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Cryotherapy for localized PCa: Indications and technique

In appropriate candidates, procedure offers a minimally invasive option with low morbidity

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In 1996, AUA recognized cryoablation as a therapeutic option for prostate cancer and removed the "investigational" label from the procedure. Cryosurgery offers the appropriate candidate a minimally invasive, outpatient treatment option with low overall morbidity and excellent overall anti-tumor activity (*Contemporary Urology* 2004; 16:46-61).

Advances in cryoablative technology in the past decade have allowed more efficient freezing of the prostate gland while reducing damage to surrounding tissues—notably, the rectum, urethra, and external urinary sphincter. The morbidity associated with this treatment alternative has become comparable with that of other available treatment options due to the development of transrectal ultrasound guidance, urethral warmers, liquid nitrogen to gas-driven probes, and a transition from cryoprobes to the smaller cryoneedles. The availability of PSA testing has allowed for better patient selection and monitoring of cancer control following treatment.

This article will review the equipment used for performing prostate cryoablation, current indications, surgical technique, outcomes, and potential side effects.

Figure 1. The patient is positioned in the dorsal lithotomy position with TRUS probe in place attached to the holding device. Cryoneedles from the cryoablation device are shown through a brachytherapy-like template into the perineum.

Available equipment

The development of third-generation cryoablation included gas-driven 17-gauge (1.47-mm) cryoneedles (Oncura, Plymouth Meeting, PA). Gas-driven cryoneedles use the Joule-Thompson principle in which different gases undergo unique temperature changes when depressurized—according to unique gas coefficients—so pressurized gas can be used to both freeze (argon gas) and actively thaw (helium gas) the prostate.

Two cryoablation devices for prostate cancer treatment are available in the United States. The SeedNet system (Oncura) uses pressurized argon gas as the cryo-

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gen, and up to 25 cryoneedles can be used to create a conformal freezing pattern. These ultra-thin cryoneedles allow for direct transperineal needle placement through a brachytherapy-like template without making incisions or using tract dilatation and insertion kits. The iceball created by the Oncura system is approximately 2 cm in diameter.

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

Patient selection

There are three indications for prostate cryoablation: primary therapy, salvage therapy, and palliation. In general, we recommend cryoablation for patients with localized, high-grade tumors and higher-volume disease who are not potent or not interested in maintaining their potency.

Cryoablation is also a reasonable therapeutic option for the following patients:

- those with clinically locally advanced disease (stage T3)
- those with no evidence of metastatic disease with a grade or stage of disease likely to progress without treatment (Gleason score of 6 and stage >A1/T1a)
- those who are poor candidates for radical prostatectomy (eg, because of Crohn's disease, ulcerative colitis, weight >350 lbs, cardiac disease, etc.)
- and patients who have no evidence of metastatic disease with >10-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.

In general, we recommend cryoablation for patients with localized, high-grade tumors and higher-volume disease who are not potent or not interested in maintaining their potency.

Local cancer recurrence following radiation therapy (external beam or brachytherapy) may be managed with cryoablation. However, complications associated with salvage cryoablation are higher than those associated with primary treatment. Cryoablation has also been used to treat local recurrences after radical prostatectomy. Patients with locally progressive disease despite hormonal manipulation can be treated with cryoablation to prevent urinary obstruction or bleeding.

Patients with high risk of metastatic disease should undergo imaging, radionuclide bone scan, or cross-sectional imaging of the abdomen and pelvis based on stage and grade, as well as serum PSA. Patients at high risk for lymph node metastases may undergo regional lymph node dissection. Patients with gross extracapsular extension or seminal vesicle invasion are treated with neoadjuvant hormone therapy to reduce the tumor volume and allow for better inclusion within the iceball.

Potential complications of cryoablation of the prostate include urethral sloughing, urinary retention, urge and/or stress incontinence, penile paresthesias, pelvic pain, scrotal swelling, impotence, and rectourethral fistulas. These complications have significantly decreased in the past years with the introduction of the urethral warming device and third-generation small-diameter cryoneedles.

