NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of high- intensity focused ultrasound for prostate cancer

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in March 2004.

Procedure name

High-intensity focused ultrasound (HIFU) for prostate cancer.

Specialty societies

British Association of Urological Surgeons*.*

British Society of Interventional Radiology.

Description

Indications:

Prostate cancer (although high-intensity focused ultrasound is also used to treat benign prostate conditions).

Cancer of the prostate gland may cause it to enlarge, resulting in symptoms such as difficulty in urinating, frequent urination, and blood in the urine. The risk of prostate cancer rises with age and it is rare in men younger than 50. It is currently the most commonly diagnosed cancer in men in the UK, with more than 25,000 cases (73.3/100,000 population) reported in 2000.[1]

Stage T1 prostate cancer is microscopic and confined within the prostate gland. Stage T2 tumours are larger but are still within the prostate gland. In stages T3 and T4, the cancer has spread beyond the prostate gland into the surrounding tissues. The Gleason system is used for histological grading of prostate cancer, giving tumours a score between 2 and 10. Low-grade tumours (2 to 4) usually grow slowly and are less likely to spread than high-grade tumours (8 to 10).

Prostate specific antigen (PSA) is a protein produced by both normal and cancerous cells in the prostate gland. In general, the higher the level of PSA the more likely it is

for cancer to be present. The PSA level may be used to monitor response to treatment.

Current treatment and alternatives:

Treatment options depend on the stage of the cancer. Current treatments for localised prostate cancer include watchful waiting, radiotherapy, and radical prostatectomy. Metastatic prostate cancer is usually treated with hormone therapy.

What the procedure involves:

HIFU for prostate cancer is carried out under a spinal or general anaesthetic. With the patient lying on his right side, an endorectal probe incorporating an ultrasound scanner and a HIFU treatment applicator is inserted. This allows the target area to be monitored and defined before being treated. The probe emits a beam of ultrasound, which is focused to reach a high intensity in the target area. Absorption of the ultrasound energy creates an increase in temperature (to between 70ºC and 100ºC), which destroys the tissue within the focal area. A cooling balloon surrounding the probe protects the rectal mucosa from the high temperature. A urethral or suprapubic catheter is used after the procedure.

Transurethral resection of the prostate may be carried out immediately before the HIFU treatment, to reduce the volume of the prostate and minimise the amount of necrotic debris left after the HIFU procedure.

HIFU treatment can be repeated, if necessary, and it does not preclude the use of other therapies to treat local recurrence.

Efficacy:

The main outcomes reported were negative biopsy rates and PSA nadir levels. Some studies reported disease-free survival rates but the criteria used to define disease varied. A systematic review, including 8 case-series, reported a negative biopsy rate of 60% (37/62) in one study with an unspecified length of follow-up, and 80% (75/94) in a study with 3 year follow-up. In three further studies in the review, the proportion of patients without clinical or biochemical evidence of disease ranged from 56% (28/50) at 24 months to 66% (67/102) at 19 months.

Three additional case-series reported negative biopsy rates between 87% (251/288) in a study with mean follow-up of 13 months and 93% (128/137) in a study with mean follow-up of 22.5 months. One of these studies, including 146 patients, also reported disease-free survival rates of 54.0% or 71.5% depending on the criteria used to define disease-free status.

The Specialist Advisors stated that long-term data are needed to establish a reduction in prostate cancer specific mortality.

Safety:

Urinary tract infections and stress incontinence were the most commonly reported complications, affecting between 4% (6/137) and 48% (46/96) and between 8% (9/111) and 23% (23/102) of patients respectively. Rectourethal fistula was reported in between 0.7% (1/137) and 2.7% (3/111) of patients. Four studies reported rates of impotence after the procedure between 24% (75/315) and 100% (62/62) but the proportion of men who were potent before treatment was rarely reported. Other complications included prolonged urinary retention, urge incontinence, urgency, bladder neck stenosis, urethral stenosis, urethritis, prostate abscess, epididymitis, asymptomatic rectal burns and chronic pelvic pain.

