

Salvage cryotherapy for recurrent prostate cancer after radiation failure: current status and future perspectives

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In the last decade, cryotherapy has emerged as a minimally invasive alternative for the treatment of localized or locally advanced prostate cancer. With better understanding of the pathophysiology of cryogenic injury and the introduction of the gas-driven systems, the procedure has been optimized to improve patient survival and reduce complication. The results of salvage cryotherapy are becoming more promising. Modifying standard cryotherapy technique by the use of a urethral warming catheter and thermocouples has resulted in the reduction in serious complications and improved quality of life following the procedure. Focal nerve-sparing cryotherapy represents a novel approach to treat prostate cancer and preserve potency. Cryoimmunotherapy and cryochemotherapy are new concepts in adjuvant therapy. Early *in vitro* studies revealed the feasibility of such an approach. Further clinical trials are essential before using these models as standard treatment.

Prostate cancer is recognized as one of the most common nondermatological male cancers in the UK, accounting for almost one in four of all new male cancers [101]. Radical prostatectomy and external-beam radiotherapy remain the two major techniques for the treatment of prostate cancer with acceptable results, although they may be associated with varying degrees of morbidity [1–4]. Patients with unfavorable presentation (prostate-specific antigen [PSA] level >20 ng/ml or Gleason score ≥8 or clinical stage >T2b) are at increased risk of clinical failure after radiotherapy [5–7]. Stamey *et al.* [8] reported that 80% of men in the high-risk group treated with radiotherapy for localized prostate cancer had an increasing PSA level at a mean follow up of 5 years. Patients with clinically localized prostate cancer, who failed their treatment either with radiotherapy or brachytherapy, have limited treatment options available. As a result, patients are left with either watchful waiting or hormone treatment in which progression to androgen independence occurs in a few years in most men [9]. Repeating radiation therapy is not successful as these tumors are radio resistant and is associated with high risk of toxicity [10]. Salvage radical prostatectomy is a technically difficult procedure and has been associated with significant comorbidities [2,11].

In the early 1960s, cryosurgery emerged as a minimally invasive alternative treatment for localized or locally advanced prostate cancer. Cryotherapy was abandoned because of high rates of significant complication, especially urethral sloughing and rectourethral fistula [12]. In

the 1990s, cryotherapy was revived following two major advances. Firstly, the development of gas-driven cryosystems based on the Joule-Thompson effect resulted in more efficient tissue destruction. Secondly, improved monitoring of the procedure by real-time ultrasound scan [13]. These technical advances markedly reduced the complication rate and led to dramatic improvement in clinical outcome. The use of a urethral warming catheter markedly reduced urethral sloughing rates following the procedure [14]. As a result, prostate cryotherapy has re-emerged as an alternative minimally invasive salvage procedure. Several reports described prostate cryotherapy as a safe, well-tolerated and effective treatment. It is less invasive than radical surgery, can be repeated and is associated with low morbidity [15–20].

Patient selection for salvage cryotherapy

Rising serum PSA level is the first sign of treatment failure in prostate cancer. The PSA may fluctuate in the first 18 months following radiotherapy [21]. Therefore, PSA should be monitored and interpreted carefully after radiotherapy. If there is a persistent rise in PSA and the possibility of lower urinary tract infection is excluded, prostate biopsy is mandatory to confirm local recurrence. Saturation prostate biopsy is more sensitive than transrectal biopsy in detecting recurrent cancer in irradiated patients [22]. If prostate biopsy reveals recurrent prostate cancer, restaging pelvic magnetic resonance imaging (MRI) scan and bone scan are mandatory to exclude any metastatic disease.

Keywords:
cryoimmunotherapy,
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future
medicine part of fsg

Table 1. Results of salvage cryotherapy series.

