

## CHAPTER THIRTEEN CRYOSURGERY

By Israel Barken, M.D. <dr@barken.com>

I have been involved from the early beginnings of cryosurgery as it unfolded from an experimental procedure, available in only one state, to a recognized procedure performed in prestigious universities and hospitals all over the U.S. and abroad. We have made a lot of progress. There is a claim being made by the opponents of cryosurgery that there are no long-term results for the procedure. Yet Boney et al (Urology 1982; 19:37-42) reported their results with 229 patients from the mid 1960s with prostatic cancer showing that stage by stage, survival rates compared favorably with those of radical prostatectomy and other modalities that included radiation.

The survival rates of these patients from the mid 60s appeared very promising. The question is then, "Why was Cryosurgery abandoned?" The answer is because of the high rate of complications back then. One of the complications was the inadvertent freezing of the rectum, which created rectal fistulas between the prostate, the rectum and the urethra. (A fistula is a connection between two different systems of tubes in the body, in this case between the urinary and the colon tract due to the freezing injury.) In the 1960s, cryosurgery was done blindly without the guidance of ultrasound. At that time the procedure was to make an incision in the perineum and place one probe against the prostate to freeze it.

The issue of efficacy nowadays, since the availability of PSA, is judged differently than in the days prior to PSA. As with any procedure, issues of efficacy and safety have to be taken into account. In the historical cryosurgery, the efficacy, as manifested by similar survival to other procedures, was very good. The safety element of the procedure was poor, which led to the complications. The primary reason for the complications was because of the technique and the primitive equipment that was available at that time. The advances in transrectal ultrasound (TRUS), the development of a computerized machine to control the freezing probes and the development of wires and tubes has enabled us to do precise cryosurgery.

New equipment and technologies are still being developed. Fig. 13-1 shows a modern system. It includes a built-in powerful computer and tanks to hold the gasses used for freezing. The systems may have from four and up to eight freezing probes. Dr. Gary Onik, of Allegheny General Hospital in Pittsburgh, developed the modern protocol. He had gained experience from work on the liver, finding out the signature of freezing on the tissue.

The border of the freezing process is seen as a high dense white line. The ice ball created in the prostate by the freezing can be easily seen with the ultrasound. It can be controlled so that it does not damage the rectum. An initial pilot study was undertaken using five dogs to evaluate the feasibility of using ultrasound to monitor the freezing of the prostate. The animals tolerated the procedure well and there were no complications. (Radiology 1988; 168: 629-631). Soon after this study, Drs. Gary Onik and Jeffrey Cohen in Pittsburgh began the modern version of cryosurgery on the prostate.

### **Advantages of cryosurgery**

- o Does not require general anesthesia
- o No significant blood loss- no need for blood transfusion .
- o Procedure takes 2-3 hours.
- o Patient may be discharged same day or next *day*.
- o Less expensive than radical prostatectomy or radiation treatments.
- o If necessary can repeat the cryosurgery and re-freeze.
- o Promising results so far as manifested by rate of negative biopsy and post procedure PSA. Compares favorably to other procedures.
- o Little or no incontinence.
- o Less traumatic than surgery. Can be performed on men who would not be able to withstand surgery.
- o Can be easily performed on obese.
- o Procedure can be tailored to preserve potency.
- o Cryosurgery has been approved for payment by Medicare and most insurance companies.

### **Disadvantages of Cryosurgery**

- o Cryosurgeon has to be very well versed in ultrasound imaging interpretation.
- o Cryosurgeon must be dedicated and experienced in performing this procedure.
- o Impotence is comparable to radical prostatectomy in the hands of those who perform an aggressive procedure without regard for preserving potency.
- o Equipment and instruments are expensive
- o No long term data.

### **Who are potential candidates for cryosurgery?**

- o Any patient with localized disease
- o Patients with localized disease that are not candidates for radical prostatectomy or radiation treatments.
- o Patients with non-localized disease when local control is desirable and patient understands that the intent is not for cure but for debulking and control. Some patients with stage C disease have been treated successfully.
- o Patients who are too ill or too old to undergo major, invasive surgery.
- o Patients, who psychologically, don't feel comfortable about having major surgery.
- o Patients who don't want to take the risk of complications associated with radical prostatectomy such as impotence or incontinence.
- o Patients who are psychologically not comfortable with radiation.

Initially, cryosurgery was used primarily to treat those patients who had failed radiation therapy or radiation salvage. Surgery after radiation is not considered a good option because of a high rate of complications. A person can only be safely exposed to a finite dose of radiation. Radiation cannot be repeated. But the disease may still be contained within the prostate in many patients. So cryosurgery seemed to be an ideal solution for these patients. Unfortunately, later experience with this group of patients demonstrated a high rate of complications when cryosurgery is done after radiation. It is very important to choose an experienced cryosurgeon who feels comfortable and knowledgeable taking care of this particular group of patients.

