Prostate Cryoablation: Update 1998

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Introduction

The use of subzero modalities for medical treatment dates from 2500 BC, when the Egyptians used cold packs on wounds to relieve pain. Arnott1 in England in the 1840s was the first physician to use cryotherapy for neuralgia and cancer, applying iced saline directly via hollow irrigating tubes to treat tumors.

Further advances in cryotherapy were related to the development of liquefied gases. In 1899, White2 used liquid oxygen at a temperature of –180°C to treat both oral and skin lesions. During the early part of this century, with the introduction of ether and ethyl chloride sprays and solidified carbon dioxide, cryosurgery was primarily a dermatologic specialty. The first closed cryosurgical device was developed in 1938 by Fay, a neurosurgeon.3

Modern cryosurgery began after World War II as liquid nitrogen became available. In 1961, Cooper and Lee4 described the use of liquid nitrogen, achieving cooling temperatures of –190°C via insulated probes attached to a circulating pump. By that time, liquid nitrogen was commonly used for the treatment of various skin disorders, brain tumors, lesions of Parkinson’s disease, and various neuromuscular disorders.

Of the various cryogens available for medical use, the most common are dichlorodifluoromethane (Freon-12) (boiling point of –29.8°C), solidified carbon dioxide (–79°C), liquid nitrous oxide (–88.5°C), and liquid nitrogen (–195.8°C).5 Liquid nitrogen is the most commonly used of these cryogens because of its availability and ease of storage.

In the 1960s Gonder and colleagues6 were the first to use liquid nitrogen cryosurgery for urologic disorders. They showed that freezing produced tissue destruction in the canine prostate. In 1966, Gonder et al7 performed prostate cryosurgery in humans, treating bladder neck obstruction from both cancer and benign prostatic hyperplasia. They used a transurethral technique with a cryoprobe shaped like a urethral sound. The procedure was considered fairly rapid with the patient under spinal anesthesia and with minimal associated blood loss.

Transurethral prostate cryosurgery was nearly abandoned at this point, how-
ever, because of complications, especially occasional fistula formation and urethral sloughing of necrotic tissue causing urinary tract obstruction that required repeat manipulation. Also, the monitoring of the procedure was imprecise, using mainly rectal palpation. Modifications of the technique, including perineal exposure to prevent rectal injury and the use of monitoring by open cystostomy, were still insufficient to prevent injury to adjacent normal structures.

Transurethral prostate cryosurgery was modified in the late 1960s by Flocks et al., who used open perineal exposure of the prostate (similar to exposure for perineal prostatectomy) to place the cryoprobes directly into the cancer. In this way the prostate tumor was destroyed directly with less sloughing of periurethral tissue. Nevertheless, control of this cryoablation was entirely visual and thus inadequate. Urethrorectal and urethrocutaneous fistulas, significant complications, occurred in up to 12% of patients. Most patients treated by Flocks and O’Donoghue had extensive lesions requiring only palliation and local control. In only a few patients was open prostatic cryosurgery indicated for cure instead of standard radical prostatectomy or irradiation.

The results of open perineal cryosurgery by Flocks and his colleagues were summarized in four published series. After 10 years of follow-up, on a stage-by-stage basis, patients treated with the open perineal technique had progression-free survival and overall survival equal to those of patients treated with either irradiation or surgery at the University of Iowa. Open perineal cryosurgery did not become popular, however, because at that time very few urologists were knowledgeable about or interested in performing radical prostatectomy, particularly by the perineal route.

The cryosurgery technique was modified further in 1974 by Megalli et al., who used a closed perineal approach with a single percutaneous probe positioned and monitored via rectal palpation. This modification avoided an open incision and resulted in less sloughing of periurethral tissues. However, again, the placement of the probe and the monitor-

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Transrectal urethral ultrasound monitoring of the prostate and improved percutaneous access to structures such as the kidney, liver, and prostate led to renewed interest in prostate cryoablation in the 1980s.

