Third-generation cryotherapy for prostate cancer in the UK: a prospective study of the early outcomes in primary and recurrent disease

JOANNE CRESSWELL, SUSAN ASTERLING, MOAZZAM CHAUDHARY, NAEEM SHEIKH and DAMIAN GREENE
Sunderland Royal Hospital, Sunderland, UK

Accepted for publication 17 November 2005

OBJECTIVE

To present the early results of the use of third-generation cryotherapy in primary and recurrent prostate cancer at one UK centre.

PATIENTS AND METHODS

Over a 14-month period 51 patients underwent cryotherapy for prostate cancer. In 31 patients cryotherapy was used as the primary treatment and in 20 as a salvage treatment after radiotherapy or hormone ablation. Data were collected prospectively and the median follow-up was 9 months.

RESULTS

The prostate-specific antigen (PSA) level decreased to <0.5 ng/mL in 79% of patients undergoing primary treatment and in 67% of patients undergoing salvage treatment. A higher Gleason grade and PSA levels were associated with a poorer outcome. No patient developed a fistula, 4% developed urinary retention requiring transurethral prostatectomy and 4% had persistent incontinence. The rates of erectile dysfunction were high (86%). The median inpatient stay was 2 days.

CONCLUSION

Early results suggest that cryotherapy offers a safe alternative for primary and recurrent prostate cancer, particularly for older and less fit patients. Long-term data are required to assess the durability of response and the effect on survival.

KEYWORDS

cryotherapy, prostate cancer, recurrence, treatment

INTRODUCTION

Cryotherapy is defined as the ablation of tissue by local induction of very low temperatures. The development of cryotherapy for localized prostate cancer provides a potentially curative option for patients with primary or recurrent disease, with less morbidity than with radical surgery.

First-generation cryotherapy using liquid nitrogen was used in the 1960s and produced equivalent results to the other treatments available at that time. Initial results showed a 41% recurrence rate, but a long-term review of these patients revealed a 78% recurrence rate [1–3]. Recurrence rates and overall survival were comparable with other treatments but complications, including urethro-rectal fistulae and sloughing of urethral tissue, were common. Technical limitations included difficulty in controlling the ice-ball and lack of monitoring of surrounding structures. Further improvements and the introduction of urethral warming catheters allowed the development of second-generation cryotherapy [4]. Subsequent technological refinements enabled percutaneous access using brachytherapy templates with TRUS guidance.

Complication rates have been reduced with the advent urethral warming catheters and temperature monitoring probes. Cryoprobes exploit the properties of inert gases to produce rapid cooling and warming. The Joule-Thompson principle dictates that rapidly expanding argon gas cools the cryoprobe tip to very low temperatures, and helium is used to induce thawing. Gas-based probes are much smaller (17 G) than their liquid nitrogen-based counterparts, a characteristic allowing percutaneous placement, and conformal cryosurgery with more probes and more accurate placement [5].

Third-generation cryotherapy has also revolutionized treatment. Long-term studies suggest a biochemical disease-free survival of ≈60% at 7 years for patients undergoing cryotherapy as a primary treatment [6]. Cryotherapy is also used as a salvage treatment for recurrence after surgery, radiotherapy or hormone treatment. The National Institute for health and Clinical Excellence issued guidance supporting the use of cryotherapy for recurrent prostate cancer in May 2005, but it was acknowledged that the effects on long-term survival remain uncertain [7]. Most studies are retrospective and with a limited follow-up, and the treatment groups are heterogeneous, therefore results are variable. One of the larger salvage series reported disease-free survival at 2 years of 28–74% [8]. Pre-treatment PSA level and Gleason grade are important in predicting outcome [9]. Whilst several reports show sustained PSA control in high-risk patient groups undergoing cryosurgery, less attention has been placed on important quality-of-life (QoL) issues such as LUTS, continence, potency and postoperative discomfort.

We present the first 51 consecutive patients to be treated at our centre. Data were collected prospectively for all patients; we believe these are the first published results of a large series of third-generation cryosurgery for prostate cancer in the UK.