This very important point must be disclosed and discussed with patients who have failed radiation.

### **How is the procedure done?**

Cryosurgery is a procedure by which extreme cold is applied to the tissue. As a result of the low temperature, the tissue is destroyed. Cryosurgery has been done on other tissues of the body such as the liver and the breast. In some cases, such as the liver, an incision is made and the freezing probes are applied directly to the tissue. Prostate cryosurgery is sometimes called percutaneous cryosurgery of the prostate. (Percutaneous means through the skin). Small probes are inserted through the skin of the perineum into the prostate. The perineum is that area between the scrotum and the anus. An ultrasound probe is placed in the rectum. A picture of the prostate and surrounding tissue is projected on a screen. The freezing probes are almost 1/8 inch in diameter. Several steps are taken before the freezing probes are introduced. By looking at the screen and using the ultrasound guidance, hollow needles are inserted into the prostate.

The prostate is somewhat like an upside down pyramid. The base or largest portion is attached to the bladder. The needles are placed equidistant from each one so that the entire prostate will be covered. Guide-wires are then inserted through these needles and left in place while the needles themselves are retracted. Dilators are gently inserted over the guide wires under visualization on the ultrasound screen. These dilators have a diameter of 3 mm (a little less than 1/8 inch, approximately the size of a drinking straw). They have an external sheath so after the dilator is placed in the appropriate position, the internal portion is removed leaving behind the external sheath. The freezing probes will be inserted through these dilator sheaths.

Some cryosurgeons make an incision so that the dilators will be easier to insert. I don't make any incisions at all but just gently dilate the tracts only. It may not sound important but it avoids the need for stitches. The stitches dissolve by themselves but they can ITCH terribly

A direct visual examination by a telescopic instrument (cystoscope) ensures that the urethra is normal and will accept a special warmer tube. The interior of the bladder is inspected at the same time that the urethra is checked just to ensure that there is no associated pathology in the bladder. A tiny tube is inserted through the abdominal wall to drain the bladder during the procedure and afterward. The tube (suprapubic tube) is very small and quite comfortable.

Prior to inserting the freezing probes, a special urethral catheter is inserted through the penis into the bladder. This special catheter is similar to a hose that is doubled. Warm fluid is continuously circulated through this catheter to keep the inside of the urethra warm and protected from freezing. (Some have called this catheter a "peter heater".) The cryo probes are inserted into the prostate through the sheaths that were a part of the dilators. These sheaths are then withdrawn so that the metal freezing probes are exposed to the tissue.

The freezing starts as the probes are turned on. Around each probe an ice ball is started. It is well visualized on the ultrasound screen. The individual ice balls from different probes coalesce to form one large ice ball. The border of the ice ball appears as an intense white line. This white line is carried down the prostate by starting first the upper probes and then starting the lower probes that are closer to the rectum. The rectal wall is also visualized as an intense white line.

The ice ball is allowed to approach the rectal wall. The prostate is very close to the rectal wall. Careful attention must be used to keep the ice ball from freezing the rectum. If the rectum is frozen, it could cause a fistula. A fistula may be very difficult to heal. In order to make sure all of the cancer is killed, the ice ball must come very close to the rectal wall.

Special temperature needles also called "thermocouple needles" are placed in strategic locations in the prostate in order to monitor the temperature during the freezing process. Areas of the prostate may be denser than other areas, especially the tumor areas. The freezing would be different in these areas. By monitoring the temperature with the thermocouples, the freezing can be increased or decreased as needed. The information from the thermocouple needles and the image of the ice ball on the ultrasound screen allows for very close control. Some of the more humorous urological cryosurgeons have called the procedure "ice sculpture". The temperatures will be taken down to  $-40^{\circ}\text{C}$  or more. Most surgeons will let the tissue thaw and then freeze it again. We define it as the double freeze procedure. The entire procedure, including preparation, may take about two hours.

#### **What to expect after surgery (The immediate post-operative period)**

Genital swelling is very common and of no clinical consequence since the swelling goes down. It usually begins at 2-4 days after the procedure. Discoloration of the scrotum may occur. The swelling and discoloration may disappear in about two weeks. There may be some irritation while voiding. Frequency and urgency are reported in most patients when starting to urinate. How well the patient urinates depends somewhat on the patient's pre-operative capability to urinate. Since the patient has a very small tube draining the bladder through the lower abdomen, it is easy to measure the residual urine in the bladder after urination. The catheter is removed only after patient demonstrates good capability to empty the bladder.

There may be a urethral discharge and some bleeding. A small amount of bleeding may be seen immediately after the procedure staining the protective pad. He may pass small fragments of tissue while urinating. This should not cause any significant problem.

