# NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

## INTERVENTIONAL PROCEDURES PROGRAMME

## Interventional procedure overview of focal therapy using cryoablation for localised prostate cancer

**Treating areas of prostate cancer using freezing (cryotherapy) needles**

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 freezing (cryotherapy) needles aims to find and destroy only the cancerous part of the prostate, avoiding treatment of healthy tissue. Freezing needles are inserted into the tumour areas, which are then destroyed. 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 September 2011 and updated in January 2012.

## Procedure name

- Focal therapy using cryoablation 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 high-intensity focused ultrasound (HIFU). All radical treatment options are associated with substantial risks of sexual, urinary or bowel dysfunction. Focal therapy using cryoablation 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 shows its precise location. With the patient under local or general anaesthesia, the bladder is catheterised. Using transrectal ultrasound and a template placed on the perineum, fine needles are inserted transperineally into the prostate. Pressurised argon is passed through the needles to freeze the targeted area of the prostate, destroying the tissue. Implantable temperature probes and transrectal ultrasound guidance are used to monitor the treatment, and the surrounding tissue are protected from the effects of freezing.

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

### *Anatomical specification of targeted lesions*

Focal therapy using cryoablation for localised prostate cancer is an evolving procedure, and several different anatomical descriptions of the targeted part of the prostate have been proposed. According to Ward (2010)[1] focal therapy may relate to the following:

- Nerve-sparing prostate ablation (unilateral or bilateral): destruction of all prostatic tissue except the posterior lateral area on one or both sides.
- Hemi-ablation: destruction of all prostate tissue within a lateralised hemisphere.

- Anterior hockey stick (3/4 ablation): hemi-ablation of the prostate plus ablation of the anterior contralateral region.
- Posterior hockey stick (3/4 ablation): hemi-ablation of the prostate plus ablation of the posterior contralateral region.
- Targeted focal therapy: minimal destruction of prostate tissue isolated to the area of known tumour, using detailed prostate mapping biopsy studies.
- Zonal ablation (anterior or posterior): destruction of anterior or posterior sextant sections containing cancer after extended prostate biopsy using spatial-targeting device.

# Literature review

## *Rapid review of literature*

The medical literature was searched to identify studies and reviews relevant to focal therapy using cryoablation for localised prostate cancer.

Searches were conducted of the following databases, covering the period from their commencement to November 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.<br>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.<br>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 using cryoablation. |
| 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 1330 patients from a register report[2] and 4 case series[3-6].

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 using cryoablation for localised prostate cancer

Abbreviations used: ASTRO, American Society for Therapeutic Radiation and Oncology; PSA, prostate-specific antigen; TURP, trans-urethral resection of the prostate. American Joint Committee on Cancer (AJCC) TNM, 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.

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Ward JF (2011)[2]<br>**Register**<br><br>USA<br>Recruitment period: analysis of the Cryo On-Line Database (COLD) Registry between 1999 – 2007.<br><br>Study population: Register included information on patients who had undergone prostate cryoablation as a primary therapy for localised, histologically identified adenocarcinoma of the prostate.<br><br>n = 5853 patients on the register (**1160 focal cryoablation)**<br>Age: Mean 67.8 years<br>Sex: Male<br>Patient selection criteria: primary unifocal prostate cancer.<br><br>Technique: Ultrasound-guided percutaneous cryosurgery with destruction of ipsilateral neurovascular bundle and sparing of contralateral neurovascular bundle.<br><br>Follow-up: **Mean 21 months**<br><br>Conflict of interest/source of funding: One author received an unrestricted research grant from Healthtronics and another author is a speaker for Healthtronics. | **Number of patients analysed: 1160**<br><br>**Biochemical disease-free survival**<br>75.7% of the patients had biochemical recurrence-free survival 2 years after treatment. Biochemical recurrence-free rate defined as per the ASTRO definition.<br><br>**Biopsy follow-up**<br>14.1% patients (164/1160) underwent a biopsy because of increased post-treatment serum PSA levels. Of those who underwent a biopsy, a positive biopsy was reported for 26.3% (43/164).<br>The mean Gleason score was 6.12 and the median 6 for the identified cancer in the 43 patients with a positive post focal cryoablation biopsy. | Safety events (at 12 months)<br>**Complication** / **%**<br>Urinary incontinence* — 1.6% (8/507)<br>New-onset erectile dysfunction — 41.9% (122/291)<br>Urinary retention (> 30 days) — 1.2% (6/518)<br>Rectourethral fistula — 0.1% (1/1160)<br>*Urinary *continence* defined as use of 0 pads | **Follow-up issues**:<br>• Numbers of patients in whom sufficient pre- and post-procedure information was available for analysis varied for the safety outcomes.<br><br>**Study design issues**:<br>• Retrospective register report<br>• Study reported the subset of focal cryoablation cohort represented 19.8% of the entire database.<br>• Participants provided details on the treatment and outcome.<br><br>**Other issues**:<br>• Study noted that a limitation of the study is the use of the ASTRO definition of biochemical recurrence (defined as 3 consecutive increases in serum PSA level > 6 months after focal cryoablation). This is a definition developed for patients treated primarily with radical radiation therapy. |

