NATIONAL INSTITUTE FOR CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedures overview of cryotherapy as a primary treatment 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 October 2004.

Procedure names

- Cryotherapy as a primary treatment for prostate cancer.
- Cryosurgery as a primary treatment for prostate cancer.

Specialty societies

- British Association of Urological Surgeons.
- British Society of Interventional Radiology.

Description

Indications

Prostate cancer.

Cancer of the prostate gland may cause it to enlarge, resulting in symptoms such as difficulty in micturating, frequent micturition, 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 that cancer is 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 management, radiotherapy, and radical prostatectomy.

Historically, cryotherapy was mainly used as a salvage procedure for local failure following radiotherapy treatment for prostate cancer. More recently, it has been used as a primary treatment for patients with localised or locally advanced prostate cancer.

What the procedure involves

Cryotherapy may be performed under general or spinal anaesthesia. A warming catheter is inserted into the urethra, to prevent it being damaged by cold. Cryoneedles or probes are inserted into the prostate, under radiological guidance. Temperature monitor probes may also be placed percutaneously through the perineum. Argon gas or liquid nitrogen is then circulated through the needles or probes generating very low temperatures and causing the formation of ice around the prostate gland, which destroys the tissue. Newer cryotherapy techniques allow for these needles to be removed or repositioned so that the frozen zone conforms to the exact size and shape of the target tissue.

After the procedure, a catheter is inserted and left in place for 1–2 weeks, depending on the post-void residual urine volume.

Efficacy

The main outcomes reported by the studies were biopsy results and survival rates, although different PSA values were used to define biochemical-free survival.

One study of 975 patients reported a 5-year actuarial biochemical disease-free survival of 52% or 63%, depending on the PSA cut-off value. Another study of 590 patients reported a 7-year actuarial biochemical disease-free survival between 62% and 89.5%, depending on the criteria used. The proportion of patients with a negative biopsy was 87% (514/590) after a mean follow-up of 5 years.

One non-randomised study reported that 6 months after standard cryosurgery or total cryosurgery 49% (24/49) and 96% (26/27) of patients respectively had a PSA level of 0.0 to 2.0, compared with 73% (61/83) of patients after radical prostatectomy.

One study reported that 96% (213/223) of patients were satisfied with their cryotherapy treatment after a mean follow-up of 2.3 years.

One Specialist Advisor noted that there were uncertainties about how the procedure affects quality of life and survival. One Specialist Advisor stated that there were too few data to establish whether total prostate ablation is achievable.

Safety

The main complications were impotence, affecting between 72% (39/54) and 100% (76/76) of patients, and incontinence in 1% (1/76) to 18% (10/54) of patients. However, not all studies reported the proportion of patients who had these conditions before the cryotherapy treatment. Five studies, including a total of 1891 patients, reported that between 4% (3/76) and 15% (4/27) of patients required a transurethral resection after the cryotherapy procedure. Four studies reported fistula as a complication, affecting between 0.3% (2/590) and 1.8% (1/54) of patients. Other complications included urinary tract infection, scrotal swelling, pelvic pain, penile tingling and numbness, stricture, stone formation in the prostatic urethra, bladder perforation, paraphimosis and paraesthesia in the legs.

The Specialist Advisors stated that potential adverse events included rectal injury and fistulae, impotence, incontinence, and urethral stricture.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to cryotherapy as a primary treatment for prostate cancer. Searches were conducted via the following databases, covering the period from 1996 to September 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 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.

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.
Patient	Patients with prostate cancer.
Intervention/test	Cryotherapy as a primary treatment.
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 one non-randomised comparative study and six case series that are summarised in Table 1. The non-randomised comparative study compared cryosurgery (with or without cryosurgical destruction of the urethra) with radical perineal prostatectomy.[2] Two large retrospective case series reported results from the USA, one of which was a multicentre study.[3,4] A more recent prospective case series included results from eight centres in the USA.[5] Two smaller prospective case series are included, along with a study that reported results of a questionnaire completed by patients undergoing cryotherapy as a primary treatment for prostate cancer.[6,7,8]

Other studies that are considered to be relevant to this procedure are listed in Appendix A.

