

Monique Gueudet-Bornstein. *When the Saints*. New Orleans 1999.

*Radioactive prostate seed
implantation is a safe,
effective treatment option
for all risk groups of
localized prostate cancer.*

Modern Brachytherapy for Treatment of Prostate Cancer

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Background: Prostate cancer is the most common cancer diagnosed in men. An increasing number of these patients are seeking minimally invasive procedures such as transperineal interstitial permanent radioactive seed prostate brachytherapy.

Methods: This paper reviews the historical perspective and the current advances in transperineal interstitial permanent radioactive seed prostate brachytherapy. The 10- to 15-year results data now published for brachytherapy alone or in combination with external-beam irradiation are also reviewed.

Results: Modern brachytherapy using transperineal interstitial permanent radioactive seed prostate brachytherapy offers patients an excellent quality of life with convenient outpatient treatment with long-term (10- to 15-year) biochemical relapse-free survival rates ranging from 67% to 87%, depending on risk stratification.

Conclusions: Modern-day brachytherapy utilizing either radioactive iodine-125 or palladium-103 alone or in combination with supplemental external-beam treatment offers patients a successful treatment outcome with acceptable toxicity.

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Abbreviations used in this paper: PSA = prostate-specific antigen, bNED = biochemical non-evidence of disease.

Introduction

Approximately 218,890 men will be diagnosed with prostate cancer in 2007.¹ Radical prostatectomy has been the most common curative treatment utilized in the past. However, the use of ultrasound-guided transperineal interstitial permanent radioactive seed prostate brachytherapy has increased dramatically, according to recent data published from the CaPSURE data base.² Brachytherapy accounts for 21.7% of all low-risk prostate cancer treatments; in men over 75 years of age, it is the preferred treatment of choice.² An increasing number of urologists in the United States are also performing this procedure.³

Historical Perspective of Brachytherapy

Seed Implantation

Radioactive seed implantation with either radioactive gold or iodine has been used to treat prostate cancer for more than 40 years. In the 1960s, Scardino and Carlton⁴ at Baylor College of Medicine began treating prostate cancer utilizing brachytherapy. In the 1970s, Whitmore et al⁵ at Memorial Sloan-Kettering Cancer Center also began to insert radioactive iodine-125 (¹²⁵I) seeds as a sole treatment, usually through open incisions. These early attempts at brachytherapy led to unacceptable outcomes due to poor-quality dosimetry with variable dose given to the prostate gland. However, one conclusion was evident: high-quality implants did result in 15-year survival rates in excess of 70% for localized prostate cancer.⁶ The subsequent development of a transperineal, ultrasound-guided approach provided the means to consistently achieve high-quality implants in an outpatient setting.

Modern Brachytherapy

Placing a transrectal ultrasound probe into the rectal area and guiding the needles and radioactive seeds into the prostate gland to various positions was reported in 1983 by Holm et al,⁷ who introduced this technique (Fig 1). In 1985, Blasko et al⁸ began their program in Seattle, utilizing the transperineal ultrasound-guided approach with consistent good quality implants resulting in relatively high success rates. The reported 10- to 12-year survival rates with radioactive ¹²⁵I range from 87% to 93% bNED (biochemical no-evidence of disease) survival.^{9,10}

In addition to seed implantation, supplemental external-beam radiotherapy given to patients with intermediate- to high-risk disease has achieved a 15-year biochemical relapse-free survival (bRFS) equal to 80.3% for intermediate-risk disease and 67.2% for high-

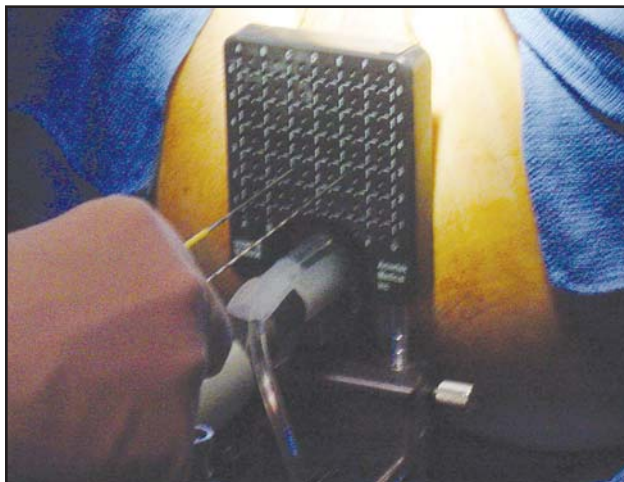


Fig 1. — Transperineal needle approach using transrectal ultrasonography.

