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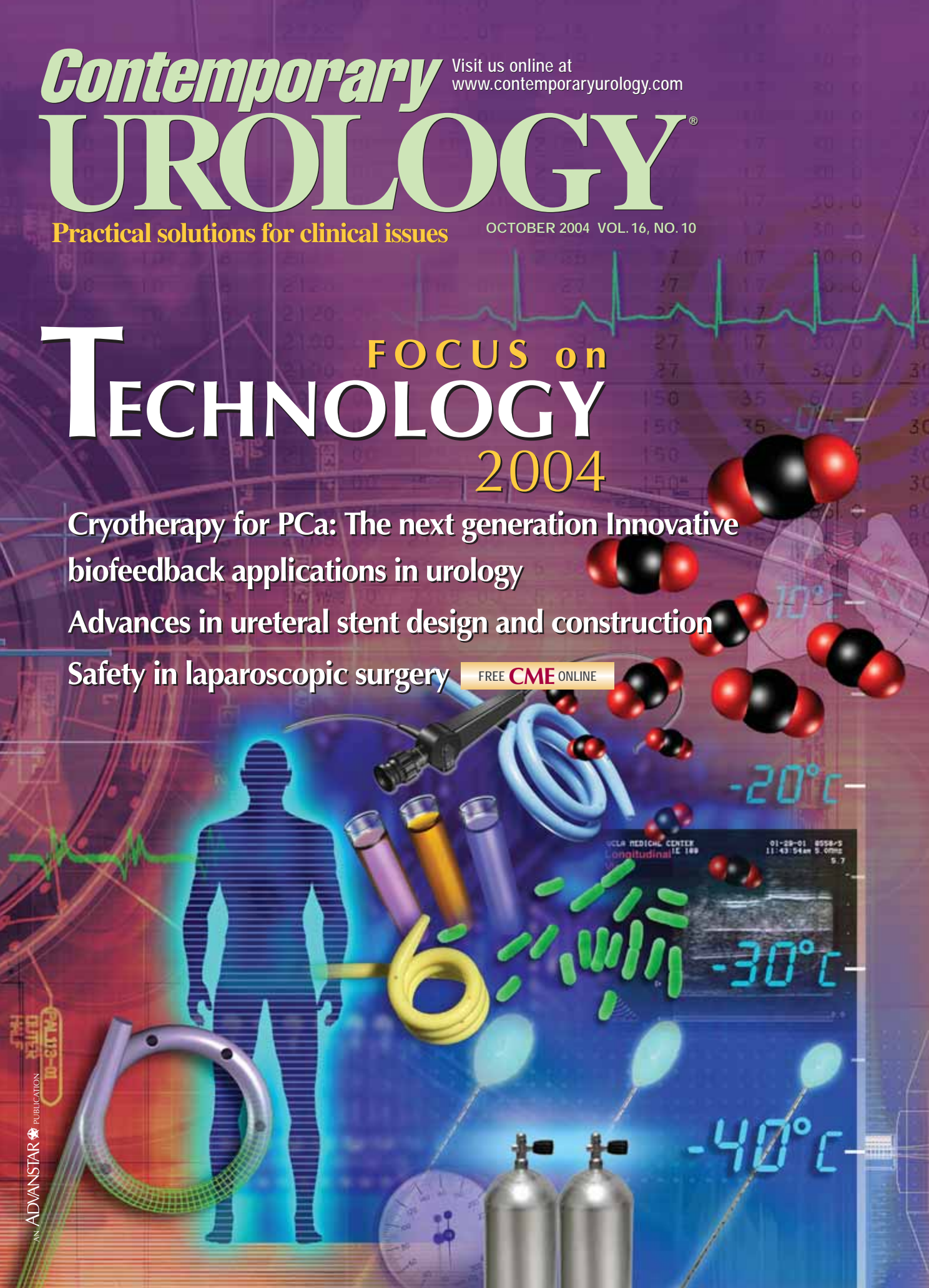
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## A new era for **CRYOTHERAPY** of **PROSTATE CANCER?**

By John S. Lam, MD, Oleg Shvarts, MD, and Arie S. Belldegrun, MD

In 2004, an estimated 230,110 new cases of prostate cancer will be detected in the United States and approximately 29,900 men will die from it, making this

*Unlike its predecessors, third-generation cryotherapy effectively eradicates primary and radiorecurrent tumors and is associated with low morbidity, with rates comparable to those of other available prostate cancer treatments. While long-term follow-up data on PSA outcome and survival are still needed, this latest generation of cryotherapy appears to be expanding the therapeutic options for a number of patients.*



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disease the most commonly diagnosed cancer and the second leading cause of cancer deaths among American men.<sup>1</sup> Treatment options for clinically localized prostate cancer include radical prostatectomy, radiation therapy (external beam radiation therapy [EBRT] and/or brachytherapy), and watchful waiting.<sup>2</sup>

Cryotherapy—the ablation of tissue by local induction of extremely cold temperatures—has recently re-emerged as a minimally invasive treatment option offering low morbidity, minimal blood loss, short hospital stay, and high rates of negative post-treatment biopsies.<sup>3-5</sup> While cryotherapy has been used for the treatment of cancer since the 19<sup>th</sup> century, the first urologic application was developed in the 1960s (see “A brief history of cryotherapy,” page 58). Over the years, technological advances have enabled more efficient freezing of the prostate gland while reducing damage to surrounding tissues—notably, the rectum, urethra, and external urinary sphincter. In 1996, the American Urological Association (AUA) recognized cryotherapy as a therapeutic option for prostate cancer and removed the label “investigational” from this procedure.

### CRYOBIOLOGY

The principles of cryotherapy, including mechanisms of cell injury and cell death, have been well studied.<sup>6</sup> The key factors involved in freezing injury

include direct mechanical shock, osmotic shock, and cellular hypoxia. Mechanisms of action include protein denaturation via dehydration, transfer of water from intracellular to extracellular space, rupture of cell membranes from ice crystal expansion, toxic concentration of cellular constituents, thermal shock from rapid supercooling, slow thawing, vascular stasis, and increased apoptosis.<sup>7</sup>

After reaching a tissue temperature of less than 0°C, the extracellular fluid begins to crystallize, increasing the osmotic pressure of the unfrozen portion of the extracellular fluid compartment. Dehydration of cells occurs due to the shift of water from the intracellular space to the extracellular space. The cellular pH changes, leading to the denaturation of cellular proteins.

At a temperature of -15°C, most of the extracellular environment is frozen, which causes trapping of tissue and shearing forces that disrupt cellular structure (mechanical shock). With further reductions in temperature, crystallization of water occurs in the intracellular space, mechanically breaking the cellular membrane.

The delayed or indirect destructive effects of cryotherapy continue primarily because of vasculature disruption, resulting in tissue hypoxia and vascular thrombosis. Zacarian and colleagues found that at temperatures below -20°C, venules were more susceptible to injury than arterioles.<sup>8</sup> Freezing promotes stasis of blood, leading to thrombosis and subsequent coagulative necrosis of tissue. This process includes local ede-

ma and activation of the inflammatory cascade. When thawing occurs, extracellular fluid shifts back into the intracellular space, leading to cellular bursting. The blood vessels around the targeted tissue initially dilate after thawing, and the vessel wall becomes hyperpermeable. Microthrombi form on the damaged vessel wall, leading to regional tissue ischemia.

