Cryo Surgery of the Prostate: An Effective, Minimally Invasive Cancer Therapy with Superior Health-related Quality-of-Life Outcomes

Martyn A. Vickers Jr
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Martyn A. Vickers, Jr.
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An Effective, Minimally Invasive Cancer Therapy with Superior Health-related Quality-of-Life Outcomes

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Introduction

You or your patient has recently been diagnosed with prostate cancer. Studies demonstrated that this cancer has not spread beyond the prostate. Many patients have a type of prostate cancer that does not demand prompt treatment, but this cancer is more aggressive and should be treated.

What is the best treatment for localized, aggressive prostate cancer? One option is Cryo Surgery, a primary option that utilizes localized freezing to destroy diseased tissue. If you or your patients wish to consider Cryo Surgery, be sure to discuss this option with an urologist who performs Cryo Surgery of the prostate. Many urologists have not observed or been trained in the performance of this procedure. Prostate cancer allows you time to carefully consider all treatment options. Make an educated decision!

This may be the second time you or your patient must choose a treatment for prostate cancer. Years ago you or your patient selected radiation therapy. Recently the PSA level has been gradually increasing. A repeat prostate biopsy may have found active cancer cells. Radical surgical removal of the prostate or salvage cryoablation of the prostate are the two potential curative options.

In this book the terms Cryo Surgery, Cryoablation, and Cryo are interchangeable.

This book presents:

- The Scientific Basis of Cryoablation.
- The Clinical Trials that support the use of Cryoablation as a Primary Therapy, a Salvage Therapy following Radiation Failure, or a Focal Therapy.
- A detailed account of the patient's Cryoablation Experience, including his time in the hospital and during his one month post-Cryo period.

The book answers many of the questions asked by health-care providers and patients:

- Who is a candidate for Cryoablation of the prostate?
- What are the prostate specific antigen (PSA) outcomes following Cryo, and how do they compare to PSA outcomes following radical surgery or radiation therapy?
- What are the advantages of Cryo compared to radical surgery or radiation therapy?
- What are the risks of Total Cryoablation of the Prostate?
- What are the PSA and Health-related Quality of Life Outcomes of patients who received Total Cryoablation for localized prostate cancer at the Penobscot Bay Medical Center?
- How do the potential adverse outcomes associated with Cryo compare to those associated with Radical Prostatectomy or Radiation Therapy?
- How will Cryo, radical open or minimally invasive prostatectomy, or any of the radiation therapies influence my Health-related Quality of Life?
- What about Hormone Therapy? Will it cure my cancer and lengthen my life?
- Am I a candidate for Active Surveillance - Monitoring and Waiting? What risks are associated with active surveillance?
- Is High-Intensity Focused Ultrasound (HIFU) a reasonable treatment option?
- How do I prepare for Cryo and what should I expect when I return home?
- How does Cryo destroy cancer cells?
- How is my prostate frozen?
• I want to remain potent. I know that if I have only one part of my prostate frozen, I will have a greater chance of remaining potent. Am I a candidate for Focal Cryoablation of the prostate?

• Will Salvage Total Cryoablation of the prostate successfully destroy the cancer cells that have reappeared in my prostate after radiation therapy?

No single treatment is the best for all patients. What was right for an acquaintance may not be the best option for you. Here are a few books and web sites that our patients have found helpful. The first three of these books have no bias toward Cryoablation of the prostate. In fact, they show little enthusiasm for, or in some cases, argue against its performance. In Complete Guide to Prostate Cancer, Dr. Kavanagh expresses concern regarding the long-term effectiveness of cryotherapy. In Questions and Answers about Prostate Cancer, Dr. P. Ellsworth questions the use and effectiveness of Cryoablation as an initial therapy for the treatment of prostate cancer. The concerns of both authors were addressed by the 2008 American Urological Association's Expert Panel on the role of Cryoablation in the treatment of prostate cancer. This 12-member panel reviewed the major peer-reviewed reports on this procedure published between 2000 and 2008. The panel concluded that "primary cryosurgery is an option, when treatment is appropriate, in men who have clinically organ-confined disease of any grade with a negative metastatic evaluation."

In the several years since the panel rendered this favorable consensus expert opinion, information continues to accrue indicating that cryosurgery is an extremely safe and effective option for many patients. In Guide to Surviving Prostate Cancer, Dr. Patrick Walsh expresses concern about the ability of Cryoablation to destroy all prostate cancer cells in the prostate. This worry has not been confirmed by short-and long-term follow-up of patients who have had total cryoablation of the prostate. For an in-depth discussion of this issue, please see Addendum #1 on pg. 71.

So why do we provide references that challenge Cryoablation? Our goal is to render a balanced presentation. These authors provide valuable information on other treatment options – radical surgery, radiation therapy, and active surveillance.

Several web sites provide valuable information on radical surgery and radiation therapy. Up to date information on Cryo can be found at www.cryocarepca.org. "Handbook of Urologic Cryoablation," edited by Rukstalis and Katz, is the most current book on this subject.

An Internet search for cryoablation of the prostate will reveal many self-proclaimed experts. Their critiques frequently fail to acknowledge or appreciate recent advances in the methodology of cryoablation of the prostate and do not provide the most current outcome data of present-day. "Third Generation Cryoablation of the Prostate."

Finally, we suggest that you go beyond data on the survival rates and PSA response for various treatments. Look at Health-related Quality-of-life issues, and then decide where you want to be in 5, 10 and 15 years.

We hope this effort will help you select the best option for you!

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Section I: Total Cryoablation of the Prostate – Is it a reasonable option for me?

1. Who are candidates for total cryoablation of the prostate?

Cryoablation is a technique for eradicating cancerous tissue by killing it with extreme cold. If your cancer has not spread outside the prostate, cryoablation is a treatment option for you. The American Urological Society convened a panel of experts to develop a best practice statement addressing the use of cryoablation for the treatment of localized prostate cancer. In 2008 the panel published a consensus opinion which stated: "Primary cryosurgery is an option, when treatment is appropriate, for men who have clinically organ-confined disease of any grade with a negative metastatic evaluation."¹

Organ-confined prostate cancer includes low-, moderate-, and high-risk prostate cancer. Please see Addendum #2 on page 72 for an explanation of Gleason grade and score and Addendum #3 on page 73 for an explanation of the D'Amico risk classification. Low-, moderate-, and high-risk prostate cancer have been successfully treated with cryoablation.

The panel and the National Comprehensive Cancer Network have stated that "salvage cryosurgery can be considered as a treatment option for curative intent in men who have failed radiation therapy."¹,²


2. How does Cryo destroy prostate cancer?

Argon gas is used to freeze the prostate. It is stored in large metal tanks and delivered to the prostate by specially designed probes. Each probe has a small-diameter, open-ended tube that, in turn, is enclosed by a larger closed-ended tube. Gas is forced through the smaller tube into the larger tube. (Figures 1 and 2) As argon exits the smaller tube, it rapidly expands. This results in its rapid cooling, with temperatures reaching -186°C or -303°F. This is the J-T effect (Joule-Thompson). The expanded gas is cycled away from the patient, through the larger, outer tube back to the cryogenic unit. The cooled gas, inside the probe, freezes the prostate tissue adjacent to the probe. Cryoprobe or freezing probe is used to describe the double tube unit. The temperature at any distance from the probe can be determined using an equation that includes the temperature of the probe, the temperature of the prostate, the radius of the probe, and the distance of the freezing interface from the probe's surface. When prostate cryoprobes are continuously infused with pressurized argon for ten minutes, a 2 centimeter (cm) by 4 cm area of
surrounding tissue is cooled to -40°C or -40°F (This is the one temperature at which Celsius and Fahrenheit have the same reading). At this temperature the tissue is destroyed. (Figure 3) The freezing process can be abruptly stopped by discontinuing the argon infusion and immediately beginning an infusion of helium through the same cryoprobe.

**Fig. 1**
Argon and helium are delivered in the same probes. All gas is returned to the cryogenic unit and away from the patient.

**Fig. 2**
Prior to placement of the cryoprobes, helium and then argon are forced through the probes that are submersed in a water bath. The integrity of the tubes and the concentration of gases is confirmed when no bubbles are seen and ice appears during the infusion of argon and disappears on the infusion of helium.

**Fig. 3**
The tissue change around the probe is called the probe's isotherm. Its' shape will vary depending on the total time that argon circulates inside the probe.
The size and shape of the prostate is obtained using an ultrasound probe that is positioned in the rectum. A computer program helps the surgeon determine the required number and ideal location of the freezing probes and the temperature-sensing probes (thermocouples). (Figure 4) The general guidelines for the cryoprobe placement are:

1. All freezing probes should be less than 21mm from their adjacent freezing probes.
2. All freezing probes should be less than 10mm from the outer margin of the prostate.
3. All freezing probes should be at least 5mm from the urethra.

Fig. 4

Fig. 4. This is a head-on image of the prostate with the computer's suggestion for the number and location of the freezing probes (1-8) and temperature sensing probes (letters). The blue line defines the roof of the rectum. The red circle outlines the urethra.
The delivery rate of argon or helium in each cryoprobe, the temperatures in and around the prostate, and the changes in the structure of the prostate are continuously displayed in real time on the computer monitor. (Figure 5)

Fig. 5. The computer monitor shows real-time temperatures detected by the temperature-sensing probes and continuously reports the gas flow through each of the freezing probes. On this photo, the temperature in area between the prostate and the rectum is 38°C (DEN). Argon is circulating continuously in cryoprobes 1, 2, 7, and 8.

Before freezing the prostate, a warming catheter is placed in the urethra. Inside the outer lining of the warming catheter, warmed sterile salt water (42°C or 107°F) is continuously circulated, thereby protecting the urethra from freezing. (Figure 6)

Fig. 6. Warmed sterile saline is continuously cycled within the outer wall of this double-walled tube during the Cryo procedure.
Figures 7-9 are side views of the prostate prior to and during the freezing process. The lethal freeze begins at the top of the prostate and continues downward. The progress of the freeze is continuously monitored by ultrasound and temperature-sensing probes. Once the ultrasound image detects that ice has extended into the space between the prostate and the rectum and out to the urethral sphincter, and the temperature probes confirm that critically low lethal temperatures have been achieved, the first freeze is complete. (Figure 9)

Fig. 7 is Nikolaus Lechenbauer's illustration of the bladder, prostate, and urethra. The rectum is very close to the prostate and temperatures in this area must be carefully monitored.

Fig. 8 is a side view of the prostate obtained by ultrasound. The white ski-shaped image is the edge of the ice as it progresses toward the rectum.

Fig. 9 shows that the ice edge has reached the prostatic capsule. The cryoablation of the prostate is complete. The rectal wall has remained intact.

Next, the prostate is warmed with helium. Once the ice crystals have dissolved, the cryoprobes and the thermocouples can again be seen on the ultrasound image and, if necessary, repositioned. Then the second freeze is begun, again using argon gas. Two freeze/thaw cycles have been shown to more reliably kill 100% of the targeted cancer than a single freeze.
3. What happens to my prostate after Cryo?

Within minutes of being exposed to extreme cold, small blood vessels in the center of the prostate close, and the tissue they supply dies.\(^1\) The outer edge of the prostate has a mixture of dead and living cells. Here, extreme cold triggers a gene-based cell death process called apoptosis.\(^2,3\) Immediately, a series of chemical reactions (caspase pathway) occur in the frozen cells that shut down the cells’ power source (mitochondria) and fracture their DNA.\(^4\) (Figure 10) Ultimately, the cancer cells cease all activity and are digested by their healthy neighboring cells. (Figure 11)

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**Fig. 10.** Within eight hours after freezing, programmed cell death (apoptosis) is evident. The caspase intrinsic pathway is activated beginning with caspase 8 and 9, then 4, 5, and 6, and finally 3 and 7. The end result is cleavage of target proteins and DNA and ultimate cell death.


4. What are the PSA results following total cryoablation and how do they compare with PSA results following radiation therapy and radical prostatectomy?

In 2003, Dr. Aaron Katz at Columbia University Medical School published a comparative review of outcomes following primary treatment of localized prostate cancer with radical surgery, brachytherapy ("seeds"), external beam radiation, and cryoablative surgery.\(^1\) (Figure 12.) Publications from 1992-2002 were included which provided data on PSA outcomes, the side effects, and quality-of-life outcomes. The PSA values of patients with low-risk and moderate-risk prostate cancer who underwent cryoablation compared favorably with those who had radical surgery or underwent radiation therapy. High-risk prostate cancer patients (two or more of the following – stage greater than 2a, Gleason score greater than 6, PSA greater than 10) treated with cryoablation had superior outcomes (lower post-procedure PSA values) than patients who had radical surgery or radiation therapy.

![Efficacy Comparison](image)

Fig. 12. Based on PSA monitoring, cryoablation compared favorably to radical surgery and radiation therapy in low-, intermediate-, and high-risk prostate cancer. The unit for vertical axis is the percent of patients that are free of recurrent cancer at 5 years after their primary treatment.

---

In 2008 Cohen reported on the 10-year biochemical disease-free status of 370 patients with prostate cancer treated with total cryoablation of the prostate. Using the Phoenix criteria (lowest post-cryo PSA plus 2), 80.5 percent, 56 percent, and 74 percent of patients with low-, intermediate-, and high-risk disease were disease-free at 10 years. Jones reported on 136 patients with prostate cancer who had a minimum follow-up of five years. Again, using the Phoenix criteria, 91%, 78%, and 62% of patients with low-, medium-, and high-risk disease were free of disease at five years.

In 2011, Mouraviev provided data on 4,321 patients from the COLD Registry who received whole gland cryoablation for localized prostate cancer between 1990 and 2010. Using the Phoenix criteria, 80%, 70%, and 48% of low, intermediate, and high-risk patients, respectively, experienced 10-year biochemical (PSA) disease-free survival.

The cornerstone article for classification of patients with localized prostate cancer into three groups (low-, intermediate-, and high-risk groups) appeared in JAMA in 1998. Using the D'Amico classification (RT), PSA biochemical outcomes after radical prostatectomy (RP), external beam radiation therapy, or interstitial radiation therapy (brachytherapy - BT) were compared. For low-risk patients the 5-year PSA biochemical free failure rates were not statistically different and were 85-87%. For intermediate-risk patients the 5-year PSA biochemical free failure rates were better for the patients treated with RP or RT than those treated by brachytherapy (60% - RP, 60% - RT, 33% - BT). Finally, for high-risk patients the 5-year PSA biochemical free failure rates were 30% for RP. There was not an adequate number of high-risk patients who received RT or BT who were followed 5 years to provide a statistically significant PSA biochemical-free failure rate.

5. What are the risks associated with Cryo?

A review by Katz of published studies (2003-2007) of third-generation total cryoablation of the prostate revealed urethral damage in 2 percent to 5 percent of patients. Two to seven percent experienced leakage of urine. Three to seven percent experienced pain in the area around the rectum. Zero to two percent of patients developed an opening between the urinary tube and the rectum. At 6 months, 80 percent of patients who were potent prior to Cryo required assistance (i.e., Viagra-type drug, vacuum constriction device, or an intra-cavernosal medication) to achieve penile firmness sufficient to permit vaginal penetration.

In 2009, Dhar reported on complication outcomes in 3,209 patients who had undergone full gland surgical cryoablation of the prostate. The incidence of urinary leakage was 5%. An opening between the urinary tube and the rectum developed in 0.3%. Sixty-six per cent of patients were sexually inactive at 12 months after treatment.

The Glickman Urological and Kidney Institute, a section of the Cleveland Clinic, presented data collected in the Cryo On-Line Data Registry involving 2,316 patients whose initial prostate volume was < 50 cc and who had received primary whole-gland cryoablation. The incidence of urinary incontinence, urinary retention, erectile dysfunction, and development of a rectal fistula were 3.3, 1.1, 7.0, and 0.6%, respectively.

6. The Penobscot Bay Medical Center Outcomes with Total Cryoablation of the Prostate

A. PSA Outcomes for Low- and Intermediate-risk Patients

Between 11/27/2006 and 4/30/2011, 47 patients with localized prostate cancer received total cryoablation of the prostate as the primary treatment for their localized prostate cancer at the Penobscot Bay Medical Center. The inclusion criteria were a pre-treatment PSA of <10 ng/ml, a Gleason Score of < 7 or a Gleason Score of 3+4=7, and tumor stage of T1c (The cancer was not felt on digital rectal exam and only detected in performance of a prostate biopsy based on an elevation in PSA) or T2a (The cancer was felt on digital rectal exam but this cancerous area comprised less than 50% of one lobe of the prostate). Patients with prostate volumes of greater than 50 cm³, determined by ultrasound performed at the time of prostate biopsy, received pre-Cryo androgen suppression therapy (AST) to decrease prostate volume. AST was not continued after the Cryo procedure.

Tables 1 and 2 present the age, the number of biopsy cores obtained and the number of cores that contained cancer, the pre-Cryo PSA, and the PSA values at 6 months and at 1-6 years of 47 consecutive patients who received Total Cryoablation of the Prostate at the Penobscot Bay Medical Center and fulfilled the inclusion criteria of this study.

Applying the Phoenix criteria (PSA nadir + 2 ng/ml), there was one biochemical failure in the Gleason <7 Group during the first 5 years following Total Cryoablation of the Prostate. The PSA of Patient #6 gradually increased following Total Cryoablation and at 5-years post-Cryo was 2.42. A prostate biopsy found benign prostatic tissue with extensive scarring, but no residual prostatic cancer. Patient #3 experienced an increase in PSA during his third post-Cryo year. By his fifth post-Cryo year it had increased to 1.36. A prostate biopsy found benign prostatic tissue with extensive scarring, but no residual prostatic cancer. The gradual increase in PSA in both patients was due to increased production of PSA by benign prostatic tissue. All the low-risk, Gleason <7 Group patients remained free of any signs or symptoms of recurrence of prostate cancer. Simply stated, all Gleason <7 Group patients remained free of recurrence of prostate cancer during the study period. Using the Phoenix criteria, the 1 to 4 year biochemical disease-free state (bDFS) is 100%. At 5 years it decreases to 92% and then rebounds at 6 years to 100%. The temporary change in the slope is the result of a patient with a PSA of 2.42 at 5 years who not available for follow-up at 6 years. The Kaplan-Meier analysis of disease-free survival using the Phoenix criteria is presented in Figure 1.