Relative contraindications are similar to those for brachytherapy and include prior transurethral resection of the prostate with a large tissue defect, large prostate size, and a history of abdominoperineal resection for rectal cancer, rectal stenosis, or other major

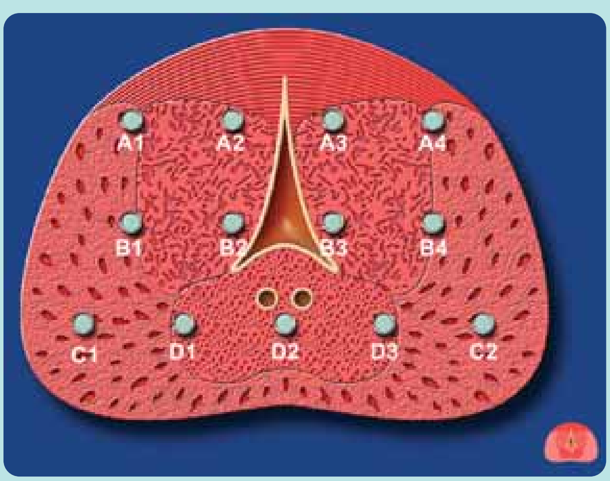

Figure 2A. Tranverse template for placement of 17-gauge cryoneedles.

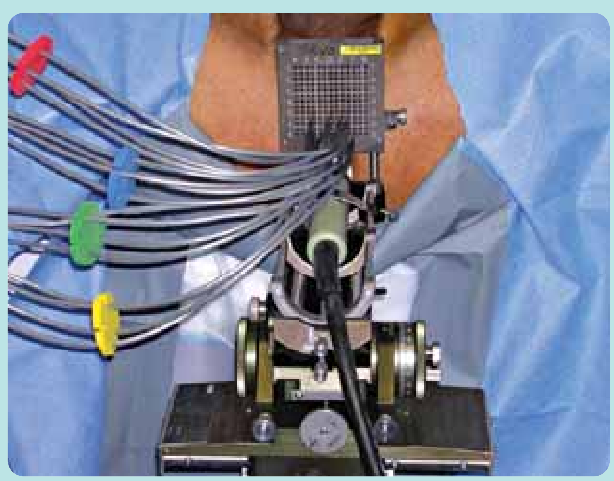

Figure 2B. Cryoneedles in brachytherapy-like template outlining the prostate with each colored marker representing a different horizontal layer group.

rectal pathology. Prior TURP is associated with an increased risk for sloughing and urinary retention. Significant preoperative obstructive symptoms increase the likelihood of postoperative urinary retention.

If the prostate size exceeds 50 cm^3, there may be pubic arch interference, and complete freezing of the prostate may be difficult. Therefore, neoadjuvant hormone therapy is indicated to reduce the target volume and allow for more effective cryoablation.

Surgical technique

Patients are placed in an exaggerated dorsal lithotomy position with careful cushioning. The perineum is placed slightly over the operating table edge at 90 degrees to the operating room floor to permit access to the TRUS probe-holding device and template (figure 1). The patient is shaved and prepped from the perineum to the umbilicus. The scrotum is fixed superiorly using two stay sutures. A 16F Foley catheter is inserted and clamped to allow the bladder to distend.

A multifrequency biplanar TRUS probe is attached to the holding device adapting cradle of the brachytherapy stepper and is used to image the prostate and measure its dimensions. The aiming grid software may be activated and projected on the TRUS image.

The attached probe is lowered posteriorly until slight resistance from the posterior rectal wall is felt or the image of the shiny anterior fibromuscular stroma is lost at 5 MHz. This maneuver opens up the distance between the prostate gland and the rectum. We believe that this prevents rectal wall ischemia during freezing and increases the safety of the procedure.

Once the adjustments are completed, the holding device is fixed in place. A brachytherapy-like template drilled with a matrix of 17-gauge holes is attached to the holding device and gently fixed against the perineum. The holes in the template are 5 mm apart and correspond to the aiming grid projected on the ultrasound image.

