NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of focal therapy using high-intensity focused ultrasound for localised prostate cancer

Treating prostate cancer using high-intensity ultrasound delivered to targeted areas of the prostate

The prostate is a small gland near a man's bladder. Symptoms of localised prostate cancer include difficulties in passing urine, although the disease is often diagnosed before symptoms develop. Focal therapy using high-intensity focused ultrasound aims to find and destroy only the cancerous parts of the prostate, avoiding treatment of healthy tissue. High-intensity ultrasound is delivered to the tumour areas, which are destroyed through heating. The procedure aims to lower the risk of side effects that can occur when radical treatment is given to the whole of the prostate gland (such as loss of bladder control and sexual function).

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make 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 June 2011.

Procedure name

- Focal therapy using high-intensity focused ultrasound (HIFU) for localised prostate cancer

Specialty societies

- British Association of Urological Surgeons

Description

Indications and current treatment

Symptoms of localised prostate cancer include difficulty in passing urine, although the condition is often diagnosed at an asymptomatic stage.

Treatment options for patients with localised prostate cancer include active surveillance, radical prostatectomy, external beam radiotherapy, brachytherapy, and ablation of the whole gland using cryotherapy or HIFU. All radical treatment options are associated with substantial risks of sexual, urinary or bowel dysfunction. Focal therapy using HIFU is intended to be used in patients with localised prostate cancer – specifically patients with tumours that are confined to one prostatic lobe.

Gleason Score: The Gleason score (1–10) is used to grade prostate cancer to aid management decisions. It is based on the degree of cellular differentiation. Higher values (particularly > 7) indicate worse prognosis.

What the procedure involves

Imaging and biopsy mapping studies are used to confirm that the tumour is suitable for focal therapy and to show its precise location. With the patient under local or general anaesthesia, the bladder is catheterised using a supra-pubic catheter and the HIFU probe is inserted transrectally. Real-time ultrasound imaging guidance is used to position the probe and to monitor the procedure. Pulses of HIFU are directed at the targeted part of the prostate, inducing tumour necrosis by a thermal effect and causing cavitation (which can be visualised by ultrasound to assess the adequacy of treatment) until satisfactory ablation of the target area is judged to have occurred.

After treatment patients are usually followed up regularly with prostate-specific antigen (PSA) measurements and repeated biopsies to detect recurrence.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to focal therapy with high-intensity focused ultrasound for localised prostate cancer.

Searches were conducted of the following databases, covering the period from their commencement to 24 June 2011: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection 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 were 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, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with localised prostate cancer.
Intervention/test	Focal therapy with 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 approximately 60 patients from 3 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on focal therapy with high-intensity focused ultrasound for localised prostate cancer

Abbreviations used: HIFU, high-intensity focused ultrasound; IPSS, international prostate symptom score; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TMN, tumour nodes metastases; TNM system: NO, the cancer has not spread to any lymph nodes; MO, the cancer has not spread beyond the regional lymph nodes; TRUS, transperitoneal ultrasound ; TURP, transurethral resection of the prostate

