Prostatic Cryoablation:

An assessment of current and future efficacy

Abstract

Prostatic cryoablation, the use of cold in the treatment of prostatic carcinoma, was first practiced during the 1960s, and, as a result of various technological advances and procedural refinements, has been regularly employed in clinical practice for the past two decades. Short-term outcomes data from recent clinical studies indicate that, in the treatment of high-risk prostatic carcinoma, cryoablation is comparable to more frequently practiced radiation therapies in terms of local disease control and acceptable complications frequency. Although the absence of long-term outcomes data prevents prostatic cryoablation from being recommended as a first-line treatment method for prostate cancer, the positive clinical results obtained thus far warrant further research and investment in this promising therapy.
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Introduction

Aside from lung cancer, prostate cancer kills more American men each year than any other form of cancer. One in six men will contract prostate cancer during their lifetime\(^33\). The National Cancer Institute estimates that in 2009 there will be 192,280 new cases and 27,360 deaths\(^27\). Fortunately, prostate cancer diagnosis and treatment methods have improved drastically over the years, but there is still a pressing need for more versatile and effective therapies\(^33\).

One of the most recent and exciting prostate cancer therapies is prostatic cryoablation, the application of cryosurgery to prostate cancer. Using the basic principles of cryosurgery, the therapeutic use of cold to destroy tissue, surgeons treat prostatic tumors by using super-cooled cryoprobes to freeze and kill malignant cells. Although this treatment is still considered experimental by some members of the medical community, it has been regularly practiced by surgeons throughout the past two decades.

Through a review of the basic biological principles behind cryosurgery and an analysis of recent clinical studies involving the use of prostatic cryoablation, this report seeks to assess the current efficacy and future potential of prostatic cryoablation in modern clinical practice.

History of cryosurgery

Cold has played an important role in medical practice for thousands of years. Even the ancient Egyptians and Hippocrates used cold as an anesthetic and anti-inflammatory treatment. However, it wasn’t until the mid-19\(^{th}\) century that James Arnott, an English physician, employed cold for the specific purpose of destroying tissue\(^10(p196)\). Using a mixture of salt and crushed ice at temperatures as low as -24°C, Arnott was able to reduce the size of tumors in accessible locations\(^15(p99)\).

While Arnott’s efforts were largely directed at inhibiting tumors’ growth and virility, he also understood the potential application of extreme cold held for providing cures\(^10(p196)\). He asserted that, “congelation arresting the accompanying inflammation, and destroying the vitality of the cancer cell, is not only calculated to prolong life for a great period, but may, not improbably, in the early stage of the disease, exert a curative action”\(^15(p99)\).

During the next century, the destructive application of extreme cold, cryosurgery, became more sophisticated with the use of liquid air, solid carbon dioxide, and liquid oxygen\(^17(p100-102)\). Then, in 1961, a major cryosurgical breakthrough was made by Dr. Irving S. Cooper, an American neurologist, when he built a liquid nitrogen cryoprobe capable of producing temperatures as low as -196°C—the direct precursor to modern day cryoprobes. Cooper achieved notable success using his cryoprobe to treat Parkinson’s disease and other neuromuscular disorders by freezing the thalamus. The potential application of Cooper’s cryoprobe in the treatment of cancer was immediately apparent and incited significant interest in cryosurgery within the medical community. Soon
cryosurgery came to be accepted as standard treatment in a number of therapeutic areas.

Evolution of prostatic cryoablation

The practice of prostatic cryoablation began when, shortly after Cooper’s breakthrough development of a liquid nitrogen cryoprobe, Gonder et al adapted Cooper’s invention for the treatment of prostatic carcinoma. This procedure’s demonstrated effectiveness in ablating tumors spurred its continued use and development during the 1960s and ‘70s.

First generation cryoablation

During this time, known as the first generation of cryoablation, cryogenic systems featured only a single cryoprobe. Although tissue freezes at about 0°C, temperatures lower than 20°C are necessary to achieve widespread destruction of cancer cells. Thus, while the insertion of a single cryoprobe may be sufficient to encapsulate a large volume of infected tissue in an ice ball, only a small portion of this ice ball is cold enough to ensure cell necrosis. To enlarge this lethal region within the ice ball, the cryoprobe was repositioned several times during surgery creating an overlapping composite freeze zone. However, the absence of effective temperature monitoring techniques made it difficult to determine the distribution of lethal temperatures within this freeze zone and, therefore, difficult to ensure uniform cell necrosis. Some surgeons attempted to mitigate this deficiency by using two cryogenic systems concurrently. Although this method increased efficacy, a large amount of guesswork was still involved in assessing the extent of uniform cell necrosis within the infected area.