Table. — Definition of the D'Amico Risk Stratification for Prostate Cancer

Risk Group	Definition
Low	cT1c-T2a and Gleason score <7 and PSA <10 ng/mL
Intermediate	cT2b or Gleason score 7 or PSA 10–20 ng/mL
High	cT2c or greater or Gleason score 8–10 or PSA >20 ng/mL

Data from D'Amico AV, et al.⁴¹
Modified from Amling CL. Advanced prostate cancer treatment guidelines: a United States perspective. *BJU Int.* 2004;94(suppl) 3:7-8. Reprinted with permission from Blackwell Publishing Ltd.

risk disease.¹¹ The D'Amico risk stratification definition is listed in the Table. These impressive long-term results appear to be producible in a variety of radiation oncology centers.¹²

The goal of transperineal permanent seed brachytherapy is to achieve the prescribed dose throughout the prostate gland while minimizing toxicity or morbidity from the procedure. Dosimetric calculations have been shown to correlate with bNED survival, particularly the D-90, which is defined as the dose given to 90% of the prostate gland.¹³⁻¹⁵

Current Advances

Stranded Seeds

In December 2006, investigators at Moffitt Cancer Center published our experience involving 272 consecutively treated patients utilizing a customized stranded product in which radioactive ¹²⁵I or radioactive palladium 103 (¹⁰³Pd) seeds are embedded in a polymer strand of glycolide, lactide, and polydioxanone spaced from 5 mm to over 50 mm apart and placed inside an 18-gauge needle (Vari-Strand, BrachySciences, Oxford, Conn).¹⁶ This was the largest study to date evaluating this customized



Fig 2. — Vari-Strand as packaged for the operating room.

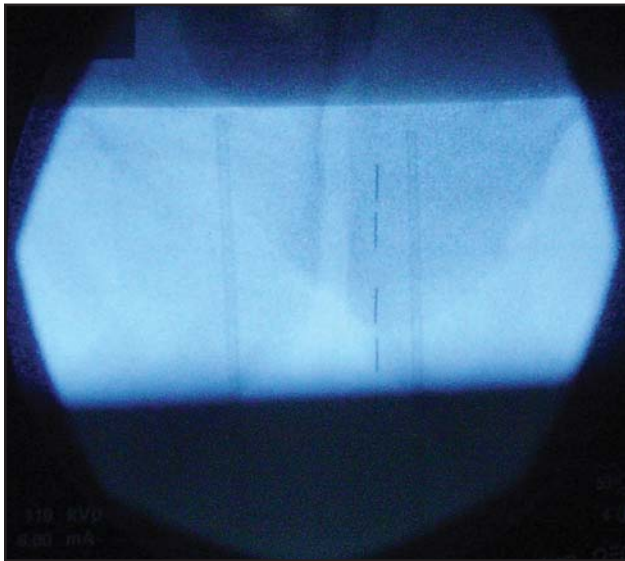


Fig 3. — Fluoroscopic image of ¹²⁵I seed allows an additional check of the seed positions in the coronal plane.

stranded technique. Previous studies used equal spacing of seeds of 10 mm and consisted of radioactive ¹²⁵I. This study showed a statistically significant improvement in the dosimetric parameter known as D-90 compared to a non-stranded product without any increase in toxicity from the polymer strand (Figs 3–5).