PATIENTS AND METHODS

Fifty-one patients were treated with cryotherapy for prostate cancer between August 2003 and May 2005. In 31 patients, cryotherapy was used as primary treatment and as salvage therapy in 17 previously treated with radiotherapy (14 external beam radiotherapy (EBRT), and three brachytherapy), and three after hormone treatment alone. The data are presented separately for primary and salvage treatment; the patients' characteristics are shown in Table 1.

TABLE 1 The patients' characteristics before cryotherapy. For the IPSS and QoL scores the values at 9 months after cryotherapy are also included

Variable	Primary (31 men)		Salvage (20 men)
	High risk (14)	Low risk (17)	
Median (range):			
Age, years	64 (51–76)		66 (56–79)
Pre-treatment PSA, ng/mL	13.9 (8–25.4)	6 (1.6–9.5)	7 (2.5–21.1)
TRUS volume, mL	30.8 (16.4–70.6)		23.3 (6.05–50.6)
IPSS			
before	16 (0–26)		6 (1–20)
at 9 months	8 (1–35)		11 (6–29)
QoL score			
before	3 (0–5)		1 (0–5)
at 9 months	1 (0–6)		2.5 (0–5)
Gleason grade, n			
<7	11	17	10
≥7	3	0	6
Pre-treatment stage, n			
T2	9	14	14
T3	5	3	5
Pre-existing ED	16/29		16/20

For primary patients, a positive biopsy, negative MRI and negative bone scan were prerequisites. For patients with radiotherapy failure (EBRT or brachytherapy), or primary hormone failure, a repeat negative MRI, bone scan and a positive re-biopsy were required. Sampling for staging the seminal vesicles could be used at re-biopsy [10]. Of the patients undergoing salvage treatment, 11 of 20 had biopsy-confirmed recurrence; this group comprised seven who previously had EBRT, two previously treated with brachytherapy and two previously treated with hormones alone. The remaining nine patients were re-biopsied elsewhere and referred to our centre for treatment.

Before surgery, patients were instructed on the use of a liquid diet and a preparation of Picolax was given. Lack of adequate bowel preparation is a difficult problem and interferes with adequate prostate visualization on TRUS. All surgery was performed under general anaesthesia, with the patient in the lithotomy position. One urologist administered all treatments using an argon-based cryotherapy system (Oncura, Amersham, UK) with imaging using TRUS. Initially cystoscopy was used and a suprapubic catheter placed; after introducing a guidewire along the urethra, a warming urethral catheter was placed before starting tissue freezing. A brachytherapy template was used to place 12–16 17-G cryoneedles and two thermosensors (one centrally within the prostate, the second in Denonvilliers' fascia, Fig. 1). The number of cryoprobes varied with prostate size, and two warming probes were inserted along the line of Denonvilliers' fascia to limit ice-ball extension toward the rectum. Cryoneedles were placed 5 mm from the prostate capsule and 1 cm apart. Particular care was taken not to place cryoneedles too close to the posterior prostate capsule, the closest relationship with the rectal wall.

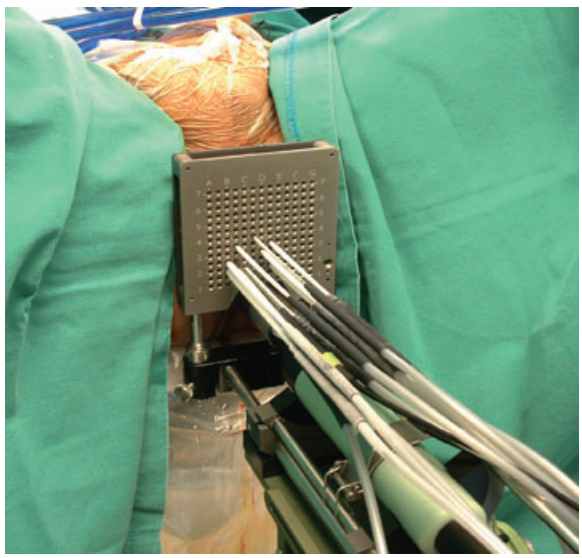


FIG. 1.
Photograph showing the intraoperative set-up with the template and cryoprobes used.

