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Systematic Review of the Efficacy and Safety of High-Intensity Focussed Ultrasound for the Primary and Salvage Treatment of Prostate Cancer

Marisa Warmuth^{a,*}, Tim Johansson^b, Philipp Mad^c

^aLudwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria

^bInstitute of General Practice, Family Medicine and Preventive Medicine, Paracelsus Medizinische Privatuniversität, Salzburg, Austria

^cLudwig Boltzmann Institute for Health Technology Assessment, Vienna, Austria; Kinderklinik Glanzing, Wilhelminenspital der Stadt Wien, Vienna, Austria

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Abstract

Context: High-intensity focussed ultrasound (HIFU) is an emerging minimally invasive treatment option for prostate cancer.

Objective: Our aim was to assess the efficacy and safety of HIFU in both primary treatment of men with localised and locally advanced prostate cancer as well as salvage treatment of men with recurrent prostate cancer following treatment failure of radical prostatectomy or external-beam radiation therapy.

Evidence acquisition: We conducted a systematic literature search for studies conducted on humans and published in either English or German in several databases from 2000 to 2010. In addition, we screened several Web sites for assessments on HIFU in prostate cancer and contacted the manufacturers of the two currently available HIFU devices for supplemental information on HIFU. We included all prospective studies with >50 study participants and assessed their quality using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Evidence synthesis: We identified 20 uncontrolled prospective case series, each of which treated between 58 and 517 patients. These studies were all conducted within the past decade. In total, 3018 patients were treated with HIFU, 93% for primary therapy and 7% for salvage HIFU. For all HIFU procedures, the biochemical disease-free survival rate at 1, 5, and 7 yr, respectively, was 78–84%, 45–84%, and 69%. The negative biopsy rate was 86% at 3 mo and 80% at 15 mo. Overall survival rates and prostate cancer-specific survival rates were 90% and 100% at 5 yr and 83% and 98% at 8 yr, respectively. Adverse events concerned the urinary tract (1–58%), potency (1–77%), the rectum (0–15%), and pain (1–6%). Quality-of-life assessment yielded controversial results.

Conclusions: Applying the GRADE approach, the available evidence on efficacy and safety of HIFU in prostate cancer is of very low quality, mainly due to study designs that lack control groups. More research is needed to explore the use of HIFU in prostate cancer.

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* Corresponding author. Ludwig Boltzmann Institute for Health Technology Assessment, Garnison-gasse 7/20, 1090 Vienna, Austria. Tel. +43 1 236 81 19 14; Fax: +43 1 236 81 19 99.
E-mail address: marisa.warmuth@hta.lbg.ac.at (M. Warmuth).

1. Introduction

Prostate cancer is the most common cancer in men in the European Union. It accounted for more than a quarter (27.1%) of all the reported cancer cases in men in the European Union in 2008 [1]. The estimated incidence of prostate cancer was 110.5 per 100 000, and the mortality rate was 21.1 per 100 000 in 2008. In contrast to the high incidence rate, the mortality rate remains low, reflecting the implementation of population screening measures for prostate cancer on the one hand and the high incidence of localised disease with a favourable prognosis on the other.

The choice of an adequate therapy option for prostate cancer depends on several factors, including tumour stage, prostate-specific antigen (PSA) value, Gleason score, patient's age, concomitant diseases, life expectancy, and patient's preference.

Depending on tumour stage and patient life expectancy, the European Association of Urology (EAU) recommends active surveillance and radical prostatectomy (RP) as standard treatment options for patients with localised prostate cancer [2]. Another option for patients with localised prostate cancer or for locally advanced prostate cancer is radiotherapy, particularly in patients who are unfit for surgery or unwilling to undergo surgery. The combination of radiotherapy with hormonal therapy improves overall survival [2].

The American Urological Association (AUA) recommendations encompass active surveillance, interstitial prostate brachytherapy, external-beam radiation therapy (EBRT), and RP for the treatment of patients with low-risk, intermediate-risk as well as high-risk localised prostate cancer [3]. It is acknowledged, based on one randomised controlled trial comparing watchful waiting and RP [4], that RP may be superior to watchful waiting due to a lower risk of cancer recurrence, cancer-related death, and improved survival.

High-intensity focussed ultrasound (HIFU) was developed in the 1990s and is a minimally invasive treatment option for prostate cancer. Ultrasound waves of high intensity are targeted at prostatic tissue via a transrectally inserted ultrasound probe. Due to thermal and mechanical effects, prostatic tissue is destroyed, leading to coagulation necrosis that is replaced by scar tissue within a few weeks following treatment [5].

Recommendations concerning HIFU in international guidelines are conflicting. Although the medical associations of France [6], Italy [7], and the United Kingdom [8] approve HIFU for the primary and/or salvage treatment of prostate cancer, the EAU [2], the AUA [3], the National Comprehensive Cancer Network [9], the National Collaborating Centre for Cancer of the National Institute for Health and Clinical Excellence in the United Kingdom [10], and the German Association of Urology (Deutsche Gesellschaft für Urologie) [11] do not recommend the routine use of HIFU in prostate cancer. Disapproval mainly stems from overall lack of data, paucity of evidence concerning improved quality of life and long-term survival, lack of long-term follow-up data, and missing comparisons of HIFU with conventional therapy options. The EAU states that focal therapeutic

options such as HIFU are currently not standard therapeutic options for localised prostate cancer and should only be performed within clinical trials, but it emphasises their future potential [2]. Since 2010 the EAU has recommended HIFU as an alternative option, in addition to salvage RP, cryosurgery, and interstitial brachytherapy, for the treatment of recurrent prostate cancer following radiotherapy in patients who are well informed about its experimental nature [2].