The 2 parameters that correlate with the likelihood of cell destruction are the cooling rate during freezing and the lowest temperature achieved (Table 1). Tatsutani and associates demonstrated that complete cell death was unlikely to occur at temperatures higher than  $-20^{\circ}\text{C}$ , and temperatures lower than  $-40^{\circ}\text{C}$  were required to completely destroy cells.<sup>9</sup> A faster freezing rate and slower thawing rate was shown to result in more cellular destruction.<sup>9,10</sup>

The duration of freezing has been

TABLE 1

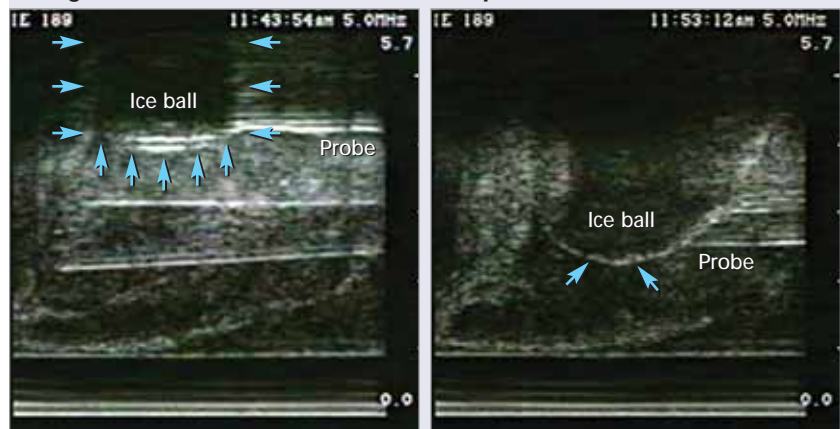
### Factors affecting tissue destruction during cryotherapy

- Duration of freezing
- Existence of heat sinks
- Lowest temperature achieved
- Number of freeze-thaw cycles
- Velocity of cooling
- Velocity of thawing

demonstrated to be an important factor leading to tissue destruction. Once the tissue temperature reaches a certain level, more cellular destruction can be achieved by prolonged freezing at this temperature. However, in a clinical setting, the number of freezing cycles, the lowest temperature achieved, and the existence of any regional "heat sinks" may be important factors relating to cancer destruction.

A double freeze-thaw cycle results in more extensive tissue damage and cell death than a single cycle.<sup>9,10</sup> Lar-

FIGURE 1  
Longitudinal view of frozen tissue on biplanar TRUS



*Left:* The leading edge of frozen tissue created by the anterior probes is seen as a bright arcuate line (arrows). *Right:* Tissue inside the frozen area is concealed by the acoustic shadow created by the leading edge.

son and co-workers reported that cryotherapy resulted in a central zone of complete cellular necrosis that is surrounded by a more peripheral zone of cell damage.<sup>11</sup> The central zone of complete cellular necrosis could be significantly enlarged by a second freezing cycle, and a double freeze at temperatures below  $-40^{\circ}\text{C}$  resulted in complete necrosis. This fact has important clinical implications because the hyperechoic edge of the iceball visualized is  $0^{\circ}\text{C}$  to  $-2^{\circ}\text{C}$ , with temperatures as low as  $-20^{\circ}\text{C}$  to  $-40^{\circ}\text{C}$  inside this edge. Therefore, the iceball should be extended beyond the edge of the prostate to ensure adequate tissue ablation. Finally, large blood vessels may act as heat sinks, and highly vascular areas may not achieve target temperatures even though they are completely enclosed in the treatment area.

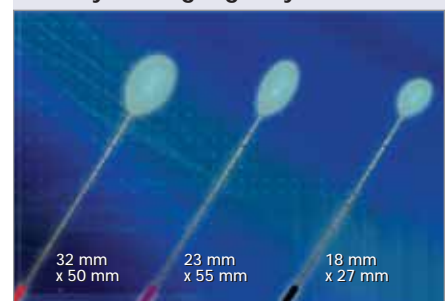
### EQUIPMENT FOR CRYOTHERAPY

Biplanar TRUS allows for transverse and longitudinal views of the prostate as well as the frozen area. Frozen tissue is significantly different from unfrozen tissue in sound impedance, resulting in strong echo reflection at the interface of frozen and normal tissue. The leading edge of frozen tissue is seen as a bright line (Figure 1).

The tissue inside is concealed in the acoustic shadow created by this boundary. As a consequence, the anterior boundary of the freezing area cannot be monitored. The refraction and reflection of the sound wave can also overestimate the lateral boundary of the iceball.

Two cryotherapy devices for prostate cancer treatment are available in the United States. The SeedNet system developed by Oncura (Plymouth Meeting, Pa) uses pressurized argon gas as the source of freezing, and up to 30, 17-gauge cryoneedles (Figure 2) can be used to create a conformal freezing pattern. The iceball created by the Oncura system is approxi-

FIGURE 2  
Family of 17-gauge cryoneedles



Use of 17-gauge cryoneedles permits the formation of iceballs of varying shapes and dimensions.

mately 2 cm in diameter. The Cryocare system (Endocare Inc, Irvine, Calif) also uses pressurized argon gas as a cryogen and can freeze up to 8, 3-mm probes simultaneously. The iceball created by the 3-mm probe is approximately 4 cm in diameter and 4 to 5 cm in length.

To protect the urethra and the external urinary sphincter, a urethral warmer is used during cryotherapy. The urethral warmer is a closed double-lumen catheter made of a polyethylene membrane through which saline, heated to 38°C to 40°C, is continuously circulated by a water pump.

### PATIENT SELECTION

As with other forms of local therapy for prostate cancer, outcome after cryotherapy correlates with disease stage and grade. In general, we recommend cryotherapy for patients with localized high-grade tumors and higher volume disease who are not potent or not interested in maintaining their potency.

We recommend brachytherapy for patients with early, nonpalpable, low-grade disease and low prostate-specific antigen (PSA) levels who are interested in maintaining their potency. Patients we consider suitable for brachytherapy as monotherapy are those with a PSA level of 10 ng/mL or less, nonpalpable tumors, maximum Gleason score of 6, and low-volume/low-stage disease.

