

Cryoablation of the prostate

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Carcinoma of the prostate is the most commonly diagnosed cancer in North America. It accounts for one in three newly diagnosed cases and is the second most common cause of cancer death in males (1). Widespread PSA screening has resulted in proportionally more men being diagnosed in the early stages of disease when a cure is possible. However, the optimal management strategy for localized cancer remains unclear and is confounded by the myriad of available treatments and lack of objective comparisons between them.

Radical prostatectomy and beam radiation therapy are historical standards of care and other treatments such as brachytherapy, conformal radiation therapy, intensity modulated radiation therapy and cryoablation have been added to the armamentarium used to battle prostate cancer.

Technology: this is not your grandfather's cryo

Since the reintroduction of cryoablation in the early 1990s, several significant technical and procedural advances have occurred, including the development of vacuum insulated cryoprobe, the introduction of systematic temperature monitoring, the evolution of intraoperative treatment planning systems and, most recently, the development of a temperature feedback automated freezing system. Each of these innovations has been

designed to assist the physician in learning and performing the three fundamental steps involved with prostate cryoablation:

1. planning the procedure based upon individual patient anatomy,
2. placing the cryoprobes and thermocouples within the prostate, and
3. freezing the prostate such that the cancer is destroyed without compromising sensitive adjacent structures such as the external sphincter, urethra and rectum.

These technical advances can be used piecemeal, in concert, or not at all, depending on the experience and skill of the physician performing the procedure and individual patient anatomy.

Smaller Cryoprobes

Most published reports establishing prostate cryoablation as a therapy with durable safety and efficacy have been based on patients treated with blunt tipped 3.4 mm diameter cryoprobes. Insertion of cryoprobes of this size necessitates the use of a dilation system that results in the consumption of a significant amount of operating room time for the less experienced physician. Cryoprobes 2.4 mm in diameter with vacuum insulated shafts are now available with thermal profiles nearly identical to those produced by 3.4 mm cryoprobes (< 1mm changes in isotherm locations).

Treatment planning

a. Placement logic

In-vivo human studies have shown that reaching a temperature of $-40\text{ }^{\circ}\text{C}$ on two successive freeze thaw cycles ensures ablation of prostate carcinoma tissue (2).

Therefore, prostate cryoablation is performed with the goal of exposing the entire gland to a temperature of $-40\text{ }^{\circ}\text{C}$ or lower while minimizing cold exposure of the rectum and external sphincter to avoid collateral damages. Determination of an optimal probe placement is a mathematical problem. The available planning algorithm utilizes the four accepted 'rules' of cryoprobe placement as reported by Ellis in 2002 (3):

1. Cryoprobes should not be placed more than 2.0 cm apart,
2. Cryoprobes should not be placed more than 1.0 cm from the margin of the prostate,
3. The distance between the urethra and any cryoprobe should not be less than 0.8 cm, and
4. The posterior cryoprobes should be placed such that their separation is less than twice the distance to the posterior capsule of the prostate.

b. Mapping patient anatomy and determining cryoprobe placement

An ultrasound transducer mounted to a stepper that is fixed in space relative to the patient is used to serially image the longitudinal plane of the prostate. Collected images are transferred to a treatment planning system. Image recognition software is used with the aid of anatomic reference points defined by the user to determine the geometric anatomy of the prostate, urethra and rectum. Utilizing this information the system generates an optimization probe placement. A brachytherapy like grid that allows for angled cryoprobe placement can be attached to the ultrasound stepper and used to assist with cryoprobe placement. Cryoprobes are inserted through the perineum and advanced to the base of the bladder in the sagittal plane. The grid can be removed from the platform and the stepper and then the ultrasound probe can be used freehand, unobstructed by a stepper or grid. Because the grid is lightweight plastic, it will not pull the probes out of the body when released from the platform. Experienced physicians may bypass this time consuming procedure and can place the cryoprobes by free hand, yet satisfying the basic “rules”.