Study details	Key efficacy findings	Key safety findings	Comments
El Fegoun 2011[1] **Case series** France Recruitment period: 1997–2000 Study population: men with localised prostate cancer n = **12** Age: mean 70 years Sex: 100% male Patient selection criteria: men with PSA ≤10ng/ml, ≤3 positive biopsies with only 1 lobe involved, clinical stage ≤T2a, Gleason score ≤7 with no predominant pattern, absence of lymphadenopathy on CT scan and negative bone scan. Technique: Patients underwent focal HIFU (Ablatherm, EDAP-TMS Vaux en Velin, France) under general anaesthesia using a 2.5 and 3.0 MHz transducer. The sphincter was always avoided and TURP was offered to patients with large prostate volumes. The median procedure time was 69 minutes and the median number of shots was 374 (161–533). Follow-up: **median 10.6 years**	Number of patients analysed: **12** *Survival* Overall survival was 83% (10/12) and cancer-specific survival was 100%. Two patients died of heart failure. Recurrence-free survival was 90% at 5 years and 38% at 10 years. *Treatment failure* (Defined as any positive biopsy and/or need for salvage therapy as indicated by rising PSA/biochemical failure) Treatment failure was observed in 5 patients: 1 was subsequently managed with focal therapy HIFU and 4 with androgen deprivation therapy. All recurrent patients were alive at between 9.5 and 11 years of follow-up (100%). *Biopsy* - 6 patients (50%) had a pre-procedure apical positive biopsy; 3 (25%) of these patients had a further positive biopsy. None of these had subsequent lympadenopathy or bone metastasis**.** - Biopsies at 1 year post-procedure were negative in 11/12 patients. 1/12 (8%) patients harboured a residual Gleason 4	There were no urethral structures. One patient experienced acute urinary retention and had a supra-pubic catheter placed for 13 days. *Urinary infection* - 2/12 (17%) patients had a urinary tract infection post-operatively. - There was 1 episode of epididymo-orchitis and 1 asymptomatic urinary tract infection. *Urinary function* No urinary incontinence was observed *IPSS scores** - 8/11 (73%) patients had a similar IPSS score compared with baseline 1 year after treatment. - 2/11 (18%) patients had a lower IPSS score compared with baseline (indicating improvement of urinary function) after 1 year. One of these patients underwent TURP before HIFU to prevent post-treatment urinary retention. - 1/11 (9%) patients had a higher IPSS score after 1 year (indicating worsening urinary function). **8-domain instrument (0–30 scale): 0–7,*	**Follow-up issues**: • Biopsy was performed at 1 year after treatment and if there was a rising PSA. Salvage therapy was introduced if a control biopsy was positive or the PSA increase to above pre-treatment failures. • Patients were offered HIFU if the recurrence was considered local. If the disease was more diffuse, they were offered androgen deprivation therapy. • PSA measurements were performed in all patients at 3 months after HIFU treatment and then every 6 months. • Clinical assessment was performed every 6 months during the first 5 years and then annually. **Study design issues**: • Initially TURP was offered prior to HIFU where patients had high

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Study details	Key efficacy findings	Key safety findings	Comments
Conflict of interest/source of funding: None declared.	(2+2) cancer. This patient was treated 4 years later with a second HIFU procedure after his PSA increased. *PSA follow-up (follow-up regimen included PSA measurement at 3 months and 6-monthly thereafter)* - Mean pre-operative PSA level was 7.3 ng/ml. - The last median PSA in the recurrence-free group was 1.63 ng/ml. - The patient re-treated with HIFU had a stable PSA at 4.6 ng/ml 4.5 years following salvage focal therapy HIFU. - The group treated with salvage androgen deprivation therapy had a mean PSA of 1.15 ng/ml.	*mildly symptomatic; 8–19, moderately symptomatic; 20–35, severely symptomatic.* *Sexual function* Authors state that this was not assessed because the majority of patients had erectile dysfunction pre-treatment (7/12) whilst for the remaining patients assessment was deemed not useful 'because of lack of objective data'.	prostate volumes. Subsequently it was done routinely as it reduces post-operative bladder obstruction. 5/11 patients underwent TURP before HIFU

Abbreviations used: HIFU, high-intensity focused ultrasound; IPSS, international prostate symptom score; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TMN, tumour nodes metastases; TNM system: NO, the cancer has not spread to any lymph nodes; MO, the cancer has not spread beyond the regional lymph nodes; TRUS, transperitoneal ultrasound ; TURP, transurethral resection of the prostate

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Muto S (2008)[2]

Case series

Tokyo, Japan

Recruitment period : 2003–2006

Study population: Men with localised prostate cancer

n = 29 treated by focal therapy, 41 treated by whole-gland HIFU

Age: median 72 years
Sex: 100% male

Patient selection criteria: Men > 60 years TNM stage T1c-T2 N0, M0 and biopsy and MRI findings indicating localised disease. Patients were not suitable for radical prostatectomy because of comorbidities or preferred the treatment with HIFU rather than surgery or radiation therapy.

