

# Cryosurgical Ablation for Prostate Cancer: Preliminary Results of a New Advanced Technique

Dan Leibovici MD, Amnon Zisman MD, Yoram I. Siegel MD and Arie Lindner MD

Department of Urology, Assaf Harofeh Medical Center, Zerifin, Israel

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## Abstract

**Background:** Cryosurgery is a minimally invasive treatment option for prostate cancer.

**Objectives:** To report on the first series of cryosurgical ablation for prostate cancer performed in Israel.

**Methods:** Cryosurgical ablation of the prostate was undertaken in 12 patients aged 53–72 diagnosed with adenocarcinoma of the prostate. The procedures were performed percutaneously and were monitored by real-time trans-rectal ultrasound. The CRYOHIT machine applying Argon gas was used with standard or ultra-thin cryoprobe. The average follow-up was 12.8 months postsurgery (range 1–24 months).

**Results:** No rectal or urethral injuries occurred and all patients were discharged from hospital within 24–48 hours. The duration of suprapubic drainage was 14 days in 10 patients and prolonged in 2. Early complications included penoscrotal edema in four patients, perineal hematoma in three, hemorrhoids in two and epididymitis in one. Long-term complications included extensive prostatic sloughing in one patient and a perineal fistula in another, both of whom required prolonged suprapubic drainage. Minimal stress incontinence was noted in two patients for the first 8 weeks after surgery. None of the patients has yet regained spontaneous potency. A prostate-specific antigen nadir of less than 0.5 ng/ml was achieved in eight patients and an undetectable PSA level below 0.1 ng/ml in five patients.

**Conclusion:** Cryoablation for prostate cancer is safe and feasible, and the preliminary results are encouraging. Further study is needed to elucidate the efficacy of the procedure.

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Cryosurgery consists of *in vivo* tumor destruction by application of cryogenic probes that generate extreme freezing temperature in the target tissue. Initial reports from the 1960s on cryoablation of the prostate for cancer or benign prostatic hyperplasia were discouraging. These early procedures were

performed using trans-urethral probes without adequate monitoring of the freezing process; alternatively, open perineal dissection facilitated access to the prostate. Due to the unacceptable rate of cancer relapse accompanied by severe complications, this approach fell out of favor [1,2].

Onik [3] revived the procedure in the early 1990s using a percutaneous trans-perineal multi-probe approach and trans-rectal real-time ultrasonography. Since then, cryosurgery is accepted as a treatment modality for prostate cancer [4]. The procedure is minimally invasive and is associated with negligible blood loss, short hospital stay and a rapid recovery phase. The goal is to eradicate all prostate tissue including malignant foci, thereby eliminating all sources of PSA. We present here the results of the first 12 patients in Israel treated by cryosurgery for prostate cancer during the last 2 years.

## Patients and Methods

Twelve patients, aged 53–72, diagnosed with adenocarcinoma of the prostate were submitted to cryosurgery. Cryosurgery was the primary treatment in 11 patients, and in the last patient was performed following brachytherapy failure [Table 1].

Pre-operative trans-rectal ultrasound examination of the prostate was performed in all patients, and three patients with prostates larger than 50 g received androgen ablation for 3 months prior to cryosurgery. The procedures were done under general or regional anesthesia in 10 and 2 patients, respectively.

A suprapubic catheter was inserted prior to the procedure to allow bladder drainage during the convalescence period. A designated warming urethral device (Advanced Polymers heat transfer sub-assemblies) was inserted over a guide-wire into the bladder via the urethra. Warm fluid at 39°C was constantly pumped in a closed circuit through the warming device at 180 ml/min to prevent the urethra from freezing throughout the procedure.

In the first five patients the procedure followed the standard approach reported by Onik et al. [5]: five needles (Cohen-Onik insertion kit) were placed trans-perineally into the prostate based on real-time TRUS imaging. Using a modification of the Seldinger technique, the needles were replaced by guide-wires, followed by tissue dilators and plastic sheaths through which the cryoprobes, 3 mm in diameter, were inserted.