Systematic Temperature Monitoring

The fundamental advancement that sparked renewed interest in prostate cryoablation was the use of real time ultrasound to visualize cryoprobe placement and iceball growth. Ultrasound, however, is not without limitation. Ice has an acoustic impedance much different than that of soft tissue. Consequently, nearly all the incident acoustic signal is reflected when the wave reaches the frozen/unfrozen interface. This allows for excellent visualization of the hyperechoic line representing the proximal iceball edge but the user is rendered blind to all distal anatomy as no signal is returned from structures within or

beyond the iceball. Temperature monitoring is used to overcome this acoustic shadowing effect.

Prior to the commencement of the freezing process, thermocouples are placed at strategic locations within and around the prostate. They are used to both ensure that adequately cold temperatures are reached within the prostate and that sensitive adjacent structures, namely the rectum and external sphincter are maintained at temperatures warm enough to ensure maintenance of their structural and functional integrity.

Automatic freezing

Keeping track of the power settings of six to eight cryoprobes, thermocouple temperature readings and progression of the iceball as visualized on ultrasound can be a daunting task for beginners. As such, automatic freezing software allows targeted temperatures to be inputted by the user as been developed. The physician selects the target temperature for each thermocouple. Typically, this is $-40\text{ }^{\circ}\text{C}$ for the thermocouples placed in zones to ensure ablation and $> 0\text{ }^{\circ}\text{C}$ for those placed in sensitive structures to ensure their preservation. All cryoprobes are controlled by a computer, which determines the optimal cryoprobe power settings based upon real time temperature feedback from the thermocouple tips. Freezing commences in an anterior to posterior manner to maximize transrectal ultrasound visualization. If at any point during the procedure the temperature reading of any thermocouple placed in a sensitive structure drops below the safety margin set by the user, all probes stop freezing and begin to actively thaw to ensure no damage.

The freezing process must still be monitored carefully by the physician and can be overridden at any point allowing the physician to stop the freeze or continue to freeze manually controlling the cryoprobe power settings. Many experienced physicians do not utilize this automatic freezing technique. They can actually sculpture the ice to make an exact fit for the prostate, resulting in a complete ablation. It is indeed an art form.

Efficacy and Morbidity

In deciding what treatment is best for them, the individual patient in concert with his physician balances the perceived risks and benefits associated with each treatment option. No therapy can guarantee a cure and unfortunately, no therapy can promise complete maintenance of quality of life. Many factors are taken into account when choosing a treatment including the stage and aggressiveness of the cancer, age, life expectancy, physical and sexual activity level and co-morbidities. The treatment decided upon is a balance of the patient's acceptance of cure probability, tolerance of potential morbidities and long-term quality of life impact.

Primary cryoablation

Randomized prospective clinical trials comparing the efficacies and morbidities of primary prostate cancer therapies are lacking. As such, unflawed comparisons of different treatment modalities are complicated by comparisons of often retrospective, single-

institution case studies with non-uniform patient selection. Further, definitions of biochemical failure (PSA based failure) vary from study to study. That being said, comparisons looking at trends in efficacy and morbidity are certainly possible and are merited.

Fortunately, many institutions have reported outcomes following prostate cancer therapy with patients stratified according to risk group. This is done by reviewing three fundamental disease state measurements: stage, Gleason sum and PSA. Each of these can be considered to be favorable or unfavorable. A favorable stage is T2a or less. Favorable Gleason sum and PSAs are < 7 and < 10 ng/ml, respectively. Low risk disease has no unfavorable characteristics, moderate risk has one and high risk has two or three.

In 2003, Katz and Rewcastle presented an analysis of the literature based upon all studies published as full manuscripts in the peer reviewed literature over a 10 year period that reported five year Biochemical Disease Free Survival (BDFS) rates following definitive prostate cancer intervention (4). Although there wasn't consistency in the definition of BDFS, the analysis was intended to look for trends and was not designed to conclusively compare the different therapies.

Figures 1 through 3 show the published range of BDFS for each therapy observed five years following treatment for low, moderate and high risk prostate cancer, respectively. Excellent local and systemic control is achieved with all therapies for low-risk disease.

Given the relative equivalence in efficacy, the treatment decision for this risk group should be based heavily on morbidity and quality of life factors.

