Cryoablation of Prostate Cancer

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Introduction

Cryosurgical ablation of the prostate using an open, perineal incision was started by Flocks and associates at the University of Iowa in 1969.[1] In this procedure, the posterior surface of the prostate, seminal vesicles and bladder base were exposed through a perineal incision. A cryoprobe was then inserted first into the prostate and/or adjacent tissues. The technique was monitored by visual and tactile inspection only. Such therapy resulted in coagulative necrosis of epithelial elements and replacement with fibrous stroma. Outcome (survival and recurrence) was related to stage and grade. Approximately 41% of patients eventually had evidence of persistent or recurrent disease.[2] Although the technique compared favorably with other treatment modalities with respect to survival, morbidity was significant. Urethral sloughing of tissue was common. Urethrorectal or urethrocutaneous fistulas developed in 13% of patients, bladder neck obstruction in 2.3% and urinary incontinence in 6.5%.

There has been renewed interest in cryosurgery as a treatment for localized prostate cancer in recent years due to an increased interest in less invasive forms of therapy for localized prostate cancer, as well as several recent technical innovations, including improved percutaneous access, expertise in transrectal ultrasound, improved cryotechnology and better understanding of cryobiology. The objective of this brief review is to summarize the results of prostate cancer cryoablation to date and make recommendations regarding future efforts and the place of cryosurgery in the treatment of prostate cancer currently.

Biological Basis of Activity

The two parameters which correlate with the likelihood of cell destruction are the cooling rate during freezing and the lowest temperature achieved.[3] Cell death may occur due to chemical damage or intracellular ice formation. Zippe summarized this destructive process as follows: freezing of the extracellular compartment and withdrawal of water from the cells occurring at -15 C, intracellular ice formation occurring at -20 C to -40 C, thawing which results in recrystallization, and tissue thrombosis.[4] Cell death is unlikely to occur at temperatures higher than -20 C. Littrup and colleagues demonstrated, in a canine model, that cryoablation resulted in hemorrhagic necrosis and the extent of cell destruction correlated with the outer edge of the iceball as demonstrated by ultrasound.5 However, it is important to note that the temperature at the edge of the iceball is 0 to -2oC, which is not adequate for consistent destruction of cancerous tissue. Therefore, the iceball is allowed to extend beyond the prostate, certainly in areas of prostatic cancer. In addition, cell death may be mediated by ischemia due to vascular obstruction precipitated by the cryoablation of the prostate's vascular supply.

Technique
Freezing of the prostate is carried out using a multiprobe cryosurgical device. Patients, after induction of regional or general anesthesia, are placed in the lithotomy position. A urethral warming device is placed to preserve the urethra and avoid sloughing of tissue postoperatively. This device circulates heated water. An ultrasound transducer is inserted into the rectum and volume measurements are made of the prostate and cancer(s). Using a biopsy guide, an 18-gauge, hollow core needle is inserted into the prostate under ultrasound guidance. Once the needle is in position, a 0.038 J-tipped guide wire is advanced through the needle to the proximal extent of the prostatic capsule. Generally, five wires are placed. Cannulas and dilators are passed over the wires. The cannula is positioned against the proximal extent of the capsule and both wire and dilator are removed. The cryoprobes (3 mm) are placed and the cannulas are retracted. Generally five probes are placed: 2 anteromedially, 2 posterolaterally and one posteriorly. Liquid nitrogen is circulated through these needles and the resulting freezing zones or "iceballs" can be monitored by ultrasound. The iceball has an elliptical shape with the maximal diameter at the tip of the cryoprobe. The anterior probes are activated first and allowed to extend posteriorly and laterally. Once these have reached the desired position, thawing is begun and the posterior probes are activated. **(Please see Figure 1)**

Most surgeons routinely perform two freeze/thaw cycles in all patients, and, if the iceball does not adequately extend to the apex of the prostate, the cryoprobes are pulled backwards into the apex and additional freezing is carried out. It has been a consistent finding that the use of 2 freeze/thaw cycles is more likely to result in prostate cancer ablation than the use of a single cycle, due to the fact that the temperature at the edge of the iceball is 0 to -2oC, while actual cell destruction requires -25 to -50oC. To ensure adequate treatment of cancer, the iceball often is allowed to extend 2 - 4 mm laterally into the periprostatic tissues, beyond the apex 6 mm and into the muscularis propria of the rectum posteriorly. In areas of extracapsular extension, greater propagation of the freeze zone is permitted laterally. If necessary, an additional probe may be placed in any area of gross extracapsular extension. Androgen deprivation before cryosurgery should be considered in patients with large glands or extensive local disease, as such therapy serves to shrink the prostate/cancer, allows for even distribution of the cryoprobes, eliminates steep temperature gradients between the probes, reduces bulky extracapsular disease, and may allow for widening of the periprostatic space and better protection of surrounding structures.