#### **Post operative monitoring**

Most cryosurgeons follow the patient with a PSA every 3 months for the first year after the procedure. If there is an indication that the PSA is rising, imaging studies and a possible biopsy may be done. If the patient is part of a protocol study, he may have multiple biopsies at intervals of three months and yearly. There is a tendency to avoid early biopsy in order to avoid creation of a fistula in the immediate post cryo period.

A new investigational tool to follow patients after cryosurgery is the Spectroscopic MRI performed only at the University of California in San Francisco. This test can map the area of question with regard to detecting and differentiating residual benign disease or residual cancer. Whenever possible the author of this article prefers to have this imaging test that provides a "map" to better direct the freezing process. Some cryosurgeons perform multiple biopsies (12-16 samples) in order to get sense of the location and extent of the tumor. This non-invasive Spectroscopic MRI serves as a tool to get the same information achieved by these biopsies without trauma to the patient.

### **Options for treatment after cryosurgery**

Whether cryosurgery followed by hormonal blockade has an advantage has not been proven or disproved. Dr. Horst Zincke did a study showing that hormonal blockade following a radical prostatectomy yielded good results. It makes sense that we can get the same good results with cryosurgery and hormonal blockade. CHT would be especially indicated if the patient's PSA began to rise and systemic disease was suspected or diagnosed.

### **Why Cryosurgery?**

There is a tremendous increase in new cases of prostate cancer every year. The radical prostatectomy has been the "gold standard" of treatment for many years. There has been a lot of disappointment with radical surgery. Surgery is not always curative. "The PSA may start to rise in 50% of patients within five years". (T. Stamey, M.D.: In personal communication). The real percentage of complications from radical prostatectomy may be considerably higher than is being presented in the literature and by practitioners. Impotence and incontinence appears to be much higher than is admitted. For many men, incontinence is a problem that severely affects their quality of life.

Because of the factors mentioned above, there is an increased desire among patients to have a treatment modality that is less invasive and has less morbidity.

### **The major postoperative complications of cryosurgery**

Urinary rectal fistula, which fortunately happens very rarely and does not happen in the hands of the experienced cryosurgeon, is the most feared complication. This complication occurs also during radical prostatectomy and again rarely in the hands of the experienced surgeon. When a communicating channel opens between the prostate or the bladder and the rectum, it may cause diarrhea due to urine in the rectum and possibly severe infection due to bacteria in the urinary bladder. Fortunately, it is a rare complication and very rare in the hands of the experienced cryosurgeons. It is a condition that can be corrected by local surgery. At times it will close spontaneously by draining the bladder with a catheter.

Urinary incontinence is also an unusual complication in the hands of an experienced cryosurgeon. It is more common in patients that have had prior radiation. There is some degree of mild stress incontinence in the immediate postoperative period.

Urethral sloughing is defined as dead tissue sloughing off from the prostate and being passed during urination. It is possible that this tissue could clog the urethra and prevent the passage of urine. There should be little or no sloughing unless the urethral walls were damaged during the freezing.

Another complication may be the loss of the ability to have an erection, or erectile dysfunction. The penile erection is dependent on the intactness of the neurovascular supply to the penis. Freezing aggressively outside of the prostate gland may injure these nerves that run along the side of the gland. The rate of impotence is similar to the rate due to radical surgery. Dr. Fowler documented an 89% rate of impotence after radical surgery. Dr. Fred Lee reported an impotence rate of 90% at 6 months. The University of San Francisco reported 84% impotence in 6 months. Some small percentage of patients regain erection capability over a longer period of time. In order to make sure that all cancer cells are frozen and killed, many doctors deliberately freeze the neurovascular bundle. Dr. Fred Lee says that if any of his patients are still potent after his treatment, then he has not done it properly.

This issue of preserving the “erection nerves” has to be discussed with the patient prior to the procedure. It is possible to do a “Nerve Sparing Cryo” in patients with a small amount of disease on one side allowing the surgeon to preserve the nerve on the opposite side. Some patients may prefer to do the procedure in two stages in order to try to preserve the nerves and repeat the freezing more aggressively if residual cancer is found later.

Some of the patients may prefer a combination of treatments by doing cryo to destroy the main portion of the cancer and then adopting a modified hormonal approach by using anti-androgens. Lupron and zoladex destroy the libido but most of the anti-androgens such as flutamide, casodex, nilutamide and proscar usually do not affect the libido.

### **Factors that are important in avoiding complications**

The training of a cryosurgeon can make a lot of difference. The cryosurgeon’s philosophy of treatment and technique is also an important factor that can affect the outcomes. You should look for a doctor who has had good training and lots of experience.