Abbreviations used: ASTRO, American Society for Therapeutic Radiation and Oncology; PSA, prostate-specific antigen; TURP, trans-urethral resection of the prostate. American Joint Committee on Cancer (AJCC) TNM, 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.

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Onik G (2008)[3]<br><br>**Case series**<br>USA<br>Recruitment period: 1995 to 2005<br>Study population: Patients with prostate cancer<br>n = **54**<br>Age: Information not available<br>Sex: Male<br><br>Patient selection criteria:<br>Men with prostate cancer confined to one prostate lobe, who had a major concern about maintenance of potency and/or continence.<br>Technique:<br>The extent of freezing was tailored to the individual patient, determined by Gleason grade, stage, PSA level and the extent and location of cancer on preoperative biopsies, aiming for a minimum 5 mm margin around tumour co-ordinates. An Endocare, Irvine, CA argon gas system was used.<br>An attempt was made to spare one neurovascular bundle on the opposite side to the tumour.<br>Tissue temperature monitoring was carried out and when the tumour had a Gleason score >7 or was adjacent to the urethra, 3 freeze thaw cycles at a temperature of at least −20°C were carried out.<br>In patients with positive midline biopsy posterior to the urethra, cryoprobes were placed into the region of the ejaculatory ducts posterior to the urethra to prophylactically prevent seminal vesicle recurrence.<br><br>A Foley catheter was left in place rather than a supra | Number of patients analysed: **48**<br><br>*Survival*<br>Overall and disease-specific survival was 100%.<br><br>*Biochemical disease-free status*<br>Mean preoperative PSA was 7.8 ng/ml and mean postoperative PSA was 2.19 ng/ml.<br><br>Of the 48 patients followed up, 45/48 (94%) had stable PSA levels at 2 years follow-up. 4/48 (8%) patients had unstable PSA levels within the first year post-procedure. All 4 patients were found to have persistent tumours in a previously unfrozen portion of the gland. They all received cryotherapy of the entire prostate gland and they subsequently had stable PSA < 0.2 ng/ml.<br>One patient who had an unstable PSA at 4 years post-procedure was demonstrated to have persistent local disease in a previously untreated area and was pending treatment when the study was reported.<br><br>*Biopsy follow-up*<br>24 patients with stable PSA had a biopsy and all biopsies were negative for both treated and untreated sides.<br>No patients had a positive biopsy from a treated portion of the gland. | *Need for additional interventional procedure*<br>One patient had subsequent transurethral prostatectomy for removal of sloughed tissue.<br><br>*Potency*<br>40 patients were potent before cryosurgical treatment and 36/40 (90%) remained potent afterwards. Of the 4 patients who required full-gland cryoablation (see efficacy column) 3 became impotent.<br><br>*Continence*<br>All patients were continent following treatment. | **Follow-up issues**:<br>• 6 patients were lost to follow-up.<br>• 48/54 (89%) patients recruited were followed up.<br>• PSA testing was carried out every 3 months for the first 2 years and then every 6 months.<br>• Patients were followed up by written questionnaire (instrument used not otherwise specified) and phone call.<br>• All patients were advised to have routine biopsy at 1 year, regardless of PSA stability. |