We feel cryotherapy is also a reasonable therapeutic option for:

- Patients with clinically locally advanced disease (stage T3).
- Patients with no evidence of metastatic disease with a grade or stage of disease likely to progress without treatment (Gleason score >5 and stage >A1/T1a) who are poor candidates for radical prostatectomy (for example, men with Crohn's disease, ulcerative colitis, weight >350 pounds, or cardiac disease).
- Patients with no evidence of metastatic disease and a greater than 10-

## UROLOGIC

- Third-generation cryotherapy, using TRUS guidance and a brachytherapy template, with argon gas (freeze) and helium gas (thaw), has a lower rate of morbidity than earlier generations of the procedure.
- Smaller 17-gauge needles permit better contouring and shaping of the iceball.
- A minimum temperature of  $-40^{\circ}\text{C}$  for 3 minutes must be reached, and 2 freeze-thaw cycles must be used for complete necrosis.
- Third-generation salvage cryotherapy is associated with minimal morbidity and may be an alternative to salvage radical prostatectomy.
- Long-term follow-up of PSA outcome and survival are needed.
- Cryotherapy may be a reasonable option for older or high-risk medical patients who would not otherwise be considered for radical prostatectomy and as salvage therapy in those who have failed EBRT or brachytherapy.

year life expectancy who, after reviewing available information on prevailing therapeutic options for new diagnoses of prostate cancer, are unsatisfied with or refuse to undergo radical prostatectomy or radiotherapy.

Local cancer recurrence following radiation therapy may also be managed with cryotherapy. However, complications associated with salvage cryotherapy are significantly higher than those associated with primary treatment.<sup>12-15</sup> Cryotherapy has been used to treat local recurrences after radical prostatectomy. Patients with locally progressive disease despite hormonal manipulation have also been treated with cryotherapy to prevent

urinary obstruction or bleeding.<sup>5,16</sup>

### PATIENT EVALUATION

Patients at high risk for metastatic disease should undergo imaging—radionuclide bone scan or cross-sectional imaging of the abdomen and pelvis—based on stage and grade, and serum PSA concentrations should be measured. Patients at high risk for lymph node metastases may undergo regional lymph node dissection if identification of disease would alter choice of treatment.

Patients with gross extracapsular extension or seminal vesicle invasion are treated with neoadjuvant hormone therapy to reduce the tumor volume and allow for easier inclusion within the iceball. If the prostate size exceeds 50 cm<sup>3</sup>, complete freezing of the prostate may be difficult, and neoadjuvant hormone therapy is indicated to reduce the target volume and allow for more effective cryotherapy.<sup>5,12,13,17-20</sup> The use of androgen deprivation 3 months prior to the procedure has also been reported to increase the distance between the base of the prostate and the anterior rectal wall.<sup>21</sup>

### SPECIAL CONCERNS FOR RADIORECURRENT DISEASE

When the PSA level rises in an irradiated patient, the optimal time for intervention is unclear. Our practice has been to wait at least 18 months following radiation and to perform a biopsy of the prostate if the PSA rises above the nadir level on 3 consecutive measurements.

If a biopsy is undertaken, multiple cores should be obtained, and the pathologist needs to be informed that the patient has had previous radiation. Severe radiation effects with both nuclear and cytoplasmic alterations are seen in many prostatic biopsies and may confound the diagnosis of residual cancer.<sup>22</sup> The incidence of positive biopsy results after primary radiation therapy varies widely

in the literature, but appears to be higher for EBRT than for brachytherapy.<sup>23</sup> If the PSA level is greater than 5 ng/mL and a prostate biopsy reveals recurrent disease, we would obtain a CT scan of the abdomen and pelvis, as well as a bone scan.

There may be a role in performing an open or laparoscopic biopsy of the pelvic lymph nodes, since between 20% and 40% of patients will have metastases to the lymph nodes.<sup>24</sup> Caution is advised for novice laparoscopic surgeons since the dissection of these nodes can be technically challenging due to potential adherence to the pelvic side wall and external iliac vessels.

#### CONTRAINDICATIONS

Relative contraindications to cryotherapy are similar to those for brachytherapy and include:

- prior transurethral resection of the prostate (TURP) with a large tissue defect,
- significant symptoms of urinary obstruction prior to treatment,
- large prostate size, and
- a history of abdominoperineal resection for rectal cancer, rectal stenosis, or other major rectal pathology.

Prior TURP is associated with an increased risk of sloughing and urinary retention. Significant preoperative obstructive symptoms increase the likelihood of postoperative urinary retention. Large prostate size may result in pubic arch interference, which may preclude adequate placement of cryoneedles. In these cases, the prostate may be cytoreduced with neoadjuvant hormonal ablation.

#### CURRENT CRYOTHERAPY TECHNIQUES FOR PROSTATE Ca

Third-generation cryotherapy using gas delivery systems and 17-gauge cryoneedles was first reported in 2000.<sup>25</sup> The full technique has previously been reported<sup>26</sup> and is summarized as follows.

Patients undergo a light bowel

preparation, consisting of oral magnesium citrate the day before and a Fleet enema the morning of the procedure. After induction of regional or general anesthesia, the patient is placed in an exaggerated dorsal lithotomy position. A Foley catheter is inserted and clamped to allow the bladder to distend. A 17-gauge brachytherapy template is stabilized with a stepper in front of the perineum. A multifrequency biplanar TRUS probe is used to image the prostate and measure its dimensions.

The 17-gauge cryoneedles are then inserted under TRUS guidance, spaced 1 cm apart, until 12 to 20 cryoneedles are placed to outline the shape of the prostate. Depending on the preference and experience of the surgeon, up to 5 thermocouples may be placed in the mid-gland, at the level of the external sphincter, in each neurovascular bundle (NVB), and in Denonvilliers' fascia. Thermocouples placed at the level of the external sphincter and in Denonvilliers' fascia are used to minimize the risk of incontinence or rectourethral fistula, while those in the mid-gland and NVBs ensure that the required temperature of  $-40^{\circ}\text{C}$  is reached. We recommend that the temperature in the sphincter is maintained above  $15^{\circ}\text{C}$ . Flexible cystoscopy is used to ensure that none of the cryoneedles have inadvertently pierced the urethra. A 0.09-mm guidewire is inserted through the cystoscope into the bladder, and a urethral warmer is inserted over the guidewire.

Two freeze-thaw cycles are used under TRUS guidance. In prostates greater than 27 mm in diameter, a "pull-back" procedure is used to cover the apex, as that is the length of the effective cytotoxic iceball isotherm. To ensure adequate cancer treatment, the iceball is often allowed to extend 2 to 4 mm laterally into the periprostatic tissues, beyond the apex, and

into the muscularis propria of the rectum posteriorly. In areas of extracapsular cancer extension, greater propagation of the iceball is permitted laterally, and, if necessary, an additional cryoneedle may be placed in such areas. When seminal vesicle invasion is present, a cryoneedle may be placed deep into the invaded seminal vesicle.

After completing the freeze-thaw cycles, the urethral warmer is left in

**The duration of freezing has been demonstrated to be an important factor leading to tissue destruction.**

place for up to 5 minutes to minimize the risk of urethral sloughing and subsequent urinary retention and irritative voiding symptoms. The cryoneedles are then removed and pressure is applied to the perineum for 2 to 5 minutes. The urethral warmer is removed, and a Foley catheter is inserted. Patients are discharged home with antibiotics and oral pain medication. The Foley catheter is removed 2 to 3 days later. In addition, patients are maintained on an  $\alpha$ -blocker for at least 1 month.

