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# The Role of Cryosurgery of the Prostate for Nonsurgical Candidates

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## ABSTRACT

**Introduction:** Technological advancements have reduced the morbidity associated with cryosurgery, leading to an increased interest in this modality for the treatment of organ-confined prostate cancer. In this study, we critically examine the current role of cryoablation of the prostate to better understand how to counsel patients regarding this treatment option.

**Methods:** A database was compiled over a 3-year period (2008–2011) of 30 patients who underwent cryoablation for organ-confined prostate cancer. Indications for cryosurgery included primary treatment, focal treatment (institutional review board–approved prospective study), and salvage cryotherapy for radiation failure. The primary outcomes were biochemical response via prostate-specific antigen (PSA) measurement and morbidity associated with cryoablation. Cryotherapy failure was defined as an increasing postcryotherapy PSA level ≥ 2 ng/mL above the post-treatment nadir, a positive prostate biopsy, or radiographic evidence of metastatic disease.

**Results:** Of the 30 patients who underwent cryoablation from 2008 to 2011, 26 patients had complete follow-up data for analysis. Of these patients, 17 (65.38%) had total gland cryotherapy, 5 (19.23%) had salvage cryotherapy for radiation failure, and 4 (15.38%) had focal cryotherapy. The mean patient age was 68 years (54–89); median preoperative PSA was 5.5 ng/mL (1.7–15.9); median prostate volume was 35 mL (15–54); mean Gleason score was 7; and the median PSA at study conclusion was 0.7 (0.02–3.4) ng/mL. Of the 17 patients who had total prostate cryotherapy, 11 (64.7%) had significant factors precluding primary treatment by a surgical and/or radiation approach, including neurological disorders (2), morbid obesity (1), rectal cancer treated with radiation (1), kidney/pancreas transplant (2), ileoanal pouch secondary to inflammatory bowel disease (IBD) (1), renal failure (1), and age (3).There were no intra- or postoperative complications. After a median follow-up of 18 months (1–40), none of the patients with multiple comorbidities had biochemical failures. Two patients from the salvage group experienced treatment failure requiring androgen deprivation therapy.

**Conclusions:** This critical analysis of a single-surgeon experience at a large academic prostate cancer program revealed that the contemporary role of cryosurgery is, in select patients with comorbidities, preventing surgical and/or radiation therapy. Additionally, cryosurgery has a role in treating radiation failures. Further studies are necessary to investigate focal cryotherapy as an option for primary treatment, but our preliminary results are promising, without any biochemical failures in our focal therapy cohort.

**Key Words:** Prostate cancer, Cryotherapy, Comorbidities.

## INTRODUCTION

Prostate cancer represents one of the most prevalent cancers in the United States. The American Cancer Society estimates a total of 2.8 million men in the United States have a history of prostate cancer, with 241 740 new cases diagnosed in 2012 alone.[1] Prostate cancer is the most common nonskin cancer diagnosed in American men and is the second leading cause of cancer deaths in men behind only lung cancer.[2] Since the introduction of PSA screening, there has been a dramatic increase in the proportion of men diagnosed with clinically localized prostate cancer, with ~90% of men having the disease confined to the prostate at the time of diagnosis.[3] Radical prostatectomy and radiation therapy (external beam and brachytherapy) are considered to be the gold standard in treatment of organ-confined prostate cancer. In 1996, the American Urological Association (AUA) recognized cryoablation as a therapeutic option for prostate cancer.[4]

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Considerable technological improvements in cryotherapy including gas-driven miniaturized equipment, ultrasonographic ice-ball monitoring, and the use of thermal sensors have allowed more efficient freezing of the prostate gland while reducing collateral damage to surrounding tissues. These improvements have led to decreased morbidity and a resurgence of cryotherapy for primary treatment of prostate cancer. In 2008, the AUA published a Best Practice Statement on the use of cryosurgery for patients with clinically localized prostate cancer and also established cryosurgery as a therapeutic option for radiorecurrent organ-confined prostate cancer.[5]

Contemporary cryotherapy offers the patient a minimally invasive treatment option with low morbidity, minimal blood loss, shorter hospital stay, and a high negative biopsy rate after treatment.[6] Additionally, the similarities between third-generation cryotherapy and brachytherapy instrumentation/setup may facilitate the adoption of this technique in suitably selected patients.

