



Monique Guedet-Bornstein. *In the Ghetto*. New Orleans 1998.

Clinical series on the use of cryoablation have reported acceptable cancer control results and acceptable morbidities for selected patients with prostate cancer.

Review of Primary and Salvage Cryoablation for Prostate Cancer

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Background: Cryosurgery has gained popularity as a minimally invasive treatment option for primary and recurrent prostate cancer. Herein we present a review and summary reports on primary cryoablation for prostate cancer and salvage cryoablation following radiation failure.

Methods: We reviewed the current published literature in the English language on these topics, along with some historic articles dating back to the 1960s for background and development of the procedure. The material is supplemented by some commentary based on our own 13-year experience with cryoablation for prostate cancer. The review is divided into two sections: primary and salvage cryoablation.

Results: For primary cryoablation, success rates are proportional to the risk categories of the primary cancers. A pretreatment prostate-specific antigen (PSA) ≤ 10 ng/mL and an undetectable PSA nadir following cryoablation are associated with a more favorable long-term outcome. Safety profile and quality of life are acceptable in carefully selected patients. Similarly, for salvage cryoablation following radiation failure, patient selection is of paramount importance. The most consistently identified predictive factors for poor cryoablation outcomes were pre-cryoablation PSA >10 ng/mL and post-cryoablation nadir PSA >1 ng/mL for salvage procedures. Side effects are more prevalent and serious than with primary cryoablation but for carefully selected patients, the long-term results are favorable.

Conclusions: Patient selection is the key to success with cryoablation, in both the primary and salvage setting. The modality can offer long-term cancer control in carefully selected patient with properly executed techniques.

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Abbreviations used in this paper: PSA = prostate-specific antigen, AUA = American Urological Association, QOL = quality of life.

Introduction

Cryosurgery has gained popularity as a minimally invasive treatment option for primary and recurrent prostate cancer. This review and summary of primary and salvage cryoablation for prostate cancer is based on the published literature in the English language. Also included is commentary based on our own 13-year experience with this modality.

History

Prostate cryosurgery was first reported in the 1960s by Gonder et al^{1,2} using a single transurethral liquid nitrogen probe to treat bladder outlet obstruction caused by benign prostatic hyperplasia and prostate cancer. However, the inability to monitor the position of the probe and control the ice-ball formation led to a high rate of urethrorectal fistula and urethral tissue sloughing. Flocks et al³ modified the technique by using an open transperineal approach with visual control of the cryoablation, but this modified approach did not improve the complication rate.

In 1974, Megalli et al⁴ were the first to use a closed perineal approach using a single 18Fr liquid nitrogen probe. The procedure was monitored by rectal palpation. This technique avoided the morbidities of an open incision and resulted in less urethral sloughing, but accurate probe placement and treatment monitoring remained difficult. Thus, cryosurgery for prostate cancer treatment was abandoned because of the high complication rates.

Onik et al⁵ revived interest in prostate cryosurgery in the early 1990s, combining endourologic percutaneous techniques with the introduction of real-time transrectal ultrasound (TRUS). This allowed accurate transperineal placement of probes, real-time monitoring and control of freezing, and adequate visualization of the rectum to protect it from injury. Improvement on cryogenic technology was the other contemporaneous major advance. In addition, improvement in thermosensors by Lee et al⁶ in 1994 allowed precise monitoring of the ice ball. Introduction of a warming catheter for urethral mucosa protection resulted in a significant reduction in sloughing and incontinence rates,⁷ thereby reducing morbidity and improving success rates.⁸ In 1995, the US Food and Drug Administration approved the urethral warming devices,⁹ and the American Urological Association (AUA) subsequently recognized cryoablation as a therapeutic option for carcinoma of the prostate in 1996.¹⁰

In the mid 1990s, the next generation multiprobe high-pressure argon-helium system was introduced.^{8,11,12} This generation of cryosurgery machines utilizes the Joule-Thomson effect in which different gases undergo

unique temperature changes when depressurized, according to unique gas coefficients. The properties of argon made it useful for cooling to below -180°C , whereas helium was ideal for thawing and re-warming. The use of gas allowed for rapid transition from freezing to defrosting, which facilitated tighter control as well as expedition of the procedure. Further improvements in technology include significant reduction in probe diameter. Ultra-thin probes with sharp tips now allow direct transperineal