Existing reviews on this procedure

A Health Technology Assessment report on the clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer was published in 2003.[9] The review stated that the quality of evidence relating to cryosurgery was not good and mostly comprised retrospective case series. The report concluded that randomised controlled trials with long term follow-up are required to draw conclusions about the relative effectiveness of cryotherapy for localised prostate cancer.

Table 1 Summary of key efficacy and safety findings on cryotherapy as a primary treatment for prostate cancer

Abbreviations used: PSA = prostate specific antigen, BFS = biochemical-free survival, bDFS = biochemical disease-free survival, BRFS = biochemical recurrence-free survival, CI = confidence interval

Study details	Key efficacy findings	Key safety findings	Comments
Gould R (1999)[2] Non-randomised comparative study 1991 onwards USA 159 patients: • 31% (49/159) standard cryosurgery • 17% (27/159) total cryosurgery • 52% (83/159) radical perineal prostatectomy Mean age: • cryosurgery = 67 years (range 53 to 78) • radical prostatectomy = 67 years (range 52 to 76) Mean PSA level: • standard cryosurgery = 10.42 (range 0.7 to 43) • total cryosurgery = 10.64 (range 1.9 to 37) • radical prostatectomy = 10.94 (range 1.4 to 43) Mean tumour grade: • standard cryosurgery = 6.42 • total cryosurgery = 6.8 • radical prostatectomy = 5.75 Follow-up: • total cryosurgery = median follow-up 12 months (range 6 to 24) • radical prostatectomy = mean follow-up 25 months	**Success defined as post-treatment PSA of 0.2 or less** PSA of 0.0 to 2.0 at 6 month follow-up: • standard cryosurgery = 49% (24/49) • total cryosurgery = 96% (26/27) • radical prostatectomy = 73% (61/83) PSA of 0.0 at 6 month follow-up: • standard cryosurgery = 16% (8/49) • total cryosurgery = 67% (18/27) • radical prostatectomy = 48% (40/83) Success in patients with pre-treatment PSA < 10: • standard cryosurgery = 67% (24/36) • radical prostatectomy = 82% (45/55) Success in patients with pre-treatment PSA ≥ 10: • standard cryosurgery = 0% (0/13) • radical prostatectomy = 57% (16/28)	**Complications** Incontinence: • total cryosurgery = 18.5% (5/27) • radical prostatectomy = 16% (4/25) Transurethral resection for obstruction at least 3 months after initial procedure: • total cryosurgery = 15% (4/27) (Early transurethral resection just after completion of total cryosurgery was performed for 12 patients) Rectal injury: • total cryosurgery = 0% (0/27) • radical prostatectomy = 4% (1/25) Fluid in the retroperitoneum: • total cryosurgery = 4% (1/27) • radical prostatectomy = 0% (0/25)	No randomisation. Retrospective study. Patients were selected based on surgeon preference and determination of clinically treatable stage T1c to T2b lesion. Of the 76 cryosurgery procedures, 49 used a standard warming catheter whereas 27 involved destruction of the urethra as well as the prostate (total cryosurgery group). Transurethral resection was used after cryosurgery as an alternative method of urethral and periurethral destruction in 33 patients. Complications were compared for the last 25 consecutive radical prostatectomy patients and the 27 total cryosurgery patients.