![Figure 1. Kaplan-Meier analysis of biochemical disease-free survival using the Phoenix criteria.](image)

Cohen published a 10-year outcome study with cryoablation as the primary treatment of prostate cancer. His low-risk patients experienced a bDFS at 3, 4, and 5 years of 94%, 90%, and 81% vs the bDFS of 100%, 100%, and 92% for patients treated at Penobscot Bay Medical Center.
There was one biochemical failure in the intermediate-risk, Gleason group 7 during the first 4 years following Total Cryoablation. Patient #36 presented with a PSA of 7.5 ng/ml and T2A disease. However, all 12 prostatic cores obtained on 11/13/2009, contained a Gleason 3 + 4 = 7 cancer. Although the original D’Amico risk classification would place this patient at intermediate-risk for prostate cancer recurrence after primary therapy, a follow-up study co-authored by D’Amico provided data that would re-classify him to “high risk for early (≤ 2 years) PSA failure.” One year following this patient’s Cryo procedure, his PSA had increased to 1.66. A post-Cryo prostate biopsy performed on 11/10/2010 failed to detect any residual cancer cells. The post-Cryo bone scan and CT scan did not detect the site of his recurrent prostate cancer. At two years post-Cryo, his PSA was 3.10 and intermittent hormonal therapy was initiated. He has remained free of any clinical signs or symptoms of recurrence of prostate cancer.

Table 1. Post-cryo PSA (ng/ml) Values in Low-risk Patients with a Gleason Score of <7 and Stage T1C or T2A, and a Pre-Cry PSA <10.

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<td>&lt;0.01</td>
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</tr>
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<td>0.3</td>
<td>0.36</td>
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<td>-</td>
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<td>1 of 12</td>
<td>5.4</td>
<td>0.06</td>
<td>0.05</td>
<td>0.08</td>
<td>0.09</td>
<td>0.11</td>
<td>0.21</td>
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</tr>
<tr>
<td>20</td>
<td>68</td>
<td>T2A</td>
<td>4 of 12</td>
<td>1.6</td>
<td>&lt;0.01</td>
<td>0.11</td>
<td>0.15</td>
<td>0.59</td>
<td>0.25</td>
<td>0.45</td>
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<td>21</td>
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<td>4 of 10</td>
<td>5.8</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.22</td>
<td>0.25</td>
<td>0.21</td>
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</tbody>
</table>

Median 65  
Mean (#) 67.3 (21)  
Range 61-81

---

1.6-9.7 <0.01-0.39 <0.01-0.8 <0.01-0.6 <0.01-1.46 <0.01-1.77 <0.01-2.42 <0.01-0.9
Table 2. PSA (ng/ml) Values of Intermediate-risk Patients with a Gleason Score of 7(3+4) and Stage T1C or T2A, and PSA <10).

<table>
<thead>
<tr>
<th>#</th>
<th>age</th>
<th>Stage</th>
<th>Cores +</th>
<th>Pre-Op</th>
<th>6 wk</th>
<th>6 mo</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
<th>5 y</th>
<th>6 y</th>
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</thead>
<tbody>
<tr>
<td>22</td>
<td>71</td>
<td>T1C</td>
<td>4 of 10</td>
<td>1.58</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.02</td>
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<td>0.47</td>
<td>0.64</td>
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</tr>
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<td>24</td>
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<td>2.1</td>
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<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.02</td>
<td>0.03</td>
<td>&lt;0.02</td>
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<td>8.05</td>
<td>0.04</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<td>&lt;0.01</td>
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<td>-</td>
<td>&lt;0.01</td>
<td>&gt;</td>
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<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<td>&lt;0.02</td>
<td>0.04</td>
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<td>&lt;0.01</td>
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<tr>
<td>30</td>
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<td>0.59</td>
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<td>0.34</td>
<td></td>
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<tr>
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<td>7.0</td>
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<td>0.75</td>
<td>0.15</td>
<td>-</td>
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<td>0.41</td>
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<td>&lt;0.01</td>
<td>&lt;0.01</td>
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<td>-</td>
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<td>&lt;0.1</td>
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<td>0.56</td>
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<td>&lt;0.02</td>
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<td>&gt;</td>
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<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&gt;</td>
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<td>75</td>
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<td>6.42</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.4</td>
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<td>4.1</td>
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<td>0.27</td>
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<td>0.26</td>
<td>0.31</td>
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<td>&lt;0.01</td>
<td>&gt;</td>
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<td>6.85</td>
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<td>67</td>
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<td>6.03</td>
<td>&lt;0.01</td>
<td>0.1</td>
<td>0.1</td>
<td>0.12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Median | 67.5 | 5.75 | 0.03 | 0.01 | 0.04 | 0.17 | 0.10 | 0.16 | 0.16 | 0.16 | 0.06|
| Mean | 70.7 (26) | 5.79 (26) | 0.09 (23) | 0.14 (22) | 0.2 (21) | 0.38 (21) | 0.16 (20) | 0.24 (15) | 0.18 (7) | 0.06 (1) |
| Range | 52-79 | 1.58-8.1 | 0.01-0.7 | 0.01-0.75 | 0.01-1.66 | 0.01-3.1 | 0.01-0.56 | 0.01-0.69 | 0.02-0.64 | 0.06 |

In table 2, > is used to indicate the death of a patient.
B. Health-related Quality of Life Outcomes for Low and Intermediate-risk Patients

Four questionnaires were mailed to 48 consecutive patients who had elected Total Cryoablation as the primary treatment for localized low- and intermediate-risk prostate cancer. Forty-two patients completed and returned at least 3 of the questionnaires.

Thirty-eight patients completed two questionnaires, one study-specific and the other a validated questionnaire designed to evaluate health-related quality of life outcomes following treatment of localized prostate cancer. The two questionnaires were designed to evaluate the patient’s sexual, urinary, and bowel function. Tables 3a and 3b present the results of these questionnaires.

<table>
<thead>
<tr>
<th>Prior to Cryo</th>
<th>No or small problem</th>
<th>Moderate problem</th>
<th>Big problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Fx.</td>
<td>24</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Urinary Fx.</td>
<td>34</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Bowel Fx.</td>
<td>35</td>
<td>3</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3a. The patient’s assessment of his sexual, urinary, and bowel function prior to total cryoablation of the prostate.

The 3 questions asked were:

1. Overall, how big a problem was getting and maintaining an erection prior to your Cryo procedure?
2. How big a problem was your bladder function prior to your Cryo procedure?
3. How big a problem was your bowel function prior to your Cryo procedure?

<table>
<thead>
<tr>
<th>After Cryo</th>
<th>No or small problem</th>
<th>Moderate problem</th>
<th>Big problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Fx.</td>
<td>11</td>
<td>4</td>
<td>23</td>
</tr>
<tr>
<td>Urinary Fx</td>
<td>36</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Bowel Fx.</td>
<td>38</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3b. The patient’s assessment of his sexual, urinary, and bowel function following his Cryo procedure.

The 3 questions asked were:

1. Overall, how big a problem has getting and maintaining an erection been for you during the last 4 weeks?
2. Overall, how big a problem has your urinary function been for you during the last 4 weeks?
3. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

Thirty-seven patients completed the questionnaire, “After Cryoablation Erectile Function/Dysfunction/Therapy.” In this group, 24 patients answered “yes” to the question, “Were you able to obtain and maintain an erection firm enough for intercourse before your cryoablation?” Fifteen of these patients regained erectile function following the cryoablation. Table 3c presents the time delay between the Cryo procedure and return of erectile function.

<table>
<thead>
<tr>
<th>Months between Cryo and return of erectile function</th>
<th># of patients (15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 6 months</td>
<td>2</td>
</tr>
<tr>
<td>6-12 months</td>
<td>7</td>
</tr>
<tr>
<td>13-23 months</td>
<td>2</td>
</tr>
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<td>24-28 months</td>
<td>2</td>
</tr>
<tr>
<td>29-36 months</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3c. Time between Cryo procedure and return of erectile function.

Four of the patients who were potent prior to cryoablation became impotent following this procedure and sought and received treatment for this problem. Table 3d lists the successful treatment options.

<table>
<thead>
<tr>
<th>Treatment</th>
<th># of patients (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral medication (PDE-5 inhibitor)</td>
<td>1</td>
</tr>
<tr>
<td>Vacuum Device</td>
<td>3</td>
</tr>
<tr>
<td>Intercavernosal therapy (Tri-mix)</td>
<td>2</td>
</tr>
</tbody>
</table>

Table 3d. Two patients were satisfied with two options (the vacuum device and Tri-mix).

Five patients who were potent prior to cryoablation and became impotent following this procedure did not seek treatment for erectile dysfunction.

Four patients were unable to obtain and maintain an erection firm enough for intercourse before and after their Cryo procedure and received treatment for erectile dysfunction. The Vacuum Device was the option that was deemed satisfactory, and this was used by 1 patient.

Nine patients were unable to obtain and maintain an erection firm enough for intercourse before and after their Cryo procedure and did not seek or receive treatment for this problem.

Table 3e provides the International Index of Erectile Function (IIEF-5) Questionnaire Score prior to and 3 years following Total Cryoablation of the Prostate for the 39 patients who competed the two questionnaires.¹

<table>
<thead>
<tr>
<th>IIEF-5 Scores</th>
<th>22-25</th>
<th>17-21</th>
<th>12-16</th>
<th>8-11</th>
<th>5-7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior to</td>
<td>18</td>
<td>8</td>
<td>7</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Following</td>
<td>3</td>
<td>5</td>
<td>5</td>
<td>3</td>
<td>23</td>
</tr>
</tbody>
</table>

Table 3e. Score of 22-25 indicates no erectile dysfunction, 17-21 (mild ED), 12-16 (mild to moderate ED), 8-11 (moderate ED), 5-7 (severe ED)
C. PSA Outcomes for High-risk Patients

Table 4 presents our experience with high-risk localized prostate cancer, cancer that has been shown to have a high probability of recurrence after Radical Prostatectomy or Radiation Therapy. Each of these 14 patients has a Gleason Score of 8 or 9. Please see addendum for an explanation of the Gleason Score. Pre-cryoablation PSAs varied from 4.1 to 38. Fifty percent of this group had a digital rectal exam which described the prostate as normal. Prior to consideration of Total Cryoablation of the prostate, each patient was carefully evaluated to be sure there was no spread of cancer beyond the prostate. This evaluation included a CT Scan of the Abdomen and Pelvis, a Bone Scan, and Laparoscopic Pelvic Node Sampling. No spread of cancer beyond the prostate was detected using these tests.

In D'Amico's classic article, "Biochemical Outcome after Radical Prostatectomy, External Beam Radiation Therapy, or Interstitial Radiation Therapy for Clinically Localized Prostate Cancer," the outcomes of 74 patients who had a radical prostatectomy and 89 patients who had received external beam radiation therapy were analyzed. At the 2 year follow-up, essentially 50% of surgical patients and 50% of the patients receiving external beam radiation had PSA evidence for recurrent prostate cancer. Seventy to eighty percent of patients receiving interstitial radiation therapy (seeds) had PSA evidence of recurrence.

We applied the Phoenix criteria (PSA nadir + 2ng/ml) in our study. At the 1 year follow-up, 1 patient (7%) had PSA evidence of recurrent prostate cancer. At the 2 year follow-up, an additional 3 patients had evidence of recurrent cancer (two patients met the Phoenix criteria, one patient had a positive repeat prostate biopsy). Comparing our results to D'Amico's, we find that 71% of our patients versus 50% of D'Amico's study group remained free of recurrent prostate cancer based on PSA values. At the 3 year follow-up visit, none of the remaining patients who underwent PSA testing showed evidence of recurrent disease. Partin's group at Johns Hopkins Medicine published their experience treating high-risk prostate cancer with open radical retropubic prostatectomy, robot-assisted laparoscopic radical prostatectomy, and laparoscopic radical prostatectomy. With a 3 year follow-up, there was no evidence of recurrence of prostate cancer in 56.3 % of patients who had the open radical prostatectomy, 67.8 % who had the robotic procedure, and 41% who underwent a laparoscopic radical prostatectomy. Of our study’s 7 patients who received a 5-year follow-up, six remained free of recurrent prostate cancer based on their PSA values and clinical status.

Two patients died during the Penobscot Bay Medical Center study. One patient's death was attributed to metastatic prostate cancer and one patient's death was due to coronary artery disease.

Table 4. Post-cryo PSA (ng/ml) Values in High-risk Patients with a Gleason Score of 8 or 9 who were free of detectable metastatic disease, determined by CT Scan, Bone Scan, and Laproscopic Sampling of Pelvic Nodes.

<table>
<thead>
<tr>
<th>#</th>
<th>Age</th>
<th>Date</th>
<th>Gl'son</th>
<th>Stage</th>
<th>Cores +</th>
<th>Pre 6 w</th>
<th>6 m</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
<th>5 y</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>10/17/2007</td>
<td>4+5=9</td>
<td>T2C</td>
<td>12 of 12</td>
<td>24.9</td>
<td>0.8</td>
<td>9.7</td>
<td>23.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
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<td>4+5=9</td>
<td>T2B</td>
<td>5 of 12</td>
<td>5.6</td>
<td>0.2</td>
<td>0.7</td>
<td>0.9</td>
<td>+BX</td>
<td>1.96</td>
<td>4.57</td>
</tr>
<tr>
<td>3</td>
<td>71</td>
<td>11/30/2007</td>
<td>4+4=8</td>
<td>T1C</td>
<td>6 of 12</td>
<td>4.4</td>
<td>0.2</td>
<td>0.3</td>
<td>0.7</td>
<td>0.5</td>
<td>0.86</td>
<td>0.94</td>
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<tr>
<td>4</td>
<td>80</td>
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<td>4+4=8</td>
<td>T1C</td>
<td>12 of 12</td>
<td>6.1</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>0.15</td>
<td>0.3</td>
<td>0.88</td>
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<tr>
<td>5</td>
<td>75</td>
<td>1/31/2008</td>
<td>4+5=9</td>
<td>T1C</td>
<td>6 of 12</td>
<td>9.6</td>
<td>0.11</td>
<td>0.07</td>
<td>0.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>77</td>
<td>4/2/2008</td>
<td>4+5=9</td>
<td>T1C</td>
<td>10 of 12</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.04</td>
<td>0.1</td>
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</tr>
<tr>
<td>7</td>
<td>73</td>
<td>7/24/2008</td>
<td>4+4=8</td>
<td>T1C</td>
<td>2 of 12</td>
<td>4.1</td>
<td>0.9</td>
<td>0</td>
<td>0.1</td>
<td>0.09</td>
<td>0.11</td>
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<tr>
<td>8</td>
<td>69</td>
<td>7/24/2008</td>
<td>4+5=9</td>
<td>T1C</td>
<td>3 of 7</td>
<td>8.1</td>
<td>0.67</td>
<td>0.46</td>
<td>0.76</td>
<td>0.64</td>
<td>0.69</td>
<td>0.68</td>
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<tr>
<td>9</td>
<td>69</td>
<td>8/14/2008</td>
<td>4+5=9</td>
<td>T2A</td>
<td>2 of 8</td>
<td>5.16</td>
<td>0.2</td>
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<tr>
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<td>T2A</td>
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<td>15.9</td>
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<td>0</td>
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<tr>
<td>11</td>
<td>76</td>
<td>10/9/2009</td>
<td>4+5=9</td>
<td>T1C</td>
<td>12 of 12</td>
<td>13</td>
<td>0.06</td>
<td>1.18</td>
<td>1.94</td>
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<td></td>
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<tr>
<td>12</td>
<td>69</td>
<td>12/4/2009</td>
<td>4+4=8</td>
<td>T1C</td>
<td>2 of 12</td>
<td>13</td>
<td>0.4</td>
<td>0.98</td>
<td>1.58</td>
<td>3.9</td>
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</tr>
<tr>
<td>13</td>
<td>76</td>
<td>9/8/2011</td>
<td>4+4=8</td>
<td>T2C</td>
<td>2 of 12</td>
<td>15</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>63</td>
<td>10/20/2011</td>
<td>4+5=9</td>
<td>T2A</td>
<td>4 of 12</td>
<td>7.89</td>
<td>0.13</td>
<td>0.13</td>
<td>0.13</td>
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</tr>
<tr>
<td>15</td>
<td>65</td>
<td>12/15/2011</td>
<td>5+4=9</td>
<td>T1C</td>
<td>12 of 12</td>
<td>7.68</td>
<td>0.05</td>
<td>0.0</td>
<td>0.0</td>
<td>0.085</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>73</td>
<td>1/12/2012</td>
<td>4+5=9</td>
<td>T2C</td>
<td>12 of 12</td>
<td>38</td>
<td>0.09</td>
<td>0</td>
<td>0.07</td>
<td>0.60</td>
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</tr>
</tbody>
</table>

In table 3, > is used to signify the death of a patient, H is used to indicate the initiation of hormonal therapy, +BX is used to represent the patient who had a post-Cryo prostate biopsy that detected recurrent prostate cancer.
7. What advantages does Cryo present when compared to Radical Surgical Prostatectomy or Minimally Invasive (Laparoscopic or Robotic) Prostatectomy?

A comparison with radical retropubic prostatectomy, using an open or laparoscopic or robotic technique, finds that Cryo patients have:

1. less pain.
2. less problems with leakage of urine.
3. a quicker return to normal activity.
4. fewer wound infections, fewer lymphoceles.
5. less need for blood transfusions or blood products.
6. shorter hospital stay.

There has not been a single report of a wound infection, lymphocele (collection of lymph fluid), or blood transfusion in any outcome report on total cryoablation of the prostate in a peer-reviewed publication. In our series of more than 150 patients, not one patient has experienced any of these problems.

During the past 10 years, minimally invasive radical prostatectomy (MIRP), performed laparoscopically with or without robotic assistance, has become the procedure of choice for men of higher socioeconomic status, despite insufficient data demonstrating its superiority over radical open retropubic prostatectomy. Men were attracted to MIRP because of smaller incisions, high technology, less analgesics, and shorter hospital stays. In 2009, Dr. Hu and colleagues identified 8,837 men who underwent radical prostatectomy from January 1, 2003, through December 31, 2007. The outcomes of these patients, including mortality/morbidity, length of stay, anastomotic strictures, incontinence, erectile dysfunction, and additional cancer therapy, were examined. The study found that MIRP patients experienced shorter length of stay (median 2 vs. 3 days), were less likely to receive donor blood transfusions (2.7 vs. 20.8 %), and were at lower risk for postoperative respiratory complications, miscellaneous surgical complications, and anastomotic strictures (5.8% vs. 14%). However, the MIRP group experienced more genitourinary complications (4.7% vs. 2.1%) and had a higher incidence of urinary incontinence (15.9 vs. 12.2 per 100 person-years) and erectile dysfunction (26.8 vs. 19.2 per 100 person-years). The need for additional cancer therapies was similar for the MIRP group and the radical retropubic prostatectomy group.