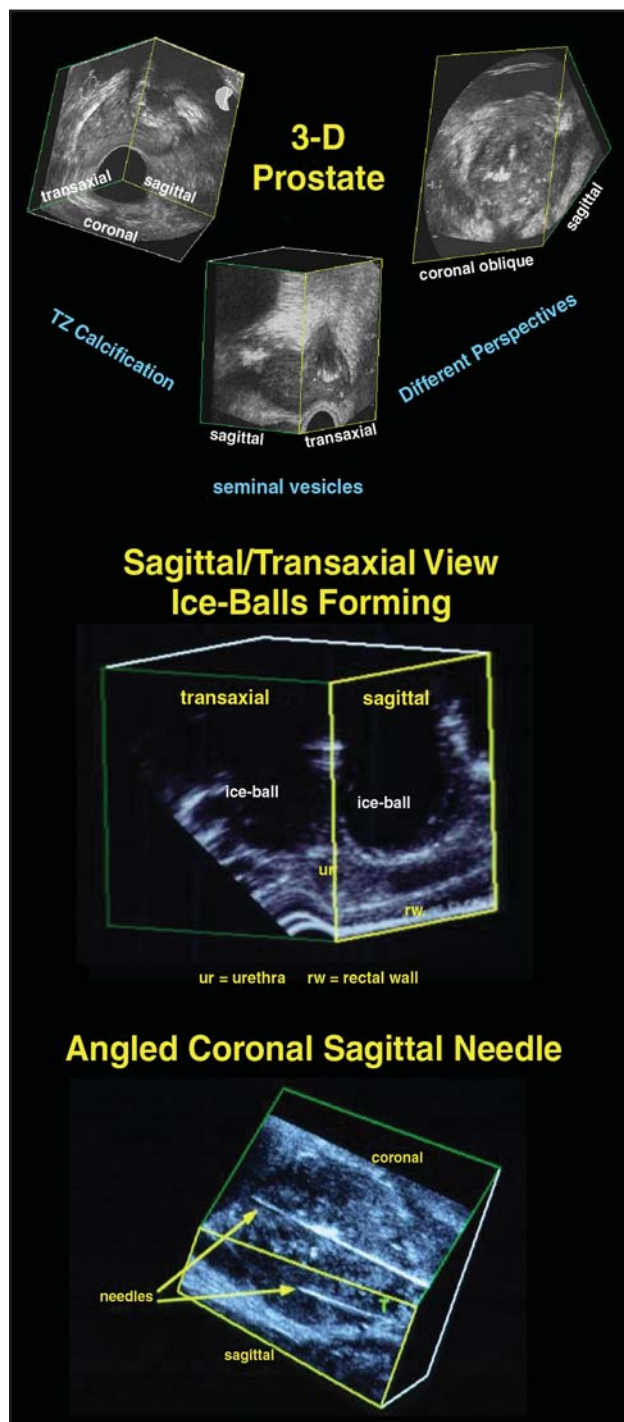


Fig 1. — Visualization of 3-D ultrasound, needle placement guidance, and monitoring of ice-ball formation during cryoablation.

probe placement through a conventional brachytherapy-type template without the need for tract dilation.^{10,13}

Some centers have incorporated software for 3-dimensional ultrasound into the system, first introduced by Chin et al^{12,14} in 1996. The reported advantage is superior accuracy in probe placement and monitoring of the freezing process, thus minimizing treatment-related complications (Fig 1).