**Salvage cryotherapy.** In patients undergoing salvage cryotherapy, previously placed radioactive seeds may result in some confusion because their sonographic appearance is similar to the tip of the cryoneedles. This can be overcome by using the sagittal view to assist in cryoneedle placement. In this view, the length of the cryoneedles can be easily followed.

Some degree of fibrosis may be encountered during placement in patients undergoing salvage cryotherapy. The gland may be adherent to the anterior rectal wall due to the previous radiation, diminishing the thickness of Denonvilliers' fascia. If the space between the anterior rectal

TABLE 2

## Contemporary primary cryotherapy series: PSA follow-up and complications

Series	Han et al, 2003 <sup>30</sup>	Chinn et al, 2004 <sup>31</sup>	Donnelly et al, 2002 <sup>32</sup>	Bahn et al, 2002 <sup>33</sup>	Long et al, 2001 <sup>34</sup>	De La Taille et al, 2000 <sup>35</sup>	Koppie et al, 1998 <sup>36</sup>
No. patients	122*	48	76	590	975 <sup>†</sup>	35	176
Cryogen	Argon	Nitrogen	Nitrogen	Nitrogen/argon	Nitrogen/argon	Argon	Nitrogen
PSA nadir, ng/mL	≤ 0.4	≤ 0.5	< 0.3	ASTRO	< 0.5	< 0.1	< 0.5
Recurrence-free rate, %							
9 mo	NR	NR	NR	NR	NR	86 (L), 70 (A)	NR
12 mo	76 (L), 73 (A)	NR	NR	NR	NR	NR	82 (L), 58 (H)
3 yr	NR	NR	NR	NR	NR	NR	69 (L), 45 (H)
5 yr	NR	NR	60 (L)	NR	60 (L), 36 (H)	NR	NR
7 yr	NR	NR	NR	92	NR	NR	NR
8 yr	NR	82 (L), 72 (I), 50 (H)	NR	NR	NR	NR	NR
Complications, %							
Fistula	0	NR	0	0.004	0.5	0	NR
Incontinence	4.3 <sup>‡</sup>	NR	1.3	4.3 <sup>‡</sup>	7.5	6	NR
Sloughing	5.8	NR	3.9	NR	NR	0	NR
Retention/LUTS	3	NR	NR	5.5	13	0	NR
Erectile dysfunction	87	NR	53	94.9	93	NR	NR

\*Recently updated to 175 patients. <sup>†</sup>Review of 5 cryotherapy series. <sup>‡</sup>Percentage using pads.

ASTRO = American Society for Therapeutic Radiology and Oncology; NR = not reported; L = low-risk (preoperative Gleason score ≤6, PSA ≤10 ng/mL, stage ≤cT2) patients; I = intermediate-risk patients; H = high-risk patients; A = all patients.

wall and posterior prostatic capsule is less than 5 mm, it may not be possible to safely drive the temperature down to  $-40^{\circ}\text{C}$ , and freezing should be terminated when the leading edge of the iceball has extended just beyond the capsule, even if the target temperature of  $-40^{\circ}\text{C}$  has not been reached.

Urologists learning to perform cryotherapy should be aware of these considerations and should maintain a high awareness of the potential increased risk of incontinence in previously irradiated patients.

#### PRIMARY CRYOTHERAPY: TREATMENT OUTCOMES

Prostate biopsy has been performed in patients 6 to 12 months following cryotherapy in several series. The positive biopsy rate following cryotherapy ranges from 7.7% to 25%.<sup>5,13,27,28</sup> Certain areas of the prostate and seminal vesicles have been reported to be more likely to be sites of treatment

failure.<sup>3,29</sup> Shinohara and colleagues reported that recurrence was more common in cancers located at the apex (9.5%) and the seminal vesicles (43.8%), in contrast to those located in the midgland (4.1%) and base (0%).<sup>29</sup>

Serum PSA levels after cryotherapy reported from several contemporary series are summarized in Table 2.<sup>30-36</sup> Serum PSA levels after cryotherapy may not immediately decrease to an undetectable level. Immediately after the procedure, the PSA level rises to a very high value due to release of intracellular PSA from cellular necrosis. PSA nadir is usually achieved in 3 months.<sup>37</sup> However, the PSA nadir that should be achieved after cryotherapy is not known with certainty.

Shinohara and colleagues correlated the rate of biochemical and biopsy failure with the PSA nadir after cryotherapy in 132 patients.<sup>29</sup> Biochemical failure was lowest in patients who

achieved PSA nadirs below 0.1 ng/mL (21%) but was common in those with higher nadir values. Biopsy failure was lowest in those with PSA nadirs below 0.1 ng/mL (1.5%) and in those with nadirs between 0.1 and 0.4 ng/mL (10%). In contrast, 55% of patients with nadirs greater than 0.5 ng/mL had a positive prostate biopsy at follow-up. Biochemical and biopsy failure tended to occur within the first 12 months after treatment (96% and 88% of biochemical and biopsy failures, respectively).

We believe that the PSA nadir after cryotherapy should be less than 0.4 ng/mL. Higher values are associated with a significant risk of continued PSA elevation and a high likelihood of residual disease detected on prostate biopsy.

Data have been accumulated on 175 patients treated with third-generation cryosurgery at several institutions in the United States.<sup>30</sup> At 12-

TABLE 3

## Contemporary salvage cryotherapy series: PSA follow-up and complications

Series	Han et al, 2003 <sup>41</sup>	Katz, 2004 <sup>40</sup>	Bahn et al, 2003 <sup>39</sup>	Chin et al, 2001 <sup>38</sup>	Pisters et al, 1997 <sup>13</sup>
No. patients	29	67	59	118	150
Cryogen	Argon	Argon	Nitrogen/Argon	Argon	Nitrogen
PSA nadir, ng/mL	≤ 0.4	< 1.0	< 0.5, < 1.0	< 0.5, < 2.0	< 0.2
Recurrence-free rate, %					
6 mo	NR	79	NR	NR	NR
12 mo	72	72	NR	NR	NR
18 mo	NR	NR	59, 69	34, 55	31
7 yr	NR	NR	NR	NR	NR
Complications, %					
Fistula	0	0	3.4	3.3	1
Incontinence	9	13	4.3	6.7	73
Sloughing	5	0	NR	5.1	NR
Retention/LUTS	3	36	NR	8.5	67
Erectile dysfunction	89	NR	85	NR	72

NR = not reported.

month follow-up, 80 of 110 (73%) patients had a PSA level of 0.4 ng/mL or less, while 42 of 65 (76%) low-risk patients (Gleason score ≤6, PSA level ≤10 ng/mL, stage ≤cT2) remained free from biochemical progression. In general, results from recent series report biochemical disease-free rates of 60% to 90% at 5-year follow-up, depending on the PSA nadir used.<sup>31-36</sup>

#### SALVAGE CRYOTHERAPY: TREATMENT OUTCOMES

As more patients select EBRT and/or brachytherapy in the hopes of avoiding the morbidity associated with radical prostatectomy, urologists will see more failures from such therapies, despite modifications in radiation delivery methods to the gland, such as intensity-modulated radiation therapy, three-dimensional conformal radiation therapy, and computer-guided seed implantation.