Freezing with argon gas to < −40°C was initiated and monitored using the thermosensors, and TRUS guidance, which revealed an acoustic shadow as the ice-ball formed (Fig. 2). After maintaining −40°C or the lowest temperature below −25°C for 10 min, a passive thaw was initiated until the temperature reached a plateau. At this point, active thawing with helium was started. Two freeze-thaw cycles were used, and for larger prostates (≈ 30 mm long or greater) retraction was used for the second cycle, providing the sphincter was not at risk.

Pressure was placed on the perineum for 15 min after withdrawing the needles. The urethral warming catheter was initially left *in situ* for 15 min [11], but this was increased to 45 min after introducing new protocols in August 2004, to reduce discomfort [10]. The suprapubic catheter was left in place for 2 weeks after cryotherapy.

The PSA level was measured and the patient clinically assessed at 6 weeks and then at 3-monthly intervals. The clinical assessment included the IPSS and disease-specific QoL

FIG. 2. Ultrasonogram of: (a) the prostate with cryoneedles in situ *before freezing; (b) transverse image of the ice-ball at the end of the freeze-cycle; and (c) longitudinal image of the ice-ball at the end of the freeze-cycle.*

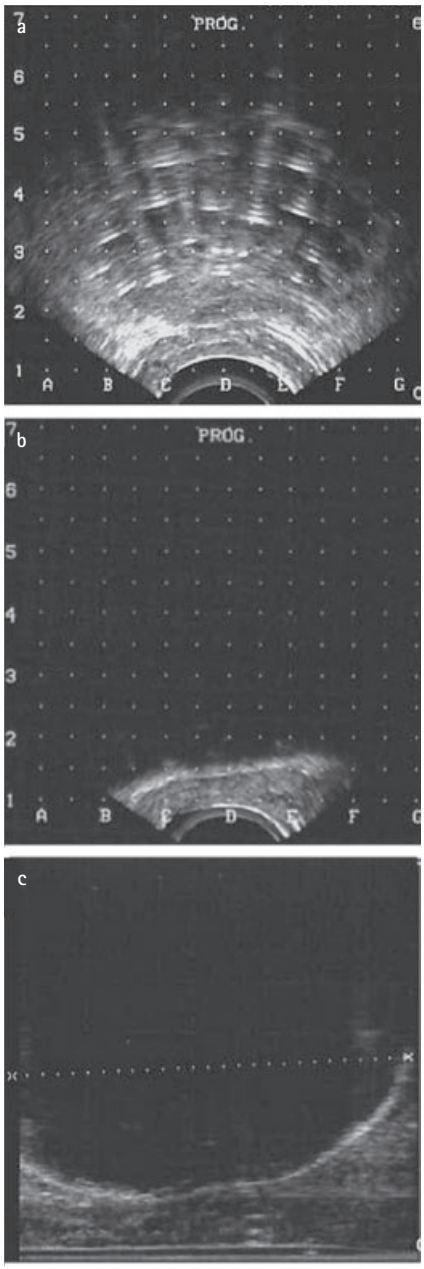
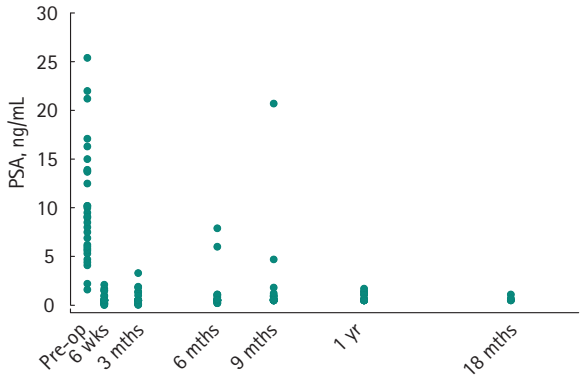


FIG. 3. Biochemical response to cryotherapy in patients undergoing primary treatment.



score [12,13] to assess urinary symptoms, the patient's assessment of erectile function, and a QoL questionnaire.

RESULTS

The Gleason grade was ≤7 in 38 patients and >7 in nine (the grade was not recorded for four patients in whom radiation therapy had failed). The median (range) PSA level for primary and salvage treatment was 9 (1.6–25.4) and 7 (2.5–21.1) ng/mL, respectively. In the primary group 23 of 31 (74%) patients had clinical stage T2 (TNM classification), and 8 (26%) had stage T3. For the salvage group 14 of 19 had stage T2 (73%) and five had stage T3 (26%) disease. For one patient (after radiotherapy) the clinical stage was not recorded.