Series	Number of patients	Follow-up months (mean)	Negative biopsy (%)	PSA failure	BDF survival (risk group) (%)			Ref.
					Low	Intermediate	High	
Ismail <i>et al.</i> (2007)	100	(33.5)	N/A	≥0.5	73	45	11	[26]
Collins <i>et al.</i> (2007)	195	46.5	70.59	ASTRO	69			[79]
Robinson <i>et al.</i> (2006)	46	24	N/A	≥0.3	48 at 2 years			[27]
Lam <i>et al.</i> (2005)	72	6	N/A	N/A	90 at 6 months			[80]
Bahn <i>et al.</i> (2003)	59	(72.5)	100	≥0.5	61	62	50	[20]
Ghafar <i>et al.</i> (2001)	38	20.7	N/A	>0.3 above nadir	74 at 2 years			[16]
Chin <i>et al.</i> (2001)	118	(18.6)	94	>0.5	34			[18]
De La Taille <i>et al.</i> (1999)	43	(21.9)	63(5/8)	<0.1	66 at 1 year			[15]
Pisters <i>et al.</i> (1997)	150	(13.5)	77(85/110)	≥0.2 above nadir	58			[32]
Bales <i>et al.</i> (1995)	23	12–23	59(13/22)	<0.3	14 at 1 year			[31]

ASTRO: American Society for Therapeutic Radiology and Oncology; BDF: Biochemical disease-free; PSA: Prostate-specific antigen.

High-risk patients (those with two or more unfavorable risk factors from a PSA level >10 ng/ml, a Gleason score ≥7 and clinical stage >2b) [23] should have pelvic lymph nodes biopsy prior to their procedure. Patients with radiological or histological evidence of pelvic lymph node involvement or metastatic disease should be excluded. All patients considered for salvage cryotherapy should be assessed in a specialized cryotherapy clinic by an experienced clinician. Detailed history and clinical examination should be obtained and prostate gland dimensions are measured by transrectal ultrasound scan. It is good practice to use hormone therapy for 3 months prior to salvage cryotherapy. This will help to reduce the size of the gland and increase the safety margin posteriorly between the rectum and the posterior prostatic capsule [24,25].

Salvage treatment for recurrent prostate cancer after radiotherapy

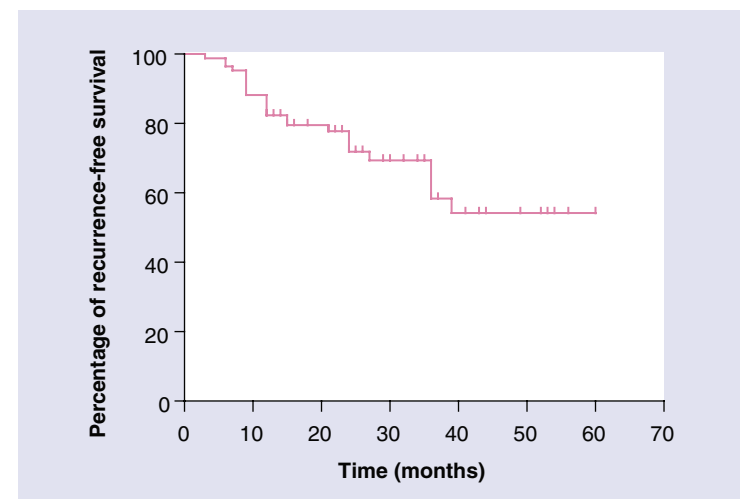
There are number of reasons that make salvage cryotherapy a more attractive option than salvage radical prostatectomy. Cryotherapy is a minimally invasive procedure. It involves transperineal insertion of ultrathin (17 gauge)

cryo needles. This approach is safe and well tolerated and associated with less postoperative complications than radical surgery [26,27].

Cryotherapy can be used to treat locally advanced prostate cancer. Extraprostatic tumor extension can be treated by allowing the ice ball to extend beyond prostatic capsule; this may potentially lead to injury to adjacent structures [28].