Technique: All patients received HIFU treatment (Sonoblate 500, Focus surgery, IN, USA) under general anaesthesia. The treatment was performed with a transrectal probe that included a 4MHz ultrasound imaging probe and a 4MHz piezoelectric treatment transducer. Contiguous HIFU shots were delivered 1.8 mm apart with a 4-s shot duration and a 12-s interval</td>
<td>Number of patients analysed (focal therapy): 29

Biochemical follow-up
Serum PSA levels decreased following focal HIFU

<table>
<tr><th></th><th>Whole-gland HIFU</th><th>Focal HIFU</th></tr>
<tr><td>Pre-HIFU</td><td>4.92±5.73</td><td>5.36±5.89</td></tr>
<tr><td>3 months</td><td>1.14±1.58</td><td>2.74±3.37</td></tr>
<tr><td>6 months</td><td>1.59±1.84</td><td>3.17±3.70</td></tr>
<tr><td>9 months</td><td>2.04±2.29</td><td>3.37±2.79</td></tr>
<tr><td>12 months</td><td>2.45±2.73</td><td>3.14±2.64</td></tr>
<tr><td>24 months</td><td>2.84±3.42</td><td>3.42±2.67</td></tr>
<tr><td>36 months</td><td>2.07±1.76</td><td>1.52±0.92</td></tr>
</table>

The 2-year biochemical disease-free survival rates in patients at low, intermediate and high risk were 85.9%, 50.9% and 0% respectively ($p < 0.005$).
No significant differences were noted in the 2-year biochemical disease-free rates for the patients at low and intermediate risk treated with whole or focal therapy.

Biopsy follow-up

- Of 28 patients who had prostate biopsy 6</td>
<td>IPSS questionnaire score*. This outcome was reported for both whole-gland and focal therapy subgroups in an aggregate fashion.

<table>
<tr><td>Pre-HIFU</td><td>10.20 ± 6.14</td></tr>
<tr><td>6 months</td><td>10.21 ± 7.11</td></tr>
<tr><td>12-months</td><td>9.25 ± 7.29</td></tr>
</table>
*8-domain instrument (0–30 scale). 0–7, mildly symptomatic; 8–19, moderately symptomatic; 20–35, severely symptomatic.

1/25 (4.0%) of patients developed urinary stricture or symptomatic urinary tract infection.

Transient urinary retention requiring TURP was noted in 4 patients who received TURP, but it is not reported how many of these patients received focal HIFU rather than whole-gland HIFU.</td>
<td>Follow-up issues:
Time to biochemical failure was defined as a midway between the PSA nadir and the first of the 3 consecutive PSA increases.

Study design issues:
• Seven patients (24.1%) were on hormone therapy at the time of the treatment.
• Impotence was not assessed following HIFU</td>
</tr>
</table>

Abbreviations used: HIFU, high-intensity focused ultrasound; IPSS, international prostate symptom score; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TMN, tumour nodes metastases; TNM system: NO, the cancer has not spread to any lymph nodes; MO, the cancer has not spread beyond the regional lymph nodes; TRUS, transperitoneal ultrasound ; TURP, transurethral resection of the prostate

Study details	Key efficacy findings	Key safety findings	Comments
between shots. The mean HIFU treatment time for focal therapy was time was 72 minutes. Follow-up: **median 32 months** Conflict of interest/source of funding: None declared	months following the procedure, 25 (89.3%) had negative biopsy and 3 (10.7% had a positive biopsy. - At 12 months post-procedure, 17 patients had a biopsy of which 13 (76.5%) were negative and 4 (23.5%) were positive.		

Abbreviations used: HIFU, high-intensity focused ultrasound; IPSS, international prostate symptom score; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TRUS, transperitoneal ultrasound ; TURP, transurethral resection of the prostate