Two HIFU devices are currently available, the Ablatherm (EDAP TMS SA, Vaulx-en-Velin, France) and the Sonablate device (Focus Surgery Inc, Indianapolis, IN, USA), which have been in use since 1993 and 1995, respectively [5,12]. Both systems are Conformité Européenne (European Conformity [CE]) marked and are predominantly used in Europe as well as in Japan, whereas in the United States HIFU is still considered experimental and its use is only approved within clinical trials [5,12]. The differences between Ablatherm and Sonablate treatments mainly concern patient positioning, treatment algorithms, imaging, and technical details. Table 1 provides a detailed comparison of the latest types of the two systems that have been employed in studies published in the literature (Ablatherm Integrated Imaging and Sonablate 500) [5,12–15].

The purpose of the present systematic review was to evaluate the evidence on the role of HIFU for the treatment of prostate cancer.

2. Evidence acquisition

2.1. Literature search

We specified the methods of the analysis and inclusion criteria in advance in a protocol. As can be seen in Table 2, we defined inclusion criteria for the literature search using the PICOS (Population, Intervention, Control, Outcome, Study design) approach. We conducted a systematic literature search on January 29, 2010, in the following databases: Medline via Ovid, Embase, Cochrane CENTRAL, and the CRD York databases (DARE, NHS EED, HTA). We combined the MeSH terms *prostatic neoplasms*; *ultrasound*, *high intensity focused*, *transrectal*; and *ultrasonic therapy* with free-text terms, such as *locally advanced/relapsed/recurrent prostate cancer*, *high-intensity focused ultrasound*, and *HIFU*. In addition, we searched for assessments on HIFU in prostate cancer on the following Web sites: Canadian Agency for Drugs and Technologies in Health (<http://www.cadth.ca/index.php/en/home>), National Coordinating Centre for Health Technology Assessment (<http://www.hta.nhsweb.nhs.uk>), National Health Service Institute for Health and Clinical Excellence (<http://guidance.nice.org.uk/>), and World Health Organisation Health Evidence Network (<http://www.euro.who.int/HEN>). The literature search included all studies conducted on humans between 2000 and 2010 and published in English or German and yielded 379 references after discarding duplicates. We contacted the manufacturers of the two currently available HIFU devices, EDAP TMS SA for Ablatherm and UKHIFU for Sonablate, requesting information on HIFU in prostate cancer. The systematic literature search was

Table 1 – Comparison of the two currently available high-intensity focussing ultrasound devices

	Ablatherm Integrated Imaging [6,14,15]	Sonablate 500 [12–15]
Company	EDAP TMS SA, France	Focus Surgery Inc, USA
Since	2005	2001
Approval	Europe: CE mark for the treatment of localised prostate cancer; Australia; Canada; Russia; South Korea	Europe: CE mark for the treatment of pts with primary prostate cancer or recurrent prostate cancer following prior therapy
Table	Integrated table	Standard operating table
Anaesthesia	General, epidural, spinal	General, epidural, spinal
Patient positioning	Right lateral decubitus	Lithotomy or supine
Mode of administration	Transrectal	Transrectal
Software	Automated: Ablaview	Semiautomated
Treatment algorithm(s)	Three	One
Power	Predefined for each treatment algorithm: primary, salvage after EBRT failure, or repeat HIFU	Adjusted manually by user
Treatment probe/transducer	Single-treatment probe containing two ultrasound transducers	Single-treatment probe containing two ultrasound transducers of different focal lengths (either 30/40 mm or 45/50 mm for larger prostate glands)
Frequency	7.5 MHz for imaging/treatment planning; 3 MHz for treatment	4 MHz for imaging/treatment planning and treatment
Focal point	45 mm from crystal	30–50 mm from crystal
Treatment planning	Prostate is divided into a series of blocks	Prostate is divided into treatment regions: anterior, middle, posterior on both right/left side
Ablation volume	Adjustable ablation volume from 19 × 1.7 × 1.7 mm to 26 × 1.7 × 1.7 mm; total: 29–36 mm ³	3 × 3 × 10–12 mm by each acoustic pulse; total: 21–47 mm ³
Ablation temperature	>85 °C	80–98 °C
Imaging	Real time	Real time
Active cooling system	Yes	Yes: Sonachill
Real-time rectal wall distance monitoring	Yes	Yes
Real-time rectal wall temperature monitoring	Yes	Yes
Postoperative treatment	Temporary urinary catheter (urethral/suprapubic), prophylactic antibiotics, analgesics	
Costs		
Device costs	€550 000	€300 000
Maintenance costs	€45 000/yr	€25 000/yr
Disposables	€550: Ablapack	€100

CE = Conformité Européenne (European Conformity); EBRT = external-beam radiation therapy; HIFU = high-intensity focussed ultrasound; pts = patients.

complemented by a hand search on February 12, 2010, using SCOPUS, offering an overall total of 435 references. Appendixes 1–4 display the full electronic search strategy.

2.2. Literature selection

We identified 435 records in our literature search. Two researchers independently screened, assessed, and included the abstracts. Two researchers independently assessed full-text articles for eligibility for inclusion in our review. In cases of disagreement, we achieved consensus through discussion or by involving a third person.

The criteria for inclusion of studies in our systematic review encompassed all prospective studies containing >50 study participants, conducted on humans, and published in English or German between 2000 and 2010. All studies identified that did not meet the inclusion criteria were excluded from our analysis. One review author extracted data from the included studies, and the second author controlled the extracted data regarding completeness and accuracy. In cases of disagreement, we achieved consensus through discussion or by involving a third person.