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| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| pubic tube.<br>Patients with a Gleason score > 7 were placed on combined hormonal therapy for 6 months prior to the procedure. After the procedure the combined hormonal therapy was stopped.<br><br>Follow-up: **Mean 4.5 years**<br><br>Conflict of interest/source of funding: Not reported. | | | |

Abbreviations used: ASTRO, American Society for Therapeutic Radiation and Oncology; PSA, prostate-specific antigen; TURP, trans-urethral resection of the prostate. American Joint Committee on Cancer (AJCC) TNM, 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.

| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Bahn DK (2006)[4]<br><br>**Case series**<br>USA<br>Recruitment period: 1995 to 2004<br><br>Study population: Patients with localised prostate cancer.<br>n = **31**<br><br>Age: Mean age 63 years<br>Sex: Male<br><br>Patient selection criteria: Patients had localised prostate cancer which was believed to be confined to one lobe of the prostate. All patients had an initial 6-8 core biopsy followed by Doppler ultrasound including targeted biopsy of all suspect lesions with nearby neurovascular bundle and seminal-vesicle biopsies if extracapsular extension of the tumour was suspected.<br>If there was no evidence of tumour on one side of the gland patients were eligible for the study, regardless of PSA level or Gleason score.<br><br>Technique: The procedure utilised two freeze cycles, urethral warming device, multiple cryoprobes and an argon-based cryomachine. Focal ablation was achieved with probes adjusted to the targeted portion of the prostate and periprostatic tissue adjacent to the treatment zone.<br>Follow-up: **Mean 70 months**<br><br>Conflict of interest/source of funding: Not reported. | Number of patients analysed: **31**<br><br>**Reporting percentages (safety and efficacy)**<br><br>*Follow-up biopsy*<br>At least 1 postoperative biopsy result was available for 25 patients.<br>Each patient underwent an average of 2.36 post-treatment biopsies of 6 cores plus a core from any region appearing suspect on colour Doppler ultrasonography.<br><br>There was no evidence of disease in 24/25 (96%) patients.<br><br>Cancer was detected in 1 patient in the apex of the untreated lobe 12 months after the procedure. The patient underwent whole-gland cryoablation and was subsequently biochemically and clinically disease free.<br><br>*Follow-up PSA*<br>Postoperative PSA levels were available for 28 patients. Biochemical recurrence-free survival according to the ASTRO definition was observed in 26/28 (92.9%) patients. | *Potency*<br>Potency was evaluated with a modified version of the Brief Male Sexual Function Index. A patient was considered potent if they answered yes to the question: 'Are you able to obtain a full erection when you are stimulated?'<br>A total of 13 men (48.1%) were potent after the procedure and a further 11 men (40.7%) were able to achieved erections sufficient for intercourse with the use of oral pharmaceuticals.<br><br>*Continence*<br>Incontinence was defined as any leakage of urine later than 3 months after the procedure.<br>There were no reports of incontinence.<br><br>*Other*<br>There were no reports of other complications. | **Follow-up issues**:<br>• All patients received PSA testing every 3 months after the procedure.<br>• All patients had prostate biopsy at 6 months and 1, 2 and 5 years after cryoablation.<br>• If there were 3 consecutive rises in a patient's serum PSA concentration, a biopsy was performed.<br>• Two patients had not returned for follow-up, as they had only recently had the procedure.<br>• Two patients refused post-treatment biopsy.<br>• One patient was lost to follow-up.<br><br>**Study design issues**:<br>• Patients were recruited if they had prostate cancer localised to one lobe of the gland.<br><br>**Study population issues**:<br>• Cases had differing grades of disease. Three patients (9.8%) had a biopsy Gleason score of 5, 20 patients (64.5%) had a Gleason score of 6 and 8 patients (25.8%) had a Gleason score of 7. |