Abbreviations used: PSA = prostate specific antigen, BFS = biochemical-free survival, bDFS = biochemical disease-free survival, BRFS = biochemical recurrence-free survival, CI = confidence interval

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Long JP (2001)[3]

Case series (retrospective)

1993–1998

USA (five centres)

975 patients

Age range not stated

Preoperative PSA levels (ng/ml):
< 4 = 13% (131/975)
4 to 10 = 54% (521/975)
> 10 = 33% (318/975)
not determined = 0.5% (5/975)

Preoperative Gleason score:
2–5 = 14% (138/975)
6 = 32% (303/975)
7 = 42% (401/975)
8–10 = 12% (115/975)
missing = 2% (18/975)

Preoperative clinical stage:
T1 = 11% (101/975)
T2 = 64% (604/975)
T3 = 24% (222/975)
T4 = 2% (15/975)
Missing = 3% (33/975)

Inclusion criteria: clinical stages T1 to T4, any PSA level, any Gleason grade

Exclusion criteria: metastatic disease, failure of previous radiation therapy

Median follow-up = 24 months</td>
<td>Primary outcome measures: biochemical-free survival (BFS) using 2 different criteria and biopsy results, stratified according to risk for biochemical relapse

• Low-risk = stage T2a or less, PSA level ≤ 10, and Gleason score ≤ 6
• Medium-risk = patients with any 1 of the following: disease at stage 2b or greater, PSA level > 10 ng/ml, Gleason score > 7
• High-risk = 2 or 3 of the following: disease at stage 2b or greater, PSA level > 10 ng/ml, Gleason score > 7

5-year actuarial BFS
<table>
<tr><th></th><th>PSA cutoff 0.5 ng/ml</th><th>PSA cutoff 1.0 ng/ml</th></tr>
<tr><td>All patients</td><td>52%</td><td>63%</td></tr>
<tr><td>Low-risk</td><td>60%</td><td>76%</td></tr>
<tr><td>Medium-risk</td><td>61%</td><td>71%</td></tr>
<tr><td>High-risk</td><td>36%</td><td>45%</td></tr>
</table>
Positive biopsy:
• Overall = 18% (denominator unclear)
• Low-risk patients = 12%
• Medium-risk patients = 12%
• High-risk patients = 24%</td>
<td>Complications

• Incontinence = 7.5% (73/975)
• Impotence = 93% (907/975)
• Transurethral resection of the prostate = 13% (127/975)
• Fistula = 0.5% (5/975)</td>
<td>Includes some patients from the same institute as Bahn et al, 2002.

Treatment protocols varied among the different study centres (in terms of number of cryoprobes, number of freeze-thaw cycles, use of thermocouples, use of liquid nitrogen or argon-based cooling systems).

Androgen deprivation therapy was used for 3 to 8 months before the procedure on 30% of patients.

Proportion of patients who were incontinent or impotent before the surgery was not stated.</td>
</tr>
</table>

Abbreviations used: PSA = prostate specific antigen, BFS = biochemical-free survival, bDFS = biochemical disease-free survival, BRFS = biochemical recurrence-free survival, CI = confidence interval

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Bahn DK (2002)[4]

Case series (retrospective)

1993–2001

Michigan, USA

590 patients

Mean age = 71 years

Preoperative PSA levels (ng/ml):
< 4 = 16% (97/590)
4 to 10 = 59% (348/590)
> 10 = 24% (145/590)

Preoperative Gleason score:
< 7 = 41% (241/590)
7 = 52% (310/590)
> 7 = 6% (35/590)
missing = 0.7% (4/590)

Preoperative clinical stage:
T1 = 2% (11/590)
T2 = 78% (461/590)
T3 = 18% (104/590)
T4 = 2% (12/590)
Missing = 0.3% (2/590)

Inclusion criteria: localised or locally advanced prostate cancer (TNM stage T1 to T3)

No exclusion criteria were described

Mean follow-up = 5.4 years</td>
<td>Primary outcome measures: biochemical disease-free survival (bDFS) using 3 different criteria and biopsy results, stratified according to risk for biochemical relapse
• Low-risk = stage T2a or less, PSA level ≤ 10, and Gleason score ≤ 6
• Medium-risk = patients with any 1 of the following: disease at stage 2b or greater, PSA level > 10 ng/ml, Gleason score > 7
• High-risk = 2 or 3 of the following: disease at stage 2b or greater, PSA level > 10 ng/ml, Gleason score > 7