The lack of effective temperature monitoring was a widely recognized deficiency of prostatic cryoablation during the 1960s and ‘70s. Freezing was often monitored simply by eyeballing or palpitation, or, as one cryosurgeon recounted, “the junior resident would place his finger in the rectum and the job was done when a tear came to his eye.” Without adequate temperature monitoring methods, surgeons were unable to place cryoprobes precisely or measure the extent of freezing accurately. Serious complications such as urinary incontinence, tissue sloughing, and rectal-urethral fistulae arising from the unintentional freezing of healthy tissue near tumors were unacceptably frequent. As a result, the practice of prostatic cryoablation was largely abandoned until the late 1980s.

Figure 1: Illustration of the freeze zone created by a liquid nitrogen cryoprobe.
Origin and development of cryoprobes

The first cryogenic medical device was created by James Arnott in the late 1840s. This device applied a mixture of two parts ice and one part sodium chloride to accessible tumors, thereby ameliorating pain and hemorrhaging. It consisted of “a waterproof cushion applied to the skin, two long flexible tubes to convey water to and from the affected part and a reservoir for the ice/water mixture and a sump.” In 1851, Arnott displayed his apparatus at the Great Exhibition in London in an exhibit titled “Mode of applying cold as a therapeutic agent” and received a prize medal.

In 1907, Dr. William Pusey, an American physician, developed a method for using carbon dioxide as a cryogen. He used steel cylinders to store liquid carbon dioxide gas under heavy pressure (80 lbs/in²). When he allowed the carbon dioxide to escape into the air, its rapid expansion caused a drastic drop in temperature—in a process called the Joule-Thomson effect—and produced carbonic acid snow. He then compressed this snow into various shapes, known as pencils, suitable for a variety of dermatological applications including the treatment of warts, vascular nevi, and epitheliomas. Adopting Pusey’s technique, Hall-Edwards, a radiotherapist from Birmingham, constructed a carbonic acid snow collecting and compressing apparatus, which he described in The Lancet in 1911.

Two years later, in 1913, Dr. Irving S. Cooper developed a “vacuum-insulated liquid nitrogen-cooled probe” capable of deep tissue freezing. The probe was equipped with controls to adjust the temperature of its freezing surface, facilitating rapid, continual heat extraction from infected tissue. Though Cooper used his probe principally to treat neuromuscular disorders by inducing lesions in the brain, modern day liquid nitrogen cryoprobes, with their myriad therapeutic applications, are based upon the same basic technology as was Cooper’s device.

Although liquid nitrogen cryoprobes are still widely used, many surgeons are now opting for gas-driven cryogenic systems. Harnessing the same relationship between temperature and gas pressure as Pusey’s and Hall-Edwards’s devices (the Joule-Thomson effect), gas-driven cryoprobes use expanding argon gas to produce subzero temperatures.
Then helium—which, unlike argon, warms rather than cools when expanded—is used to rapidly modulate the temperature of the cryoprobe in response to computer-automated input from the surgeon. This system is able to shift temperatures from -186°C to +40°C in approximately 30 seconds.

The use of argon gas instead of liquid nitrogen allows for development of very small cryoprobes (1.5mm diameter), often called cryoneedles. This small size enables surgeons to more precisely map the lethal freezing zone during surgery, thereby further minimizing the risk to adjacent healthy tissue. While argon gas cryoprobes are not able to produce nadir temperatures as low as those of liquid nitrogen ones, their advocates argue that this deficiency can be easily mitigated by the application of additional probes.

![Argon gas cryoneedles being percutaneously inserted into the prostate](image)
Second generation cryoablation

The second generation of prostatic cryoablation began in 1988 with the development of real-time transrectal ultrasound (TRUS)\(^9\)\(^{21}\). Using TRUS, surgeons were able to ensure the proper placement of cryoprobes by monitoring them during insertion and, perhaps more importantly, to protect the rectum and other vital structures by monitoring their temperature during surgery\(^{31}(p27)\).

Another major development, the introduction of a urethral catheter warming device, helped preserve the urethra during cryoablation. The catheter circulates warm saline solution to keep the urethra above freezing temperatures and preserve a thin layer of urethral mucosa. There is evidence that complete destruction of the prostate gland, which is prevented by the catheter, increases the effectiveness of prostatic cryoablation; however, most reports still advocate the use of a catheter because it drastically reduces the frequency of procedural complications, especially urinary incontinence and urethral sloughing\(^{31}(p31)\).

Several years later, in the mid-1990s, thermocouples began to be used adjunctively to TRUS. Thermocouples record when maximum lethal temperatures (\(<40^\circ C\)) have been reached and ensure warmer, nondestructive temperatures are maintained in adjacent structures, particularly in the rectum and external sphincter\(^2(p5)\).