The Specialist Advisors listed urinary incontinence, rectal fistula, bowel perforation and erectile dysfunction as potential adverse events but noted that this procedure appears to be safer than alternative radical treatments for prostate cancer. Two Specialist Advisors noted that there were concerns regarding control of local heating and limiting sound energy to the target area.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to high intensity focused ultrasound for prostate cancer. Searches were conducted via the following databases, covering the period from their commencement to February 2004: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and Science Citation Index. Trial registries and the Internet were also searched. No language restriction was applied to the searches.

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with prostate cancer.
Intervention/test	High-intensity focused ultrasound.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on a systematic review including eight case-series studies, summarised in Table 1. Three of the case-series reported in the review have been described in detail in Table 2.[3,4,5,10] Four of the case-series studies in the review appear to be reporting on the same study at different time -points.[7-10]

An additional three case-series studies published after the date of the systematic review are also included in this overview [12,13,14]. Of the additional studies, one is a multi-centre European trial, which probably includes patients described in separate studies published by the individual centres.[12]

Existing reviews on this procedure

A systematic review on the clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer was published in 2003 (Table 1).[2] The review concluded that there was insufficient evidence to draw conclusions regarding the effectiveness of high-intensity focused ultrasound.

Table 1 Summary of key efficacy and safety findings from a systematic review on treatments for early localised prostate cancer

Study Details	Key efficacy findings	Key safety findings	Comments
Hummel et al., 2003[2] Systematic review Literature search date: February 2002 8 case-series studies on HIFU included: • Beerlage et al., 1999 (n = 111, The Netherlands and Germany)[3] • Chaussy and Thüroff, 2000 (= n = 184, Germany)[4, 5] • Chaussy and Thüroff, 2001 (n = 184, Germany)[6] • Gelet et al., 1996 (n = 14, France)[7] • Gelet et al., 1999 (n = 50, France)[8] • Gelet et al., 2000 (n = 82, France)[9] • Gelet et al., 2001 (n = 102, France)[10] • Kiel et al., 2000 (n = 62, Germany)[11]	Negative biopsy: • 60% (no follow-up specified) (Beerlage et al) • 80% over 3 years (Chaussy & Thüroffl) No evidence of disease (biochemical): • 55% (no follow-up specified) (Beerlage et al) • 61% over 3 years (Chaussy & Thüroff) No evidence of disease (clinical or biochemical): • 56% at 24 months – 66% at 19 months (overall) (Gelet et al) 40% – 83% at 17 or 19 months (according to pre-treatment risk group) (Gelet et al) • 68.7% over 15-month median follow-up (Kiel et al)	Postoperative complications including rectourethral fistulae, urethral stenosis and stress incontinence: 12% (Beerlage et al) Stress incontinence: 13% (Gelet et al) Total incontinence: 4% (Gelet et al) Loss of potency: 23% (Gelet et al)	Small study populations. Most of the series include patients who have also had some hormonal deprivation therapy, or who are undergoing HIFU as a salvage procedure. Short follow-up periods. “Insufficient evidence to draw conclusions regarding the effectiveness of this procedure.”

Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for prostate cancer (1)

