The Modern Radioactive Seed Implant for Prostate Cancer Treatment

By Jamie A. Cesaretti, MD, MS and Mitchell D. Terk, MD
Terk Oncology, Jacksonville, FL

Abstract: *Prostate transperineal brachytherapy has become an effective treatment option for the cure of prostate cancer. A well done implant offers a very high cure rate and low morbidity compared with surgery and external beam radiation therapy. Over the past several decades the technology surrounding the seed implant technique has improved dramatically. Today's implant technology allows the physician and their physics team to continuously adjust the dose delivered to the prostate gland and surrounding tissues thereby allowing doses of radiation to the prostate gland to rise to levels not possible using either proton or photon based techniques. The seed implant also allows for the body to maintain its normal anatomic relationships which in turn allows for maintenance of a person's normal physiological functions such as urination, normal anal tone and rectal function. Clinical results have been impressive in the long term with data from several institutions confirming impressive data from the 1990s using this minimally invasive treatment modality as a worthy standard option to the robotic assisted radical prostatectomy or external beam irradiation using either protons or photons. In addition to the experience in the United States (US), other health systems have embraced the seed implant as a standard option such as Japan and most European countries.*

Introduction

The prostate seed implant has been part of the prostate oncology arsenal since the 1970s offering excellent results for most presentations of prostate cancer.[1] The modern implant techniques afford very good long term results with morbidity that is almost always temporary in nature when compared to other proven treatment options such as surgery and external beam radiation using either protons for photons.[2]

Whitmore and Hilaris in the 1970s describe I-125 seed implants that used a thoughtful open retropubic approach to the gland whereby the surgeon, under direct visualization, implanted radioactive seed without the help of modern imaging modalities.[3,4] With the development of the trans-rectal ultrasound in the 1980s, Holm et al. applied this new imaging technology to the seed implant which has allowed for the implant procedure to become a very popular treatment option.[5,30]

In addition to the continued application of imaging modalities to the implant technique, the development of the modern computer has also further advanced the field. Today's implant procedure is done with a full three dimensional appreciation of anatomy in real time using not just a high quality biplanar ultrasound probe, but also fusion imaging technology that takes advantage of MRI and functional imaging modalities. The computer software available for real time implant guidance and planning allows for instantaneous corrections of doe inhomogeneity within the gland and avoidance of functional organs that in the past we were not able to visualize, such as the penile bulb and neurovascular bundles. These advances combine to allow the modern urology team to give unprecedentedly efficacious doses of radiation straight where the cancer occurs without having to rely on probability models to determine whether a radiation dose might be effective.[2]

History of the Seed Implant Procedure

Alexander Graham Bell, in the early 1900s, speculated on the use of radioactive sources implanted directly into tumors in order to achieve a cure for cancer.[6] Hugh Hamptom Young, a noted urologist at the Johns Hopkins Medical School who is credited with performing several of the first prostatectomies in the US also published successful prostate tumor regression with the repeated use of a small radium rod using a transrectal approach in a large series of patients who had very symptomatic and locally advanced prostate tumors in the first quarter of the 20th century.[7,8] The early processes for enriching a radioactive brachytherapy source was very expensive and labor intensive; it was not until the late 1960s that permanent radioactive sources were available. The first such sources consisted of encapsulated radon gas within a gold container; the field has gone on to produce several other models with characteristics that are useful in different clinical context.[7]

Address Correspondence to: Jamie A. Cesaretti, MD, MS
Terk Oncology, Jacksonville, FL
jamie@jcesaretti.com