2.3. Quality of evidence

One researcher assessed the quality of the available evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach, and a second researcher reviewed the evidence tables. According to GRADE, the evidence is graded separately for each important outcome [16]. However, evidence from observational studies should first be graded as low quality. Depending on the quality of the studies, the evidence might be upgraded to moderate or high quality or downgraded to very low quality. Reasons for downgrading the evidence include study limitations, inconsistency of results, indirectness of evidence, imprecision, and publication bias. Upgrading the evidence may be achieved if there is a large or very large magnitude of effect, a dose–response relationship, or if plausible confounders are present that would lead to an underestimation of the treatment effect [16]. The results concerning the efficacy and safety of HIFU for the treatment of prostate cancer are presented separately for primary and secondary therapy for both Ablatherm HIFU and Sonablate HIFU, respectively. Data for HIFU in recurrent prostate cancer are

Table 2 – Inclusion criteria

Population	Men with localised (T1–T2, N0–Nx, M0) and locally advanced (T3–T4, N0–Nx, M0) prostate cancer Men with recurrent prostate cancer after treatment failure of radical prostatectomy or external-beam radiation therapy
Intervention	High-intensity focussed ultrasound Ablatherm (prototypes, Maxis, Integrated Imaging) by EDAP TMS, France, and/or Sonablate (200, 500) by Focus Surgery Inc, USA
Control	Radical prostatectomy with/without dissection of pelvic lymph nodes External-beam radiation therapy (with/without hormone therapy) or interstitial brachytherapy Active surveillance/watchful waiting
Outcomes	
Efficacy	Clinical (surrogate outcomes): PSA kinetics, biopsy results Patient relevant: 5-yr survival, disease-free survival, overall survival, quality of life
Safety	Morbidity: acute/chronic urinary retention, urinary incontinence, urinary tract infection, stricture/stenosis (bladder neck/ureter), erectile dysfunction, rectourethral fistula, chronic pain Mortality
Study design	
Efficacy	All prospective studies, >50 patients
Safety	All prospective studies, >50 patients

PSA = prostate-specific antigen.

sparse, and only data for Ablatherm HIFU (not for Sonablate HIFU) are available in this patient population.

We assessed the available evidence for each important outcome. In addition to surrogate outcomes such as biochemical disease-free survival and negative biopsy rate, patient-relevant outcomes such as overall survival, prostate-cancer specific survival, adverse events, and quality of life were considered.

3. Evidence synthesis

Fig. 1 shows the detailed literature selection process. We identified and included 20 studies that met our inclusion criteria, all of which were prospective case series. We were not able to identify any prospective (randomised) controlled trials in our literature search. Because all the studies were conducted in an uncontrolled manner, we downgraded them

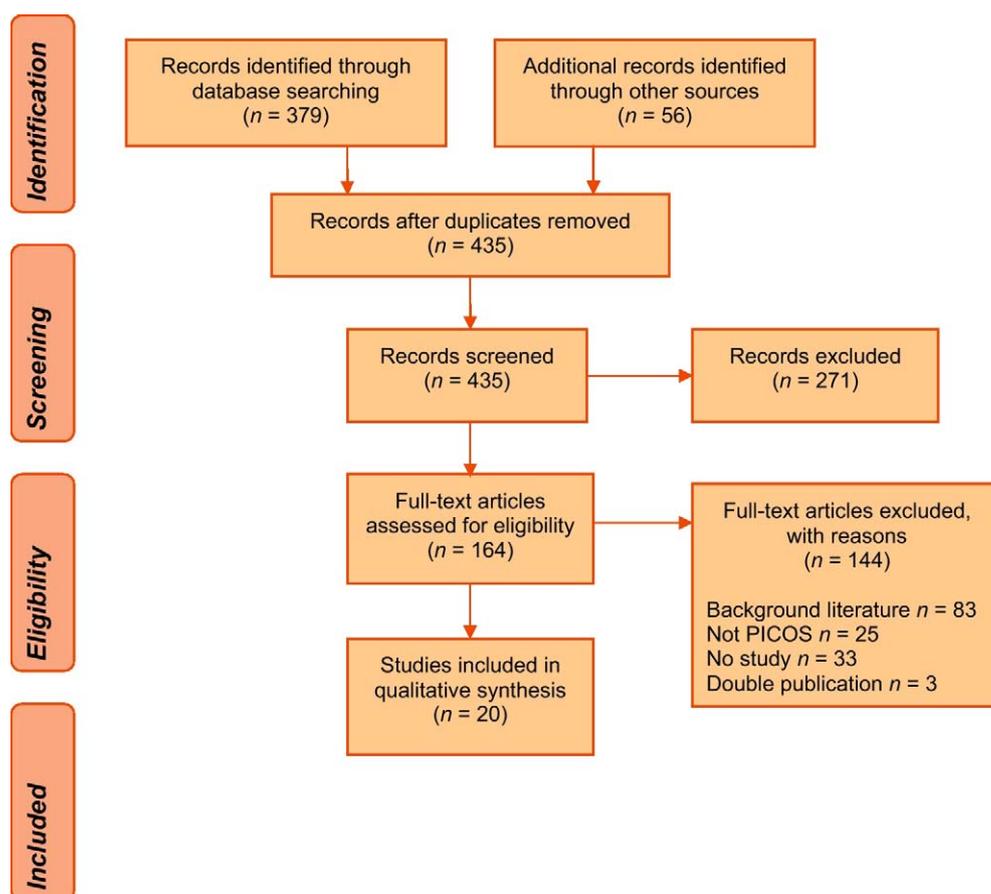


Fig. 1 – Literature selection process (PRISMA flow diagram).

PICOS = Population, Intervention, Control, Outcome, Study design; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

from low quality to very low quality. Further factors lowering the quality of evidence also applied, such as the high likelihood of publication bias or the lack of precise data.

In all studies included in our review, 3018 patients were treated with HIFU, of whom 2794 (93%) underwent HIFU for primary therapy [17–33] and the remaining 227 (7%) underwent salvage HIFU [34–36]. Most patients (56%) undergoing HIFU for primary therapy were treated with the Ablatherm device [18,19,21,24,27,28,33,34]; 44% were treated with the Sonablate device [17,25,26,29–32]. All salvage HIFU treatments were conducted with the Ablatherm device [34–36]. Adverse events concerned the urinary tract (1–58%) [17–36], potency (1–77%) [17–21,23,27–33,35], the rectum (0–15%) [17,19,20,22,23,25,28,30–33,35,36], and pain (1–6%) [18,19,23,27,33–35]. Patient-relevant outcomes such as quality of life were assessed using validated questionnaires. However, these scores either changed little from pre- to post-HIFU treatment or yielded controversial results [17,19–21,25,26,29,33]. For all HIFU procedures, the biochemical disease-free survival rate was between 78% and 84%, 0% and 91%, 20% and 86%, 45% and 84%, and 69% at 1, 2, 3, 5, and 7 yr, respectively [18,25–27,29–32]. The negative biopsy rate was 86% at 3 mo and 80% at 15 mo [18–23,25–30,32–36]. Overall survival rate and prostate-cancer specific survival rate were only reported in 1 of 20 studies and were 90% and 100% at 5 yr and 83% and 98% at 8 yr, respectively [18].

