

BRACHYTHERAPY OR RADIOACTIVE SEED IMPLANTATION

CANCER OF THE PROSTATE

Prostate cancer, like other cancers, is a disease of the body's cells. Normal cells reproduce themselves by dividing--facilitating growth and replacing worn-out and injured tissue. Cancer is characterized by the uncontrolled growth of abnormal body cells. Occasionally, cells grow abnormally into a tumor mass. Some tumors are benign (non-cancerous); others are malignant, or cancerous. Cancers invade and destroy nearby tissues and organs or spread to other parts of the body.

Prostate cancer is now the most common type of cancer of the male. If not treated early and effectively, however, prostate tumors can start to grow and spread into other tissues such as lymph nodes and bone. Although only a small proportion of prostate cancers progress to this severe stage, the ones that do can spread relatively quickly and are not easily treated or cured. The cancer can grow without symptoms for years, even decades. Prostate cancer is rare before the age of 40, and the risk increases with age. Its cause is unknown.

GOALS OF PROSTATE CANCER TREATMENT

Ideally, treatment for any cancer should cure the disease, be easily tolerated, and cause minimal or no problems. This concept is particularly important in prostate cancer for several reasons. Some men have an aggressive form of cancer that can lead to death from this disease. In other men, prostate cancers can grow so slowly that it causes few if any problems during a patient's natural lifetime. However, there is no absolute way to determine if prostate cancer will be aggressive or slow growing. Therefore, for most men whose disease is confined to the prostate, treatment is preferable to waiting and watching, especially since, as our life expectancies continue to increase, even slow-growing cancers could in time become life-threatening.

In other words, the ideal treatment for prostate cancer should effectively arrest or cure the disease particularly in men with aggressive cancer, but cause little if any problems, especially for men with slow-growing disease. Furthermore, since many men with prostate cancer are older or have other medical problems that make it impossible for them to undergo radical treatment, a treatment that minimizes trauma and complications is essential.

CURRENT TREATMENT OPTIONS

To ensure that prostate cancer does not develop further and is halted soon after diagnosis, physicians recommend early treatment to either remove or kill the tumor. The three main treatment options for early stage prostate cancer are

radical prostatectomy, external beam radiation therapy, and radioactive seed implants.

Some physicians and patients will employ an observational strategy termed Watchful Waiting or Observation. This may be a good choice in older men (over 75 or in poor health) who have cancers that are slow-growing, meaning Gleason Score 2, 3, or 4. Evidence shows that younger men with Gleason Score cancers of 5-10 will require treatment for advanced prostate cancer about 65% of the time in less than 10 years if they don't die of something else. Since the hormonal treatment used for advanced cancers is not curative and still has side effects, most healthy younger men with more aggressive cancers prefer to be treated earlier when the potential for cure is higher.

RADICAL PROSTATECTOMY

Radical prostatectomy is currently the most common treatment for early-stage prostate cancer in the U.S. It is a major surgical procedure in which the surgeon removes the prostate gland, usually through an incision in the lower abdomen.

Advantages:

Surgery is a one-time procedure that may cure early prostate cancer. It has been considered the "gold standard" for treatment. However, this is not based on clinical studies comparing surgery to either external beam or brachytherapy. Cure rates for those who undergo surgery for early, localized cancer (T1-T2) are only roughly 75% at 5 years and roughly 60% at ten years after treatment. However, if the operation is done in men with advanced disease, only 35 to 50% might be cured with surgery alone.