7-year actuarial bDFS
<table>
<tr><th></th><th>PSA cutoff 0.5 ng/ml</th><th>PSA cutoff 1.0 ng/ml</th><th>ASTRO criteria</th></tr>
<tr><td>All patients</td><td>62%</td><td>76%</td><td>89.5%</td></tr>
<tr><td>Low-risk</td><td>61%</td><td>87%</td><td>92%</td></tr>
<tr><td>Medium-risk</td><td>68%</td><td>79%</td><td>89%</td></tr>
<tr><td>High-risk</td><td>61%</td><td>71%</td><td>89%</td></tr>
</table>
ASTRO (American Society for Therapeutic Radiology and Oncology) criteria: biochemical failure of 3 successive increases in PSA

Negative biopsy (stratified by preoperative characteristics):
• PSA <4 ng/ml = 92% (89/97)
• PSA 4–10 ng/ml = 89% (310/348)
• PSA >10 ng/ml = 79% (115/145)
• Gleason score 3–6 = 92% (221/241)
• Gleason score 7 = 84% (262/310)
• Gleason score 8–9 = 80% (28/35)
• Stage T1 = 100% (11/11)
• Stage T2 = 90% (414/461)
• Stage T3 = 74% (77/104)
• Overall = 87% (514/590)</td>
<td>Complications

• Impotence after surgery in patients who were potent before the surgery = 95% (354/373)

(5% [19/354] of patients recovered their potency with an average recovery time of 16 months)

• Persistent incontinence (any leakage) after surgery in patients who were continent before the surgery = 16% (85/533)

• Persistent incontinence (use of pads) after surgery in patients who were continent before the surgery = 4% (23/533)

• Fistula = 0.3% (2/590)

• Transurethral resection of the prostate = 6% (32/590)</td>
<td>Consecutive patients.

The procedure evolved over the study period. Initially, patients were treated with a liquid nitrogen cryomachine. This was later changed to an argon-based cryomachine.

Curative intent.

The paper states that 2 patients had a fistula, with a rate of 0.004%. It is unclear what denominator was used to achieve this result.

Seven-year data were available for 33% (196/590) of patients. Losses to follow-up are not described.

Number of patients who underwent biopsy at different time intervals:
<table>
<tr><th>Time since cryotherapy (months)</th><th>Number of patients biopsied</th></tr>
<tr><td>6</td><td>436</td></tr>
<tr><td>12</td><td>403</td></tr>
<tr><td>24</td><td>301</td></tr>
<tr><td>48</td><td>78</td></tr>
<tr><td>60</td><td>41</td></tr>
</table>
</td>
</tr>
</table>

Abbreviations used: PSA = prostate specific antigen, BFS = biochemical-free survival, bDFS = biochemical disease-free survival, BRFS = biochemical recurrence-free survival, CI = confidence interval