The second generation of prostatic cryoablation also features the application of multiple cryoprobes as standard procedure. Cryogenic systems equipped with multiple 3-mm liquid nitrogen cryoprobes allowed surgeons, through careful probe placement, to create a synergistic freezing effect that produced uniform, effectively distributed lethal temperatures throughout the ice ball. This thermal uniformity greatly increased the lethality of the procedure. Furthermore, the use of numerous, small cryoprobes—in contrast to one or two large ones—enabled surgeons to shape the ice formation around the patient’s unique anatomy, which further reduced the risk of damaging adjacent structures\(^{31}(p29)\).

Third generation cryoablation

The relatively new third generation of cryoablation is characterized by the use of gas-driven cryoprobes rather than those using liquid nitrogen. These cryoprobes use pressurized gas to produce rapid decreases (argon) or increases (helium) in temperature\(^{19(p14)}\). They have two primary advantages over liquid nitrogen systems: First, gas-driven cryoprobes are more responsive to user inputs and, thus, able to raise or lower temperatures more quickly\(^{31}(29-30)\). Second, gas-driven systems permit the use of thinner cryoprobes, which allow for more finely shaped ice formations\(^2(p6)\). Although argon gas driven cryoprobes have been in clinical use since 2000, many surgeons still opt to use liquid nitrogen, often citing its ability to produce lower minimum temperatures\(^1(p928),31(p30)\).

How cold kills cells

As is evident in cases of frostbite, extreme cold harms cells. This harm is caused by two primary mechanisms: injury to cells caused by ice crystal formation during the freezing period and microcirculatory failure occurring during the thawing period\(^{31(p187)}\).
The freezing period

When cells are exposed to freezing temperatures, water in the intracellular areas between the cells freezes. The formation of these extracellular ice crystals creates an osmotic environment that draws water from within the cells, which, in turn, freezes into additional ice crystals. As the ice crystals accumulate, the dehydrated cells shrink. The resulting high concentration of solutes within the cells damages their membranes and organelles. Given sufficient time, this process, known as solution-effect injury, will usually destroy the cells\(^\text{16(p172)}\).

While the formation of extracellular ice crystals certainly poses a significant threat to cells, the formation of intracellular ice is almost always lethal. If cells are exposed to extremely low temperatures rapidly enough, water within the cells will freeze before it can escape through osmosis. These intracellular ice crystals substantially disrupt cell membranes and organelles and nearly always result in cell necrosis\(^\text{3(p1187),16(p172-173),20(42)}\).

How prostatic cryoablation works

The objective of prostatic cryoablation is to freeze the entire prostate gland—thereby, destroying the cancerous cells within it—while leaving the prostatic urethra unharmed. Metal cryoprobes, super-cooled by argon gas or liquid nitrogen, are placed in contact with the prostate gland via percutaneous insertion through small incisions in the perineum\(^\text{7(p201)}\).

The subzero temperatures produced by the cryoprobes create ice balls that engulf the prostate gland and induce tissue necrosis\(^\text{18(p15)}\). To protect the prostatic urethra from these subzero temperatures, a warming catheter is inserted through the urethra into the bladder\(^\text{7(p202)}\). After lethal temperatures have been achieved, the frozen tissue is thawed, and...
then the entire freeze-thaw cycle is repeated\cite{16(p171)}.

The entire prostatic cryoablation process is planned and monitored using TRUS. By emitting sound waves into the body and measuring both the speed and amplitude of these waves when they reflect back, TRUS detects both the size and shape of both organ structures and tumors. This information is used to strategically place cryoprobes and, during freezing, to monitor the temperatures of both the prostate gland and prostatic urethra—because sound travels faster through frozen than unfrozen tissue, ultrasound waves will accelerate when passing through frozen tissue\cite{7(p197)}. Thermocouples are often used to assist TRUS with temperature monitoring in sensitive areas such as Denonvilliers’ fascia and the external sphincter\cite{2(p10)}.

**Advantages of prostatic cryoablation**

When compared to more traditional methods of prostatic cancer treatment, cryoablation offers several distinct advantages:

- It is less invasive. Because only small percutaneous incisions are required, pain, bleeding, and scarring are minimized\cite{11,21(p8)}.

- The duration of surgery and recovery time are shorter. Cryoablation can usually be performed as an outpatient procedure with surgery lasting two to three hours and, when hospitalization is required, it is usually only for one day. Most patients are able to return to normal activity two weeks after the surgery\cite{2(p43)}.

- It is less expensive\cite{11}.

- Fewer anesthetics are needed—the cold itself acts as an anesthetic\cite{21(p8)}.

- Healthy tissue can usually be left unharmed. Unlike chemotherapy or radiation therapy, cryoablation affects only a targeted area, which reduces the likelihood that healthy cells will be destroyed\cite{11}.