The 17-gauge cryoneedles are inserted under TRUS guidance, each spaced about 1 cm apart until 12 to 20 cryoneedles are placed to outline the shape of the prostate (*Urology* 2001; 58:988-93). Cryoneedles are inserted in either three horizontal layers (prostate height, 3.5 cm or less) or four layers (prostate height, greater than 3.5 cm) about 1 cm apart. Each layer groups two to five cryoneedles according to prostate width (figures 2a and 2b).

Since the iceballs progress longitudinally 5 mm past the needle tip, the needles are advanced into the prostate base and positioned 5 mm caudal to the bladder neck. The most posterior layer is ideally located 5 to 7 mm anterior to the prostate capsule. Given the propensity of prostate cancer to expand through the capsule in locations pierced by the branches of the neurovascular bundle (NVB), we place lateral needles to permit extraprostatic freezing and facilitate killing by early shutdown of the arterial supply to the gland.

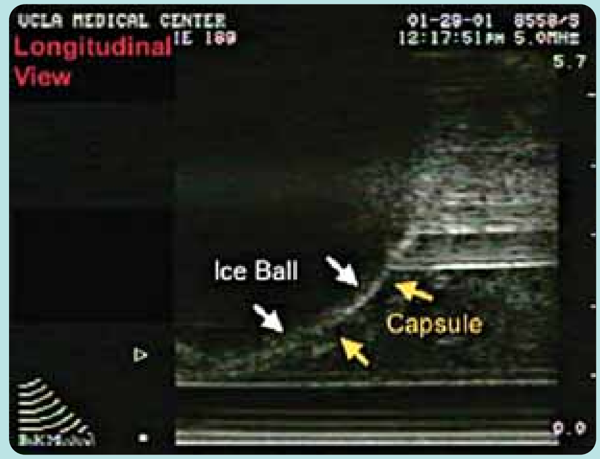

Figure 3. An ultrasound image showing the leading edge of freezing tissue created by the anterior probes. The edge of frozen tissue is seen as a bright arcuate line. Tissue inside the frozen area is concealed by the acoustic shadow created by the leading edge. (Photographs courtesy of John S. Lam, MD, and Arie S. Belldegrun, MD)

The prostatic urethra is identified by TRUS in both the longitudinal and the transverse views, and the cryoneedles are placed about 1 cm away from the urethra. The only cryoneedle permitted in the same sagittal plane as the urethra is the middle probe of the posterior layer when an uneven number of probes is used.

Depending on the preference and experience of the surgeon, up to five thermocouples may be placed in the midgland, at the level of the external sphincter, each NVB, and 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 midgland and NVBs ensure that the required temperature of –40°C is reached. We recommend that the temperature in the sphincter be maintained above 15ºC.

In patients undergoing salvage cryoablation, previously placed radioactive seeds may cause some confusion, because their sonographic appearance is similar to the tip of the cryoneedles. This can be overcome by utilizing the sagittal view to assist in placing the cryoneedles. In this view, the length of the cryoneedles can be easily followed.

Some degree of fibrosis may also be encountered during placement in patients undergoing salvage cryoablation. The gland may be adherent to the anterior rectal wall due to the previous radiation, diminishing the thickness of the Denonvilliers' fascia. If the space between the anterior rectal wall and posterior prostatic capsule is less than 5 mm, it may not be possible to drive the temperature down to –40ºC safely. Freezing should be terminated when the leading edge of the iceball has extended just beyond the capsule, even if the target temperature of –40ºC is not reached. Urologists learning to perform cryoablation should be aware of these considerations and maintain a high awareness of the potential increased risk of incontinence in previously irradiated patients.

After all the cryoneedles have been positioned, the Foley catheter is gently removed. Any difficulty may indicate that a probe is wrongly positioned and is potentially piercing the urethra. A meticulous 360-degree examination of the urethra and bladder is performed using a flexible cystoscope.

If a misplaced cryoneedle is visualized in the urethra or a wall hematoma is detected, repositioning is indicated to avoid the detrimental outcome of direct urethral freezing or freezing the circulating urethral warmer fluid into a standstill position. If the surgeon chooses, a soft 10F to 12F suprapubic catheter may be inserted under vision, closed, and secured to the skin. We do not routinely use a suprapubic catheter and discharge the patient with a Foley catheter for few days.