Results
Biopsy Data The positive biopsy rate after cryoablation ranges between 7.7 % and 23%. (See Table 1) Although not reported routinely, many of these biopsies may contain benign epithelial elements. Benign epithelium, often very focal, has been seen in up to 71% of patients after cryotherapy. The significance of benign epithelium is unknown; such findings may represent areas of the prostate not frozen, perhaps, in the area of the urethral warmer. Alternatively, Littrup and colleagues noted, in a canine model, occurrence of re-epithelialization by urethral surface epithelium of necrotic glandular elements.

Table 1 - Positive Biopsy Rates After Cryosurgery

Study	Patients	3 - 6 mos	12 mos	> 21 mos
Bahn et al6/ Lee et al7*	130/136	7.7/3.3	2.3/9	---
Coogan and McKiel8	76	17	---	---
Cohen et al9	114	---	---	18
Bales et al10	23	14	---	---
Weider et al11/Schmidt et al12*	61/179	13.1/21	21	---
Shinohara et al13/*	91/121	23/8.6	3.4	9.1
Long et al14	137	201	---	---
Pisters et al15	113	23	---	---
*Update 13 to 20 mos				

The relationship between clinical stage and the likelihood of a positive biopsy is summarized in Table 2. Certain areas of the prostate and/or seminal vesicles may be more likely to be sites of treatment failure. At UCSF, sixty-eight patients had pre- and post-treatment ultrasound guided biopsy mapping of the prostate and each seminal vesicle to define sites of disease. The presence of residual disease was correlated with the initial site(s) of the cancer.

Recurrence was more common in cancers located at the apex (9.5%) and seminal vesicles (44%), in contrast to those located in the mid-gland (4%) and base (0%). Similarly, Bahn and colleagues noted that the apex, and to some extent, the seminal vesicles were more likely to harbor residual Biopsy: disease compared to the rest of the prostate.[13]

Table 2 - Relationship of Clinical Stage and Likelihood of a Positive Biopsy[13,15,16,18,20]

Stage	Patients	Positive Biopsy: Patients (%)
A (T1)	67	6 (9)
B (T2)	203	18 (8.9)
C (T3)	133	28 (21)

Serum PSA after definitive treatment such as radical prostatectomy or radiotherapy has been shown to be an important determinant of outcome. What constitutes an acceptable PSA following cryotherapy has not been well defined. It is known that as many as 60% of patients who undergo cryotherapy will have benign epithelial elements noted on biopsy. Therefore, a low, but stable, PSA may not be associated with disease progression. A similar situation has been noted for patients who undergo radiotherapy where PSA nadir levels in excess of 2.0 ng/ml following treatment are associated with an increased risk of prostate cancer recurrence compared to those patients who achieve detectable, but very low values, < or = 0.5 ng/ml.[16]

What PSA nadir level should be achieved after cryosurgery is not known with certainty, as yet. We recently addressed this issue at UCSF. The rates of biochemical and biopsy failure were correlated with the PSA nadir after cryosurgical treatment in 132 patients

who underwent 145 procedures. Follow-up included prostatic specific antigen (PSA) at 3, 6, and 12 months and every 6 months thereafter. Biopsies were performed at six months or with biochemical failure defined as PSA nadir > or = 0.5 ng/ml or subsequent PSA elevation > or = 0.2 ng/ml. Biochemical and biopsy failures were correlated with PSA nadir values following cryosurgery (< 0.1 ng/ml, 0.1 - 0.4 ng/ml, 0.5 - 1.5 ng/ml, and > 1.5 ng/ml). Biochemical failure was lowest in those who achieved PSA nadirs < 0.1 ng/ml (21%), but was noted in 54% to 58% of those with higher nadir values. Biopsy failure was lowest in those with nadirs < 0.1 ng/ml (1.5%) and < or = 0.4 ng/ml (10%). In contrast, 55% of the patients with nadir values > or = 0.5 ng/ml had biopsy failure. Both biochemical and biopsy failure tended to occur within the first 12 months after treatment (i.e. 96% and 88% of the biochemical and biopsy failures, respectively). Based on this single study, a PSA nadir of < or = 0.4 ng/ml. should be achieved following cryotherapy. Higher values are associated with a significant risk of PSA elevation and a high likelihood of residual disease detected on biopsy.