Medicare began reimbursement for cryotherapy as a treatment modality for prostate cancer in 1999, but cryosurgery is seldom used in community urological practice. According to AUA polls, the percentage of urologists performing cryosurgery from 1997 to 2001 remained constant at 2%, but the average annual number of procedures performed by each urologist increased from 4 to 24. In contrast, the percentage of urologists performing brachytherapy over the same period rose from 16% to 51%.[7]

Cryotherapy offers certain advantages to patients with comorbidities discouraging alternative primary therapies, including patients with inflammatory bowel disease (IBD), prior gastrointestinal or pelvic surgery, pelvic irradiation, cardiac disease, and morbid obesity.

## MATERIALS AND METHODS

Between January 2008 and September 2011, 30 prostate cryoablation procedures were performed at our institution. All patients had biopsy-proven organ-confined prostate cancer as well as a negative metastatic workup. Most commonly, patients had significant cardiovascular, neurological, gastrointestinal, or pulmonary risk factors that prevented surgical or radiation therapy. Preoperative PSA, gland size, and Gleason scores were recorded. Mean and median patient age was 68 and 67 years, respectively (range 54–89 years).

Indications for cryosurgery included primary total gland or focal treatment as well as salvage cryotherapy for radiation failures of the 30 patients undergoing cryotherapy; 26 had complete follow-up data for analysis, including 5 with local recurrence after radiation therapy, 17 having total gland therapy, and 4 patients undergoing focal primary therapy. The study was approved by the institutional review board.

### Technique

All patients underwent prostate cryosurgery by a single surgeon using the CRYOcare system (Endocare, Irvine, California, USA) and the technique previously described by Onik et al.[8] The CRYOcare system is an argon gas–based system that works via pressurized gas expansion at the tip of the cryoneedle. Per the Joule-Thompson effect, argon gas cools rapidly as it expands, creating the ice balls used for cryoablation. In contrast, helium gas heats rapidly as it expands and was thus used to reverse ice-ball formation rapidly. In this manner, argon and helium gases are used sequentially for rapid freezing and thawing; this process creates the freeze–thaw cycle.[9] Two freeze–thaw cycles were used in cryoablative therapy per the manufacturer's recommendation.

Because third-generation cryotherapy uses pressurized gas for ice-ball formation, it allows for use of ultrathin probes offering more precise prostatic ice-ball formation than in previous generations of cryosurgery. This advancement gives the surgeon flexibility to place more probes where necessary, depending on the size and anatomy of the prostate.

All patients underwent a light bowel preparation the evening before surgery consisting of oral magnesium citrate and a Fleet enema (C.B. Fleet Company, Inc., Lynchburg, Virginia, USA) the morning of treatment. Bowel preparation was performed with the aim of reducing fecal contents and air in the rectum to enhance transrectal ultrasonographic (TRUS) imaging of the prostate. All patients were given preprocedure antibiotics.

After induction of general anesthesia, the patient was placed in the dorsal lithotomy position. The scrotum was fixed superiorly using two stay sutures, and a 16-French Foley catheter was inserted and clamped to distend the bladder, displace the peritoneal contents from the treatment area, and facilitate clear identification of the urethra and bladder. A 17-gauge brachytherapy template was stabilized with a stepper in front of the perineum, and a real-time biplanar TRUS probe was used to visualize the insertion of cryoprobes and actively monitor the freeze–thaw cycles. The ultrathin 17-French cryoprobes were then inserted under ultrasonographic guidance, spaced approximately 1 cm apart. Typically, 6 to 8 needles are

