Salvage cryotherapy for recurrent prostate cancer after radiation failure: a prospective case series of the first 100 patients

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OBJECTIVE

To report the short- to intermediate-term experience of using salvage targeted cryoablation of the prostate (TCAP) for the recurrence of localized prostate cancer after radiotherapy.

PATIENTS AND METHODS

Between May 2000 and November 2005, 100 patients had salvage TCAP for recurrent prostate cancer after radiotherapy; the mean follow-up was 33.5 months. All patients had biopsy-confirmed recurrent prostate cancer. Biochemical recurrence-free survival (BRFS)

was defined using a prostate specific antigen (PSA) level of <0.5 ng/mL and by applying the American Society for Therapeutic Radiology and Oncology (ASTRO) definition for biochemical failure. Patients were stratified into three risk groups, i.e. high-risk (68 men), intermediate-risk (20) and low-risk (12).

RESULTS

There were no operative or cancer-related deaths; the 5-year actuarial BRFS was 73%, 45% and 11% for the low-, intermediate- and high-risk groups, respectively. Complications included incontinence (13%), erectile dysfunction (86%), lower urinary tract

symptoms (16%), prolonged perineal pain (4%), urinary retention (2%), and recto-urethral fistula (1%).

CONCLUSION

Salvage TCAP is a safe and effective treatment for localized prostate cancer recurrence after radiotherapy.

KEYWORDS

cryoablation, prostate cancer, PSA, recurrence, survival

INTRODUCTION

Prostate cancer is the most common non-dermatological male cancer in the UK, accounting for almost a quarter of all new male cancers. The average risk of developing prostate cancer in UK is ≈7% [1]. Radical prostatectomy and external-beam radiotherapy (RT) remain the most common primary treatments for localized prostate cancer, with acceptable results, although they can have significant morbidity [2–5]. An increasing PSA level after RT is the earliest evidence of inadequate local control in about three-quarters of patients [6,7], and when combined with biopsy after RT, substantially many patients will be at greater risk of clinical failure [8]. Stamey *et al.* [9] reported that 80% of men treated with RT for localized prostate cancer had an increasing PSA level at a mean follow-up of 5 years.

Options for curative salvage therapy for these patients are limited. Repeating RT is not successful, as these tumours are radio-resistant, and it is associated with a greater risk of complications [10]. Salvage radical

prostatectomy is a technically difficult procedure and has been associated with significant comorbidity [3,11]. With a better understanding of the cellular pathophysiology after exposure to cold injury, modern cryosurgery has emerged as an alternative option to treat patients with recurrent prostate cancer after RT, with the intention to provide local control and to prolong survival. It is minimally invasive, can be repeated and has a relatively short hospitalization time. Using cryotherapy as salvage treatment for prostate cancer, the 2-year disease-free survival was reported to be 30–70% [12,13]. The National Institute for Clinical Excellence issued guidance in May 2005 [14] stating that evidence of efficacy measured by the reduction in PSA levels and biopsy finding appeared to be adequate to support the use of this procedure in patients with recurrent prostate cancer. Further research into the quality of life, outcome and long-term survival was recommended. In the present prospective case series we report our experience, evaluating the biochemical outcome and complications after salvage targeted cryosurgery of the prostate (TCAP).

PATIENTS AND METHODS

Between May 2000 and November 2005, 100 patients had salvage TCAP for prostate cancer; six had a second procedure for local recurrence, giving 106 procedures in all. The patients were initially assessed in the cryosurgery clinic, prostate dimensions were measured using TRUS, and all had biopsy-confirmed recurrent prostate cancer and were re-staged before surgery with pelvic MRI and bone scans. Patients at greater risk of having locally advanced disease had pelvic lymph node biopsy before their procedure. Patients with evidence of pelvic lymph node involvement or metastatic disease were deemed unsuitable for salvage TCAP, and hence were excluded.