In terms of clinical advances, in the 1970s, the prostate cancer group at the Memorial Sloan Kettering Cancer Center developed a freehand technique of implanting iodine-125 in the prostate gland using direct visualization. The accurate placement of radioactive sources was not possible because of a lack of three dimensional imaging of the gland; in addition it was as yet unknown what the optimal radiation dose should be which resulted in unacceptably low cure rates. A retrospective analysis of these men has identified a subset who did receive a high quality implant. These men were found to have good,long term prostate cancer control which is remarkable considering that neither the PSA test nor the histological stratification scheme (Gleason Scoring) were available.[9] This series confirmed what most brachytherapists suspected which is that in order to achieve success a high dose of radiation is needed.[10] Holm et al. applied the single plan transrectal ultrasound probe to the problem of achieving a good prostate implant in the early 1980s. By using the axial real-time image his team could visualize needle placement relative to the bladder, urethra and rectum, and for the first time properly avoid relatively radiosensitive structures. In addition, he used a perineal template approach rather than the open or trans-rectal approach bringing a high level of reproducibility and precision to the procedure.[5] In the mid-1980s, this initial image-guided technique was further refined and popularized by the Seattle group; they codified and widely taught a pre-planned approach which was highly reproducible and robust.[11] Their technique required that a treatment plan was generated a few days before implantation and was carried out in the operating room by the brachytherapy team. A different approach was developed by a group of clinicians at the Mount Sinai Hospital in New York in the early 1990s; their technique relied on the use of an intraoperative nomogram which performed the implant procedure in real time. It also relied heavily on using both the transverse and saggital image sets during the procedure.[12]

It is generally accepted today that there should be some form of intraoperative adjustment of a prostate seed implant. This is usually done by evaluating the plan mid-course or upon its near completion for areas of under dosing and applying extra dose to these areas. In addition, it is common in all implant strategies to take into account anatomic variation during the implant and make reasonable modifications based on clinical judgement and/or computational insights.[13]

Isotope Selection

Prostate brachytherapy is the only way to use radiation to treat prostate cancer currently which avoids high radiation doses to the bladder, rectum, bowel, penile bulb, femoral heads and associated vascular and neuronal structures. The use of external beam radiation and proton therapy can avoid dose to most of the above structures, but not all because external beam radiation or proton therapy must enter the body from the outside. A low dose rate radioactive source, if placed correctly, has a very small area of activity, akin to a very small bead in three dimensional terms. The size of the bead of radiation is determined by the isotope selected and the baseline energy of that isotope. A highly active source of any isotope could give off a marble or golf ball sized area of biologically meaningful dose. In the brachytherapy field most clinicians have elected to use bead sized energy fields and isotopes. This decision gives the clinician a very high safety threshold should a seed be slightly out of place and it also allows the user to place seeds very close to important structures without damaging them.

The isotopes used today for prostate cancer treatment emit gamma ray energy and decay at a rate which allows them to become completely inactive between two to 12 months. High-energy gamma ray sources with a long half-life (the amount of time it takes for half of the energy of an isotope to decay) are used for temporary implants or high dose rate (HDR) brachytherapy. Low-energy sources, with much shorter half-lives, are used for permanent implants or low dose rate (LDR) brachytherapy. The LDR type of implant is commonly referred to as a seed implant whereas the HDR type of implant, which relies on the use of removable catheters, is referred to as a temporary implant.

The most widely used isotopes for the treatment of prostate cancer are iodine-125 (LDR), palladium-103 (LDR) and iridium-192 (HDR). There are other isotopes whose properties are of interest which will also be reviewed below, but the field is continuously developing and new radionuclides such as cesium-131, gold-198, and californium-252 may find a useful place in the treatment paradigm going forward.[14]

Iodine-125 (I-125)

Radioactive Iodine-125 has a physical half-life of 59.4 days and the photon energy produced by its decay is relatively low, 0.028MeV. The majority of its radiation (87.5 percent) will be delivered in six months and in a year it becomes totally inactive. It can be used for monotherapy or in combination with external beam radiotherapy. In addition, it is the isotope which we know most about because it has been in use continuously longer than the other available isotopes.

Generally, the radioactive sources are completely encapsulated within a titanium cylinder. The seeds external dimensions are 4.5 mm in length and 0.8 mm in diameter,

with a marker inside making the seed identifiable during fluoroscopy. Most of the variability among manufacturers has to do with variations in the internal structure of the seed. These differences can manifest as differences in the dose distribution of each source. The oncological minimum dose recommended for I-125 monotherapy is 145 Gy and 100-110 Gy when used in conjunction with external beam irradiation to 45 Gy.[15,16] There has been a recent development from seed manufacturers which is to put external structures on the outside of the standard seed in order to make them more sticky within the prostate gland such as the Capseed from Bard Urological.