Erectile dysfunction is the most frequently occurring complication following prostate cryotherapy [26,27], primarily due to the ice ball extending into the neurovascular bundles when attempting to completely eradicate the tumor. In salvage cryotherapy, most patients suffer from a degree of erectile dysfunction owing to previous hormone therapy and pelvic irradiation [29]. The rate of impotence in most salvage prostatectomy series is not well reported. In one study by Link *et al.* [30] the percentage was as high as 100%.

In an early reported series of salvage cryotherapy, urinary incontinence was reported to be as high as 95% [31]. This may be related either to the lack of protection of the urethra and external sphincter or periurethral scarring postradiation therapy [32]. The urinary incontinence rate has dropped dramatically with better temperature

Figure 1. BRFs according to ASTRO definition.

ASTRO: American Society for Therapeutic Radiology and Oncology;
BRFS: Biochemical recurrence-free survival.
Adapted with permission from [26].

control around the external sphincter and the use of a urethral warming catheter. A recent study reported incontinence rates of 8% [20]. Urinary incontinence is still common following salvage radical prostatectomy and 44% of the patients treated remain incontinent at median follow up of 7 years [33].

The most serious complication of salvage cryotherapy is the development of rectourethral fistula. New treatment advances and better control of the procedure have significantly reduced this complication and recent studies report fistula rates ranging from 1–3% [18,20,26]. An early series of salvage radical prostatectomy reported rectal injury rates of 15%. The majority were primarily repaired at the time of operation [34]. A more recent series reported rectal injury rate of 4% [33].

Urethral slough rates have been reduced from 40 [31] to 5% [15,18] since the introduction of the urethral-warming catheter, which protects urethral mucosa during cryotherapy. Although urethral warming has been successful in reducing urinary morbidity, it can compromise cancer control by protecting a rim of prostatic tissue around the urethra from freezing [35]. Gould *et al.* showed a significant improvement in biochemical disease-free survival in men undergoing total cryotherapy (without warming catheter) and men who underwent standard cryotherapy (with warming catheter) [36]. Despite the obvious benefit of total cryotherapy, the use of urethral warming device became a standard practice in prostate cryotherapy.

Almost all patients following salvage cryotherapy will have some degree of lower urinary tract symptoms (LUTS) secondary to urethral slough most of which will return to the pre-treatment level in the first 6 months after the treatment [26].

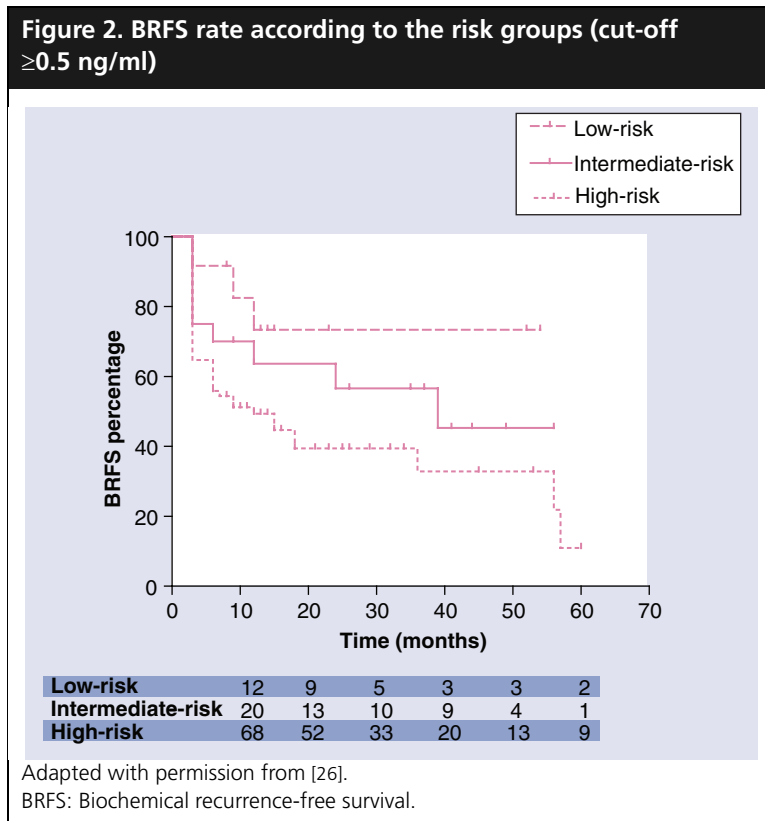
Cryotherapy may be a cost-effective approach to control locally advanced prostate cancer. It has been estimated that the total cost of cryotherapy procedure is approximately half of the usual cost of radical prostatectomy [37]. The cost saving reflects the length of hospital stay, 1.1 days for cryotherapy versus 3.5 days for radical prostatectomy [37]. Transrectal high-intensity focused ultrasound (HIFU) has recently emerged as an exciting salvage treatment for local recurrence after radiotherapy. Gelet *et al.* [38] reported a case series of 71 patients with local recurrence of prostate cancer and treated with HIFU. At a mean follow up of 14.6 months, 80% of the patients had negative biopsy rate and 44% had no evidence of PSA recurrence. The rectourethral fistula and urinary incontinence rates were unexpectedly high (6 and 35%, respectively). Further research on the long-term follow up is essential.