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| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| Ellis DS (2007)[5]<br><br>**Case series**<br>USA<br>Recruitment period: 2000 to 2005<br>Study population: Patients with prostate cancer at stage T1 to T3, NO, MO.<br><br>n = **60**<br>Age: Mean 69.0 years<br>Sex: Male<br>Patient selection criteria: Patients with T1 to T3, NO, MO disease who were relatively young and unwilling to undergo any standard treatment option that would put their potency at risk; or were older, but uncomfortable with watchful waiting.<br>Technique: Three probes were usually used on the side of the prostate targeted for ablation. A fourth probe was usually placed at the posterior medial position on the non-involved side in stick mode and warmed to assist in freezing ice under the urethra.<br>Patients were discharged on the day of cryosurgery or (rarely) the following morning with a suprapubic catheter.<br><br>Follow-up: **Mean 15.2 ± 7.4 months**<br>Conflict of interest/source of funding: The first author is a proctor for Endocare, Inc. The other authors have no financial arrangement or affiliation with a corporate organisation or manufacturer of a product used for this procedure. | Number of patients analysed: **60**<br><br>**Reporting percentages (safety and efficacy)**<br>**PSA**<br>Of the 51 patients with sufficient follow-up to determine biochemical disease-free status, 41 (80.4%) patients were biochemically disease free according to the ASTRO definition at follow-up (number of patients not stated in the paper and calculated by analyst).<br>Mean PSA before treatment 7.2 (+/- 4.7) ng/ml. Nadir mean post-treatment PSA 2.15 ng/ml.<br><br>**Biopsy**<br>After surgery, 35 patients underwent biopsy, 14 (40%) of whom had positive findings. This was 23.3% of the starting population. 11 of these patients underwent a second cryoablation and 8 (72.7%) of these were biochemically disease free at last follow-up. Of the 3 remaining patients, 1 was lost to follow-up.<br>Only 1 patient had a positive biopsy result from a specimen from the lobe that was treated. | There were no postoperative deaths.<br>There were no rectal fistulas reported.<br><br>**Incontinence**<br>All patients were continent before they underwent cryoablation. 55 were followed up for ≥6 months and 2 (3.6%) developed incontinence (but neither required pads).<br><br>**Impotence**<br>40 patients were known to be potent before treatment. All patients became impotent immediately after cryoablation. At 6 months, potency information was available for 36 patients, and 22 (61%) were potent with or without oral pharmaceutical assistance. At 12 months, potency data was available for 34 patients, of whom 24 (70.6%) were potent.<br>Of 5 patients that received 2 focal cryoablation procedures, all regained potency at follow-up. | **Follow-up issues**:<br>• Patients were followed up actively at 6 weeks, 3, 6, 9 and 12 months post cryosurgery and then every 6 months.<br>• Sufficient follow-up to determine biochemical disease-free survival was available for 51 patients with a mean follow-up or 16.7 ± 6.8 months.<br>• 35 patients were biopsied following treatment.<br><br>**Study design issues**:<br>• This study included penile rehabilitation following surgery.<br><br>**Study population issues**:<br>• Patients were recruited prospectively. The recruitment criteria took into account the wishes of the patient. In particular, patients who were not content with watchful waiting were offered the procedure. These patients are likely to have had lower grade tumours and be more health conscious.<br>• Patients were encouraged to take part in a penile rehabilitation programme which involved either oral pharmaceutical assistance or |

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| Study details | Key efficacy findings | Key safety findings | Comments |
|---|---|---|---|
| | | | a vacuum therapy device to maintain an erection for at least 10 minutes per day.<br><br>**Other issues**:<br>• It is not clear whether patients received androgen ablation therapy prior to, or after, surgery. |

Abbreviations used: ASTRO, American Society for Therapeutic Radiation and Oncology; PSA, prostate-specific antigen; TURP, trans-urethral resection of the prostate. American Joint Committee on Cancer (AJCC) TNM, 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.

### Study details

Lambert EH (2007)[6]

**Case series**

USA

Recruitment period: 2002 to 2005

Study population: Patients with primary unifocal prostate cancer with Gleason score of 6 or 7 who had cancer confined to one lobe in one or two contiguous biopsy cores and a tumour volume of < 10% in a 12-core biopsy. All patients had clinical state T1c. Patients received focal cryosurgery with freezing confined to a single lobe of the prostate.

n = **25**

Age: Mean 69 years

Sex: Male

Patient selection criteria: primary unifocal prostate cancer.

Technique: Ultrasound-guided percutaneous cryosurgery with destruction of ipsilateral neurovascular bundle and sparing of contralateral neurovascular bundle.

Follow-up: **Median 28 months**

Conflict of interest/source of funding: One author is a proctor for Oncura who supply services for prostate brachytherapy.