Patients were stratified into three risk groups according to their PSA level, Gleason score and clinical stage before RT [15]. The low-risk group comprised those with a PSA level of ≤10 ng/mL, a Gleason score of ≤6 and clinical stage ≤T2b; the intermediate-risk group had one unfavourable factor from a PSA level of >10 ng/mL, a Gleason score of ≥7

Characteristic	Value	
Mean (range) age, years	66.8 (54–78)	**TABLE 1**
PSA level, ng/mL, %		*The patients' characteristics*
Median	5.4	*before TCAP*
<4	50	
4–10	27	
>10	23	
Gleason score before RT, %		
6	30	
= 7	33	
8–10	37	
Clinical stage before RT, %		
T1c	6	
T2a	20	
T2b	27	
T2c	17	
T3	30	
Mean (range) prostate volume, mL	23 (11–58)	
Pelvic lymph node biopsy, %	20	
Open	13	
Laparoscopic	7	
Risk groups, %		
Low	12	
Intermediate	20	
High	68	
Neoadjuvant hormones before TCAP, %	46	

and clinical stage >T2b, and the high-risk group had two or more unfavourable risk factors.

All TCAP procedures were performed by one urological surgeon; with the patient under general anaesthesia, and in the extended lithotomy position, diagnostic flexible cystoscopy was used initially. Under TRUS guidance (B-K Medical, Copenhagen, Denmark), several percutaneous cryoneedles were placed transperineally into the prostate. Two cryoablation systems were used; the Cryocare™ system (Endocare, Inc., Irvine, CA, USA) in 45 men, and the Seednet™ (Oncura Inc., Plymouth Meeting, PA, USA) in 100. The procedure was monitored by TRUS and four thermocouples were placed in four critical positions, i.e. the anterior prostate, the apex, Denonvilliers' fascia and the external sphincter. Once all probes were in place flexible cystoscopy was used again to ensure that all the probes were in place and none had traversed through the urethra. Over a guidewire a double-lumen urethral warming catheter was placed and warm normal saline (40°C) circulated to protect the urethra. Double freeze-thaw cycles were applied in all patients.

Patients were discharged either on the day of TCAP or the following day with an indwelling urethral catheter in place, which was removed 2 weeks later. All patients were prescribed 2 weeks of antibiotics (quinolones) and 4 weeks of α-blockers.

Patients were followed at 6 weeks, and then every 3 months for the first year and 6-monthly thereafter, with PSA measurements at each visit. Biochemical recurrence-free survival (BRFS) was defined as a PSA level of <0.5 ng/mL and by the American Society for Therapeutic Radiology and Oncology (ASTRO) definition for biochemical recurrence. Patients with three consecutive increases in PSA level were re-staged by bone scan, pelvic MRI and prostate biopsy. TCAP was repeated in men with a positive biopsy and no evidence of metastatic disease.

Actuarial survival curves were used to calculate the time to biochemical recurrence, with Kaplan-Meier survival analysis; the log-rank test was used to determine differences in the survival curves among the risk groups. We defined the time to biochemical recurrence as the time from surgery to PSA recurrence for those who had recurrence, and as the time

from surgery to the last follow-up visit for those who were biochemically free. Fisher's exact test was used to compare the two cryoablation systems. A Cox proportional-hazard regression model was used to define the predictors of outcome; in all tests, $P < 0.05$ was taken to indicate a statistically significant difference.
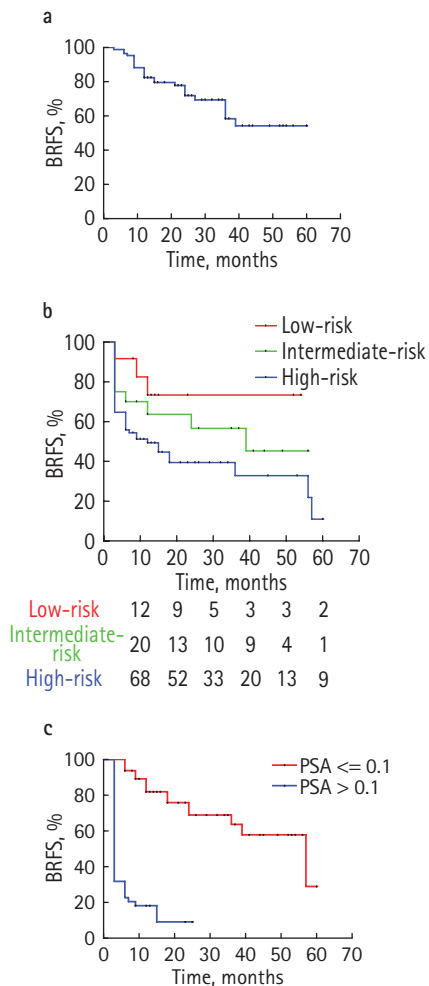
RESULTS