Salvage prostatectomy is associated with significant morbidity, and salvage brachytherapy or radiotherapy have the potential for increased rectal and urinary toxicity. As a result, patients are often left with the option

of either watchful waiting or temporary palliation with hormone deprivation therapy and its attendant toxicity. Recent modifications in the technique of salvage cryotherapy have led to the ability to eradicate radio-recurrent prostate cancer safely and with decreased morbidity.

Many of the published salvage cryotherapy series from the early 1990s reported a significant number of complications.<sup>5,12,13,19,20</sup> The use of argon gas-based systems has led to the current generation of salvage cryotherapy series (Table 3).<sup>13,38-41</sup> At UCLA, 29 patients have undergone salvage cryotherapy using the SeedNet system. The complication rates were either comparable to or less than those previously reported by other investigators.<sup>41</sup> All patients had biopsy-proven recurrence without metastatic spread. At 12-month follow-up, 13 of 18 (72%) patients who had salvage cryotherapy have maintained a PSA of 0.4 ng/mL or less.

Similarly, Katz recently reported on the 6-year Columbia-Presbyterian experience with 67 men who underwent salvage cryotherapy.<sup>40</sup> Multi-

ple thermocouples were used and all patients received 3 months of hormone deprivation therapy. Based on a PSA cutoff value of greater than 1.0 ng/mL, 48 (72%) patients remained free of biochemical recurrence at 12 months.

Chin and co-workers recently reported on the Western Ontario experience using an argon-based system in 118 patients with biopsy-proven local recurrence following radiation therapy.<sup>38</sup> Nearly all patients underwent post-treatment prostate biopsy, which identified persistent disease in only 3.1%. The post-treatment PSA nadir was less than 0.5 ng/mL in 114 (96.6%) patients, with 34% showing no biochemical evidence of disease at a mean follow-up of 18 months. Chin and associates also reported on the serial biopsy results on 106 patients who underwent salvage cryotherapy.<sup>42</sup> Of 818 biopsy cores, 23 (2.8%) from 15 patients (14.2%) were positive.

#### COMPLICATIONS OF CRYOTHERAPY

Erectile dysfunction (ED) following cryotherapy of the prostate is com-

mon.<sup>3</sup> Although some series have reported rates ranging from 40% to 47%,<sup>3,43</sup> more contemporary series report rates greater than 80%.<sup>30,33,34</sup> This is likely due to the use of multiple freeze-thaw cycles and the extension of the iceball beyond the prostate, into the area of the NVBs.

Donnelly and co-workers reported that 47% of their patients had return of erectile function at 3-year follow-

up.<sup>32</sup> Despite this report, we do not routinely perform cryotherapy in patients interested in maintaining their potency. We feel that total ablation of the NVB is necessary to ensure complete eradication of tissue at the periphery of the prostate gland.

**The major risk of salvage cryotherapy remains incontinence, but the risk is significantly lower than with salvage prostatectomy.**

up.<sup>32</sup> Despite this report, we do not routinely perform cryotherapy in patients interested in maintaining their potency. We feel that total ablation of the NVB is necessary to ensure complete eradication of tissue at the periphery of the prostate gland.

The incidence of incontinence varies among series, probably owing to varying definitions of incontinence. Han and associates reported an incontinence rate of 3%,<sup>30</sup> while Cox and Crawford reported a rate of 27%.<sup>44</sup> Prior TURP increases the risk of urinary incontinence in patients undergoing cryotherapy. Shinohara and colleagues reported that 12 of 25 (48%) patients who underwent TURP after cryotherapy developed urinary incontinence.<sup>5</sup>

The major risk of salvage cryotherapy remains incontinence, but this risk is significantly lower than with salvage radical prostatectomy. The reported postsalvage cryotherapy urinary incontinence rates range from 0% to 83%.<sup>13,19,20,30,34</sup> However, the use of an external sphincter thermocouple has decreased urinary incontinence rates to less than 5% in the most recently reported salvage

cryosurgery series.<sup>21,38,41</sup> Tissue sloughing has been reported to occur in 3.8% to 23% of cases.<sup>4,5,14,30,37,43</sup> Treatment consists of antibiotics and adequate drainage of urine. Self-intermittent catheterization may lead to spontaneous tissue dislodgment. However, transurethral resection or removal of the necrotic tissue may be required if the condition persists.

Urethral stricture rarely forms after cryotherapy when an effective urethral warming device is used. However, if extensive tissue sloughing occurs, stricture at the bladder neck or the middle of the prostatic urethra can develop. Transurethral incision or balloon dilation is usually successful. Calcification of the stricture may also occur, necessitating transurethral resection.

Pelvic or rectal pain after the procedure and has been reported by 0.4% to 11% of patients.<sup>4,5,14,30,37,43</sup> Pain has been reported to be more common in previously irradiated patients, with rates ranging from 26% to 77.3%.<sup>13,35,45</sup> Generally, such patients are best managed with anti-inflammatory agents, once a urinoma or abscess has been excluded by imaging.

Han and associates reported that 3% of patients treated with cryotherapy developed transient penile numbness.<sup>30</sup> Penile numbness is caused by damage to the dorsal nerve of the penis due to close proximity of the cryoprobe. This complication generally resolves spontaneously.

Rectourethral fistula formation has been reported to occur in 0% to 3% of men who undergo cryotherapy of the prostate.<sup>34,44</sup> This complication is most commonly seen in patients previously treated with radiation. However, due to the high accuracy of modern-day TRUS combined with temperature monitoring at the anterior rectal wall, the complication rate is near 0% in contemporary se-

ries. This complication may occur either early after the procedure or several months later. Watery diarrhea or pneumaturia should alert the clinician to the possibility of fistula formation. A voiding urethrogram or CT scan is used to confirm the diagnosis and location of the fistula.

Conservative treatment with Foley drainage is sometimes successful and should be tried initially. If the fistula tract matures and epithelializes, fulguration may facilitate spontaneous closure. Formal fistula repair should be delayed until the inflammatory process has resolved completely, usually in 4 to 6 months. A transperineal or posterior approach for closure is recommended.<sup>46</sup>

Hydronephrosis is not a common complication. However, extensive freezing of the bladder neck area or placing of a cryoprobe deep into the seminal vesicle may result in freezing of the ureteral orifices or distal ureters.<sup>12</sup> Small bowel obstruction after cryotherapy of the prostate has been reported.<sup>36</sup> This complication may occur if the iceball is allowed to extend into the cul-de-sac of the peritoneal cavity. Distention of the bladder with normal saline during the procedure generally prevents this complication by moving the peritoneal contents away from the freezing process.

#### NERVE-SPARING CRYOTHERAPY

Onik and associates recently reported on 9 patients treated with focal, unilateral nerve-sparing cryotherapy.<sup>47</sup> At a mean follow-up of 36 months, all 9 had stable PSA levels; 6 patients who subsequently underwent biopsy had negative results, and 7 of 9 were potent.