Biology of Cryoablation

Cryosurgery kills cells and ablates tissue by (1) direct cell injury from ice crystal formation and related deleterious effects, and (2) vascular stasis caused by microcirculatory failure. As temperatures fall, direct cellular injury occurs as a result of cellular metabolism failure. As the temperature reaches -20°C , water in the extracellular environment crystallizes into ice, and withdrawal of water from the system results in a hyperosmotic extracellular environment. Consequently, denaturation and electrolyte imbalances occur.¹⁵ During thawing, ice crystals fuse to form larger crystals, which eventually disrupt the cell membrane. At the extracellular level, vasoconstriction occurs initially secondary to decreased temperatures, followed by vasodilatation, increased cellular permeability, and edema as temperatures rise. Endothelial damage leads to platelet aggregation and microthrombi formation, which in turn leads to stagnation of circulation.¹⁵

Histopathologic changes in the cryoablated prostate can be divided into an earlier degenerative phase and the subsequent reparative phase.¹⁶ The main feature of the degenerative phase, a direct result of the damage from freezing, is coagulative necrosis. Features of the reparative phase include fibrosis, calcification, and hyalinization,¹⁷ with fibrosis being most common.

Recent molecular-based research has focused attention on apoptosis as a mechanism of cell death in the periphery of the cryogenic lesion. Its recent recognition may add credence to the potential use of adjunctive therapy to enhance the efficacy of cryosurgery.¹⁸ Gage and Baust¹⁵ recommended a minimum freezing temperature of -40°C for at least 3 minutes for complete eradication of the tumor and a minimum of two freeze-thaw cycles. This led to modification of cryotherapy techniques that in turn has resulted in improved biochemical and histologic outcomes.¹⁹ The number of cryoprobes used also affects completeness of glandular ablation, with Lee et al²⁰ recommending more cryoprobes in some cases to achieve better results.

Results with newer techniques and technologies have been more promising. Technical advances included double freezing, more lateral placement of cryoprobes, and more aggressive freezing towards the prostatic capsule.

Patient Selection

Although the AUA recognizes cryoablation as a therapeutic option for carcinoma of the prostate, no consensus has been reached on guidelines for indications or patient selection for either primary or salvage cryoablation. Patient inclusion criteria at various centers have been variable. Furthermore, no randomized trials have been published comparing primary cryoablation against any of the "standard" treatment modalities. A randomized trial is close to completion in Calgary, Canada, that is comparing primary cryoablation and radical prostatectomy (personal communication, B. Donnelly, 2007). Also, at the 2006 AUA annual meeting, Chin et al²¹ reported results of a randomized study that compared primary cryoablation against external beam radiotherapy in cT2C-N0-M0 to cT3B-N0-M0 disease.²¹

Clinical Outcome of Primary Cryoablation

The long-term outcomes (mean follow-up of 93.7 months) of primary cryosurgery with the first generation machines showed a high failure rate of 78.4%, with 67% local recurrence and 47.1% of patients dying of their prostate cancer.²² These results may not be relevant in view of the improvements and modifications that have since taken place. A retrospective analysis of pooled data of 975 patients from five centers showed that, with a PSA threshold of <0.5 ng/mL, the 5-year actuarial biochemical-free survival rate was 36% to 61%, depending on the risk category.²³ The positive biopsy rate was 18%.

Ellis²⁴ reported on 93 patients who underwent cryoablation, 75 of whom had primary procedures. A nadir PSA value of 0.4 ng/mL or less was achieved in 84% of the entire population. Shinohara et al²⁵ found that the best results with cryosurgery were in patients with low-volume disease (stage T2 or less and PSA values of 10 ng/mL or less). In their series, patients with a pretreatment PSA level of less than 10 ng/mL demonstrated a negative biopsy rate of 84%. However, PSA was detectable after cryosurgery in 36% of patients with stage T1c disease and in more than 40% with a PSA of 4 to 10 ng/mL. Biochemical and biopsy failure tended to occur within 18 months after treatment. The same group subsequently updated their findings on 176 patients with clinically localized disease (8.7% T1, 30% T2, 59% T3, and 2.3% T4).²⁶ With a mean follow-up of 30.8 months, nadir PSA level was undetectable in 49% of patients, between 0.1 and 0.4 ng/mL in 21%, and >0.5 ng/mL in 30%. Neoadjuvant androgen deprivation was used in 57% of the patients, the residual effects of which had to be taken into account when interpreting the PSA results. More noteworthy was the 38% positive biopsy rate after the procedure.