Study details	Key efficacy findings	Key safety findings	Comments
Ahmed (2011)[3] **Case series** London, UK Recruitment period: 2006 to 2008 Study population: Men with a prostate cancer confirmed by MRI and histology ('template trans-perineal mapping biopsies') to be unilateral. n = **20** Age: Mean 60.4% Sex: 100% male Patient selection criteria: Men who had unilateral prostate cancer and were free of erectile dysfunction Technique: HIFU was used for hemiablation. Men had 1 sterile urine culture within 6 weeks of the procedure and received prophylactic antibiotics at the time of surgery. Lobar ablation to midline with or without 5 mm extension over midline as indicated by tumour localisation. Suprapubic catheterisation was used until urethral voiding encouraged after 2 days. Follow-up: **12 months** Conflict of interest/source of funding: No commercial conflicts of interest declared.	Number of patients analysed: **20** *Histology follow-up:* 17/19 (90%) men biopsied had no histological evidence of cancer at 12 months. *Biochemical follow-up:* Mean PSA decreased 80% to 1.5 ng/ml at 12 months. *MRI follow-up:* Extensive fibrosis was seen in 18 cases by multiparametric MRI (mp-MRI) at 6 months. And 10 patients had evidence of necrosis. Two men (10%) had positive 6-month mp-MRI and were demonstrated to have low volume disease. The first patient decided on a period of active surveillance. The other patient underwent further focal therapy HIFU to the treated side and had a resultant decrease in PSA. He refused further biopsy, but the PSA remained stable and he had a further negative mp-MRI.	All men were able to void their bladder through the urethra on postoperative day 2 Sexual, urinary and bowel function were assessed using validated questionnaires at 1, 3, 6, 9 and 12 months. For all outcomes and instruments, significant decrements in function were observed at 1 month but function scores improved to baseline levels typically by 3 to 6 months. In detail: **Sexual function:** 19/20 (95%) men had a return of erections sufficient for penetrative sex at 12-month follow-up. A decrease in erectile dysfunction score (using the International Index of Erectile Dysfunction scoring system on a scale of 0–30; lower value indicates worse function) was reported from a mean of 20.9 points at baseline to 14.3 points at 1 month (p = 0.004). However, scores at 3, 6, 9 and 12 months were not significantly different from baseline (mean scores of 17.9 [p = 0.278], 21.7 [p = 0.705], 23.3 [p = 0.198] and 21.8 [p = 0.619] respectively). **5-domain instrument (0–30 scale, 25–30 indicate 'normal' function, and for values <25, lower scores indicating more severe erectile dysfunction)* **Urinary function:** IPSS scores* were significantly lower (i.e. better) at 6 months	**Follow-up issues**: • Contrast-enhanced MRI was performed within 1 month to confirm the area of ablation. • Follow-up consisted of clinic visits at 1 month and PSA level testing, questionnaire and adverse event reporting every 3 months • A further MRI and TRUS-guided biopsy was scheduled at 6 months post-procedure. If a new, suspicious lesion was seen, a biopsy of the contralateral side was permitted. • One patient refused biopsy. **Study design issues**: • Quality of life, impotence and incontinence were measured as outcomes in this study • The study was powered to detect changes in erectile dysfunction. • 75% of men in the study were assessed as at intermediate risk from

Abbreviations used: HIFU, high-intensity focused ultrasound; IPSS, international prostate symptom score; MRI, magnetic resonance imaging; PSA, prostate-specific antigen; TMN, tumour nodes metastases; TNM system: NO, the cancer has not spread to any lymph nodes; MO, the cancer has not spread beyond the regional lymph nodes; TRUS, transperitoneal ultrasound ; TURP, transurethral resection of the prostate

Study details	Key efficacy findings	Key safety findings	Comments
		compared with baseline (p = 0.021). UCLA–EPIC (Expanded prostate cancer index composite) urinary incontinence scores indicated no significant difference between baseline and 6 months (p = 0.450). 18/20 (90%) of men were pad-free and leak-free by 6 months and 19/20 (95%) were pad-free by 3 months. *7-domain instrument (0–30 scale): 0–7, mildly symptomatic; 8–19, moderately symptomatic; 20–35 severely symptomatic.* A pre-sphincteric stricture requiring dilation developed in 1 man. **Bowel function** There were no recto-urethral fistulae. Functional assessment of cancer therapy – prostate (FACT-P) scores were no different at 6 months (p = 0.792).	prostate cancer, based on TRUS biopsy and template prostate mapping. **Study population issues**: • Men identified with erectile dysfunction refractory to pharmaceutical aid were excluded from the trial.

Efficacy

Survival

A case series of 12 patients followed for a median of 10.6 years reported overall and cancer-specific survival following the procedure, which was 83% (10/12) and 100% respectively[1]. Recurrence-free survival was 90% at 5 years and 38% at 10 years (absolute numbers not reported).

In a case series including 29 patients, there was no significant difference in 2-year biochemical disease-free survival (determined by PSA levels) for the patients at low and intermediate risk by focal or whole-gland HIFU[2].