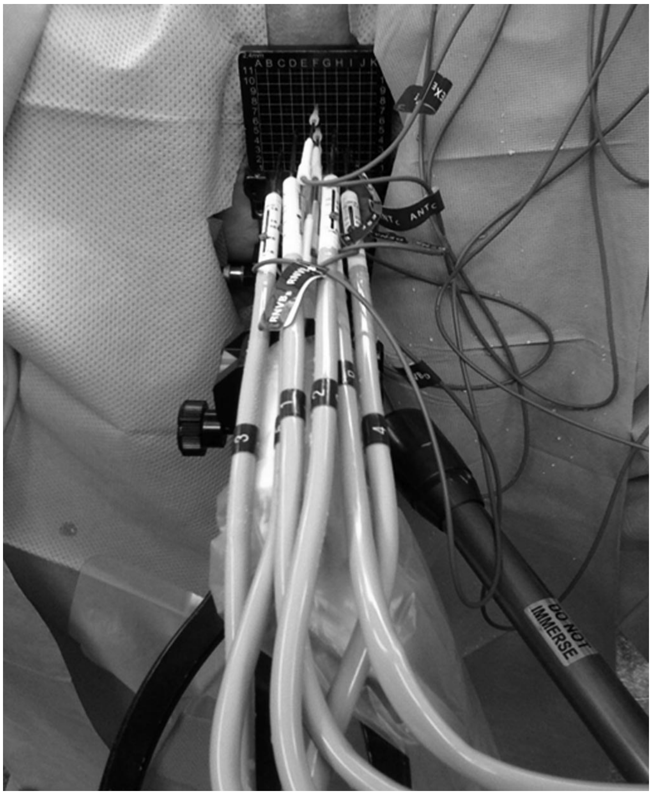


**Figure 1.** Intraoperative setup with placement of cryoneedles using radiotherapy template.

placed, depending on the gland size and anatomy to outline the shape of the prostate. The needles were inserted in a fashion that allows sufficient overlap of adjacent ice balls for optimal tissue ablation.

**Figure 1** illustrates intraoperative setup with the template and cryoprobes used. Typically, up to 5 thermocouples are placed at the level of external sphincter, left neurovascular bundle, right neurovascular bundle, mid gland, and Denonvilliers' fascia, but the number of thermosensor probes is adaptable to surgeon preference and patient characteristics.

After placement of the cryoneedles, flexible cystoscopy is performed to ensure that none of the cryoprobes have perforated the urethra or bladder, as well as to place a guide wire in the bladder for insertion of the urethral warmer. Warm saline irrigation is started through the warmer in a continuous-flow manner to avoid urethral freezing and thereby prevent urethral sloughing after treatment. Two freeze–thaw cycles are used with ice-ball formation performed under TRUS guidance.

**Figure 2** illustrates transrectal sonogram of the prostate

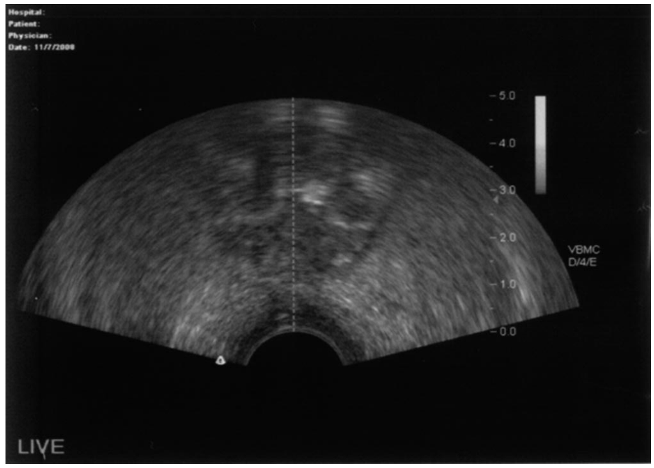


**Figure 2.** Transrectal ultrasonographic image of the prostate during cryotherapy showing ice-ball formation.

illustrating ice-ball formation; ice balls in the prostate create an ultrasonographic shadow obscuring anatomic detail anterior to the ice, and thus the anterior probes are activated first. After two freeze–thaw cycles, the urethral warmer is kept in place for 5 minutes. The cryoprobes are then removed, and pressure is applied to the perineal region to minimize blood loss.

The Foley catheter is left in place for 5 to 7 days, and patients are treated on an outpatient basis. Postcryotherapy follow-up is scheduled for every 3 mo and includes a focused history, digital rectal examination, serum PSA measurement, and radiological imaging if indicated. Cryotherapy failure is defined as an increasing postcryotherapy PSA level of ≥2 ng/mL above the nadir value, a positive prostate biopsy, or radiographic evidence of metastatic disease.