Previous series stratified patients having primary treatment into high-risk (PSA level ≥10 ng/mL or Gleason grade >7) and low-risk (PSA level <10 ng/mL and Gleason grade ≤7) [14]. Using these criteria, in the present series 14 patients were considered high-risk and had a median PSA level of 13.9 (8–25.4) ng/mL, with a Gleason grade of ≥7 in three and <7 in 11. In this high-risk group nine men had clinical stage T2 and five had clinical stage T3 disease. There were 17 patients (55%) stratified as low-risk; these patients had a median PSA of 6 (1.6–9.5) ng/mL and a Gleason grade of <7 in all. In the low-risk group 14 had a clinical stage of T2 and three of T3.

As for brachytherapy, large prostate glands are not usually treated with cryotherapy; in the present series the median volume was 30.8 (16.4–70.6) mL for primary treatment and 23.3 (6.05–50.6) mL for salvage cases. Patients with prostates significantly >50 mL were treated with bicalutamide for ≈3 months before cryotherapy to reduce prostate size. The prostate volume was measured again by TRUS before treatment to ensure that the prostate size was suitable for treatment.

Sixteen of the patients undergoing primary treatment had pre-existing erectile dysfunction (ED), with 13 reporting no problems; in two patients this was not recorded. For the salvage patients, 16 reported ED before cryotherapy.

The IPSS was recorded before cryotherapy in 20 patients in the primary treatment group, with a median score of 16 and a wide variation among patients. For 18 of the salvage patients the median IPSS was 6 (1–20). The median stay after cryotherapy was 2 days, with 20 patients discharged on the first day, 28 on the second and three on the third day. The median follow-up was 9 (1.5–18) months. For primary treatment, 23 of 29 (79%) patients had a complete response to cryotherapy by 6 weeks (a complete response was recorded if the PSA level was <0.5 ng/mL; Fig. 3). For the group stratified as low-risk there was a complete response in 12 of 15, and for the high-risk group in 10 of 14. A further two patients had a PSA level of <1 ng/mL, and all showed a marked reduction in PSA level. Overall at 3 months, 21 of 27 (78%) patients, and at 1 year nine of 15, had a PSA level of ≤0.5 ng/mL (Fig. 3). Within the low-risk group, 11 of 13, and in the high-risk group 10 of 14 maintained a PSA level of <0.5 ng/mL at 3 months. At 1 year after cryotherapy the low- and high-risk groups had the same response rate, at six of 10 and three of five patients, respectively. There was a sustained rise in PSA level (>0.1 ng/mL increase on two consecutive serum analyses) after cryotherapy in six of 25 patients (24%). Where practical, disease recurrence was detected using MRI, bone scans or re-biopsy of the prostate. One of the patients with a rapidly rising PSA level developed metastatic prostate cancer after 1 year, detected on a bone scan. One patient was re-biopsied and residual cancer was confirmed, and MRI showed extracapsular extension. A further patient is due to have his prostate re-biopsied. To date no patient has had repeat cryotherapy for

residual cancer. One patient who had primary treatment and had a complete response subsequently died from a stroke at 6 months after cryotherapy.

For salvage treatment, 12 of 18 (67%) patients had a complete response to cryotherapy by 6 weeks (Fig. 4); at 3 months this response persisted in 10 of 15 and in four of six at 1 year (Fig. 4). Three patients failed to respond to cryotherapy, with PSA levels continuing to increase afterward. One of these patients had pelvic MRI showing lymph node involvement, and was subsequently treated with androgen blockade. Another patient opted for phytotherapy (saw palmetto). One patient had a rapidly rising PSA level (20.1 ng/mL before cryotherapy, rising to 122.6 ng/mL at 3 months after), and MRI showed spinal metastases. He was subsequently treated with bisphosphonates and chemotherapy, and died from metastatic prostate cancer 9 months after cryotherapy. A further three patients were re-biopsied, having initially responded to cryotherapy and then developed rising PSA levels. In one of these patients biopsies showed a Gleason 4 + 4 cancer, and in the other two no viable tumour was seen. Pelvic MRI showed seminal vesicle invasion in one of these men. The other patient has had transurethral biopsies and once again there was no evidence of cancer. Overall, re-biopsies were taken in four of the patients with a rising PSA level, but only two of these sets of biopsies were positive.