Disadvantages:

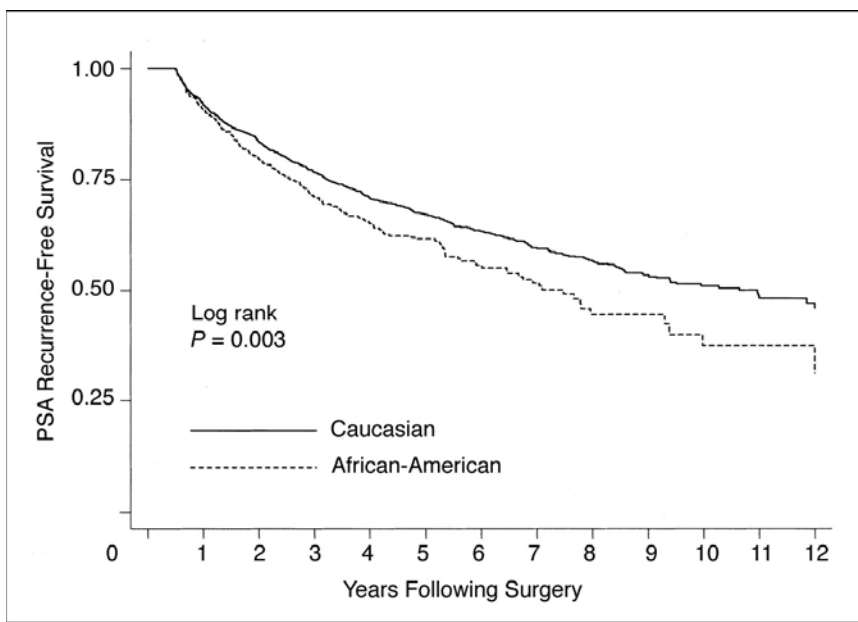
Radical prostatectomy requires hospitalization and is not tolerated well in older men who are not in overall excellent health. The side effects from surgery include impotence (inability to have an erection) in a high percentage of patients (generally more than 75 to 80%) and incontinence (a loss of urinary control) in a small percentage (1-2% severe, up to 20% mild or moderate). Recovery from surgery takes 4 to 6 weeks, and a catheter is usually maintained in the bladder for two to three weeks after the operation. In virtually all series, even recent ones, the mortality of the surgery alone results in 1% of men dying, usually from blood clots to the lungs.

Laparoscopic and Robot-assisted Laparoscopic Prostatectomy

Some surgeons are learning to remove the prostate with "less invasive" procedures. Patients may return to activities more quickly. However, to date, failure to cure by having positive margins does not appear to be lessened with

either technique, occurring in as many as 25 to 28% of patients undergoing these forms of surgical treatment. Incontinence is still an issue after these approaches.

What percentage of men are cured after radical surgery? A number of factors determine the outcome after surgery. Five and 10-year cure rates are shown in the table near the end of this file. The likelihood of cure goes down as PSA, Gleason Score, and extent of cancer go up. Other factors such as race and obesity may also have an impact. In a recent series of over 3,100 men undergoing surgery, Amling and associates showed that African-Americans and obese males had a worse outcome than Caucasians. However, among non-obese and Caucasian men, the cure rate after surgery was no better than 66-67% by 5 years, and only 51% at 10 years after surgery:

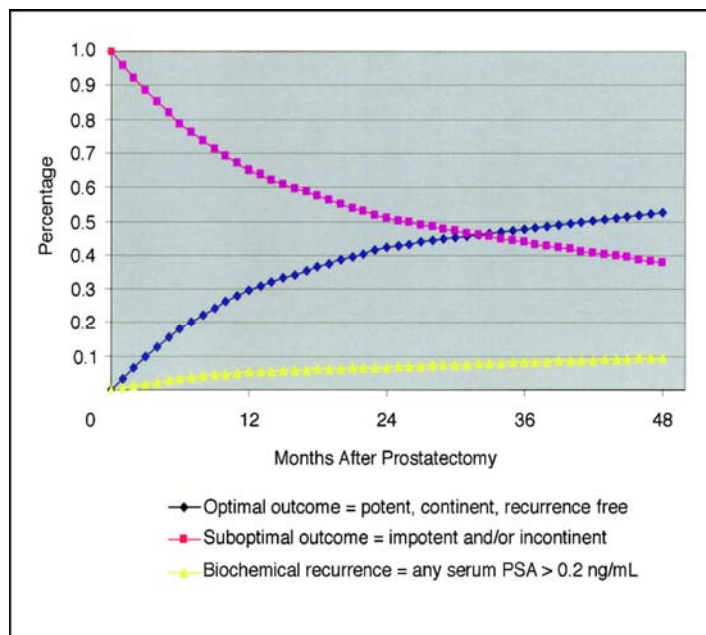


Amling et al: Pathologic Variables and Recurrence Rates As Related to Obesity and Race in Men with Prostate Cancer Undergoing Radical Prostatectomy. J Clin Oncol 22:439-445, 2004. Copyright American Society of Clinical Oncology.