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The ultrasound characteristics of cryoablation were described as a hyper-echoic rim with anterior acoustic shadowing, and the final destroyed prostate tissue was described as hypoechoic compared with normal surrounding tissues. Onik et al.\(^2\) then adapted their technique to the treatment of human prostate cancer. Their early findings indicated that the technique improved local control of freezing and, in turn, decreased complications. The problem of sloughing of the periurethral tissues was diminished further with the use of an investigational intraoperative urethral warming device. The procedure was completed fairly rapidly with the patient under regional or general anesthesia, was associated with minimal blood loss, and resulted in a short period of hospitalization.

The enthusiasm for a minimally invasive procedure was offset by the prolonged learning curve required to complete the technique accurately. Many investigators in their initial experience had results and morbidity that were unacceptable for treatment of localized prostate cancer. Political issues and reimbursement problems soon followed, leading to a decline in prostate cryoablations in all but a few institutions. However, individuals who have continued to evaluate and refine the technique have presented and published longer-term results that are comparable to those of radiation therapy and radical prostatectomy.

This update describes the mechanisms of action of cryoablation, the technique of the authors and others, results to date, complications, and the status of this alternative modality for the treatment of localized prostate cancer.

### Mechanisms of Action

The principles of cryoablation, including mechanisms of cell injury and cell death, have been well studied.\(^4,6,23\) The three key factors involved in freezing injury are direct mechanical shock, osmotic shock, and cellular hypoxia. The various documented mechanisms of action of cryoablation are listed in Table 1.

Cryoablation can be defined as the in situ freezing and devitalization of tissues. The freezing process must be applied and precisely controlled to produce a predictable zone of necrosis that will destroy...
the target lesion and an appropriate margin of surrounding tissue. Studying an in vitro model of cold-induced cellular injury, Zacarian in 1973 showed that cryotherapy is both time and temperature dependent and that two freeze-thaw cycles are more damaging to cells than is one freeze-thaw cycle.

Because temperature is a measure of the kinetic energy of molecular motion, as intracellular temperature is lowered, the molecular processes are slowed and thus can be arrested. With a rapid freeze and slow spontaneous-thaw technique, the two primary effects noted are direct destruction and indirect destruction. During the period of direct damage, at temperatures below –15 to –20˚C, tissue goes through both hypothermia and true freezing.

Hypothermic effects are divided into the following two categories: metabolic uncoupling and compromise of structural integrity. Freezing begins in the intracellular and extracellular compartments and in the microvascular network. At a temperature of –15˚C, most of the extracellular environment is frozen, causing trapping of tissue and production of shearing forces that disrupt cellular structure. This process is known as mechanical shock.

As ice is formed of pure solid water by the exclusion of electrolytes and organic chemicals, the cells are exposed to an extremely hyperosmotic environment. This extracellular hyperosmotic fluid allows water to be drawn out of the cells, resulting in increased tissue ice content along with cell shrinkage. This process then further damages cell membranes and causes protein denaturation. The latter process is known as osmotic shock.

The slower process of spontaneous thawing is also a damaging environment for cells. As the ice melts, any remaining intact cells are exposed to a relatively hypotonic environment as the water reenters the remaining cells, causing cellular rupture.

The delayed or indirect destructive effects of cryosurgery continue mostly because of disruption of vasculature resulting in tissue hypoxia and vascular thrombosis. Zacarian et al found that, at temperatures below –20˚C, venules were more susceptible to injury than were arterioles. Freezing promotes stasis of blood, leading to thrombosis and subsequent coagulative necrosis of tissue. This process includes local edema with activation of the inflammatory cascade. Later, tissue macrophages invade to resorb the lesion. The histopathologic changes seen after cryotherapy are detailed later in this article.

Further information on the cryobiology related to this treatment is beyond the scope of this article, but interested readers are encouraged to refer to the work of Gage.