Study details	Key efficacy findings	Key safety findings	Comments
Beerlage H et al., 1999[3] The Netherlands and Germany Case-series 111 patients • 49 selective treatments • 62 global treatments (whole prostate) 14 additional patients were treated with HIFU before a radical prostatectomy to evaluate effect of HIFU on prostate tissue Mean follow -up: 12 months (range 6 to 27 months) Inclusion criteria: patients with biopsy-proven prostate cancer, clinical stage T1–-3 without metastasis, PSA less than 25 ng/ml, unfit or unwilling to undergo radical prostatectomy, with life expectancy exceeding 5 years.	Negative biopsy and PSA < 4 ng/ml (Complete response): selective treatment = 25%, global treatment = 60% Negative biopsy and PSA >4 ng/ml (Partial response): selective treatment = 3%, global treatment = 8% Positive biopsy and PSA <4 ng/ml (Partial response): selective treatment = 37%, global treatment = 26% Positive biopsy and PSA >4 ng/ml (Failure): selective treatment = 35%, global treatment = 6% Local control (complete or partial response): selective treatment = 65%, global treatment = 94% PSA nadir < 0.5 ng/ml: selective = 19%, global = 55% PSA nadir 0.5 to 4 ng/ml: selective = 50%, global = 36% PSA nadir > 4 ng/ml: selective = 30%, global = 9% Focus of vital tumour seen on histological examination after HIFU and prostatectomy = 28.6% (4/14)	**Complications:** Rectourethral fistula = 2.7% (3/111) Urethral stenosis = 0.9% (1/111) Stress incontinence = 8.1% (9/111) Impotence = 100% (62/62) after global treatment but only a small minority of men were potent prior to procedure	This study is included in the systematic review. [2] Method of patient recruitment not clear. Study partially funded by EDAP-Technomed, Lyon, France – provided equipment. Patient group may also be included in Thüroff S et al., 2003.[12]

Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for prostate cancer (2)

Study details	Key efficacy findings	Key safety findings	Comments
Chaussy C and Thüroff S, 2000[4,5] Germany 1996 – 1999 Case -series 315 patients • 184 patients with local disease Mean age: 72 years (range 59 to 81 years) Mean follow -up: 193 days (range 0 to 903 days) Inclusion criteria: patients unsuitable for surgery with biopsy-proven localised prostate cancer of any Gleason grade, a gland volume of < 30 cc, no calcifications > 5 mm, a total PSA concentration < 20 ng/ml, a life expectancy of at least 5 years and normal rectal anatomy. In addition to patients with local disease, some patients were treated for local recurrence and some for local adjuvant debulking.	Negative biopsy: • 2.25 MHz = 40% (36/90) • 3.0 MHz = 80% (75/94) PSA nadir < 4 ng/ml: 97% (178/184) PSA nadir < 0.5 ng/ml: 61% (112/184)	**Complications**: Rectourethral fistula = 1.3% (4/315) Stress incontinence grade 1 = 9.8% (31/315) Stress incontinence grade 2 = 1.6% (5/315) Stress incontinence grade 3 = 1.0% (3/315) Urge/incontinence = 2.9% (9/315) Urgency = 14.3% (45/315) Bladder neck stenosis = 3.5% (11/315) Urethral stenosis = 2.2% (7/315) Urinary tract infection = 24.8% (78/315) Epididymitis = 6.7% (21/315) Prostatitis = 0.3% (1/315) Prostate abscess = 0.6% (2/315) Urethritis = 2.9% (9/315) Rectal wall burn (asymptomatic) = 20.6% (65/315) Perineal discomfort = 9.2% (29/315) Total impotence = 23.8% (75/315)	This study is included in the systematic review. [2] Method of patient recruitment not clear. Patient group may also be included in Thüroff S., 2003.[12] Short follow -up. Single injection of LHRH agonist given to 48% of patients prior to procedure. 2.25 MHz without rectal cooling used between April 1996 and Oct 1997 (learning curve), 3.0 MHz with rectal cooling used from Nov 1997 to Apr 1999. Efficacy data is presented for 184 patients with localised disease only, safety data is presented for all 315 patients. Complications decreased after treatment was modified during the study period. Only minor complications were seen in the last 100 patients to be treated.

Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for prostate cancer (3)