What percentage of patients undergoing surgery have an Optimal Outcome, that is, are cured, potent, and continent?

In a landmark paper, Saranchuk studied 647 continent, potent men who underwent surgery. Cancer-free status with full continence and potency was achieved in 30% at 12 months, 42% at 24 months, 47% at 36 months, and only 53% at 48 months after surgery. 38% were impotent or incontinent, and 12% had a rising PSA at this early point:

Fig 5. Results of Markov model



Saranchuk, J. W. et al. J Clin Oncol; 23:4146-4151 2005

EXTERNAL BEAM RADIATION THERAPY or IMRT

Radiation to stop the growth of cancer cells is delivered using a machine (usually a linear accelerator) that shoots a beam of radiation from outside the body through normal body tissue to reach the cancer. The radiation is given in short sessions over a long period, normally once a day, five days a week over a seven- or eight-week period, to minimize damage to the normal tissue. Newer techniques may allow improved delivery and energy to the prostate, such as the Peacock device, Proton therapy, or IMRT.

Advantages:

External beam radiation therapy has a cure rate similar to surgery for early prostate cancer, perhaps 50 to 60% at ten years after treatment. Because it is not a surgical procedure, it is better tolerated, especially in older men. Hospitalization and anesthesia are not required and there are no life-threatening complications. When compared to radical prostatectomy, the risk of impotence is lower and the incidence of incontinence is approximately the same.

Disadvantages:

Although hospitalization is not necessary, the patient must make daily visits to the radiation center for nearly two months. There is still a significant risk of impotence and external radiation damage to healthy tissue, such as the rectum and the bladder. While most of these are minor and disappear shortly after therapy stops, they include fatigue, skin reactions in the treated areas, frequent and painful urination, upset stomach, diarrhea and rectal irritation or bleeding. In some cases, damage to the rectum or bladder can be severe and permanent.

BRACHYTHERAPY OR RADIOACTIVE SEED IMPLANTS

In the early 1970s, a new approach was developed to confine radiation exposure to the prostate gland, increase radiation dosage to the tumor in order to kill the cancer, and minimize side effects. Cancer specialists began to implant radioactive iodine (I-125) seeds directly into the prostate, thereby providing internal radiation therapy exactly where it was needed. In these early attempts, surgery was performed to expose the prostate gland and the radioactive seeds were implanted freehand, without the aid of imaging techniques now available. This early method of prostate implantation began at New York's Memorial Sloan-Kettering Cancer Center. The results were not satisfactory due to incomplete coverage due to the uneven distribution of seeds placed in that fashion. In the 1980's, several groups began to use trans-rectal ultrasound to map the prostate, plan effective distribution of the seeds, and then do the implantation using ultrasound to guide seed placement in order to achieve an even distribution of radiation. Ten year data is now available from several centers, and results with this technique are at least as good as with surgery for prostate cancer (see table below). In addition to I-125, a newer agent, palladium or Pd-103 is now used. Both iodine and palladium appear to be well suited for prostate implantation. They give off very low energy radiation over several months which does not travel far outside the prostate and poses no threat to patients or those near them. This is termed low dose rate (LDR) permanent brachytherapy implantation.