If the patient has had prior radiation treatment it predisposes him to a higher risk of rectal/urinary fistula. Having a prior TURP predisposes the patient to urethral sloughing of tissue. The type of equipment can make a difference in outcomes. The newer cryo machine manufactured by EndoCare has built in thermocouple monitoring which provides better control of the freezing process. Fig. 13-1 is a photo of a machine from EndoCare. The type of ultrasound equipment and the urethral warmer used can make a difference. The technique in using the equipment can make a difference. For instance, if the urethral warming catheter is removed prior to the iceball being thawed, this may cause sloughing later.

It is best if you get to know your doctor before treatment and discuss all of these important matters. Ask questions. Talk to some of his patients.

### **Results of Cryosurgery**

Dr. Gary Onik reported negative biopsies in 82.6% of his patients at 3 months following cryosurgery. Dr. Fred Lee found no cancer in 92% of his patients at 3 months. The University of California San Francisco reported that 89% had negative biopsies at 3 months. Dr. Jeff Cohen showed 69% negative biopsy at 21 or more months after the cryo. Overall Fred Lee et al reported negative biopsy rate at 5 years at 82%.

### **Targeted Ablation of Prostate Cryosurgery: A new and improved procedure**

There is a new cryosurgery machine manufactured by EndoCare. Their CryoCare unit uses Argon instead of liquid nitrogen, is smaller and can use 6-8 probes, enabling treatment of larger glands. The new EndoCare machine has a new built in feature -Thermocouples. These are needles that enable us to measure temperature in strategic locations. The panel of this new machine shows a display of temperature. The target is -40 degree Celsius. At this temperature, it was found all living cells die. Hence the name **targeted cryoablation of the prostate (TCAP)**. The target refers to target temperature.

### **Tailored Cryosurgery**

If we take it as a given that cryosurgery can achieve the same results as radical prostatectomy, there still remains the question: Is it worth while to risk the same complications that result from radical prostatectomies. The patient should be a partner in the treatment decision. All patients are different. Some want to make sure every last cancer cell is killed at any cost. Others may want to preserve their potency and accept the risk. The patient must decide how much risk he is willing to accept. Cryosurgery's advantage over surgery is that the procedure is much easier to perform. It is less traumatic. There is no blood loss. There is very short hospitalization of 1-2 days. It heals much quicker, and one can return to work or normal activities almost immediately. These are significant advantages.

The cryosurgical procedure produces good control of local disease, with a good potential for cure. But if we allow complications such as impotence and incontinence to occur at the same rate as radical surgery, then many of the advantages of cryosurgery are lost. I perform cryosurgery after a candid discussion with the patient who has to decide what objectives the patient feels comfortable with. What does he want to achieve? What can he reasonably expect to achieve? And how much risk is he willing to accept to achieve his objectives? I try to explain to my patients all of the options that he may have such as radical surgery or any of the various types of radiation. I explain the various treatments, the advantages and disadvantages of each. I know that I am a bit biased, but I believe that what I am doing is the best for the patient. But it must be the patient's decision whether he wants to undergo cryosurgery, radical surgery or radiation.

I view cryosurgery as an excellent alternative for patients who have a good understanding of the various procedures. I view cryosurgery mainly as a de-bulking

of local tumor (destroying as much as possible the tumor volume). If cure is achieved after first attempt, that is wonderful. I tell my patients, after all the years in practice, I cannot promise to cure everyone. But I tell them that I can avoid most postoperative complications if I am given the freedom to treat fairly non-aggressively. If patient wishes to take the most aggressive approach regardless of complication, I am able to do that for him.

How to correlate the question of efficacy of the procedure compared to the safety of the procedure is very much tailored to the individual. Overall, I don't think that cure is attainable in every case. My motto is: Control the disease by conservative treatments but try to do no harm to the patient or detract from his quality of life, and at the same time provide treatments aggressive enough to allow the patient to live out his normal life span. I can't justify the high rate of impotence after cryo that I see in other centers. I think that the patient himself should decide about this very important issue of potency. All men are frightened when diagnosed with prostate cancer. They may panic and act immediately out of fear, only to regret later their loss of their ability to have normal erections because of aggressive treatment.

### **The future**

There is further research going on to improve the destruction of the prostate cancer cells by having better mapping to indicate where the location of the cancer is in the prostate gland. If we know exactly where the tumor is, then we can have more success in killing it and perhaps become more selective in our targets of destruction. Spectroscopic MRI may be one of the tools to help us in locating the tumor. Many new developments are in progress. Researchers are working to develop better imaging of the prostate.

Other areas of research including immune therapy, gene therapy and anti-angiogenesis offer non-aggressive approaches. In combination with cryosurgery I believe we will develop more effective and safer treatment options that preserve quality of life. For prostate cancer patients it will be a better tomorrow.