There also appears to be less migration of seeds outside of the prostate when using a stranded product. The incidence of seed migration to the lungs has been reported at 10% to 55% with loose seeds compared with a 0.1% incidence with a stranded product.¹⁷⁻²⁰ There is also a case report of seed migration to a coronary artery with the loose seed technique (Fig 2)²¹ and a case report of seed migration to the right coronary artery resulting in an acute myocardial infarction.²² The migration issue is an important distinction between stranded and unstranded seeds since many institutions

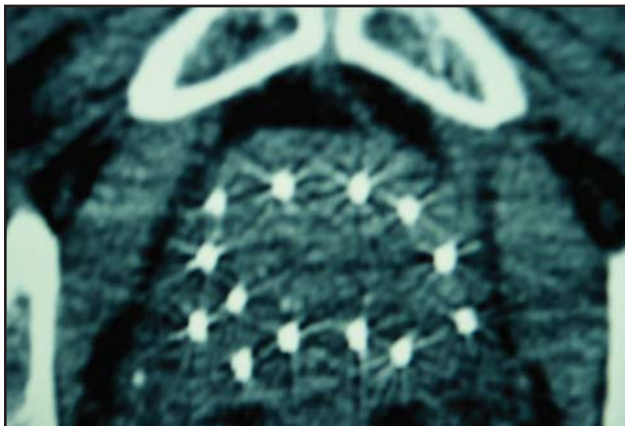


Fig 4. — Customized stranded seeds: computed tomography image 21 days post implant. Note the well-defined position and satisfactory spacing of the seeds. From Heysek RV, Gwede CK, Torres-Roca J, et al. A dosimetric analysis of unstranded seeds versus customized stranded seeds in transperineal interstitial permanent prostate seed brachytherapy. *Brachytherapy*. 2006;5:244-250. Reprinted with permission from Elsevier.

and physicians still utilize the loose seed technique in the treatment of prostate cancer.

Post-Implant Cystoscopy

At our institute, we have also omitted the routine cystoscopy evaluation following the insertion of radioactive prostate seeds. Cystoscopic evaluation is now primarily reserved for fluoroscopic evidence of inadvertent seed placement into the bladder/urethra or for excessive urethral bleeding during the procedure. In addition, a number of institutions are using flexible cystoscopies rather than rigid cystoscopies following placement of radioactive seeds in an attempt to reduce urethral trauma and lower the incidence of morbidity following seed implantation.

Seed Activity Strength

In the mid 1990s shortly after beginning our implant program, the average number of seeds placed per patient was approximately 120 with an average needle count of 30. As time evolved, higher activity radioactive seeds have been used, resulting in a lower average seed count of approximately 70 with a decrease in the average needle count to 15. Although controversial, one study reported that higher activity per seed has been shown to improve overall prostate dose, particularly D-90.²³

Ultrasound Equipment/Fluoroscopic Imaging

The development of higher resolution ultrasound equipment with wider-angle field of view has resulted

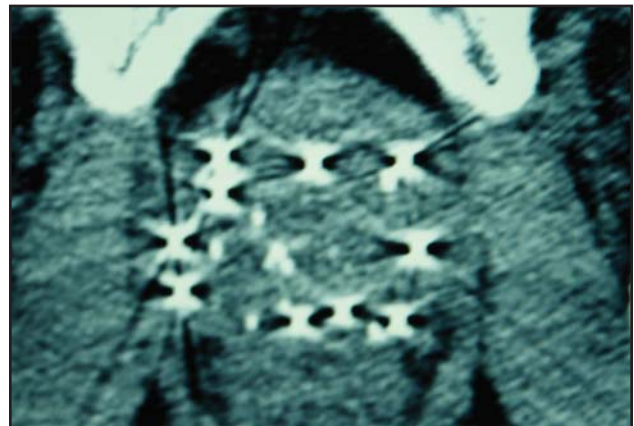


Fig 5. — Unstranded or loose seeds: computed tomography image at 21 days post implant. Note the seed clumping and migration outside of the prostate gland. From Heysek RV, Gwede CK, Torres-Roca J, et al. A dosimetric analysis of unstranded seeds versus customized stranded seeds in transperineal interstitial permanent prostate seed brachytherapy. *Brachytherapy*. 2006;5:244-250. Reprinted with permission from Elsevier.

in improved visualization of the prostate during seed implantation. It is now possible to visualize, through color Doppler ultrasound, the neurovascular bundles surrounding the prostate gland and therefore spare certain critical areas the trauma associated with needle or source placement. Fluoroscopic x-ray imaging with magnified views is used in all patients at our institute; this additional check ensures accuracy of seed placement into the prostate gland.