## RESULTS

**Tables 1** and **2** highlight the patient demographics and disease characteristics; we categorized our patients using the D'Amico criteria for risk stratification.[10] Per this classification scheme, none of our patients were in the high-risk group, 14 (54%) had intermediate risk, and 12 (46%) had low-risk prostate cancer.

Of the 26 patients who had complete follow-up data available, the Gleason score was ≤7 in all patients.

The median PSA level for total gland, salvage, and focal-treatment patients was 6.9 (1.8–15.9), 5.17 (2.5–5.7), and 5.8 (4.7–8.2) ng/mL, respectively. Of the 17 patients in the primary group, with the exception of the focal-therapy

**Table 1.**
Patient Demographics

| Characteristic | Value (% of total when applicable) |
|---|---|
| Age (y) | |
| Median | 68 |
| Range | 54–89 |
| Indication | |
| Primary treatment (total) | 21 (80.7) |
| Total cryotherapy | 17 (65.3) |
| Focal cryotherapy | 4 (15.38) |
| Salvage cryotherapy | 5 (19.23) |
| Baseline PSA (ng/mL) | |
| Median | 5.5 |
| Range | 1.7–15.9 |
| TRUS volume (mL) | |
| Median | 35 |
| Range | 14.6–54 |
| Gleason Score | |
| 3+3 | 13 (50) |
| 3+4 | 10 (38) |
| 4+3 | 3 (11) |
| D'Amico risk group low | 12 (46) |
| Focal | 4 (33) |
| Salvage | 2 (16.6) |
| Primary | 6 (50) |
| D'Amico risk group intermediate | 14 (54) |
| Focal | 0 |
| Salvage | 3 (21.4) |
| Primary | 11 (78.57) |
| D'Amico risk group high | 0 |

group, 11 had comorbidities that precluded robotic radical prostatectomy and/or external beam radiation.

The median volume of the prostate was 35 (17–52) mL for the total gland primary group treatment, 25 (14.6–32) mL for salvage cases, and 48 (44–54) mL for the focal group.

Furthermore, 11 of the 17 patients in the primary treatment group (64.7%) had pre-existing ED, 3 patients (17.64%) reported no problems, and 2 patients had unrecorded data for this dysfunction.

For the salvage patients, all reported ED before cryotherapy. One of the 4 patients in the focal-therapy group (25%) reported ED before therapy.

**Table 2.**
Comorbidities of Total Cryotherapy Group

| Comorbidities | Value (% of total) |
|---|---|
| Total patients with comorbidities | 11 (64.7) |
| Neurological disorders | 2 (18.18) |
| Morbid obesity | 1 (9.09) |
| Pelvic radiation | 1 (9.09) |
| Kidney/pancreas transplant | 2 (18.18) |
| Ileoanal pouch | 1 (9.09) |
| Renal failure | 1 (9.09) |
| Advanced age | 3 (27) |

Preoperative AUA symptom scores were available in half of the total study population, with a median score of 7 (range 0–17), and the median follow-up for our study was 18 months (range 1–40).

None of the patients in the total gland primary treatment group had biochemical failures at last follow-up. Two patients from the salvage group (40%) had biochemical failures requiring salvage hormonal therapy. None of the patients in the focal-therapy group had biochemical failure or recurrence on repeat biopsy.

The cryoablation was tolerated well by all patients, with no intraoperative complications. Similarly, no patients experienced postoperative complications, including urethroectal fistula, urethral stricture, chronic pelvic pain, or urinary retention.

## DISCUSSION

Our report presents a single-institution study of 30 consecutive patients treated by a single surgeon who used third-generation cryotechnology to treat prostate cancer (PCa) as primary, focal, or salvage therapy. Cryotherapy represents another notch in the evolutionary timeline of clinical therapy for prostate cancer and is increasingly being used as an alternative to the current surgical "gold standard" for treatment of prostate cancer, radical prostatectomy.[11] As mentioned previously, cryotherapy was approved for Medicare reimbursement in 1999, yet its implementation as part of clinical practice has been slow as evidenced by a low overall rate of physician application. Thus, the data for long-term outcomes of cryotherapy are limited, but there are an increasing number of reports in the literature of recent years that may provide more insight into the role of cryosurgery in the treatment of prostate cancer. Therefore, our study, although small, provides another glimpse at the early outcomes of cryotherapy for prostate cancer.