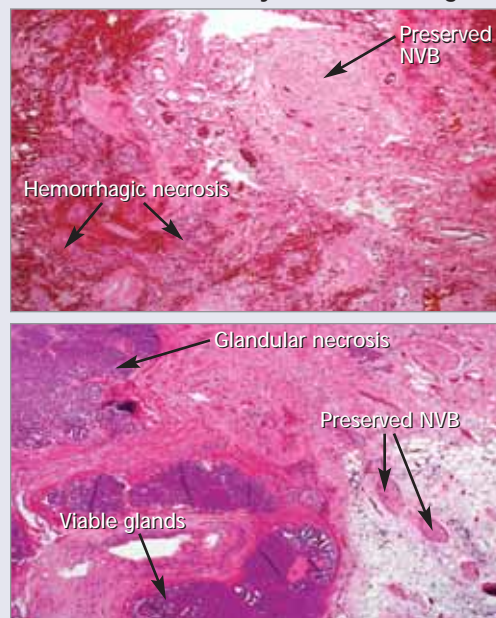
While these results are certainly provocative and intriguing, we do not recommend nerve-sparing cryotherapy at present. We have evaluated the feasibility of nerve-sparing cryotherapy by active warming of the NVB in a canine model.<sup>48</sup> Cryotherapy was performed using 17-gauge gas-driven

cryoneedles on 9 prostate lobes from 5 dogs. Seven lobes were treated with active warming of the NVB, and 2 lobes were treated without active warming. All 7 prostate lobes treated with active warming demonstrated complete or partial NVB preservation; however, 4 prostate lobes demonstrated adjacent gland preservation (Figure 3). All prostate lobes treated with a double freeze-thaw cycle demonstrated complete and uniform ablation of prostate tissue, whereas 1 of 3 prostate lobes treated with a single freeze-thaw cycle demonstrated incomplete ablation of the prostate tissue. Future studies include the feasibility of injecting antifreeze proteins<sup>49</sup> or saline to protect or separate the NVB.

#### CRYOTHERAPY VERSUS OTHER MINIMALLY INVASIVE OPTIONS

In 2001, Long and co-workers reported on a 5-year retrospective, multi-institutional pooled analysis of 975 patients who had cryotherapy and compared the results with those in recently published series of brachytherapy and EBRT.<sup>34</sup> The 3 techniques were compared after stratifying patients into similar risk groups and using similar or matching definitions of biochemical freedom. The biochemical survival rates for those at low risk of progression were 75% to 85% for EBRT, 65% to 85% for brachytherapy, and 76% for cryotherapy. For patients in the high-risk group, the biochemical-free survival rates were 15% to 65% for EBRT, 0% to 58% for brachytherapy, and 45% for cryotherapy. For 75 patients, who primarily had second-generation cryotherapy, the 5-year biochemical freedom from recurrence rate was 76% when the PSA threshold was 1.0 ng/mL. These results were similar to those reported by the combined 8 series that used EBRT or

FIGURE 3  
Preservation of NVB by active warming



Top: Preserved NVB adjacent to hemorrhagic necrosis of the prostate.

Bottom: Viable prostate glands can be seen immediately adjacent to preserved NVBs.

brachytherapy.

The review also concluded that the rate of ED following cryotherapy (93%) was higher than the rates reported by other investigators following EBRT (37% to 70%) and brachytherapy (10% to 40%). Fistula rates for EBRT, brachytherapy, and cryotherapy were 1% to 9%, 0% to 7%, and 0.5%, respectively, and incontinence rates were 0% to 13%, 0% to 5%, and 7.5%, respectively.<sup>34</sup>

#### QUALITY OF LIFE

The importance of assessing quality of life (QOL) in evaluating treatment outcome is now well established. Robinson and colleagues assessed 69 patients treated with cryosurgery for localized prostate cancer.<sup>50</sup> Patients were asked to complete the Functional Assessment of Cancer Treatment-Prostate (FACT-P) questionnaire before treatment and again at 6 weeks and 3, 6, and 12 months afterward. Total FACT-P scores showed a significant decline from baseline at 6 weeks,

with a steady increase over the year of follow-up to scores not significantly different from baseline. However, the sexual function scores were significantly below baseline at 1 year; only 1 of the 46 sexually active participants who were potent before treatment had recovered the ability to have erections sufficient for intercourse at 12 months.

The authors compared these results with those of Litwin and associates evaluating QOL outcomes in men treated with radical prostatectomy, radiotherapy, or observation.<sup>51</sup> Although there were differences between the studies, the authors "tentatively" concluded that QOL scores at 1 year after treatment were at least as high after cryotherapy as after surgery, radiotherapy, or observation.<sup>50</sup> Subsequently, the same authors reported the 3-year follow-up QOL data from this same group of patients,<sup>52</sup> with QOL remaining stable over the following 2 years. At 3 years, 13% of patients had regained erectile function and an additional 34% of patients were sexually active with the help of aids.

Perrotte and co-workers evaluated QOL after salvage cryotherapy using a modified UCLA Prostate Cancer Index that measured health-related QOL.<sup>15</sup> Treatment without an effective urethral warming catheter was highly associated with urinary incontinence ( $P < 0.003$ ), perineal pain ( $P < 0.001$ ), tissue sloughing ( $P < 0.003$ ), and an AUA symptom score greater than 20 ( $P < 0.004$ ). ED was more common in the double freeze-thaw cycle group ( $P < 0.05$ ). However, this study was performed on patients who had undergone cryotherapy with older-generation technology.

Anastasiadis and colleagues compared QOL in 81 patients who underwent primary or salvage cryother-

## A brief history of cryotherapy

Human cancers were first managed by cryotherapy in the 19th century, when cervical and breast cancers were treated with a salt and ice mixture.<sup>1</sup> Since then, cryotherapy has been applied to a wide variety of neoplasms, including brain, cervix, skin, kidney, prostate, and liver.<sup>2</sup> Cooper and Lee built the first liquid-nitrogen cryoprobe in 1961 and used it to treat patients with Parkinson's disease and other neuromuscular disorders.<sup>3</sup>

The first urologic application of cryotherapy in the prostate was performed by Gonder and colleagues,<sup>4</sup> who developed probes suitable for transurethral freezing of prostate tissue for benign prostatic hyperplasia (BPH) and prostate cancer. First-generation cryotherapy for the prostate was used in the 1960s and 1970s with no transrectal ultrasound (TRUS) guidance or urethral warming.<sup>4,5</sup> Complications were common and significant, including incontinence, urethral sloughing, and rectourethral fistulas.<sup>6</sup> The inability to precisely place cryoprobes or to monitor the extent of freezing resulted in the abandonment of the technology until the late 1980s.