Figures 2 and 3 compare the range of reported BDFS for patients with moderate and high-risk disease. Comparing with Figure 1, a drop in efficacy is observed for all therapies with increasing disease risk. However, the drop is not as substantial for cryoablation as it is for both surgical and radiation series. Based on this comparison, the efficacy of cryosurgery appears to be at least equivalent to all forms of radiation therapy and surgery for moderate and high risk patients.

Another measure of efficacy is the positive biopsy rate which was also reviewed by Katz and Rewcastle(4). The positive biopsy rates recently reported following cryoablation have been reported to be between 2 and 18%. The mean follow up of these studies was 5.1 and 2 years, respectively. The positive biopsy rates reported in the literature for brachytherapy, conformal beam radiation, and external beam radiation tend to be higher. Studies of brachytherapy found positive biopsies to range from 5-26%, with mean follow-up periods of 18 months to 10 years. One study reporting positive biopsy rates following conformal beam radiation found it to be 48% at a mean follow-up of > 30 months. Following external beam radiation therapy the rates ranged from 20%-71%, with a mean follow-up of 2-6.8 years. However, positive biopsy rates following radiation therapy can be misleading as radiation protocols are continuously changing and these rates may reflect outmoded dosing strategies.

It can be concluded that the efficacy of cryoablation is at least equivalent to radical prostatectomy and all forms of radiation therapy. It also appears to be superior in the treatment of higher risk disease. Katz and Rewcastle provided a hypothesis as to why this may be so. There are two fundamental shortcomings to the standard therapies that can limit their ability to effectively treat locally extensive or biologically aggressive prostate cancer: positive margins observed after radical prostatectomy and the preferential killing of lower Gleason grade cancer by radiation therapy. The ability of radical prostatectomy to cure prostate cancer is defined by its ability to remove all tumor cells. Following prostatectomy, positive surgical margin rates are observed in up to 40% of patients. Lateral freeze beyond the capsule of the prostate is usually done during cryoablation in case there is microscopic capsular penetration by the tumor. Seminal vesicle freezing is also possible if tumor involvement is confirmed. This decreases the probability of cancer remaining in the patient. The disease extent defines how aggressively the user freezes laterally.

Radiation therapy ablates tissue by damaging the nucleus of individual cells. The more aggressive the cancer is, the harder the cells are to kill. Certainly any cell will be irreversibly damaged if exposed to enough radiation but the sensitivity of the anatomic neighborhood of the prostate limits the lifetime dose of radiation that can be delivered to the gland. Clinical results indicate that efficacy of radiation therapy declines significantly if a patient's Gleason score is greater than 7 or has an aneuploid tumor. In fact, if cancer recurs following a trial of radiation therapy it is often a more aggressive form, which indicates a preferential killing of less aggressive cells only to leave those that are more

radioresistant. Recently, Bahn and his colleague reported that the efficacy of cryoablation is independent to the ploidy. Cryoablation offers mechanical destruction of tissue by forming a lethal iceball and ischemic necrosis by interrupting the blood flow during the procedure.

Procedural and technical advances, along with increasing experience of individual physicians have resulted in a steady decline of cryoablation morbidity. Urethrorectal fistula was a great concern during cryoablation. Of the three latest cryoablation studies (5-7), only one found rectal complications (Bahn et al with fistula < 0.1%). This is directly related to an increased use of temperature monitoring of the Denonvillier's fascia and improved ultrasound technology. Incontinence in the three studies ranged from 1.3% to 5.4% and rates of post operative impotence ranged from 82.4% to 100%.

Table 1 compares the different forms of rectal injury and their rates for the different therapies (4). Urinary morbidity among radical surgery patients included permanent incontinence in 7-52%, while urinary morbidity among brachytherapy and beam radiation patients included incontinence ranging from 0-19% and 0-15%, respectively. Impotence occurred at a rate of 51-96% in radical surgery studies, and at a range of 50-61% and 14-66% in beam radiation and brachytherapy studies, respectively.

A three year prospective quality of life impact analysis is available following cryoablation (8). The authors administered two scales, the FACT-P, and the SNQ. A return to pre-surgical functioning in all areas, with the exception of sexual functioning

was observed one year post cryoablation. At three years, 47% of impotent men who were previously potent prior to the procedure returned to having intercourse with or without assistance. All other areas of functioning remained high. There was no delayed-onset morbidity associated with cryoablation. These results imply that post cryoablation quality of life is comparable, if not superior, to that of other treatments.