3.1. Ablatherm high-intensity focussed ultrasound

3.1.1. Primary therapy

We identified 11 case series assessing Ablatherm HIFU as a primary therapy option in prostate cancer, which were conducted by four study groups in Germany, France, and the Republic of Korea [18–24,27,28,33,34]. Study characteristics are shown in Table 3. Between 58 and 402 patients with localised prostate cancer (T1–T2, N0–Nx, M0) with a mean age of 66–72 yr were treated with HIFU. In 4 of 11 case series, patients were recruited consecutively [19,23,27,33]. The mean preoperative PSA level was 7–12 ng/ml, Gleason score was ≤7 in most patients, and the mean preoperative prostate volume was 21–37 ml. Between 0% and 43% of men received neoadjuvant androgen-deprivation therapy (ADT), and 65–100% of patients underwent transurethral resection of the prostate (TURP) before or in combination with HIFU. Patients received between one and three HIFU treatments; most patients (57–96%) underwent one treatment. The mean follow-up period varied between 6 and 77 mo.

Table 4 shows the evidence profile of Ablatherm HIFU as a primary therapy option in prostate cancer. The biochemical disease-free survival rate was 66% and 77% after 5 yr [18,27] and 69% after 7 yr [18]. The negative biopsy rate was assessed in all but one study and varied between 65% and 94% [18–23,27,28,33,34]; the point in time of biopsy was not specified. In one case series the negative biopsy rate was 86% at 3 mo [34].

The evidence concerning the patient-relevant outcomes, overall survival, and prostate cancer-specific survival is

Table 3 – Ablatherm high-intensity focussed ultrasound: primary therapy

Study	Blana et al [18]	Poissonnier et al [27]	Colombel et al [34]	Lee et al [24]	Blana et al [19]	Walter et al [33]	Chaussy et al [21]	Thüroff et al [28]	Chaussy et al [20]	Gelet et al [23]	Chaussy et al [22]
Country	DE/FR; 2 centres	FR	FR	KR	DE	DE	DE	DE/FR/NL; 6 centres	DE	FR	DE
Patients, No.	140	227	242	58	146	70	271 (A: prospective; HIFU 96; B: retrospective; TURP + HIFU 175)	402	184	102	65 (A: global, n = NA vs B; selective treatment, n = NA)
Patients, age, yr (range)	M: 70 (45–87)	Ø 69 ± 6	Ø 71 ± 6	Ø 70 ± 6	Ø 70 ± 7	Ø 67 ± 6	A: Ø 66 ± 8; B: Ø 68 ± 7	Ø 70 ± 7	Ø 72 (59–81)	Ø 71 ± 6	NA
Tumour stage	T1a–T2cNxM0	T1–T2	T1cT2	T1–T2	T1–T2N0M0	T1–T2bN0M0	T1–T2c	T1–T2N0–NxM0	T1–T2NxM0	T1b–T2	Localised
Neoadjuvant ADT, % of pts	16	33	NA	29	43	NA	NA	0	NA	8	NA
TURP prior to/combined with HIFU, % of pts	NA	78	100	91	NA	100	65	NA	NA	NA	NA
Follow-up, mo (range)	Ø 77 ± 12	Ø 28 ± 20; M: 21 (12–107)	NA	Ø 14 ± 4	Ø 23 (4–62)	Ø 15 ± 7	A: Ø 19 ± 12; B: Ø 11 ± 6	Ø 14 (0–51)	Ø 6, M: 4 (0–30)	Ø 19 (3–76)	Ø 10 (1–18)

ADT = androgen-deprivation therapy; DE = Germany; FR = France; HIFU = high-intensity focussed ultrasound; KR = Republic of Korea; M = median; NA = not available; NL = Netherlands; Ø = mean plus or minus standard deviation; pts = patients; TURP = transurethral resection of the prostate.

Table 4 – Evidence profile: Ablatherm high-intensity focussed ultrasound

No. of studies/patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors ¹	Level of evidence
2/367	Observational, case series	Serious limitations ² (–1)	No important inconsistency	Direct	66–77 at 5 yr, 69 at 7 yr	Publication bias likely	Very low
Outcome: biochemical disease-free survival rate							
10/1849	Observational, case series	Serious limitations ² (–1)	Important inconsistency	Direct	86 at 3 mo, 65–94 (point in time not specified)	Publication bias likely; lack of precise data	Very low
Outcome: negative biopsy rate							
1/140	Observational, case series	Serious limitations ² (–1)	Only one trial	Direct	90 at 5 yr, 83 at 8 yr	Publication bias likely	Very low
Outcome: overall survival rate							
1/140	Observational, case series	Serious limitations ² (–1)	Only one trial	Direct	100 at 5 yr, 98 at 8 yr	Publication bias likely	Very low
Outcome: prostate-cancer specific survival rate							
4/702–11/1907 ⁴	Observational, case series	Serious limitations ² (–1)	Important inconsistency	Direct	2–58	Publication bias likely	Very low
Outcome: adverse events urinary tract ³							
8/1714	Observational, case series	Serious limitations ² (–1)	Important inconsistency	Direct	18–0	Publication bias likely	Very low
Outcome: adverse events potency ⁵							
1/184–6/969 ⁷	Observational, case series	Serious limitations ² (–1)	Important inconsistency	Direct	0–15	Publication bias likely	Very low
Outcome: adverse events rectum ⁶							
6/927	Observational, case series	Serious limitations ² (–1)	No important inconsistency	Direct	1–6	Publication bias likely	Very low
Outcome: pain							
Outcome: IEFF (30-point scale) No evidence							
4/671	Observational, case series	Serious limitations ² (–1)	Important inconsistency	Direct	Improved by 1–4 points, or worsened by 3 points (baseline vs last follow-up)	Publication bias likely	Very low
Outcome: IPSS (35-point scale)							
3/525	Observational, case series	Serious limitations ² (–1)	No important inconsistency	Direct	Changed by ±1 point (baseline vs last follow-up)	Publication bias likely	Very low
Outcome: IPSS-Quality of Life (6-point scale)							

IEFF = International Index of Erectile Function; IPSS = International Prostate Symptom Score.

