising the radiation to normal tissue. EBRT utilises 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 maximise irradiation of the tumour while minimising radiation to normal tissue [11]. In low-dose rate brachytherapy (LDRB), radioactive seeds are permanently implanted. It is widely used in combination with EBRT. High-dose rate brachytherapy (HDRB) requires the temporary insertion of radioactive sources, and is used mainly in patients with high-risk PCa [5].

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

A major claimed benefit of HIFU is the lack of induction of apoptosis, avoiding late complications of treatment, and a lack of cumulative effect with the possibility of repeating treatment [4]. It is claimed that HIFU treatment has a significantly lower AE profile (erectile and urinary dysfunction) [9], and reduces toxicity (because of less damage to the adjacent or intervening tissues) compared with other ablation techniques [7, 10].

HIFU has the potential to ablate internal tumour tissue with great precision, because the tumour can be visualised during treatment [4]. HIFU is also able to treat only a small focus; thus, 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 [2].

Although AS and WW are options to avoid overtreatment and, thus, treatment-related AEs, they can also carry an increased risk of psychological distress (anxiety and depression), which might considerably affect QoL. Apart from psychological distress, untreated patients can have a higher level of obstructive urinary symptoms compared with patients treated with definitive therapies. Consequently, appropriate patient selection is crucial [1, 2].

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

The first description of HIFU concerning its ability to destroy tissue was published in 1944 [4], but the technology was only approved for clinical indications some years later. The first experiments on the prostate were performed during the early 1990s, while the first treatments in men were performed in 1992. The results of a pilot study on PCa treatment were first published in 1996 [4]. HIFU devices have been available commercially since the early 2000s. The first two commercially available HIFU devices (Ablatherm[®] and Sonablate[®]) used US-imaging guidance. FocalOne[®] was the first device to implement MRI/TRUS image fusion to guide transrectal treatment. HIFU performed with real-time MRI is the newest and most precise imaging to localise and ablate PCa. In addition,

this allows real-time temperature monitoring and visualisation of treatment effects [4]. To date, there are two MRI-guided HIFU systems that have a CE mark: TULSA PRO[®] and ExAblate[®]. HIFU is not yet established as standard treatment option according to guidelines [1, 12, 28].

[B0004] – Who administers HIFU and in what context and level of care is it provided?

Although a multispecialist team is required to deliver the whole HIFU procedure, the urology surgeon performs the HIFU treatment itself. For image fusion, the radiologist performs pretreatment MRI and provides the image data that the software of the HIFU system requires. If HIFU is performed under MRI guidance, the urological surgeon, radiologist and their teams work hand in hand. Internal technical support is needed to set up, tear down and disinfect the system after the procedure. The manufacturers require that, as part of the training for surgeons, a certain number of procedures need to be done with the assistance of a supervisor/specialist. Afterwards, the surgeon becomes a certified HIFU user and is able to use the device without the assistance of the supervisor [39-41].

Although HIFU can be delivered in a day-surgery setting, patients usually spend 2–4 days in hospital because of local reimbursement practices and preoperative evaluations, 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 [43].

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

[B0009] – What equipment and supplies are needed to use HIFU?

HIFU treatment can be performed wherever the required resources (anaesthesia, power, internet, nursing, recovery room, etc.) are available [44]. It is usually done in a urological day-case suite with cystoscopy facilities, degassed water (<3 ppm oxygen) and nonsterile sheaths [5]. 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 that 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 [4]. Most devices require a few disposables, usually tubing and covers, gels and fluids.

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

The CE mark has been awarded to the HIFU technology for the treatment of patients with primary localised PCa or recurrent localised PCa following prior therapy. The various HIFU systems and their regulatory status with the verbatim wording of the indications are presented in [Table A12](#) in [Appendix 2](#). Contraindications are also presented in [Table A12](#), described only for one device, Sonablate[®] 500. However, they are generalisable to all transrectal HIFU devices.

HIFU has also received a 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) [8].

[A0021] – What is the reimbursement status of HIFU?

Detailed information on the reimbursement status of HIFU and recommendations are included in [Table A13](#) in [Appendix 2](#).

4 HEALTH PROBLEM AND CURRENT USE OF THE TECHNOLOGY (CUR)

4.1 Research questions

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 are the symptoms and the burden of disease for patients with prostate cancer?
A0006	What are the consequences of prostate cancer for society?
A0024	How prostate cancer is currently diagnosed according to published guidelines and in practice?
A0025	How prostate cancer is 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 patients belong to the clinically localised prostate cancer (cT1a-T2, N0-Nx, M0) and locally relapsed/recurrent prostate cancer (cT1a-T2, N0-Nx, M0) groups?
A0011	How much is high-intensity focused ultrasound utilised?

4.2 Results

Overview of the disease or health condition

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

PCa is the most common non-skin cancer in men in Europe [1]. The malignancy usually originates from glandular epithelial cells, often multifocal and multiclonal. Depending on parameters, such as tumour grade, tumour volume and PSA concentration at the time of diagnosis, risk stratification is possible [45]. Small low-grade cancer is a frequent finding, usually characterised 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 PCa shows rapid local growth and a high likelihood of metastasis [1, 46-48].

In its early stage, PCa is localised and organ confined [49]. Depending on the risk of progression, the cancerous lesion increases in volume and produces more PSA over time. PCa is called ‘locally advanced’ when it 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 metastasise early or late, into regional or distant lymph nodes. Metastatic PCa is also likely to produce bone metastases with high variation in size and numbers, in any location [46-48].

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 [50]. By contrast, low-risk PCa, particularly in older men, can usually be left untreated. It might never cause any problems or affect overall survival (OS) [12, 13]. However, given that risk stratification is based on biopsy findings, there is a risk of under- or overestimation because of sampling error. During follow-up, a shift of grading can also occur [51].

Recurrence of PCa can be either local or the result of 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, no PSA is produced. After RT or any other procedure that leaves healthy or non-cancerous prostatic tissue behind, PSA is still detectable, the lowest value occurring during follow-up being named the 'nadir'. After RT, any PSA above zero is proof of recurrence or remaining prostate tissue, either locally or metastatic. In most cases, this is a sign that the initial tumour was understaged. After RT, the definition of recurrence is more difficult, and is based on consecutive measures of increasing PSA (Phoenix definition) [52]. 'Biochemical recurrence' is a term used for patients who had a nadir after RP of zero and show some PSA increase to a low value, which stays at a low level during further follow-up, with no detectable lesion [53]. The term is also used for recurrence after other therapies, usually with low tumour burden.

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

PCa can be divided into three groups: hereditary, familial and sporadic. Positive family history is a strong epidemiological risk factor for PCa. Gene-environment interactions also have a crucial role in cancer development. Hereditary PCa, which is high-risk PCa, is demonstrated only in 5% of cases with family history, whereas familial PCa accounts for approximately 13%–25% of cases. Patients with hereditary PCa 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 6–17 years earlier than spontaneous cases. Epidemiological studies have also shown strong evidence for a genetic predisposition to PCa based on ethnic background [1, 54].

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

[A0004] – What is the natural course of prostate cancer?

The natural history of PCa is not yet fully clarified. It might arise from damaged prostate epithelium and develop progressively over many decades, but its heterogeneity and multifocal nature makes it difficult to fully understand its progression. Approximately one-third of men over the age of 50 display histological evidence of PCa. However, most of these cases remain clinically insignificant. The likelihood of disease progression is difficult to predict. Although progression of the disease is usually slow, certain high-grade tumours proceed on a more aggressive course compared with low-grade, well-differentiated tumours [13]. Nevertheless, PCa can lead to both metastases and death.

Effects of the disease or health condition

[A0005] – What are the symptoms and burden of disease for patients with prostate cancer?

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 a primary diagnosis of locally advanced or metastatic disease might have symptoms

of these conditions, such as haematuria, incontinence, urinary retention, uni- or bilateral hydro-nephrosis, urinary tract infection, and skeletal pain at various locations. PCa (especially localised disease) is usually diagnosed as a result of PSA screening, rather than on the perceived symptoms. Symptoms of problems with the prostate can be similar to those of PCa [55].

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

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

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 in the economic burden of the disease. There will also be an increased need for resources, such as treatment facilities and trained specialists [12].

The mean direct costs per patient for initial treatment for PCa have been estimated at approximately €2800 in the UK, €2900 in Spain, €3600 in Germany, €4650 in Italy and €5200 in France. The total estimated costs for all patients in the first year from diagnosis, when the highest proportion of the costs occurs, were estimated to be €106 million in the UK, €223.3 million in Germany and €352 million in France. This does not include indirect costs, such as time and productivity loss (because of cancer-related illnesses, or the impact of the physical and mental suffering of both patients and relatives during diagnosis and follow-up), or end-of-life costs [12]. It is estimated that the total economic costs of PCa in Europe exceeded €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?

PCa is suspected on the basis of digital rectal examination (DRE) and/or PSA levels; however, a definitive diagnosis is based on histopathological verification in prostate biopsy cores or specimens 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 over the benefit of PSA screening or over the cut-off value at which to perform a biopsy, it is obvious that higher PSA concentrations indicate a greater likelihood of a positive result, but not a definitive sign of PCa [1].

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 (TRUS and mpMRI), PSA level and biopsy are tools to predict the final pathological stage of PCa.

- *N staging*: this should only be performed when it might directly influence treatment decisions. High PSA values, T2b–T3 stage, poor tumour differentiation and perineural invasion are associated with a high risk of nodal metastasis. CT scans or MRI are used to predict the N stage.
- *M staging*: evaluation of bone metastases of PCa using bone scans, positron emission tomography (PET)/CT or MRI.