Palladium-103 (Pd-103)

Radioactive palladium-103 has a physical half-life of 17 days and photon energy of 0.021MeV. Therefore, the dose rate of Pd-103 is higher than that of I-125. The Pd-103 seed has a similar biological effect to I-125 with minor clinical differences. There are currently no studies that show that one isotope is better than the other in terms of acute and late side effects or oncological efficacy.[17] In addition, both isotopes can be used in combination therapy (brachytherapy plus external beam irradiation) where implantation acts as a "boost" for the total dose. Pd-103 is theoretically preferable to I-125 as salvage prostate seed implant therapy for patients who have failed external beam radiation therapy because the energy of the isotope is less than I-125. The energy of Pd-103 is less penetrating and is therefore less likely to penetrate to a heavily pre-treated rectum. Of note, the suggested dose by the American Brachytherapy Society for Pd-103monotherapy is at least 124 Gy and 90-100 Gy when used in combination with 45 Gy of external beam irradiation.[16]

Iridium-192 (Ir-192)

Iridium-192 has a physical half-life of 73.8 days and emits high energy gamma energy of 380 KeV. Because of the very high energy the isotope is always used for temporary implantation in the form of transperineal catheters.[18] The catheters are placed through the perineum and the Ir-192 source is allowed to dwell for short pre-determined lengths of time. Once the treatment is complete the catheters are removed, and the source can be used on another person.

Cesium-131 (Cs-131)

Cesium-131 has now been in use for seed implant therapy for more than 10 years. It has a significantly shorter half-life of 9.7 days and a gamma energy of 0.029-0.034MeV. Radiobiology, the study of the interaction between radiation and normal tissues and cancers, can be used to make a persuasive argument that the quick delivery of a high dose of radiation is the most effective way to kill prostate cancer. In terms of normal tissues, radiobiology is instructive because it predicts that the same quick delivery of radiation to normal non-cancerous tissues is deleterious. In addition, because the normal tissue effects which concern patients most are late effects such as erectile dysfunction, chronic urinary bother, rectal ulceration and fistulazation, the use of Cs-131 will have to continue to be tested in a large number of patients by high volume practitioners over many years to assure that the advances we have made with the use of I-125 and Pd-103 are not diminished by the widespread adoption of the technology before its late side effect consequences have been clarified.[19] From a practical standpoint, its use had been limited because of the need to perform the implant within a relatively strict timeframe because of the very short half-life.

Gold-198 (Au-198)

Au-198 has a half-life of 2.69 days and gamma energy of 1.2MeV. The use of radioactive gold as an isotope for the treatment of prostate cancer can be traced back to 1952 when Flocks inserted Au-198 colloidal suspension in the gland during an open surgery.[20] The next step was the use of solid Au-198 combined with EBRT by Carlton in 1965, and introduction of transrectal ultrasound allowed gold to be applied also transperineally. During past years the evolution of other cost-effective isotopes (iodine, iridium) has limited its usage.

Californium-252 (Cf-252)

Cf-252 has a physical half-life of 2.7 years and gamma energy 0.7MeV. Radiosensitivity is dependent upon intracellular concentration of oxygen. Cancer cells are less saturated with oxygen than healthy ones and thus require a higher energy source to kill them. Irradiation with high linear energy transfer (2-10KeV) can be more effective for poor oxygenated cells. It may be better to use neutrons with high linear energy transfer where secondary radiation is formed as a result of interaction of neutrons with biological tissue. Cf-252 neutrons can be used for this purpose, and that is why investigations are under way to prove this concept. Several problems have prevented the introduction of Cf-252 sources into clinical practice. Development of an appropriate sized delivery mechanism and limiting harmful radiation to medical personnel are two of them.[21]

Radiobiology

The goal of radiation is to damage DNA of cancer cells by producing lethal double strand breaks. In order to maintain genome stability, human cells are capable of repairing these lesions by a process called DNA repair, usually within a few hours. If this pathway is not successful, cell death will result.[22] Cancer cells are more radiosensitive than normal ones because they are less efficient in successful DNA repair and more easily become synchronised in radiosensitive phases of cell cycle.