- It is more tolerable to the body. Because cryoablation is localized and less physically demanding than traditional treatment methods, it can be used for patients who, because of age or medical complications are poor candidates for other types of treatment\cite{11}.

- The treatment can be repeated if it is not effective initially\cite{11}.
Disadvantages of prostatic cryoablation

Despite the many advantages mentioned above, there are several drawbacks to prostatic cryoablation. Perhaps the most significant of these is the uncertainty surrounding the procedure’s long-term effectiveness. Long-term clinical outcomes data is currently minimal, so the effectiveness of cryoablation at halting microscopic cancer spread is still unknown. Because of this lack of concrete data, many members of the medical community still regard cryoablation as strictly experimental, which may limit insurance coverage for the procedure. Lastly, prostatic cryoablation is associated with several potential complications that can significantly affect a patient’s life after treatment.

Complications

There are a number of adverse side effects associated with prostatic cryoablation; however, the most significant ones are urethral sloughing, urinary incontinence, urethrorectal fistula, and impotence. Fortunately, advances made during the second and third generations of cryoablation have substantially reduced the frequency of most of these complications.

Urethral sloughing

The most frequent serious side effect of cryoablation is urethral sloughing. Sloughing is the separation of dead tissue from healthy tissue. When cell necrosis is induced by lethal temperatures during cryoablation, small clumps of dead tissue may fall into the urethra. This tissue may cause urinary obstruction and, in some cases, require medical treatment. The use of a warming catheter during cryoablation greatly reduces the occurrence of urethral sloughing.

Urinary incontinence

Another potential side effect is urinary incontinence. The urethra and urinary sphincter may be damaged during cryoablation, resulting in some loss of control over urinary function. Urinary incontinence may be characterized by leaking or a complete loss of urinary control; medical treatment may be necessary in more severe cases.

Urethrorectal fistula

One of the more serious and rarer possible complications of cryoablation is urethrorectal fistula. Urethrorectal fistula occurs when widespread tissue necrosis causes an unnatural channel to form between the urethra and rectum. This channel allows urine, ejaculate, and fecal matter to flow freely between these two structures, causing significant problems. The unacceptably high frequency of urethrorectal fistulae led to the abandonment of cryoablation in the mid-1970s until the development of TRUS in 1988 greatly reduced their occurrence.

Impotence

Impotence, the inability for men to perform sexual intercourse, is a very common immediate side effect of cryoablation. Because
the entire prostate gland is engulfed within an ice ball during cryoablation, neurovascular nerve bundles that control erections are nearly always severely damaged. However, these nerve bundles can often regenerate over time, particularly in younger men, restoring sexual function\textsuperscript{5(p45),27}.

### Primary cryoablation

While still not a first-line recommended treatment for prostatic carcinoma, cryoablation is now widely recognized as a valid, minimally invasive primary treatment option that may be best for some patients.

### Patient selection

Prostatic cryoablation has been considered a viable treatment alternative for all stages of clinically localized prostatic carcinoma; however, because cryoablation is a focal treatment, it is generally not effective against metastatic carcinomas\textsuperscript{3(p11)}. Cryoablation is most often recommended for patients with high-risk carcinomas (defined as PSA >10 ng/mL, Gleason score >6, or stage T2 or higher) or for patients who are poor candidates for radical prostatectomy or external beam radiotherapy due to preconditions such as rectal disorders, obesity, or a prior history of pelvic surgery\textsuperscript{2(p12),5(p43)}.

However, when determining whether prostatic cryoablation is appropriate for a given patient, a wide variety factors must be considered including:

- the characteristics of the tumor
- the patient’s life expectancy
- the patient’s desire for long-term cancer control
- the patient’s fear of complications
- the patient’s desire to avoid invasive surgery
- the time the patient is able or willing to commit to treatment and recovery

In many cases, patients may choose cryoablation to avoid the extensive hospitalization and discomfort associated with more invasive treatment methods, even if the potential for long-term cancer control is lower\textsuperscript{5(p43)}.

#### PSA levels, Gleason grades, and T stages

PSA levels, Gleason grades, and T stages are useful metrics for assessing different characteristics of prostatic tumors. They are often used compositely to evaluate the overall threat and prognosis of individual cases.

#### PSA levels

Prostate-specific antigen (PSA) is a protein enzyme involved in the liquefaction of semen. It is manufactured exclusively in the prostate gland, and, under normal conditions, is only present in other parts of the body in very small amounts\textsuperscript{28}.

Cells lining the lumen of the prostate gland are tightly-packed together to serve as a barrier between the prostate and adjacent blood vessels. However, a developing tumor will generally disrupt this tightly-packed formation, allowing greater quantities of PSA to leak into the blood stream. Thus, elevated PSA levels in the blood may indicate the presence of cancer\textsuperscript{28,33}.