Table 1 summarizes the patients' characteristics before surgery. Patients with a prostate volume of ≥50 mL received hormone therapy before TCAP to reduce the prostate size. 22 had hormone therapy to reduce the prostate, which was stopped before TCAP, and only 24 were already on hormone therapy on the time of referral, and this was stopped 3 months after TCAP. The commonest hormone treatments were bicalutamide and LHRH analogue.

The mean (range) follow-up was 33.5 (12–79) months; there were no operative or cancer-related deaths. The overall BRFS rate using the ASTRO definition for biochemical failure was 83% at 12 months, 72% at 24 months and 59% at 36 months (Fig. 1a). The 5-year actuarial BRFS using a PSA threshold of 0.5 ng/mL was 73%, 45% and 11% for the low-, intermediate- and high-risk groups, respectively (Fig. 1b). The median (range) PSA nadir was 0.1 (0.003–6.1) ng/mL and half the patients achieved an undetectable PSA nadir (≤0.1) at 3 months. BRFS rates differed between the group of patients who had an undetectable PSA nadir and those who had a PSA nadir of >0.1 ng/mL ($P < 0.001$, 95% CI 18.45–19.55; Fig. 1c). In the multivariate analysis a PSA nadir of >0.1 ng/mL and Gleason score before RT were statistically significant factors for biochemical recurrence after TCAP (Table 2).

Comparing the two cryoablation systems, the BRFS rate using a PSA level of <0.5 ng/mL was 49% for the Endocare system and 43% for the Seednet system at 24 months ($P = 0.54$).

The complications associated with TCAP are summarized in Table 3. Perineal discomfort was common after TCAP, with most cases resolving within 6 weeks. Four patients had prolonged perineal pain, and were treated successfully with oral analgesia. Urethral sloughing causing urinary retention occurred

FIG. 1. *The BRFS according to: **a**, the ASTRO definition (95% CI 37.23–47.96); **b**, the risk groups (P = 0.045); **c**, the PSA nadir after cryosurgery (P < 0.001).*

a

b

Low-risk | 12 | 9 | 5 | 3 | 3 | 2
Intermediate-risk | 20 | 13 | 10 | 9 | 4 | 1
High-risk | 68 | 52 | 33 | 20 | 13 | 9

c

Variable	P	SEM	95% CI
Cryoablation system	0.991	0.981	0.148–6.919
PSA level before RT	0.948	0.032	0.936–1.063
PSA nadir	0.037	0.086	1.011–1.418
PSA before TCAP	0.525	0.071	0.832–1.098
Gleason score before RT	0.001	0.385	1.617–7.316
Clinical stage	0.592	0.713	0.169–2.761
Time from RT to TCAP	0.374	0.011	0.970–1.012
Time to PSA nadir	0.116	0.103	0.695–1.041

TABLE 2

The multivariate analysis for factors predicting the outcome after TCAP

Morbidity	Rate, n (%) Overall	Endocare	Seednet	P
No. of patients	100	45	55	
Incontinence	13	9 (20)	4 (7)	0.057
LUTS	16	9 (20)	7 (13)	0.230
Prolonged perineal pain	4	2 (4)	2 (3.6)	0.610
ED	86	36 (80)	50 (91)	0.042
Recto-urethral fistula	1	0	1 (2)	0.550
Urinary retention	2	2 (4)	0	0.770