The TNM classification nomenclature is presented in [Table 5](#).

Table 5: TNM classification of prostate cancer

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 PSA level)
T2	Tumour confined within the prostate ³⁷
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 ³⁸
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 nodes³⁹
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis ⁴⁰
M	Distant metastasis⁴¹
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymph node(s)
11	
M1b	Bone(s)
M1c	Other site(s)

Source: EAU-ESTRO-SIG Guidelines on Prostate cancer, 2016 [1]

³⁷ Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.

³⁸ Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

³⁹ The regional lymph nodes are the nodes of the true pelvis, which are essentially the pelvic nodes below the bifurcation of the common iliac arteries.

⁴⁰ Laterality does not affect the N classification.

⁴¹ When more than one site of metastasis is present, the most advanced category should be used.

Diagnosis of disease recurrence

BCR after curative primary treatment can be a sign of relapse because it universally precedes progression, but an increase in PSA is not a surrogate for survival endpoints. Treatment failure defined by the PSA level differs depending on the primary treatment modality that the patient received. Following primary RP, there is international consensus that recurrent cancer can be defined by two consecutive PSA values of >0.2 ng/mL and increasing. 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) have been proposed by consensus groups [1].

Once a PSA relapse has been diagnosed, it is important to determine whether the recurrence has developed at local or distant sites [1]. mpMRI is the first step in current clinical practice to diagnose PSA relapse 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].

As detailed above, biochemical failure is defined according to the Stuttgart definition (an increase of 1.2 ng/mL or more above the nadir PSA) and the Phoenix definition (an increase of 2 ng/mL or more above the nadir PSA).

The management of PCa depends on the TNM stage of the disease as well as both biochemical (e.g., PSA) and pathological information (e.g., Gleason score), which have prognostic value. The optimum treatment for a patient with PCa requires an assessment of the risk of both metastatic spread and local recurrence [12].

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

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

- Anatomic extent of the disease (TNM stage)
- Histological 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.

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

- AS
- RT
 - EBRT or
 - LDRB
- RP with optional lymph node dissection.

Other ablative techniques, such as cryotherapy and HIFU, are not standard.

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

- RT with optional ADT
 - External beam (EBRT) or
 - HDRB or
 - Combination of EBRT and brachytherapy
- RP with pelvic lymph node dissection WW if the life expectancy is limited based upon age and comorbidities [11].

Other ablative techniques, such as cryotherapy and HIFU, are not standard.

The treatment algorithm for localised prostate cancer is presented in [Figure 2](#).

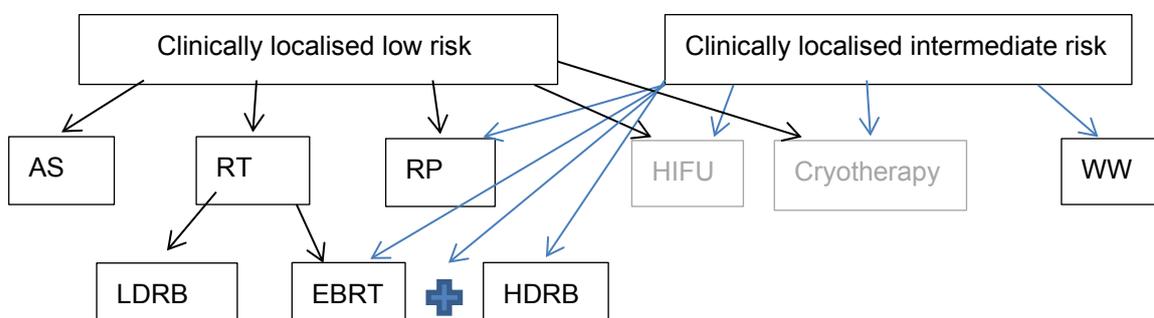


Figure 2: Treatment algorithm for localised prostate cancer

There are no standards for patient selection for salvage treatments; however, most investigations include patients with BCR, local disease and no metastasis and there are some further considerations that can help determine the treatment decision [59].

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

Treatment options for locally recurrent PCa are:

- Local salvage therapy:
 - RP
 - RT.

Other ablative techniques, such as cryotherapy and HIFU, are not standard.

- *Systemic therapy*: hormonal therapy (ADT) is only recommended to patients who have metastasis, a PSA doubling time of <3 months, or who have symptomatic local disease progression [12]. Given that systemic therapy offers no prospect of cure, patients should fully explore curative salvage options before initiating systemic therapies [59].

The treatment algorithm for relapsed/locally recurrent prostate cancer is presented in [Figure 3](#).

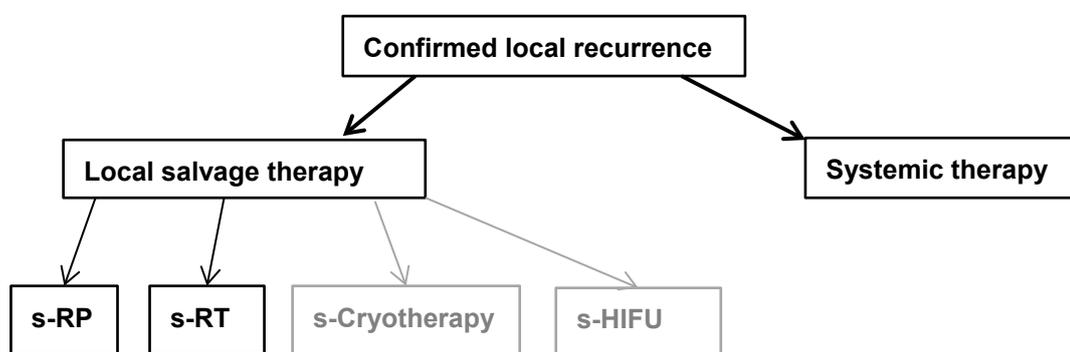


Figure 3: Treatment algorithm for relapsed/locally recurrent prostate cancer

Considering only HIFU in the guidelines, the EAU guideline [1], along with guidelines from selected European countries (Germany [28], United Kingdom [12]), as well as the American Urologists guideline [60] all recommend the use of HIFU only in the course of clinical trials because it is an experimental treatment (the same applies for cryotherapy). Available guidelines on HIFU are provided in [Table A1](#) in [Appendix 1](#).

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)?

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

- ‘Low risk’ is defined as PSA<10 ng/mL, GS<7 and cT1a–T2a.
- ‘Intermediate risk’ is defined as PSA 10–20 ng/mL, or GS 7, or cT2b [1].

The reasons for the choice of the target population are outlined in the [Scope](#).

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

The incidence of PCa is higher in Northern and Western Europe (>200 per 100,000 men), although rates in Eastern and Southern Europe are increasing (average annual percentage change from 1998 until 2010 was between three and seven percentages in countries of the two regions) [15]. 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 around 35 per 100,000 men in Poland and Slovakia [16].

A recent study [15] described a rapid increase in the incidence of PCa, including a pronounced peak, in Austria over the past three decades. The annual average localised PCa incidence in Austria is approximately 2600 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 percentage change of 19.3% and with the most rapid increase for men aged less than 65 years [15].

Incidence rates of recurrent PCa 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 experience BCR within 10 years [14].

[A0011] – How much is HIFU utilised?

Data are available for the two biggest manufacturers in terms of the approximate number of treated patients. Sonacare Medical claim that their Sonablate[®] is used by over 300 physicians worldwide and over 15,000 procedures had been completed as of 2015 [34].

EDAP TMS claim that their three generations of commercial devices [Ablatherm[®] Maxis (from 1993 to 2005), Ablatherm[®] Integrated Imaging (since 2005) and Focal One[®] (since 2013)] have been routinely used for more than 20 years throughout the world, with more than 40,000 treatments performed [62].

According to the information of the submitting hospital, total utilisation rate in Austria is unclear. However, in the submitting hospital (with 1200 beds and 88,000 inpatients annually), approximately 30 procedures are delivered annually.

5 CLINICAL EFFECTIVENESS (EFF)

5.1 Research questions

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 the technology affect progression (or recurrence) of localised and locally recurrent prostate cancer?
D0011	What is the effect of HIFU on patients' bodily 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 HIFU?

5.2 Results

The inclusion criteria for assessing the clinical effectiveness of HIFU were exclusively restricted to studies with a comparison group, including RCTs and non-RCTs. The systematic literature search (Figure 1: Flow chart) 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 PCa, including 70 patients in each treatment arm [20]. Characteristics of the included study and the results are presented in Table A2 in the Appendix.

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

The critical outcomes to evaluate the evidence were OS, PCa-specific survival and local disease recurrence. All three outcomes reflect the most important aims of PCa treatment: that is, that patients do not die in general or as a result of the cancer and that patients do not experience tumour recurrence. Thus, the success of the treatment can be largely measured by these three endpoints. Generally, the three outcomes were measured by the study investigators or study assessors.

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 significant older than patients in the control group ($p < 0.01$). Tumour stage was between T1a and T2b for all patients, whereas only 12 versus 9 patients had an intermediate-risk PCa with stage T2b. The GS was 6 or below in 72.9% and 7 in 27.1% of the patients included 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 before the actual treatment. The 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 treatment was performed by the use of the Ablatherm[®] device. However, the first series of patients was treated with Ablatherm[®] Maxis, which is no longer commercially available [62]. The second series was treated with Ablatherm[®] Integrated Imaging. The control group was treated by a permanent transperineal interstitial preloaded-free needle implantation of Iode¹²⁵ using a real-time biplanar US-guided system [20].