#### Gleason score

Gleason scores are used to measures the aggressiveness of prostatic tumors and, thus, the probability that they will spread to other
organs. Once a biopsy is performed, a pathologist will assess the microscopic tumor patterns found in the specimen and, “based upon the degree of loss of the normal glandular tissue architecture (i.e. shape, size, and differentiation of the glands),” assign them a grade using the following scoring system:

**Pattern 1:** Pale glands beginning growing closely together.

![Pattern 1](image1)

**Figure 7:** Pattern 1 cancer cells.

**Pattern 2:** Glands are more loosely aggregated and may invade surrounding muscle tissue.

![Pattern 2](image2)

**Figure 8:** Pattern 2 cancer cells.

**Pattern 3:** Glandular invasion of muscle tissue is widespread.

![Pattern 3](image3)

**Figure 9:** Pattern 3 cancer cells.

**Pattern 4:** The normal gland unit is disrupted; individual glands are no longer clearly differentiated.

![Pattern 4](image4)

**Figure 10:** Pattern 4 cancer cells.

**Pattern 5:** Individual glands cannot be discerned; tissue features are indistinguishable from cancerous tissues in other organs.

![Pattern 5](image5)

**Figure 11:** Pattern 5 cancer cells.

A patient’s Gleason score is the sum of their primary and secondary Gleason grades (e.g. 4 + 3 or 3 + 4 = 7). The primary Gleason grade must be observed in at least 50% of the biopsic tissue, while the secondary Gleason grade, the second most common pattern, must be visible in at least 5% of the tissue.

**T stages**

Pathologic T stages are a metric used to quantify the size and invasiveness of prostatic tumors. The four different T stages are characterized as follows:

**T1:** The tumor is not felt during a digital rectal exam, but a biopsy reveals the presence of cancer cells.
**T2:** The tumor can be felt during a digital rectal exam, but is probably confined to the prostate.24

**T3:** Cancer cells have spread to connective tissues and seminal vesicles surrounding the prostate but have not invaded any other organs.24

**T4:** Cancer cells have spread to tissues adjacent to the prostate, such as the bladder neck or rectum.24

**Clinical results**

The clinical studies on primary prostatic cryoablation investigated in this report were obtained from the following institutions:

- Allegheny General Hospital
- Tom Baker Cancer Centre
- University of Calgary
- New England Medical Center
- University of California at San Francisco
- Urologic Institute of New Orleans
- Crittenton Hospital
- Alhambra Hospital
- Columbia-Presbyterian Medical Center

Because the resurgence of cryoablation in clinical practice is relatively recent, the results from these studies concern only short-term outcomes of primary prostatic cryoablation (<10 years after treatment). Published data on long-term outcomes of prostatic cryoablation is currently very limited.

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**Allegheny General Hospital**

The most extensive published studies on prostatic cryoablation outcomes are from Allegheny General Hospital. In a study involving 261 men with high-risk, clinically localized prostatic carcinoma, 240 received at least one post-treatment biopsy. Of these patients, 165 (68.7%) had negative results. After one year, 52% of the 261 men maintained a PSA below 0.4 ng/mL, while 71.8% maintained a PSA below 1.0 ng/mL. After five years, the percentage of men who maintained a PSA below 0.4 ng/mL dropped to 42.3%, and the percentage of those with a PSA below 1.0 ng/mL dropped to 57.7%.24

The most common complication was urethral sloughing, which occurred in approximately 15% of these patients, and when a urethral warming catheter was not used, the sloughing rate increased to about 50%. Urinary incontinence was reported in 5.9% of patients, and in 24% of patients when a urethral warming catheter was not used. While impotence was initially observed in the vast majority of cases, 33% of patients younger than 65 years old were eventually able to recover their erectile function while only 15% of patients aged 65 or older were able to do so. Urethrorectal fistula was rare, occurring in only 0.3% of cases.24

**Tom Baker Cancer Centre and University of Calgary**

In another study conducted in Calgary, AB (Canada), cryoablation was performed on 76 men with prostatic carcinoma. Seventy-three received post-treatment biopsies and, of these, all but one (98.6%) tested negative for malignancies. Five years after treatment, 58.8% of the 76 patients retained a PSA level below 0.3 ng/mL, and 79.8% retained a PSA level below 1.0 ng/mL.24

In general, procedural complications were minimal. Urethral sloughing occurred in 3.9%
of patients, and urinary incontinence occurred in 1.3% of patients. None of the patients experienced urethrorectal fistula. Although all patients experienced impotence immediately following surgery, 47% of patients capable of unassisted intercourse prior to surgery resumed sexual intercourse within three years—five spontaneously and thirteen with sexual aids\textsuperscript{14}\textsuperscript{(p646-647)}.