TABLE 3

The complication rate after TCAP, including that for patients treated with the two cryoablation systems

in two patients and was treated by prolonged urethral catheterization. At the last follow-up, 16% of the patients had LUTS in the form of urgency and frequency. Incontinence was defined as a lack of urinary control which needed at least one pad in 24 h. Thirteen patients developed persistent incontinence after TCAP, in seven being mild to moderate (three or fewer pads in 24 h). Two patients with severe incontinence had transurethral collagen injection and subsequently became dry. A recto-urethral fistula developed in one patient 6 months after TCAP. Erectile dysfunction (ED) was assessed using the International Index of Erectile Function; of 63 patients who completed a baseline questionnaire, 38 (60%) had ED before TCAP, 37 (59%) of these remained with ED after

TCAP, and surprisingly one regained good erectile function. Of 14 (22%) patients who reported adequate erectile function with no assistance before their operation, six regained the same activity, six had reduced erectile function and two had complete loss of erectile function. Eleven patients needed assistance to maintain their erection before TCAP; five remained the same and six completely lost their erectile function. The overall rate of ED after TCAP was 86%.

Although the follow-up was shorter for the Seednet group, the complication rates are compared for the two systems in Table 2; apart from ED, there was no statistically significant difference between the groups.

Before TCAP the median (range) IPSS for all patients was 7 (1–27); after TCAP the IPSS was available for 69 patients, and the median was 13 (0–34). There was no significant difference in the IPSS before and after TCAP (Fig. 2).

DISCUSSION

The aim of any salvage treatment for prostate cancer is to achieve local tumour control and prolong patient survival [16]. Patients with clinically localized prostate cancer, in whom treatment either with RT or brachytherapy has failed, have limited treatment options. As a result, patients are left with either 'watchful

FIG. 2. *The IPSS after TCAP (P = 0.133).*
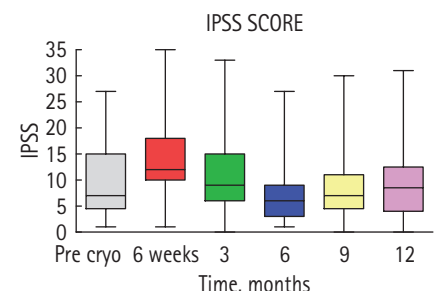
waiting' or hormone treatment, in which progression to androgen independence occurs in a few years in most men [16]. In the last decade TCAP has re-emerged as an alternative option for salvage treatment. A renewed interest in the procedure has increased with new technical advances, which markedly reduced the complication rate and improved patient survival [8,13,16–21]. In the present study we report our experience from the first 100 patients, evaluating the biochemical outcome and complications after salvage TCAP. To our knowledge this is the largest UK series of salvage TCAP.

There is no established agreed definition for biochemical failure after cryosurgery. Threshold PSA levels of 0.1, 0.2 above nadir, 0.3, 0.4 and 0.5 ng/mL have been used in previous studies [8,13,16–21]. The PSA level, biopsy results and clinical assessment are

essential to define failure after TCAP [11]. In TCAP, a rim of prostatic tissue is preserved around the protected urethra, and therefore the serum PSA level is unexpected to decrease to undetectable levels after the procedure. The ASTRO definition of biochemical recurrence might be a reasonable method to measure biochemical failure after TCAP. In the present series we used both the ASTRO definition and a serum PSA level of ≥0.5 ng/mL to define biochemical failure. Using the ASTRO definition, more than half of the patients remained disease-free at 3 years of follow-up. From our results, a PSA level of >10 ng/mL before TCAP, clinical stage >T2b, and Gleason grade of ≥7, would predict an unfavourable outcome with salvage TCAP. The high-risk group had the least favourable outcome, as most patients had biochemical recurrence at their last follow-up. It is not clear why this group had a high failure rate; it might reflect undetected subclinical systemic disease, persistent local cancer progression [12], or involvement of the seminal vesicle, which was not routinely treated. Hence careful patient selection for TCAP is crucial. Most of the patients in this series were in the high-risk group (69%) and this might have affected the overall results. In the low-risk group, most of the patient remained free from biochemical recurrence at 5 years of follow-up; the results were favourable but there were few patients.