No patient had intraoperative complications; one developed significant haematuria immediately after cryotherapy and returned to theatre for a cystoscopic bladder washout. There were no cases of urethro-rectal fistula. Forty-one patients successfully voided on clamping their suprapubic catheter at 2 weeks after cryotherapy; the remaining 10 had a second trial of clamping and by 6 weeks only one had a catheter *in situ*. Four patients had episodes of urinary retention. Two patients subsequently required a TURP; both of these patients had large prostates, slightly above the recommended 50-mL upper limit (52.1 and 54 mL) before cryotherapy. Histology of the prostate chips showed chronic prostatitis and necrosis. One of these patients continued to have dribbling incontinence immediately after TURP, but this resolved over 3 months and he no longer requires the use of pads. The other patient had no further urinary symptoms after TURP. Most patients had LUTS after treatment, ranging from incontinence to frequency. In most the LUTS were temporary and this is reflected in the IPSS at 9 months. Two patients continued to have incontinence, requiring the use of pads, beyond 9 months (4%); both had flexible cystoscopy and video-urodynamic studies, and in both cases sphincter function appeared normal but there was significant detrusor instability, and this was treated medically.

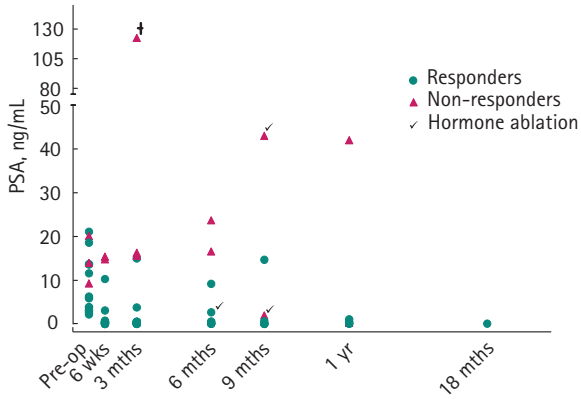


FIG. 4.
Biochemical response to cryotherapy in patients undergoing salvage treatment

Of the patients undergoing primary treatment, 16 of 29 reported pre-existing ED and 13 reported normal erections (Table 1). All of these patients reported ED after cryotherapy. Four patients (with normal erections before surgery) regained partial erectile function at 3–9 months after treatment (two were using phosphodiesterase-5 inhibitors). Interestingly, two patients reporting ED before cryotherapy reported partial erections at 1 year afterward. Sixteen patients undergoing salvage cryotherapy also reported pre-existing ED, with four denying ED before cryotherapy (three of these were taking LHRH analogues and one had had previous radical radiotherapy). After cryotherapy all of the patients treated for recurrent disease had ED, with no improvement noted with pharmacological therapy.

Before cryotherapy the median IPSS in the 20 men having primary treatment was 16 (0–26), and was 6 (1–20) in the 18 in the salvage group. The lower IPSS for the salvage group may reflect the use of hormone therapy, with a reduction in prostate size. At 9 months after cryotherapy the median IPSS was 8 (1–35) for 15 patients having primary treatment and 11 (6–29) in six salvage patients. These data suggest an improvement (from 16 to 8) after cryotherapy in the primary treatment group, and a deterioration in the salvage group (from 6 to 11; Table 1).