A 2012 article, published in the Journal of Clinical Oncology, evaluated and compared urinary continence and sexual function in 626 Medicare enrollees who had undergone surgical removal of a cancerous prostate. Two hundred and twenty patients had an open retropubic radical prostatectomy (ORRP), and 406 had a robotic-assisted laparoscopic radical prostatectomy (RALRP). The two key questions were: 1. “Since this prostate surgery, how much of a problem have you had with leaking or dripping urine?” 2. “Since this prostate surgery, how much of a problem have you had with sexual functioning, such as problems with erections?” Possible responses were “No problem,” “A very small problem,” “A moderate problem,” and “A big problem.” An analysis of the questionnaire revealed that 27.1% of men who had undergone ORRP reported a moderate or big problem with continence, versus 33.3% of men who had RALRP. For sexual function, 89.0% of ORRP patients reported a moderate or big problem compared to 87.5% of RALRP patients. The authors concluded that Medicare-age men should not expect fewer adverse effects following robotic prostatectomy.
Comparing this data to outcome analysis for patients treated with total surgical cryoablation of the prostate reveals that the incidence of urinary incontinence and anastomotic strictures is less in patients treated with cryoablation. However, erectile dysfunction remains a commonly experienced problem in patients who elected prostatectomy or total surgical cryoablation of the prostate.

Cryo is significantly less expensive than radical surgery. The cost advantages associated with Cryo include a shorter hospital stay, absence of pathology charges, and absence for need of blood products. Cryo is performed on one day in an outpatient setting.

8. What advantages does Cryo present when compared to Conformal, or External Beam Radiation Therapy, or Intensity-Modulated Radiation Therapy (IMRT), or Proton Therapy, or Brachytherapy in the primary treatment of localized prostate cancer?

A comparison with radiation therapy finds that Cryo patients avoid:

1. the risk of radiation-induced inflammation of the colon which results in frequent bowel movements, bloody stool, and chronic diarrhea.
2. the risk of radiation-induced inflammation of the bladder which results in frequent voiding and bloody urine.
3. a 67% increased risk of hip fractures following external beam radiation.\(^1\)
4. the increased risk of developing a second cancer (colon, bladder, lung) that occurs following radiation therapy.\(^2,3\)
5. the unnecessary administration of salvage therapy or enrollment in clinical trials due to a bounce in PSA following brachytherapy, which mimics biochemical failure.\(^4\)
   (See Addendum #4. PSA Bounce Following Brachytherapy, pg. 74)

A 2011 review of radiation therapy for clinically localized prostate cancer in the Annals of Internal Medicine asked two questions:

1. What are the benefits and harms of radiation therapy for clinically localized prostate cancer compared with no treatment or no initial treatment (Active Surveillance)?
2. What are the benefits and harms of different forms of radiation therapy for clinically localized prostate cancer?

The conclusion was that a lack of high-quality comparative evidence precludes conclusions about the efficacy of radiation treatments compared with no treatments for localized prostate cancer.\(^5\) In fairness, it must be pointed out that the "lack of a randomized control group" is a problem for all accepted prostate treatments of localized prostate cancer. Radical prostatectomy is the only treatment option that has been compared in a randomized controlled manner with watchful waiting.\(^6\)

In 2012, researchers at the University of North Carolina compared the morbidity and prostate cancer control of Conformal, External Beam Radiation (EXBR), Intensity-modulated Radiation Therapy (IMRT), and Proton therapy (PT).\(^7\) The fact that the adoption of minimally invasive radical prostatectomy, intensity-modulated radiation therapy and proton therapy increased the US health expenditures in 2005 by $350 million played a key role in motivating them to undertake this study. A previous study by Hu found that the theoretical advantages of minimally invasive prostatectomy vs. the older open prostatectomy did not necessarily translate into clinical benefit.\(^8\) Many authorities, entrusted with national budgetary management, wondered if IMRT and Proton therapy were cost effective.

The patients' information was retrieved from the Surveillance, Epidemiology, and End Results (SEER)-Medicare data-base. The study group was composed of 6310 patients in the EXBR group, 6666 in the IMRT group, and 684 in the PT group. Outcomes were reported in rates per 100 patient years. Here, the specific outcome is divided by some number of persons at risk during some time period. It is not probability, because the denominator multiples persons by time. IMRT patients were less likely to experience GI problems and hip fractures than EXBR
patients (13.4 vs. 14.7) and (0.8 vs. 1.0), respectively. However, they were more likely to experience ED (5.9 vs. 5.3). IMRT patients had fewer GI problems than PT patients (12.2 vs. 17.8). There were no significant differences in rates of other morbidities between IMRT and PT therapy.

Cryo is significantly less expensive than radical surgery, radiation therapy, or hormonal therapy. The cost advantages associated with Cryo include a shorter hospital stay, absence of pathology charges, and absence for need of blood products. Cryo is performed on one day in an outpatient setting. In 2012, a cost-utility analysis was performed of primary treatments for clinically localized prostate cancer. Costs were determined from the USA payer perspective. Radiation therapy methods were consistently more expensive than surgical methods: costs ranged from $19,901 (robot-assisted prostatectomy for low-risk disease) to $50,276 (three-dimensional conformal radiation therapy combined with brachytherapy for high-risk disease). Importantly, the analysis found small differences in outcomes.

9. How will my health-related quality-of-life be changed by each treatment option (radical surgery, external beam radiation, brachytherapy, total surgical cryoablation of the prostate) for localized prostate cancer?

Quality-of-life issues have been meticulously evaluated following Brachytherapy, External Beam Radiation Therapy, Radical Prostatectomy, and Total Surgical Cryoablation of the prostate. In 2007, a UCLA group studied 580 men before and 24 months after treatment with Radical Prostatectomy (RP), External Beam Radiation (EBRT), or Brachytherapy (BT). BT patients had moderate voiding symptoms throughout the 24 months after treatment. At one week following BT, 34% of patients were unable to void spontaneously. At 6 months after BT, 10% continued to be unable to empty their bladder without using a catheter. Eight to 35% of RP patients experienced urinary incontinence. At 2 years, 40% of RP patients, 37% of BT patients, and 30% of EBRT patients reported “severe bother” with their sexual function. Bother scores measure the distress associated with the dysfunction. At 2 years, 2% of RP patients, 10% of BT patients, and 14% of EBRT patients reported severe bother with their bowel function.

The American Urological Association published “Guidelines for the Management of Clinically Localized Prostate Cancer: 2007 Update.” The expert panel screened 13,888 citations and abstracts which reported outcomes of prostate cancer treatment. Five hundred and ninety-two articles met the panel’s criteria. The panel summarized the complications in graphs which displayed the percentage of patients with complications associated with Brachytherapy, External Beam radiation Therapy, and Radical Prostatectomy. Bowel and bladder problems were the most commonly reported problems noted after Brachytherapy and External Beam Radiation therapy, varying from 3-70%. Impotence occurred in 10-90% of patients treated with Radiation Therapy. Impotence and urinary incontinence were the two most commonly reported problems following Radical Prostatectomy, with percentages varying from 20-100% and 5-75%, respectively.

In 2008, the quality of life and satisfaction with outcome among prostate cancer survivors was analyzed in 1,201 patients at multiple academic centers. The patients had elected prostatectomy, brachytherapy, or external-beam radiotherapy as primary treatment for their localized prostate cancer. The study had three objectives: 1. Characterize the quality of life after radical prostatectomy, external beam radiation therapy, and brachytherapy 2. Identify factors that influence these outcomes 3. Determine how quality of life relates to overall satisfaction with the outcome of treatment from the perspective of the patient and his partner. Each prostate cancer treatment (Radical prostatectomy, Brachytherapy, External Beam Radiation Therapy) was associated with a distinct pattern of change in quality of life domains related to urinary, sexual or bowel function, and vitality.
Table 1. The percentage of patients and the percentage of the patients’ partners reporting a “Moderate Problem” (MR) or a “Big Problem” (BP) with a specific function following primary treatment of their localized prostate cancer. Urinary Inc. is urinary incontinence; urinary Irr. refers to urinary irritation or obstruction. Vitality function relates to hot flashes, breast problems, depression, lack of energy, weight change. Many patients receiving radiation therapy also received hormonal therapy. The responses were collected by a third-party phone-survey facility before treatment and at 2, 6, 12, and 24 months after the start of treatment.

<table>
<thead>
<tr>
<th>Type of Rx.</th>
<th>Patient’s Report</th>
<th>Partner’s Report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sexual Fx.%</td>
<td>Urinary Inc.%</td>
</tr>
<tr>
<td>-Prostatectomy</td>
<td>MP</td>
<td>BP</td>
</tr>
<tr>
<td>24</td>
<td>26</td>
<td>6</td>
</tr>
<tr>
<td>-EXRT</td>
<td>15</td>
<td>16</td>
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<tr>
<td>-Brachy</td>
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<td>16</td>
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<tr>
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<td>12</td>
<td>10</td>
</tr>
<tr>
<td>-Brachy</td>
<td>7</td>
<td>6</td>
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</tbody>
</table>

Symptoms related to sexual function, vitality, and urinary function were independently associated with prostate cancer treatment outcome satisfaction.

In a 2009 study published in the British Journal of Medicine, a total of 1347 potential controls, matched by age and postal code of residence to patients with localized prostate cancer, were randomly selected from the New South Wales, Australia, electoral roll. The controls and the patients who received treatment for their cancer were closely monitored for 3 years. The objective of the study was to quantify the risk and severity of negative effects of treatment for localized prostate cancer on long-term quality of life. After adjusting for age, baseline function, and comorbidity score, all treatment groups (radical prostatectomy, external beam radiation therapy, brachytherapy, hormonal therapy, active surveillance) experienced a higher proportion of men with urinary incontinence, moderate or severe bowel problems, and impotence than their matched controls. Sexual dysfunction three years after diagnosis was common in all treatment groups. Bowel function was most compromised in those who had external beam radiotherapy.

A multicenter 2011 study found that at 2 years following treatment of localized prostate cancer, 35% of the radical prostatectomy patients, 37% of the external beam radiotherapy patients, and 43% of the brachytherapy patients reported the ability to attain functional erections suitable for intercourse with the aid of medication or devices.

The New England Journal of Medicine published the Prostate Cancer Outcomes Study (PCOS) in 2013. This study enrolled 3533 men in whom prostate cancer had been diagnosed in 1994 or 1995. The functional status of a subgroup of these men, those between ages 55 and 74 years who had undergone either radical prostatectomy (RP) or radiotherapy (RT), was assessed at baseline and at 2, 5, and 15 years after diagnosis. At 5 years, 13.4% of the RP patients and 4.4% of the RT patients had no bladder control or experienced frequent urinary leakage. At 5 years, 75.7% of the RP patients and 71.9% of the RT patients had erections insufficient for intercourse. Finally, at 5 years, 16.3% of RP patients and 31.3% of RT patients had bowel urgency.
An article in the New England Journal of Medicine in 2012 compared the effectiveness of therapy in 731 men with localized prostate cancer who were randomly assigned to radical prostatectomy or observation and followed for a median of 10 years. At 2 year follow-up, 17.1% of patients who had a radical prostatectomy versus 6.3% on observation experienced urinary incontinence ("have a lot of problems with urinary dribbling," "lose larger amounts of urine than dribbling but not all day," "have no control over urine," or "have an indwelling catheter"). In the surgical group, 81.1% experienced erectile dysfunction, versus 44.1% in the observation group. "Moderate" or "big" problems with bowel function were reported by 12.2% of radical prostatectomy patients versus 11.3% of the patients on observation.

In 1999 and again in 2002, Robinson evaluated quality-of-life outcomes for men treated with cryosurgery for localized prostate cancer. Bowel function returned to pre-cryo baseline function by 3 months in all cryo patients. Bladder function returned to pre-cryo baseline function by 8 months in all 69 patients. Forty-six patients were sexually active and able to have erections prior to Cryo. All men reported a complete loss of erectile function at 6 weeks post-treatment. At 12 months, only 1 participant had recovered erectile function sufficient for intercourse. At 36 months, 13 percent of the participants reported return of erectile function. An additional 34 percent were able to have erections with assistance (vacuum erection device or vaso-active drugs). Physical well-being, social/family well-being, emotional well-being, and functional well-being scores of Cryo patients were better than the scores of patients who were treated with radical prostatectomy, primary pelvic radiation, brachytherapy, or active surveillance at 12 and 36 months following the treatment.

In 2009 Robinson reported on 244 men with newly diagnosed localized prostate cancer who were randomly assigned to cryoablation or external beam radiation therapy (EBRT). All patients completed questionnaires during the months following their therapy. Patients in both groups recovered their baseline levels of urinary and bowel function by 36 months post-treatment. By 36 months, 22 percent of cryoablation patients and 36 percent of radiation therapy patients were having unassisted or assisted intercourse.

Please see page 20 for the Penobscot Bay Medical Center data on Health-related Quality of Life scores following total cryoablation of the prostate.


10. Each of the primary active treatment options can potentially adversely impact the quality of my life. Can I avoid or defer therapy and have my urologist check me periodically to make sure that my cancer is not becoming more aggressive. (Active Surveillance)

Am I someone who can safely forego immediate treatment and choose Active Surveillance?

In 2004, 9.8% of patients with low-risk prostate cancer opted for Active Surveillance. This percentage increased to 18.6% in 2011. We discuss Active Surveillance with patients who meet the criteria established at Johns Hopkins Medical Center:

1. Life expectancy less than 20 years.
2. Cancer cannot be felt on digital rectal examination (stage T1c).
3. PSA density (PSA divided by prostate volume is less than 0.15).
4. Gleason score is 6 or less with no Gleason pattern 4 or 5.
5. No more than 2 cores with cancer, or cancer involving no more than 50% of any core on at least a 12 core biopsy.
   OR
   1. Life expectancy less than 10-15 years.
   2. Cancer not felt on digital rectal examination and/or small nodule (stage T1c or T2a).
   3. PSA below 10ng/ml.
   4. Gleason score of 6 or less with no Gleason pattern 4 or 5 on a least a 12 core biopsy.

If you decide on Active Surveillance, several recommendations are made for follow-up of your cancer by Johns Hopkins:

1. 12-14 core prostate biopsy annually until age 75 years.
2. PSA and free PSA every 6 months.
3. Digital rectal examination at least yearly.

Other medical centers incorporate PSA velocity, change in digital rectal exam, and overall health status before making a final recommendation regarding the frequency of prostate biopsy.

If I select AS, what is the likelihood I will remain on it? What would prompt my urologist to recommend Active Treatment?

In 2008, a peer-reviewed article presented the outcomes of 321 men who selected Active Surveillance as their initial management at the University of California at San Francisco. Patients were considered to have a progression of their cancer if their follow-up biopsies had a Gleason Score of 7 or greater or their PSA increased more than 0.75ng/ml/year. One hundred twenty men (37%) met at least 1 criterion for disease progression. Seventy-eight (24%) received secondary treatment at a median of 3 years. The median patient follow-up was 3.6 years.
Why is going from a Gleason score of 6 to a score of 7 or higher so important? Dr. Albertsen’s group answered this question. In 2005, he published the 20-year outcomes of 767 patients with localized prostate cancer who were simply observed or received immediate or delayed hormonal therapy. Two hundred and ninety-four patients had a Gleason score of 6. Prostate cancer was the cause of death in 81 (27%) of these patients. One hundred and thirty-seven patients had a Gleason score of 7. Prostate cancer was the cause of death in 62 (45%) of these patients. In an earlier study by the same group, maximum estimated lost life expectancy increased as the Gleason score increased.

Four academic centers in Europe provided data for 616 men who selected AS. All patients had PSA values of ≤10, PSA density <0.2 ng/ml, stage T1/T2, Gleason score ≤6, and <2 positive biopsy cores. Within a mean of 2.55 yrs (range 0.29-10.86), one hundred eighty-two men received active treatment, 80 had radical prostatectomy, 89 had radiation therapy, and 13 patients received hormonal therapy. One hundred and ten men opted out of AS and elected radical surgery or radiation therapy, despite favorable PSA and PSA doubling times. A change in the tumor stage prompted opting out of AS in only 9 patients. Information on re-biopsy was known in 27 patients and played no role in opting out of AS.

In 2010, the Toronto group led by Klotz published their experience with 450 patients on AS. The criteria for entering the study were a Gleason Score of ≤6 and a PSA of ≤10. The median follow-up was 6.8 years. The 10-year prostate cancer specific survival was 97.2%. Thirty percent of patients demonstrated disease progression based on an increase in Gleason Score (4+3=7 or greater), PSA doubling time of <3 years, or the development of an unequivocal palpable prostatic nodule.

Patients on AS are also at risk for experiencing psychological morbidity. Burnet and colleagues used the Hospital Anxiety and Depression Scale to evaluate 329 consecutive patients with localized prostate cancer. One hundred were on AS, 81 were currently receiving radiotherapy and hormonal therapy, and 148 had previously received radical radiotherapy. Overall, 16% met criteria for anxiety, and 60% met criteria for depression. There were no significant differences in anxiety and depression between the treatment groups.

Protocol requires patients on AS to undergo periodic PSA measurements and follow-up prostate biopsies. Each has been shown to evoke an increase in anxiety. Dale and associates performed a systematic review of 29 peer-reviewed publications that examined anxiety levels in men with prostate cancer. They found the anxiety levels in these men were substantially higher than men who were simply at risk for prostate cancer. A Sloan-Kettering study of 88 men who chose AS between 1984 and 2001 found 7 patients who did not show progression of their cancer but received definitive therapy because of their anxiety. Finally, a multi-center study, using CaPSURE data from 105 patients, identified that decisions about treatment for some men were significantly influenced by cancer-related anxiety rather than clinical presentation and disease progression.
Long-term quality-of-life outcomes after radical prostatectomy (RP) in 182 patients or AS in 167 patients were analyzed in the Scandinavian Prostate Cancer Group-4 randomized trial, with a follow-up of more than 12 years. The study included a population-based control group numbering 281. High self-assessed quality of life was reported by 35% of men who had been treated with radical prostatectomy, 34% of men on AS, and 45% of the control group. Prevalence of erectile dysfunction was 84% in the RP patients, versus 80% in the AS patients, and 46% in the control group. The prevalence of urinary leakage was 41%, 11%, and 3%, respectively. This data strongly suggests that cancer itself has a significant adverse impact on quality-of-life, even when active therapy is avoided.