The development and implementation of TRUS guidance<sup>7</sup> and urethral warming<sup>8,9</sup> significantly reduced the number of complications with second-generation cryotherapy (see the accompanying table). TRUS guidance allowed for accurate placement of probes, real-time monitoring, control of freezing, and visualization of the rectum to protect it from injury. Urethral warmers using a continuous irrigation system significantly reduced urethral sloughing and stricture formation. In addition, the availability of prostate-specific antigen (PSA) testing allowed for better

selection of patients and monitoring of cancer control following treatment.<sup>10</sup>

The development of third-generation cryotherapy included gas-driven 17-gauge cryoneedles, which signaled the transition from liquid nitrogen to gas-driven systems. Using the Joule-Thompson effect (different gases undergo unique temperature changes when depressurized according to unique gas coefficients), pressurized gas was frozen (argon) and actively thawed (helium). The transition from liquid nitrogen to gas-driven cryoneedles also permitted the use of smaller diameter probes; 17-gauge (1.47 mm) cryoneedles that allow for direct transperineal needle placement through a template without making incisions or using tract dilatation and insertion kits.

### REFERENCES

1. Gage AA. History of cryosurgery. *Semin Surg Oncol*. 1998;14(2):99-109.
2. Gage AA, Baust JG. Cryosurgery for tumors - a clinical overview. *Technol Cancer Res Treat*. 2004;3(2):187-200.
3. Cooper IS, Lee AS. Cryostatic congelation: a system for producing a limited, controlled region of cooling or freezing of biologic tissues. *J Nerv Ment Dis*. 1961;133:259-263.
4. Gonder MJ, Soanes WA, Smith V. Experimental prostate cryosurgery. *Invest Urol*. 1964;14:610-619.
5. Flocks RH, Nelson CM, Boatman DL. Perineal cryosurgery for prostatic carcinoma. *J Urol*. 1972;108(6):933-935.
6. Bonney WW, Fallon B, Gerber WL, et al. Cryosurgery in prostatic cancer: survival. *Urology*. 1982;19(1):37-42.
7. Onik G, Cobb C, Cohen J, et al. US characteristics of frozen prostate. *Radiology*. 1988;168(3):629-631.
8. Cohen JK, Miller RJ. Thermal protection of urethra during cryosurgery of prostate. *Cryobiology*. 1994;31(3):313-316.
9. Cohen JK, Miller RJ, Shuman BA. Urethral warming catheter for use during cryoablation of the prostate. *Urology*. 1995;45(5):861-864.
10. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. *N Engl J Med*. 1987;317(15):909-916.

### Evolution of prostate cryotherapy

Generation	TRUS	Urethral warmer	PSA	Cryogen	Small-diameter probes
1 <sup>st</sup> (1960s)	No	No	No	Liquid nitrogen	No
2 <sup>nd</sup> (1990s)	Yes	After 1995	Yes	Liquid nitrogen	No
3 <sup>rd</sup> (2000s)	Yes	Yes	Yes	Argon*	Yes (1.47 mm)

\*Joule-Thompson effect.

apy.<sup>53</sup> Primary cryotherapy patients fared significantly better regarding physical ( $P=0.005$ ) and social ( $P=0.024$ ) functioning than salvage cryotherapy patients. The most prominent prostate-related symptom in both groups was sexual dysfunction, followed by urinary symptoms, which were signifi-

cantly more severe in the salvage group ( $P=0.001$ ). Incontinence rates were 5.9% and 10% in the primary and the salvage groups, respectively. Severe ED was reported in 86% and 90% of the primary and salvage groups, respectively.

### CONCLUSIONS

Cryotherapy of the prostate appears to have low morbidity and is effective in eradicating primary and radio-recurrent tumors. With the development of TRUS guidance, urethral warmers and smaller needles, the morbidity associated with this treat-

ment alternative is now comparable with that of other available treatment options. The use of 17-gauge cryoneedles in third-generation cryotherapy may offer more precise prostate ice-ball formation and offer the flexibility to place more cryoneedles where necessary. Long-term follow-up of PSA outcome and survival are still needed. At present, third-generation cryotherapy should be considered in older or high-risk medical patients who would not otherwise be considered for radical prostatectomy and as salvage therapy in patients who have failed EBRT or brachytherapy. □