Study details	Key efficacy findings	Key safety findings	Comments
Han KR (2003)[5] Case series (prospective) 2000–2002 USA (8 centres) 122 patients Mean age = 69.7 years (range 53 to 85) Preoperative PSA levels (ng/ml): ≤ 10 = 74.6% (91/122) > 10 = 25.4% (31/122) Preoperative Gleason score: 2–5 = 15.6% (19/122) 6 = 45.9% (56/122) 7 = 23.8% (29/122) 8–10 = 14.7% (18/122) Preoperative clinical stage: T1 = 43.8% (53/122) T2 = 52.1% (63/122) T3 = 4.1% (5/122) Inclusion criteria: biopsy-proven prostate cancer Follow-up: 12 months	**Primary outcome measures: biochemical recurrence-free survival (BRFS) defined as PSA 0.4 ng/ml or less, stratified according to risk for biochemical relapse** • Low-risk = stage T1 or T2, PSA level ≤ 10, and Gleason score < 7 • High-risk = stage T3, PSA level > 10 ng/ml, Gleason score ≥ 7 BRFS at 3 months: • Overall = 81% (96/118) • Low-risk = 86% (50/58) • High-risk = 77% (46/60) • Primary cryotherapy = 81% (82/101) BRFS at 12 months: • Overall = 75% (76/106) • Low-risk = 78% (42/54) • High-risk = 71% (37/52) • Primary cryotherapy = 74% (66/89)	**Complications (primary cryotherapy only)** • Incontinence requiring pads = 3% (3/99) • Urge incontinence (no pads) = 5% (5/99) • Urethral sloughing = 5% (5/102) • Penile tingling/numbness = 2% (2/100) • Impotence = 87% (83/95) • Pelvic pain = 6% (6/100) • Scrotal swelling = 5% (5/101)	It is not clear whether patients were consecutive. 3rd generation cryosurgery. Salvage cryotherapy was performed on 15% (18/122) of patients. Approximately one-third of patients received preoperative hormone therapy. Proportion of patients who were incontinent or impotent before the surgery was not stated. 3-month results may have been biased by the effect of neoadjuvant hormone therapy. 87% (106/122) of patients were available for 12-month follow-up. Losses to follow-up were not described.

Abbreviations used: PSA = prostate specific antigen, BFS = biochemical-free survival, bDFS = biochemical disease-free survival, BRFS = biochemical recurrence-free survival, CI = confidence interval

Study details	Key efficacy findings	Key safety findings	Comments
Donnelly B (2002)[6] Case series (prospective) 1994–1998 Alberta, Canada 76 patients (87 cryosurgical procedures) Mean age = 65 years (range 51 to 77) Mean PSA level = 9.7 ng/ml (range 1.5 to 30) Preoperative Gleason score: 5 to 6 = 45% (34/76) 7 = 38% (29/76) 8 to 10 = 17% (13/76) Preoperative clinical stage: T1–2 = 88 % (67/76) T3 = 12% (9/76) Inclusion criteria: histologically proven adenocarcinoma of the prostate, PSA level ≤ 30 ng/ml Exclusion criteria: gland size > 60g, prior radiotherapy, evidence of metastatic disease, inability to give informed consent Median follow-up = 60.8 months (range 35 to 85)	**Primary outcome measures: 5-year survival rate, biopsy results and PSA levels, stratified by risk group** • Low-risk = stage T2a or less, PSA level < 10, and Gleason score ≤ 6 • Moderate-risk = patients with any 1 of the following: disease at stage 2b or greater, PSA level > 10 ng/ml, Gleason score ≥ 7 • High-risk = 2 or 3 of the following: disease at stage 2b or greater, PSA level > 10 ng/ml, Gleason score ≥ 7 5-year overall survival rate = 89% (95% CI, 83% to 97%) 5-year cancer-specific survival rate = 98.6% (95% CI, 96% to 100%) Negative biopsy after one or more treatments = 98.6% (72/73) Three patients did not have biopsies; one had developed metastases, one declined, and one had postoperative sloughing 14% (10/73) patients required two treatments 1.4% (1/73) patients required three treatments **PSA levels < 0.3 ng/ml (Kaplan-Meier analysis):** • Low-risk patients (n = 13) = 60% (95% CI, 38% to 95%) • Moderate-risk patients (n = 23) = 77% (95% CI, 60% to 97%) • High-risk patients (n = 40) = 48% (95% CI, 34% to 68%) **PSA levels < 1.0 ng/ml (Kaplan-Meier analysis):** • Low-risk patients = 75% (95% CI, 54% to 100%) • Moderate-risk patients = 89% (95% CI, 76% to 100%) • High-risk patients = 76% (95% CI, 64% to 91%)	**Complications** • Incontinence = 1.3% (1/76) • Testicular abscess = 1.3% (1/76) • Sloughing requiring transurethral resection of the prostate = 3.9% (3/76) • Impotence = 100% (76/76) At 3 years, 47% (18/38) of patients capable of unassisted intercourse at the time of cryosurgery had resumed sexual intercourse, 5 spontaneously and 13 with sexual aids	Consecutive patients. Twenty six patients had a 3-month course of neoadjuvant hormone treatment prior to cryosurgery. Follow-up biopsies were performed 5 to 6 months after the procedure or of the PSA level rose to greater than 1.0 ng/ml. Repeated cryosurgery was performed if a positive biopsy was found and there was no evidence of metastatic disease. The authors note that there is a lengthy learning curve.