In 2014, two studies presented relatively long term follow-up data regarding patients on AS. The medical records of all patients (47) who were commenced on AS in UK at a District General Hospital from 2002-2003 were reviewed. Data to January 2011 was gathered. Eighty-one percent of patients had a Gleason score of 6 or less. Only 10.6% remained on AS during the follow-up period. Forty percent progressed to radical therapy, either radical prostatectomy or radical radiotherapy. Thirty per cent of patients went onto hormone treatment. Death from prostate cancer occurred in 15% of patients.

Between 1989 and 1999, 695 men with early prostate cancer were randomly assigned to watchful waiting or radical prostatectomy by the Scandinavian Prostate Cancer Group. Primary end points of the study (SPCG-4) were death from any cause, death from prostate cancer, and the risk of metastases. A total of 347 men were randomly assigned to the radical prostatectomy group (RPG) and 348 men were assigned to the watchful-waiting group (WWG). The average follow-up was 13.4 years. By the end of 2012, 200 men in the RPG and 247 men in the WWG had died. The cumulative incidence of death at 18 years was 56.1% in the RPG versus 68.9% in the WWG. Sixty-three men in the RPG and 99 men in the WWG had died from prostate cancer. The cumulative incidence of death, again at 18 years, was 17.7% in the RPG versus 28.7% in WWG. The cumulative incidence for distant metastases, again at 18 years, was 26.1% in the RPG versus 38.3% in the WWG. Among men with low-risk prostate cancer, there was a significant absolute reduction of 15.6% in the rate of death from any cause and 10.6% reduction in the risk of metastases in the RPG. Among men with intermediate-risk cancer there was a significant absolute reduction of 15.5% in overall mortality, a 24.2% in the rate of death from prostate cancer, and a 19.9% in the risk of metastases in the RPG. Among men in the high-risk group, there was no significant reduction with respect to any of the 3 end points.

The bottom line is if you select Active Surveillance make sure you strictly comply with the follow-up guidelines! You have a cancer and this cancer has the potential to adversely impact the quality and length of your life!


**11. Will Primary Androgen Deprivation Therapy (Hormone Therapy) cure my cancer and lengthen my life?**

The answer is NO! A study of 19,271 men who did not receive definitive local therapy (radiation or surgery) for localized prostate cancer was published in JAMA in 2008.¹ The diagnosis was made between 1992 and 2002. Overall and prostate cancer-specific survival was available through December 31, 2006, and December 31, 2004, respectively. Forty-one % (7901) of the population received Androgen Deprivation Therapy (PADT). There were 1,560 prostate cancer deaths and 11,045 deaths from all causes in the study. The longer the duration of PADT, the lower overall and cancer-specific survival among 5,826 PADT users who survived at least 3 years. Patients receiving PADT were more likely to die within 10 years due to prostate cancer than patients who did not receive PADT. Additionally, PADT did not improve 10-year overall survival.


**12. High-intensity Focused Ultrasound (HIFU) for the Primary Treatment of Localized Prostate Cancer: Technology, Post-HIFU PSA Outcomes, Biopsy Findings, and Quality of Life Issues.**

**Background:**
High-intensity Focused Ultrasound (HIFU) was developed in the 1940s to destroy tissue. Transrectal HIFU was first used to treat prostate cancer in 1966. Presently HIFU is utilized in Europe, Japan, and Canada, but has not been approved by the Food and Drug Administration in USA for the primary treatment of localized prostate cancer. We present this information because patients are beginning to inquire about it.
Mechanism:
HIFU uses a transducer to direct high energy, compressed sound waves with a frequency of 3.0 or 4.0-MHz at a specific point in the body. The transducer function is perhaps analogous to a magnifying glass as it concentrates light waves on a specific target. A cigar shaped area of coagulation necrosis ranging from 1.7x1.7x26 mm (0.08 cc) to 2.0x2.0x10mm (0.04 cc) of tissue is ablated, depending on whether the Ablatherm or Sonablate HIFU device is used. The targeted tissue absorbs the sonic energy and converts it to thermal energy. To be precise, the sound waves strike molecules in the targeted tissue and make them vibrate. This vibration produces heat. When human tissue reaches or exceeds 56°C for 1 second, the tissue dies.  

Biochemical (PSA) Outcomes Following HIFU:
One of the first published HIFU reports with a significant number of patients was provided by the University of Perugia, Torino, Italy. Between 2004 and 2007, 163 men with localized prostate cancer underwent one or two treatments with HIFU. PSA testing was performed at 1 month and then every 3 months after treatment. Biochemical failure was defined according to Phoenix criteria (PSA nadir + 2 ng/ml). The patients were stratified on the basis of the D'Amico criteria. Patients in whom the prostate cancer was not felt during the pretreatment digital rectal exam, or if felt, comprised only a small area on one side of the prostate, and had a Gleason score of less than 7, and had a PSA of 10 or less were classified as low-risk for biochemical PSA recurrence following treatment of their prostate cancer. Patients whose cancer could be felt in both lobes, or with a PSA greater than 20, or with a Gleason score of greater than 7 were classified as high-risk for biochemical PSA recurrence. Patients in whom the prostate cancer could be felt in more than half of one lobe, but not both lobes, or a Gleason score of 7, or a PSA greater than 10 but less than or equal to 20 were classified as intermediate-risk for biochemical PSA recurrence. The 3-year biochemical failure-free rate was 86%, 79%, and 56% for low-, intermediate-, and high-risk patients.

A multi-center report on the “10 year Outcome and Morbidity of High-Intensity Focused Ultrasound (HIFU) as a Primary Therapy for Localized Prostate Cancer: Outcomes from 2552 Men Followed with the @-Registry” appeared in 2011. Patients were followed for a mean (average) of 39.6 months. The median (the "middle" value in the list of numbers) PSA nadir was 0.11 and was reached at 3 months. Patients were stratified according to D'Amico’s 2003 risk groups. At a 5-year follow-up, there was an 84% biochemical failure-free rate for low-risk patients, a 77% failure-free rate in moderate-risk patients, and a 68% failure-free rate in high-risk patients using the Phoenix definition (PSA nadir + 2 ng/ml).

Urologists at the University Hospital Hamburg-Eppendorf, Hamburg, Germany, reported on the 5-year outcomes of 191 consecutive patients who received a single HIFU application as a first-line therapy for clinically localized prostate cancer. HIFU was classified as a failure in patients whose PSA equaled or exceeded a PSA nadir + 1.2 ng/ml (Stuttgart definition), or who experience a rise in PSA level to ≥0.5 if PSA doubling time was ≤6 months. The patients were stratified by risk group, using the D'Amico criteria, as low-, intermediate-, and high-risk. Post HIFU PSA measurements occurred at 2, 3, and 6 months, and every 3 months thereafter. Only 2 patients were lost to follow-up. The 5-year biochemical failure-free rates were 85%, 65%, and 55% for the low-, intermediate-, and high-risk groups, respectively. The authors concluded that the principal use for HIFU should be in patients with low-risk prostate cancer.

In 2012, “Long-Term Follow-up and Complications Rate” of 74 patients with prostate cancer who had been treated with HIFU at the University of Parma, Italy, was published. The mean
post-HIFU PSA nadir was 1.12 ng/ml, with a median of 0.95, and was obtained within a mean range of 3 months. The nadir value was ≤1.0 in 76.6% of patients, while a nadir value of ≤0.2 was obtained in 31.6%. Based on the Phoenix criteria for biochemical failure (PSA nadir + 2), 26.6% (#16) of patients failed during a mean follow-up of 29.9 months. Using the D’Amico criteria for risk stratification, 83% of the low-, 80% of the intermediate-, and 12% of the high-risk group were biochemically failure-free. Forty-five patients had follow-up biopsies and of these patients, 15.5% had cancer cells present in their post-HIFU biopsies.

The Department of Surgery at McMaster University in Toronto published its data from 447 consecutive patients who were treated with a single session of HIFU between May 2005 and December 2010. The study’s objective was to assess 4-year biochemical failure rate (BCF) in patients after HIFU using the Horwitz (two consecutive PSA increases of at least 0.5 nl/ml) and Stuttgart definition (PSA nadir + 1.2 ng/ml). The mean and median absolute PSA nadir levels were 0.36 and 0.1 ng/ml, respectively, and were achieved in a median time of 3 months. Patients were stratified using the D’Amico criteria. Based on the Stuttgart definition, BCF failure-free rate for low-risk patients was 75% and 62% for intermediate-risk patients at 4 years. Using the Horwitz definition, it was 76% for low-risk patients and 69% for intermediate-risk patients. The study noted that at a 4-year follow-up, the biochemical failure-free rates were significantly lower for a PSA nadir ≤0.5 ng/ml and a pre-treatment prostate volume of ≤ 30 ml.

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HIFU Failure-free Rate (%) in low-, intermediate-, and high-risk patients with localized prostate cancer. *FR - failure-free rate, **NR – not reported or not included in the study population.

An analysis of 804 patients with localized prostate cancer who were treated with HIFU at multiple academic centers was published in 2011. The objective of this study was to determine if the PSA nadir after HIFU could be used as a predictor of biochemical disease-free survival (DFSR). The inclusion criteria included a minimum follow-up of 3 years; localized disease; no previous hormone therapy; Gleason score ≤7; and PSA level ≤20. Patients were placed into four PSA nadir groups: group 1, ≤0.2 ng/ml; group 2, 0.21 - 0.5 ng/ml; group 3, 0.51-1 ng/ml; group 4, >1. At 5 years, the DFSR was 84, 64, 40, and 30% for the four groups, respectively. The study concluded that PSA nadir after HIFU was a statistically significant predictor of biochemical DFSR.

Histopathological Findings after HIFU:
As part of the study’s protocol, 163 HIFU patients at the University of Perugia underwent post-HIFU prostate biopsy at 6 months. Residual cancer was observed in 33.9% of patients after a single treatment.

In 2008, Muto and associates at Teikyo University School of Medicine in Tokyo, Japan, published their experience with whole prostate gland HIFU in 41 patients. The selection criteria
were as follows: > 60 years old, MRI of the prostate that indicated localized cancer. Low-, intermediate, and high-risk patients were included. Biopsies were routinely performed 6 and 12 months following the procedure. Cancer cells were detected in 12% and 18% of patients at 6 and 12 months, respectively.\(^9\)

Four years later, Blana reported the biopsy results for 226 of 356 patients treated with whole prostate gland HIFU.\(^{11}\) Each patient had either a T1 or T2 cancer with a prostate AP diameter of \(\leq 24\) mm, a criterion that excluded patients with prostate volumes of greater than 35ml. Biopsy was recommended at 3-6 months post HIFU and/or if a PSA level was recorded that was considered clinically relevant by the treating physician. Residual cancer was noted in 44 of the 226 patients (19.5%).\(^{10}\)

In 2010 a group of pathologists from the United States and Europe analyzed 25 consecutive prostate cancer patients who were treated by HIFU from 2002 to 2006 at a single institution.\(^{11}\) Inclusion criteria included pathologically confirmed prostate cancer, Gleason score 7 or less, pre-treatment PSA 10 ng/ml or less, and stages T1-T2 (D’Amico’s low- and intermediate-risk groups). Prostatic biopsies were obtained 6 months after the HIFU therapy. Eleven patients (44%) had residual prostatic carcinoma. In 88% of these patients with residual cancer, the prostate tissue did not show any microscopic changes.

A second group of pathologists at the Bon Secours Hospital in Cork, Ireland, reviewed post-HIFU prostate biopsies that were performed in 22 patients who had rising or elevated PSA.\(^{12}\) A standard definition of biochemical failure was not universally employed. Seventy-seven percent (17/22) contained adenocarcinoma. Eight patients without rising post-HIFU PSA also were biopsied. Twenty-five percent (2/8) contained adenocarcinoma. In 29 of the 30 sets of post-HIFU biopsies, benign prostate tissue was present, confirming incomplete ablation of the prostate.

Quality of Life Issues:
In the following reports, urinary incontinence is reported as simply present or absent in some studies, while in other reports urinary incontinence when present is graded. The commonly used grading system is: grade I = safety pad during the day; grade II = 2-3 pads daily, dry at night; grade III = >3 pads daily and/or wet at night.

The Muto and associates study (2008) of 70 patients found that 11.4% of patients experienced a clinical urinary tract infection, and 8.6% developed a urethral stricture. Fifty-two patients were continent of urine prior to HIFU. Three patients (6%) were incontinent following HIFU.\(^{10}\) In the Mearini study of 163 patients, 18 patients (16%) experienced grade I or II urinary incontinence, and 1 patient developed grade III urinary incontinence.\(^3\) Urethral stricture developed in 24 patients (15%) and was treated with dilation in 5 and transurethral surgery in 19. A recto-urethral fistula occurred in 1 patient.\(^3\)

In May, 2011, Ganzer reported on the outcomes of 2552 men who received HIFU as a primary treatment for their localized prostate cancer at nine European Centres and whose follow-up data was stored in the @-Registry.\(^5\) Patients were followed for an average of 39.6 months. Grade I, II, and III incontinence was observed in 12.4%, 6.4%, and 1.8% of the population, respectively. Urethral or bladder neck strictures were present in 18.5% of patients. Urinary retention occurred in 11%. Potency data was inconsistent and is not presented herein.
In the Parma University report (2012), 7 of 74 patients (9%) with prostate cancer who had been treated with HIFU continued to experience urinary incontinence 12 months after their procedure. Sixteen of the 74 patients were potent prior to HIFU. Twelve of these 16 men (75%) were impotent after HIFU. One patient developed a recto-vesical fistula.

The University Hospital Hamburg-Eppendorf study, with a follow-up of 189 patients, determined that 99 patients (51.5%) experienced voiding difficulties within 12 months of single-session HIFU, with 36 (18.7%) requiring transurethral surgery. Grade II urinary incontinence was experienced by 12 patients (6.3%), and Grade III in 2 patients (1.6%). Recurrent urinary tract infection occurred in 51 (26.5%) patients, and 3 (1.6%) developed recto-urethral fistulas. Sung’s study (2012) reported that none of the 126 study patients required blood transfusions, had wound problems, or experienced strokes, deep vein thrombosis, or bowel problems. The incontinence rate was 6.3%, and the impotence rate was 73.7%.

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Quality of Life issues following HIFU as the primary treatment for localized prostate cancer. NR – not reported in this study.

A 2012 review article on HIFU from the Department of Urology at Tokai University Hachioji Hospital, Hachioji, Tokyo, Japan, reports the complications associated with HIFU. The common and usually transient complication was the inability to void, reported in 3.9 - 22.3% of cases. A narrowing of the urethra or bladder neck was experienced in 0 - 41.2% of patients. Other complications included urinary tract infections and epididymitis (0 - 48%), recto-urethral fistula (0.6 - 0.9%), urethral stricture or bladder neck contracture (0 - 41%), urinary incontinence (1 - 18%), and erectile dysfunction (18 - 53%, median 33%). The significant variation in complication rates in the cited studies raises questions about methodology within the studies.

In 2010, Marisa Warmuth, Tim Johansson, and Philipp Mad reported their systematic literature search for studies conducted on humans which were published in either English or German in several databases from 2000 to 2010. They included all prospective studies with >50 study participants and assessed their quality using the Grading of Recommendations Assessment, Development, and Evaluation approach. They concluded that the available evidence on efficacy and safety of HIFU in prostate cancer is of very low quality, mainly due to study designs that lack control groups. This grading means that any conclusions about the efficacy and safety of HIFU in prostate cancer are very uncertain.

Gänzer and Blana responded to Warmuth’s review of HIFU. The "lack of control groups," they state, is a problem for all accepted prostate treatments of localized prostate cancer. They point out that radical prostatectomy is the only treatment option that has been compared in a randomized controlled manner with watchful waiting. Further, they note that it has been 100 years since the invention of radical prostatectomy. Finally, they reveal that there are two
controlled trials going on in the United States. One study compared HIFU with brachytherapy in organ-confined prostate cancer with the primary end point being absence of biochemical failure at 24 months. The second study compares biochemical outcome through a 24-month period between HIFU and cryotherapy.

Section II: The Cryoablation Experience

13. What can I expect at the visit just prior to my procedure?

Two weeks before your procedure, you will have your medical history reviewed and your physical exam performed in the office. Bring a list of all your medications, including over-the-counter drugs and herbal preparations. You will be given several prescriptions for new medications that you will begin on returning home after Cryo. These medications are in addition to your routine medications.

14. What do I need to do during the ten days before my Cryo procedure?

1. We recommend that you stop taking all medication that influences how your blood clots. Plavix is tops on this list and should not be taken for ten days prior to Cryo. As a general rule, stop Coumadin (warfarin) 5 days before the procedure. We commonly ask your primary-care provider or cardiologist to guide us in managing your blood thinners. If you have a mechanical heart valve, you will receive an injectable anticoagulant during this period.

   Motrin, Advil, Naprosyn, aspirin, and other similar drugs, used to treat pain or swelling in your muscles or joints, must be discontinued 10 days prior to your procedure.

   A few herbal supplements “thin the blood.” To be safe, avoid all supplements for a week before your procedure.

2. On the day before the cryoablation procedure, please avoid solid foods. Drink only clear (clear liquids are those you can see through) non-carbonated liquids. These include water and clear soup broths, such as chicken soup broth. Avoid all milk products. Additional details are included in your Bowel Preparation Handout. Between 4 p.m. and 6 p.m. begin drinking the bowel cleansing liquid. Please follow the bowel preparation instructions.

3. Do not eat or drink anything (no solids or liquids or even water) after midnight the night before the cryoablation.

4. On the day of the procedure, use an over-the-counter saline enema in the privacy of your home between 1 to 3 hours before leaving your home. This enema is available at any drugstore. The cleaner the bowel is at the time of your procedure, the better the ultrasound image of the prostate. The better the ultrasound image, the easier it is to precisely position each probe. If your travel time to the hospital is longer than 1 hour, administer the enema after your arrival at the hospital.
15. What can I expect during my time in the hospital?