Mortality**[D0001] – What is the expected beneficial effect of HIFU on mortality?**

Two outcomes were considered relevant to assess the expected beneficial effect of HIFU on mortality: OS and PCa-specific survival. After 5 years, OS in the brachytherapy group compared with HIFU was not significantly different (88% vs. 97.5%, HR 0.24, 95% CI 0.01–1.34) [20].

Regarding PCa-specific survival, after 5 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, 95% CI 0.32–1.29) [20].

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 and locally recurrent prostate cancer?**

BCR-free survival (BCRFS) 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% versus 68.5% according to the Phoenix and 51.3% versus 60.9% according to the Stuttgart definitions (HR 0.41, 95% CI 0.19–0.81 for Phoenix; HR 0.39, 95% CI 0.19–0.74 for Stuttgart; $p < 0.05$ for both) [20]⁴².

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'.

[D0011] – What is the effect of HIFU on patients' bodily functions? and**[D0016] – How does the use of HIFU affect activities of daily living?**

These two research question are answered in the next chapter, by presenting the functional outcomes on urinary, bowel and sexual (dys)function (see research question **C0008**).

⁴² Phoenix criteria: PSA nadir +2ng/mL; Stuttgart criteria: PSA nadir +1.2 ng/mL). See also **A0024**.

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 these research questions.

Satisfaction

[D0017] – Were patients satisfied with HIFU?

No evidence was identified to answer this research question.

6 SAFETY (SAF)

6.1 Research questions

Element ID	Research question
C0008	How safe is HIFU in relation to AS, WW, RT and RP?
C0002	Are the harms related to the dosage or frequency of applying HIFU?
C0004	How does the frequency or severity of harm 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?

6.2 Results

Included studies

The study inclusion criteria for assessing safety differed from those used for assessing clinical effectiveness. In addition to RCTs and non-RCTs, prospective studies without a control group (single-arm studies, case series, and registry studies) with at least 50 patients were considered. In the systematic literature search ([Figure 1: Flow chart](#)), we identified four prospective single-arm studies [21-24] and one non-RCT (matched-pair analysis) [20] regarding primary HIFU and one prospective single-arm study regarding s-HIFU [25], which met our inclusion criteria. The single-arm primary HIFU studies applied hemiablation, the matched-pair analysis and the s-HIFU study applied whole-gland ablation of the prostate. Characteristics of the included studies and the results are presented in [Table A3](#) in [Appendix 1](#).

The critical outcomes used to evaluate the evidence were functional outcomes (urinary and sexual functions) and SAEs. Functional outcomes were measured with various tools:

- Urinary (dys)function was defined as the loss of continence (measured by 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 using the IPSS, which is based on the answers to seven questions concerning urinary symptoms (frequency, emptying, intermittency, urgency, weak stream, straining, and nocturia) and one question concerning QoL. Each question concerning urinary symptoms allowed the patient to choose one out of six answers indicating the increasing severity of the particular symptom. The answers were assigned points from 0 to 5. Therefore, the total score could range from 0 to 35 (asymptomatic to very symptomatic) [63].
- Sexual (dys)function was defined as the loss of erectile function (reported as the number of patients with new-onset 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). The questions were focused on erectile function and intercourse satisfaction. The possible scores for the IIEF-5 ranged 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 erectile dysfunction (22–25) [64].

Adverse events were reported in all included studies, although three primary HIFU studies [20, 23, 24] reported exclusively the number of events and the number of patients for whom this outcome was collected, but did not report the event per patient number. The events were categorised into Grade 1, 2, 3, and 4 classes according to the Clavien-Dindo risk categories, where Grade 1 represented any deviation from the normal intraoperative or postoperative course, including need for pharmacological treatment other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, or physiotherapy; Grade 2 represented complications needing only the use of intravenous medication, total intravenous nutrition, or blood transfusion; Grade 3 complications were those where surgical, endoscopic or radiological intervention under local or general anaesthesia was needed; and Grade 4 complications were life-threatening and required intensive care unit management [25].

Primary HIFU

Study characteristics

The single-arm primary HIFU studies [21-24] reported on a total of 279 patients treated with Ablatherm[®], originating from France, Germany and Belgium. The matched-pair analysis [20] study reported on 70 patients treated with the Ablatherm[®] HIFU device and 70 patients treated with brachytherapy in Belgium.

Patient characteristics

Mean patient ages ranged between 63.4 and 73 years in the single-arm studies [21-24]. The median patient ages were 74 years in the HIFU group and 69 years in the brachytherapy group in the matched-pair analysis [20]. Tumour stages T1–T2 were 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) [23, 24] and in the matched-pair analysis [20], two studies did not report the tumour stage [21, 22]. The GS for patients treated with HIFU was 6 or below in 221 (60%) of the included patients, 7 in 85 patients (23%) and unknown for the rest of the patients (one study [22] stated only the number of patients with GS 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 [22] excluded patients with previous ADT according to the exclusion criteria of the study. The matched-pair analysis [20] reported that 27% of patients treated with HIFU received ADT before treatment, whereas 20% of patients treated with brachytherapy received ADT. Mean pre-HIFU PSA level ranged between 6.2 ng/mL and 6.6 ng/mL (one study [21] reported the median, which was 6.1 ng/mL) in the single-arm studies, and was not reported in the matched-pair analysis (only the number of patients with a pre-HIFU PSA level 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 was not reported in the matched pair analysis.

HIFU procedure and follow-up

All studies used the Ablatherm[®] device in the procedure, except for one [22], which used both Ablatherm[®] and the newer device from the same manufacturer, FocalOne[®]. Hemiblention was applied in the single-arm studies [21-24], whereas the matched-pair analysis [20] applied whole-gland ablation of the prostate. Only one study [23] reported on TURP performed before or in combination with HIFU. This study reported that 60% of patients had TURP before or in combination with HIFU treatment because of a large prostate volume. The duration of the treatment was reported in two studies [21, 22]: mean treatment time was 62.2 min in one study [22] and an average of 120 min

in the other study [21]. Catheterisation time was also reported in two studies [22, 24] and ranged between 2.8 days and 2.9 days. The mean follow-up ranged between 17.41 months and 39 months (one study [21] reported the median rather than mean follow-up time, 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 treatments per patient was reported in two studies [22, 23] and was comparable within the studies: 90% of patients had only one intervention and 10% had two HIFU treatments.

Salvage HIFU

Study characteristics

The s-HIFU study [25] reported on 84 patients treated with the Sonablate® device in the United Kingdom and Canada. Whole-gland ablation was applied.

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, tumour stage was lower than T3a. A total of 30 patients (36%) received neoadjuvant ADT before the s-HIFU. The median GS was 7, ranging from 6 to 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 [25].

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 min with a mean of 1.4 days of hospital stay. Over 90% of patients (78) were treated with one s-HIFU intervention and 7% (6 patients) had two s-HIFU treatments [25].

Patient safety

[C0008] – How safe is HIFU in relation to AS, WW, RT and RP?

Comparative study

The only available evidence that compared HIFU with any of the comparators was the matched-pair analysis study that reported on whole-gland HIFU and brachytherapy [20]. We found no comparative evidence on HIFU in relation to other treatment options, such as RP, AS or WW.

Intervention-related death

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

Urinary (dys)function

There was no significant difference in urinary in patients treated with HIFU compared with those who received brachytherapy (occurred in 7.2% of patients in the HIFU group and 3.8% in the brachytherapy group, $p = 0.44$).

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

The most frequent AEs reported were urinary retention, urinary tract infection, urethral stricture, and storage or voiding LUTS. Urinary retention and urethral stricture (particularly in patients treated with the first-generation device) were significantly higher in the HIFU cohort compared with the brachytherapy cohort ($p = 0.02$ and ≤ 0.01 , respectively). Urinary tract infection and storage or voiding LUTS were the most frequent early and late postoperative complications, with no statistically significant difference across the two cohorts ($p = 0.07$ and $p = 1.0$, respectively). One patient per each cohort developed a rectourethral fistula, which was managed surgically. One patient in the brachytherapy cohort had haemorrhagic cystitis, which was managed by endoscopic fulguration.

When comparing the severity of AEs, the rate of Grade 3 AEs was higher for patients treated by HIFU than for patients treated by brachytherapy (35% vs. 13%, see also [Table 6](#)). In particular, acute urinary retention and stricture occurred more often in the HIFU group than in the brachytherapy group (>20% vs. <6% each). However, information on statistical significance was not provided [20].

Single-arm observational studies

All four single-arm studies on primary HIFU applied hemiablation [21-24]. The study on s-HIFU [25] applied whole-gland ablation.

Intervention-related mortality

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

Urinary (dys)function

Urinary symptoms with the IPSS score were reported in three studies, of which two studies [21, 22] concluded that there was no significant change in urinary function (even without TURP) because there was no change in mean IPSS score from baseline post-HIFU to the 3–12 months follow-up visit, and one study [23] 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 s-HIFU [25] did not show any significant effect on the IPSS score at 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 [24] 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 [21-23] of which two studies [22, 23] had a follow-up of 12 months and both reported that one patient was incontinent pre-HIFU and three (3% and 5.9%, respectively) patients had persistent incontinence at 12 months' follow-up. One study [21] reported that none of the patients had incontinence at follow-up, although 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 [21-23] used the IIEF-5 scale, of which two [21, 22] 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 patients who had been potent pre-intervention; whereas one study [21] 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 s-HIFU study [25] also reported a significant negative effect on sexual function based on the IIEF-5 scores 6 months after the intervention ($p < 0.001$).