DISCUSSION

This is the first published series reporting results of third-generation cryotherapy for prostate cancer in the UK, from the first 51 consecutive patients treated with cryotherapy for prostate cancer at one centre. The data show the early outcomes and complication rates for patients treated for primary and recurrent disease, and show that for primary treatment there was an initial reduction in PSA level for all patients at 6 weeks after treatment, and a PSA nadir of <0.5 ng/mL in 79%. At 3 months, 78% of patients had a PSA of <0.5 ng/mL, and this was maintained in two-thirds of patients at 1 year after treatment. Figure 3 shows the reduction in PSA levels for all patients; these results are comparable to those in other published series of early outcomes [11,14]. Twelve men in the primary treatment group had pretreatment PSA levels of >10 ng/mL, and three had Gleason grades of >7. Both of these factors have been associated with poorer outcome [6], and therefore we stratified these patients as high-risk. However, a recent study showed that PSA responses in 80% of patients can be achieved even in the presence of a PSA level of >10 ng/mL and Gleason grade >8 [15]. In the present study, six of the patients with a PSA level of >10 ng/mL and all three with high Gleason grades had evidence of biochemical recurrence after an initial response. The PSA levels at 6 weeks and 3 months were compatible with the better prognosis expected with low-risk patients. However, at 1 year there were few patients, and this may have precluded detecting a difference between high- and low-risk patients. For the

primary treatment group the results are immature, but we would suggest that high pretreatment PSA level and Gleason grade are associated with poorer outcome, and this should be carefully considered during patient selection. Undoubtedly there are difficulties in staging prostate cancer before any radical treatment. Higher PSA levels may reflect underlying micrometastatic disease that is not identified on bone scan, and local extension not evident on MRI, which has a low sensitivity and specificity. This is particularly problematic in the salvage group, where seminal vesicle involvement is common. Pathological examination of specimens from salvage radical prostatectomy indicates seminal vesicle involvement in 30–40% [16]. For this reason it may be advisable to take seminal vesicle biopsies particularly in salvage patients. For those patients failing to respond to cryotherapy or developing evidence of biochemical recurrence, we found MRI and bone scans helpful in confirming residual/recurrent prostate cancer, particularly when prostate re-biopsies were negative.

The results of third-generation cryotherapy also depend on a sound knowledge of TRUS of the prostate, and a good understanding of the anatomy and distribution pattern of prostate cancer. Technical difficulties are encountered at the apex of the prostate where the prostate volume is small and the ice-ball may extend closest to the rectum, increasing the risk of fistula. The lateral extent of the ice-ball can be controlled by needle placement; nevertheless, careful judgement must be exercised in this area to balance cancer clearance against complications.

By contrast with the rapid decrease in PSA to undetectable levels after radical prostatectomy, immediately after cryotherapy the PSA levels may increase and then reach a nadir at 3 months [17]. In the present series the rise in PSA level after cryotherapy was not detected despite routine measurement of PSA at 6 weeks. There was a further reduction in PSA level at 3–6 months after cryotherapy in four patients. The target nadir after cryotherapy is not clearly defined, and detectable levels afterward are not necessarily associated with disease persistence. Studies have shown that PSA levels of >0.5 ng/mL are associated with biopsy-confirmed disease in 55% of cases, compared to <10% positive biopsies with a PSA level of <0.5 ng/mL [18]. A PSA level of ≤0.5 ng/mL was therefore used as a threshold for response, as has been the case for other series [6]. The salvage treatment group reached a PSA nadir of <0.5 ng/mL at 6 weeks in two-thirds of patients, and that was maintained at 3 months, and in a similar proportion of patients followed to 1 year. Three patients failed to respond to cryotherapy and it seems likely that they had metastatic disease at the time of treatment, despite negative bone scans. All three not responding had a short PSA doubling time, known to be associated with metastatic disease [19], and two were subsequently shown to have lymph node or bony metastases on MRI. Once again, PSA levels of >10 ng/mL and a Gleason grade >7 were associated with a poorer outcome [8]. As for other salvage therapies, the challenge remains to identify those with biochemical relapse secondary to localized recurrence. The use of cryotherapy may be beneficial after other methods (e.g. radiotherapy or brachytherapy), as the mechanisms of cellular damage are very different and therefore cancer cells resistant to radiotherapy may be susceptible to very low temperatures. An additional advantage is that the pinpoint localization of cryotherapy allows for further treatment cycles if there is local recurrence after cryotherapy. Repeated treatments have not yet been used in the present series. Despite an anticipated increase in the complication rate, studies so far of patients requiring re-treatment with cryotherapy appear to show no increase in morbidity. In a study incorporating biopsies after treatment, 39 patients (13%) were found to have residual cancer and had further cryotherapy, with no increase in complications [6].