You will be informed of the time that you should arrive at the hospital. Bring all the medications that you routinely use to the preoperative holding area for the surgical team to review. You will have an opportunity to ask your anesthesiologist and surgeon questions. Once all your questions have been answered to your satisfaction, you will be asked to sign an operative permit. A needle will be inserted into a vein in your arm. This will allow you to receive sterile solutions and antibiotics before and during your procedure. Cryo can be performed under spinal, or general, or a combination of spinal/general anesthesia. You will make this choice. The Cryo procedure commonly takes 2-3 hours. After the procedure, you will awake in the recovery room. Customarily, patients remain there for 2-3 hours. Once awake, alert, and medically stable, you will be transferred to your hospital room.

You will probably be hungry for the evening meal and you can order any food on the menu. You will have a urethral catheter. Your urine will be a reddish-orange due to the medication, Pyridium. You may experience discomfort in your lower belly and penis. Pain medication will be available. You will stay in the hospital overnight for observation. A medication to help you sleep is available if you request it.

16. What medications will I take when I go home?

Please resume all medications that you were routinely taking before this procedure, unless directed otherwise. The following medications are commonly prescribed following Cryo. If you have an allergy to any of these medications, please alert your physician.

1. Flomax (tamsulosin) 0.4mg tablet. This drug will help you urinate after the catheter is removed. Take one Flomax at bedtime each day for 31 days.
2. Pyridium 100mg capsule. This drug will decrease bladder discomfort and the burning sensation when you urinate. Take one pill every 8 hours, beginning the day you return home from the hospital. Take this medication for 10 days.
3. Ciprofloxin 500mg tablet. This drug is an antibiotic that will minimize the risk of a urinary tract infection. Take one tablet 1 hour before you remove your catheter and a second tablet 8 hours after you have removed your catheter.
4. Macrobid 100mg tablet. This drug is an antibiotic. It will minimize the chance you will experience a urinary infection during the first month after Cryo. Take one tablet at bedtime for 31 days, starting the day after you remove your catheter.
17. What will I experience 2-4 weeks after the Cryo procedure?

1. You may experience constipation. Water, high-fiber foods, prune juice, Metamucil, and MOM will help. Do not use suppositories or enemas!
2. You may experience mild discomfort in the lower belly or penis. Tylenol or Motrin will usually control this.
3. Swelling and bruising of the scrotum and penis may occur. This will usually disappear in 10-14 days.
4. Your urine will be reddish-orange due to the medication Pyridium.
5. You may experience mild to moderate discomfort in the anal area and base of the scrotum. Ice packs to the area will decrease or eliminate the discomfort. You can also minimize the discomfort by sitting on a pillow or a foam cushion at least 6 inches thick. This discomfort commonly disappears within 2-3 weeks after your procedure.
6. You may need to hurry to the bathroom. Pyridium helps lessen the urgency sensation. If you are bothered by frequent voiding, call us. Medication is available to control this symptom.
7. You can have a low-grade temperature elevation. This does not mean you have an infection. The freezing process releases chemicals that cause a temperature elevation. The temperature increase can occur several days after the cryo procedure and last for several days. Call us if your temperature is greater than 101.5°F.

Occasionally, patients will notice a bloody discharge from their penis or small clots in the urine. Rarely, a patient will lose some sensation to touch in the penis. These symptoms will customarily gradually resolve within 4-6 weeks.

18. What can I do during the first 4 weeks after my Cryo procedure?

1. Immediately after returning home, you can resume activities that are not strenuous. These activities include taking walks, stair-climbing, and going out in public for social events.
2. You may shower.
3. Avoid activities that put pressure on the area near your rectum/anus – for example, avoid cycling, rowing, weight lifting, or paddling a kayak.
4. Avoid driving while you have a catheter.
19. How do I remove my catheter?

Prior to leaving the hospital, you will receive instructions on catheter care. Routinely, the catheter is removed on the 5th-7th day following your procedure. Many patients choose to remove their catheter at home, thus avoiding the travel and saving the time required to return to the urologist’s office. If you decide on this option, follow these instructions:

1. Disconnect the catheter from the drainage bag.
2. Cut the short side-arm of the catheter between the main tube and the hard plastic ring.
3. Allow the water that filled the catheter’s balloon to squirting into the toilet.
4. When the water stops squirting from the side-arm, gently and slowly remove the catheter.

You may notice a small amount of blood on the tip of the catheter. You will likely feel the urge to void within 1-2 hours. Most patients will void frequently for several weeks. You may have a mild burning sensation in the penis as you void.

20. What should I do if I can’t void after I remove my catheter?

A few patients will be unable to void during the first few days after they remove their catheter. If you feel the need to void, but can’t:

1. Wash your hands and penis with soapy water.
2. Straddle the toilet.
3. Apply the lubricant you were given to the opening in your penis (urethra) and to the tip of the new catheter that you were provided at the time of discharge from the hospital. Be sure the curve on the tip of the catheter points up toward the ceiling.
4. Insert the catheter into the opening in your penis (urethra). The knob on the end of the catheter should point up, in the same direction as the tip of the catheter. Gradually advance the catheter until urine begins dripping from the catheter. Then advance the catheter another inch into your penis. Tip the catheter downward toward the toilet while holding it in place.
5. Once urine stops flowing through the catheter, remove the catheter.
6. Rinse the catheter with soapy water and allow it to air dry. Save the catheter in case you need to use it again.

21. Will I be able to have intercourse after Cryo?

It is very rare to regain normal erectile function for the first six months after the cryoablation procedure. At your seven-week visit, we will discuss treatment options (Viagra, Levitra, Cialis, the vacuum device, or intercavernosal therapy) that will assist you to have intercourse.
22. How will I be checked for cancer after Cryo?

We realize that you will be very concerned about your PSA value. Please wait at least six weeks after your procedure before having this blood test. Why? PSA is released from prostate cells during cryoablation. Immediately after the procedure your PSA value will exceed several hundred (ng/ml). The half life of PSA is three days. If, for example, your peak PSA value were 500, three days later it would be 250, at six days 125, at 9 days 62.5, at 12 days 31.25, and so forth. Depending on your highest PSA value after cryo, it may take up to 6-12 weeks before the lowest PSA value is achieved. You will have a second PSA value obtained at 3 months after the procedure and then again every 3 months during the first year following Cryo.

You will be seen in our office at seven weeks after the procedure and then again at 6 and 12 months. During your follow-up visits we may perform a digital rectal exam in order to confirm that the swelling in the area of the prostate is subsiding.

Assuming the PSA falls to less than 0.6ng/ml and remains less than 1.0ng/ml during the first year, we will obtain a PSA every 6 months for the subsequent year and then yearly. Please see Addendum #5 on page 75 for additional information regarding post-cryo PSA values.

![Fig. 14](image1.png) ![Fig. 15](image2.png)

Fig. 14. This is a prostate biopsy under the microscope. The tissue has been bathed in a special stain that colors the prostate cells blue. In this picture the blue cells are packed together, a hallmark of prostate cancer.

Fig. 15. This is prostate tissue after Cryo. The prostate cancer cells have been replaced by scar tissue (collagen), the pink tissue. In this slide there are a few cholesterol clefts and dystrophic calcifications.
23. When was extreme cold first used to treat prostate cancer?

The era of cryoablation of the prostate began in 1964. The freezing agent, liquid nitrogen, was delivered through probes that were inserted through the urethra into the prostate.¹ (Figure 16)

In 1972, Flocks made an incision in the skin and exposed the prostate.² He then directly inserted freezing probes into the prostate. Again, liquid nitrogen was the freezing agent. These cancer patients experienced cure rates comparable to patients treated with radiotherapy and radical surgery. However, cryoablation did not become a widely accepted therapy because many cryo patients experienced post-operative voiding problems due to injury of the urethra, and a number of patients developed an opening between the urinary tube and the rectum (urethro-rectal fistula).

24. What changes have been made in the past twenty years to improve the safety and effectiveness of cryoablation of the prostate?

Landmark advances in the cryoablative technique were made between 1990 and 2000. Liquid nitrogen was replaced by a combination of argon (freezing gas) and helium (warming gas) gases. (Figure 17)

![Cryo Probes](image)

**Fig. 17**

Fig. 17. The two large tanks contain argon and helium. The gray probes to the left of the computer are closed circuits that circulate these gases. The computer provides continuous monitoring of the temperatures in and around the prostate.

Liquid nitrogen did not permit precise control of the targeted tissue because the area frozen continued to expand after the flow of nitrogen was stopped. With the two new gases, the area frozen was contained by shutting off the argon and turning on the warming gas, helium.
Temperature sensors were added to permit continuous real-time temperature measurements in and around the prostate. A rectal ultrasound probe was introduced to provide real-time images of ice formation in the prostate. (Figure 18)

![Image](image1.png)

**Fig. 18**

Fig. 18. This is an ultrasound image of the prostate. The white double U is the lowest edge of the ice. The white edge is continuously used to determine the amount of prostate that has been destroyed.

These images, in combination with temperature measurements provided by the temperature sensors, help the physician determine when the cryoablative procedure is complete, while protecting nearby critical tissue. (Figure 19)

![Image](image2.png)

**Fig. 19**

Fig. 19. The blue temperature-sensing probes to the external sphincter (ES), the anterior prostate (ANT or A), and Denonvilliers' fascia (DEN) surround the gray probes that carry argon and helium to and from the prostate. The monitor reports that cryo probes #1 and #2 are active and freezing 100% of each cycle. Probes #3-6 are inactive. The temperature in the external sphincter is 38°C or 100°F.
Finally, surgeons began warming the urethra, the urinary tube, during the procedure with a double lumen catheter. (*Figures 20 and 21*) This device minimized the chances that the urethra would be frozen during the cryo procedure.

![Fig. 20](image1.png)  ![Fig. 21](image2.png)

**Fig. 20.** The warming tube has a central core that is surrounded by a thin plastic sheath. A warm solution (42 °C or 107°F) continuously circulates in the tube and protects the urethra from freezing.  
**Fig. 21.** This is the ultrasound image of the warming tube in the urethra.

Recent studies report that less than 0.5% of patients developed a fistula.


25. *Technical Details of the Total Cryoablation of the Prostate Procedure at the Penobscot Bay Medical Center*

Preoperative evaluation includes serum PSA level, digital rectal exam, and trans-rectal guided twelve-core prostate biopsy with coincident determination of prostate volume. Hormonal therapy is instituted prior to Cryo therapy in patients with a prostate volume >50 ml. This therapy is not continued following the cryoablation. Bone scan, pelvic computed tomography, and laproscopic pelvic node sampling are performed in patients with high-risk prostate cancer to exclude metastatic disease.

**Technique:**  
Cryoablation is performed using the Cryocare CS System (Endocare, Inc., Irvine, CA). Argon and helium are the freezing and thawing agents. Multiple 2.4 mm cryoprobes (6 to 8) and 17-gauge thermocouples are placed under trans-rectal ultrasound (TRUS) guidance, utilizing the brachytherapy template. A urethral warming catheter containing a +42°C solution is placed prior to initiating the freeze. A double freeze/thaw cycle is performed under TRUS and thermocouple guidance. The target temperature throughout the prostate is -40°C. The argon freeze is initiated in the anterior probes and continued toward the rectum. In the anterior probes, freeze is present 100% of each cycle for at least 5 minutes and then lowered to 75%. In the lateral probes the
freeze time begins at 75% for each cycle. In the posterior probes, the freeze is active 25% of each cycle. The edge of the ice ball is carried down to the anterior rectal wall and out to the external sphincter. The temperature in Denovillier’s fascia is kept above -5°C. The sphincter temperature is kept above 20°C. Once the target temperature is achieved, a passive thaw is permitted for 3 minutes, followed by an active thaw with helium. The active thaw is discontinued once the prostatic architecture, the cryoprobes, and thermocouples are clearly identified. After the second freeze, again a passive thaw is permitted for 3 minutes, followed by an active thaw. Following the thaw, the urethral warming catheter is replaced by a 3-way #18F Foley. The patient is then transferred to the recovery room. See Addendum #6 on page 76 for an analysis of various cryosurgical techniques utilized in cryoablation of the prostate.
Section IV: The Scientific Foundation of Cryosurgery

26. How does extreme cold destroy cells?
To answer this question, the cryo-researchers evaluated the changes that occur in cancerous organs and individual cancer cells following exposure to extreme cold. Their studies included an analysis of:
1. The shifts of water from inside to outside the cell.
2. The electrolytes (sodium, chloride, magnesium, and potassium)
3. The changes in the protein structure and function within the cell's nucleus.
4. The changes in blood flow to the targeted tissue.
5. The response of white blood cells in the targeted tissue.
6. The formation and growth of ice.
7. The ultimate fate of the frozen cancer cells.
So, how does extreme cold kill cancer? The simplest answer is that the ice formed within the cancer breaks down the walls of the cancer cells. However, this is not the major mechanism. At the cooling rates utilized during cryoablation of the prostate, most ice is formed in the spaces between the cells and in the blood vessels that supply the cancer with nutrients. (Figure 22)

Fig. 22. Location of ice crystals. As the tissue cools, ice crystals are formed between the cells and inside the blood vessels.

Each ice crystal is composed of oxygen and hydrogen molecules, and each crystal is attracted (bonded) to nearby ice crystals. (Figure 23)

Fig. 23. The structure of ice. Sodium, potassium, magnesium, and chloride are not part of the crystal.
The dissolved chemicals (sodium, potassium, magnesium, and chloride) remain in the unfrozen liquid. As more ice crystals form outside the cancer cells, the unfrozen liquid outside the cells becomes more concentrated. The concentration of chemicals inside and outside the cells must always be equal. To maintain this balance, water is drawn out from the cell. The cell and the cell's nucleus shrink. (Figure 24) The concentration of chemicals within the cell increases. This causes the proteins within the nucleus to change their shape. Once the protein's shape (alpha helix) is lost, cellular activity halts. (Figure 25) The longer the time the protein is deformed, the more likely the cell will not recover from the injury.

Fig. 24

Fig. 24. As water moves out from inside the cell, the cell and the cell's nucleus shrink. The solutes within the cell become more concentrated. Na, Cl, Mg, K are abbreviations for sodium, chloride, magnesium, and potassium, respectively.

Fig. 25

Fig. 25. The elevated salt concentration in the cell causes the protein to uncoil. The S-shaped protein cannot send or receive critical, cell-sustaining messages from other cells.
The third mechanism, and perhaps the most important, involves cutting off the blood supply to the cancer. The blood vessels to the prostate run along the side walls, the capsule, of the prostate before penetrating into the central part of the prostate. *(Figure 26)* The freeze must extend to and through the capsule to destroy all these vessels. Temperature sensors are placed next to the capsular vessels, and the freeze is continued until the sensors register -20°C (-4°F) or less.

![Blood Supply](image)

*Fig. 26*

Fig. 26. The blood supply to the prostate originates from vessels that hug the prostatic capsule.

When a blood vessel is exposed to temperatures of -20°C (-4°F), it initially narrows and then expands. *(Figure 27)* The ice that forms within the vessel injures its lining cells (endothelium). Soon, circulating minute oval discs, called platelets, coat the injured cells. Within four hours, the channel becomes plugged by the platelets, and the “lifeline” for the cancer is blocked.

![Vascular changes](image)

*Fig. 27*
Cryosurgery has also been shown to trigger a fourth, potentially lethal, mechanism in cancer cells, an autoimmune response – one group of cells in the body destroying another group of cells. Chemicals (antibodies – immunoglobulins) and lymphocytes (T cells) produced by the immune system invade the prostate after this tissue is frozen.

Section V: Focal Cryoablation of the Prostate

Targeted Focal Cryoablation of the Prostate (TFCP) is a minimally invasive cancer therapy which treats only the area of the prostate that contains cancer. The most common focal procedure freezes one lobe of the prostate, in contrast to Total Cryoablation of the Prostate (TCP), which freezes both lobes. (*Figure 28*)

![Figure 28](image)

*Fig. 28. In this FCP, the left lobe of the prostate was frozen, but the right lobe was preserved.*

27. *What are the advantages of targeted focal cryoablation of the prostate (TFCP) when compared to radical surgery, radiation therapy (external beam or intensity-modulated radiation therapy, or proton beam therapy, or brachytherapy), or total cryoablation?*

1. TFCP is less likely to cause erectile dysfunction than radical surgery, radiation therapy (external beam or seeds), or TCP.\(^1\)\(^-\)\(^5\)
2. TFCP is less likely to cause incontinence than radical surgery or TCP.\(^1\)\(^-\)\(^6\)
3. TFCP is less likely to cause bowel problems than radiation therapy (external beam or seeds) or TCP (0.4 percent, versus 2-5 percent).\(^1\)\(^-\)\(^5\)
4. TFCP has a shorter recovery time than surgery, radiation therapy (external beam or seeds), or TCP.
5. The overall cost of TFCP is less than radical or robotic prostatectomy and significantly less than radiation therapy.\(^7\)


28. Who are potential candidates for TFCP?

TFCP has not been approved by the Food and Drug Administration in the USA for the primary treatment of localized prostate cancer. The application for approval is currently under review. Cancer treatment centers in Europe, Japan, and the USA have published the results of their initial clinical trials with this therapy. No strict criteria have been universally agreed upon for this procedure. However, the baseline characteristics of patients in published peer-reviewed reports include:

1. Cancerous cells detected in only one lobe of the prostate.
2. Gleason Score of 6 or 7.
3. PSA of < 10.
4. Clinical Stage of T1c or T2a.
5. D'Amico risk classification of low- or intermediate-risk.

Various academic centers have included additional selection criteria:

1. No more than 2 adjacent regions positive for cancer.
2. Total length of cancer < 10mm and < 7 mm in any one core; <1/3 of cores positive for cancer.
3. PSA density <0.15 ng/ml/cc.
4. PSA velocity < 2 ng/ml/yr in the year prior to diagnosis.
5. No Gleason Grade 4 or 5.

Well, I know I have prostate cancer. What's the chance it is in only one lobe of my prostate and has a Gleason Score of 6 or 7? Let me give you a little background.