Abbreviations used: PSA = prostate specific antigen, BFS = biochemical-free survival, bDFS = biochemical disease-free survival, BRFS = biochemical recurrence-free survival, CI = confidence interval

Study details	Key efficacy findings	Key safety findings	Comments
Aus G (2002)[7] Case series (prospective) 1995–1997 Sweden 54 patients Mean age = 68.1 years (range 50 to 78) Preoperative PSA levels (ng/ml): 0 to10 = 31.5% (17/54) >10 = 66.7% (36/54) not determined = 1.8% (1/54) Preoperative Gleason score: 2– 4 = 25.9% (14/54) 5–6 = 37.0% (20/54) 7–10 = 37.0% (20/54) Preoperative clinical stage: T1 = 14.8% (8/54) T2 = 44.4% (24/54) T3 = 40.7% (22/54) Median follow-up = 58.5 months	**Primary outcome measures: actuarial progression-free survival (PSA of > 1 ng/ml or positive biopsy was interpreted as progression)** Actuarial progression-free survival at 58.5 months = 38.9% At last follow-up: • Progression-free = 35.2% (19/54) • Local or biochemical recurrence only = 51.8% (28/54) • Alive with metastatic disease = 5.6% (3/54) Positive biopsy during follow-up period = 28% (14/50) At the last visit, 38.8% (21/54) of patients had started hormonal therapy and 4 underwent radiation treatment for local failure	**Complications** • Incontinence requiring pads = 18.5% (10/54) • Sloughing needing treatment = 14.8% (8/54) • Stricture = 16.7% (9/54) • Stone formation in prostatic urethra = 9.3% (5/54) • Urinary tract infection = 33.3% (18/54) • Fistula/abscess = 1.8% (1/54) • Impotence = 72.2% (39/54) • Bladder perforation = 1.8% (1/54) • Paraphimosis requiring surgery = 1.8% (1/54) • Paraesthesia in both legs = 1.8% (1/54)	75.9% (41/54) of patients received neoadjuvant hormonal therapy. 5.6% (3/54) of patients had received previous radiation therapy. Proportion of patients who were incontinent or impotent before the surgery was not stated. The authors note that they have stopped using this treatment modality because of the high complication rates and poor oncological outcome.

Abbreviations used: PSA = prostate specific antigen, BFS = biochemical-free survival, bDFS = biochemical disease-free survival, BRFS = biochemical recurrence-free survival, CI = confidence interval

Study details	Key efficacy findings	Key safety findings	Comments
Badalament R (1999)[8] Case series (questionnaire mailed to patients 1993–1994 USA 223 patients Mean age = 65.2 years (range 46.4 to 91.7) Mean follow-up = 2.3 years (range 1.3 to 3.1)	Overall patient satisfaction = 96% (213/223)	**Complications** • Incontinence requiring pads = 4.3% (9/208) • Impotence = 85% (168/198) • Urethrorectal fistula = 0.4% (1/223) • Bladder outlet obstruction caused by bladder neck contracture or sloughing, requiring transurethral resection = 10% (22/223) • Scrotal swelling = 18% (41/223) • Penile tingling = 15% (34/223) • Pelvic pain = 12% (27/223)	Consecutive patients. This study is likely to include some of the same patients as Bahn et al (2002). Response rate for questionnaire = 92% (267/290). 16% (44/267) patients were excluded because of prior treatment.