Investigators are attempting to improve the results using more innovative imaging (MRI and three-dimensional ultrasound).[17,l8] More efficient and effective freezing may be accomplished by the use of antifreeze proteins. Use of such proteins in an in vitro system resulted in complete destruction of prostate cancer at high subzero temperatures irrespective of cooling rates.[19]

Complications

Table 3 - Complications of Cryosurgery

Complication	Incidence (%)
Impotence*	77
Urinary Retention	9
Incontinence	16
Infection	7
Pain	3
Fistula	3

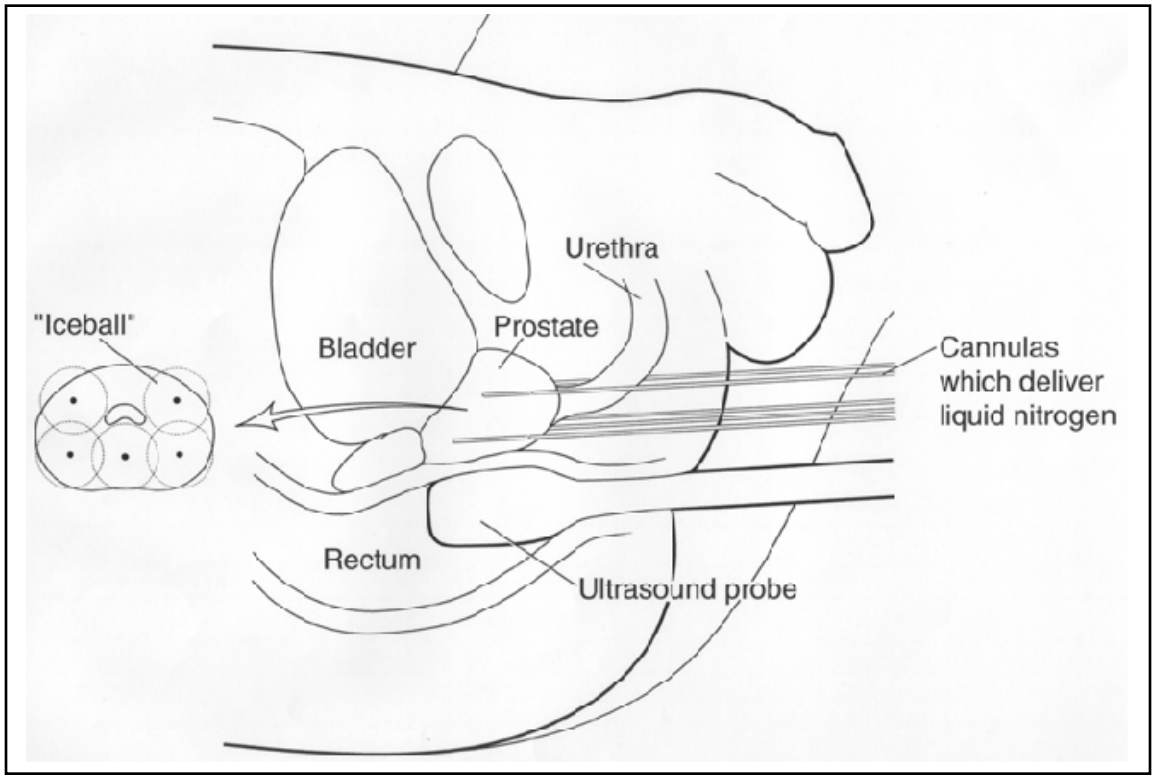
*Of those potent preoperatively

Impotence is very common after the procedure and is a product of damage to the neurovascular bundles during the freezing process. Clearly, some patient who are impotent following the procedure will regain erectile function with time. Sloughing of tissue occurs in approximately 3% to 10% of patients. The likelihood of either urinary retention due to necrotic tissue obstruction or stricture formation is related to the type of urethral warmer used. Sloughing of urethral tissue (and retention and stricture disease) is much less common in those patients treated with commercially available urethral warming devices compared to those managed with "home made" warmers (9.9% vs. 37.6%).[20] Sosa in a multicenter review reported the following incidence of early complications: urinary retention > one month 6.8%, pain 9.4%; infections 13.4% and fistula formation 1.4%. Complications from published, individual series are summarized in Table 3.

Summary
Cryosurgical ablation of the prostate results in significant epithelial destruction. Although early- and intermediate-term results strongly suggest that cryoablation of the prostate is therapeutic in a substantial number of patients, long-term results of the procedure are unknown and patients need to be advised of this. With improvements in technology, imaging and freezing techniques, PSA undetectability and negative biopsy rates have improved and the risk of complications has been reduced.

As the cryosurgical technique has not been completely established, cryosurgery remains an evolving modality. Specific issues which must be addressed include: patient selection; the role of thermocouples, both to confirm adequate freezing and to protect the bladder neck and voluntary sphincter; the long-term significance of residual benign glands on biopsy; the impact of new imaging techniques; and prospective comparison (cost, quality, and cure) with existing techniques. Prospective trials of cryotherapy for localized/regional prostate cancer are justified based on the information now available.

Figure 1



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