Table 2
Indications for Prostate Cryoablation at the University of California, San Diego

| Primary treatment of clinically localized carcinoma (T1–T3) |
|----------------------------------------------------------------|
| Salvage therapy for local failures after radical prostatectomy, external beam irradiation, brachytherapy, or other techniques |
| Debulking of large primary tumors with or without metastatic disease |
Indications
Indications for prostate cryoablation at our institution fall into three broad categories (Table 2). The first and largest of the three groups consists of patients with localized disease who were not treated previously and who either are advised to or elect to undergo this procedure rather than radical prostatectomy or irradiation. The same type of patient made up the smaller group in the series by Flocks et al.13

The second category includes patients who have had recurrent or relapsing local prostate cancer after radical prostatectomy, cryosurgery, or irradiation, including external beam therapy, interstitial therapy, and combinations of these two types of radiation therapy. The third and smallest group consists of patients with large local lesions, often in the presence of metastatic disease, in whom the procedure is indicated for the control and prevention of local complications such as repeated hematuria, bladder outlet obstruction, and urinary retention. This group was the largest category of patients treated with the open perineal approach by Flocks et al.13

Surgical Techniques and Patient Care
The ultimate objective of prostate cryoablation is the destruction of the entire gland. In some cases, the goal includes ablation of areas of local tumor extension. The procedure is done with the AccuProbe 450 SP instrument (Cryomedical Sciences, Rockville, MD), which uses cryoprobes 3 mm in diameter. Although other instruments are available,27 most cryosurgeons use the AccuProbe system, achieving probe tip temperatures of –160°C. We perform transrectal ultrasound monitoring with the Bruel and Kjaer instrument using a 7.5-MHz transducer.

Preoperatively, patients undergo digital rectal examination, prostate biopsy, urinalysis, chest radiography, complete blood count, blood chemistry tests, and measurement of their prostate-specific antigen (PSA) level. Selected patients undergo further imaging techniques to identify possible extraprostatic extension or regional pelvic lymph node involvement. Patients with prostate glands larger than 40 to 50 g are started on induction endocrine therapy to reduce the target volume. The gland size can be decreased up to 50% with this method. Induction therapy continues for at least 3 months using luteinizing hormone-releasing hormone agonists (LHRH-agonists) with or without an antiandrogen.

Three different types of freezing techniques have been used, including single and double freeze-thaw cycles and a pullback freeze. Our preferred technique consists of a single long freeze-thaw cycle with an apical pullback freeze for patients with large prostates (more than 4 cm). Cryoablation is more intense in areas of known prostate cancer based on the initial sextant biopsies.

The freezing process must be precisely applied and controlled to produce a predictable zone of necrosis that will destroy the target lesion and an appropriate margin of surrounding tissue.
SINGLE FREEZE-THAW CYCLE

Patients receive either regional or general anesthesia and perioperative antibiotics. The dorsal lithotomy position is used, and cystoscopy is performed initially to determine the local anatomy and to identify any unrecognized pathology. A percutaneous suprapubic catheter is inserted under cystoscopic guidance, and a large-bore Foley catheter is placed per urethra over a guidewire. The scrotum may be sutured to the anterior abdominal wall to allow access to the perineum if necessary. Sterile saline warmed to 40°C is infused at this time through either the suprapubic or the urethral catheter and later as a closed system through the urethral warming device. This warm irrigation prevents urethral freezing and subsequent necrosis and stricture.

The surgeon uses transrectal ultrasound of the prostate to look for asymmetry and evidence of any extraprostatic disease and to assess the overall prostate dimensions. Five cryoprobes are generally used, two placed anterolaterally, two posterolaterally, and one in a suburethral midline location. Additional probes can be placed in extraprostatic positions, such as the seminal vesicles, if evidence of disease in those areas is present. To reduce the risk of urethrorectal fistula yet encompass the entire prostate to its capsule, we try to keep a 1-cm margin from the probe tip to the adjacent capsule.