Early series using first-generation cryotherapy reported high rates of urethro-rectal fistulae. Third-generation cryotherapy has virtually eliminated this complication, with the incorporation of rectal and urethral warming catheters. No patients developed fistulae in the present series, consistent with the risk of <1% reported in a recent study [20].

Urinary retention developed in four patients, with two requiring TURP (4%). Most patients had temporary LUTS, which resolved by 9 months, reflected in the low IPSS. Two patients continued to have urinary incontinence after this time (4%), compared to the published rate of 4.4% [20]. Although neither of these patients had external sphincter injury on postoperative urodynamics, it has been suggested that the use of thermocouple devices placed percutaneously at the external sphincter with cystoscopic visualization may significantly reduce incontinence rates by maintaining 15 °C in the region of the sphincter [10]. In both patients in our series who had persistent episodes of urinary incontinence there was evidence of detrusor instability on urodynamic studies after cryotherapy. As we did not use routine urodynamic studies in our patients before cryotherapy it is not possible to determine whether this occurred as a result of cryotherapy, but the lack of symptoms beforehand infers that this was the case. An interesting future study incorporating urodynamics before and after cryotherapy would be helpful in answering this question.

The most common complication was ED, with 86% of patients reporting it. In four patients this had at least partly resolved after 9 months, albeit with pharmacological therapy. Two-thirds of patients had ED before treatment, particularly in the salvage group. Other groups reported similar rates of ED, at 94% in one of the larger series [6]. This complication occurs more frequently after cryotherapy than other local treatments, e.g. nerve-sparing radical prostatectomy, and previously potent patients should be counselled accordingly.

Previous studies have focused on the PSA response and major complications such as fistula. Less attention has been given to side-effects such as LUTS, pelvic discomfort and scrotal swelling. As the techniques are refined to eliminate the major complications, it becomes more important to assess the rates of less severe morbidity, to help patients assess the potential outcomes of a therapy. We carefully documented these side-effects and while many patients have some LUTS and discomfort, in most this was transient and easily managed with simple analgesics.

The hospital stay was much shorter (median 2 days) than for radical prostatectomy. This is comparable to brachytherapy and may be preferred to repeated attendance for EBRT. The oldest patient in the primary group was 76 years old, and there is little doubt that cryotherapy offers a curative option for older patients and those with significant comorbidity. The treatment options for recurrent prostate cancer are limited and cryotherapy provides a further potentially curative option for patients with relapse, with

favourable response rates compared to those for salvage radiotherapy [19]. The technologies available continue to develop, both to reduce the associated morbidity (e.g. the use of thermocouple devices placed into the sphincter) and to increase the efficiency of the procedure (e.g. the development of ice-rod technology) with the potential to eliminate the requirement for a retraction procedure in larger prostates. Investigative work continues into the augmentation of cryotherapeutic effect with chemotherapeutic agents and cytokines [21,22].

In conclusion, the present preliminary results suggest that cryotherapy offers a safe and effective alternative for the primary and secondary treatment of prostate cancer. Response rates are better for primary treatment than salvage therapy, which is consistent with results from other forms of prostate cancer treatment. Patients should be counselled that rates of ED are high, and that an initially high PSA level and Gleason grade predict a less favourable outcome. Advantages include a shorter hospital stay and lower morbidity than for radical surgery, therefore allowing consideration of older and less fit patients who seek curative therapy. A long-term follow-up is required to assess the durability of response and therefore the probability of cure.