PSA = prostate-specific antigen

TRUS = trans-rectal ultrasound

**Table 1.** Patients' pre-operative data

Patient no.	Age (yr)	Gleason score	PSA (ng/ml) (current level)	Clinical stage	Prostate size (g)*	Bone scan
1	67	2+3	8.5	B1	29	Negative
2	72	3+3	14.3	B2	40	Paget**
3	69	4+5	7.9****	B1	53	Negative
4	66	3+3	38.0	C	20	Equivocal***
5	67	3+3	8.2****	B1	57	Negative
6	71	3+3	2.8****	B2	76	Negative
7	65	3+3	56.0	C	18	Negative
8	64	3+3	12.5	B2	32	Negative
9	53	3+3	10.1	B1	24	Negative
10	61	3+4	7.41	B1	39	Negative
11	60	2+2	4.49	B2	46	Negative
12	58	4+5	8.9	C	46	Negative

\* Prostate size was measured by two of us (A.Z. and D.L.) by TRUS.

\*\* This patient's bone scan was not interpretable due to Paget's disease.

\*\*\* This patient had a suspect lesion in the right 8th rib but was normal on X-ray.

\*\*\*\* Androgen ablation was given to patients 3, 5 and 6 prior to cryosurgery but was discontinued postoperatively. Their PSA shown here was measured 2 years after discontinuation of androgen ablation.

In the other seven patients a modified technique of cryoablation was applied that included the use of 1.5 mm probes (cryoseeds) [6]. These needle-size probes are inserted by direct puncture, obviating the need for the more cumbersome Cohen-Onik insertion kit. Cryoseed positioning was facilitated by a template similar to the placement technique applied in brachytherapy and was guided by TRUS. The miniscule size of the cryoseeds enables more probes to be placed into the prostate, resulting in a more homogenous freezing with lesser thermal gradients. In the last seven procedures with the cryoseed system, 6–24 cryoprobes were used as compared to 5–6 with the former technique.

Individual ice balls that formed at the tip of each probe were allowed to coalesce, forming a large ice ball that encompassed the whole volume of the prostate. Real-time TRUS imaging was used throughout the phase of probe insertion as well as during the entire freezing process. Freezing progressed until the border of the ice ball reached the muscularis layer of the rectal wall. Two freezing cycles, with a full spontaneous thaw phase between cycles, were performed in all cases. Tissue temperature was monitored by 1–3 thermosensors. TRUS imaging was performed using the B&K-3535 machine and the 8558 probe. Cryogenic temperatures were generated by a CRYOHIT machine that utilizes the Joule-Thompson principle: namely, a pressurized gas that is released to the ambient pressure through a narrow nozzle absorbs thermal energy and thereby cools. Argon gas was used for cooling and helium for warming. Rapid temperature changes – from  $-187^{\circ}\text{C}$  to  $+37^{\circ}\text{C}$  – can be achieved within a few seconds, allowing precise control.

Following the procedure, urethral warming was continued for 20 minutes until full passive tissue thawing was reached. All patients remained with suprapubic catheters for at least 14 days

**Table 2.** Postoperative results

Patient no.	Follow-up duration (mo)	PSA (ng/ml)	Current androgen ablation	Digital rectal examination
1	24	0.01	None	EPF
2	24	0.5	None	EPF
3	24	0.5	None	+ 1, normal texture
4	14	0.06	LHRH agonist	EPF
5	24	0.7	None	EPF
6	24	0.08	None	EPF
7	11	0.0	None	EPF
8	6	0.6*	None	EPF
9	3	0.01	None	EPF
10	1.5	1.4	None	**
11	1	0.1	None	**
12	1	0.8	None	**

\* Patient no. 8 had a nadir PSA of 0.34 ng/ml at 3 months postsurgery, but his current PSA is 0.6 and prostate biopsy is scheduled.

\*\* These are the most recent patients and follow-up is 1 month at the time of writing.