### Key efficacy findings

Number of patients analysed: **25**

**Biochemical disease-free survival**

Mean pre-treatment PSA: 6 ng/ml (range 1-13.1)

| Criteria for biochemical disease-free status | Number of biochemical disease-free patients | Per cent biochemical disease-free patients |
|---|---|---|
| PSA nadir <1.0 ng/ml | 9 | 36 |
| PSA nadir <2.0 ng/ml | 12 | 48 |
| PSA nadir <3.0 ng/ml | 18 | 72 |
| ≥50% nadir reduction | 21 | 84 |

**Biopsy follow-up**

7 patients were eligible for repeat biopsy (based on a rise in PSA nadir plus 2 ng/ml or a PSA nadir of less than 50%) and recurrent or residual cancer was detected in 3 of these patients (2 related to the contralateral side and 1 was on the ipsilateral side of the cryosurgery). All of these patients underwent repeat cryosurgery and were biochemically disease free at the last follow-up examination.

### Key safety findings

There was no evidence of incontinence, rectal pain perineal discomfort or fistula formation.

**Postoperative complications n = 25**

| Complication | Number of patients |
|---|---|
| Incontinence | 0 |
| Impotence | 7/24* |
| Rectal pain | 0 |
| Perineal discomfort | 0 |
| Urinary retention | 1 |
| Fistula | 0 |
| Death | 0 |

*****24/25 patients were potent preoperatively

**Potency**

Of 25 patients, 24 (96%) were potent preoperatively, (4 with the aid of pharmaceuticals). Postoperatively, 17 (71%) patients were potent (7 with pharmaceutical aid) and 7 patients were impotent following surgery.

### Comments

**Follow-up issues**:

- Patients were followed up postoperatively with a questionnaire and physical examinations and serial PSA measurements at 3, 6, and 12 months. They were then followed up every 6 months.

**Study design issues**:

- This was a case series that was analysed retrospectively.
- Standard sexual function questionnaires were not used.

**Study population issues**:

- All patients had a desire for minimally invasive treatment and no evidence of metastases.
- All the patients had prostate cancer confined to one or two cores with less than 50% tumour volume in those cores.

Patients had prostate cancer of clinical stage T1c and a Gleason score of 6 or 7(3+4).

## *Efficacy*

*Survival*

Only 1 case series (54 patients, 48 followed up) reported overall and disease-specific survival following the procedure, which was 100%[3].

*Biochemical control*

One retrospective register[2] and 4 case series reported biochemical disease-free survival in the majority of patients[3-6].

The study in which 48 patients were followed up reported that 45/48 (94%) patients had stable serum prostate-specific antigen (PSA) levels at 2 years post-procedure. Of the patients with stable PSA, 53% (24/45) of patients had a biopsy and had negative biopsy results on both the treated and untreated sides. The 4 patients with unstable serum PSA levels at follow-up were diagnosed with persistent tumour in a previously unfrozen portion of their gland and treated with further (total) cryotherapy, following which they had stable PSA levels. One patient developed an unstable PSA at 4 years post-procedure and was shown to have persistent local disease in a previously untreated area[3].

A case series of 31 patients had PSA levels available for 28 patients. Using the American Society for Therapeutic Radiology and Oncology (ASTRO) definition, 93% (26/28 ) of patients demonstrated biochemical disease-free survival[4].

In a case series of 60 patients, 51 patients were followed up and 80% (41/51) of these were biochemically disease free at follow-up according to the ASTRO definition[5].

In a register report of 1160 patients treated by focal cryoablation (total 5853 patients), the biochemical recurrence-free rate was 76% (absolute numbers not reported) at 3-year follow-up according to the ASTRO definition[2].

In a case series of 25 patients, biochemical disease-free survival was determined by varying criteria based on PSA levels. In this study, 36% (9/25) of patients were considered biochemically disease free (defined as a PSA nadir of 1.0 ng/ml or less) [6].

*Biopsy follow-up*

In the register report of 1160 patients, 164 patients underwent biopsy because of increased post-treatment serum PSA levels[2]. Of these patients 26% (43/164) had a  positive biopsy.

In the case series of 54 patients there were no patients with a positive biopsy in a treated portion of the gland at follow-up[3].