Adverse events

The most frequent AEs reported in the single-arm studies [21-24] were: urinary tract infection, dysuria, anejaculation, pain and urinary retention. Additionally, in the s-HIFU study [25], bladder outlet obstruction and rectal fistula were common AEs. Compared with the matched-pair analysis [20], the rates of storage or voiding LUTS [23, 24] (Grade 1 complication), acute urinary retention [21, 23, 24] and stricture [22-24] (Grade 3 complications) were considerably lower in the single-arm studies. Rectal fistula (Grade 3 complication) occurred only in the matched-pair analysis [20] and in the s-HIFU study [25], which both applied whole-gland ablation. Bladder outlet obstruction, another Grade 3 complication, was observed only in the s-HIFU study [18], 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 salvage HIFU study [18]. The AEs are presented in [Table 6](#) categorised by study and severity

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

No evidence was found relating either the dosage or frequency of either primary or s-HIFU to the harms associated with either treatment.

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

One single-arm study [21] reported that all complications were encountered within the first post-operative month. Another single-arm study [24] and the matched-pair analysis [20] did not report when the complications occurred first, but reported that seven, respectively one patient had transient incontinence during follow-up after HIFU. This transient incontinence was self-resolving in three of seven patients in the single-arm study and in the one patient in the matched-pair analysis at 12 months postoperatively. The reported complications were likely to occur shortly after treatment and were only temporary in most of the patients. The matched-pair analysis [20] reported that storage and voiding LUTS developed immediately after 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.

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

No evidence was found to answer this research question.

[C0007] – Is HIFU associated with user-dependent harms?

The included studies did not report explicitly on user-dependent harms. One study [20] stated that the technical improvements with the introduction of the new Ablatherm® device and the changes in surgical protocol had lowered the high rate of urinary tract infection and bladder outlet obstruction encountered with earlier HIFU interventions. The incidence of rectal fistula has decreased over the past decade, mainly because rectal bleeding has been managed better [20]. This was also underlined by the s-HIFU study [25], which reported that rectourethral fistulae occurred early in the learning curve in the first 20 patients.

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

No evidence was found to answer this research question.

Table 6: 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 [20]		Van Velthoven, 2016 [24]	Rischmann, 2017 [23]	Ganzer, 2017 [22]	Feijoo, 2015 [21]	Uddin Ahmed, 2012 [25]
		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 ⁴³)	20 (28.6) ⁴³	9 (18)	7 (6.7)	—	—	—
Haematospermia	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)	—	—
Haematuria	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) ⁴³	18 (25.7) ⁴³	—	—	—	—	—
Urinary tract infection	49/313 (15.6)	15 (21.4)	5 (7.1)	3 (6)	18 (17.1)	9 (42.9)	4 (6)	—

⁴³ 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 [20]		Van Velthoven, 2016 [24]	Rischmann, 2017 [23]	Ganzer, 2017 [22]	Feijoo, 2015 [21]	Uddin Ahmed, 2012 [25]
		HIFU	Brachytherapy					
Orchitis	8/105 (7.6)	—	—	—	8 (7.6)	—	—	—
Prostatitis	8/105 (7.6)	—	—	—	8 (7.6)	—	—	—
Haematuria	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)	—	—	—	—	—
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) ⁴³	—	—	—	—	—
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)	90⁴⁴ (128)	59⁴⁴ (84.3)	22 (44)	106⁴⁴ (109)	26⁴⁴ (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: [20-25].

⁴⁴ The study reported a higher number of total adverse events than the total number of patients.

7 DISCUSSION

HIFU is a technology that uses US waves to destroy tissue, particularly cancer tissue. The present report focused on the treatment of PCa with HIFU. US can be applied for the ablation of the whole gland or in parts, so-called 'hemiblention' or 'focal therapy'. Treatment planning can be done under the assistance of US or MRI, whereas the latter is more appropriate for FT.

In 2010, the LBI-HTA published a report on the use of HIFU for PCa [17], 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 no earlier than 2 years after that report, based on the estimated completion date of the identified ongoing studies. The aim of the present assessment was to update the LBI-HTA report from 2010 to examine the evidence published since 2010. Nevertheless, the scope of the present assessment notably changed in two aspects: the population was limited to low- and intermediate-risk patients according to the latest guidelines and more patient-relevant outcomes formed the basis of our conclusions.

Interpretation of findings

The present assessment does not alter the general conclusions of the 2010 LBI-HTA report. Overall, we identified 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 50–111 patients and had a mean or median follow-up of 12–39 months. The matched-pair analysis included 70 patients in each study arm and had a median follow-up of 83 months in the HIFU arm and 44 months in the brachytherapy arm. Therefore, there is still a lack of comparative studies for the most common comparators.

The single available comparative study [20] showed slightly lower PCa-specific survival rates after 5 years, as well as overall survival rates in patients treated with HIFU compared with those treated with brachytherapy. Although the differences were not significant, the given confidence intervals indicated considerable harm resulting from the use of HIFU. However, patients in the HIFU group were significantly older than patients treated with brachytherapy, which could have had a confounding effect on survival rates. Local disease recurrence, a critical effectiveness-related outcome, was not reported in the study.

Although QoL was not measured in the single comparative study included in the present assessment, three single-arm studies (two primary HIFU [22, 23] and one s-HIFU study [25]) reported on this outcome. All three studies used various outcome measures. One primary study reported a significant improvement in the QoL scores 12 months post-treatment [23], whereas the other primary HIFU study and the s-HIFU study could not show any significant change in either the depression and anxiety scores, or in the global QoL scores at 12 months post-HIFU.

In terms of safety-related functional outcomes, the matched-pair analysis did not show a significant difference in urinary incontinence between HIFU and brachytherapy. In the absence of data relating to bowel and sexual (dys)function outcomes, it was not possible to draw any conclusions in terms of these functional outcomes in a comparison of the HIFU and the brachytherapy cohorts. However, the single-arm primary studies [21-24], as well as the s-HIFU study [25], reported a significant negative impact on sexual function. Concerning complications, in the matched-pair analysis [20], considerably more AEs were observed in patients treated with HIFU compared with those treated with brachytherapy, with more-severe complications occurring more often.

Comparing the matched-pair analysis [20] with the single-arm studies [21-24] suggests that storage or voiding LUTS, acute urinary retention and stricture were more frequent in the matched-pair analysis. More-severe, Grade 3 and 4 complications, such as rectal fistula and bladder outlet obstruction, did not occur in any of the primary single-arm studies. The ablation type applied might have influenced the severity of AEs because the matched-pair analysis [13] and the s-HIFU study [18] both applied whole-gland ablation, whereas the primary single-arm studies [21-24] applied hemiablation.

Study quality, validity, and level of evidence

The overall quality of evidence for HIFU as a primary treatment for clinically localised low-risk and intermediate-risk PCa as well as for HIFU as salvage treatment for locally recurrent PCa is low. Studies lack sufficiently high patient numbers, comparators, and sufficiently long periods of follow-up. The small numbers considerably limit the generalisability of the findings and only two studies reported on outcomes with a follow-up of 5 years; therefore, no significant conclusion can be drawn on disease control. All outcome estimates of the efficacy of primary HIFU compared with brachytherapy, a type of RT, were based on only one comparative study. However, this comparative study comprised two matched single-arm studies, which does not represent a high evidence level. Moreover, the safety outcome estimates of primary HIFU were based on single-arm studies in addition to the comparative study. In terms of s-HIFU, all outcome estimates were based on one single-arm study. Direct prospective comparisons between deferred treatment modalities (AS and WW) and RP or RT for salvage treatment are lacking.

There was also considerable heterogeneity in the HIFU studies because of 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 endpoints (biochemical, variable definitions of PSA endpoints, and/or biopsy data, and various survival endpoints: overall, actuarial recurrence-free, BCRFS, PCa specific, metastases-free, progression-free, and radical treatment-free). Definition of treatment failure was not universal among the studies, with some defining it as positive biopsy control (indicating local relapse [6]), whereas others used the need for salvage treatment, initiation of definitive treatment, or presence of clinically significant cancer. BCR rates were defined according to Phoenix or Stuttgart criteria, but there is currently no consensus regarding the drop in PSA level, which could indicate treatment success. In addition, Phoenix criteria are not validated for treatments other than radiotherapy, which tends to generate lower rates of recurrence. It might also be less sensitive in terms of focal ablation because the nadir might have less relevance, given the preservation of a large proportion of the prostate tissue [9]. The Stuttgart criteria ($>PSA \text{ nadir} + 1.2 \text{ ng/mL}$) have been proposed to define BCR after HIFU treatment, although are not yet validated.

Similarly for the safety endpoints, there is no standard measurement tool and the studies showed heterogeneity in the outcome measures used for sexual and urinary function and at what time point the outcome was measured. Sexual function was measured with the IIEF-5 score and/or physician-reported rates of – erectile dysfunction of previously potent patients at 3 or 12 months post-treatment. Urinary function was measured based on the usage of pads and/or with IPSS at 3 or at 12 months post-treatment. 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 [23], only the mean difference before and 12 months after treatment was stated, whereas, in another study, the values after treatment were missing [21].

Additional limitations that hinder the generalisability 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 AE profile (more frequent toxicities, incontinence, and erectile problems) compared with hemiablation [26, 27] (see also applicability table, [Table A11](#)).

Overall, the lack of comparative studies, the lack of standardisation, the heterogeneity in the type of ablation and the type of HIFU device and used (and device generations), the poor reporting of additional interventions (TURP and ADT), the heterogeneity in the follow-up schedule and outcome measures do not allow support a meta-analysis of the available evidence or a stratification to different generations of HIFU (and MRI guidance), and additional interventions.