EPF = empty prostatic fossa.

to permit adequate bladder drainage. Patients were followed every 3 months with serum PSA and physical examination. Postoperative values of PSA higher than  $> 0.5$  ng/ml were considered evidence of biochemical failure.

Potency status was assessed pre- and postoperatively, with potency considered adequate when spontaneous erections sufficient for vaginal penetration were reported. Urinary continence was defined as being completely dry with no need of pads.

## Results

The average operating time was 140 minutes and adequate freezing temperatures were obtained in all cases. No probe failure occurred and no emergency thawing was required. Pre-operative androgen ablation was given in three patients to reduce the prostate size and was discontinued after cryosurgery.

Four patients were hospitalized for 2 days following the procedure; the other eight were discharged the next morning. No blood transfusions were necessary and no rectal or urethral injuries occurred. Postoperative analgesia included a single oral dypirone in four patients. Early postoperative complaints were marked penoscrotal edema in four patients and perineal hematoma in three, which subsided within one week. Hematuria was minimal and did not necessitate specific therapy. Two patients developed hemorrhoids and one was diagnosed with orchitis 2 months following treatment. Suprapubic bladder drainage was maintained for 14 days in 10 patients and removed when residual volumes measured less than 50 ml.

Long-term complications included massive necrotic tissue sloughing in one patient, which was dislodged into the bladder and managed by trans-urethral morcellation. Another patient

developed a perineal fistula that dried out within 3 months. Both patients required prolonged suprapubic drainage – for 6 weeks and 3 months, respectively. Significant obstructive voiding was reported by one patient, but improved within a year. Average maximal urinary flow rate was 12 ml/sec (range 8–13 ml/sec).

Mild stress incontinence requiring 1–2 pads per day was noted in two patients. Both regained full continence 2 months postoperatively. None of the five patients who had been potent prior to cryosurgery regained erections sufficient for intercourse during the follow-up period. However, two patients had intercourse following treatment with sildenafil.

A PSA nadir of 0.5 ng/ml or less was reached in 8 of the 12 patients [Table 2]. One patient with a pre-operative PSA level of 38 ng/ml had a modest initial decline to 24 ng/ml postoperatively, with an early subsequent rise. He was deemed to have systemic disease and androgen ablation was initiated. In another patient (no. 3) PSA level fluctuated, with a nadir value of 0.2 and a slow rise to 1.0 ng/ml at 8 months postsurgery and subsequent decrease to 0.5 ng/ml. Trans-rectal prostate biopsy did not disclose prostate cancer but showed viable benign prostatic glands. Patient no. 8 had an initial nadir PSA level of 0.34 ng/ml and a moderate rise to 0.6 ng/ml 6 months after cryosurgery. Prostate biopsy is pending in this patient. Digital rectal examination disclosed an empty prostatic fossa in eight patients – a finding observed after radical prostatectomy.

## Discussion

The best treatment option for localized prostate cancer remains a matter of debate despite the vast experience gained in various treatment strategies [7]. The complexity of this therapeutic decision is further complicated by the advent of relatively new treatment modalities including brachytherapy and cryosurgery. While initially considered experimental, cryosurgery has won its role as a legitimate and acceptable option for prostate cancer. As stated by the 1997 American Urological Association position form: “Cryosurgical ablation of the prostate is an accepted form of treatment for prostate cancer and should no longer be considered experimental” [8].

To be considered a successful therapy for cancer, a procedure must show an impact on disease-specific mortality and must be safe. However, given the long natural course of prostate cancer, at least 15 years of follow-up are needed to assess such an impact. Few randomized prospective studies encompass such long follow-up on prostate cancer patients and none have reported on cryosurgery. Therefore, the ability to achieve a low PSA level postoperatively is accepted as a comparative endpoint. Connolly et al. [9] suggested that PSA below 0.5 ng/ml be considered a successful endpoint for cryosurgery. Although the reported PSA results following cryosurgery depend on patient selection and length of follow-up, a 60–80% rate of PSA below 0.5 ng/ml is acceptable [10]. Cohen and colleagues [11], reporting on 383 patients with a 21 month follow-up, found that 60% had an undetectable PSA and 77% had a PSA < 1.0