Using needles passed through the skin behind the scrotum (the perineum), pellets or seeds containing the radioactive iodine or palladium are permanently implanted directly into the prostate where they give off low-level radiation continuously for several months. Using trans-rectal ultrasound guidance, these seeds can be positioned so that radiation is distributed evenly throughout the prostate gland. Since only a small area is irradiated by each seed, relatively little radiation reaches the adjacent normal organs-the colon, which is directly under the prostate gland, or the bladder, lying on top of the gland. The entire prostate is radiated, since more than half the time, there are second or third cancers in addition to the one that might have been found on needle biopsy. The total dose

of radiation delivered to the prostate exceeds that which can be delivered by external beam therapy.

The implant procedure does not require a surgical incision. Instead, the seeds are contained in thin needles which are passed into the prostate gland through the skin between the scrotum and rectum. The location of the needles can be seen on the screen of the ultrasound machine and can be accurately guided to the desired position. While the needles are being inserted, the ultrasound probe is in the rectum. When each needle is in its correct position in the prostate, the needle is slowly withdrawn and the individual seeds are injected into the prostate gland. The ultrasound probe and the needles are removed when the procedure has been completed. The numbers of needles and seeds required varies depending upon the size and shape of the prostate gland. Thus, treatment is truly tailored to each patient individually.

Depending upon the size of the prostate and the extent of cancer in it, implant therapy may be performed as the only therapy used, or it may be used in combination with androgen blockade (hormonal) therapy or external beam radiation. In rare cases, all three modes of treatment might be combined. Most prostates are small enough to be implanted without needing to shrink them. However, big prostates may be hard to get the needles into because the pelvic bone blocks part of the gland. In such cases, hormonal treatment is used for several months to shrink the prostate and allow successful implantation.

Advantages:

Results from centers using I-125 and palladium since 1985 show a higher percentage of implant patients remaining disease-free than with either radical prostatectomy or external beam therapy.

Seed implantation is normally done as an outpatient procedure taking about one hour to perform. The patient usually leaves the hospital the same day as the implant procedure or stays in the hospital for one night and then resumes normal activities within several days.

Because they are placed inside the prostate, seeds actually deliver 2 to 4 times more radiation to the cancer than external radiation therapy or IMRT, which must use a lower dose because they may damage healthy tissue.

This procedure is well suited to older patients because it is much easier to undergo than surgery or external radiation. It is well suited to younger patients who would prefer to avoid the rigors and potential complications of radical prostatectomy.

Disadvantages:

There is little information yet on the effectiveness of the implant treatment after 10 years. While the current clinical data show good results through 10 years, younger men often are advised more strongly to consider radical prostatectomy. However, randomized comparisons of surgery to seed implant therapy are not underway, nor are they likely to take place. There is actually no factual basis on which to base the statement that younger men should undergo surgical removal of the prostate rather than seed implantation.

It is common to experience problems with urination after seed implantation. Most are discharged without a catheter but 2-3% of men may need a bladder catheter to drain the urine for a few days after the procedure. Burning on urination as well as an ache from the prostate may occur as the radiation effect on the tissue occurs. Some increase in frequency of urination is to be expected. These symptoms will gradually disappear after a few weeks to 6 months, and by one year, most men are voiding at their pre-treatment levels.

Incontinence occurs in less than 1% of patients who have not had prior surgery. If a patient has had a prior TURP or needs one later, some degree of urinary leakage may occur. Impotence occurs in less than 15% of patients under the age of 70. For patients over the age of 70, impotence occurs more often.

Rectal irritation is frequent after an implant, but usually transient and self-limited. Bleeding from radiation changes can occur one or more years later and usually requires colonoscopy and cauterization. Serious injury to the rectum can occur and may require colostomy. This is less common with brachytherapy seeds (less than 1%) than with external radiation alone (5%), but higher (3%) in patients receiving brachytherapy combined with external beam. Fortunately, the addition of external radiation to the seeds as combination therapy is necessary in only less than 5% of patients.

WHO ARE BEST CANDIDATES FOR IMPLANTATION?