Limitations of the present report

Limitations of the present report are the lack of stratification to different generations of HIFU (and MRI guidance), and additional interventions (TURP and ADT) because this information was often lacking. The MRI guidance, for instance, is a relatively new approach and studies evaluating its effectiveness and safety are ongoing. Moreover, we included a comparative study [20] in which patients were initially treated with an older version of device that is no longer commercially available. However, it can be expected that the device used, the type of guidance, and any concomitant treatments will have a considerable effect on the effectiveness and safety of HIFU.

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

As a result of changes to the project protocol, the present report slightly differs from the original version, 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, remaining at a very low level.

Evidence gaps and ongoing studies

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 only recently been completed and its effectiveness and safety are currently being analysed.

A search for ongoing studies identified two RCTs and three non-RCTs, of which one non-RCT was terminated because of poor recruitment and two had unknown status, although, according to the registry data, completion was planned for 2008 for one non-RCT and 2014 for an RCT (but no published results were identified). 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 A5](#)). It is often claimed that ethical considerations hinder the implementation of RCTs. To overcome this problem, there are alternative approaches that can be considered, such as cohort-embedded multiple RCTs or preference-based randomisations. A pragmatic approach would be to implement other trial designs, such as patient preference trials and parallel prospective cohort studies [9].

8 CONCLUSION

There is insufficient evidence to determine whether primary HIFU is more effective than (or at least as effective as) AS, WW, RP, or RT.

There is insufficient evidence to determine whether salvage HIFU is more effective than (or at least as effective as) AS, WW, s-RP, or s-RT.

There is insufficient evidence to determine whether primary HIFU has a better (or at least similar) safety profile to that of AS, WW, RP, or RT.

There is insufficient evidence to determine whether s-HIFU has a better (or at least similar) safety profile to that of AS, WW, s-RP, or s-RT.

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

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APPENDIX 1: METHODS AND DESCRIPTION OF THE EVIDENCE USED

DOCUMENTATION OF THE SEARCH STRATEGIES

Cochrane:

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

106 Hits

CRD

Date: 01/12/2017

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
13 Hits

Embase

Date: 01/12/2017

No.	Query	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 ultra*sound*':ti,ab	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

Ovid MEDLINE(R)

Date: 01/12/2017

- 1 exp Prostatic Neoplasms/ (123427)
- 2 (prostat* adj2 (cancer* or neoplasm* or carcinoma* or tumor* or adenoma*)).mp. (155384)
- 3 1 or 2 (155384)
- 4 exp High-Intensity Focused Ultrasound Ablation/ (1788)
- 5 exp Ultrasound, High-Intensity Focused, Transrectal/ (486)
- 6 high-intens* focus?ed ultra?sound*.mp. (3138)
- 7 high-intens* focal ultra?sound*.mp. (8)
- 8 HIFU.ti,ab. (2072)
- 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 (4054)
- 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. (4743197)
- 24 22 not 23 (648)
- 25 limit 24 to (english or german) (577)
- 26 remove duplicates from 25 (**501**)

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

DESCRIPTION OF THE EVIDENCE USED

Guidelines for diagnosis and management

Table A1: 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.	C

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)
			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.	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 <ul style="list-style-type: none"> • 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 minimise 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

Abbreviations: AUA American Urological Association, ASTRO American Society for Radiation Oncology, EAU European Association of Urology, ESTRO European Society for Radiotherapy & Oncology, HIFU High-intensity focused ultrasound, SIOG International Society of Geriatric Oncology, SUO Society of Urologic Oncology

Sources: [1, 12, 28, 60]

Evidence tables of individual studies included for clinical effectiveness and safety

Table A2: Characteristics of non-randomised controlled studies for the domain effectiveness and safety for primary HIFU

Author, year, reference number	Aoun, 2015 [20]
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 Iodine ¹²⁵)
Study design	Prospective matched-pair analysis ⁴⁵
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	NA (74 ± 4.47 vs. 69 ± 6.5) [62-86] vs. [54-79], (p<0.01)
Mean (median) [IQR]	
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)

⁴⁵ 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.

	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 ⁴⁶
Risk categories n (% of pts) according to	<u>D'Amico:</u> 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 ⁴⁷
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
Hospital stay (d)	NA
Catheterisation time (d)	NA

⁴⁶ PSA ≤10: 50 vs. 57 patients, PSA>10 ≤20: 20 vs. 13 patients.

⁴⁷ Pre-HIFU prostate volume was only given for the 110 patients of the initial HIFU study.

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	<u>After 5 years:</u> 62 vs. 68 ⁴⁸ (88 vs. 97.5 %), HR 0.24, CI 0.01-1.34, p = N.S.
Prostate cancer specific survival n (%) at X years	<u>After 5 years:</u> 62 vs. 64 ⁴⁸ (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	<u>After 5 years⁴⁹:</u> 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 ⁴⁸ (68 % vs. 77.5 %), HR 0.31, CI 0.09-0.94, p = 0.05 , intermediate risk: 31 vs. 41 ⁴⁸ (44.9 vs. 58.8 %), HR 0.47, CI 0.17-1.13, p = 0.12] Stuttgart: 36 vs. 43 ⁴⁸ (51.3 vs. 60.9 %), HR 0.39, CI 0.19-0.74, p < 0.05 [low risk: 39 vs. 54 ⁴⁸ (56.3 vs. 77.5 %), HR 0.31, CI 0.10-0.84, p = 0.03 , intermediate risk: 29 vs. 41 ⁴⁸ (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	

⁴⁸ Own calculations.

⁴⁹ Study reported biochemical recurrence-free survival.

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	<u>Events</u> ⁵⁰ : Erectile dysfunction: 5 ⁵¹ vs. NA (11.6 vs. NA), p = NA
Complications/adverse events (AEs) (grade 1-2) n at x months	43 vs. 31 ⁵² , p = NA within 1 year post-intervention; 22 vs. 13 , p = NA after more than 1 year post-intervention
Urinary tract infection	Urinary tract infection: 15 vs. 5 (21.4 vs. 8.5 %), p = 0.07 within 1 year post-intervention
Storing or voiding lower urinary tract symptoms (LUTS)	LUTS: 28 vs. 25 (40 vs. 42.4 %), p = 0.93 within 1 year post-intervention; 19 vs. 13 (27.5 vs. 26.4 %) ⁵³ , p = 1 after 1 year post-intervention
Acute/ chronic urinary retention	Burn, injuries, bleeding: NA
Burn, injuries, bleeding	Proctitis: NA
Proctitis	Pain ⁵⁴ : 3 vs. 0 (4.3 vs. 0), p = 0.34 after 1 year post-intervention
Pain	Anaesthesia-related complications: NA
Anaesthesia-related complications	Thromboembolic disease (phlebitis): NA
Thromboembolic disease (phlebitis)	Gastrointestinal toxicity ⁵⁵ : 0 vs. 1 (0 vs. 1.7%) within 1 year post-intervention
Other AEs	

⁵⁰ Method to document erectile dysfunction was not stated.

⁵¹ Measured in 43 patients

⁵² 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.

⁵³ Study did not report p values separately for grade 1-2 and grade 3-4 events after 1 year post-intervention.

⁵⁴ Study reported chronic pelvic pain

⁵⁵ Study reported gastrointestinal toxicity. The p value (p=0.59) was reported for all events (grade 1-3).

Serious adverse events (SAEs) (grade 3-4) n at x months	17 vs. 5 within 1 year post-intervention; 18 vs. 4 after 1 year post-intervention
Bladder neck/ urethral stricture/stenosis	Stricture: 17 vs. 2 (24.6 vs. 3.8 %), p < 0.01 ⁵⁶ after 1 year post-intervention
Bladder neck obstruction	Bladder neck obstruction: NA
Rectal fistula	Rectal fistula: 1 vs. 1 (1.4 vs. 1.9 %), p = 1 ⁵⁷ after 1 year post-intervention
Other SAEs	Acute urinary retention: 16 vs. 4 (22.9 vs. 6.8 %), p = 0.02 within 1 year post-intervention LUTS/haematuria: 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

⁵⁶ Study reported urethral stricture.

⁵⁷ Study reported rectourethral fistula.

Table A3: Characteristics of other relevant studies for the domain safety for primary HIFU

Author, year, reference number	Van Velthoven, 2016 [24]	Rischmann, 2017 [23]	Ganzer, 2017 [22]	Feijoo, 2015 [21]
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	<p>Inclusion: ≤T2, PSA<15 ng/ml, ≥5 y life expectancy, prostate volume <40 cm³.</p> <p>Exclusion: extraprostatic extension disease on mpMRI, suspected regional lymph nodes, or distant metastases, previous HIFU or RT.</p>	<p>Inclusion: treatment naïve, T1/T2, unilateral cancer, Gleason score ≤7.</p> <p>Exclusion: biopsy confirmed mpMRI lesion located <6 mm from the apex or <5 mm from the sagittal midline.</p>	<p>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.</p> <p>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.</p>	<p>Inclusion: unilateral cancer, T1c-T2a, max positive biopsies <33%, Gleason scores≤7, PSA<15 ng/ml, >10 y life expectancy.</p> <p>Exclusion: previous PCa related treatment, extraprostatic extension disease on mpMRI.</p>
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	T1c : 16 (32)	T1 : 77 (69)	NA	NA

pts)	T2 : 34 (68)	T2 : 33 (30) Unknown : 1 (1)		
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	<u>D'Amico:</u> low 24 (48) intermediate 26 (52)	<u>NA:</u> low 75 (68) intermediate 36 (32)	<u>NA:</u> low NA intermediate NA	<u>NA:</u> low: 67 (100)
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 ⁵⁸	Spinal, general	General	NA
Number of treatments/ patient n (% of pts)	NA	NA	NA	NA

⁵⁸ Procedure described in Van Velthoven, 2014

Duration of treatment (min) ± SD	NA	NA	62.2 ± 20.3	∅ 120
Hospital stay (d)	4 ⁵⁹	NA	NA	NA
Catheterisation time (d)	2.8 ⁶⁰	NA	2.9 ± 4.3	NA
Follow-up (m) Mean ± SD (median) [range]	39 (34) [IQR: 13-58] ⁶¹	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) ⁶² 32 (29) over 2 y	0	15 (22.4) over 16 m
Effectiveness-related outcomes				
Overall survival n (%) at X years	46 ⁶³ (87)/ 5 y	109 (98.2) ⁶⁴ / 1 y	51 (100)/ 1 y	NA
Prostate cancer specific survival % at X years	100/ 5 y	NA	100/ 1 y	NA
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

⁵⁹ Procedure described in Van Velthoven, 2014

⁶⁰ Procedure described in Van Velthoven, 2014

⁶¹ 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.