Treatment Planning

Brachytherapy treatment planning is based in proper ultrasound measurement of prostate volume and careful identification of anatomic relationships. The brachytherapy field has been using image guidance for the placement of radioactive seeds since the mid-1980s in contrast the modern image guided era of external beam radiation which began when onboard imaging technology because widely available in the early 2000s.

After the initial work of Holm who used an axial ultrasound for guidance in seed placement,[5] the private practice from Seattle further refined his technique and developed a preplanned ultrasound guided prostate brachytherapy technique.[11] According to the "Seattle method," the treatment plan is created a few days before the implant based upon axial images of the prostate every five mm measured in the urologist's office. These images were originally digitized by physicists with the aid of computer software prior to the introduction of the CT scanner into the radiation department. The plan is then used in the operating room where the physician team attempts to put the patient in the same position as he was when the preplan was created. The needles are inserted through the template and via perineum into the prostate. The ultrasound is used to recreate the preplan and make certain that the needles are positioned in the predetermined positions. The early implantations of the Seattle group were performed by placing the seeds uniformly throughout the prostate according to the Quimby dosimetry system.[23] Later a peripheral weighting was used in order to achieve homogeneous dose distribution, and avoid high doses to central part of the gland were urethra is located so to decrease urinary complications.[24]

The group at Mount Sinai Hospital developed a prostate brachytherapy method called the Real – Time technique.[1,12,15] This method is also referred to as the "nomogram method" because it originally used a nomogram table in order to find the proper amount of activity to implant. The planning of this method is done in the operating room and does not rely on a preplan. Seeds are placed mainly in the periphery (75 percent of total activity) according to the principles of Paterson and Parker[24] in order to avoid urethral and rectal hot spots. The remaining[25] percent is placed in the interior for coverage of base and apex of the gland. Initially the prostate volume is measured in the urologist's office and used for the seed order with an additional measurement taken at the beginning of the case. The seeds are inserted using a Mick applicator under continuous ultrasound guidance in longitudinal imaging that allows for immediate adjustment of seed placement.

Both methods have evolved substantially from their initial approach and now integrate modern computer imaging and dose calculation technology; the original approaches using the limited computer technology and low quality imaging devices of the early 1990s have revealed during the past two decades that the original treatment offered excellent long term results.[1,13,15,25]

Doses

Radiation dosing and dose limitations are of major importance in order to achieve an optimal and successful implant. The goal of prostate brachytherapy is to deliver the highest dose to the target with the greatest precision. This way tumor control is achieved and morbidity risk is minimized.[2,15] The recommended doses of American Brachytherapy Society for I-125 and Pd-103 are 145Gy and 125Gy respectively when monotherapy is applied, and 100-110Gy and 90-100Gy respectively when brachytherapy acts as a boost to external beam irradiation.[16] Dose to a prostate is expressed as a percentage of the volume of the prostate in Gray units (1Gy = 100 Rads). For example, D90 that is often used and represents the quality of an implant equals the dose received by 90 percent of prostate gland. For normal tissues VGy (fraction of volume receiving a specific dose) is used to assess the effects of radiation toxicity. For example, V100 refers to the volume of a structure in percent receiving the prescription dose.[15,25]

Patient Selection

Success in prostate brachytherapy depends highly on patient selection because dose delivered by seeds travels only a few millimeters (three to five mm) around the gland and a small amount reaches the surrounding tissues.[2,12,26]

Low risk patients are defined as those who present with PSA ≤ 10ng/ml, Gleason ≤ 6 and clinical stage ≤ T2a. This group of men has a high possibility that the disease is confined to the prostate.[27] It is now generally accepted that patients with organ confined disease have excellent long term results regardless of the treatment method employed, and the final decision should be taken by the patient after taking in consideration the expected morbidity of each procedure.[26,28]

Patients with a risk of extracapsular extension will not be adequately treated with implantation alone and require further screening before appropriate treatment is selected. If one or more of the following intermediate disease features are present, PSA: 10-20ng/ml, Gleason 7 or clinical stage T2b, the patient should be treated with either implant and short course of hormonal therapy (six months) or implant plus external beam irradiation.