Patients with early-stage and small prostate tumors are the best candidates for implant alone. That means that about 60 to 70% of men with prostate cancer will fit these criteria. The development of more sensitive tumor detection techniques means that prostate cancer patients are being diagnosed at earlier stages, permitting more patients to become potential candidates for seed implantation. More importantly, many men with low PSA and limited cancer will be found, after surgical removal of the prostate, to have extension of the cancer into the capsule, leading to "positive margins" with cancer left behind if the prostate is removed surgically. The Partin Tables can and should be used to help each patient understand his probability of having his cancer invade the capsule of the prostate

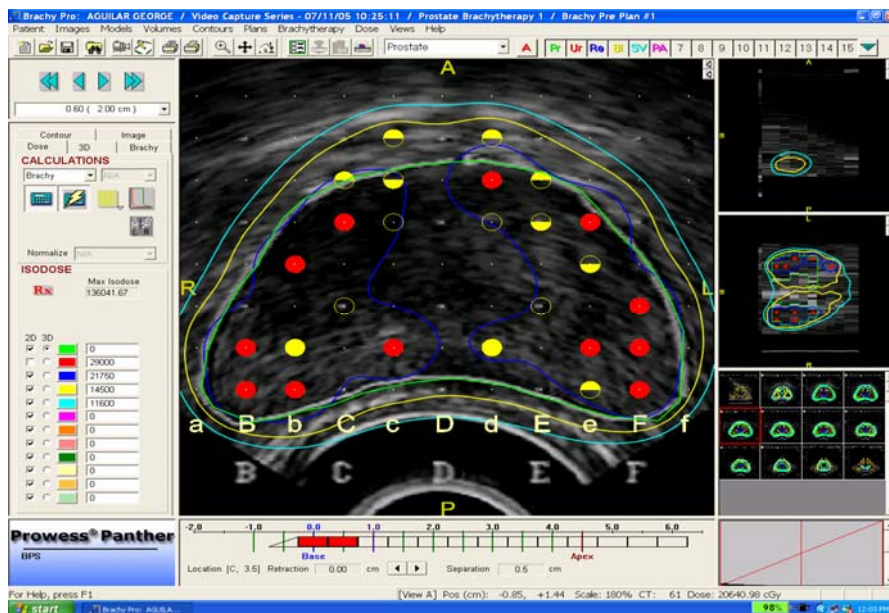
before a decision is made for surgery. This is the major reason for failure in most of those who fail to be cured by surgery. Even with positive margins, it may be several years after surgery before the PSA begins to rise again. That is why the percentage of patients cured by surgery averages only 75% five years after surgery, and drops further to 50 to 70% at 10 years, and a low 44% 15 years after surgery (see Table below). Since radiation with seeds alone or seeds with a low dose of external beam has the potential for killing the cancer that has invaded the capsule, many patients who would appear to be good candidates for surgery might be even better treated with brachytherapy. The fact that overall side effects with brachytherapy are less is an additional benefit of brachytherapy.

The Radioactive Seed Implant Procedure: Before, During and After

Before the Implant

A volume study to determine the shape and size of the cancer will usually be performed about three weeks before the implant. Using a trans-rectal ultrasound unit, we will locate your prostate and a computer will make an exact 3-D model of the gland. This will allow the radiation physicist to determine the number of seeds needed to treat the prostate and exactly where they should be placed.

A single slice (1 of 8 to 10) showing locations of seeds and the shape of the radiation field (yellow = 145 Gy, blue = 116 Gy) surrounding the prostate (green line):