Prepelica et al²⁷ reported on 65 men with organ-confined disease associated with high-risk features (defined as PSA ≥ 10 ng/mL and/or Gleason score ≥ 8). Durable biochemical disease-free survival was noted in 83.3% of patients based on the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria. In contrast to the report from Koppie et al,²⁶ post-cryosurgery biopsies were positive in only 12.5%.

Longer-term follow-up was provided by Bahn et al,²⁸ who reported on 590 patients. Surprisingly, there was no difference in the 7-year actuarial biochemical disease-free survival (bDFS) (PSA < 0.5 ng/mL) for low-, medium-, and high-risk patients at 61%, 68%, and 61%, respectively. The bDFS probability using the ASTRO definition was 92%, 89%, and 89%, respectively. The rate of positive biopsy was 13% (the majority detected within 6 months postoperatively). For the locally advanced cohort (stage T3 or T4) with mean preoperative PSA of 21.8 ng/mL, 48% achieved an undetectable PSA 6 months postoperatively, although 23% had a positive biopsy in this higher-risk subgroup. Of interest (and possibly concern) was the finding of benign epithelial elements in 71% of biopsies.

Donnelly et al²⁹ reported on 76 patients with PSA levels under 30 ng/mL. Eleven patients required repeat treatment. The 5-year overall and cancer-specific survival rates were 89% and 98.6%, respectively. PSA values were < 0.3 ng/mL in 60% at 5 years for low-risk patients, 77% for moderate-risk patients, and 48% for high-risk patients.

Han et al³⁰ described the preliminary experience using the multiple small-caliber ice needles. In this multicenter study, 88 of the 106 treated patients had primary cryoablation. The initial results were encouraging, although longer follow-up and larger series from individual centers are pending.

Adverse Effects of Primary Cryoablation and Treatment-Related Quality of Life

Due to the anatomic relationship of the prostate and the cavernous nerve bundles, erectile dysfunction (ED) is likely if the apex of the prostate and periprostatic tissue are aggressively frozen. As expected, ED has been reported in 84% to 93% of preoperatively potent patients.^{23,24,28,29,31} Slow recovery of erectile function over time was anticipated in some cases following cryoablation, given that nerve regeneration is possible.³² Robinson et al³³ performed a meta-analysis of the rates of ED after local treatments that offers some data for comparison. They reported the predicted probability of maintaining erectile functioning 1 year after cryoablation at 14% compared to brachytherapy at 84%, external-beam radiotherapy at 67%, and radical prostatectomy at 38%. At 36 months, 13% of patients

had regained erectile functioning, and an additional 34% of patients were sexually active with the help of pharmacologic or mechanical aids.^{34,35} Similarly, Kang et al³⁶ found that 11.8% of their patients had "recovery" from ED, and an additional 14.7% were able to achieve erection with the use of phosphodiesterase type 5 (PDE5) inhibitor.

Urethral sloughing and bladder outflow obstruction requiring transurethral resection occurred in 13% to 23%, the incidence of which had drastically improved with the use of approved urethral warming catheters. Some degree of incontinence developed in under 10%. The most serious complication, ie, rectourethral fistula formation, occurred in less than 1%.^{23,24,28,29}

Quality of life (QOL) is a crucial outcome measure in the evaluation of different anticancer therapies. A number of studies assessing QOL after cryoablation of the prostate have been published.³⁴⁻³⁶ With a phase II clinical trial of primary cryosurgery for localized prostate carcinoma, Robinson et al³³ found that by 12 months after cryosurgery, most FACT-P subscales had returned to pretreatment levels. QOL remained stable over the subsequent 2 years, except for persistent impairment in measures of social/family well-being.