Treatment failure

In a case series of 12 patients, treatment failure (defined as any positive biopsy and/or need for salvage therapy prompted by rising PSA levels) was observed in 42% (5/12) of all patients[1]. In 1 patient prostate cancer was managed by further focal HIFU treatment and in 4 patients by androgen deprivation. All 5 patients were alive at follow-up between 9.5 and 11 years.

Biopsy

In the case series including 29 patients who received focal HIFU for localised prostate cancer, 89% of patients (25/28) who had a biopsy at 6 months post-procedure were cancer-free[2]. At 12 months, 77% of patients (13/17) who had a biopsy were cancer-free.

In the case series of 20 patients, 90% of the men (17/19) who had a biopsy had no histological evidence of cancer at 12 months[3]. Mean PSA levels reduced by 80% to 1.5 ng/ml at 12 months. Two men had positive 6-month multiparametric magnetic resonance imaging (mp-MRI) and were demonstrated to have low-volume recurrence of disease: 1 decided on a period of active surveillance and 1 underwent further HIFU with a resultant decrease in PSA (he refused further biopsy but his PSA level remained stable at the time of reporting and mp-MRI was negative for disease).

In the case series of 12 patients, 92% (11/12) had a negative biopsy 1 year after the procedure[1]. The patient with a positive biopsy had a Gleason 4 (2+2) cancer. He received active surveillance with biochemical monitoring and was treated with a second HIFU procedure when his PSA level rose 4 years later.

PSA

In the case series of 12 patients, the mean preoperative PSA level was 7.3 ng/ml[1]. This was reduced to a median of 1.63 ng/ml in men who were recurrence-free and 1.15 ng/ml in men who received salvage androgen deprivation therapy.

The patient who underwent a second HIFU procedure had a stable PSA level of 4.6 ng/ml 4.5 years after the procedure.

In the case series including 29 patients who received focal HIFU, preoperative median PSA levels reduced from 5.36 ng/ml to 3.42 ng/ml and 1.52 ng/ml at 2 and 3 years respectively[2].

In the case series of 20 patients, the mean PSA level decreased by 80% to 1.5 ng/ml[3].

Safety

Sexual dysfunction

The case series of 20 patients reported a decrease in erectile dysfunction score (using the International Index of Erectile Dysfunction scoring system on a scale of 0–30; lower value indicates worse function) from a mean of 20.9 points at baseline to 14.3 points at 1 month (p = 0.004). However, scores at 3, 6, 9 and 12 months were not significantly different from baseline (mean scores of 17.9 [p = 0.278], 21.7 [p = 0.705], 23.3 [p = 0.198] and 21.8 [p = 0.619] respectively). 95% (19/20) of patients had erectile function sufficient for penetrative sex at 12-month follow-up.

Urinary dysfunction

No urinary incontinence was observed in the case series of 12 patients[1]. In the case series of 20 patients, 90% (18/20) of men were pad-free and leak-free continent by 6 months following the procedure and 95% (19/20) were pad-free by 3 months[3].

Infection

In the case series including 29 patients who received focal HIFU, the authors note that 4% (1/25) developed a symptomatic urinary tract infection or symptomatic urinary stricture. No further details are provided[2].

In the case series of 12 patients, 17% (2/12) developed a urinary tract infection post procedure, there was 1 episode of asymptomatic urinary tract infection and 1 episode of epididymo-orchitis[1].

No urinary tract infections were reported in the series of 20 patients[3].

Fistula formation

There were no reports of fistula formation in any of the 3 case series[1–3].

Urethral stricture

In the case series of 20 patients, there was 1 pre-sphincteric stricture which required dilatation[3].