Salvage cryoablation

Radiation therapy is widely used to treat localized prostate cancer. However, recurrence and residual disease have been recorded in 25% to 93% of radiation cases and the procedure may not be repeated (9). The unique characteristics of radioresistant prostate cancer leave patients with limited options if the disease does recur. Primary radiation therapy results in micro and macroscopic tissues changes that often result in the unfortunate situation of aggressive disease located in a challenging surgical environment. Radical prostatectomy following failed radiation therapy can be performed with curative intent but is associated with significant morbidity. Hormonal therapy (androgen deprivation) may reduce tumor size and slow the growth but is ultimately not curative and is too associated with significant quality of life impact. Considering the limitations of these treatments, an alternative approach to cure recurrent prostate cancer with minimal morbidity is desired. Significant interest in the potential ability of cryoablation to fill this therapeutic void has resulted in much work in the past decade that has established cryoablation as the preferred therapy for localized radiorecurrent prostate cancer.

Comparing the outcomes of salvage cryoablation and salvage radical prostatectomy is limited to comparing similar reports. Again, no comparative trials exist. Table 2 lists the ranges of BDFS, rectal injury and incontinence as published in the literature. For both therapies, the efficacy is lower and morbidity higher than that when prostates that have not been irradiated are treated. Efficacies appear to be similar and a conclusion other than equivalence would be inappropriate. The difference arises when one looks at the morbidity. Although statistical comparison would be ineffectual the differences are compelling: essentially five and ten fold reductions in rectal injury and incontinence rates, respectively.

Although patients are carefully assessed prior to salvage therapy, be it cryoablation or radical prostatectomy, occult metastatic disease remains a concern. Treatment failure is often thought to be due to micrometastatic disease overlooked in salvage therapy work-up. These micrometastatic cells, found most often in bone marrow or lymph nodes, spread concurrently with radiation treatment and being outside of the prostatic capsule, remain beyond the realm of any salvage prostate cancer treatment. Several studies have correlated an elevated Gleason score in the primary tumor with an increased prevalence of micrometastatic cells and reverse-transcription polymerase chain reaction amplification of PSA mRNA has been proven to characterize metastatic cell proliferation. Cher et al. have found an association between androgen ablation and a reduced prevalence of metastatic cells that could be useful in adjuvant primary therapies (10). A phenotypic characterization assay performed in addition to standard bone scans would detect distant metastases earlier and improve treatment plans in patients likely to have

micrometastatic bone marrow or lymphatic cancers. It is plausible that patients who fail definitive salvage therapy may have an etiology based on preexisting extracapsular or systemic cancers. With more careful screening and patient work-up, the success of cryosurgery to fully ablate localized radioresistant cancer may be greater than reported.

Personal Experience

We have published 7-year outcomes of 590 patients who underwent cryoablation as a primary prostate cancer therapy (5) and 59 patients who had the procedure following biopsy proven post radiation therapy recurrence (9). A summary of these results are contained in table 3.

As a primary therapy the results are comparable or superior to the rates of efficacy of all conventional radiation therapy modalities for prostate cancer. There are also other advantages to cryoablation in comparison to conventional prostate cancer therapies. The procedure is extremely well tolerated. Only a short hospital stay is required with most patients being discharged within 24 hours. Cryoablation provides hope for those patients with locally advanced prostate cancer due to its ability to ablate laterally outside the glandular margin. It is also possible to ablate the seminal vesicles allowing the treatment of stage T3 disease. An interesting psychology is at play after the procedure. In terms of quality of life and continence specifically, patients tend to improve over time. This yields a patient who tends to be happier than one whose morbidity increases or quality of life decreases following the procedure as can occur after radiation therapy (regardless of

delivery modality). Impotence post procedure was high in our series. This was not surprising as the average age was 71 years and many patients had aggressive and/or bulky disease. Recent reports indicate that impotence post procedure may not be as high as once thought when baseline and post procedure sexual function is objectively quantified. There are no known latent complications following cryoablation. We believe that the results we and others have published will lead to a greater acceptance and utilization of cryoablation as a primary treatment option for localized prostate cancer.