**Columbia-Presbyterian Medical Center**

At Columbia-Presbyterian Medical Center, 65 men with advanced, clinically localized prostatic carcinoma underwent prostatic cryoablation. After a median follow-up of 35 months, 83.3% of these patients were found free of biochemical recurrence under the American Society for Therapeutic Radiology and Oncology definition of biochemical failure (three consecutive increases in PSA level). Eight of these patients also underwent biopsies, of which seven (77.5%) received negative results. Two years after surgery, 94.44% of the 65 patients had a PSA level under 1.0 ng/mL, while 80.55% had a PSA level under 0.4 ng/mL\textsuperscript{25}\textsuperscript{(p1626-7)}.

Of these patients, only two (3.1%) experienced urinary incontinence, and there were no instances of urethrorectal fistula\textsuperscript{25}\textsuperscript{(p1527-8)}.

**New England Medical Center, University of California at San Francisco, Urologic Institute of New Orleans, Crittenton Hospital, and Alhambra Hospital**

In a multi-institutional pooled analysis, Long et al compiled outcomes data from five institutions (New England Medical Center, University of California at San Francisco, Urologic Institute of New Orleans, Crittenton Hospital, and Alhambra Hospital) for 975 patients who underwent prostatic cryoablation. The negative post-treatment biopsy rate for these men was 86%. After five years, 76% of low-risk patients (defined as PSA < 10, Gleason score < 7, and stage T1-2) maintained a PSA below 1.0 ng/mL, while 53.6% of high-risk patients (defined as PSA > 10, Gleason score > 6, and stage T2a or higher) maintained a PSA below 1.0 ng/mL\textsuperscript{22}\textsuperscript{(p519,521)}.

The procedural complications reported in these studies were as follows: urinary incontinence occurred in 7.5% of cases, urethrorectal fistula occurred in 0.5% of cases, and impotence occurred in 93% of cases\textsuperscript{22}\textsuperscript{(p522)}.

<table>
<thead>
<tr>
<th>Study</th>
<th>&lt;1.0 ng/mL</th>
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<tr>
<td>Allegheny</td>
<td>57.7</td>
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<tr>
<td>New England Medical Center, etc.</td>
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</tr>
<tr>
<td>Calgary</td>
<td>80.7</td>
</tr>
<tr>
<td>Columbia-Presbyterian</td>
<td>31</td>
</tr>
</tbody>
</table>

\textsuperscript{NA = Information not available}
Prostatic Cryoablation

Table 2: Primary cryoablation complication rates\textsuperscript{5,14,22,25}

<table>
<thead>
<tr>
<th>Study</th>
<th>Sloughing</th>
<th>Incontinence</th>
<th>Urethrorectal Fistula</th>
<th>Impotence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegheny</td>
<td>15.6%</td>
<td>5.9%</td>
<td>0.3%</td>
<td>NA</td>
</tr>
<tr>
<td>New England Medical Center, etc.</td>
<td>NA</td>
<td>7.5%</td>
<td>0.5%</td>
<td>93%</td>
</tr>
<tr>
<td>Calgary</td>
<td>3.9%</td>
<td>1.3%</td>
<td>0%</td>
<td>100%</td>
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<tr>
<td>Columbia-Presbyterian</td>
<td>14.4%</td>
<td>3.1%</td>
<td>0%</td>
<td>NA</td>
</tr>
</tbody>
</table>

\textit{NA} = Information not available

Salvage cryoablation

Nearly one-third of men diagnosed with prostate cancer will choose some form of radiation therapy as their primary treatment method. Unfortunately, for approximately one-third of these men, radiation therapy will fail to control their local disease. However, salvage cryoablation, treatment with cryoablation after primary treatment has failed, may still offer these men a second treatment option with curative potential\textsuperscript{2}(p20).

Patient selection

Salvage cryoablation is often recommended for men who, after radiation therapy, experience a local recurrence of cancer that is detected early and has not metastasized. However, because of the increased risk of complications, patients who have a life expectancy of less than ten years are generally advised against undergoing this procedure\textsuperscript{2}(p20, 23).

Clinical results

The salvage prostatic cryoablation outcomes data analyzed in this report were obtained from two clinical studies: one at Allegheny General Hospital, and the other at Columbia-Presbyterian Medical Center. Because long-term outcomes data for salvage prostatic cryoablation is still largely unavailable, these studies only cover short-term results (<10 years after treatment).

**Allegheny General Hospital**

Upon failing radiation therapy, 87 men underwent prostatic cryoablation at Allegheny General Hospital. After surgery, 72 of these patients received a biopsy, and 69.4% tested negative for malignancies. A follow-up examination five years later showed that 66.7% of the 87 patients had a PSA level below 1.0 mg/mL\textsuperscript{5}(p44).