Oncological outcome of salvage cryotherapy

There has been controversy in evaluating clinical response following cryotherapy of the prostate. Serum PSA level, biopsy results and clinical assessment are essential to define failure post-cryotherapy [11]. PSA level cut offs of 0.1, 0.2 (above nadir), 0.3, 0.4 and 0.5 ng/ml have been used to define biochemical failure [15,16,18–20]. Connolly *et al.* demonstrated that a PSA cut off value of ≥ 0.5 ng/ml is a strong predictor of positive biopsy at 12 months post cryotherapy [39].

In our center, the first 100 salvage cryotherapy patients were followed with 3-monthly serum PSA level over a mean follow-up period of 33 months. We used the American Society for Therapeutic Radiology and Oncology (ASTRO) definition and cut off value ≥ 0.5 ng/ml to define biochemical failure. Using the ASTRO definition, 60% of treated men remained disease-free at 3 years follow up (Figure 1).

In our experience, high-risk patients (those with two or more unfavorable risk factors from PSA level of >10 ng/ml, a Gleason score of ≥ 7 and clinical stage of $>T2b$) showed the least favorable outcome as most patients had biochemical recurrence at their last follow up (Figure 2). This may reflect undetected subclinical systemic disease, persistent local cancer progression or involvement of the



seminal vesicle [32]. A total of 73% of low-risk patients with no risk factor remained disease-free from biochemical recurrence at 5 years follow up.

Bales *et al.* demonstrated PSA decline in 86% of patients and an 86% negative biopsy rate at 3 months [31]. Bahn *et al.* presented the longest follow-up series of salvage cryotherapy [20]. At 7 years follow up, the combined biochemical disease-free survival using PSA cut-off of 0.5 ng/ml was 59%. Robinson *et al.* have published the most recent case series of salvage cryotherapy for recurrent prostate cancer [27]. Half of their 46 patients maintained their PSA level below 0.3 ng/ml. Pisters *et al.* reported the largest series of salvage cryotherapy in 150 patients that demonstrated 66% biochemical recurrence-free survival and 93% negative biopsy rate [32].

Advances to reduce complication rates following cryotherapy

Focal nerve sparing cryotherapy

In prostate cryotherapy, the whole prostate gland is frozen, including the periprostatic tissue with neurovascular bundles to eradicate all tumor cells. As a result, the incidence of erectile dysfunction is high. In an attempt to preserve potency, Onik *et al.* described focal nerve sparing prostate cryotherapy where they treated the part of the prostate

that contained the tumor. After a mean follow-up of 50 months, 95% of the treated patients had stable PSA and 80% maintained their potency [40]. In a different approach, the neurovascular bundle was successfully preserved by active warming, but this resulted in an incomplete ablation of prostate tissue [41]. Lambert *et al.* presented 28 months (range 9 to 72 months) follow up of 25 patients treated with primary focal cryotherapy [42]. A total of 84% of patients had not experienced biochemical failure and 14% showed positive biopsy on the treated site. Potency was maintained in 71%, and no patient reported any worsening LUTS or incontinence. Focal nerve sparing cryotherapy has not been applied in salvage treatment.