⁶² 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.

⁶³ 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.

⁶⁴ Two patients died from other causes: pancreatic and ethmoidal bone cancers.

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	<u>EORTC QLQ-C28 at 0 m/ 12 m FU (n = 76):</u> mean increase 0.4 (95% CI: -1.0; 1.7)	<u>Global health status/quality of life score (± SD) at 0 m/ 12 m FU:</u> 74.6 ± 17.8 / 73.9 ± 22.0, p = 0.39 <u>HADS-D depression score (± SD) at 0 m/ 12 m FU:</u> 8.8±4.7 / 10.1 ± 3.2, p = 0.276 <u>HADS-D anxiety score (± SD) at 0 m/12 m FU:</u> 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 3 rd 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	<u>Physician reported rate: incontinent pre-HIFU/ 12 m post-HIFU, n (%) (n = 50):</u>	<u>Usage of pads pre-HIFU/ 12 m post-HIFU, n (%) (n = 102):</u> 1 (1) / 3 (3)	<u>Usage of pads pre-HIFU/ 12 m post-HIFU, n (%) (n = 51):</u> 1 (2) / 3 (5.9)	<u>Usage of pads pre-HIFU/ x m post-HIFU, n (%) (n = 67):</u> 0 (0) / 0 (0)

	0 (0) / 3 (6) (transient incontinence before 12 m post-HIFU: 7 (14))	<u>IPSS pre-HIFU/ 12 m post-HIFU (n = 80):</u> improvement with a mean decrease of 3 (95% CI: 1.6; 4.4)	<u>IPSS pre-HIFU/ 12 m post-HIFU:</u> No significant change	<u>IPSS (range) pre-HIFU/ 3 m post-HIFU:</u> 6.24 (0-26)/NA, p = 0.217 <u>ICS (range) pre-HIFU/3 m post-HIFU:</u> 0.42 (0-8)/NA, p = 0.840
Functional outcomes: sexual (dys)function according to	<u>Physician reported rate pre-HIFU potent/ NA m post-HIFU potent (n = 50):</u> 30 / 24 De novo erectile dysfunction n (% of previously potent): 6 (20)	<u>IIEF-5 pre-HIFU / 12 m post-HIFU:</u> mean difference 1.2 (95% CI: -0.4; 2.7) <u>Physician reported rate pre-HIFU potent/ NA m post-HIFU potent (n = 51):</u> 51 / 40 De novo erectile dysfunction n (% of previously potent): 11 (21.6)	<u>IIEF-5 score (± SD) pre-HIFU / 12 m post-HIFU:</u> 17.6±6.1/ 13.6±8.6, p<0.001 <u>ICS-male score at 0 m/ 12 m FU:</u> 0.9±2.3/ 1.4±3.0, p = 0.131	<u>IIEF-5 score (range) pre-HIFU/3 m post-HIFU:</u> 17.97 (0-25)/NA, p < 0.001 <u>Physician reported rate pre-HIFU potent/ NA m post-HIFU potent (n = 21):</u> 21 / 11 De novo impotence n (% of previously potent): 10 (47.6)
Complications/adverse events (AEs) (grade 1-2) n at x months	16/ NA m (n = 50)	100/ 12 m (n = 105)	25/ NA m (n = 21)	8 within 1 m (n = 67)
Urinary tract infection	Urinary tract infection: 3	Urinary tract infection: 18	Urinary tract infection: 9	Urinary tract infection: 4
Storage or voiding lower urinary tract symptoms (LUTS)	LUTS: 9 Chronic urinary retention: 4	LUTS: 7 Urge incontinence: 4 Gross haematuria: 5 Transient dysuria: 17 Chronic urinary retention: 3	Transient haematuria: 4 Urge incontinence: 2 Dysuria: 1 Chronic urinary retention: 5	Urinary retention: 4
Acute/ chronic urinary retention		Haemospermia: 2	Anejaculation: 1 Pelvic pain: 2	
Burn, injuries, bleeding		Anejaculation: 16	Aspermia: 1	
Proctitis				
Pain				

Anaesthesia-related complications Thromboembolic disease (phlebitis) Other AEs		Orchitis: 8 Proctitis: 8 Transient anal and perineal pain: 10 Deep phlebitis: 1 Superficial phlebitis: 1		
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 A4: Characteristics of studies for the domain safety for salvage HIFU

Author, year, reference number	Uddin Ahmed, 2012 [25]
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 ⁶⁵

⁶⁵ Data available only on 40 patients

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)	<u>RAND-SF36 at 0m / 6 m (n = 39):</u> 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
Safety-related outcomes	
Intervention-specific mortality	0
Functional outcomes: urinary (dys)function according to	<u>IPSS pre-salvage-HIFU/ 6 m post-salvage-HIFU (n = 39):</u> 8.3 (7)/ 11.6 (9.5), p = 0.06
Functional outcomes: bowel (dys)function according to	NA

Functional outcomes: sexual (dys)function according to	<u>IIEF-5 pre-salvage-HIFU/ 6 m post-salvage-HIFU (n = 43):</u> 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 Storage or voiding lower urinary tract symptoms (LUTS) Acute/ chronic urinary retention Burn, injuries, bleeding Proctitis Pain Anaesthesia-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

List of ongoing and planned studies
Table A5: List of controlled ongoing studies with HIFU for prostate cancer treatment

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	<ul style="list-style-type: none"> • 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. A subject with a histological grading of primary 4 is not permitted for enrolment, • 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 require- 	<p>Primary:</p> <ul style="list-style-type: none"> • 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). <p>Secondary:</p> <ul style="list-style-type: none"> • 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).

Study Identifier	Estimated completion date	Study type	Number of patients	Intervention	Comparator	Patient population	Endpoints
						ments, including HIFU or cryotherapy treatment and all follow up visit requirements through 24 months of follow up.	
NCT00770822	December 2017 (terminated due to lack of inclusions) ⁶⁶	Non-randomised (concurrently) controlled study	466	HIFU (Sonablate)	Brachytherapy	<ul style="list-style-type: none"> • 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)
NCT03348722	November 2019	Non-randomised controlled study (cohort study)	3000	Active surveillance	Radical prostatectomy, radiotherapy, Other radical treatments (HIFU, cryotherapy, others)	<ul style="list-style-type: none"> • Newly diagnosed low risk PCa patients, defined according to the presence of all the following criteria: <ul style="list-style-type: none"> ○ 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 ran- 	Primary: <ul style="list-style-type: none"> • Treatment-Free Survival Secondary: <ul style="list-style-type: none"> • Quality of life

⁶⁶ See: [http://www.eu-focus.europeanurology.com/article/S2405-4569\(15\)00031-0/pdf](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
						dom sampling and ≤ 2 lesions for target biopsies (even if the number of positive samples if >2) <ul style="list-style-type: none"> ○ 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. 	
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: <ul style="list-style-type: none"> ● HRQoL changes over time Secondary: <ul style="list-style-type: none"> ● Urinary symptom score and erectile function over time
DRKS00005179	NA (recruiting planned)	RCT	60	HIFU (Ablatherm [®])	No intervention	<ul style="list-style-type: none"> ● Male, ● 18–80 years, ● High risk patients (PSA<20 ng/ml, Gleason Score ≥ 8) ● Life expectancy ≥ 10 years. 	Primary: <ul style="list-style-type: none"> ● Biochemical disease free survival Secondary: <ul style="list-style-type: none"> ● 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

Risk of bias tables

Table A6: Risk of bias – non-randomised study (matched pair analysis) comparing HIFU versus RT (brachytherapy): Aoun, 2015

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 information 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
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		
<p>2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?</p> <p>If N/PN to 2.1: go to 2.4</p>	<p>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).</p>	<p>PY</p>
<p>2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?</p>	-	N
<p>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?</p>	-	-
<p>2.4. Do start of follow-up and start of intervention coincide for most participants?</p>	-	-
<p>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?</p>	-	-
<p>Risk of bias judgement</p>		Moderate
<p>Optional: What is the predicted direction of bias due to selection of participants into the study?</p>		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
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 <i>and</i> 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
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 <i>measurements</i> within the outcome domain?		N
7.2 ... multiple <i>analyses</i> of the intervention-outcome relationship?		N
7.3 ... different <i>subgroups</i> ?		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 A7: Risk of bias – single-arm studies (IHE-20-Criteria checklist)