In 2009, the Division of Urologic Oncology at New York University Medical Center reviewed the records of 1467 consecutive men who underwent open radical prostatectomy for localized prostate cancer. Cancer was identified under the microscope in both lobes of the prostate in 1154, and in only one lobe in 313 patients. Of these 313 patients, only 246 had a very small area of the cancerous lobe containing cancer. Overall, 163 men (11.1%) had cancer in one lobe and had low-risk disease (defined as a PSA level <10 ng/ml, Gleason score < 7, percentage of tumor involvement of <10%). This work highlighted that only a small minority of men who were candidates for radical surgery would be suitable candidates for focal cryoablation of the prostate.

Okay, but my biopsy found cancer in only one lobe. How certain can I be that cancer was not missed on biopsy of the other lobe? In 2011, researchers at Patras University Hospital in Patras, Greece, reviewed 161 patients with prostate cancer in only one lobe in biopsies performed prior to the patients undergoing a radical prostatectomy. When they studied the whole prostate in the pathology laboratory, they found that 39 patients had cancer limited to one lobe. All 39 patients had a PSA density of ≤0.2 and a percentage of cancer in the biopsy material (proportion of cancer out of all cores examined) of ≤ 35%. The PSA density is obtained by dividing your PSA value by the volume of your prostate determined at the time of your biopsy. For example, if your PSA was 6 mg/ml and your prostate volume was 40 ml, your PSA density would be 0.15.

Hofner and colleagues at the University of Heidelberg analyzed 438 patients with unilateral prostate cancer in prostate biopsy samples from patients who were treated with radical prostatectomy. Of these patients, 30.8% had bilateral prostate cancer or cancer outside the covering of the prostate. The researchers found that if the PSA density was <0.056, there was a 98% likelihood the patient had cancer in only one lobe of his prostate. However, none of the patients in the Patras study had a PSA density of <0.056.
The ability of Diffusion-weighted Magnetic Resonance Imaging to exclude the presence of cancer in a lobe of the prostate that did not contain cancer on biopsy was evaluated at Tokyo Medical University Graduate School. 270 prostate lobes that were free of cancer on pre-radical prostatectomy biopsy were analyzed. When 14-core biopsy was combined with MRI, the combination accurately (95.7%) predicted the absence of cancer in the lobe that was free of cancer on the pre-radical prostatectomy biopsy. Two additional studies demonstrated that multiparametric MRI (mpMRI) has the ability to localize significant areas of prostate cancer. 

Area deemed to lack cancer on mpMRI have a 95% probability of having no clinically significant disease as defined by the presence of any Gleason pattern 4 and/or a lesion volume of ≥0.5 ml.

A 2009 Duke University Medical Center study reviewed 538 patients with low- and intermediate-risk prostate cancer (PSA <10, biopsy Gleason score ≤7, and clinical state of T1c-T2b) treated with a radical prostatectomy. Two pretreatment clinical variables were significantly predictive of unilateral prostate cancer: negative family history of prostate cancer and prostate biopsy unilaterality.

How can I be 100% sure I don't have cancer in the lobe that will not be treated? To achieve a 99% likelihood that all areas in the prostate that contain cancer will be found, including tumors as small as 0.5cc, a “saturation biopsy” technique (SBT) would be required. Forty-eight or more biopsy samples would be required, depending on the height and width of your prostate. A sample would be taken every 3mm. This technique is performed in the OR under anesthesia. The major problem with SBT is that it detects both significant (index) and insignificant lesions.

Insignificant lesions have a volume of less than 0.5cc. These lesions are unlikely to spread beyond the prostate. Their presence does not alter the outcome of therapy for a significant lesion, a lesion that is 0.5cc or greater. The significant lesion contains 80 percent of all cancer cells in the prostate and exhibited the dominant Gleason score in 92 percent of patients who underwent a radical prostatectomy. This lesion is believed to be the source of cancer cells that spread to lymph nodes and bone and must be detected to allow selection of the most beneficial therapy.
Assuming, then, that the goal of screening is to detect the significant (index) tumor, what is the best way to detect it? Twelve core biopsy procedures accurately detect the index lesion in 78.9 percent of patients. The 12 cores are obtained from the posterior lobes and the apex. In determining the precise location of cancers within prostates removed during radical surgery, it was determined that 72 percent of index lesions were located in the posterior lobes, and 28 percent were found at the apex and in the anterior lobe. If 20 cores of tissue had been obtained rather than the standard 12 cores, it has been hypothesized that nearly all, if not all, index lesions would be detected. The additional cores would come from the posterior lobe, the apex, and the anterior lobe. It is critical to point out that the 20 core biopsy technique, performed prior to radical prostatectomy, has not yet been proven to detect all these index tumors.

In 2012, Hou compared the accuracy of primary systematic template-guided transperineal biopsy of the prostate predicting the Gleason Grade assigned based on microscopic inspection of radical prostatectomy specimens. Typically 22-24 cores were taken which included 3 cores from the transitional zone and 3 cores from the apex/distal half of the prostate. In 25.6% of cases, the Gleason Grade was upgraded following examination of the surgical specimen, while downgrading occurred in 8.8%. This raises concern that patients could potentially be erroneously thought to be or conversely not thought to be suitable candidates for focal therapy.


29. What are the PSA outcomes and post-TFCP biopsy results?

The COLD Registry study included 795 patients undergoing targeted focal cryoablation (TFCP) of the prostate. The average follow-up was 1 year. Using the ASTRO definition (three consecutive PSA increases following the post-treatment nadir), 84 percent were free of biochemical failure at three years. Biopsy-proven recurrence was present in 4.5% of 199 patients.

Between 2002 and 2009, 77 patients received TFCP at Columbia University by one surgeon. The mean follow-up was 30.8 months. Eighty-seven per cent of patients experienced biochemical-free survival.

In 2012, the researchers at the Institute of Urology at the University of Southern California reported on 73 patients with biopsy-proven, clinically unilateral, low-intermediate risk prostate cancer. Post-TFCP follow-up included measuring PSA level every 3-6 months; prostate biopsies at 6-12 months and yearly, as indicated; and validated symptom questionnaires. The
pre-cryo mean PSA was 5.9 ng/ml and the Gleason score was 3+3=6 in 28 patients (41%), 3+4=7 in 24 patients (35%), and 4=3=7 in 16 patients (24%). Post-cryo mean PSA was 1.6 ng/ml. Of the 48 patients who had post-cryo biopsy, residual cancer was discovered in the treated lobe in one patient. The criterion for determining biochemical failure-free rates was not part of this study.

Ward published the Cryosurgery On-Line Database Registry data of 1,160 patients who received focal cryoablation of the prostate. Forty-seven percent had low-risk disease, 41% has intermediate-risk, and 12 had high-risk disease. The 3-year biochemical-free survival was 75%, using the ASTRO criteria. Prostate biopsy was performed after Cryo because of increased post-treatment serum PSA level in 14% of patients. Residual cancer was detected in 3% of patients (125/4099).

In 2013, researchers in the Section of Urologic Oncology, MD Anderson Cancer Center Orlando reported on 26 patients with documented minimal disease on saturation prostate biopsy (performed under monitored anesthesia) in only one lobe of the prostate. A mean of 35 cores were obtained from the prostate. Twenty-three had low-risk cancer and 3 had intermediate-risk prostate cancer. PSA failure was defined as an increase of 0.50 ng/ml over nadir. Mean follow-up was 19.1 months. Three patients (11.5%) experienced biochemical failure, and these patients underwent repeat post-Cryo biopsy. In 2 of the 3 patients, cancer was present.

30. What are the risks associated with TFCP?

There are several risks associated with TFCP. The first potential adverse outcome is ED. Several studies have revealed that 0 - 30% of patients following TFCP experience erectile dysfunction. There may be a delay of 6 - 12 months before return of this function. Urinary incontinence occurred in 0.0-3% of patients. A rectourethral fistula occurred in 0.0-0.6% of patients.


31. Conclusion.

The most common reason for selection of TFCP is a desire to preserve erectile function. As with all treatments for prostate cancer, follow-up monitoring with PSA and digital rectal exam are essential. If either or both of these monitors subsequently become abnormal, a repeat prostate biopsy may be suggested. If cancer is then detected, several treatment options will be available, including radical prostatectomy, radiation therapy, or total cryoablation of the prostate.

A thorough review of Focal Therapy was published in European Urology.

Section VI: Treatment of Recurrent, Localized Prostate Cancer after Radiation Therapy

Introduction.

Radiotherapy is a primary treatment option for men diagnosed with localized prostate cancer. This can be in the form of traditional External Beam Therapy, Conformal Therapy, Intensity-Modulated Radiation Therapy (IMRT), Proton Therapy, or Brachytherapy. The five-year recurrence rate of prostate cancer, determined by three sequential increases in PSA after the post-treatment lowest PSA, approaches 25 percent in patients with stage T1c/T2a disease and Gleason score of less than 6, but reaches 50 percent in patients with stage T2b/T3 disease and Gleason score of greater than 7. In 2007, The Cancer of the Prostate Strategic Urological Research Endeavor (CaPSURE) reviewed 935 patients who had received external beam radiation therapy. Sixty-three percent (587) of these patients experienced biochemical failure – a progressive rise in PSA – within a mean of 3-4 years.

This review is intended to help you select therapy for prostate cancer that was not totally eradicated by radiotherapy. We have summarized the outcomes and the factors that influence the outcomes of the various treatment options, including hormonal therapy, salvage radical prostatectomy (SRP), and salvage cryoablation of the prostate (SCP).

32. Who are candidates for salvage therapy?

If you received radiotherapy as the primary treatment for localized prostate cancer and

1. your PSA is gradually rising, and/or,
2. your urologist detected a change in the shape of your prostate,

you may wish to consider a repeat prostate biopsy to determine if prostate cancer has recurred. If you are pursuing curative therapy, at the time of the biopsy ask your urologist to include tissue from your seminal vesicles. If the microscopic exam finds cancer cells in the prostate but not in the seminal vesicles and your Gleason Score is equal to or less than 7, your next step is to be sure that a CT scan and bone scan do not detect cancer outside the prostate.

Before considering salvage radical prostatectomy (SRP) or salvage cryoablation of the prostate (SCP), ask your primary-care giver whether it is likely that you will live more than 10 years, if salvage therapy is successful in eradicating the prostate cancer. If the answer is yes, and you have:

1. no prostate cancer cells in the seminal vesicles,
2. no evidence of metastatic disease on CT scan and bone scan,
3. a post-radiation PSA of <10 ng/ml,
4. a PSA doubling time of greater than or equal to (≥) 12 months,
5. a Gleason score of less than or equal to (≤) 7 (Figure 30),
6. a clinical stage of T1 or T2 (Figure 31), and

you have a greater than 50 percent probability of being cancer-free for at least 5 years following salvage therapy.
Fig. 30. The Gleason Grading System. The normal glands within the prostate look like small rings and are similar in size. The Gleason grade 2 cancerous glands vary in size but are still round. The Gleason grade increases as the structure of the glands looks less and less like small rings. The Gleason score is obtained by adding the Gleason grade of the predominant pattern of abnormal glands to the Gleason grade of the less common pattern of abnormal glands seen on your biopsy. For example, if the predominant pattern was a Gleason 3, and the less common pattern was a Gleason 4, then the Gleason score for that patient would be 7.

Fig. 31. T1 is the first stage of cancer. Cancer is present in the prostate but cannot be felt on digital rectal exam (DRE) or imaged. Most commonly, T1 cancer is detected on needle biopsy performed due to an elevated PSA. T2 prostate cancer can be felt on digital rectal exam, but still appears to be confined to the prostate. In stage T3, the cancer extends into the outer covering of the prostate or into the seminal vesicles. In T4 disease, the cancer has grown into tissue next to the prostate, such as the urethral sphincter, the rectum, or inner wall of the pelvis.
33. The treatment options.

The most common salvage therapy for locally recurrent prostate cancer has been hormonal therapy, either with a luteinizing hormone-releasing hormone (LHRH) agonist alone or in combination with an anti-androgen. The energy source for most prostate cancer cells is testosterone. The LHRH agonists lower the concentration of testosterone in the blood. The most commonly prescribed agonists are Zoladex, Eligard, Lupron, and Trelstar. The anti-androgens prevent testosterone from stimulating the prostate cancer cells. The most commonly used are Eulexin, Anandron, and Casodex. Hormone therapy has been proven to be beneficial in patients with prostate cancer that has spread beyond the prostate, but it has not been recommended by the National Comprehensive Cancer Network or the Hormone Study Group as a primary treatment for localized, organ-confined prostate cancer. In 2009, an observational study of 16,535 men was published which used the Surveillance, Epidemiology, and End Results Medicare data (SEER). In one group (4316), hormonal therapy – androgen deprivation therapy (ADT) – was the sole modality. The other group (12,219) did not receive any treatment. After adjusting for tumor characteristics, co-morbidities, and demographics, patients who received ADT had a worse overall survival rate.

The Cancer of the Prostate Strategic Urological Research Endeavor investigators reviewed salvage therapy for prostate cancer. In their database, 430 patients had received and failed external beam radiation therapy. Four hundred and two patients (93.5 percent) received androgen deprivation therapy (ADT), 13 (3 percent) received cryotherapy, and 4 (0.9 percent) had salvage radical prostatectomy. Disease progression after salvage therapy was defined as a PSA level of >0.2 ng/ml. Three hundred and nineteen (74 percent) failed salvage androgen deprivation therapy. The mean survival of this “failed” group was 81.1 months, versus 103.2 months for those who did not fail.

The Veterans Affairs Medical Center in Memphis, TN, reviewed the charts of 206 men who had received salvage androgen deprivation therapy. The overall survival (the probability the patient would not die of any cause) was 85 percent at 5 years and 70 percent at 10 years. The disease-specific survival (the probability that the cause of death would not be prostate cancer) was 93 percent at 5 years and 89 percent at 10 years. The publication concluded that “as most patient deaths in the present series were unrelated to prostate cancer, the true survival value of androgen deprivation therapy in these patients remains unclear.” Other authors have shown that among patients 65 years or older treated with external beam radiation therapy, brachytherapy, or cryotherapy, ADT was associated with a higher cumulative incidence of death from cardiovascular causes.

Two less commonly selected, but potentially curative, options for patients with rising PSAs following radiation therapy are salvage radical prostatectomy (SRP) and salvage cryoablation of the prostate (SCP). Three high-volume referral centers have published their experience with SRP. In 2004 and 2005, Memorial Sloan-Kettering Cancer Center reported data collected from 100 consecutive patients who had undergone an SRP between 1984 and 2003. Patients were considered to be free of biochemical progression (BD-FP) following SRP if their PSA remained <0.2 ng/ml. The 5-year BD-FP rate for patients with a preoperative PSA level of <4, 4-10, or >10 was 86 percent, 55 percent, and 37 percent, respectively. The study examined whether a higher
percentage of patients had biochemical disease-free progression as the experience of the surgeon increased. It also examined whether the procedure-associated morbidity decreased as the experience of the surgeon increased. Patients treated after 1993 demonstrated improved biochemical (PSA) control, but the difference was not statistically significant. During the first 10 years of the study, the urinary incontinence rate was 43 percent, versus 32 percent for the subsequent 10 years. This was not statistically significant (p=0.71). The incidence of rectal injury significantly decreased from 15 percent to 2 percent (p=0.01). The urethral stricture rate was 30 percent and did not change during the study. The 5-year potency rate was 45 percent in patients who were potent preoperatively. Potency was defined as erections that were satisfactory for intercourse, with or without sildenafil.

In 2005, the Mayo Clinic presented its 33-year experience with 138 patients who were treated with SRP. Patients were considered to be free of biochemical progression following SRP if their PSA remained <0.4ng/ml. The 5-year BD-FP rate was 58 percent. The urinary incontinence rate ranged from 44 percent to 57 percent, depending on the year the procedure was performed. The frequency of rectal injury decreased from 6 percent (years 1967-1990) to 3 percent (years 1990-2001). However, the urethral stricture rate increased from 14 percent to 26 percent. No data on erectile function was provided.

In 2006, the University of Southern California reviewed their 20-year experience with 51 patients treated with SRP. Patients were considered to be free of biochemical progression following SRP if their PSA remained <0.4ng/ml. At 5 years following SRP, the BD-FP rate was 47 percent. Fifty-four percent of patients experienced urinary incontinence. Rectal injury occurred in 1 patient (2 percent). A urethral stricture was identified in 21 of 51 patients (41 percent). Forty-six percent of these patients were incontinent of urine. The UCLA Prostate Cancer Index was used to evaluate sexual function outcome. In this validated questionnaire, the higher the score, the greater was the preservation of sexual function. Men who had undergone an SRP had significantly lower scores than healthy, aged-matched controls.

Salvage cryoablation of the prostate (SCP) is the second potentially curative option for patients whose cancer has continued to grow despite radiotherapy. In 2003, Bahn published a seven-year follow-up of 59 patients who had SCP. Patients were considered to be free of biochemical progression following SCP if their PSA remained ≤0.5ng/ml. At 5 years, 59 percent of the “combined-risk group” (patients with pre-SCP PSA of less than or greater than 10, Gleason grade 3-9, T Stage of T1-T4) remained free of disease progression. For the 45 patients with a PSA of <10, the BD-FP rate was 62 percent. For the 14 patients with PSA >10, the BD-FP rate was 50 percent. The BD-FP rate was 66 percent for patients with a Gleason grade of 7, versus 52 percent for patients with a Gleason grade of 8-9. Four percent of the patients experienced urinary incontinence, 3 percent of patients developed a rectal fistula. No erectile function data was provided. The mean follow-up for this study was 72.5 months. There were no prostate cancer-related deaths reported.

In 2007, St. Luke’s Cancer Centre in Guildford, Surrey, UK, reported on 100 patients who had SCP between May 2000, and November 2005. Patients were stratified into three risk groups according to their PSA level, Gleason score, and clinical stage before radiation therapy. The low-risk group consisted of those with a PSA level ≤ 10, a Gleason score of ≤ 6, and clinical stage of
\( \leq T2b \). The intermediate-risk group demonstrated one unfavorable factor – a PSA level of >10 ng/ml, a Gleason score of \( \geq 7 \), or a clinical stage of greater than T2b. The high-risk group had two or more unfavorable risk factors. Patients were considered to be free of biochemical progression (BD-FP) following SCP if their PSA remained \( \leq 0.5 \) ng/ml. The 5-year BD-FP rate was 73 percent, 45 percent, and 11 percent for the low-, intermediate-, and high-risk groups, respectively. Thirteen patients (13 percent) developed persistent incontinence. A rectal fistula developed in one patient (1 percent). Sixteen percent of patients experienced urgency and frequency. Fifty-seven percent of the patients who reported adequate erectile function with no assistance before SCP had reduced or complete loss of erectile function following SCP. The mean follow-up was 33.5 months.