A 0.038-inch guidewire is inserted through the working channel of the cystoscope, which is then withdrawn, and a heavily lubricated urethral warming catheter is introduced into the bladder over the guidewire. The urethral warmer is a closed double-lumen catheter made of a polyethylene membrane in which saline heated to 43°C is continuously circulated through it by a water pump. During the procedure, the bladder is kept nearly full to prevent injury from the rigid tip of the warmer device.

TRUS visibility

To maintain TRUS visibility, the freezing is started at the anterior probe layer and continued posteriorly. Uncovered areas may be visualized and a correcting maneuver may be used.

On TRUS, 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 3). The tissue inside is concealed in the acoustic shadow created by this boundary. Therefore, 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 10-minute freezing cycles are performed. Between the cycles, the prostate may be allowed to thaw passively (15 to 20 minutes) or actively using helium (7 to 8 minutes). The SeedNet cryoneedles provide 27-mm long, –20°C isotherm at 10 minutes of continuous freezing. Therefore, in glands longer than 27 mm, a "pullback" maneuver is used to cover the apex.

In a current phase I study, we are evaluating the safety and efficacy of modified 17-gauge cryoneedles (IceRod, Oncura) that form an elongated iceball (32 mm × 56 mm) for cryoablation of large prostate glands (longer than 40 mm), which will eliminate the need for a pullback.

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 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 afterwards, or alternatively, the suprapubic catheter is opened.

Patients are discharged on the same day or on postoperative day 1 with antibiotics (usually a fluoroquinolone), oral pain medications, an alpha-blocker (maintained for at least a month), and a Foley catheter to be removed in 2 to 3 days. If a suprapubic catheter was placed, it is kept open for 72 hours and then closed. The patient documents the urinary rests, and once normal voiding is regained, the suprapubic catheter is removed.

Patients are followed with clinical examinations and serial PSA measurements at 3-month intervals. Serum PSA after cryoablation may not immediately decrease to an undetectable level. Immediately after the procedure, PSA rises to a very high value due to release of intracellular PSA from cellular necrosis. PSA nadir is usually achieved in 3 months. However, the PSA nadir level that should be achieved after cryoablation is not known with certainty. We define failure as an inability to achieve and maintain a PSA value of 0.4 ng/mL. We do not routinely perform follow-up biopsies.

Outcomes

Data have been accumulated on 175 patients prospectively studied in a multicenter clinical trial using the third-generation cryoneedles (*J Urol* 2003; 170:1126-30; *BJU Int* 2004; 93:14-8). At 12-month follow-up, 80 of 110 patients (73%) remained with a PSA of ≤0.4 ng/mL, while 32 of 45 (72%) high-risk patients (Gleason ≥7, PSA >10.0 ng/mL, ≥cT3) remained free from biochemical progression at 1 year.

Results of recent series report biochemical disease-free rates of 60% to 90% at 5-year follow-up, depending on the PSA nadir used. The rate of urethral sloughing in our study cohort of 175 patients was 6% (10 patients). Five patients (3%) required the use of pads for incontinence; seven patients (4%) had transient pelvic pain; and five patients (3%) had transient urinary retention. There were no cases of urinary-rectal fistulas. The impotence rate of 84% in the current series is comparable with that previously reported by others.

Twenty-nine patients underwent salvage cryoablation for radiation failure. At 12-month follow-up, 13 of 18 patients remained with a PSA of ≤0.4 ng/mL. Complications included urethral sloughing (5%), incontinence requiring pads (5%), transient penile/pelvic pain (23%), transient urinary retention (3%), and impotence (89%). There were no cases of urinary-rectal fistulas. These results were either comparable or less than those previously reported.

Cryoablation of the prostate appears to have a low overall morbidity comparable with other available treatment options and is effective in eradicating primary and radiorecurrent tumors. Urologists should familiarize themselves with this treatment option, since it is a procedure that incorporates techniques we commonly perform, such as TRUS of the prostate, needle placement under TRUS guidance, and cystoscopy. UT