During the ultrasound visualization, five 18-gauge needles are positioned percutaneously in the prostate down to the prostatovesical junction, using a perineal biopsy guide. The stylets are withdrawn.
and replaced with 0.038-inch J-tip guidewires, which are inserted through the needles. After the needles are removed, small skin incisions are made at the perineal skin level to allow entry of the dilators and cannulas over the guidewires. When tract dilation is complete to the level of the prostatovesical junction, the guidewires and dilators are removed and five cannulas are left in place.

Next, the cryoprobes are inserted through the cannulas under ultrasound monitoring, and the proximal insulating ends of the cannulas are pulled back at least 2 cm over the cryoprobes, exposing the working freezing element. The position of the cryoprobe tips is verified by ultrasound, then the probes are activated and fixed to the tissue at a temperature of -50 to -70˚C. This part of the procedure, which is called sticking, is completed within 2 minutes (Fig. 1).

The prostate is then frozen by a quick decrease of probe temperatures to approximately -196˚C for 5 to 10 minutes. To diminish the risk of urethrorectal fistula, we deactivate the suburethral probe at 5 minutes. Freezing is begun anteriorly so that the freeze zone does not interfere with the ultrasound imaging of the yet-unfrozen gland. Ultrasonic visualization is continued throughout the procedure to determine adequate ablation of the gland and tumor and to prevent injury to surrounding tissues such as the anterior rectal wall, bladder neck, and trigone.

After satisfactory freezing and devitalization of tissue, the cryoprobes are thawed slowly, then withdrawn. Generally the probes need 5 to 10 minutes to thaw before they are removed; however, the reconstitution of the ultrasound image may take up to 30 minutes. The small perineal skin incisions are closed with interrupted 3-0 chromic suture, and the urethral warming device is removed and replaced with a large-bore urethral catheter. Both suprapubic and urethral catheters are irrigated, then placed to straight drainage. Typically, the urethral catheter can be removed either in the recovery room or on the first postoperative day after the gross hematuria subsides.

**Double Freeze-Thaw Cycle**

As mentioned earlier, cryobiology data suggest that a repeat or double freeze-thaw cycle can provide more thorough destruction if any cellular elements remain after the first cycle. Selected patients with large tumors or glands (usually more than 35 to 40 g) may be treated with this modification even after preoperative induction endocrine therapy.

In this technique, the cryoprobes are thawed slowly, and when the prostate tissue image begins to reconstitute on ultrasound, after about 30 minutes, the cryoprobes are maintained in their initial position and reactivated as in the first freeze. The total freeze time can then reach 15 minutes. Transrectal ultrasound monitoring continues through the second cycle. In this fashion, at least theoretically, any surviving cancer cells will be freeze-sensitized and forced to undergo an additional cycle of freezing.

**Pullback Freeze**

In patients with large prostate glands, the prostatic apex may not be ablated sufficiently with the initial placement of five cryoprobes. To make sure the apical area is ablated, after the cryoprobes are thawed and the prostate image is reconstituted on ultrasound, the surgeon visually repositions the cryoprobes more distally. Again, the cryoprobes are fixed to the tissue at -50 to -70˚C, and another cycle of freezing and thawing takes place in the apical area.

**Patient Care**

The urethral catheter is removed and the patient is discharged home within the first 24 hours after the cryoablation. Two weeks of oral broad-spectrum antibiotics is prescribed. The patient is instructed to clamp his suprapubic cystostomy tube after the first 7 to 10 days and to begin void-
ing trials with measurement of both the voided and the residual urine volumes. When the postvoid residual volumes are between 50 and 100 ml or less, the suprapubic cystostomy can be removed.

Patients are typically followed at 1, 3, and 6 months and at 6-month intervals after that for the first several years. Follow-up examination includes a full history of voiding habits and sexual function, digital rectal examination, urinalysis, and determination of PSA level. Cryoablation, similar to other significant manipulations of the prostate, increases the serum PSA level immediately; thus a new baseline for PSA should not be established until at least 4 to 6 weeks postoperatively. Follow-up ultrasound-guided biopsy is recommended at 6 months and again at 1 to 2 years. If induction endocrine therapy was given, it is stopped at the time of the cryoablation.