Urethral sloughing was the most common complication, occurring in 26.4% of these patients. Slightly less frequent was urinary incontinence, which was reported in 23% of cases. No patients developed urethoro rectal fistula\textsuperscript{5}(p45).

**Columbia-Presbyterian Medical Center**

At Columbia-Presbyterian Medical Center, prostatic cryoablation was performed on 43 men after radiation therapy failed to control their local disease. Of these patients, eight underwent a post-treatment biopsy, of which 5 (62.5%) received negative results. After two years, 60% of the 43 patients maintained a PSA level below 1.0 ng/mL\textsuperscript{13}(p80-81).
Of these patients, 9.3% experienced urinary incontinence, and there were no instances of urethrorectal fistula\textsuperscript{13}(p82).

### Table 3: Salvage cryoablation complication rates\textsuperscript{13,22}

<table>
<thead>
<tr>
<th>Study</th>
<th>Sloughing</th>
<th>Incontinence</th>
<th>Urethrorectal Fistula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allegheny</td>
<td>26.4%</td>
<td>23%</td>
<td>0%</td>
</tr>
<tr>
<td>Columbia-Presbyterian</td>
<td>NA</td>
<td>9.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>

NA = Information not available

### Indications

When determining the effectiveness and significance of cryoablation as a treatment for prostate cancer, it is necessary to compare it to other treatment alternatives. Comparing results from different studies can be difficult because researches use varying metrics for determining biochemical-free survival (BFS) rates (e.g. PSA <1.0 ng/mL, PSA <0.4 ng/mL, two consecutive rises in PSA level, etc.), but, despite these discrepancies, such comparisons can still be useful indicators of the relative efficacy of different treatment methods. Currently, some of the standard primary treatment methods are radical prostatectomy, external beam radiation therapy (EBRT), and brachytherapy.

A comparison of BFS rates, using a uniform BFS definition of PSA <1.0 ng/mL, for low-risk patients (Gleason score <7, T1-2) is provided in Table 4.

### Table 4: BFS rate comparison for low-risk patients\textsuperscript{12,22}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BFS rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoablation</td>
<td>76%</td>
</tr>
<tr>
<td>Radical Prostatectomy</td>
<td>88%</td>
</tr>
<tr>
<td>EBRT</td>
<td>85%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>87%</td>
</tr>
</tbody>
</table>

Results obtained at 5-year evaluations, except for radical prostatectomy (obtained at 8-year evaluations)

As evidenced by these results, cryoablation generally provides less local disease control than other proven therapies for low-risk patients. Because of this lack of efficacy—and the high rates of impotency associated with cryoablation—primary cryoablation is rarely recommended for low-risk patients.

However, in the case of high-risk patients (PSA >10 ng/mL, Gleason score >6, stage T2 or higher) the average cryoablation BFS rates from studies investigated in this report compare more favorably to those of other treatment methods. A comparison of these BFS rates is provided in Table 5 (because radical
prostatectomy is a very invasive therapy, and, thus, not often recommended for high-risk patients, it is not considered in this comparison).

### Table 5: 5-year BFS rate comparison for high-risk patients\textsuperscript{14,22}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>BFS rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoablation</td>
<td>54.8%</td>
</tr>
<tr>
<td>EBRT</td>
<td>39.5%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>68%</td>
</tr>
</tbody>
</table>

**BFS Definitions:**
- Cryoablation: PSA \(<1.0\) ng/mL
- EBRT: 2 consecutive rises in PSA level
- Brachytherapy: 3 consecutive rises in PSA level

While there is significant divergence in these results, much of this may be attributable to the varying definitions of BFS used and the varying tumor characteristics of the patients involved. It is notable that the BFS rates for cryoablation fall almost directly in-between the rates for EBRT and brachytherapy, two well-proven treatments for prostatic carcinoma.

The average occurrence of complications arising from cryoablation, as derived from the studies in this report, is also comparable—in most respects—to those from EBRT and brachytherapy. Table 6 provides a comparison of complications frequency.

### Table 6: Comparison of complication rates\textsuperscript{22}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Incontinence</th>
<th>Urethral Fistula</th>
<th>Impotence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryoablation</td>
<td>6.5%</td>
<td>0.4%</td>
<td>93.5%</td>
</tr>
<tr>
<td>EBRT</td>
<td>6.5%</td>
<td>5%</td>
<td>53.5%</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>2.5%</td>
<td>3.5%</td>
<td>25%</td>
</tr>
</tbody>
</table>

As is apparent from these results, the frequency of urethralrectal fistula is substantially lower for cryoablation than either of the other two therapies. However, the low frequency of urethralrectal fistula resulting from cryoablation is highly dependent upon the use of a warming catheter to protect the urethra; without this safeguard, the incidence of urethralrectal fistula becomes much higher than in either EBRT or brachytherapy\textsuperscript{5(p45)}. However, if cryoablation is used to treat cancers that have spread to the urethra and bladder neck, the use of a urethral warming catheter will usually allow some malignant cells to survive. For this reason, cryoablation should be considered a poor treatment option in these cases\textsuperscript{14(p648)}.