High risk patients are patients with at least one of the followings: PSA > 20ng/ml, Gleason score ≥ 8, clinical stage ≥ T2c. Disease with two or more of the intermediate risk characteristics should be considered high risk and treated with the high risk protocol (trimodality approach) consisting of nine months hormonal therapy, three given neoadjuvantly, brachytherapy boost (107 Gy) and external beam irradiation (45 Gy). Another excellent option is to treat the patient with definitive high dose radiation in conjunction with hormone therapy to greater than 80 Gy using image guidance and intensity modulated radiation therapy.[29,30]

In addition to the criteria related to the stage of the disease, exclusion criteria for seed implant therapy were developed mainly because the implant techniques could not overcome very specific technical-anatomical problems such as having a prostate size > 50 cm^3 and prior TURP before implantation.[13]

Hormonal Therapy and Brachytherapy

The basis for the use of complete androgen blockage and prostate seed implantation came from the experience with hormonal therapy combined with external beam irradiation.[31] The mechanism of synergistic effect of hormonal therapy and radiation is increased therapeutic ratio, cytoreduction and apoptotic synergism.[32]

Treatment Results

The results of patients undergoing prostate brachytherapy depend on several variables. Patient selection, the use of hormonal therapy, the addition of external beam irradiation and the definition of failure used will influence the final outcome. Most investigators use the ASTRO definition (1997) of three consecutive rises to identify patients failed after radiation treatment and others suggest that a nadir value of 0.2ng/ml is more appropriate. ASTRO (2006) revised the original definition to a 2ng/ml or more rise from the nadir (revised Phoenix definition) suggesting that the old definition was not linked to clinical progression or survival, and that the new is not influenced by hormonal therapy usually added in radiation receiving patients.[35] Special attention should be given to a single or double PSA value rises since not always constitute a failure (PSA bounce).[36]

Low risk patients (PSA ≤ 10ng/ml, Gleason ≤ 6 and clinical stage ≤ T2a) are the best candidates for prostate monotherapy brachytherapy. Most investigators report a 76-96 percent PSA failure free rate at 5-13 years (Table 1).

Patients presenting one of the intermediate risk features (PSA: 10-20ng/ml, Gleason: 7 or Stage: T2b) can also be candidates for seed implantation usually in conjunction with hormonal therapy or external beam irradiation. Patients with two or more intermediate characteristics should be considered high risk and treated with the trimodality protocol (hormonal therapy, brachytherapy boost and external beam irradiation) (Table 1). High risk patients are considered those having at least one of the followings: PSA > 20ng/ml, Gleason: 8-10, clinical stage ≥ T2c. Data from experienced groups performing brachytherapy have reported results superior to monotherapy surgery or EBRT in intermediate and high risk patients (Table 1).

Morbidity

Prostate brachytherapy is a minimally invasive procedure that both eradicates the tumor and maintains quality of patient's life. Short and long term complications, however, can also occur with prostate seed implantation. The rate and severity reflect particular institution's and individual practitioner's experience.

Urinary retention occurs in two to 10 percent and highly correlates with large prostate size or significant urinary symptoms (high IPSS scores) before the procedure. The risk greatly decreases if patients are treated with an alpha blocker prior and after the procedure.2,45 Persistent urinary retention will require surgical intervention (TURP) that is better to be performed after three to four half-lives of the isotope are delivered (two to three months for Pd-103 and six to eight months for I-125). Postimplant TURP rates are 0.8-3 percent.