Validity and generalisability of the studies

- There is no evidence from randomised control trials or from non-randomised comparative studies.
- Only 1 case series reports long-term data on mortality from prostate cancer following this procedure.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- High-intensity focused ultrasound for prostate cancer. NICE interventional procedures guidance 118 (2005). Available from www.nice.org.uk/guidance/IPG118
- Cryotherapy for recurrent prostate cancer. NICE interventional procedures guidance 119 (2005). Available from www.nice.org.uk/guidance/IPG119
- Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedures guidance 132 (2005). Available from www.nice.org.uk/guidance/IPG132
- Cryotherapy as a primary treatment for prostate cancer. NICE interventional procedures guidance 145 (2005). Available from www.nice.org.uk/guidance/IPG145
- High dose rate brachytherapy in combination with external-beam radiotherapy for localised prostate cancer. NICE interventional procedures guidance 174 (2006). Available from www.nice.org.uk/guidance/IPG174
- Laparoscopic radical prostatectomy. NICE interventional procedures guidance 193 (2006). Available from www.nice.org.uk/guidance/IPG193

Clinical guidelines

- Prostate cancer: diagnosis and treatment]. NICE clinical guideline CG58 (2008). Available from www.nice.org.uk/guidance/CG58

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr Simon Brewster (British Association of Urological Surgeons) and Mr Rajendra Persad (British Association of Urological Surgeons).

- One Specialist Adviser stated the existence of inter-specialty controversy over the procedure but gave no further comment.
- Both Specialist Advisers had performed whole gland HIFU and only one Specialist Adviser had performed focal therapy using HIFU a few times.
- Both Specialist Advisers considered the procedure to be definitely novel and of uncertain safety and efficacy.
- The Specialist Advisers listed relevant comparators as active surveillance, whole gland radiotherapy/brachytherapy, radical prostatectomy or whole gland HIFU.
- One Specialist Adviser stated that the procedure is only performed by two or three urologists in the United Kingdom, mainly in clinical research.
- Key efficacy outcomes: Biochemical failure-free survival, absence of viable cancer on repeat biopsy and MRI evidence of cancer ablation.
- Adverse events reported in the literature: bladder neck stenosis, acute retention and erectile dysfunction in those who are preoperatively potent.
- Theoretical adverse events: infection, voiding obstruction, bleeding, debris *per urethram* and failure to cure the cancer.
- Training: transperineal template biopsy and HIFU delivery.
- Facilities: template biopsy facility, multiparametric MRI and HIFU machine.
- One Specialist Adviser thought that the procedure is likely to have a major impact on the NHS; one considered the potential impact to be minor.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent 50 questionnaires to one Trust for distribution to patients who had HIFU. NICE received 38 completed questionnaires.

The patient commentaries reported some instances of sexual dysfunction.

Issues for consideration by IPAC

- There is no accepted definition of focal therapy.
- Only a small number of case series have been published on this procedure at present.
- Only 1 case series provides long-term (> 10 years) survival data following this procedure.

References

1. El Fegoun AB, Barret E, Praptnich D et al. (2011). Focal therapy with high intensity focused ultrasound for prostate cancer in the elderly. A feasibility study with 10 years follow-up. Brazilian Journal of Urology 37; 213–22

2. Muto S, Yoshii T, Saito K et al. (2008) Focal therapy with high-intensity focused ultrasound in the treatment of localized prostate cancer. Japanese Journal of Clinical Oncology 38; 192–9

3. Ahmed HU, Freeman A, Kirkham A et al. (2011) Focal therapy for localized prostate cancer: a Phase I/II trial. Journal of Urology 185; 1245–55

Appendix A: Additional papers on focal therapy with high-intensity focused ultrasound for localised prostate cancer

There were no additional papers identified

Appendix B: Related NICE guidance for focal therapy using high-intensity focused ultrasound for localised prostate cancer

Guidance	Recommendations
Interventional procedures	**High-intensity focused ultrasound for prostate cancer. NICE interventional procedures guidance 118 (2005).** Available from www.nice.org.uk/guidance/IPG118 • Current evidence on the safety and efficacy of high-intensity focused ultrasound (HIFU), as measured by reduction in prostate-specific antigen (PSA) levels and biopsy findings, appears adequate to support the use of this procedure for the treatment of prostate cancer provided that the normal arrangements are in place for consent, audit and clinical governance. • The effects of HIFU for prostate cancer on quality of life and long-term survival remain uncertain. Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options. Use of the Institute's Information for the public is recommended. • Interpretation of the data was difficult because it was not clear from the literature when the procedure was used for primary or for salvage treatment. Further research and audit should address clinical outcomes, long-term survival and indications for treatment (differentiating between the use of the procedure for primary and for salvage treatment). **Cryotherapy for recurrent prostate cancer. NICE interventional procedures guidance 119 (2005).** Available from www.nice.org.uk/guidance/IPG119 • Current evidence on the safety and efficacy of cryotherapy, as measured by a reduction of prostate-specific antigen (PSA) levels and biopsy findings, appears adequate to support the use of this procedure in patients with recurrent prostate cancer provided that the normal arrangements are in place for consent, audit and clinical governance. • The effects of cryotherapy for recurrent prostate cancer on quality of life and long-term survival remain uncertain. Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options. Use of the Institute's *Information for the public* is recommended. Further