Recurrent prostate cancer following definitive radiation therapy tends to be extremely aggressive and dangerous. We have found that salvage cryosurgery is a promising form of treatment and we routinely offer it to patients who have failed radiation therapy. Our 7-year data shows biochemical control rates comparable with salvage radical prostatectomy series. The compelling case for salvage cryoablation is when one considers the morbidity associated with both procedures. Incontinence and rectal injury rates following salvage radical prostatectomy are significantly higher. Indeed some cryoablation series have been published with high incontinence and fistula rates but these should be considered historic and are not reflective of outcomes achieved with the modern procedure performed with advanced technology. Cryoablation is a curative therapy with acceptable morbidity for a very hard to manage patient population. We encourage physicians to follow patients treated with radiation therapy closely as there is a window of opportunity in which the disease is still localized and a cure is possible.

Conclusion:

Technical and procedural modifications of cryoablation have led to a procedure today that is very different than what it was ten years ago. It is a minimally invasive procedure, requiring a short hospital stay, with most patients discharged within 24 hours. Modern cryoablation, as a definitive therapy for both primary and radiorecurrent prostate cancer, is associated with minimal morbidity and no known latent complications. In fact, quality of life seems to continually improve following the procedure.

Cryoablation should be considered as a viable option for any patient who has been diagnosed with localized prostate cancer. Like all other options, it is not best for everyone but certainly there is sufficient evidence that it should be considered by everyone.

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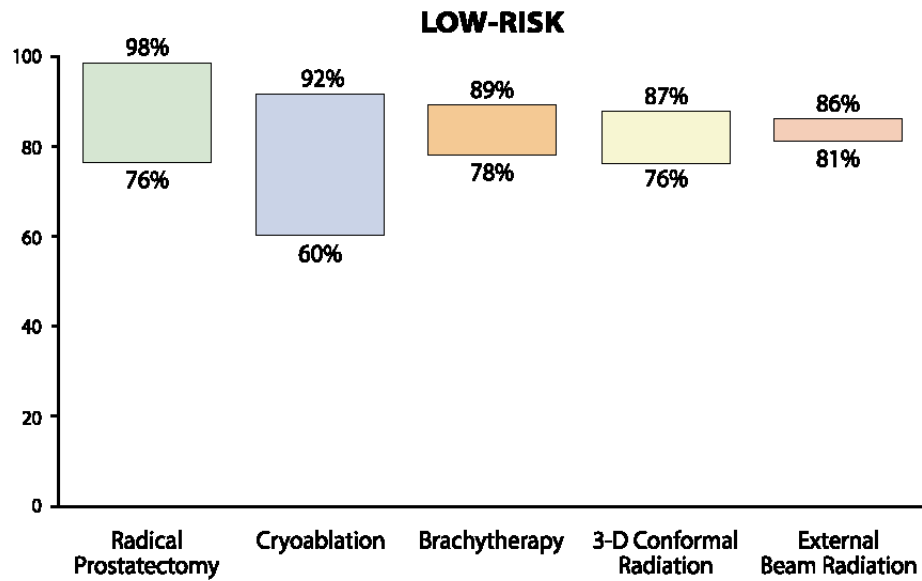