Study details	Key efficacy findings	Key safety findings	Comments
Gelet A et al., 2001[10] France 1993 – 1998 Case-series 102 patients Mean age: 71 years (range 55 to 86 years) Mean follow -up: 19 months (range 3 to 76 months) Inclusion criteria: Patients with prostate cancer clinical stage T1b, T1c or T2, positive biopsy regardless of Gleason grade, PSA < 20ng/ml, negative preoperative bone scan and unsuitable for radical prostatectomy. Watchful waiting was either not indicated or refused. 8 patients with local recurrence after radiotherapy included.	At last follow -up: Negative biopsy: 75% (76/102) **Disease-free survival**: Overall = 66% Initial PSA ≤ 10 ng/ml = 73% Initial PSA > 10 ng/ml = 50%, p =0.02 Gleason score 2 – 6 = 81% Gleason score 7 – 10 = 46%, p <0.001 1 – 4 positive samples in pre-treatment sextant biopsy = 68% 5 – 6 positive samples in pre-treatment sextant biopsy = 40%, p =0.01 Failure defined as any positive biopsy regardless of PSA levels, or 3 successive increases of the PSA level with a PSA velocity ≥ 0.75 ng/ml/year for patients with negative biopsies	**Complications:** Impotence = 61% (25/41) Stress incontinence grade 1 = 9% (9/102) Stress incontinence grade 2 = 10% (10/102) Stress incontinence grade 3 = 4% (4/102) Prostate urethra stenosis = 17% (17/102) Febrile urinary infection = 8% (8/102) Persistent urinary retention = 5% (5/102) Transient perineal pain = 2% (2/102) Rectourethral fistula = 1% (1/102)	This study is included in the systematic review. [2] Consecutive recruitment. Some patients with very short follow -up. Losses to follow -up not clearly described. Continence and potency were evaluated using a self-administered questionnaire. Some patients may also be included in Thüroff S., 2003.[12]

Table 3 Summary of key efficacy and safety findings on high-intensity focused ultrasound for prostate cancer (4)

Study details	Key efficacy findings	Key safety findings	Comments
Thüroff S et al., 2003[12] Case series Six European sites – France, Germany and The Netherlands 1995 – 1999 402 patients Mean age: 69.3 years Mean follow -up: 407 days 52.7% (212/402) patients with 6 month follow -up Inclusion criteria: Patients with biopsy-proven localised prostate cancer who were not suitable candidates for radical prostatectomy.	**Negative biopsy:** Overall = 87.2% (251/288) Prostate volume ≤ 40cc = 88.4% Prostate volume > 40cc = 85.0%, p = not significant Partial treatment = 87.2% Complete treatment = 91.7%, p = not significant Low- risk patients (stage T1-2a and PSA ≤ 10 ng/ml and Gleason score ≤ 6) = 92.1% Intermediate risk patients (stage 2b or PSA between 11 and 20, or Gleason score 7) = 86.4% High risk patients (stage T2c or PSA >20 ng/ml or Gleason score ≥ 8) = 82.1%, p = not significant **Mean nadir PSA (ng/ml) for patients with 6 month follow -up (n = 212)**: Overall = 1.8 Prostate volume ≤ 40cc = 1.5 Prostate volume > 40cc = 2.9, p = 0.0001 Partial treatment = 1.8 Complete treatment = 1.4, p = 0.016 Low- risk patients = 1.3 Intermediate- risk patients = 1.4 High- risk patients = 3.1, p = not significant Nadir PSA defined as the lowest concentration measured after the last HIFU session.	**Complications:** Rectourethral fistula = 1.2% (5/402) Stress incontinence grade 1 = 10.6% (43/402) Stress incontinence grade 2 = 2.5% (10/402) Stress incontinence grade 3 = 1.5% (6/402) Urinary tract infections = 13.8% (56/402) Prolonged urinary retention = 8.6% (35/402) At follow -up: Urethral stenosis = 3.6%	European Multicentric Study – prospective, multi-centre, open-labelled, uncontrolled clinical trial. Trial recruited patients between 1995 and 2000. This report presents interim analysis for patients recruited up to 1999. It is likely that patient groups from this study have also been described in separate reports. [4-11, 13] 71.6% (288/402) patients assessable for biopsy results. Changes in clinical procedure and technical protocols over the course of the study. Mean 1.47 sessions/patient. To reduce post-treatment retention, a transurethral resection of the prostate (TURP) is now being performed immediately prior to HIFU.

Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for prostate cancer (5)

Study Detailsdetails	Key efficacy findings	Key safety findings	Comments
Chaussy C and Thüroff S, 2003[13] Germany Case -series 271 patients • 96 treated with HIFU only • 175 treated with HIFU preceded by transurethral resection of the prostate (TURP) Mean age: • HIFU = 65.8 years • TURP and HIFU = 68.4 years Mean follow -up: • HIFU = 18.7 months • TURP and HIFU = 10.9 months Inclusion criteria: Clinically organ-confined prostate cancer with initial PSA level at diagnosis ≤ 15 ng/ml.	Retreatment rate: • HIFU = 25% • TURP and HIFU = 4% Negative biopsy after first HIFU: • HIFU = 66.3% • TURP and HIFU = 70.6% Negative biopsy at last follow-up: • HIFU = 87.7% • TURP and HIFU = 81.6% Mean PSA nadir 15 weeks after treatment (ng/ml): • HIFU = 0.48 • TURP and HIFU = 0.26 Stable PSA at last follow-up: • HIFU = 84.2% • TURP and HIFU = 80.0%	Incontinence grade 1: • HIFU = 9.1% • TURP and HIFU = 4.6%, $p < 0.05$ • Incontinence grade 2 : • HIFU = 6.3% • TURP and HIFU = 2.3% • Urinary tract infections: • HIFU = 47.9% • TURP and HIFU = 11.4%, $p < 0.001$ Additional deobstruction procedures (mainly for the removal of necrotic debris or bladder neck stenosis): • HIFU = 27.1% • TURP and HIFU = 8.0%	Method of patient recruitment not clear. Short follow -up in TURP and HIFU group. Same protocol for HIFU used for all patients and throughout study period. PSA stability assessed according to the 1997 American Society for Therapeutic Radiology and Oncology (ASTRO) definition. Some patients may also be included in Thüroff S., 2003.[12]

Table 2 Summary of key efficacy and safety findings on high-intensity focused ultrasound for prostate cancer (6)

Study Detailsdetails	Key efficacy findings	Key safety findings	Comments
Blana A et al., 2004[14] Germany 1997 – 2002 Case -series 146 patients Mean age: 66.9 years Mean follow-up: 22.5 months (range 4 to 62 months) Inclusion criteria: Clinical stage T1—-T2 N0M0 biopsy-proven localised prostate cancer, serum PSA level < 15 ng/ml, and Gleason score 7 or less. All patients were unsuitable for radical prostatectomy or unwilling to risk the potential morbidity of the operation.	At follow up: Negative biopsies: 93.4% (128/137) PSA nadir < 0.1 ng/ml: 56% (77/137) PSA nadir < 0.5 ng/ml: 83% (114/137) PSA nadir < 1.0 ng/ml: 92% (126/137) PSA level > 4.0 ng/ml: 1.5% (2/137) Disease-free survival rate: Event occurrence defined as any positive biopsy, and/or a PSA rise of greater than 0.2 ng/ml = 54.0% Event occurrence defined as any positive biopsy, and/or a PSA rise of greater than 0.4 ng/ml = 71.5%	**Complications:** Rectourethral fistula = 0.7% (1/137) Stress incontinence grade 1 directly after procedure = 10.2% (14/137) Stress incontinence grade 1 at last follow -up = 5.8% (8/137) Urinary tract infection = 4.8% (6/137) Infravesical obstruction = 11.7% (16/137) Chronic pelvic pain = 1.5% (2/137) Postoperative impotence noted in 52.7% of patients who were potent preoperatively (number not stated)	Consecutive recruitment. 6.2% (9/146) lost to follow -up: 7 patients had no control biopsy and 2 patients had no follow -up owing to other medical problems. Mean 1.17 sessions/patient. Disease-free survival rate reported using two different criteria for defining an event.. Prototype device used prior to Oct 2000.

Abbreviations used: HIFU = high intensity focused ultrasound, PSA = prostate specific antigen, TURP = transurethral resection of the prostate

Validity and generalisability of the studies

Different criteria are used for determining response to treatment and for defining disease-free status, which makes it difficult to compare efficacy.

Treatment protocols varied within and between studies and some of the earlier patients were treated with prototype devices, making it difficult to generalise about safety outcomes.