	research and audit should address quality of life, clinical outcomes and long-term survival. **Low dose rate brachytherapy for localised prostate cancer]. NICE interventional procedures guidance 132 (2005).** Available from www.nice.org.uk/guidance/IPG132 • Current evidence on the safety and short- to medium-term efficacy of low dose rate brachytherapy for localised prostate cancer appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. • Most of the evidence on the efficacy of low dose rate brachytherapy for localised prostate cancer relates to the reduction of prostate-specific antigen (PSA) levels and to biopsy findings. The effects on quality of life and long-term survival remain uncertain. Clinicians should ensure that patients understand these uncertainties and the alternative treatment options. Use of the Institute's *Information for the public* is recommended. • A multidisciplinary team should be involved in the planning and use of this procedure. The Institute has issued a cancer service guideline on *Improving Outcomes in Urological Cancers* (www.nice.org.uk/csguc). • Further research and audit should address quality of life, clinical outcomes and long-term survival. **Cryotherapy as a primary treatment for prostate cancer. NICE interventional procedures guidance 145 (2005).** Available from www.nice.org.uk/guidance/IPG145 • Current evidence on the safety and efficacy of cryotherapy, measured by reduction of prostate specific antigen (PSA) levels and biopsy findings, appears adequate to support the use of this procedure as a primary treatment in patients with prostate cancer provided that normal arrangements are in place for consent, audit and clinical governance. • The effects of cryotherapy as a primary treatment for prostate cancer on quality of life and long-term survival remain uncertain. Clinicians should therefore ensure that patients understand the uncertainties and the alternative treatment options. They should provide them with clear written information and, in addition, use

	of the Institute's *Information for the public* is recommended. • Further research and audit should address quality of life, clinical outcomes and long-term survival. **High dose rate brachytherapy in combination with external -beam radiotherapy for localised prostate cancer. NICE interventional procedures guidance 174 (2006).** Available from www.nice.org.uk/guidance/IPG174 • Current evidence on the safety and efficacy of high dose rate (HDR) brachytherapy in combination with external-beam radiotherapy for localised prostate cancer appears adequate to support the use of this procedure provided that the normal arrangements are in place for consent, audit and clinical governance. • A multidisciplinary team should be involved in the planning and use of this procedure. **Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedures guidance 132 (2005).** Available from www.nice.org.uk/guidance/IPG132 • Current evidence on the safety and short- to medium-term efficacy of low dose rate brachytherapy for localised prostate cancer appears adequate to support the use of this procedure, provided that the normal arrangements are in place for consent, audit and clinical governance. • Most of the evidence on the efficacy of low dose rate brachytherapy for localised prostate cancer relates to the reduction of prostate-specific antigen (PSA) levels and to biopsy findings. The effects on quality of life and long-term survival remain uncertain. Clinicians should ensure that patients understand these uncertainties and the alternative treatment options. Use of the Institute's Information for the public is recommended. • A multidisciplinary team should be involved in the planning and use of this procedure. The Institute has issued a cancer service guideline on Improving Outcomes in Urological Cancers

	(www.nice.org.uk/csguc). • Further research and audit should address quality of life, clinical outcomes and long-term survival. **Laparoscopic radical prostatectomy (2006) NICE interventional procedures guidance 193 (2005).** Available from www.nice.org.uk/guidance/IPG193 • Current evidence on the safety and efficacy of laparoscopic radical prostatectomy appears adequate to support the use of this procedure provided that normal arrangements are in place for consent, audit and clinical governance. • Clinicians should ensure that men understand the benefits and risks of all the alternative treatment options. In addition, use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG193publicinfo). • Clinicians undertaking laparoscopic radical prostatectomy require special training. The British Association of Urological Surgeons has produced training standards.