Most patients will experience voiding irritative symptoms such as dysuria, frequency and nocturia. Their intensity peaks at about one to two months postimplant, but a year after the procedure most patients normalize their urinary complaints.[45,46] However, a late transient exacerbation of urinary symptoms may occur till the fifth year postimplant.[47]

Long term complications include urethral scarring, chronic irritative urinary symptoms and urinary incontinence (18 percent, associated with TURP after implantation). They highly correlate to the dose delivered to urethra (urethral volume should receive less than 150 percent of prescription dose).[2,12,15,45,46]

Radiation proctitis (grade one or two) may also occur after brachytherapy (two to 24 percent) although is usually mild[45] and correlates with the delivered dose (volume of rectum receiving prescription dose should be less than 1.3cm^3 for monotherapy patients and less than 1cm^3 in combination). It consists of tenesmus, urgency to defecate and minor intermittent rectal bleeding. More severe complications such as ulcer (grade 3) or rectal fistula (grade 4) may occur after biopsy of anterior rectal wall or electrocautery (treatment attempt of rectal bleeding).

It is critically important that patients should not have any rectal procedures before notifying the physician that performed the implant.

All treatment modalities of prostate cancer cause some form of erectile dysfunction. Seed implantation though, has been associated with the lowest impotence rates. Impotence may occur in 15 to 30 percent of patients with normal preimplant sexual function, although a small decrease may occur from the third till the fifth year after implantation.[45] Since normal anatomy is preserved, brachytherapy patients usually respond to the administration of sildenafil citrate and potency rates increase further.[48]

Genetic Predictors of Side Effects

The side effects of prostate radiotherapy are a major concern of patients undergoing this form of cancer treatment and a main reason why some of them elect other approaches for curing their disease. A lot of work has been done during the last few years regarding genetic tests that predict which patients are most likely to develop radiation-induced responses based on genetic alterations in genes, such as ATM gene (Ataxia Teleangiectasia Gene). In a series of studies it is validated that there is a strong relationship between expression of ATM gene and fibrosis which in turn is associated with increased urinary symptoms, erectile dysfunction and rectal bleeding. These initial findings may prove critically important in the future and genetic screening of patients might serve as a predictor of presence or severity of side effects after prostate brachytherapy or EBRT.[49,59]

Conclusions

Permanent radioactive prostate seed implantation is accepted as a safe and effective treatment modality for localized prostate cancer that maintains the patient's quality of life.[51] Well controlled randomized trials are needed to determine if it is better than a modern robotic radical prostatectomy.

Table 1: Freedom from PSA failure (rate percent) after only brachytherapy or in combination with external beam irradiation and/or hormonal therapy in low, intermediate and high risk patients.

Author	Patient Number	Risk	Treatment	Rate (percent)	Follow-up (years)	PSA definition of failure (ng/ml)
Ragde[37]	Low: 441 High: 178	Low, High	Low: I-125 BTx, High: Pd-103 BTx No HT	Low: 76 High: 80	13	ASTRO modified (3rd PSA rise > 0.5)
Critz[38]	1469	Low, Intermediate, High	BTx + EBRT No HT	Low: 93 Intermediate: 80 High: 61	10	> 0.2
Sylvester[39]	232	Low, Intermediate, High	BTx + EBRT	Low: 85 Intermediate: 77 High: 45	10	ASTRO modified (2 consecutive rises)
Stone[40]	279	Low, Intermediate, High	BTx + HT	78	10	ASTRO
Zelefsky[41]	367	Low, Intermediate	BTx	Low: 96 Intermediate: 89	5	ASTRO
Sharkey[42]	1707	Low, Intermediate, High	BTx	Low: 89 Intermediate: 89 High: 78	12	ASTRO
Stock[43]	132	High	BTx + EBRT + HT	86	5	ASTRO
Dattoli[44]	243	High	BTx + EBRT	81	13	> 0.2

(BTx: brachytherapy, EBRT: external beam radiation therapy, HT: hormonal therapy)

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