¹ Low incidence, lack of precise data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible.

² All observational studies have been downgraded from low quality to very low quality because of case series with lack of control group; further factors lowering the quality of evidence apply, such as the likely occurrence of publication bias.

³ Adverse events urinary tract: bladder neck/urethral stricture/stenosis, prolonged urinary retention, urinary tract infection, urinary incontinence.

⁴ Not all adverse events concerning urinary tract were assessed in all studies.

⁵ Adverse events potency: impotence/erectile dysfunction.

⁶ Adverse events rectum: rectal burn, rectourethral fistula.

⁷ Not all adverse events concerning rectum were assessed in all studies.

scarce because these factors were only assessed in one case series [18]. Adverse events of the urinary tract included bladder neck/urethral stenosis/stricture (2–17%), prolonged urinary retention (3–14%), urinary tract infection (2–58%), and urinary incontinence (2–34%). Adverse events of the

rectum included rectal burn (0–15%) as well as rectourethral fistula (0–3%). In six case series, outcomes in terms of quality of life were assessed using self-administered questionnaires that yielded either little differences from pre- to post-HIFU treatment or controversial results [19–21,23,27,33].

Table 5 – Ablatherm high-intensity focussed ultrasound: salvage therapy

Study	Colombel et al [34]	Gelet et al [36]	Gelet et al [35]
Country	FR	FR	FR
Patients, No.	71	71	82
Patients, age, yr	NA	Ø 67 ± 6	Ø 71 ± 6
Tumour stage	Local recurrence	Local recurrence (T1–T3)	T1–T2
Primary treatment	EBRT	EBRT	EBRT
Neoadjuvant ADT, % of pts	NA	30	9
TURP prior to/combined with HIFU, % of pts	NA	NA	NA
Follow-up, mo (range)	Ø 15	Ø 15 (6–86)	Ø 18

ADT = androgen-deprivation therapy; EBRT = external-beam radiation therapy; FR = France; HIFU = high-intensity focussed ultrasound; NA = not available; Ø = mean plus or minus standard deviation; pts = patients; TURP = transurethral resection of the prostate.

3.1.2. *Salvage therapy*

Ablatherm HIFU as a salvage therapy option in recurrent prostate cancer after EBRT failure was assessed in three case series, all of which were published from one study centre in France [34–36]. Study characteristics are shown in Table 5.

Between 71 and 82 patients were treated with HIFU following recurrence of prostate cancer after EBRT. In one case series patients were recruited consecutively [35]. Mean patient age was 67–71 yr; mean preoperative PSA level was 8 ng/ml, Gleason score was ≤8 in most patients, and

Table 6 – Evidence profile: salvage high-intensity focussed ultrasound

No. of studies/patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors ¹	Level of evidence
Outcome: biochemical disease-free survival rate							
No evidence							
3/224	Observational, case series	Serious limitations ² (–1)	Outcome: negative biopsy rate Important inconsistency	Direct	80 at 15 mo, 78–80 (point in time not specified)	Publication bias likely; lack of precise data	Very low
Outcome: overall survival rate							
No evidence							
Outcome: prostate-cancer specific survival rate							
No evidence							
1/82–3/224 ⁴	Observational, case series	Serious limitations ² (–1)	Outcome: adverse events urinary tract ³ Important inconsistency	Direct	1–35	Publication bias likely	Very low
1/82	Observational, case series	Serious limitations ² (–1)	Outcome: adverse events potency ⁵ Only one trial	Direct	77	Publication bias likely	Very low
3/224	Observational, case series	Serious limitations ² (–1)	Outcome: adverse events rectum ⁶ No important inconsistency	Direct	1–6	Publication bias likely	Very low
1/82	Observational, case series	Serious limitations ² (–1)	Outcome: pain Only one trial	Direct	1	Publication bias likely	Very low
Outcome: IEFF (30-point scale)							
No evidence							
Outcome: IPSS (35-point scale)							
No evidence							
Outcome: IPSS-Quality of Life (6-point scale)							
No evidence							

IEFF = International Index of Erectile Function; IPSS = International Prostate Symptom Score.

¹ Low incidence, lack of precise data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible.

² All observational studies have been downgraded from low quality to very low quality because of case series with lack of control group; further factors lowering the quality of evidence apply, such as the likely occurrence of publication bias.

³ Adverse events urinary tract: bladder neck/urethral stricture/stenosis, prolonged urinary retention, urinary tract infection, urinary incontinence.

⁴ Not all adverse events concerning urinary tract were assessed in all studies.

⁵ Adverse events potency: impotence/erectile dysfunction.

⁶ Adverse events rectum: rectourethral fistula.