Y/N/Partial/Unclear		Van Velthoven, 2016 [24]	Ganzer, 2017[22]	Rischmann, 2017 [23]	Feijoo, 2015 [21]	Ahmed, 2012 [25]
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	<i>Were additional interventions (co-interventions) clearly described?</i>	Yes	Partial	Yes	Yes	Partial
Outcome measure						
10	<i>Were relevant outcome measures established a priori?</i>	Yes	Yes	Yes	Yes	Yes
11	<i>Were outcome assessors blinded to the intervention that patients received?</i>	No	No	No	No	No
12	<i>Were the relevant outcomes measured using appropriate objective/subjective methods?</i>	Yes	Yes	Yes	Yes	Yes
13	<i>Were the relevant outcome measures made before and after the intervention?</i>	Partial	Yes	Yes	Yes	Yes
Statistical analysis						
14	<i>Were the statistical tests used to assess the relevant outcomes appropriate?</i>	No	Yes	Yes	Yes	Yes
Results and conclusions						
15	<i>Was follow-up long enough for important events and outcomes to occur?</i>	Partial	Partial	Partial	Partial	Partial
16	<i>Were losses to follow-up reported?</i>	Yes	Yes	Yes	Yes	Yes
17	<i>Did the study provided estimates of random variability in the data analysis of relevant outcomes?</i>	No	Yes	Yes	Yes	Yes
18	<i>Were the adverse events reported?</i>	Yes	Yes	Yes	Yes	Yes
19	<i>Were the conclusions of the study supported by results?</i>	Unclear	Yes	Yes	Yes	Yes
Competing interests and sources of support						
20	<i>Were both competing interests and sources of support for the study reported?</i>	Partial	No	Yes	Yes	Yes

Table A8: GRADE assessment of primary HIFU matched-pair analysis

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 ⁶⁹	NA (only one trial)	Serious ⁶⁹	Serious ⁶⁷	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 ⁶⁸	NA (only one trial)	Serious ⁶⁹	Serious ⁷⁰	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 ⁶⁸	NA (only one trial)	Serious ⁶⁹	Serious ⁷¹	None	0/70 (0%)	0/70 (0%)	Not estimable	NA	Very low	Critical

⁶⁷ Imprecision was set "serious" for this particular endpoint, since the confidence interval (0.01 to 1.34) indicates considerable harm due to HIFU.

⁶⁸ 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.

⁶⁹ 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.

⁷⁰ 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.

⁷¹ 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.

Functional outcomes: urinary dysfunction (physician reported events) (follow up: median 83 vs. 44 months)												
1	Observational study (matched-pair analysis)	Serious ⁷²	NA (only one trial)	Serious ⁶⁹	Serious ⁷³	All plausible residual confounding would reduce the demonstrated effect	5/69 (7.2%)	2/53 (3.8%)	RR 1.92 (0.39 to 9.51) ⁷⁴	34 more per 1,000 (14 fewer to 359 more)	Very low	Critical
Functional outcomes: sexual dysfunction (events) (follow up: median 83 vs. 44 months)												
1	Observational study (matched-pair analysis)	Serious ⁷⁵	NA (only one trial)	Not serious ⁷⁶	Serious ⁷⁰	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 ⁷⁷	NA (only one trial)	Serious ⁶⁹	Serious ⁷⁸	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 ⁷⁷	NA (only one trial)	Serious ⁶⁹	Serious ⁷⁸	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: [20]

⁷² 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.

⁷³ Imprecision was set "serious" for this particular endpoint, since the confidence interval (0.39 to 9.51) indicates considerable harm due to HIFU.

⁷⁴ Calculated with MedCalc[®] (http://www.medcalc.org/calc/relative_risk.php).

⁷⁵ 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.

⁷⁶ Indirectness cannot be assessed, because study exclusively reported sexual (dys)function for HIFU-patients.

⁷⁷ 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.

⁷⁸ Imprecision was set "serious" for this particular endpoint, because the patient number was too low to detect rare adverse events.

Table A9: GRADE assessment of primary HIFU single-arm studies

Quality assessment							Summary of findings					Importance
							Number of patients		Effect		Quality	
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 ⁷⁹	Not serious	Serious ⁸⁰	Serious ⁸¹	None	0/279 (0.0%)	0/279 (0.0%)	Not estimable	NA	Very low	Critical
Functional outcomes: urinary dysfunction (follow up: 12 months; assessed with usage of pads)												
4	Observational study	Serious ⁷⁹	Not serious	Serious ⁸⁰	Serious ⁸¹	None	2/270 (0.7%)	9/270 (3.3%)	Not estimable	NA	Very low	Critical
Functional outcomes: urinary dysfunction (follow up: range 3 months to 12; assessed with IPSS, Scale from 0 to 26 worse)												
3	Observational study	Serious ⁷⁹	Serious ⁸²	Serious ⁸⁰	serious ⁸¹	None	198 ⁸³	198	Not pooled	NA	Very low	Critical
Functional outcome: sexual dysfunction (follow up: range 3 months to 12; assessed with IIEF-5, Scale from: 0 to 25 worse)												
3	Observational study	Serious ⁷⁹	Not serious	Serious ⁸⁰	Serious ⁸¹	None	NA ⁸⁴	NA	Not pooled ⁸⁵	NA	Very low	Critical

⁷⁹ No control group.

⁸⁰ 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).

⁸¹ Low sample size.

⁸² 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.

⁸³ The number of patients answering the questionnaire pre- and post-treatment.

⁸⁴ The number of patients answering the questionnaire was not available.

⁸⁵ The range of effect: 1.2 to 4

Quality assessment							Summary of findings					Importance
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Number of patients		Effect		Quality	
							Pre-HIFU	Post-HIFU	Relative (95% CI)	Absolute (95% CI)		
Functional outcomes: sexual dysfunction (follow up: 3 months; assessed with physician reported rates of de novo erectile dysfunction)												
3	Observational study	Serious ⁷⁹	Serious ⁸⁶	Serious ⁸⁰	Serious ⁸¹	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 ⁷⁹	Serious ⁸⁷	Serious ⁸⁰	Serious ⁸¹	None	0/273 (0.0%)	15/273 ⁸⁸ (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: [21-24]

⁸⁶ 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.

⁸⁷ 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.

⁸⁸ Number of events in the total number of patients.

Table A10: GRADE assessment of salvage HIFU single-arm studies

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 ⁸⁹	NA (only 1 study)	Serious ⁹¹	Very serious ⁹²	None	0/84 (0.0%)	0/84 (0.0%)	not estimable	NA	Very low	Critical
Functional outcomes: urinary dysfunction (follow up: 6 months; assessed with IPSS)												
1	Observational study	Serious ⁹⁰	NA (only 1 study)	Serious ⁹¹	Very serious ⁹²	None	39 ⁹³	39	NA	NA	Very low	Critical
Functional outcomes: sexual dysfunction (follow up: 6 months; assessed with IIEF-5)												
1	Observational study	Serious ⁹⁴	NA (only 1 study)	Serious ⁹¹	Very serious ⁹²	None	43 ⁹³	43	NA	NA	Very low	Critical
Serious adverse events (follow up: mean 19.8 months; assessed with number of events)												
1	Observational study	Serious ⁸⁹	NA (only 1 study)	Serious ⁹¹	Very serious ⁹²	None	0/84 (0.0%)	55/84 (65.5%) ⁸⁸	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: [25]

⁸⁹ No control group.

⁹⁰ No control group, follow-up data available only for 39 patients (46%).

⁹¹ 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.

⁹² Very low sample size.

⁹³ Number of patients answering the questionnaire pre- and post-treatment.

⁹⁴ No control group, follow-up data available only for 43 patients (51%).

Applicability tables

Table A11: Summary table characterising 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 generalisable 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 salvage HIFU study. 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. There was more harm associated with this older version of the device. 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, local disease recurrence, 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. For local disease recurrence it was often not stated when it was measured. 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. Local disease recurrence and 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 inexperienced surgeons will perform the intervention.

Abbreviations: HIFU high-intensity focused ultrasound, IIEF-5 international index of erectile function, IPSS international prostate symptom score, TURP transurethral resection of the prostate

APPENDIX 2: REGULATORY AND REIMBURSEMENT STATUS

Table A12: 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	<p>Sonablate[®]: transrectal treatment of prostate cancer⁹⁵</p> <p>Sonablate[®] 500: for treatment of primary and focal prostate cancer.⁹⁶</p> <p>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.⁹⁷</p>	<p>Sonablate[®]: >10mm fluid-filled cavities, large reflective surfaces observed in the ablation zone.</p> <p>Metal implants or stents in the urethra.</p> <p>Brachytherapy seeds adjacent to the posterior prostate capsule, the Denonvilliers' fascia, or the rectal wall.</p> <p>Pre-existing inflammatory disease of the colon or rectum.</p> <p>Prior significant rectal surgery.</p> <p>Inability to insert or tolerate a transrectal ultrasound probe.</p> <p>Active urinary tract infection.</p> <p>Urethral stricture.</p> <p>Latex allergy.⁹⁸</p> <p>Sonatherm[®] is not to be used to spare intervening tissue.</p>	Sonablate [®] 500: 2001 ⁹⁹ Sonatherm [®] : March, 2015 ¹⁰⁰	Yes
Sonablate [®] 5	USA	FDA	Sonablate [®]	Sonablate [®] 500: transrectal high	-	Sonablate [®]	yes

⁹⁵ http://sonacaremedical.com/index.php?option=com_content&view=article&id=38&Itemid=36

⁹⁶ <https://www.fusfoundation.org/news/728-sonacares-devices-treat-prostate-cancer-other-uological-conditions>