ng/ml. Salliken et al. [12] observed that 67% of their patients had an undetectable PSA almost 2 years after treatment. While PSA above 1.0 is commonly associated with persistent cancer, some patients may have a detectable but stable PSA that may be attributed to persistent prostate glands but not necessarily of viable malignant cells [13]. Some authors perform routine prostate biopsies 6 months following the procedure. While a positive biopsy must be regarded as evidence of failure, a negative biopsy is less specific [14].

Prognosis is affected by tumor grade and stage at presentation, and pre-operative PSA. For patients with favorable parameters at diagnosis (i.e., PSA < 10 ng/ml, Gleason score < 6, and stage B2 or less), long-term results are comparable between various treatment options [7]. In the unfavorable group the likelihood of extra-prostatic tumor extension is significant, and therefore radical surgery has less curative potential. Since freezing may be allowed to include peri-prostatic tissues such as the tips of the seminal vesicles and laterally up to the levator muscles, cryosurgery may have an advantage in this subset of patients. Although performing cryosurgical prostate ablation requires TRUS skills and a thorough understanding of both anatomy and cryobiology, this procedure has a rapid learning curve. The use of the 1.5 mm probes and the template insertion system simplifies the procedure. Based on thermodynamic models, it is speculated that the application of multiple probes, up to 30, allows for a more homogenous thermal sink and approaches the lethal isotherm to the visible edge of the ice ball. This may result in more efficient freezing with less damage to surrounding tissues. Evidence that increasing the number of probes results in more effective freezing has been provided by Lee et al. [15], who showed that increasing the number of probes from 5 to 6–8 is associated with better glandular ablation [15].

The most feared complications associated with cryosurgery of the prostate are rectal fistula and urethral sloughing and stricture. The former is totally operator dependent and is rare today thanks to meticulous preservation of the rectal wall and its real-time inspection with TRUS. The surgeon's experience is a crucial factor in preventing this mishap. And the latter has practically disappeared since the FDA approval of the designated urethral warmer catheters [16]. The risk for fistula formation is 0.33–0.4% [10,17]. We presume that the occurrence of a urethro-perineal fistula in one of our patients reflects the early stage in our learning curve.

The inflammatory response to the act of freezing results in marked prostatic edema soon after surgery. It is therefore prudent to assure bladder drainage by a suprapubic catheter as a standard part of the operation. Obstructive symptoms may persist for up to 3 months in 20% of cases [12]. Previously, such patients underwent trans-urethral resection of the prostate to remove the obstructing necrotic tissue, but this was associated with an unacceptable rate of urinary incontinence. It seems more prudent to wait for spontaneous resolution of the obstruction with concomitant suprapubic drainage.

Impotence is common following cryosurgery and is a significant drawback. However, erectile dysfunction may occur

following any treatment option for prostate cancer. Since perfusion causes a thermal leak of coldness, it is important to freeze both neurovascular bundles and thereby “shut-down” the blood supply to the prostate. This also enhances prostatic ischemia, which is crucial to the success of treatment [18].

Cryosurgery may be used as a salvage therapy when previous treatment options have failed. Such patients have an overall 20–25% chance of being cured with a salvage cryosurgical procedure, and presently this is their sole curative option albeit with a higher risk for complications [14,19].

## Conclusion

Cryosurgical ablation is a treatment option for prostate cancer and our initial results demonstrate that it is feasible and safe. The new technology of ultra-thin cryoprobes and argon-based freezing holds promise that this procedure will become even safer and more effective.

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**Correspondence:** Dr. A. Lindner, Dept. of Urology, Assaf Harofeh Medical Center, Zerifin 70300, Israel. Phone: (972-8) 977-9409, Fax: (972-8) 977-9402, email: oshoval@asaf.health.gov.il