The case series of 31 patients demonstrated no evidence of disease at post-procedure biopsy in 96% (24/25) of patients. In this case series cancer was detected in 1 patient in the apex of the untreated lobe 12-months after the procedure. This patient had further treatment and was subsequently clinically disease free[4].

In a case series of 60 patients, 35 patients underwent biopsy of whom 40% (14/35) had positive findings. (tumours were in the untreated lobe except for 1 patient who had a positive biopsy result from the lobe that was treated by the procedure; this patient was treated with whole gland cryoablation). Eleven of these patients were treated with a second cryoablation and 8 were biochemically disease free at last follow-up. One patient was lost to follow-up. [5].

In of the case series of 25 patients, those with a rise in PSA nadir plus 2 ng/ml, or a PSA nadir of less than 50% were eligible for biopsy. Residual or recurrent cancer was found in 3 of the 7 patients eligible, 1 of which was on the ipsilateral side of the cryoablation All of these patients underwent cryoablation and were biochemically disease free at the last follow-up[6].

## *Safety*

*Sexual function*

Studies varied in how impotence was measured, but 4 case series demonstrated that most (61–90%) patients maintained or regained potency[3-6]. In the case series of 60 patients, 67% (40/60) of patients who were sexually potent before treatment became impotent immediately after treatment[5]. 71% (24/34) of patients for whom data were available at 12 months had regained potency. In the case series of 54 patients 90% (36/40) of the patients who were potent before treatment remained potent after treatment[3].

*Urinary continence*

In 3 case series, all patients were continent following treatment[3,4,6]. The case series of 60 patients reported incontinence in 4% (2/55) of patients, although the patients did not require incontinence pads[5]. The register report of 1160 patients reported urinary incontinence in 2% (8/507) of patients at 12 months[2].

*Fistula formation*

Rectourethral fistula was reported in less than 1% (1/1160) of patients in the register report at 12 months[2]. In all 4 case series, there were no reports of fistulae developing after the procedure[3-6].

*Prolonged urinary retention*

Prolonged urinary retention (> 30 days) was reported in 1.2% (6/518) of the patients in a register report at 12 months[2].

*Post-procedural urethral obstruction*

The case series of 54 patients reported that 1 patient required a transurethral prostatectomy for the removal of sloughed tissue[3].

## *Validity and generalisability of the studies*

- There is no evidence from randomised control trials or from non-randomised comparative studies.
- There are no long-term data on mortality from prostate cancer following this procedure.
- There are several variations of the technique which differ regarding the amount of prostate tissue that is destroyed.
- There are differing definitions of biochemical disease-free survival and impotence.

## *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 John Davies and Mr Damian Greene (British Association of Urological Surgeons).

- Both Specialist Advisers have performed this procedure regularly.
- One of the Specialist Advisers stated appropriate comparators are total gland cryotherapy or active monitoring. The other Specialist Adviser stated HIFU as an appropriate comparator.
- Key efficacy outcomes noted were a significant reduction in serial PSA and biopsy-proven evidence of absence of cancer.
- Adverse events reported in the literature and/or own experience were erectile dysfunction and incontinence.
- Theoretical adverse events noted were urinary tract infection, lower urinary tract symptoms and pain.
- This is a minor variation on an existing procedure which is unlikely to alter that procedure's safety and efficacy.
- Special consent is needed to explain the experimental nature of focal cryotherapy and the lack of long-term outcomes.
- There is evidence of the safety of the procedure, the low risk of side-effects and short-term outcomes which are good.

## Patient Commentators' opinions

NICE's Patient and Public Involvement Programme sent ten questionnaires to one trust for distribution to patients who had the procedure (or their carers). NICE received six completed questionnaires.

The patient commentaries reported some instances of sexual dysfunction.

## Issues for consideration by IPAC

- There is no accepted definition of focal ablation using cryotherapy and the studies included used procedures that differed in the amount of prostate tissue destroyed and exact technique used.
- There are only a small number of studies published on this procedure at present.
- There are no studies of long-term survival, for example survival over 10 years following this procedure.