Repeat Treatment
During follow-up care, a percentage of patients will be found to have evidence of persistent or recurrent prostate cancer. Among alternative therapies at that point, a second attempt at cryotherapy can be offered.

The retreatment technique is similar to that of the initial treatment except that the target volume, both gland and tumor, is generally much smaller than that of the initial treatment. Thus, it requires either fewer cryoprobes or a shorter freezing duration. At our institution, retreatment cryosurgery has been performed in 6% of patients. Postcryotherapy follow-up for patients who have had retreatment is similar to that for men who have had only a single cryoablation.

Results
Experience at the University of California, San Diego
At the University of California, San Diego Medical Center since March 1993, 296 men with prostate cancer have been treated with prostate cryoablation in a total of 316 procedures. Their clinical stages included T1 to T4, N0 to N1, and M0 to M1. Their average age was 68 years. Five cryoprobes were used in the cryoablation in 80% of cases. Most men voided spontaneously with removal of the suprapubic cystostomy tube by 10 to 14 days. Of the 137 men who had a follow-up biopsy at 1 year or later, 110 (80%) had cumulative negative biopsies, and 27 (20%) had persistent cancer documented by a positive biopsy.

Patients with persistently elevated or rising PSA levels, with or without abnormal findings on digital rectal examination, are more likely to undergo follow-up biopsy. Conversely, patients doing well clinically with low or undetectable PSA levels and “negative” findings on digital rectal examination (e.g., flat or empty prostate fossae) are less likely to require follow-up biopsy.

At the 1-year follow-up, of 63 patients biopsied, 48 (76%) were negative.

Cryosurgery can be considered as a primary treatment alternative to surgery or irradiation, as salvage treatment for recurrent cancer after irradiation, and for debulking of large symptomatic primary tumors.
and 15 (24%) were positive for malignancy. Of 52 patients biopsied between 2 and 3 years after cryoablation, 42 (81%) were negative and 10 (19%) were positive. Finally, of 22 men with follow-up biopsies at 3 years or later, 20 (91%) were negative and 2 (19%) were positive.

As stated earlier, PSA levels typically rise initially, probably secondary to prostate infarction, but subsequently fall. In 83% of patients, PSA levels were in the normal range, and 50% of these were in the undetectable range of less than 0.5 ng/ml. Thus far there seems to be no statistical difference relating the pretreatment PSA level to the results of follow-up biopsy.

Among 21 patients who underwent prostate cryoablation for relapses after radiation therapy, 18 (86%) have had negative biopsies after cryoablation. PSA levels have been in the normal range in 67% of these patients, and of these 40% have been in the undetectable range. Thus far in our experience, the rates of negative and positive biopsy results are the same in patients who have cryosurgery for recurrent disease after irradiation and in patients with no previous therapy. In the entire series, no perioperative deaths have occurred and no patients have required transfusion.

Experience at Other Institutions

Miller et al29 and Cohen et al30 have recently updated results on 383 patients who have undergone 443 cryosurgical procedures. Of 354 men biopsied at 3 months, 53 (15%) were positive for carcinoma. Positive biopsies at 3 months were seen in 11.3% of men who had had no previous treatment, in 18% of men who had received hormone therapy, in 27% of men who had previously had irradiation, and in 27% of men who had had both irradiation and hormone treatment before cryoablation.

These authors also looked at the results of biopsies in relation to the initial clinical stage. They found positive biopsies at 3 months in 9% of patients with stage A (T1) prostate cancer, in 9% of those with clinical stage B1 (T2a), in 15% of those with stage B2 (T2b), and in 22% of men with stage C (T3). Their overall negative biopsy rate at 2 years is 85%. The negative biopsy rate in patients who did not have previous therapy is 83%.