Clinical guidelines	**Prostate cancer: diagnosis and treatment. NICE clinical guideline CG58 (2008).** Available from www.nice.org.uk/guidance/CG58 • Healthcare professionals should adequately inform men with prostate cancer and their partners or carers about the effects of prostate cancer and the treatment options on their sexual function, physical appearance, continence and other aspects of masculinity. Healthcare professionals should support men and their partners or carers in making treatment decisions, taking into account the effects on quality of life as well as survival. • To help men decide whether to have a prostate biopsy, healthcare professionals should discuss with them their prostate specific antigen (PSA) level, digital rectal examination (DRE) findings (including an estimate of prostate size) and comorbidities, together with their risk factors (including increasing age and black African or black Caribbean ethnicity) and any history of a previous negative prostate biopsy. The serum PSA level alone should not automatically lead to a prostate biopsy. • Men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance. • Men undergoing radical external beam radiotherapy for localised prostate cancer[1] should receive a minimum dose of 74 Gy to the prostate at no more than 2 Gy per fraction. • Healthcare professionals should ensure that men and their partners have early and ongoing access to specialist erectile dysfunction services. • Healthcare professionals should ensure that men with troublesome urinary symptoms after treatment have access to specialist continence services for assessment, diagnosis and conservative treatment. This may include coping strategies, along with pelvic floor muscle re-education, bladder retraining and pharmacotherapy. • Healthcare professionals should refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter. • Biochemical relapse (a rising PSA) alone should not necessarily prompt an immediate change in treatment. • Hormonal therapy is not routinely recommended for men with prostate cancer who have a biochemical relapse unless they have: – symptomatic local disease progression, or – any proven metastases, or – a PSA doubling time < 3 months.

	• When men with prostate cancer develop biochemical evidence of hormone-refractory disease, their treatment options should be discussed by the urological cancer multidisciplinary team (MDT) with a view to seeking an oncologist and/or specialist palliative care opinion, as appropriate. • Healthcare professionals should ensure that palliative care is available when needed and is not limited to the end of life. It should not be restricted to being associated with hospice care. [1] This may also apply to some men with locally advanced prostate cancer.

Appendix C: Literature search for focal therapy with high-intensity focus ultrasound for localised prostate cancer.

IP: 839 Focal therapy using high-intensity focused ultrasound for localised prostate cancer

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	11/05/2011	May, 2011	3
Database of Abstracts of Reviews of Effects – DARE (CRD website)	11/05/2011	N/A	7
HTA database (CRD website)	11/05/2011	N/A	7
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	11/05/2011	May, 2011	13
MEDLINE (Ovid)	11/05/2011	1948 to May Week 1 2011	255
MEDLINE In-Process (Ovid)	11/05/2011	May 12, 2011	26
EMBASE (Ovid)	11/05/2011	1980 to 2011 Week 18	629
CINAHL (NLH Search 2.0 or EBSCOhost)	11/05/2011	N/A	28
BLIC (Dialog DataStar)	11/05/2011	N/A	0

Trial sources searched on 13/05/2011

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched on 13/05/2011

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

MEDLINE search strategy

The MEDLINE search strategy was adapted for use in the other sources.

# ▲	Searches	Results
1	High-Intensity Focused Ultrasound Ablation/	128
2	HIFU.tw.	678
3	(high adj4 intens* adj4 focus* adj4 ultrasound*).tw.	915
4	(high* adj4 intensit* adj4 focal* adj4 therap*).tw.	4
5	(hemi* adj3 ablat*).tw.	62
6	hemi-ablat*.tw.	4
7	1 or 2 or 3 or 4 or 5 or 6	1069
8	Prostatic Neoplasms/	75145
9	(prostat* adj3 (neoplasm$ or cancer$ or carcinoma$ or adenocarcinom$ or tumour$ or tumor$ or malignan$)).tw.	71211
10	8 or 9	86364
11	7 and 10	263
12	sonablate.tw.	24
13	Ablatherm Robotic HIFU.tw.	0
14	11 or 12 or 13	269
15	animals/ not humans/	3498061
16	14 not 15	255