# References


1. Ward JF (2010) Contemporary outcomes of focal therapy in prostate cancer: what do we know so far...World Journal of Urology 28; 593–7

2. Ward JF, Jones JS. Focal cryotherapy for localized prostate cancer: a report from the national Cryo On-Line Database (COLD) Registry. British Journal of Urology International 2011 Oct 28. doi: 10.1111/j.1464-410X.2011.10578.x. [Epub ahead of print]

3. Onik G, Vaughan D, Lotenfoe R et al. (2008) The ‘male lumpectomy’: Focal therapy for prostate cancer using cryoablation results in 48 patients with at least 2-year follow-up. Urologic Oncology: Seminars and Original Investigations 26: 500–505

4. Bahn DK Silverman P Lee Sr F et al. (2006). Focal prostate cryoablation: Initial results show cancer control and potency preservation. Journal of Endourology 9; 688–692

5. Ellis DS, Manny Jr TB, Rewcastle JC (2007) Focal cryosurgery followed by penile rehabilitation as primary treatment for localized prostate cancer: Initial results. Urology 70 (Suppl 6A): 9–15

6. Lambert EH, Bolte K, Masson P et al. (2007) Focal cryosurgery: Encouraging health outcomes for unifocal prostate cancer. Urology 69: 1117–1120

# Appendix A: Additional papers on focal therapy using cryoablation for localised prostate cancer

| Article | Study features | Direction of conclusions | Reason for inclusion in Appendix A |
|---|---|---|---|
| Abreu, A. L. C., Bahn, D., Hung, A. J., Silverman, P., Gill, I. S., and Ukimur, O. 8-Year experience of focal cryotherapy in 75 men with unilateral low-intermediate risk prostate cancer.<br><br>JOURNAL OF ENDOUROLOGY Conference: 29th World Congress of Endourology and SWL WCE 2011 Kyoto Japan. Conference Start: 20111130 Conference End: 20111203. Conference Publication: (var.pagings) A99-2011. | n = 75<br><br>Follow up = 8 years | At up to 8 years following, oncologic and functional outcomes were encouraging. No patient died or developed metastases. Positive biopsies in follow-up: treated lobe (n = 1; 1.8%), untreated lobe (n = 11; 20%). Of the 12men with positive biopsies, 75%(9/12) were followed with active surveillance (n = 7) or repeat focal cryoablation (n = 2); 1 year functional data: Continence rate: 100%. Sexual intercourse rate: 86% in pre-operatively potent men. | Conference publication. |
| **[Chinese].** Guo, Z., Wang, H. T., Xing, W. G., Liu, F., Li, Y., and Yu, H. P. A preliminary clinical study of targeted cryoablation of prostate in the treatment of T3N0M0 prostate cancer]. Zhonghua yi xue za zhi 90 (40) 2815-2819.2010. | n = 40<br><br>Follow up = 3 years | The result of quality of life showed that the sexuality scores decreased at 6 months post-TCAP, but there was no statistical significance ($p = 0.06$) and recovered to baseline level at 12 months. Urinary symptoms improved significantly ($p < 0.01$). The clinical progression rate in this study at 3 years was 24.4% (11/45). To be specific, local recurrence rate was 54.5% (6/11) and distant metastasis rate 45.5% (5/11). Repeated cryoablation was performed for the patients with local recurrence and satisfactory results were achieved during a follow-up of 10–15 months. | Foreign-language paper. |

| Article | Study features | Direction of conclusions | Reason for inclusion in Appendix A |
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| Onik G ( 2008) Rationale for a "male lumpectomy," a prostate cancer targeted approach using cryoablation: results in 21 patients with at least 2 years of follow-up. Cardiovasc Intervent Radiol. 31(1):98-106. | Case series n = 21 Follow-up: range: at least 2 years' follow up | Of the 21 patients, 19 had postoperative biopsies at 1 year. All 19 patients had negative biopsies on both the treated and untreated side. Potency was maintained in 85% (17/20). No complications occurred. | Appears to be including patients already included in Onik (2008) included in table 2 |

# Appendix B: Related NICE guidance for focal therapy using cryoablation for localised prostate cancer

| Guidance | Recommendations |
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| Interventional procedures | **High-intensity focused ultrasound for prostate cancer. NICE interventional procedures guidance 118 (2005).** Available from www.nice.org.uk/guidance/IPG118<br><br>• 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.<br>• 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.<br>• 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).<br><br>**Cryotherapy for recurrent prostate cancer. NICE interventional procedures guidance 119 (2005).** Available from www.nice.org.uk/guidance/IPG119<br><br>• 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.<br>• 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 |