Factors Predictive of Success of Primary Cryoablation

In general, success rates are proportional to the risk categories of the primary cancers. A pretreatment PSA ≤ 10 ng/mL and an undetectable PSA nadir following cryoablation are associated with a more favorable outcome.^{24,26,28,29}

Patient Selection for Salvage Cryoablation

For salvage cryoablation, all patients should have biochemical evidence of local treatment failure, ie, rising PSA levels on three consecutive determinations at least 2 years after radical radiation therapy, in addition to histologic proof of local cancer recurrence.^{12,37} All patients should be judged to have reasonable life expectancy and acceptable anesthetic risks. All should have a negative pelvic and abdominal computed tomography (CT) study as well as radionuclide bone scan. PSA levels preferably should be < 10 ng/mL at the time of consideration for cryoablation of the prostate to minimize the probability of occult distant metastatic disease. Patients with serum PSA levels between 10 and 20 ng/mL should have a negative pelvic lymphadenectomy or a negative CT-guided aspiration biopsy of pelvic nodes. An unfavorable biochemical outcome is predicted by precryoablation PSA levels over 10 ng/mL, preradiation Gleason score of 8 or greater,

and T3/T4 disease.¹ Prior transurethral surgery is a significant risk factor for incontinence, although it is not a contraindication for cryoablation of the prostate.^{12,37}

Clinical Outcomes of Salvage Cryosurgery

From these various studies, preoperative PSA levels, biopsy Gleason scores, and clinical stage appear to correlate with biochemical outcome. A precryotherapy PSA level <10 ng/mL and a lower-grade Gleason score (Gleason ≤8) were predictors of sustained biochemical response.³⁷⁻⁴⁰ In addition, patients with a preradiotherapy clinical stage of lower than T3 had superior biochemical relapse-free rates.^{37,40} As with primary cryoablation, PSA nadir values postcryosurgery is a positive predictor of long-term biochemical response.³⁹ Patients who have also received hormonal therapy, mostly already hormone-resistant, appeared to have a poorer outcome than those receiving radiotherapy alone,⁴⁰ although this was not an undisputed finding.

There is no consensus on the definition of “success” with salvage cryoablation.³⁷ The 5-year biochemical no evidence of disease (bNED) rate for salvage cryosurgery was 40% in the M.D. Anderson Cancer Center series, where failure was defined as a PSA of 2 ng/mL above nadir.³⁸ Chin et al³⁷ reported on 118 patients with a bNED (PSA >0.5 ng/mL) rate of 40% at 20 months. Updated results were presented on 187 patients at the AUA 2006 meeting by this group, reporting 5- and 8-year biochemical recurrence-free survival (bRFS) rate of 56% and 37%, respectively, for patients with precryoablation PSA <4 ng/mL. In contrast, if the PSA value was >10 ng/mL, the 5- and 8-year bRFS rates were only 14% and 7%, respectively (Fig 2).⁴¹

Ghafar et al⁴² reported a “success” rate of 74% at 2 years with failure defined as 0.3 ng/mL above nadir. Whereas an undetectable PSA would be the optimal benchmark if it is assumed that all prostate tissue is completely ablated, it has been demonstrated that complete ablation is not usually attained. In fact, similar to the finding with primary cryoablation, Chin et al⁴³ and Izawa et al⁴⁴ identified, at two institutions, that viable benign prostatic tissue was present in a substantial number of cryoablated prostates even when biopsies were negative for malignancy.

The rate of local negative biopsies reported for salvage cryosurgery was generally more favorable than the figures on biochemical control. The M.D. Anderson group reported a positive biopsy rate of 23% on 150 patients.⁴⁰ Miller et al⁴⁵ reported a positive biopsy rate of 37% on 33 patients at 3 months postoperatively with an 11-core biopsy technique. Studies involving more limited biopsies have reported positive rates from 14% to 37%.⁴⁶⁻⁴⁸ Chin et al⁴³ conducted serial biopsies on all salvage cryosurgery patients at 6, 12, and 24 months postoperatively and thereafter as indicated by PSA levels. The rate of positive biopsy was found to be 14.2% compared to a 40% biochemical NED rate. The majority of positive biopsies (73.9%) were reported within 1 year of cryoablation.⁴⁵

Similarly, de la Taille et al⁴⁶ reported on 43 patients with a mean follow-up of 21.9 months (range 1.2 to 54 months). Sixty percent reached a serum PSA nadir of <0.1 ng/mL. The biochemical recurrence-free survival rate was 79% at 6 months and 66% at 12 months. Using multivariate analysis, a PSA nadir >0.1 ng/mL was an independent predictor of PSA recurrence.