Table 7 – Sonablate high-intensity focussed ultrasound: primary therapy

Study	Ahmed et al [17]	Mearini et al [25]	Uchida et al [32]	Muto et al [26]	Uchida et al [31]	Uchida et al [30]	Uchida et al [29]
Country	GB	IT	JP	JP	JP	JP	JP
Patients, No.	172	163	517	70 (A: full ablation 41; B: focal ablation 29)	181	63	72
Patients, age	64 ± 8 (47–88)	M (IQR): 72 (68–75)	M: 68 (45–88)	M: 72 (61–80)	M: 70 (45–88)	M: 71 (45–87)	M: 72 (45–79)
Tumour stage	≤T1c–T3bN0M0	T1c–T3aN0M0	T1c–T3N0M0	T1c–T2N0M0	T1c–T2bN0M0	T1c–T2bN0M0	T1c–T2bN0M0
Neoadjuvant ADT, % of pts	29	0	66	34	52	0	0
TURP prior to/combined with HIFU, % of pts	0	0	NA	NA	NA	0	NA
Follow-up, mo. (range)	0–12 ± 8 (5–25)	M: 24 (12–41)	M: 24 (2–88)	M: 34 (8–45)	M: 18 (4–68)	M: 22 (3–63)	M: 14 (2–24)

ADT = androgen-deprivation therapy; GB = United Kingdom; HIFU = high-intensity focussed ultrasound; IQR = interquartile range; IT = Italy; JP = Japan; M = median; NA = not available; pts = patients; Ø = mean plus or minus standard deviation; TURP = transurethral resection of the prostate.

preoperative prostate volume was between 21 and 35 ml. Neoadjuvant ADT was administered to between 9% and 30% of the men. Patients were treated with HIFU one (41%) to five (1%) times and were followed up for a mean of 15–18 mo.

Table 6 shows the evidence profile of Ablatherm HIFU in the salvage setting in prostate cancer. The negative biopsy rate was 80% at 15 mo in one trial [34] and between 78% and 80% in the remaining studies; the point in time of biopsy was not shown [35,36]. Evidence concerning patient-relevant outcomes is limited to adverse events concerning the urinary tract, such as bladder neck/urethral stricture/stenosis (17%), prolonged urinary retention (6%), urinary tract infection (1–6%), urinary incontinence (7–35%), as well as potency, the rectum, and pain. One case series assessed the quality of life by self-administered questionnaires, but data were not presented [35].

We were not able to identify any evidence concerning the use of Ablatherm HIFU in recurrent prostate cancer following RP.

3.2. Sonablate high-intensity focussed ultrasound

3.2.1. Primary therapy

We retrieved seven case series assessing Sonablate HIFU as a primary therapy option in prostate cancer that were carried out by three study groups in the United Kingdom, Italy, and Japan [17,25,26,29–32]. As shown in Table 7, between 63 and 517 patients were treated with Sonablate HIFU who were recruited consecutively in four case series [25,29,30,32]. Both localised (T1–T2, N0, M0) as well as locally advanced (T3, N0, M0) prostate cancers were treated using the Sonablate device. Median patient age, reported in all but one study, was between 68 and 72 yr [25,26,29–32]. The remaining study reported a mean age of 64 yr [17]. Median PSA level was 5–10 ng/ml in six studies [25,26,29–32]; mean PSA was given in one study and was 8 ng/ml [17]. Gleason score was ≤7 in most patients, and median preoperative prostate volume was 22–33 ml. Between 29% and 66% of men received neoadjuvant ADT. TURP was either not carried out or no information was provided. Patients received one to four HIFU treatments, but most (79–86%) were treated once. Median follow-up was between 14 and 34 mo [25,26,29–32]; mean follow-up was 12 mo as reported in one study [17].

The evidence profile of Sonablate HIFU as a primary treatment option for prostate cancer is shown in Table 8. The biochemical disease-free survival rate was given in six case series and varied between 78% and 84% at 1 yr, 0–91% at 2 yr, 20–86% at 3 yr, and 45–84% at 5 yr [25,26,29–32]. The negative biopsy rate was assessed in five studies [25,26,29,30,32], but the point in time of biopsy was only presented in three of them [25,26,29]. The negative biopsy rate was 19–89% at 6 mo and 77–84% at 12 mo [25,26,29]. There is lack of evidence concerning overall survival and prostate cancer-specific survival. Adverse events reported included urinary tract with bladder neck/urethral stricture/stenosis (4–30%), prolonged urinary retention (1–13%), urinary tract infection (4–24%), and urinary incontinence (1–2%). Impotence/erectile dysfunction and retrograde ejaculation occurred in 20–39% and 1–20% of men, respec-

Table 8 – Evidence profile of Sonablate high-intensity focussed ultrasound

No. of studies/ patients	Study design	Methodological quality	Consistency of results	Directness of evidence	Magnitude of effect, %	Other modifying factors ¹	Level of evidence
6/1066	Observational, case series	Serious limitations ² (–1)	Important inconsistency		78–84 at 1 yr, 0–91 at 2 yr, 20– 6 at 3 yr, 45– 4 at 5 yr	Publication bias likely	Very low
5/885	Observational, case series	Serious limitations ² (–1)	Important inconsistency		19–89 at 6 mo, 77–84 at 12 mo	Publication bias likely	Very low
					Outcome: overall survival rate No evidence		
					Outcome: prostate-cancer specific survival rate No evidence		
2/242–7/1238 ⁴	Observational, case series	Serious limitations ² (–1)	Important inconsistency	Direct	1–30	Publication bias likely	Very low
4/833–5/1005 ⁶	Observational, case series	Serious limitations ² (–1)	Important inconsistency	Direct	1–39	Publication bias likely	Very low
1/72–5/1096 ⁸	Observational, case series	Serious limitations ² (–1)	No important inconsistency	Direct	0–2	Publication bias likely	Very low
					Outcome: pain No evidence		
1/172	Observational, case series	Serious limitations ² (–1)	Only one trial	Direct	Worsened by 6 points (baseline vs 12 mo post HIFU)	No	Very low
4/671	Observational, case series	Serious limitations ² (–1)	No important inconsistency	Direct	Changed by ± 1 point (baseline vs 12 mo post HIFU)	Publication bias likely	Very low
					Outcome: IPSS-Quality of Life (6-point scale) No evidence		

HIFU = high-intensity focussed ultrasound; IEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score.
¹ Low incidence, lack of precise data, strong or very strong association, high risk of publication bias, dose-efficacy gradient, residual confounding plausible.
² All observational studies have been downgraded from low quality to very low quality because of case series with lack of control group; further factors lowering the quality of evidence apply, such as the likely occurrence of publication bias.
³ Adverse events urinary tract: bladder neck/ urethral stricture/ stenosis, prolonged urinary retention, urinary tract infection, urinary incontinence.
⁴ Not all adverse events concerning urinary tract were assessed in all studies.
⁵ Adverse events potency: impotence/ erectile dysfunction, retrograde ejaculation.
⁶ Not all adverse events concerning potency were assessed in all studies.
⁷ Adverse events rectum: rectal burn, rectourethral fistula, stool incontinence.
⁸ Not all adverse events concerning rectum were assessed in all studies.

tively. All case series assessed quality of life by self-administered questionnaires. Results were only presented in four of the seven trials, however [17,25,26,29].