In 2007, the University of Western Ontario published its experience with 187 patients having locally recurrent prostate cancer after radiotherapy who were then treated with SCP.\(^{14}\) The procedures were performed between March 1995, and September 2004. The group included three brachytherapy patients, 183 external beam radiation patients, and one patient who had both brachytherapy and external beam radiation. Patients were considered to be free of biochemical progression following SCP if their PSA remained <2 ng/ml above the lowest PSA level following SCP (Houston or Phoenix Definition). Patients with pre-cryoablation PSA of <4 ng/ml had a 5-year BD-FP rate of 56 percent. Patients with a pre-cryoablation PSA of \( \geq 10 \) ng/ml had a 5-year BD-FP rate of 14 percent. Sixty-nine patients (37 percent) had mild to moderate incontinence, and 3 percent had severe urinary incontinence. Four patients (2 percent) developed a rectal fistula. Eighteen patients (10 percent) experienced urgency and frequency, which responded to medication. No erectile function data was presented.

The Cryo On-Line Data (COLD) Registry is composed of four academic medical centers and 34 community urologists who submit patient data through a secure on-line link. The COLD registry consists of detailed case report forms. In 2008, the registry published its data on 279 patients who had undergone SCP.\(^{15}\) Patients were considered to be free of biochemical progression if their PSA did not increase in three consecutive assays subsequent to the lowest post-SCP PSA value (ASTRO Definition). Patients were also considered to be free of biochemical progression if their PSA did not increase more than 2 ng/ml above the lowest PSA value achieved following SCP (Houston or Phoenix Definition). Thirty-two patients (12 percent) had previously undergone brachytherapy, 218 (78 percent) had undergone external beam radiation, and 20 (7 percent) had undergone combination radiotherapy. The 5-year BD-FP rate for the SCP patients was 59 percent (ASTRO criteria), and 55 percent (Phoenix criteria). The urinary incontinence rate was 4.4 percent. The rectal fistula rate was 1.2 percent. Three percent of patients required a transurethral prostate resection to remove sloughed tissue. Sixty-nine percent of patients who were potent prior to SCP experienced erectile dysfunction following SCP.

Outcomes of 156 patients who had undergone salvage prostate cryotherapy was captured in the COLD Registry and published in 2013. Biochemical disease-free survival (bDFS) was assessed using the Phoenix definition. At 1, 2, and 3 years, the bDFS was 89.0, 73.7, and 66.7%, respectively. Using \( \leq 5 \) and \( \geq 5 \) ng/ml, the study population was stratified into two groups. At 3 year follow-up, the subgroup with a pre-salvage PSA of \( \leq 5 \) had a 78.3% bDFS rate versus 52.9% rate in the group with a pre-salvage PSA of \( \geq 5 \) ng/ml. The data supports early salvage intervention once recurrence of prostate cancer following radiation therapy is detected.
<table>
<thead>
<tr>
<th>SRP</th>
<th>PSA ng/ml Cutoff for Disease Progression</th>
<th>SCP</th>
<th>Prostate Inst’t (4)</th>
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</thead>
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<td>(4)</td>
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<td>UWO (6)</td>
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<td>COLD Registry (7)</td>
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<td>(ASTRc criteria)</td>
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The grouping of patients by pre-salvage PSA ng/ml.

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<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>Low</td>
<td>Int’e</td>
</tr>
<tr>
<td>3</td>
<td>≤5</td>
<td>5.1-10</td>
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<tr>
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<td>7</td>
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<td>to &gt;10</td>
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The percent of patients who remained free of biochemical progression at 5 years.

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The percent of patients who experienced urinary incontinence following salvage therapy.

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The percent of patients who developed a urethral stricture following salvage therapy.

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<td>4</td>
<td></td>
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<td></td>
<td></td>
<td>7</td>
<td>NR</td>
</tr>
</tbody>
</table>

The percent of patients who experienced erectile dysfunction following salvage therapy.

<table>
<thead>
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<th>NR</th>
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<td>4</td>
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</tr>
<tr>
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<td></td>
<td>NR</td>
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<td></td>
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<td>IN</td>
<td></td>
<td>7</td>
<td>IN</td>
</tr>
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</table>

The percent of patients who experienced a rectal injury following salvage therapy.

<table>
<thead>
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<td>7</td>
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<td></td>
<td>7</td>
<td>1.2</td>
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</tbody>
</table>

**Fig. 32.** Summary of 5-year biochemical disease-free progression rates and morbidity in the 3 salvage radical prostatectomy and 4 salvage cryoablation of the prostate publications reviewed. If the potential morbidity was not addressed in the publication, NR was entered. In the COLD Registry study, 74 patients were potent prior to SCP. Post-SCP potency data was available for only 8 patients, an insufficient number by which to determine erectile dysfunction percentages. This limitation is listed as IN.
34. Conclusion.

A significant number of patients who have localized prostate cancer will experience recurrence of the cancer following primary radiation therapy. If the PSA is less than 10ng/ml, the PSA doubling time is greater than 12 months, the Gleason score is ≤7, and the stage is ≤T2, the recurrent cancer will very likely be inside the prostate. Traditionally, hormonal therapy has been prescribed, yet this approach has not been proven to be curative. In fact, it can shorten survival and increase the risk of cardiovascular death. Two potentially curative options, salvage radical prostatectomy and salvage cryoablation of the prostate, are included in the guidelines of the National Comprehensive Cancer Network. If favorable criteria are met, both options offer a greater than 50 percent probability that the patient will remain free of recurrence or progression of his prostate cancer at 5 years after the salvage therapy. A recent study revealed that patients, who failed radiation therapy and had a PSA of <5 at the time of salvage cryotherapy, experienced a 78.3% rate of biochemical disease-free survival at 3 years. Each option can adversely impact the quality of your life.


Addendum

1. **Dr. Patrick Walsh's Concern:**

*Discussion of Dr. Patrick C. Walsh's concern that cryoablation could not destroy all cancer cells in the prostate without also destroying the urethra, an outcome that would cause serious voiding difficulties.*

A theoretical challenge to the value of cryoablation comes from Dr. Patrick C. Walsh in *Guide to Surviving Prostate Cancer*. He cites a publication that reviewed 350 radical prostatectomy specimens and found that in more than 50 percent of the specimens, cancer cells were within 5 millimeters of the urethra. Dr. Walsh was concerned that cryoablation could not destroy these cells without destroying the urethra, an outcome that would adversely influence the patient's ability to void.

Data provided in recent clinical trials published in peer-reviewed journals dispel this fear. First, prostate biopsies, performed routinely following cryoablation, reveal that 85 percent of patients do not have any detectable cancer cells remaining in the prostate. In these same studies, the incidence of urethral injury was less than 15 percent.

Second, the PSA values following total cryoablation of the prostate in patients with low-risk disease are commonly less than 0.2 ng/ml, the benchmark for a curative radical prostatectomy determined by the Johns Hopkins group. Please see post cryo PSA values in **Addendum 5**.

Third, Jones reported that 91 percent of cryo-patients with low risk prostate cancer had no evidence of recurrent prostate cancer 5 years after their procedure, based on PSA testing. Both Cohen in 2008 and Mouraviev in 2011 reported an 80% 10-year biochemical (PSA) disease-free survival for low risk disease.


71
2. **Gleason Grade and Gleason Score or Sum:**

Will cancer influence the quality and length of your life? Several factors must be considered before your doctor can answer this question. In 1966, Dr. Donald F. Gleason at the University of Minnesota helped answer this question when he devised a scoring system to help determine the aggressiveness of prostate cancer. The Gleason grade is based on a pathologist's microscopic examination of the prostate tissue.

The prostate is composed of many cells that are arranged in small groups around a central opening. This grouping of cells is a gland. The prostate is composed of hundreds of glands. The pathologist examines the structure of the glands and assigns a numerical grade. The grade depends on how closely the abnormal glands resemble non-cancerous prostate glands. If the glands very closely resemble normal glands, they will be given a Gleason 2 grade. If the glands have a very bizarre, disorganized arrangement, they will receive a Gleason 5 grade. Glands in between these two extremes will be assigned a Gleason grade 3 or 4, depending how bizarre their appearance.

Most tissue will contain two or more abnormal types of glands. The pathologist will assign a **Gleason grade** to the most common group and then another Gleason grade to the less common group of abnormal glands. The sum of these two numbers is the **Gleason score**. The higher the score is, the more aggressive the cancer is, the faster it tends to grow, and the more likely it is to spread beyond the prostate.

3. Prostate Cancer Outcome Risk Classification:

What is the likelihood that the initial treatment you select will cure your cancer? Based on an extensive review of PSA values in patients who had received radiation therapy or radical prostatectomy, D’Amico, in 1998, formulated criteria that predict PSA outcomes in patients considering treatment for their recently discovered prostate cancer. In this setting, PSA values strongly correlate with the presence or absence of residual prostate cancer. He predicted that patients with prostate cancer which:

1. was not felt during the pretreatment digital rectal exam, or if felt, comprised only a small area on one side of the prostate (T1C or T2A) and,
2. had a Gleason score of less than 7 and,
3. had a PSA of 10 or less,

would likely have a low or non-detectable PSA following their treatment and that it would remain so in the following years. This was his low-risk group.

He also predicted that patients with cancer which:

1. could be felt in both lobes of the prostate (T2C) or,
2. with a PSA greater than 20 or,
3. with a Gleason score greater than 7.

would be at risk of a post-treatment PSA value that would gradually increase, indicating the presence of residual prostate cancer. This was his high-risk group.

Patients with prostate cancer which:

1. could be felt in more than half of one lobe, but not both lobes (T2B),
2. a Gleason score of 7 or,
3. a PSA greater than 10 but less than or equal to 20

were more likely to have residual cancer than the low-risk group and less likely than the high-risk group. This was his intermediate-risk group.

The D’Amico classification has been accurate in predicting outcomes in patients receiving external beam radiation therapy, brachytherapy (seeds), radical prostatectomy, and total cryoablation of the prostate.

The PSA value during the first few months following successful, curative, primary therapy for localized prostate cancer varies according to the modality. For patients who had a radical prostatectomy, the PSA should be <0.2 ng/ml within days of the procedure. With either external beam radiation (EBRT) or brachytherapy, the PSA will gradually decrease over the first post-treatment year. In fact, it may take up to 5 years after treatment before the lowest PSA value is achieved. If an EBRT patient achieves a PSA of less than 0.5 ng/ml, he has a 75% chance of remaining free of documented local or metastatic disease for the next 8 years. If the patient's PSA begins to rise following EBRT, he likely has active prostate cancer. Unlike EBRT, in patients who received brachytherapy the PSA may fluctuate and increase for a short time during the few years following treatment before returning to or below its lowest post-treatment value.

Mitchell reported on 205 patients who had received \(^{125}\)I permanent seed implants. PSA bounce occurred in 79 (37%), with the median peak PSA of 1.8 ng/ml and a bounce magnitude of 0.91 ng/ml.

The problem comes in determining whether the increase in PSA is simply a “bounce” or is, in fact, an indicator of failure of the treatment to eradicate the prostate cancer. Anxiety in the patient and the treating physician builds as successive PSAs are obtained. Should a CT scan or bone scan be performed? When should salvage therapy be considered? Only when the PSA falls to, or less than the lowest post-treatment PSA value can the physician reassure the patient that a bounce rather than progression of the cancer occurred. A 2011 study of 820 patients found that patients who experienced treatment failure (nadir PSA value plus 2 ng/ml) had their PSA begin to increase at 22.3 months, but the range was 5.9-65.9 months. A present recommendation is to withhold salvage intervention within the first 24 months after brachytherapy. This delay in initiating therapy has the potential of lowering the salvage rates of radical surgery or cryoablation of the prostate.

Simply stated, in our experience, Cryo patients do not have a “bounce” in PSA.

5. Post-cryo PSA critical values:

Levy reviewed the records of 2,427 patients treated with cryoablation. When the post-cryo PSA nadir (lowest) value was less than 0.1 ng/ml, the 60-month biochemical disease-free survival based on the Phoenix Criteria (lowest post-cryo PSA value + 2) was 91.8% for patients with low-risk prostate cancer, 76% for patients with intermediate-risk disease, and 71% for high-risk patients. When the post-cryo PSA nadir value was less than 0.6 ng/ml, the numbers were 86%, 67%, and 51% for low-, intermediate-, and high-risk disease, respectively. When the post-cryo PSA nadir value was 0.6 to 1.0 ng/ml, the 24-month biochemical disease-free survival was 70.5%, 56.1%, and 46.7%, respectively. The PSA outcomes study from the Penobscot Bay Medical Center, presented on pages 16-19, compares very favorably with Levy's finding.

Based on more than 150 cases, we have found that PSA values at 3 and 6 months are very reliable in determining the outcome from total surgical cryoablation of the prostate. Hormone shots, administered prior to the cryo procedure to shrink the prostate, can lower post-cryo PSA values for up to 6 to 9 months. In this situation, PSA values at 9 and 12 months are more reliable in judging ultimate outcomes.

6. Various Modifications of the Cryosurgical Technique in Cryoablation of the Prostate

The Impact of Various Modifications of Cryosurgical Technique on Biochemical Disease-free Survival, QoL Outcomes, and Complication Rates

Introduction:
The cryogenic method for maximizing cancer cell injury in the research laboratory is generally accepted. The freezing rate, the critical lethal tissue temperature, the duration of the freeze, the critical temperature range for maximizing re-crystallization injury, the thawing rate, and number of freeze-thaw cycles have been defined in cell suspensions, tissue slices, and in animal models. However, the relationship of the prostate to adjacent organs and the value of operating time have prompted several modifications. The clinical outcomes of these modifications have been published but not compared.

The ultimate goal of this study is not to compare the efficacy of the three cryo systems, Cryomedical Sciences (Rockville, MD); Cryocare CS System (Irvine, CA); and the Galil Medical System (Yokneam, Israel), but rather to determine if a specific freeze/thaw technique consistently trended to produce a superior biochemical disease-free survival rate (bDFS), health-related quality of life outcome (QoL), and fewer complications.

To minimize the potential of extra-prostatic prostatic cancer cells confounding our outcome analysis, this study focused on patients with low-risk prostate cancer - that is patients with stage T1c or T2a, Gleason score <7, PSA <10 (D'Amico classification - 1998).

Methods
Peer-reviewed studies that presented the bDFS for low-risk prostate cancer patients who received total cryoablation of the prostate were reviewed and compared. Each surgical technique was analyzed.

Health-related quality of life data utilizing the Functional Assessment of Cancer Treatment-Prostate (FACT-P), or the University of California, Los Angeles, Prostate Cancer Index (UCLA, PCI), when available, were compared.

The complication rate solely for patients with low-risk prostate cancer was not present in the published references. Since the same technique was used for patients with high-, intermediate-, and low-risk cancer in these publications, the complication rate for the total study population was recorded.

In a similar fashion, the unpublished technique and outcomes of 21 consecutive patients with low-risk prostate cancer who underwent TCP by a single surgeon at a community-based hospital were analyzed and compared with the published reports. All procedures were performed using third-generation cryosurgical technology. All used ultrasonic guidance for placement of the cryoprobes and monitoring the ablation. A significant majority of cases were performed with temperature sensors and a urethral warmer.
Results
1. Techniques

Three referenced publications reported pooled data from institutions which used divergent techniques. The Long study contained data from all patients undergoing cryoablation at 5 institutions. "Aspects such as the number of cryoprobes (5 to 8), number of freeze-thaw cycles/case (1 to 3), length of apical pull-back, use of thermocouples for real-time temperature monitoring during freezing, and use of liquid nitrogen or argon-based cooling systems varied among different institutions to a measurable degree." The Jones and the Dhar studies extracted data from 4 academic medical centers and 34 community urologists. The precise method of freezing and thawing was determined by the individual urologist. Han's work included contributions from 8 institutions. The remaining studies report data from a single institution.

Six referenced publications provided outcomes from groups of cryo surgeons who used a standardized technique. Table 1.

Bhan reported on 92 patients who received targeted cryoablation as a primary treatment for localized prostate cancer. All patients were treated with 2 complete freeze/thaw cycles. Five to eight 3.4 mm cryoprobes were used. The target temperature was -40. Commonly 75-100% gaseous flow was utilized for 5 minutes or longer in the anterior probes, while 50-75% was used in the posterior probes. The end point was -20 to -40°C. Each freeze lasted approximately 10 minutes and each thaw lasted 20 minutes. Androgen ablation therapy was given before the procedure to downsize the gland, but not continued after the procedure.

Cohen used 5 cryoprobes (3.4 mm). The Onik procedure was used. When the rim of ice had passed through the prostatic capsule, before reaching the rectal wall, the probes were deactivated. A passive thaw then occurred. Although the published study did not report a double freeze/thaw method, Dr. Cohen informed me in a recent conversation that his group did add a second freeze and thaw cycle.

In the Donnelly study 5 cryoprobes (3.4 mm) were utilized. Twelve percent of patients were treated with one freeze, the remainder with a double freeze. The thawing was passive. Hubosky used six to eight (2.4 mm) cryoprobes. "Double freeze/thaw cycles were carried out with the goal of exposing prostate tissue to -40°C temperatures." However, an active thaw was initiated immediately after the target temperature and the ideal ice edge position were achieved. This was followed by a second freeze. Following the second freeze, again an active thaw was initiated after the targeted temperatures and ice edge appearance were achieved and continued for 4 to 5 minutes. At that point the cryoprobes were removed, and then a passive thaw followed.

The Han group used ten to fifteen 1.47 mm cryoprobes. The Zisman technique was used. Double freeze/thaw cycles were performed, using argon and helium, with the goal of exposing prostate tissue to -20°C. Between cycles the prostate was allowed to thaw passively (15 to 20 minutes) or actively (7 to 8 minutes) using helium.