The development of third-generation cryoablation systems was marked by the use of smaller cryoneedles (17 g, 1.47 mm). In our centre we started using the Endocare system in 1999 with 2- or 3-mm cryoprobes. Up to eight probes were used to cover the prostate. From January 2004 we started using the Seednet system, with 1.47 mm cryoneedles; a mean of 15 needles were used to cover the prostate. Comparing the two systems in terms of BRFS and complication rates, there was no significant difference between them. However, these results must be interpreted with caution, as there are differences in the 'learning curve' and the follow-up between the systems.

Salvage TCAP is technically more challenging than primary treatment and the risk of complications is significantly greater [22]. Complication rates in this series were comparable to those in other published series [8,13,16–21]. In early series of salvage TCAP, urinary incontinence was reported to be high (73%). This might be related either to the lack of protection of the urethra and external sphincter, or periurethral scarring after RT [12]. The urinary incontinence rate has declined dramatically with better temperature control around the external sphincter and the use of a urethral warming catheter. A recent study reported an incontinence rate of 11% [20]. In the present series 13% of patients reported stress incontinence at their last follow-up, where the use of a urinary pad was necessary. Symptoms tended to resolve during a follow-up of >1 year [23]. Recto-urethral fistula represent the most serious complication of TCAP, but new treatment advances and better control of the procedure have significantly reduced this complication [23,24]. Previous studies reported a fistula rate of 1–3% [12,18,21]; in the present series, one patient with locally advanced disease (T3c) developed a recto-urethral fistula in the first 6 months after TCAP, and he was treated with a suprapubic catheter and colostomy.

Most of the present patients developed some degree of LUTS after TCAP, which generally resolved quickly and required no treatment; only 16% had persistent LUTS. One patient developed severe urgency and urge incontinence, in whom a urodynamic study showed a severe reduction in bladder capacity; this was treated with suprapubic catheterization, and at the last follow-up he had a dramatic improvement.

ED is the most frequent complication after cryosurgery; the ice-ball is allowed to extend to the neurovascular bundle to completely eradicate the tumour at the edge of the prostate. Thus TCAP is not ideal for patients who are interested in maintaining their erectile function. Donnelly et al. [25] reported that the nerves have the potential to recover after primary TCAP, and half of their patients had recovered erectile fucntion by 36 months. In salvage TCAP most patients already have ED secondary to hormone therapy and RT, which makes it difficult to assess the true incidence of the problem. In an attempt to preserve the neurovascular bundle and hence erectile function, Onik et al. [26] described focal nerve-sparing cryosurgery for primary prostate cancer; after a mean follow-up of 36 months, 77% of the men maintained erectile function. The rate of ED in the present study is comparable to other published results [20].

Quality of life is increasingly becoming a well recognized outcome measure in cancer treatment. There are few published data on the effect of TCAP on quality of life. Robinson et al. [27] reported that quality of life had generally returned to the level before treatment by 1 year after primary TCAP. In the present series there was no significant change in the IPSS after TCAP from before; further research into the quality of life is recommended.

In conclusion, the present series suggests that TCAP is safe, well-tolerated and effective for the salvage treatment of prostate cancer. It is minimally invasive, can be repeated and is associated with low morbidity (except for ED), and for patients in whom RT has failed, it offers an additional hope of cure. High-risk patients had the least favourable outcome, and hence patient selection is essential before TCAP. Further research into long-term survival and quality of life is recommended.

CONFLICT OF INTEREST

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