The discrepancy between biochemical and histologic results suggests possible selective sampling, with

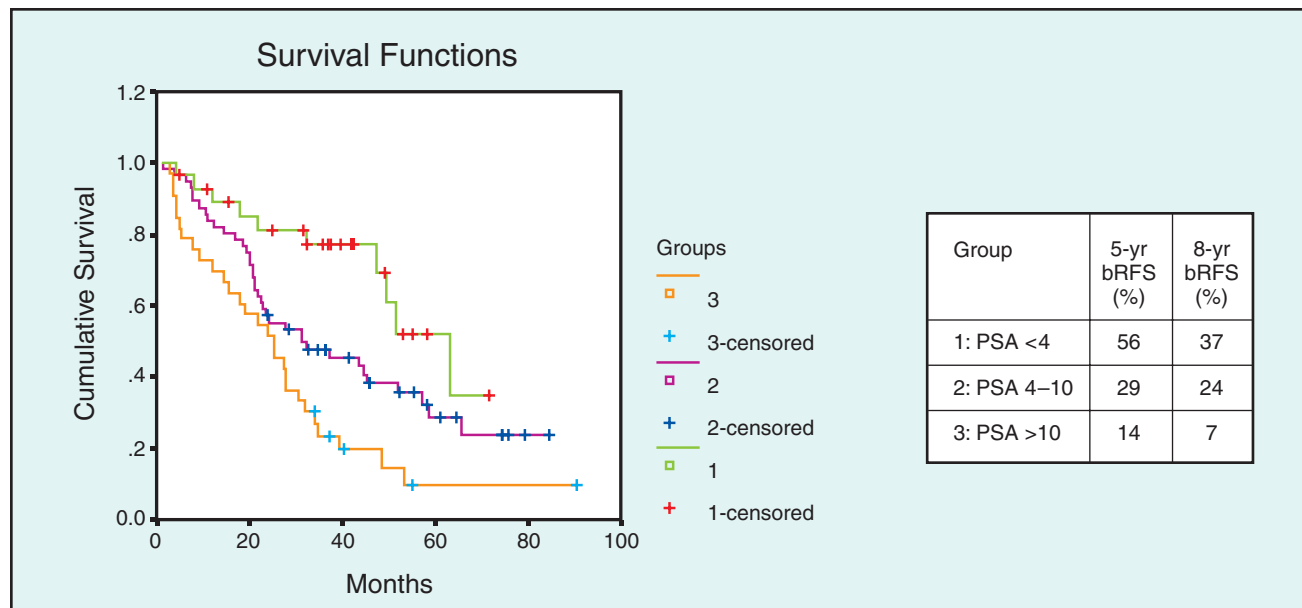


Fig 2. — Intermediate-term follow-up salvage cryoablation results on 187 patients. bRFS = biochemical recurrence-free survival.

postcryoablation biopsy (despite multiple serial biopsies) as a possible reason. A more likely explanation is the presence of as yet radiographically undetected but biochemically active metastatic disease.

Spieß et al⁴⁹ reported on 49 patients with T2 and T3 disease and median presalvage cryotherapy serum PSA levels of 5.9 ng/mL. Biochemical failure (PSA >2 ng/mL above postoperative nadir) occurred in 26 patients. A presalvage cryotherapy serum PSA level >10 ng/mL and PSA doubling time of less than 16 months were predictive factors for subsequent risk of biochemical failure in their study.