Laser-assisted cryotherapy

Laser-assisted cryotherapy (LAC) is a new technique that protects healthy tissue around the prostate without limiting the cryoablation of unwanted tissue. Laser rays irradiated from the urethra into the prostate during the freezing process maintain the temperature in the urethral wall and surrounding region above the damaging level, and at the same time lethal temperature is achieved in the surrounding prostate tissue. The margin of the laser-protected area increases with injecting light absorbing dye into the periurethral tissue [43].

Rectal wall protection

The rate of rectourethral fistula following prostate cryotherapy remains low. Avoiding excessive freezing at the posterior margin of the prostate protects the rectum from freezing injury. Therefore, whole-gland ablation, which is necessary for complete eradication of prostate cancer will always be associated with risk of fistula. Modification of the cryotherapy technique to achieve lethal temperature (lower than -40°C) posteriorly while avoiding potential rectal injury was investigated by Cytron *et al.* [44]. They inserted two cryo needles into the Denonvillier's fascia for active warming using the thawing phase when the temperature drops below 0°C in the posterior prostate. This approach successfully maintained a PSA level of less than 0.5 ng/ml in 80.6% of the patients treated and no rectal injury was reported. Other studies have addressed this issue by manipulating the transrectal ultrasound probe to increase the distance between the rectal wall and the prostate. The mean distance was increased by 7.1 mm without impairing the ultrasound quality image and no patients developed rectourethral fistula [45].

Table 2. Complication associated with salvage cryotherapy.

Series	Impotence (%)	Incontinence (%)	Rectourethral fistula (%)	Urethral slough (%)	Pain (%)	Stricture/retention (%)	Ref.
Ismail <i>et al.</i> (2007)	86	6 (severe)	1	16	4	2	[26]
Collins <i>et al.</i> (2007)	N/A	6.6	0	0	10.26	2	[79]
Robinson <i>et al.</i> (2006)	56	29 (moderate to severe)	2 (from early series)	24 (from early series)	16	6 (from early series)	[27]
Lam <i>et al.</i> (2005)	83.3	17.5	0	N/A	5	9	[80]
Bahn <i>et al.</i> (2003)	N/A	8	3.4	N/A	N/A	N/A	[20]
Ghfar <i>et al.</i> (2001)	N/A	7.9	0	0	39.5	0	[16]
Chin <i>et al.</i> (2001)		6.7	3.3	5.1		8.5	[18]
De La Taille <i>et al.</i> (1999)	N/A	9	0	N/A	26	5	[15]
Pisters <i>et al.</i> (1997)	72	73	1	22	8	67	[32]
Bales <i>et al.</i> (1995)	100	95.5	N/A	N/A	N/A	40.9	[31]

Advances to increase the efficacy of prostate cryotherapy

The critical temperature required for complete ablation of the prostate tissue is not well defined. Early reports demonstrated a temperature of -20°C or less is essential to kill the cells [46,47]. More recently, studies have shown that -40°C is required for complete destruction of prostate tissue [48–50]. The effect of freezing on tissue varies depending on four thermal parameters: target temperature, thawing rate, freezing rate and duration of freezing [48,51,52]. The area adjacent to the centre of the cryo probe is exposed to rapid freezing, lower temperature and slow thawing rate. Tissues in this area show coagulative necrosis (kill zone). At the periphery, tissues are exposed to sub-lethal temperature and show inflammation and hemorrhage (damage zone) [53]. Apoptotic cells were identified in the peripheral zone of the cryogenic lesion where complete ablation of prostate cancer was difficult to achieve [54–56].