The study populations consist mainly of patients with localised prostate cancer who were not candidates for radical prostatectomy.

None of the studies reported a mean follow-up period longer than two 2 years.

Patients included in the multicentre European study are also likely to be included in the separate studies published by the individual centres. There is considerable overlap between the studies and it is difficult to ascertain the total number of patients treated overall.

Some studies reported that a transurethral resection of the prostate was performed immediately prior to the high intensity focused ultrasound treatment, in order to reduce postoperative urinary retention.

Specialist Advisors' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

The Specialist Advisors commented that this is an experimental procedure and that longer term data is needed before efficacy can be established.

Issues for consideration by IPAC

None other than those identified above.

References

1 National Statistics. Cancer statistics registrations Series MB1 no. 31. London: Office for National Statistics, 2003.

2 Hummel S, Paisley S, Morgan A, Currie E, and Brewer Net al. Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review. *Health Technology Assessment* 2003; Vol.7: No. 33.

3 Beerlage HP, Thüroff S, Debruyne FMJ, Chaussy C, and de la Rosette JJMCHet al. Transrectal high-intensity focused ultrasound using the Ablatherm device in the treatment of localized prostate carcinoma. *Urology* 1999; 54: 273 – 277.

4 Chaussy C, and Thüroff S. High-intensity focused ultrasound in prostate cancer: results after 3 years. *Molecular Urology* 2000; 4: 179 – 182.

5 Thüroff S, and Chaussy C. High-intensity focused ultrasound: complications and adverse events. *Molecular Urology* 2000; 4: 183 – 187.

6 Chaussy C, and Thüroff S. Results and side effects of high-intensity focused ultrasound in localized prostate cancer. *Journal of Endourology* 2001; 15: 437 – 440.

7 Gelet A, Chapelon JY, Bouvier R, Souchon R, Pangaud C, Abdelrahim AF, et al. Treatment of prostate cancer with transrectal focused ultrasound: early clinical experience. *European Urology* 1996; 29: 174 – 183.

8 Gelet A, Chapelon JY, Bouvier R, Pangaud C, and Lasne Yet al. Local control of prostate cancer by transrectal high intensity ultrasound therapy: preliminary results. *The Journal of Urology* 1999; 161: 156 – 162.

9 Gelet A, Chapelon JY, Bouvier R, Rouvière O, Lasne Y, Lyonnet D, et al. Transrectal high-intensity focused ultrasound: minimally invasive therapy of localized prostate cancer. *Journal of Endourology* 2000; 14: 519 – 528.

10 Gelet A, Chapelon JY, Bouvier R, Rouvière O, Lyonnet D, and Dubernard JMet al. Transrectal high intensity focused ultrasound for the treatment of localized prostate cancer: factors influencing the outcome. *European Urology* 2001; 40: 124 – 129.

11 Kiel HJ, Wieland WF, and Rossler W. Local control of prostate cancer by transrectal HIFU-therapy. *Archivo Italiano di Urologia, Andrologia* 2000; 72: 313 – 319.

12 Thüroff S, Chaussy C, Vallancien G, Wieland W, Kiel HJ, Le Duc A, et al. High-intensity focused ultrasound and localized prostate cancer: efficacy results from the European multicentric study. *Journal of Endourology* 2003; 17: 673 – 677.

13 Chaussy C, and Thüroff S. The status of high-intensity focused ultrasound in the treatment of localized prostate cancer and the impact of a combined resection. *Current Urology Reports* 2003; 4: 248 – 252.

14 Blana A, Walter B, Rogenhofer S, and Wieland WF. High-intensity focused ultrasound for the treatment of localized prostate cancer: 5-year experience. *Urology* 2004; 63: 297–-300.