Figure 1: Comparison of Biochemical Disease Free rates for low-risk disease

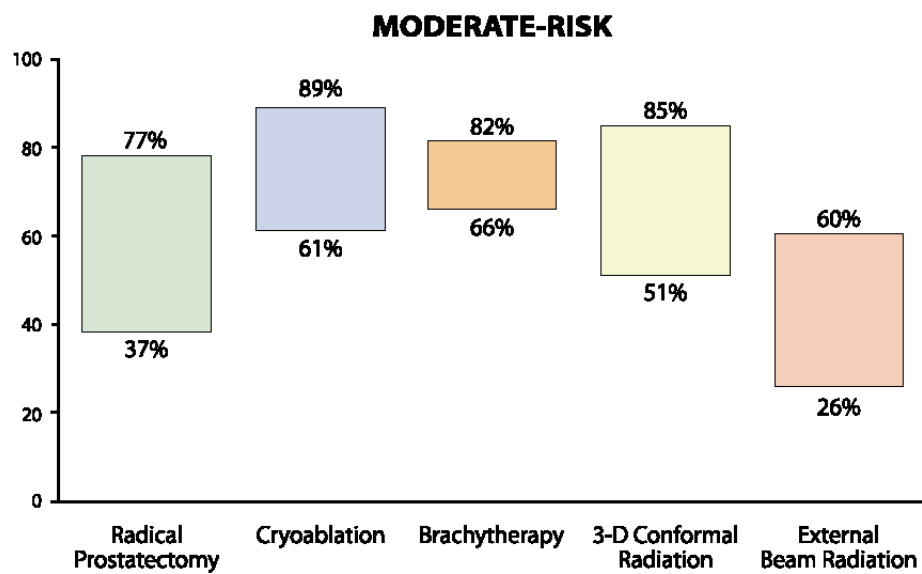


Figure 2: Comparison of Biochemical Disease Free rates for moderate-risk disease

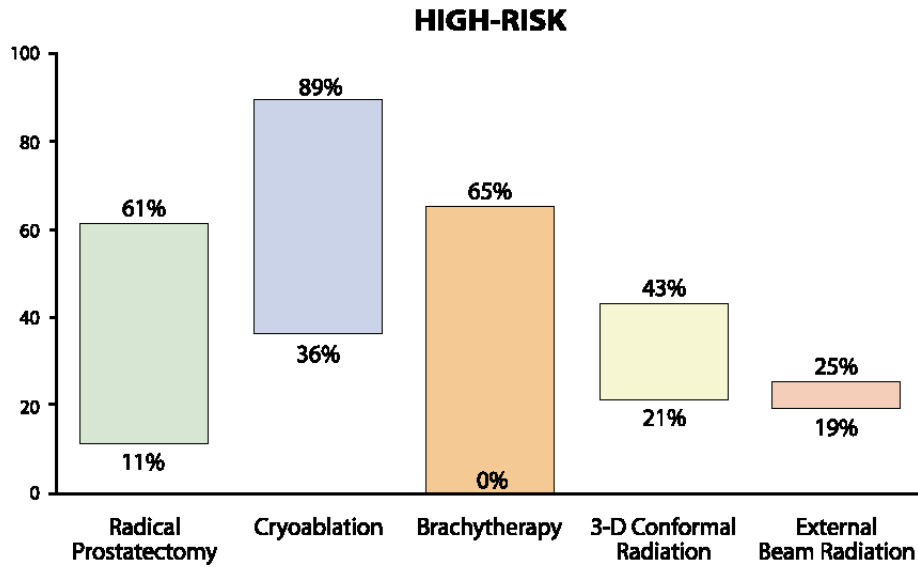


Figure 3: Comparison of Biochemical Disease Free rates for high-risk disease

Table 1: Comparison of the range of published rectal injury rates following definitive prostate cancer therapy

	Fistula	Urgency	Bleeding	Diarrhea
Radical Prostatectomy	1-3 %	6-16 %	1-3 %	6-19 %
Beam Radiation		19-43 %	13-17 %	12-42 %
Brachytherapy	0-3 %		4-11 %	
Cryoablation	0-0.5 %			

Table 2: comparison of published ranges of BDFS, rectal injury and incontinence rates following salvage cryoablation and salvage radical prostatectomy

	Salvage Cryoablation	Salvage Radical Prostatectomy
BDFS	59 – 69 %	30 – 82 %
Rectal injury	0 – 2 %	1 – 10 %
Incontinence	4.3 – 7.9 %	0 – 64 %

Table 3: Summary of our personal cryoablation experience

		Primary	Salvage
n		590	59
median PSA		6.8 ng/ml	5.6 ng/ml
median Gleason		7	7
median stage		T2b	T2c
7-year BDFS	ASTRO	89%	N/R
	PSA < 1.0	76%	69%
	PSA < 0.5	62%	59%
Negative biopsy rate		87%	100%
Incontinence		4.3%	8%
Fistula		<0.1%	3.4% (early in experience)
Impotence		95%	N/R

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