## REFERENCES

- Jemal A, Tewari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin*. 2004;54(1):8-29.
- Middleton RG, Thompson IM, Austenfeld MS, et al. Prostate Cancer Clinical Guidelines Panel Summary report on the management of clinically localized prostate cancer. The American Urological Association. *J Urol*. 1995;154(6):2144-2148.
- Bahn DK, Lee F, Solomon MH, et al. Prostate cancer: US-guided percutaneous cryoablation. Work in progress. *Radiology*. 1995;194(2):551-556.
- Cohen JK, Miller RJ, Rooker GM, et al. Cryosurgical ablation of the prostate: two-year prostate-specific antigen and biopsy results. *Urology*. 1996;47(3):395-401.
- Shinohara K, Connolly JA, Presti JC Jr, et al. Cryosurgical treatment of localized prostate cancer (stages T1 to T4): preliminary results. *J Urol*. 1996;156(1):115-120.
- Gonder MJ, Soanes WA, Smith V. Experimental prostate cryosurgery. *Invest Urol*. 1964;14:610-619.
- Cooper IS, Hirose T. Application of cryogenic surgery to resection of parenchymal organs. *N Engl J Med*. 1966;274(1):15-18.
- Zacarian SA, Stone D, Clater M. Effects of cryogenic temperatures on microcirculation in the golden hamster cheek pouch. *Cryobiology*. 1970;7(1):27-39.
- Tatsutani K, Rubinsky B, Onik G, et al. Effect of thermal variables on frozen human primary prostatic adenocarcinoma cells. *Urology*. 1996;48(3):441-447.
- Gage AA, Baust J. Mechanisms of tissue injury in cryosurgery. *Cryobiology*. 1998;37(3):171-186.
- Larson TR, Robertson DW, Corica A, et al. In vivo interstitial temperature mapping of the human prostate during cryosurgery with correlation to histopathologic outcomes. *Urology*. 2000;55(4):547-552.
- Bales GT, Williams MJ, Sinner M, et al. Short-term outcomes after cryosurgical ablation of the prostate in men with recurrent prostate carcinoma following radiation therapy. *Urology*. 1995;46(5):676-680.
- Pisters LL, von Eschenbach AC, Scott SM, et al. The efficacy and complications of salvage cryotherapy of the prostate. *J Urol*. 1997;157(3):921-925.
- Long JP, Fallick ML, LaRock DR, et al. Preliminary outcomes following cryosurgical ablation of the prostate in patients with clinically localized prostate carcinoma. *J Urol*. 1998;159(2):477-484.
- Perrotte P, Litwin MS, McGuire EJ, et al. Quality of life after salvage cryotherapy: the impact of treatment parameters. *J Urol*. 1999;162(2):398-402.
- Cohen JK, Rooker GM, Miller RJ Jr, et al. Cryosurgical ablation of the prostate: treatment alternative for localized prostate cancer. *Cancer Treat Res*. 1996;88:167-186.
- Baust J, Gage AA, Ma H, et al. Minimally invasive cryosurgery—technological advances. *Cryobiology*. 1997;34(4):373-384.
- Onik GM, Cohen JK, Reyes GD, et al. Transrectal ultrasound-guided percutaneous radical cryosurgical ablation of the prostate. *Cancer*. 1993;72(4):1291-1299.
- Miller RJ Jr, Cohen JK, Shuman B, et al. Percutaneous, transperineal cryosurgery of the prostate as salvage therapy for post radiation recurrence of adenocarcinoma. *Cancer*. 1996;77(8):1510-1514.
- Cespedes RD, Pisters LL, von Eschenbach AC, et al. Long-term followup of incontinence and obstruction after salvage cryosurgical ablation of the prostate: results in 143 patients. *J Urol*. 1997;157(1):237-240.
- Ghafari MA, Johnson CW, De La Taille A, et al. Salvage cryotherapy using an argon based system for locally recurrent prostate cancer after radiation therapy: the Columbia experience. *J Urol*. 2001;166(4):1333-1337.
- Cheng L, Chevillie JC, Bostwick DG. Diagnosis of prostate cancer in needle biopsies after radiation therapy. *Am J Surg Pathol*. 1999;23(10):1173-1183.
- Stone NN, Stock RG, Unger P, et al. Biopsy results after real-time ultrasound-guided transperineal implants for stage T1-T2 prostate cancer. *J Endourol*. 2000;14(4):375-380.
- Rogers E, Ohori M, Kassabian VS, et al. Salvage radical prostatectomy: outcome measured by serum prostate specific antigen levels. *J Urol*. 1995;153(1):104-110.
- Zisman A, Leibovici D, Siegel YI, et al. Prostate cryoablation without an insertion kit using direct transperineal placement of ultrathin freezing probes. *Tech Urol*. 2000;6(1):34-36.
- Zisman A, Pantuck AJ, Cohen JK, et al. Prostate cryoablation using direct transperineal placement of ultrathin probes through a 17-gauge brachytherapy template-technique and preliminary results. *Urology*. 2001;58(6):988-993.
- Connolly JA, Shinohara K, Carroll PR. Cryosurgery for locally advanced (T3) prostate cancer. *Semin Urol Oncol*. 1997;15(4):244-249.
- Wong WS, Chinn DO, Chinn M, et al. Cryosurgery as a treatment for prostate carcinoma: results and complications. *Cancer*. 1997;79(5):963-974.
- Shinohara K, Rhee B, Presti JC Jr, et al. Cryosurgical ablation of prostate cancer: patterns of cancer recurrence. *J Urol*. 1997;158(6):2206-2209.
- Han KR, Cohen JK, Miller RJ, et al. Treatment of organ confined prostate cancer with third generation cryosurgery: preliminary multicenter experience. *J Urol*. 2003;170(4 Pt 1):1126-1130.
- Chinn DO, Wong WW, Chinn M, et al. Temperature monitored prostate cryosurgery: 8 year accrued clinical experience. *J Urol*. 2004;171(4 Suppl):219. Abstract 831.
- Donnelly BJ, Saliken JC, Ernst DS, et al. Prospective trial of cryosurgical ablation of the prostate: five-year results. *Urology*. 2002;60(4):645-649.
- Bahn DK, Lee F, Badalament R, et al. Targeted cryoablation of the prostate: 7-year outcomes in the primary treatment of prostate cancer. *Urology*. 2002;60(2 Suppl 1):3-11.
- Long JP, Bahn D, Lee F, et al. Five-year retrospective, multi-institutional pooled analysis of cancer-related outcomes after cryosurgical ablation of the prostate. *Urology*. 2001;57(3):518-523.
- De La Taille A, Benson MC, Bagiella E, et al. Cryoablation for clinically localized prostate cancer using an argon-based system: complication rates and biochemical recurrence. *BJU Int*. 2000;85(3):281-286.
- Koppie TM, Shinohara K, Grossfeld GD, et al. The efficacy of cryosurgical ablation of prostate cancer: the University of California, San Francisco experience. *J Urol*. 1999;162(2):427-432.
- Wieder J, Schmidt JD, Casola G, et al. Transrectal ultrasound-guided transperineal cryoablation in the treatment of prostate carcinoma: preliminary results. *J Urol*. 1995;154(2 Pt 1):435-441.
- Chin JL, Pautler SE, Mouraviev V, et al. Results of salvage cryoablation of the prostate after radiation: identifying predictors of treatment failure and complications. *J Urol*. 2001;165(6 Pt 1):1937-1941.
- Bahn DK, Lee F, Silverman P, et al. Salvage cryosurgery for recurrent prostate cancer after radiation therapy: a seven-year follow-up. *Clin Prostate Cancer*. 2003;2(2):111-114.
- Katz AE. Targeted cryosurgical ablation of the prostate (TCAP) for patients failing radiation: 6-year observations. *J Urol*. 2004;171(4 Suppl):272. Abstract 1028.
- Han KR, Belldegrin AS. Third-generation cryosurgery for primary and recurrent prostate cancer. *BJU Int*. 2004;93(1):14-18.
- Chin JL, Touma N, Pautler SE, et al. Serial histopathology results of salvage cryoablation for prostate cancer after radiation failure. *J Urol*. 2003;170(4 Pt 1):1199-1202.
- Coogan CL, McKiel CF. Percutaneous cryoablation of the prostate: preliminary results after 95 procedures. *J Urol*. 1995;154(5):1813-1817.
- Cox RL, Crawford ED. Complications of cryosurgical ablation of the prostate to treat localized adenocarcinoma of the prostate. *Urology*. 1995;45(6):932-935.
- De La Taille A, Hayek O, Benson MC, et al. Salvage cryotherapy for recurrent prostate cancer after radiation therapy: the Columbia experience. *Urology*. 2000;55(1):79-84.
- Nyam DC, Pemberton JH. Management of iatrogenic rectourethral fistula. *Dis Colon Rectum*. 1999;42(8):994-997.
- Onik G, Narayan P, Vaughan D, et al. Focal "nerve-sparing" cryosurgery for treatment of primary prostate cancer: a new approach to preserving potency. *Urology*. 2002;60(1):109-114.
- Janzen N, Han KR, Perry KT, et al. Feasibility of nerve-sparing prostate cryoablation: applications and limitations. Presented at the Annual Meeting of the Society of Urologic Oncology/NCI: December 5-6, 2003; Bethesda, Md.
- Jia Z, Davies PL. Antifreeze proteins: an unusual receptor-ligand interaction. *Trends Biochem Sci*. 2002;27(2):101-106.
- Robinson JW, Saliken JC, Donnelly BJ, et al. Quality-of-life outcomes for men treated with cryosurgery for localized prostate carcinoma. *Cancer*. 1999;86(9):1793-1801.
- Litwin MS, Hays RD, Fink A, et al. Quality-of-life outcomes in men treated for localized prostate cancer. *JAMA*. 1995;273(2):129-135.
- Robinson JW, Donnelly BJ, Saliken JC, et al. Quality of life and sexuality of men with prostate cancer 3 years after cryosurgery. *Urology*. 2002;60(2 Suppl 1):12-18.
- Anastasiadis AG, Sachdev R, Salomon L, et al. Comparison of health-related quality of life and prostate-associated symptoms after primary and salvage cryotherapy for prostate cancer. *J Cancer Res Clin Oncol*. 2003;129(12):676-682.

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