3.2.2. *Salvage therapy*

We were not able to identify any evidence concerning the use of Sonablate HIFU as a salvage therapy option in recurrent prostate cancer.

3.3. *Discussion*

Although HIFU has been used for the treatment of prostate cancer since the 1990s, good-quality evidence concerning its efficacy and safety is still lacking. The available evidence identified in our literature search has some limitations. First,

up-to-date evidence solely stems from uncontrolled case series. Prospective (randomised) controlled trials comparing HIFU with established surgical (RP) and nonsurgical (radiotherapy) treatment options or with no treatment (active surveillance) have not been published. Unlike the framework applied to the investigation of new drugs, at present the development and assessment of surgical innovations takes place in an unstructured and unregulated manner [37]. Taking into consideration the challenges associated with the evaluation of surgical procedures [38], the IDEAL recommendations have recently been proposed to structure the investigation of surgical innovations [39]. The IDEAL model suggests five interconnected stages related to the development and assessment of surgical innovations, namely innovation, development, exploration, assessment, and

long-term study. In addition, the authors present various study designs to overcome obstacles associated with the feasibility of randomised trials as well as potential improvements for reporting [39]. Second, because the 20 case series we identified were only published by seven international study groups, publication bias is very likely. Hence no definite conclusion can be drawn about the overall patient population treated with HIFU so far. Third, in seven case series, patients were treated with various models of either the Ablatherm or Sonablate device within one trial, making a comparison of outcomes difficult even across one study population. Fourth, patients were recruited consecutively in only nine case series, which could introduce selection bias. Further bias could have been introduced by including heterogeneous patient populations with variations in prognostic factors and neoadjuvant treatments, such as hormonal therapy or TURP. Fifth, the number of HIFU treatments varied between one and five. Recurrent HIFU treatment, however, has not been judged as a HIFU failure. Data on long-term follow-up after HIFU treatment are sparse, and the quality of available data is insufficient. In the case series identified, the efficacy of HIFU was mainly assessed using surrogate outcomes, such as biochemical disease-free survival rate and negative biopsy result. It remains questionable whether surrogate outcomes correlate with patient-relevant outcomes such as overall survival, prostate-cancer specific survival, and quality of life. In addition, in the studies identified, biochemical treatment failure was either not defined [17,19,20,22,28,33,34] or defined according to the Phoenix criteria [18,25,32], the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria [21,24,26, 29–31,36], or predefined criteria [23,27,34,35]. Both the Phoenix criteria and the ASTRO criteria have been validated in PSA failure after radiotherapy only. Recently, a new definition, the so-called Stuttgart definition—a PSA increase of 1.2 ng/ml above the PSA nadir value—has been suggested to judge PSA failure following HIFU treatment [40]. However, this definition remains to be validated in prospective trials.

A direct comparison of patient-relevant outcomes between patients undergoing conventional treatment for prostate cancer, such as RP, radiotherapy, or active surveillance, and those undergoing HIFU is not achievable due to lack of comparative studies. Although studies comparing the various treatment options for prostate cancer would be of great value, only one randomised controlled trial comparing RP and watchful waiting has been published so far. It showed that RP is superior to watchful waiting in terms of overall survival, disease-specific survival, and the risk of local and systemic disease progression [4]. However, the available literature indicates that most of the limitations reported for HIFU treatment here also apply for RP, including the radical retropubic prostatectomy (RRP), laparoscopic radical prostatectomy (LRP), and robot-assisted laparoscopic radical prostatectomy (RARP) approach [41–43]. Adverse events associated with RRP, LRP, and RARP are similar to those observed in HIFU treatment. Using a standardised reporting methodology, the overall rate of medical and surgical complications in patients undergoing RRP or LRP has been reported to be

10% and 20%, respectively [44]. However, LRP was associated with a lower incidence of major surgical complications compared with RRP [44]. Furthermore, when applying standardised criteria, early complications were observed in 22% of patients undergoing RARP for clinically localised prostate cancer [45]. Although most patients experienced minor adverse events, about 3% suffered from severe adverse events [45]. It has been shown that the overall complication rate decreases as the surgeon's experience increases [45,46].

In terms of complication rates associated with radiotherapy, about 16% of patients experience significant genitourinary toxicity including cystitis (5%), haematuria (5%), urinary stricture (7%), and urinary incontinence (5%). In addition, approximately 10% of patients suffer significant gastrointestinal toxicity, most often proctitis (8%), followed by chronic diarrhoea (4%) and small bowel obstruction (1%). Leg oedema occurs in about 2% of patients [2].

HIFU as a treatment option for prostate cancer is controversial among urologic experts, which is reflected in the differing guidelines concerning its use over the whole of Europe. However, HIFU is a promising new treatment option for prostate cancer, and its technology has been evolving over the past decade. Nevertheless, considering the biology and natural course of prostate cancer, the technology is too young and the follow-up of published series in the literature is inadequate to assess patient-relevant outcomes.