⁹⁷ <http://sonacaremedical.com/index.php/surgeons/peer-reviewed-library>

⁹⁸ <http://sonacaremedical.com/index.php/surgeons/starting-my-hifu-practice>

⁹⁹ <http://drstevenskinurology.com/blog/hifu-high-intensity-focused-ultrasound-for-prostate-cancer/>

¹⁰⁰ 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
00 Sonatherm®			500: yes Sonatherm®: is 510(k) cleared. ¹⁰¹	intensity focused ultrasound (HIFU) ablation of prostatic tissue ^{102,103}		: Oct, 2015	
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 ¹⁰⁴ .	-	Ablatherm® Maxis : 2000 ^{105,106} Ablatherm® Integrated Imaging: 2005 ¹⁰⁷	yes
Ablatherm®	USA	FDA	Yes	Ablation of the prostate tissue ¹⁰⁸	-	Oct, 2015 ¹⁰⁹	Yes
Focal One®	Europe	CE mark	Yes	Focal therapy of prostate cancer ¹¹⁰ , non-invasive treatment of prostate cancer ¹¹¹		June, 2013 ¹¹²	Yes
Focal One®	USA	FDA	No ¹¹³	-	-	-	EDAP filed for new 510(k) application ¹¹⁴
ExAblate® system	Europe	CE mark	Yes	Treating locally-confined prostate cancer ¹¹⁵	-	December, 2016 ¹¹⁶	Yes

¹⁰¹ <http://sonacaremedical.com/index.php/blog/press-releases/62-us-hifu-announces-name-change-to-sonacare-medical>

¹⁰² <http://sonacaremedical.com/index.php/surgeons/our-products/sonablate-ablation-tool>

¹⁰³ https://www.accessdata.fda.gov/cdrh_docs/pdf16/K160942.pdf

¹⁰⁴ http://www.fusfoundation.org/images/pdf/Prostate_System_Comparison_Chart_Jan2016.pdf

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

¹⁰⁶ http://www.fusfoundation.org/images/pdf/Prostate_System_Comparison_Chart_Jan2016.pdf

¹⁰⁷ http://www.fusfoundation.org/images/pdf/Prostate_System_Comparison_Chart_Jan2016.pdf

¹⁰⁸ https://www.accessdata.fda.gov/cdrh_docs/pdf15/k153023.pdf

¹⁰⁹ https://www.accessdata.fda.gov/cdrh_docs/pdf15/k153023.pdf

¹¹⁰ <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>

¹¹¹ <https://www.medgadget.com/2013/06/focal%E2%80%A2one-robotic-high-intensity-focused-ultrasound-for-prostate-cancer-gets-green-light-in-eu.html>

¹¹² <https://www.edap-tms.com/en/about-edap-tms/a-tradition-of-innovation>

¹¹³ <https://www.edap-tms.com/news/40/71/First-Focal-One-HIFU-Device-in-North-America-First-Focal-One-HIFU-Device-in-North-America>

¹¹⁴ <https://www.edap-tms.com/news/98/151/EDAP-Announces-Filing-of-New-510K>

¹¹⁵ <https://www.massdevice.com/insightecs-exablate-wins-ce-mark-approval-prostate-treatment-japanese-approval-essential-tremor/>

	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	USA	FDA	No	-	-	-	No
TULSA-PRO®	Europe	CE mark	Yes ¹¹⁷	Ablation of prostate tissue ¹¹⁸	-	April, 2016 ¹¹⁹	Yes
TULSA-PRO®	USA	FDA	No ¹²⁰	-	-	-	No: TACT trial is expected to support Profound's FDA application ¹²¹

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

Table A13: Summary of (reimbursement) recommendations in European countries for the technology

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

¹¹⁶ <https://www.insightec.com/news-events/press-releases/2016/insightec-receives-ce-mark-for-the-exablate-prostate-for-treating-locally-confined-prostate-cancer>

¹¹⁷ <http://www.profoundmedical.com/new-tulsa/>

¹¹⁸ <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>

¹¹⁹ <https://globenewswire.com/news-release/2016/05/19/841557/0/en/FDA-Grants-Profound-Medical-Corp-IDE-Approval-for-TULSA-PRO.html>

¹²⁰ <http://www.profoundmedical.com/new-tulsa/>

¹²¹ <http://www.biotuesdays.com/features/2017/3/23/profound-medicals-tulsa-pro-pilot-ous-launch-paving-the-way-for-global-growth>

Country and issuing organisation e.g. G-BA, NICE	Summary of (reimbursement) recommendations and restrictions	Source
Romania	HIFU is used for the treatment of prostate cancer in few private clinics and the treatment is not reimbursed by health insurance.	-
Germany	<p>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 3467 €, which includes between 2 and 11 days of hospital stay.</p> <p>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.</p>	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/
RIZIV, Belgium	There is currently no reimbursement for HIFU in Belgium.	-

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, RIZIV Rijksinstituut voor ziekte- en invaliditeitsverzekering, VASPV State Health Care Accreditation Agency under the Ministry of Health, ZIN Zorginstituut Nederland

APPENDIX 3: CHECKLIST FOR POTENTIAL ETHICAL, ORGANISATIONAL, PATIENT AND SOCIAL AND LEGAL ASPECTS

1. Ethical	
1.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new ethical issues?	Yes
<p>The introduction of the HIFU technology could give rise to ethical issues especially in the low-risk patient group. Keeping in mind that the main goal is to achieve the best balance between cancer control and maintenance of quality of life, a common dilemma arises between standard curative gland therapy, focal therapy and active surveillance for this group of patients.</p> <p>Although there is no consensus yet on candidate selection or on treatment modality, the use of focal therapy has been proposed for low-risk patients with visible lesions at mpMRI and/or significant cancer at biopsy (cancer core length >3 mm and/or Gleason Score 3+4) [23]. Patients not presenting these features are more likely to be harmed through over- or under-treatment. Patients with lower risk could be over-treated whereas for high-risk patients the intervention would carry a higher risk due to a possible inadequately ablated tissue which could cause persistent residual progression and metastasis [20]. Low-risk patients could receive unnecessary radical intervention and experience subsequent side-effects. With the introduction of the technology the side-effects of radical intervention might possibly be avoided with cancer control possibly reached. On the other hand, radical intervention is not indicated for patients with a life expectancy less than 10 years and patients showing contraindications. Furthermore there are patients who do not accept to undergo radical treatment. The new technology might be an additional option for them (besides active surveillance and radiation therapy).</p> <p>With the more accurate diagnosis and increasing screening for prostate cancer, the number of patients diagnosed with very early PCa is expected to increase which give rise to the issue of overtreatment. HIFU being considered as a non-invasive or minimally invasive treatment, it might be used excessively instead of AS which might offer comparable oncological efficacy with a lower adverse event rate [5].</p>	
1.2. Does comparing the new technology to the defined, existing comparators point to any differences that may be ethically relevant?	Yes
<p>Possible ethical issues may arise when comparing the standard medical therapy with HIFU due to the probability to preserve sexual function and continence. This could have physical and psychological consequences for individual patients and their families.</p>	
2. Organisational	
2.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) require organisational changes?	Yes
<p>Introduction of the HIFU technology requires the device and training for the staff. If a hospital plans to set up MRI-guided HIFU, MRI device is also required. Also, one of the HIFU devices, Ablatherm[®] requires plenty of space in an operating room (because the system is built in the treatment table).</p> <p>As not all of the centres will have this technology (especially MRI-guided), patient transportation issues from one place to another may arise.</p>	
2.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be organisationally relevant?	Yes
<p>RP requires longer hospital stay, typically 3 days, whereas HIFU requires 0-1 night spent in hospital.</p> <p>Brachytherapy requires a team composed of an urologist, a radiation oncologist and/or physicist). MRI-</p>	

guided HIFU requires a team composed of an urologist and an MRI-trained radiologist.	
3. Social	
3.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any new social issues?	Yes
The number of localised prostate cancer patients is expected to increase due to better screening and therefore more low to intermediate-risk patients will be detected. The target population for HIFU will hence also increase.	
3.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be socially relevant?	No
4. Legal	
4.1. Does the introduction of the new technology and its potential use/non-use instead of the defined, existing comparator(s) give rise to any legal issues?	Yes
Introduction of the HIFU and comparing it to the defined alternatives rise legal issues concerning a person's rights to choose the optimal treatment and the states' duties to guarantee the right of equality in health care. To assure autonomy of the patient – legal requirements to providing patient with sufficient information about treatment (potential harms) must be met. Informed consent forms together with defined clinical HIFU protocols should be implemented in health care institutions. In order to guarantee equal access to the HIFU for all patients there should be ensured mechanisms of national reimbursement.	
4.2. Does comparing the new technology to the defined, existing comparator(s) point to any differences that may be legally relevant?	Yes
The HIFU technology might possibly be recommended to selected patients. The selection of these patients must be carefully evaluated. One difficulty in the comparative assessment might arise, when different outcome definitions with different states of validation (e. g. for DFS) will be compared between the technologies, or when reduced side effects must be valued against less certainty about oncologic efficacy.	

Appendix 4: 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 μm 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	CCL ≥ 3 mm and/or Gleason ≥ 7 / CCL ≥ 5 mm and/or Gleason ≥ 7
[33] (2014) ^a	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.
^a Definition 4 was used.
^a Publications from the same centre.

Source: Fütterer [65]

For the purpose of transparency, a separate document with comments on the 2nd draft assessment from external experts and the MAH/manufacture(r)s (fact check), as well as responses from authors, is available on the EUnetHTA website.