CONFLICT OF INTEREST

D. Greene is a paid consultant to sponsor; proctor for Oncura.

REFERENCES

1 **Gonder MJ, Soanes WA, Shulman S.** Cryosurgical treatment of the prostate. *Invest Urol* 1966; **3**: 372–8
2 **Flocks RH, Nelson CM, Boatman DL.** Perineal cryosurgery for prostate carcinoma. *J Urol* 1972; **108**: 933–5
3 **Porter MP, Ahaghotu CA, Leoning SA, See WA.** Disease-free and overall survival after cryosurgical monotherapy for clinical stages B and C carcinoma of the prostate: a 20-year followup. *J Urol* 1997; **158**: 1466–9
4 **Cohen JK, Miller RJ.** Thermal protection of urethra during cryosurgery of prostate. *Cryobiology* 1994; **31**: 313–6
5 **Baust JG, Gage AA.** The molecular basis of cryosurgery. *BJU Int* 2005; **95**: 1187–91
6 **Bahn DK, Lee F, Badalament R, Kumar A, Greski J, Chernick M.** Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology* 2002; **60** (Suppl. 2): 3–11
7 **National Institute for Health and Clinical Excellence (NICE).** Cryotherapy for recurrent prostate cancer. Interventional Procedure Guidance (IPG) May 2005: 119
8 **Pisters LL, von Escenbach AC, Scott SM *et al.*** The efficacy and complications of salvage cryotherapy of the prostate. *J Urol* 1997; **157**: 921–5
9 **Chin JL, Pautler SE, Mouraviev V, Touma N, Moore K, Downey D.** Results of salvage cryoablation of the prostate after radiation: identifying predictors of treatment failure and complications. *J Urol* 2001; **165**: 1937–42
10 **Katz AE, Mohamed A, Ghafar MD.** Selection of salvage cryotherapy patients. *Rev Urol* 2002; **4** (Suppl. 2): S18–S23
11 **Zisman A, Pantuck AJ, Cohen JK, Belldegrun AS.** Prostate cryoablation using direct transperineal placement of ultrathin probes through a 17-gauge brachytherapy template – technique and preliminary results. *Urology* 2001; **58**: 988–93
12 **Barry MJ, Fowler FJ Jr, O'Leary MP *et al.*** The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. *J Urol* 1992; **148**: 1549–57
13 **Mebust W, Roizo R, Schroeder F *et al.*** Correlations between pathology, clinical symptoms and the course of the disease. In Cockett AT, Chatelain AY, Denis L, Griffiths K, Khoury S, Murphy G eds, *Proceedings of the International Consultation on Benign Prostatic Hyperplasia.* Channel Islands: Scientific Communication International, 1992: 53–62
14 **Han KR, Cohen JK, Miller RJ *et al.*** Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience. *J Urol* 2003; **170**: 1126–30
15 **Prepelica KL, Okeke Z, Murphy A, Katz AE.** Cryosurgical ablation of the prostate: high risk patient outcomes. *Cancer* 2005; **103**: 1625–30
16 **Brenner PC, Russo P, Wood DP, Morse MJ, Donat SM, Fair WR.** Salvage radical prostatectomy in the management of locally recurrent prostate cancer after 125I implantation. *Br J Urol* 1995; **75**: 44–7
17 **Leibovici D, Zisman A, Lindner A, Stav K, Siegel YI.** PSA elevation during prostate cryosurgery and subsequent decline. *Urol Oncol* 2005; **23**: 8–11
18 **Shinohara K, Rhee B, Presti JC Jr, Carroll PR.** Cryosurgical ablation of prostate cancer: patterns of cancer recurrence. *J Urol* 1997; **158**: 2206–10
19 **Leventis AK, Shariat SK, Kattan MW, Butler BE, Wheeler TM, Slawin KM.** Prediction of response to salvage radiation therapy in patients with prostate cancer recurrence after radical prostatectomy. *J Clin Oncol* 2001; **19**: 1030–9
20 **Rees J, Patel B, MacDonagh R, Persad R.** Cryosurgery for prostate cancer. *BJU Int* 2004; **93**: 710–4
21 **Clarke DM, Baust JM, Van Buskirk RG, Baust JG.** Addition of anticancer agents enhances freezing-induced prostate cancer cell death: implications of mitochondrial involvement. *Cryobiology* 2004; **49**: 45–61
22 **Chao BH, He X, Bischof JC.** Pre-treatment inflammation induced by TNF-alpha augments cryosurgical injury on human prostate cancer. *Cryobiology* 2004; **49**: 10–27

Correspondence: Damian Greene, Sunderland Royal Hospital, Sunderland, UK.
e-mail: Damien.Greene@chs.northy.nhs.uk

Abbreviations: **QoL**, quality of life; **EBRT**, external beam radiation therapy; **ED**, erectile dysfunction.