Validity and generalisability of the studies

- The technology involved in this procedure is continually evolving and there have been a number of modifications to the procedure initially described in the literature, including the use of thermocouple monitoring, urethral warming systems and cryoneedles.

- As such, earlier studies may have less favourable outcomes, particularly in terms of morbidity – and later studies will have shorter-term follow-up and perhaps reflect a learning curve.

- The treatment protocols varied within and between studies.

- Some studies reported that a proportion of patients were treated with neoadjuvant hormone therapy prior to cryosurgery.

- Two studies reported that patients were excluded if they had had prior radiotherapy. [3,6] One study stated that 6% (3/54) of patients had received previous radiation therapy.[7] The remaining studies did not state whether any of the patients had already received radiotherapy.

- One study reported that some patients received more than one cryotherapy session and presented the results after multiple treatments.[6]

- Different definitions were used to describe outcomes. This is particularly evident in terms of the PSA level used as an indication of a cure or a biochemical failure, where the cut-off points used in the studies ranged from 0.2–1.0 nanograms/ml.

Specialist Advisors' opinions

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

- Cryotherapy of the prostate has been around for a long time, but the technology has advanced. Newer cryotherapy machines use smaller needles and are more controllable than earlier versions.

- The key efficacy outcomes are 5- and 10-year biochemical-free survival and PSA levels.

- This procedure is likely to have a minor to moderate impact on the NHS.

- Cryotherapy is only one of a number of options available for the treatment of prostate cancer.

Issues for consideration by IPAC

A Cochrane systematic review of cryotherapy for localised prostate cancer is in progress and is due to be published in 2005 (Issue 4).[10]

Salvage cryotherapy for recurrent prostate cancer has previously been considered by IPAC.

References

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

2 Gould RS. Total cryosurgery of the prostate versus standard cryosurgery versus radical prostatectomy: comparison of early results and the role of transurethral resection in cryosurgery. *Journal of Urology* 1999; 162: 1653–7.

3 Long JP, Bahn D, Lee F, et al. Five-year retrospective, multi-institutional pooled analysis of cancer-related outcomes after cryosurgical ablation of the prostate. *Urology* 2001; 57: 518–23.

4 Bahn DK, Lee F, Badalament R, et al. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology* 2002; 60: 3–11.

5 Han KR, Cohen JK, Miller RJ, et al. Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience. *Journal of Urology* 2003; 170: 1126–30.

6 Donnelly BJ, Saliken JC, Ernst DS, et al. Prospective trial of cryosurgical ablation of the prostate: five-year results. *Urology* 2002; 60: 645–9.

7 Aus G, Pileblad E, Hugosson J. Cryosurgical ablation of the prostate: 5-year follow-up of a prospective study. *European Urology* 2002; 42: 133–8.

8 Badalament RA, Bahn DK, Kim H, et al. Patient-reported complications after cryoablation therapy for prostate cancer. *Urology* 1999; 54: 295–300.

9 Hummel S, Paisley S, Morgan A et 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.

10 Dublin N, Shelley M, Wilt TJ, et al. Cryotherapy for localised prostate cancer. *The Cochrane Database of Systematic Reviews* 2004, Issue 4.

Appendix A: Additional papers on cryotherapy as a primary treatment for prostate cancer not included in the summary tables