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| | *Information for the public* is recommended. Further research and audit should address quality of life, clinical outcomes and long-term survival.<br><br>**Low dose rate brachytherapy for localised prostate cancer. NICE interventional procedures guidance 132 (2005).** Available from www.nice.org.uk/guidance/IPG132<br><br>• 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.<br>• 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.<br>• 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).<br>• Further research and audit should address quality of life, clinical outcomes and long-term survival.<br><br>**Cryotherapy as a primary treatment for prostate cancer. NICE interventional procedures guidance 145 (2005).** Available from www.nice.org.uk/guidance/IPG145<br><br>• 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.<br>• 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 |

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| | 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.<br>• Further research and audit should address quality of life, clinical outcomes and long-term survival.<br><br>**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<br><br>• 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.<br>• A multidisciplinary team should be involved in the planning and use of this procedure.<br><br>**Laparoscopic radical prostatectomy (2006) NICE interventional procedures guidance 193 (2005).** Available from www.nice.org.uk/guidance/IPG193<br><br>• 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.<br>• 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).<br>• Clinicians undertaking laparoscopic radical prostatectomy require special training. The British Association of Urological Surgeons has produced training standards. |

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| Clinical guidelines | **Prostate cancer: diagnosis and treatment. NICE clinical guideline CG58 (2008).** Available from www.nice.org.uk/guidance/CG58<br><br>• 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.<br>• 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.<br>• Men with low-risk localised prostate cancer who are considered suitable for radical treatment should first be offered active surveillance.<br>• 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.<br>• Healthcare professionals should ensure that men and their partners have early and ongoing access to specialist erectile dysfunction services.<br>• 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.<br>• Healthcare professionals should refer men with intractable stress incontinence to a specialist surgeon for consideration of an artificial urinary sphincter.<br>• Biochemical relapse (a rising PSA) alone should not necessarily prompt an immediate change in treatment.<br>• Hormonal therapy is not routinely recommended for men with prostate cancer who have a biochemical relapse unless they have:<br>– symptomatic local disease progression, or |

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| | – any proven metastases, or<br>– a PSA doubling time < 3 months.<br>• 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.<br>• 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.<br>[1] This may also apply to some men with locally advanced prostate cancer. |

# Appendix C: Literature search for focal therapy using cryoablation for localised prostate cancer

**IP: 968** Focal therapy using cryoablation for localised stage prostate cancer_ Overview

| Database | Date searched | Version/files |
|---|---|---|
| Cochrane Database of Systematic Reviews – CDSR (Cochrane Library) | 29/11/2011 | Issue 4 of 4, Oct 2011 |
| Database of Abstracts of Reviews of Effects – DARE (CRD website) | 29/11/2011 | n/a |
| HTA database (CRD website) | 29/11/2011 | n/a |
| Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library) | 29/11/2011 | Issue 4 of 4, Oct 2011 |
| MEDLINE (Ovid) | 29/11/2011 | 1948 to November Week 3 2011 |
| MEDLINE In-Process (Ovid) | 29/11/2011 | November 28, 2011 |
| EMBASE (Ovid) | 29/11/2011 | 1980 to 2011 Week 47 |
| CINAHL (NLH Search 2.0) | 29/11/2011 | n/a |
| Zetoc | 29/11/2011 | n/a |

### MEDLINE search strategy

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

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| 1 | Cryoablat*.tw. |
| 2 | Cryosurgery/ |
| 3 | cryosurg*.tw. |
| 4 | cryotherap*.tw. |
| 5 | (cryogen* adj3 surg*).tw. |
| 6 | or/1-5 |
| 7 | focal*.tw. |
| 8 | Local*.tw. |
| 9 | focus*.tw. |
| 10 | Lumpect*.tw. |

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| 11 | or/7-10 |
| 12 | Prostatic Neoplasms/ |
| 13 | (Prostat* adj3 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignant*)).tw. |
| 14 | or/12-13 |
| 15 | 6 and 11 and 14 |
| 16 | animals/ not humans/ |
| 17 | 15 not 16 |
| 18 | limit 17 to ed=20110523-20111130 |