4. Conclusions

High-quality evidence on the efficacy and safety of HIFU in prostate cancer is still lacking. To assess the true role of HIFU in prostate cancer, (randomised) controlled trials of good quality and sufficient size comparing HIFU with conventional surgical (RP) and nonsurgical (radiotherapy) treatment options or to no treatment (active surveillance) are urgently required. Such studies must include previously overlooked data on patient-relevant outcomes like overall survival, prostate-cancer specific survival, adverse events, and quality of life if they are to be truly meaningful.

Author contributions: Marisa Warmuth had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Warmuth, Johansson, Mad.

Acquisition of data: None.

Analysis and interpretation of data: Warmuth, Johansson.

Drafting of the manuscript: Warmuth.

Critical revision of the manuscript for important intellectual content: Johansson, Mad.

Statistical analysis: None.

Obtaining funding: None.

Administrative, technical, or material support: None.

Supervision: Warmuth.

Other (specify): None.

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Appendix A. Electronic search strategy for Medline via Ovid

```
Database: Ovid MEDLINE(R) <1996 to January Week 3 2010>
Search Strategy:
1 exp Prostatic Neoplasms/ (46006)
2 locally advanced prostate cancer*.mp. (473)
3 locally advanced prostate neoplasm*.mp. (1)
4 relapsed prostate cancer*.mp. (51)
5 relapsed prostate neoplasm*.mp. (0)
6 recurrent prostate cancer*.mp. (301)
7 recurrent prostate neoplasm*.mp. (0)
8 1 or 2 or 3 or 4 or 6 (46019)
9 exp Ultrasound, High-Intensity Focused, Transrectal/ (200)
10 high-intensity focused ultrasound.mp. (640)
11 HIFU.mp. (504)
12 Ablatherm.mp. (32)
13 Sonablate.mp. (18)
14 EDAP.mp. (55)
15 Focus Surgery.mp. (12)
16 exp Ultrasonic Therapy/ (3267)
17 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (3475)
18 8 and 17 (283)
19 limit 18 to yr="2000 - 2010" (261)
20 limit 19 to (humans and (english or german)) (215)
21 from 20 keep 1-10 (10)
22 from 20 keep 1-215 (215)
*****
29.01.2010.
```

Appendix B. Electronic search strategy for Embase

```
Embase
Session Results
No. Query Results Results Date
#25. #24 AND ([english]/lim OR [german]/lim) AND 323 29 Jan 2010
[humans]/lim AND [2000–2010]/py
#24. #14 AND #23 502 29 Jan 2010
#23. #15 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 12,795 29 Jan 2010
#22. 'ultrasound therapy'/exp 12,540 29 Jan 2010
#21. 'focus surgery':df 28 29 Jan 2010
#20. edap:df 69 29 Jan 2010
#19. sonablate 55 29 Jan 2010
#18. ablatherm 77 29 Jan 2010
#17. 'hifu'/exp OR hifu 1,129 29 Jan 2010
#15. 'high intensity focused ultrasound'/exp OR 'high 1,253 29 Jan 2010
intensity focused ultrasound'
#14. #1 OR #2 OR #3 OR #5 OR #6 OR #7 OR #10 OR #11 93,359 29
Jan 2010
#13. 'recurrent prostate neoplasms' 29 Jan 2010
#12. 'recurrent prostate neoplasm' 29 Jan 2010
#11. 'recurrent prostate cancers' 10 29 Jan 2010
#10. 'recurrent prostate cancer' 375 29 Jan 2010
#9. 'relapsed prostate neoplasms' 29 Jan 2010
#8. 'relapsed prostate neoplasm' 29 Jan 2010
#7. 'relapsed prostate cancers' 3 29 Jan 2010
#6. 'relapsed prostate cancer' 59 29 Jan 2010
#5. 'locally advanced prostate neoplasms' 1 29 Jan 2010
#4. 'locally advanced prostate neoplasm' 29 Jan 2010
#3. 'locally advanced prostate cancers' 13 29 Jan 2010
#2. 'locally advanced prostate cancer' 654 29 Jan 2010
#1. 'prostate tumor'/exp 93,338 29 Jan 2010
```

Appendix C. Electronic search strategy for Cochrane CENTRAL

```
Search Name: HIFU
Comments: MEL 2010
Save Date: 2010-01-29 10:47:33

ID Search
#1 MeSH descriptor Prostatic Neoplasms explode all trees
#2 "locally advanced prostate cancer*"
#3 "locally advanced prostate neoplasm*"
#4 "relapsed prostate cancer*"
#5 "relapsed prostate neoplasm*"
#6 "recurrent prostate cancer*"
#7 "recurrent prostate neoplasm*"
#8 (#1 OR #2 OR #4 OR #6)
#9 MeSH descriptor Ultrasound, High-Intensity Focused,
Transrectal explode all trees
#10 "high-intensity focused ultrasound"
#11 HIFU
#12 Ablatherm
#13 Sonablate
#14 EDAP
#15 "Focus Surgery"
#16 MeSH descriptor Ultrasonic Therapy explode all trees
#17 (#9 OR #10 OR #11 OR #12 OR #14 OR #16)
#18 (#8 AND #17)
#19 (#18), from 2000 to 2010
#20 (#19)
```

Appendix D. Electronic search strategy for CRD

```
MeSH Prostatic Neoplasms EXPLODE 1 2 3 4
"locally advanced prostate cancer*"
"locally advanced prostate neoplasm*"
"relapsed prostate neoplasm*"
"relapsed prostate cancer*"
"recurrent prostate cancer*"
"recurrent prostate neoplasm*"
#1 OR #2 OR #6
MeSH Ultrasound, High-Intensity Focused, Transrectal EXPLODE 1 2 3
"high-intensity focused ultrasound"
HIFU
Ablatherm
Sonablate
EDAP
"Focus Surgery"
MeSH Ultrasonic Therapy EXPLODE 1 2
#9 OR #10 OR #11 OR #12 OR #14 OR #16
#8 AND #17
#18 RESTRICT YR 2000 2010
english:la
german:la
#20 OR #21
#19 AND #22
29.01.2010.
```

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