Polascik used 1.47 mm cryoprobes. Freezing was stopped when the ice-ball reached the anterior rectal wall and the posterior prostatic capsule was at least -20°C. A passive thaw followed, and then a second active freeze was followed by a second passive thaw.
In the Pen Bay technique, the identical technique used by Aaron Katz, M.D., the double freeze/thaw cycle was performed under TRUS guidance. The target temperature was -40°C. In the anterior probes (2.4 mm), freeze was present 100% of each cycle for at least 5 minutes and then was lowered to 75%. In the lateral probes the freeze time began at 75% for each cycle. In the posterior probes, the freeze was active 25% of each cycle. The edge of the ice ball was carried down to the anterior rectal wall. The temperature in Denovillier’s fascia was kept above minus 5°C. The sphincter temperature was kept above 20°C. The solution in the warming catheter was 42°C. Once the target temperature was achieved, a passive thaw was permitted for 3 minutes, followed by an active thaw with helium. The active thaw was discontinued once the prostatic architecture was re-identified. After the second freeze, again a passive thaw was permitted for 3 minutes, followed by an active thaw.

The Shinohara, Ellis, Al Ekish, and Pitman studies were not included in this analysis because a D’Amico low-risk subgroup was not identified, or the bDFS outcome data for this group was not provided.

<table>
<thead>
<tr>
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Table 1. The method used to thaw tissue between and following the two active freezes.

*Han’s thawing technique varied from case to case.

2. bDFS

The Pen Bay PSA bDFS data for 21 consecutive patients with low-risk prostate cancer is presented in table 2. The minimal FU was 4 years. Two patients experienced a PSA >1.0 ng/ml in this study. In both cases, the post-cryo 12 core prostate biopsy found benign prostatic tissue with extensive scarring, but no residual prostatic cancer.

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<td>0.31</td>
<td>0.49</td>
<td>0.42</td>
</tr>
<tr>
<td>Mean</td>
<td>6.33</td>
<td>0.08</td>
<td>0.23</td>
<td>0.23</td>
<td>0.35</td>
<td>0.38</td>
<td>0.48</td>
<td>0.66</td>
<td>0.46</td>
</tr>
<tr>
<td>Range</td>
<td>1.8-9.7</td>
<td>&lt;0.01-0.39</td>
<td>&lt;0.01-0.8</td>
<td>&lt;0.01-0.6</td>
<td>&lt;0.01-0.88</td>
<td>&lt;0.01-1.46</td>
<td>&lt;0.01-1.77</td>
<td>&lt;0.01-2.42</td>
<td>&lt;0.01-0.9</td>
</tr>
<tr>
<td># of Pts.</td>
<td>21</td>
<td>17</td>
<td>20</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>21</td>
<td>12</td>
<td>7</td>
</tr>
</tbody>
</table>

Table 2. The PSA data of the Pen Bay Study, including the number of patients available for evaluation at each post-cryo follow-up visit.
A review of the data from cited publications and the Pen Bay data permits a comparison of the bDFS of patients with low-risk prostate cancer. (Table 3) The mean age for the published studies was 69.5 years. Hormonal therapy was utilized prior to Cryo in patients with prostate volumes of greater than 50ml, but it was not continued following the Cryo procedure. The PSA threshold used to determine the bDFS rate varied in the studies.

The critical values used included 0.4 ng/ml, 0.5 ng/ml, 1.0 ng/ml, the ASTRO definition (three consecutive rises in PSA after a nadir), and the Phoenix definition (nadir + 2).22,23

<table>
<thead>
<tr>
<th>Author - yr</th>
<th>#</th>
<th>1yr %</th>
<th>2yr %</th>
<th>3yr %</th>
<th>4yr %</th>
<th>5yr %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pen Bay -2013</td>
<td>21</td>
<td>80a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hubosky -2007</td>
<td>22</td>
<td>74a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Han - 2003</td>
<td>65</td>
<td>78a</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polascik - 2007</td>
<td>36</td>
<td>95b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahn - 2002</td>
<td>94</td>
<td>76b</td>
<td>68b</td>
<td>67b</td>
<td>66b</td>
<td>65b(61)</td>
</tr>
<tr>
<td>Pen Bay -2013</td>
<td>21</td>
<td>85b</td>
<td>71b</td>
<td>79b</td>
<td>71b</td>
<td>67b(12)</td>
</tr>
<tr>
<td>Long - 2001</td>
<td>158</td>
<td>92c</td>
<td>92c</td>
<td>86c</td>
<td>85c</td>
<td>85c(26)</td>
</tr>
<tr>
<td>Pen Bay -2013</td>
<td>21</td>
<td>100c</td>
<td>100c</td>
<td>95c</td>
<td>89c</td>
<td>82c(12)</td>
</tr>
<tr>
<td>Donnelly - 2002</td>
<td>13</td>
<td>93c</td>
<td>93c</td>
<td>93c</td>
<td>83c</td>
<td>83c(?)</td>
</tr>
<tr>
<td>Bahn - 2002</td>
<td>94</td>
<td>92d</td>
<td>92d</td>
<td>92d</td>
<td>92d</td>
<td>92d(61)</td>
</tr>
<tr>
<td>Pen Bay -2013</td>
<td>21</td>
<td>95d</td>
<td>81d</td>
<td>95d</td>
<td>94d</td>
<td>90d(12)</td>
</tr>
<tr>
<td>COLD - 2008</td>
<td>123</td>
<td>92d</td>
<td>90d</td>
<td>88d</td>
<td>84d</td>
<td>85d(29)</td>
</tr>
<tr>
<td>COLD - 2011</td>
<td>127</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>82d(?)</td>
</tr>
<tr>
<td>COLD - 2008</td>
<td>123</td>
<td>96e</td>
<td>95e</td>
<td>92e</td>
<td>92e</td>
<td>92e(29)</td>
</tr>
<tr>
<td>Cohen - 2008</td>
<td>36</td>
<td>100e</td>
<td>96e</td>
<td>94e</td>
<td>90e</td>
<td>81e(36)</td>
</tr>
<tr>
<td>Pen Bay - 2013</td>
<td>21</td>
<td>100e</td>
<td>100e</td>
<td>100e</td>
<td>100e</td>
<td>92e(12)</td>
</tr>
<tr>
<td>COLD - 2011</td>
<td>127</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75e(?)</td>
</tr>
</tbody>
</table>

Table 3. Author, year of publication, and percent of patients with bDFS based on several thresholds. The number of patients evaluated at a specified follow-up is in parentheses. A question mark indicates that the number of patients actually evaluated at the 5 year post-Cryo visit was not provided in the publication.

- a - Biochemical threshold = 0.4 ng/ml
- b - Biochemical threshold = 0.5 ng/ml
- c - Biochemical threshold = 1.0 ng/ml
- d - Biochemical threshold = ASTRO22
- e - Biochemical threshold = Phoenix23

In the a-group (0.4ng/ml), the thaw was achieved by three different methods. The bDFS outcomes are similar. The short-term follow-up does not provide a trend for determining a superior technique.
In the b-group (0.5ng/ml), the Bahn and Pen Bay bDFS percentages are similar over a 5 year follow-up. Bahn used a passive thaw for 20 minutes. Pen Bay used a passive thaw for 3 minutes followed by an active thaw. However, both methods allowed time for maximum re-crystallization that occurs between -40°C and -20°C.

In the c-group (1.0ng/ml) the bDFS percentages are complementary. Yet, the thawing method varied from a total passive thaw to a partial passive thaw followed by active thaw.

In the ASTRO-group, the bDFS percentages for the studies that used a total passive thaw or a partial passive thaw are 5 to 10% greater than in studies that used pooled data with varied thawing techniques. However, it is impossible to determine the percentage of Cryo surgeons in the COLD study who used passive or active thawing. Therefore, no trend can be detected with reasonable certainty.

In the Phoenix-group, the bDFS percentages are similar. The bDFS outcomes following methods incorporating a passive thaw are not superior to those which use an active thaw. (Figure 1)

![Biochemical Disease-Free Survival](Image)

**Figure 1. Using the Kaplan-Meier analysis, at 3, 4, and 5 years, the % of patients with bDFS in the Cohen study was 94, 90, 81% vs 100, 100, 92% in the PBM Series.**

3. Health-related QoL
Quality of life analysis of the patients in the Donnelly study was performed utilizing the Functional Assessment of Cancer Treatment-Prostate (FACT-P) questionnaire. FACT-P revealed that bowel function returned to baseline function by 3 months in all patients. Bladder function returned to baseline function by 8 months. All patients reported a complete loss of erectile function at the 6-week follow-up. The sexual function score showed very slight increases during the first post-operative year. At 36 months, 5 of 38 patients (13%) reported a return to baseline erectile function.

Only two studies utilized the UCLA, PCI questionnaire. In the Pen Bay Study, twenty-one consecutive low-risk prostate cancer patients were mailed two questionnaires that assessed pre- and post-total cryoablation health-related QoL parameters.
The study specific pre-cryo questionnaire asked 3 questions:
1. Overall, how big a problem was getting and maintaining an erection prior to your Cryo procedure?
2. How big a problem was your bladder function prior to your Cryo procedure?
3. How big a problem was your bowel function prior to your Cryo procedure?
Nineteen patients answered these questions. (Table 4) The interval between the Cryo procedure and completion of the study-specific questionnaire varied from 3 to 5 years.

<table>
<thead>
<tr>
<th>Prior to Cryo</th>
<th>No or small problem</th>
<th>Moderate problem</th>
<th>Big problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Fx.</td>
<td>13</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Urinary Fx.</td>
<td>18</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Bowel Fx.</td>
<td>18</td>
<td>1</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4. A majority of the patients did not have erectile dysfunction. The post-cryo questionnaire was the University of California, Los Angeles, Prostate Cancer Index (UCLA, PCI).

The questions asked were:
1. Overall, how big a problem has getting and maintaining an erection been for you during the last 4 weeks?
2. Overall, how big a problem has your urinary function been for you during the last 4 weeks?
3. Overall, how big a problem have your bowel habits been for you during the last 4 weeks?

Nineteen patients returned the competed questionnaires. Table 5.

<table>
<thead>
<tr>
<th>After Cryo</th>
<th>No or small problem</th>
<th>Moderate problem</th>
<th>Big problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexual Fx.</td>
<td>8</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Urinary Fx.</td>
<td>18</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Bowel Fx.</td>
<td>19</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 5. Cryo did not adversely impact urinary or bowel function. Surprisingly, 50% of the responding patients replied that their erectile function had returned to pre-cryo status within 3 to 5 years.

Hubosky also used the UCLA, PCI as part of the follow-up for third-generation cryoablation of the prostate. One year post-treatment sexual domain scores remained “well below baseline” (sexual bother 45%). Bladder and bowel scores were comparable to baseline.
4. Complications

The complication rates provided in the cited studies were for patients with low-, intermediate-, and high-risk cancer. (Table 6) It was impossible to dissect out the complication rate for only the low-risk patients. However, each investigator used the same method to totally cryoablate the prostate in patients with low-, intermediate-, and high-risk prostate cancer.

<table>
<thead>
<tr>
<th>Author</th>
<th>ED %</th>
<th>Incontinence %</th>
<th>Fistula %</th>
<th>TURP %</th>
<th>Pain %</th>
<th>Slough %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long</td>
<td>93%</td>
<td>7.5%</td>
<td>0.4%</td>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahn</td>
<td>95% at 16 months</td>
<td>4.3%</td>
<td>&lt;0.1%</td>
<td>5.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donnelly</td>
<td>54% at 36 months</td>
<td>1.3%</td>
<td>1.3%</td>
<td></td>
<td>3.9%</td>
<td></td>
</tr>
<tr>
<td>Han</td>
<td>87%</td>
<td>3%</td>
<td>6%</td>
<td>5%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Hubosky</td>
<td>2%</td>
<td>1%</td>
<td>0%</td>
<td>6%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>COLD-08</td>
<td>93%</td>
<td>2.9%</td>
<td>0.4%</td>
<td>2.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>COLD-11</td>
<td>89%</td>
<td>0.9%</td>
<td>0.1%</td>
<td>1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polascik</td>
<td>100%</td>
<td>3.7%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Pen Bay</td>
<td>66% at 36 months</td>
<td>0%</td>
<td>0%</td>
<td>4.7%</td>
<td>4.7%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table 6. All publications recorded the complication rates for their total study group, independent of their risk category.

Discussion:

This study examined various third-generation techniques used to treat localized, low-risk prostate cancer, utilizing the Cryomedical Sciences, or the ENDOcare, or Galil systems. The Cryomedical system used the 3.4 mm probe, the ENDOcare system used a 2.4 mm probe, and the Galil system a 1.47 mm probe. Laboratory research has demonstrated that the larger the circumference of a probe, the larger its freezing surface area, and the larger the volume of tissue which can be frozen. This principle explains why the ENDOcare system used 6-8 probes to cryoablate a 35 ml prostate while the Galil system used 12-15 probes.

Rapid freezing which produces intracellular ice has proven to be more lethal than gradual cooling in the laboratory. However, in Cryosurgery, rapid freezing, i.e. of the order of 50°C or more per minute occurs only in tissue immediately adjacent to the cryosurgical probe. It is impossible to achieve rapid freezing throughout the prostate. The time required and the details of the freeze have rarely been described in detail. Onik did not present how rapidly he froze the prostate. Lee provided a precise description of his 10-minute, aggressive freezing technique, a technique that was utilized in the Bahn study. The other cited studies provide the end point of the freeze but not how it was achieved. Recognizing human nature, it is more probable than not that freezing rates used by various surgeons varied. Yet, the outcomes from the divergent methods presented in this study were similar, again adding support to the thermal principle that the cooling rate is not the primary factor in determining cell survival.
The second issue is how long should the targeted tissue be kept frozen? Gage demonstrated that with a single freeze, tissue cooled to -30°C and held at that temperature for 3 minutes incurred greater cellular injury than tissue that was cooled to -30°C and then immediately thawed. This 3 minute delay allows small ice crystals to fuse into large ice crystals, a process called recrystallization. The larger ice crystals maximize the mechanical disruption of cells. In the cited studies, the delay time between active freezing and active thawing varied. Bahn maintained the ice ball at a static size for up to 10 minutes if possible without endangering the rectal wall. However, Hubosky initiated an active thaw immediately after the target temperature and the ideal ice edge position were achieved. Han allowed the prostate to thaw passively (15 to 20 minutes) or actively (7 to 8 minutes) using helium. The Pen Bay study allowed 3 minutes of passive thawing immediately following achievement of the -40°C. The threat of a post-Cryo urethral rectal fistula is felt by every Cryo surgeon and remains a powerful stimulus to begin active thawing.

How rapidly should the tissue be thawed? Research has shown that slow thawing maximizes cellular damage by maximizing recrystallization. The cited studies included thawing methods that varied from two passive thaws to two active thaws to part active/part passive thaws. Accepting the fact that the various clinical cryosurgical techniques do not exactly mirror the ideal laboratory technique, does one technique tend to be better based on biochemical disease-free status (bDFS), lowest complication rate, and highest rate of preservation of health-related QoL?

The bDFS outcomes of the various techniques, using five different thresholds and follow-ups of 1-5 years, fail to favor one method. For example, the Hubosky study using active thawing, the Pen Bay study using a partial passive thaw, and the Han study using either a passive or active thaw had similar 1-year outcomes with the 0.4ng/ml threshold. At 5-year FU, the outcomes for the Long, Pen Bay, and Donnelly studies were complementary, although the freeze method varied from passive, to active, to part passive. The bDFS of Han and Hubosky are similar using the 1.0ng/ml threshold. Using the ASTRO criteria, bDFS for patients in Bahn’s passive freeze study were similar to the Pen Bay study (92 vs 90). With the Phoenix threshold, the bDFS outcomes for the COLD study that utilized various thawing methods were similar to the Pen Bay study.

Regarding the complication rates, the rate of ED, incontinence, and fistula formation are similar using the various techniques in the published studies and Pen Bay study. The decision to intervene with a TURP in a patient with post-Cryo urinary retention is influenced by the patient’s and surgeon’s tolerance of relatively long-term clean self-catheterization. Finally, the Hubosky and Pen Bay studies using the UCLA, PCI questionnaire, and the Donnelly study using the FACT-P questionnaire reveal that urinary and bowel function are not compromised by various thawing techniques. In the Hubosky study, 49% of patients experienced “sexual bother,” versus 50% in the Pen Bay study. In the Hubosky study, 20% had regained erectile function by 1 year. In the Donnelly study, 13% had regained erectile function at 3 years. A longer follow-up (3-5 years) with the Pen Bay study found that 50% of patients had experienced return of erectile function.
This study is retrospective. The techniques were not randomized. The experience of the Cryosurgeons varied. This study could not capture the surgeon’s interpretation of the ultrasound image as the ice edge approached the anterior rectal wall and external sphincter and the importance the surgeon placed on the thermocouples’ readings. The number of patients entering each study and the mean, median, minimal length of follow-up of each study, and the percent of patients available for evaluation at yearly follow-up visits varied.

Conclusion: From this analysis, it is not apparent that one thawing technique is superior. The rate of freeze, the rate of thaw, and the time the temperature of the prostate tissue is between -40°C and -20°C, do not appear to dramatically influence bDFS, complication rates, and QoL outcomes. The critical factor for successful cryoablation of the prostate is a nadir temperature of -20°C to -40°C during each freeze.

References:


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I am indebted to Aaron Katz, M.D., for sharing his extensive experience with cryoablation of the prostate. I am grateful for Ingrid Ellison’s artistic work. I thank Elizabeth Borch, RN, for her care of our Cryo patients and for managing the follow-up questionnaires. The skilled OR team at the Penobscot Bay Medical Center played a critical role in the success of the Cryo procedures. Finally, I acknowledge the time, commitment, and skill of the reviewer Thomas Minehan, M.D. and the editor, my wife, Margaret.

Conclusion

The advent of Robotic Radical Prostatectomy, Conformal Radiation Therapy, Intensity-modulated Radiation Therapy, Proton Therapy, High-intensity Focused Therapy, and Cryoablation of the Prostate has made the selection of a primary therapy for localized Prostate Cancer extremely difficult. Cynthia Geppert, M.D., in her essay, “Prudence: The Guide for Perplexed Physicians in the Third Millennium,” addressed the issue of character in an age of complexity and change. She quoted from the Meditations of Marcus Aurelius in stating that, “One thing hastens into being, another hastens out of it... In such a running river, where there is no firm foothold, what is there for a man to value among all the many things that are racing past him?” This question was answered by Sir William Osler who described the prudent man as, “one who had coolness and presence of mind under all circumstances, calmness amid the storm, clearness of judgment in moments of grave peril...”

The goal of this book was to inform you of the various, ever-changing therapies for Prostate Cancer. We attempted to provide you with peer-reviewed outcome data that will help you judge if Cryo Surgery is the best option for you.