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Anastasiadis AG, Sachdev R, Salomon L, et al. Comparison of health-related quality of life and prostate-associated symptoms after primary and salvage cryotherapy for prostate cancer. *Journal of Cancer Research & Clinical Oncology* 2003; 129: 676–82.	131 patients.	Question-naire response rate = 62%	Primary cryotherapy patients had significantly better physical and social function than salvage patients. Incontinence = 6% Erectile dysfunction = 86%
Cohen JK, Miller RJ, Rooker GM, et al. Cryosurgical ablation of the prostate: two-year prostate-specific antigen and biopsy results. *Urology* 1996; 47: 395–401.	383 patients. Follow-up = 2 years.	Case series.	79% negative biopsy after 1 or more treatments. 88% negative biopsy for patients with prior hormone treatment.
De la Taille A, Benson MC, Bagiella E, et al. Cryoablation for clinically localized prostate cancer using an argon-based system: complication rates and biochemical recurrence. *BJU International* 2000; 85: 281–6.	35 patients. (16 primary)	Case series.	Biochemical recurrence-free survival = 70% at 9 months.
Derakhshani P, Neubauer S, Braun M, et al. Cryoablation of localized prostate cancer. Experience in 48 cases, PSA and biopsy results. *European Urology* 1998; 34: 181–7.	48 patients. Median follow-up = 15 months.	Case series.	Positive biopsy: T1 tumours = 0% T2 tumours = 17% T3 tumours = 27% 10% transurethral resection.
Ellis D. Cryosurgery as primary treatment for localized prostate cancer: a community hospital experience. *Urology* 2002; 60: 34–9.	93 patients (75 parimary)	Case series.	PSA level < 0.4 ng/ml = 84%.
Koppie TM, Shinohara K, Grossfeld GD, et al. The efficacy of cryosurgical ablation of prostate cancer: the University of California, San Francisco experience. *Journal of Urology* 1999; 162: 427–32.	176 patients. Mean follow-up = 31 months	Case series.	Positive biopsy = 38%. Biochemical disease-free survival at 3 years: Low risk = 69% High risk = 45%
Long JP, Fallick ML, LaRock DR, et al. Preliminary outcomes following cryosurgical ablation of the prostate in patients with clinically localized prostate carcinoma. *Journal of Urology* 1998; 159: 477–84.	145 patients. Mean follow-up = 36 months.	Case series.	Overall actuarial progression-free rate at 60 months = 56%. 87% negative biopsy.
Robinson JW, Saliken JC, Donnelly BJ, et al. Quality-of-life outcomes for men treated with cryosurgery for localized prostate carcinoma. *Cancer* 1999; 86: 1793 –801.	69 patients.	Question-naire	With the exception of sexual function, all aspects of well-being had returned to pre-treatment levels by 12 months.

Article title	Number of patients/ follow-up	Comments	Direction of conclusions
Saliken JC, Donnelly BJ, Brasher P, et al. Outcome and safety of transrectal US-guided percutaneous cryotherapy for localized prostate cancer. *Journal of Vascular & Interventional Radiology* 1999; 10: 199–208.	71 patients. Follow-up = 10 to 36 months.	Case series.	99% (68/69) negative biopsy. 67% (43/64) undetectable PSA level at 1 year.
Wong WS, Chinn DO, Chinn M, et al. Cryosurgery as a treatment for prostate carcinoma: results and complications. *Cancer* 1997; 79: 963–74.	83 patients.	Case series.	High failure rate for patients who did not have temperature monitoring. 90% negative biopsy for patients who had temperature monitored.
Zisman A, Pantuck AJ, Cohen JK, et al. Prostate cryoablation using direct transperineal placement of ultrathin probes through a 17-gauge brachytherapy template – technique and preliminary results. *Urology* 2001; 58: 988–93.	92 patients (71 primary)	Case series.	No major complications. 8% minor complications.

Appendix B: Literature search for cryotherapy 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.

31. cryotherapy/
32. cryotherapy.tw.
33. cryoprobe.tw.
34. freez$ therapy.tw.
35. cryo$ ablation.tw.
36. cryoablation.tw.
37. cryosurgery/
38. cryosurgery.tw.
39. cold therapy.tw.
40. or/31-39
41. (prostat$ adj3 carcinoma$).tw.
42. (prostat$ adj3 tumo?r).tw.
43. (prostat$ adj3 cancer$).tw.
44. *prostatic neoplasms/
45. prostat$ neoplasm$.tw.
46. or/41-45
47. 40 and 46
48. limit 47 to human