The high probability of impotence remains a significant problem and should always be considered when choosing between cryoablation and other therapies. Because the success of cryoablation generally requires the
entire prostate gland to be exposed to lethal temperatures, the destruction of the neurovascular nerve bundles that control erections is inevitable. While these nerve bundles may regenerate over time in some men, particularly young men, a return to sexual potency can never be guaranteed.

Although clinical results seem to indicate that prostatic cryoablation is comparable to both EBRT and brachytherapy in efficacy and complication rates, these results are based solely on 5-year studies. Because published outcomes data on the efficacy of cryoablation after 10- or 15-years are extremely limited, the long-term outcomes of cryoablation are still unknown. This uncertainty is another important factor that should be considered before cryoablation is recommended over other proven therapies.

Future Developments

The short-term outcomes from prostatic cryoablation indicate that the procedure holds significant therapeutic potential, and, as a result, many researchers are energetically working toward further improving and perfecting cryosurgical technology and technique. Several of the most important developments on the horizon for prostatic cryoablation are focal nerve sparing, MRI monitoring, and improved adjunctive therapy.

Focal nerve sparing

Focal nerve sparing refers to a new cryoablation technique aimed at retaining potency after surgery. Rather than aggressively freeze the entire prostate gland, the surgeon attempts to produce uniform lethal temperatures on only one side of prostate gland—the side containing the tumor—and, thereby preserve the neurovascular nerve bundle on the other side of the prostate. Leaving this neurovascular nerve bundle largely unharmed allows patients to either retain or quickly restoring their sexual functionality. When this technique is used, there is a risk that malignant cells will also be preserved on the less aggressively treated side of the prostate; however, clinical studies conducted thus far by Onik et al have demonstrated surprising effectiveness in both treating cancer and preserving potency using this technique.

MRI monitoring

Experiments have shown that the use of MRI technology in cryoablation offers significantly improved imaging ability over TRUS. MRI offers true three-dimensional imaging—unlike TRUS, which provides pseudo-three-dimensional images by gathering data from multiple angles—allowing for much more accurate information about temperatures and freezing volume. This additional information enables surgeons to better determine the extent of lethal temperatures achieved during surgery and, thereby adjust the procedure to ensure that all targeted tissues are affected without placing healthy structures at additional risk. Unfortunately, the expense of MRI devices makes it unlikely that this technology will be regularly used for cryoablation.

Improved adjunctive therapy

While chemotherapy and radiation therapy are often used in conjunction with cryoablation, there may be unrealized potential in a carefully harnessed synergistic reaction between these therapies. Studies have
shown that apoptosis (programmed cell death) may play an important role in cellular destruction during cryoablation. While this role is not fully understood, it is believed that the freezing procedure causes some cells to enter an apoptotic state and die several hours, days, or weeks later. The potential for chemotherapy to trigger apoptosis has been recognized for some time, and many researchers have suggested that these two therapies could be used to in conjunction to achieve greater lethality through instigated apoptosis. For instance, Benson and Ikekawa et al have shown that if pharmaceuticals are administered during microcirculatory cessation—just as after the thawing process commences—they will become sequestered within the tumor, both enhancing their desired therapeutic effect and reducing their undesired side effects4(p98).

Researchers have suggested that similar synergistic effects may be achieved using radiation therapy and cryoablation in tandem. In vitro experiments have demonstrated that cells become more sensitive to radiation when cooled; however, the appropriate time to irradiate the cells and potentially capitalize on this vulnerability is not yet known4(p98).

Conclusion

The practice of cryosurgery has progressed rapidly since Arnott’s bold experiment nearly a century and a half ago. Through an incremental refinement of technique and breakthrough inventions, cryosurgery has evolved from an exciting, but problematic, experimental procedure into a vital cancer therapy.

Short-term clinical results indicate that prostatic cryoablation may have equal or even greater therapeutic potential than radiation therapies for the treatment of high-risk prostatic cancer. These results are particularly surprising and exciting when one considers the relative lack of experience, research, and interest afforded to cryoablation compared to that of radiation therapy22(p523). However, these results must be tempered with the recognition that long-term outcomes are still unknown.

For now, prostatic cryoablation provides an effective alternative treatment option to patients who have high-risk prostatic carcinomas, are poor candidates for more invasive treatments, or have failed radiation therapy. However, until long-term outcomes data are available, cryoablation cannot be recommended as front-line treatment method. Nonetheless, the positive short-term results achieved in clinical studies should be sufficient to spur future research and interest in this promising therapy.
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