At the University of Texas M.D. Anderson Cancer Center, prostate cryoablation has been done primarily for salvage, that is, after failure of previous treatment such as irradiation. Von Eschenbach et al31 reported on 89 patients treated with salvage cryoablation after radiotherapy had failed. An average of 3.5 years elapsed before the documented treatment failure, and about half the patients had Gleason scores of 8 to 10. Forty-seven of the 89 patients underwent a single freeze-thaw cycle, and the remaining 42 underwent a double freeze-thaw cycle.

Sixty-seven patients underwent biopsy 6 months after their cryoablation. Fifty-two (78%) of the biopsies have been negative. However, biopsy findings were negative in only 69% of patients who had the single freeze-thaw cycle compared with 92% of those who had the double freeze-thaw cycle. Twenty-five percent of the patients have undetectable PSA levels, and results are similar in the single-freeze and double-freeze groups.

Bahn et al32 and Lee et al33 reported prostate cryoablation results in patients treated with combined LHRH-agonist and antiandrogen therapy for at least 3 months before cryoablation. Residual cancer (i.e., a positive biopsy at 3 months) was found in only 2 of 134 patients (1.5%) who were clinically stage T2 or less before treatment. The positive biopsy rate at 1 year is 4%, for an overall residual cancer rate of 3%. For patients with clinical stage T3 disease, the positive biopsy rate was 11% at 3 months and 14% at 1 year. Patients with negative biopsies had significantly lower PSA levels; these patients on average had a PSA level of 0.4 ng/ml 1 year after
cryoablation.\textsuperscript{32,33} Long et al\textsuperscript{34} reported on 84 cryoablation procedures in 80 patients with clinical stage T1 to T3 prostate cancer. Of their last 50 procedures, they reported undetectable PSA levels in 90% of patients at 3 to 6 months and a 15% positive biopsy rate. These authors also performed 23 cryoablations on 21 patients who had relapses of cancer after irradiation.\textsuperscript{35} Their positive biopsy rate after cryoablation is 30%, and in each case, the positive biopsies were seen only in the seminal vesicles. Two-thirds of these patients had undetectable PSA levels.

Shinohara and Carroll\textsuperscript{36} reported on 70 cryoablation procedures in 65 patients, documenting persistent or residual cancer at 3 months in 18%. After changing their technique to include standard double freeze-thaw cycles as well as extensive periprostatic and apical freezing, they reported a reduction in positive biopsies to only 4%, with undetectable PSA levels in 64% of patients.

Shinohara et al\textsuperscript{37} recently updated their results of 147 cryoablations in 134 patients, concluding that the greatest chance of success occurred in men who had a nadir PSA of 0.4 ng/ml or less. Most local failures of treatment were at the prostatic apex and seminal vesicles. Lastly, these authors reported that induction combination endocrine therapy reduced the risk of biochemical failure in patients with stages T1 and T2 (A and B) cancers.

The use of thermosensors to monitor the freezing process has been reported by Wong et al.\textsuperscript{38} These authors increased their negative biopsy rate from 17% to 90% using this modification of the technique. Second (repeat) cryoablations were done in 12 patients with a cumulative success rate of 91%.

Miller et al\textsuperscript{39} reported the impact of cryoablation as salvage therapy for 33 patients with relapses after irradiation. After cryoablation, 24 (73%) converted to biopsy-negative status. Repeat cryoablations converted an additional 2 patients to biopsy-negative status for an overall success rate of 79%.

Additional reviews on the technique, results, and complications of prostate cryoablation have been published by Patel et al,\textsuperscript{40} Dinney et al,\textsuperscript{41} Pisters and von Eschenbach,\textsuperscript{42,43} Zippe,\textsuperscript{44,45} Cohen,\textsuperscript{46} Greene et al,\textsuperscript{47} Connolly et al,\textsuperscript{48} and Shinohara et al.\textsuperscript{49}

### Complications

Table 3 lists the complications reported after prostate cryoablation.

At our institution, 169 patients were evaluated by Wieder et al\textsuperscript{50} for complications. More than 50% of the patients reported no complications.