Cryochemotherapy

Three mechanisms are responsible for freezing results in necrotic cell death:

- Extracellular ice crystal formation that leads to cell hyperosmolarity and posthypertonic lysis;
- Direct cell damage caused by intracellular ice crystal formation;

- Vascular stasis and tissue ischemia [51].

The use of chemotherapeutic agents as an adjuvant therapy to enhance apoptotic cell death at the peripheral zone of the cryogenic lesion may enhance the efficacy of cryotherapy. Clarke *et al.* [57] demonstrate that the combination of cryotherapy and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) resulted in enhanced prostate cancer cell death at -10°C . The synergistic effect of both treatments was primarily due to increased apoptosis. Exposure to either treatment alone resulted in minimal cell death. Another study by the same group demonstrated enhanced efficacy of cryotherapy when combined with sub-lethal concentration of 5-fluorouracil *in vitro* [58]. Goel *et al.* investigated the ability of tumor necrosis factor- α (TNF- α) to enhance cryoinjury *in vivo* [59]. Temperature threshold for necrosis was increased with the addition of TNF- α prior to cryotherapy and the combined treatment resulted in growth delay of the tumor in the experimental animals. Systemic toxicity of TNF- α was reduced by delivering the drug combined with gold nanoparticles. Cryochemotherapy may represent a potentially effective therapeutic model for the treatment of prostate cancer and further studies and clinical trials are required.

Cryoimmunotherapy

Systemic antitumor immune response has been postulated following prostate cryotherapy. Early clinical reports observed regression of metastatic disease and symptom relief following prostate cryotherapy which implies that a protective immune response may be induced [60–62]. The mechanism of such clinical observation was not clear. Local tumor destruction by cryotherapy results in the release of a large amount of cryonecrotic tissue and tumor antigens. This may enhance the uptake of these antigens by local dendritic cells (DC) and priming of naive T cells in regional lymph nodes resulting in tumor-specific immune response and tumor eradication [63]. The cryoimmune response has been studied in several animal models. Both immunostimulatory and immunoinhibitory effects have been reported [64–73].

The precise mechanism of the immunostimulatory effect is not clear. Early cytokine-mediated response was reported [64,65]. The involvement of T-cell immunity and enhanced NK cell cytotoxicity was also described [65,66,81]. Other reports suggested the development of anti-tumor antibodies [74,75].

On the contrary, other reports suggest suppressed immunity and enhanced tumor growth and metastases following cryotherapy [72,73,76].

In an attempt to develop an effective immunotherapy for prostate cancer, Udagawa *et al.* [77] attempted administration of stimulated dendritic cells into cryotreated tumors in animal model. There was a significant increase in tumor-specific immune response for both the treated and untreated tumors that resulted in tumor eradication. Another report described strong antimetastatic effects and prolonged survival in mice treated with cryoimmunotherapy [78]. Those results warrant further studies and application of similar protocols in clinical trials.

Conclusion

Cryotherapy is a safe, well-tolerated and effective option for salvage treatment of prostate cancer. Compared with salvage radical prostatectomy, cryotherapy is a minimally invasive procedure, can be repeated and offers additional hope of cure for patients with recurrent prostate cancer after radiation failure. With better understanding of the cellular pathophysiology of freezing injury, future improvement in cryosurgical techniques are expected. Recent studies of cryotherapy combined with chemotherapy or immunotherapy have been extremely encouraging, and further research into the long-term effects and quality of life after cryotherapy is needed.

Future perspective

It is an interesting challenge to look at the future of salvage cryotherapy for recurrent prostate cancer after radiation failure. The application of cold temperature in the treatment of cancer is not a new concept. Cryotherapy of the prostate developed rapidly over the last decade. With modern cryo technology, the current status of salvage cryotherapy of the prostate is promising. It is increasingly able to provide improving results, while reducing the side effects. Potential future developments include further research on cryoimmunotherapy and cryochemotherapy as an alternative model, which may lead to advancement in salvage cryotherapy by increasing treatment efficacy. Further modification of the procedure is needed to reduce the side effects, in particular, erectile dysfunction.

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