Appendix A: Additional papers on high intensity focused ultrasound for prostate cancer not included in the summary tables

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Thüroff S, and Chaussy C. Transrectal focused ultrasound (HIFU) in prostate cancer. *European Urology Supplements* 2003; 1: 135	576 patients Mean follow - up between 28.6 weeks and 59.7 7 weeks	Case -series Conference abstract	Negative biopsy rate for localised cancers (n =396): 74.4% – 93.5% depending on disease risk level
Gelet A, Poissonnier L, Chapelon JY, Bouvier R, Rouviere O, Lyonnet D, et al. High intensity focused ultrasound for the treatment of localized prostate cancer: efficacy and impact on sexual function. *Andrologie* 2003; 13: 242 – 251.	Group 1: - 120 patients with T1- T2 prostate cancer, PSA <10 ng/ml Group 2: - 167 patients with PSA < 30 ng/ml	Case -series Article in French. Data from English abstract only	Treatment improved from 2000 onwards with combination of TURP. Disease-free survival rates: Group 1 = 76.9% Group 2 = 66%
Chapelon J, Rouviere O, Bouvier R, Dubernard J, and et al.Gelet A. Localized prostate cancer treated with high-intensity focused ultrasound (HIFU): 5-year results. *Ultrasound in Medicine and Biology* 2003; 29: S40 – 41.	245 patients 24 month mean follow - up	Case -series Conference abstract	Disease-free survival: 55.6% – 76.7% depending on disease risk level
Conti G, Paulesu A, Nespoli R, Lancini V, and Comeriet al G. High intensity focused ultrasound (HIFU) for the treatment of localized prostate cancer. *Urology Supplements* 2003; 1: 135	157 patients	Case -series Conference abstract	At 6 months: 79% PSA nadir <0.5 ng/ml. nNegative biopsies 87% (88/101)
Chaussy and Thüroff S. High-intensive focused ultrasound in localized prostate cancer. *Journal of Endourology* 2000; 14: 293 – 299.	65 patients 10 month mean follow - up	Case -series	Residual cancer in 35% patients treated selectively and in 17% with global treatment.
Madersbacher S, Pedevilla M, Vingers L, Susani M, and Marberger Met al. Effect of high-intensity focused ultrasound on human prostate cancer *in vivo*. *Cancer Research* 1995; 55: 3346 – 3351.	29 patients 12 month follow -up	Case -series Histological effects of HIFU	Coagulative necrosis seen within target area.
Sanghvi NT, Gardner TA, and Koch MO. High-intensity focused ultrasound for treatment of organ-confined (T1/T2) prostate cancer. *Ultrasound in Medicine and Biology* 2003; 29: S102.	20 patients 30-day follow - up	Case -series Conference abstract	1 patient with positive biopsy at 6 months No rectal injuries
Uchida T, Sanghvi NT, Gardner TA, Koch MO, Ishii D, Satoh T, et al. Transrectal high-intensity focused ultrasound for treatment of patients with stage T1b-2N0M0 localized prostate cancer: a preliminary report. *Urology* 2002; 59: 394 – 399.	20 patients 13.5 month mean follow - up	Case -series	100% (20/20) postoperative negative biopsies 5% (1/20) rectourethral fistula 10% (2/20) urethral stricture 5% (1/20) prolonged urinary retention
Beerlage HP, van Leenders GJLH, Oosterhof GON, Witjes JA, Ruijter ET, van de Kaa C, et al. High-intensity focused ultrasound (HIFU) followed after one to two weeks by radical retropubic prostatectomy: results of a prospective study. *Prostate* 1999; 39: 41 – 46.	9 patients	Case -series Histological effects of HIFU	Incomplete tissue destruction at dorsal side – small residual tumours seen in 22% (2/9) patients.

Appendix B: Literature search for high intensity focused ultrasound for prostate cancer

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in EMBASE, Current Contents, PreMedline and all EMB databases.

For all other databases a simple search strategy using the key words in the title was employed.

1. PROSTATE/
2. high intensity focused ultrasound.mp.
3. exp ULTRASOUND, HIGH-INTENSITY FOCUSED, TRANSRECTAL/
4. HIFU.mp.
5. prostate.mp. [mp=ti, ab, ot, rw, sh]
6. 1 or 5
7. 2 or 3 or 4
8. 6 and 7