A major goal of our study was to showcase the possible role of cryotherapy as treatment for patients with comorbidities defining them as poor candidates for surgery or radiation therapy. As shown in Table 1, of the 17 patients in our total cryotherapy group, 11 had known significant comorbidities at the time of treatment. These included neurological disorders, morbid obesity, rectal cancer status postradiation, kidney/pancreas transplant, ileoanal pouch secondary to IBD, renal failure, and advanced age. In our short-term follow-up, none of these patients had biochemical failure.

Neither the American Urological Association (AUA) nor the European Association of Urology (EAU) recognizes any absolute contraindications to robotic-assisted laparoscopic prostatectomy, but both organizations state that certain conditions can be challenging. Two of the comorbidities that we encountered, obesity (BMI >30) and history of pelvic surgery/radiation, are known to create challenges for even the most experienced surgeons and thus can be potentially limiting factors in surgical management of PCa.[5,12] Robotic-assisted radical prostatectomy (RARP) in this patient population has a significantly higher complication rate and poorer functional outcomes such as urinary continence than other options.[12] Given the difficulties with primary treatment in these clinical situations, cryotherapy may offer an excellent alternative mode of therapy. Furthermore, our preliminary results specifically with this patient population offer encouraging oncologic outcomes without significant post-treatment functional sequelae at 18 months.

Prostate cancer is increasingly prevalent in the elderly population, and guidelines for both cryotherapy and RARP state that therapy should be undertaken only in patients with a life expectancy >10 years. Such an indication can potentially limit therapy options for patients with advanced age but excellent functional status and potential longevity. Recent literature, however, shows that prostate cancer-specific survival is consistent with previous estimations regardless of age at therapy initiation. For example, Labanaris et al.[13] found that patients aged >75 years undergoing RARP could potentially experience only ~4.5% biochemical recurrence at 17 months, which was consistent with the literature findings of 6% recurrence at 10 years. Our study group had 6 patients who were 75 years or older with an average follow-up of 18.8 months, none of whom has experienced biochemical failure. This further supports cryotherapy as a viable alternative to RARP with similar results in patients 75 years and older who seek a treatment option for their condition.

Of the 5 patients who underwent salvage cryotherapy after initial radiation therapy, 2 (40%) experienced biochemical failure with a mean follow-up of 20.8 months. Our disease-free survival of 60% at 20.8 months is consistent with previous findings of 55% and 57% at 5 years by Pisters and Wenske, respectively.[14,15] Because of our limited sample size, the value of our data is diminished in comparison with previous studies, yet the consistency in results lends more confidence to the literature. It is also worth noting that none of our 5 patients experienced any significant postoperative complications, an occurrence that warrants a more thorough study.

None of our 4 patients who underwent focal cryotherapy for localized PCa experienced recurrence on repeat biopsy with a mean follow-up of 24 months. This outcome once again points toward a favorable short-term profile of prostate cryoablation outcomes and is consistent with previous studies demonstrating disease-free survival between 84% and 94% with a minimum follow-up of 28 months.[16] Furthermore, all 3 of our patients who were potent before having focal cryotherapy maintained satisfactory erectile function after treatment. Although focal cryotherapy is in its relative infancy, our results suggest that focal cryotherapy for localized PCa may be a viable alternative to other primary treatment modalities.

## CONCLUSION

Our study represents the experience of one surgeon at a large-volume academic center using cryotherapy as primary total gland therapy, salvage therapy after radiation failure, and focal ablation for localized prostate cancer. We found that cryotherapy is a viable means of primary therapy of PCa patients and can be an excellent option in those patients who have comorbidities that preclude them from safe execution of more traditional means of therapy. Our study also shows that cryotherapy shows promise as a medium for salvage therapy and focal ablation of localized PCa. It is especially encouraging considering there were no intra- or postoperative complications even when applied to a complicated patient population more susceptible to such events. Ultimately, we believe that cryotherapy can benefit from more studies with longer follow-up times.

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