Thirty-four patients (approximately 50% of those who had normal sexual function) reported some degree of impotence (in those potent preoperatively). Incontinence, bladder outlet obstruction, urethral stricture, hematuria, thrombosed hemorrhoids, urethritis, epididymitis, urinary tract infection, prolonged sloughing of periurethral tissue, penile numbness, osteitis pubis, persistent cancer, and ureteral obstruction have been reported as complications of prostate cryoablation.
function before cryoablation) reported impotence. Complications requiring further operative management occurred in 6% of all patients treated. In the immediate postoperative interval, perineal ecchymosis, urinary stress or urge incontinence, and genital edema were seen but were usually transient. The rates of significant complications (including urinary incontinence, urethral stricture, bladder neck contracture, and rectourethral fistula) have been higher in patients with relapses of prostate cancer after irradiation.

Increased complications, including the finding of persistent cancer requiring radical prostatectomy, have been reported by Cox and Crawford\textsuperscript{51} and Grampsas et al.\textsuperscript{52} However, these authors’ series included many patients with clinical stage T3 disease and those with relapsed cancer after radiation therapy. Our experience with salvage surgery or radiation therapy for cryoablation failures is described later in this update.

Miller et al\textsuperscript{39} reported urethral sloughing syndrome (15%) and incontinence (10%) as the major complications in their series of patients receiving salvage cryoablation for relapsed cancer after irradiation.

Pisters et al\textsuperscript{53} reported that a double freeze-thaw cycle was more effective than a single cycle as salvage therapy for local tumor control but resulted in more complications. Incontinence was seen in 73% of patients, obstructive symptoms in 67%, impotence in 72%, and severe perineal pain in 8%.

In summary, the complications of prostate cryoablation in previously untreated patients seem to be modest and manageable. However, the evidence to date suggests that in spite of the ability of salvage cryoablation to eradicate residual disease, the procedure in previously irradiated patients results in significantly higher rates of incontinence, urethral obstruction, impotence, rectourethral fistula, and local pain. The mechanisms involved include ischemic necrosis, a noncompliant (“pipe-stem”) bladder outlet and prostatic urethra, and direct sphincteric damage.

### Histopathologic Changes

The first report of histologic changes after prostate cryoablation is credited to Hansen and Wanstrup.\textsuperscript{54} These authors described most of the early histologic findings, showing that the epithelial elements

| Stromal Components                  | Epithelial Components          |
|-------------------------------------|--------------------------------|
| Fibrosis                            | Basal cell hyperplasia         |
| Hemosiderin pigment deposition      | Squamous metaplasia            |
| Chronic inflammation                | Residual carcinoma             |
| Hyalinization                       |                                |
| Necrosis                            |                                |
| Hemorrhage                          |                                |
| Calcification                       |                                |

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seen on biopsies represented the initial or precryoablation morphology. Petersen et al\textsuperscript{55} reported on postcryoablation prostate biopsies, emphasizing cancer recurrences but not other histologic changes.

More recently, Shabaik et al\textsuperscript{56} reported on 64 patients from our institution, where biopsies were performed from 5 to 48 weeks after cryoablation. The significant findings in the stroma and epithelial components are listed in Table 4.

The earliest and most frequent changes noted were stromal fibrosis, basal cell proliferation in regenerating acini, and the presence of hemosiderin granules in the stroma. Other changes observed were squamous metaplasia, stromal hemorrhage, inflammation, necrosis, dystrophic calcification, and recurrent or residual cancer. Eight patients had persistent cancer, and these recurrences correlated with initial higher grade and stage but did not correlate with the patient’s baseline PSA levels. The absence of cryoablation background in 6 of 8 (75\%) positive postcryoablation biopsies was significant. Cryoablation background was present in 87.5\% of patients with negative biopsies.