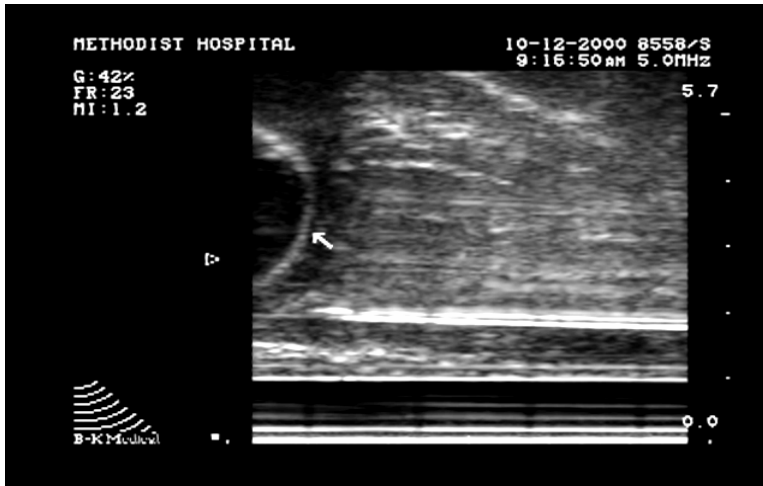
Approximately one week prior to the implant, you will have blood tests done and possibly an electrocardiogram (EKG) and chest X-ray. The test results are used to inform the anesthesiologist of your ability to tolerate anesthesia. You also will be given specific instructions regarding diet and enemas, and when to arrive at

the hospital. The enemas will help remove fecal material from your lower bowel and rectum so that the ultrasound image of your prostate will be optimal.

During the Implant

The implant procedure is performed in the operating room and lasts about 45 minutes. You will probably receive general anesthesia. You may also receive medication through an intravenous (I.V.) line, which will make you feel drowsy before the anesthetic takes over.

An ultrasound probe will be inserted into the rectum to image the prostate on a television monitor. The seeds, usually numbering about 75 to 125, are then inserted into the prostate through 18 to 30 needles. The needles are inserted through the skin between the scrotum and the rectum and, with the transrectal ultrasound device, are guided with pin-point accuracy directly to their intended locations. After the seeds have been placed, a flexible scope is passed into the bladder to make sure that no seeds are loose in the urine channel or in the bladder itself. After that, a catheter is temporarily placed in your bladder to drain urine.



After the Implant

After the implant you will go to the recovery room for one to two hours, until you have awakened and are alert and medically stable for discharge. The urinary catheter is usually removed when you are alert and the urine is clear.

Since seed implants are an outpatient procedure, you can go home or to your hotel after you have recovered from the anesthesia. Because you may feel a little weak, it is recommended that you do not drive for at least 12 hours.

You may resume eating and have visitors as soon as you wish, but you should avoid heavy lifting or strenuous physical activity for the first two days you are home. After that, you will probably be ready to return to your normal activity

level. You will be placed on antibiotics for several days after the procedure. Most men return to work the next day.

Possible Side Effects

There is surprisingly little discomfort after the implant, although mild soreness is expected between the legs for one to two days. You may experience some slight bleeding or burning beneath the scrotum, or blood in the urine. These side effects are caused by the needles used to place the seeds. The seeds themselves, the catheter and other instruments used during the procedure also can contribute to these side effects. It is normal for some blood to appear in the urine draining from the catheter, which may continue for several days. While this slight bleeding is no cause for alarm, if it should become severe or there are large blood clots, call your urologist. Drinking plenty of water helps prevent blood clots and flushes the bladder.

Other side effects that may occur after the implant, such as frequent urination or burning on urination, are generally due to the radiation from the seeds in the prostate. If severe, we will want to check your urine soon for infection. If not due to an infection, these symptoms will gradually decrease as the seeds lose their strength. Drinking plenty of fluids and avoiding caffeine may help to relieve these symptoms. If you have significant trouble urinating before or after the implant, you might be given medication to help, such as Hytrin or Flomax. As with all medical procedures, there is a small chance that there could be other longer term, or even permanent, side effects.

Radiation Safety

Many patients are concerned about whether an implant poses any potential dangers of radiation exposure to their family and friends. The seeds used in implant therapy emit a very low energy radiation that does not travel far; in fact, the vast majority of the radiation does not go beyond the prostate itself.

Very small amounts of radiation, however, can reach other people either from a seed being passed in the urine or if a tiny amount of radiation escapes from the prostate and travels a short distance through the air. Because the amount that might escape is so small, it is not considered a risk for most people, and there are no restrictions on a patient's travel or physical contact with other adults. Small children and pregnant women, however, may be more sensitive to the effects of radiation. It is usually recommended that young children and pregnant women not be on the lap of the patient for the first two months following the implant.