Factors Predictive of Success of Salvage Cryoablation

The most consistently identified predictive factors for poor cryoablation outcomes were precryoablation PSA >10 ng/mL and postcryoablation nadir PSA >1 ng/mL for salvage procedures.^{37,39,43,46}

Adverse Effects and Treatment-Related Quality of Life of Salvage Cryoablation

Because salvage cryoablation is technically more challenging, it understandably has a higher complication rate than primary cryoablation due to the preexisting radiation-induced tissue damage and anatomic changes and, in many cases, more advanced local disease involvement. Nevertheless, these complication rates have also improved with time as the procedure has become safer, as surgeons have become more experienced technically, and as patient selection has improved.

Rectourethral fistula and total urinary incontinence are the most serious adverse effect of cryoablation. Published data and a review^{37,50} indicate a 1% to 3% rate in salvage cryoablation procedures. In terms of urinary function, up to 20% of the patients had some form of incontinence. The likelihood of incontinence is substantially higher if the patient has had prior transurethral resection of the prostate.^{37,50} Adverse effects reported by de la Taille et al⁴⁶ included incontinence (9%), obstruction (5%), urethral stricture (5%), rectal pain (26%), urinary infection (9%), scrotal edema (12%), and hematuria (5%).

Robinson et al³⁵ assessed QOL prospectively over 2 years subsequent to salvage cryosurgery. QOL scores returned to baseline by 24 months after cryosurgery in all domains, scales, and individual items included in the EORTC-QOL-C30. In a comparison of 51 patients after primary cryoablation and 30 patients after salvage cryoablation, Anastasiadis et al³¹ reported that the overall QOL scores were high in both groups. Primary cryotherapy patients fared significantly better regard-

ing physical and social functioning compared with salvage cryotherapy patients. Incontinence rates were 5.9% and 10% in the primary and the salvage groups, respectively. Severe ED was prevalent in both groups (86% and 90%, respectively).

Based on data from patients treated with older techniques and technology (eg, inconsistent use of urethral warming), Perrotte et al⁵¹ found that QOL of a majority of patients who undergo salvage cryotherapy of the prostate is compromised by side effects. They reported 72% of patients had some degree of incontinence, 85% who were potent before cryotherapy became impotent, and 26% had moderate to significant perineal pain.

One important QOL benefit has emerged from longer-term follow-up data. Although a substantial proportion of patients eventually receive androgen ablation therapy, the average delay in institution of endocrine therapy was 31 months.⁴¹ This postponement of androgen ablation resulted in superior QOL for those patients for a meaningful period of time and probably resulted in delay in the eventual onset of androgen resistance of their disease.

Erectile Function: Sparing Cryoablation

Janzen et al⁵² conducted nerve-sparing experiments in a canine model by studying the utility of placing warming probes in the neurovascular bundle (NVB) to prevent freezing. They found that NVB preservation with active warming was possible but not consistently reproducible. In some cases, NVB preservation with active warming may result in incomplete peripheral tissue ablation. Other methods are being studied, including the feasibility of injecting antifreeze proteins⁵³ or saline to protect or separate the NVB.

Onik et al⁵⁴ was first to report a clinical pilot study on focal nerve-sparing cryosurgery in 9 patients who had unilateral prostate cancer based on detailed biopsy "mapping." Unilateral cryoablation was performed on the side of the positive biopsy, while the contralateral side was not treated. All 9 patients were considered "stable" in their PSA course, with a mean follow-up of 36 months. Six of the patients underwent routine postoperative biopsy, and all had negative biopsies. Seven of the 9 patients were considered potent, using the criteria that they had erections sufficient for vaginal penetration and were satisfied with their sexual functioning. Until longer follow-up data on more patients are available, nerve-sparing cryosurgery should be considered investigational.

Conclusions

Cryoablation has been available as a treatment modality for prostate cancer as primary therapy and as salvage

therapy. Although no randomized trials or high-level evidence is available to confirm its efficacy, clinical series have emerged with acceptable cancer control results and acceptable morbidities. The procedure demands careful patient selection and technical expertise to achieve satisfactory cancer control, patient satisfaction, and acceptable quality of life. Ongoing critical appraisal of results, combined with further refinement in technology and in patient selection criteria, should result in further improvement in outcome.

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