Shuman et al\textsuperscript{57} recently reported on the dysplastic changes and unaltered prostatic glandular epithelial elements after prostate cryoablation. These authors noted that a postoperative increase in PSA level often indicated residual glandular elements and not necessarily residual carcinoma. Conversely, an undetectable postcryoablation PSA level correlated with a low risk of both residual glandular elements and carcinoma.

**Salvage Therapy after Failure of Cryoablation**

We recently analyzed our cryoablation series to examine the results of secondary or adjuvant treatments in 38 patients with positive follow-up biopsies. Eight patients were lost to follow-up, and among the remaining 30, additional treatments included salvage radical retropubic prostatectomy (4), salvage radiotherapy (6), endocrine therapy (10), repeat cryotherapy (8), and observation (2). We were particularly interested in the 10 patients who underwent salvage surgery or radiation therapy.

As expected, residual prostate cancer was found in all four who underwent salvage retropubic prostatectomy. Significantly, three of the four also had periprostatic and seminal vesicle invasion. Two of the four patients continue to be free of disease with undetectable PSA levels. The other two are on endocrine therapy for their progressive local and metastatic nodal disease.

Of the six patients undergoing salvage external beam irradiation for cryotherapy failure, five are reported to be free of recurrent disease based on digital rectal examination and undetectable PSA levels. The remaining patient has been lost to follow-up.

**Socioeconomic Factors**

At our institution, the typical charge for prostate cryoablation is approximately $13,000, including all professional fees and the hospital and technical components. This is one-half or less of the usual total cost for either radical prostatectomy or radiation therapy. However, a major financial impediment has been the general reluctance of Medicare and private insurance carriers to authorize and reimburse for the procedure. Most of our patients have said they would undergo the procedure again if given the opportunity and have had a good quality of life, although we have not used specific quality-of-life instruments.

**Proposed Clinical Trial Evaluating Prostate Cryoablation**

Based on the many noncontrolled series reported to date and because of pressure exerted by patient advocate...
groups, a randomized, prospective clinical trial is currently being formulated. Under the auspices of the Health Care and Financing Agency (HCFA) of the federal government and the American Urological Association (AUA), eligible patients with localized prostate cancer will be randomized to receive either cryoablation or external beam irradiation (XRT) (Fig. 2). Patients entered into the trial will be followed by PSA determinations, local biopsies, disease-free survival, overall survival, and comparison of posttherapy complications such as impotence. This trial is scheduled to begin in 1998; results, therefore, will not be available for many years.

**Summary and Conclusions**

Transrectal ultrasound-guided percutaneous transperineal prostate cryoablation has many attractive features both to the patient and to the urologist. The procedure typically can be done in a period of 2 hours or less on an outpatient basis with minimal blood loss and with the patient under regional or general anesthesia. With more experience in using the equipment and the techniques described, urologists can treat all stages of localized prostate cancer with relatively little morbidity.

The results of this technique in the treatment of prostate cancer continue to appear promising. With follow-up of 5
years or more available in several series, cryoablation appears to be an effective modality for the eradication of localized prostate cancer, particularly low-volume cancer (PSA less than 10 ng/ml and Gleason score less than 7).

Improved results, i.e., undetectable postcryoablation PSA levels and negative biopsies, may occur with modifications such as double freezing and pull-back apical freezing. However, the complication rate also may increase with increased tissue destruction. To date, most complications reported have been relatively minor and require limited intervention. Notably, complications, especially incontinence, are significantly greater, in spite of successful eradication of residual tumor, in patients who undergo salvage cryoablation for recurrent disease after radiation therapy. In our experience, transrectal ultrasound-guided prostate cryoablation appears to be effective in controlling local prostate cancer in 81% of patients with minimal morbidity.

As with radical prostatectomy and irradiation techniques, longer follow-up is required; however, at this time prostate cryosurgery can be considered in the following situations: as a primary treatment alternative to surgery or irradiation, as salvage treatment for recurrent cancer after irradiation, and for debulking of large symptomatic primary tumors. We look forward to the prospective randomized clinical trial comparing prostate cryoablation with external irradiation.

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