Suggested Follow-Up Schedule

After a seed implant, follow-up with your urologist and radiation oncologist should be done on a regular basis. Both of us will work together to provide you with the best care possible. The follow-up schedule usually includes a visit at 3 weeks to check for seed placement using a CAT scan. Further visits are then usually scheduled every three to six months for the first five years, to monitor treatment progress. Physical examination and blood tests will be performed periodically.

BRACHYTHERAPY USING HIGH DOSE RATE AFTERLOADING WITH IRIIDIUM

A variation of brachytherapy is called HDR or High Dose Rate Afterloading. In this technique, which is used in only a few centers in the US, needles are placed into the prostate. The position of the needles is then checked with ultrasound or CAT scan and a dose plan is created. The patient is transferred to a special lead lined room that protects the staff from the radiation. A computer driven device then places a radioactive substance, usually Iridium-192, into the needles for a measured length of time. This appears to give a more exact dose of radiation to the prostate than external beam therapy. The patient will receive one to four treatments. External beam therapy must be added to this type of radiation. Data from HDR treated patients is much too early to determine how effective it might be. The major detraction is that the patient is awake and confined to a bed while the needles are held in place between the legs. For patients who need to have a pelvic lymph node dissection done prior to radiation, such bedrest and high dose therapy may not be unreasonable. However, most patients needing seed implants do not require lymph node dissection, so confinement to bed for this period to accomplish HDR therapy seems excessive compared to the ease of implant therapy.

CRYOSURGERY OR FREEZING

Freezing the prostate while it is still in the body is erroneously termed "cryosurgery", since it is not a surgical procedure. It is being developed as a non-surgical method of treating prostate cancer. Under anesthesia, probes are placed into the prostate and it is frozen and thawed twice to literally turn the prostate into a ball of ice. Cell death occurs, and this can be effective in the short-term in controlling some cancers, though moderate morbidity and side effects may result. It may be useful to treat men who have failed external beam therapy. A major practical limitation is that the freeze line cannot be taken beyond the prostate for fear of causing damage to adjacent structures, and it is clear that most of the failures to surgery are due to disease that is already outside the prostate at the time of surgery. A clear role for cryo in the treatment of early, localized prostate cancer has not been defined clearly.

Percent of Patients With Undetectable PSA after Surgery
or < 0.5 after Brachytherapy

Physician/Institution	<u>5 years</u>	<u>10 years</u>	<u>15 years</u>
<u>Radical Prostatectomy for T1-T2</u>			
Catalona/ Wash. U.	78%	68%	n.a.
Ohori / Baylor	76%	73%	n.a.
Partin / Hopkins	83%	70%	n.a.
Paulson / Duke	75%	n.a.	n.a.
Trapasso / UCLA	69%	47%	n.a.
Zincke / Mayo	77%	54%	44%
Amling et al, 2004	65%	48%	n.a.
AVERAGE	75%	58%	44%
<u>Brachtherapy for T1-T3</u>			
Grimm / Northwest Inst. (1988-90)	91%	87%	84%
Blasko et al, 2000 (Seeds only)	87%	85%	
Critz, 2002 (PSA < 0.2)	87%	84%	

adapted from Ragde et al, Cancer 83:989-1001, 1998

The Partin Table

The Partin Table is a useful guide to predict the pathologic findings if a man were to have his prostate removed for cancer. It is based upon several thousand men who had cancer and underwent surgery. Ideally, the cancer would be contained or confined to the prostate, and not involve the capsule, seminal vesicles, or lymph nodes. We will fill this in when you visit with us. Based upon your Stage _____, Gleason Score _____, and PSA _____, the Partin Table predicts for you:

- Organ-contained cancer in _____ %;
- Extension outside the prostate in _____ %;
- Seminal vesicle involvement in _____ %;
- Cancer in the lymph nodes in _____ %.