Medication

The use of alpha blockers such as Flomax or Uroxatral in the perioperative period has significantly reduced the urinary morbidity following prostate seed implantation. These alpha 1A adrenoreceptor antagonists of the prostate gland are typically used for 2 to 12 months following the brachytherapy procedure, depending on how quickly urinary symptoms resolve.

In addition, androgen blockade is utilized in some patients to downsize the prostate prior to brachytherapy. We have found that a short course of a luteinizing hormone-releasing hormone (LHRH) agonist 1 to 3 months combined with Avodart, a selective inhibitor of both type 1 and type 2, 5-alpha reductase, results in dramatic reduction in prostate size, averaging 25% to 30% within 8 to 10 weeks following initiation of this medication regimen. A rapid reduction in prostate size facilitates the expedient scheduling of patients for seed implantation.

Sexual Functioning

Preserving sexual functioning has become increasingly important to our patient population. Younger and more sexually active men are seeking treatment for their prostate cancer that does not affect sexual function. Recent studies reveal the dose given to the penile bulb directly correlates with the incidence of sexual dysfunction.²⁴ A multi-institutional trial by the Radiation Therapy Oncology Group (RTOG 94-06) examined the dose given by external-beam treatment and concluded that a median penile bulb dose less than 52.50 Gy resulted in the ability to maintain sexual functioning in 75% of cases at 5 years compared with 50% of cases at 5 years when the median dose was greater than 52.50 Gy.²⁵ Therefore, we are trying to not only limit radiation dose to the neurovascular bundles/plexus but also avoid significant dosing to the penile bulb. We have recently included this anatomical landmark as an avoidance structure for radiation planning on a routine basis. Sexual dysfunction rates following brachytherapy alone range from 10% to 40%.^{26,27}

Intraoperative/Interactive Treatment Planning

Planning can be performed successfully either prior to the procedure (preplanned) or at the time of the procedure (intraoperative). Intraoperative treatment planning, which is simply preplanning in the operating room (not real time) has evolved in some institutions such as Memorial Sloan-Kettering Cancer Center (MSKCC). Recently published 5-year data are promising.²⁸ Instead of the prostate volume measurements being completed several weeks before the seed implantation, planning and measurements are done in the operating room just prior to the procedure while the patient is anesthetized. This can result in less variability of prostate position, and some brachytherapists believe accuracy is improved. Lower maximum urethral doses were also noted at MSKCC with intraoperative planning compared with a preplan volume study approach.^{29,30} However, there is no evidence that this technique is superior to the preplanning technique in terms of cancer control or complications.

Although there are apparent advantages to intraoperative planning, many disadvantages exist. The intraoperative planning procedure can add significant time (20 minutes or more for a procedure that normally takes less than 60 minutes in the preplan setting), resulting in an increase in operating room time and personnel. Also, the physicist must plan under significant time constraints in the operating room and loses the ability to critically review and double-check a plan several days prior to the implant. There can be a significant waste of unneeded seeds at the time of the procedure since an approximate number of seeds is ordered based on a nomogram.³¹ Most important, a majority of the seeds used for intraoperative planning are loose seeds, which have a higher propensity for migration.

Isotopes

The two commonly used isotopes for permanent prostate seed brachytherapy are radioactive ¹²⁵I and ¹⁰³Pd. ¹²⁵I has a half-life of 60 days with an average energy of 28 KeV. ¹⁰³Pd has a half-life of 17 days with an average energy of 21 KeV. Iodine has been available since 1970, well before the start of ultrasound-guided seed implantation, while palladium has been available since 1985. There appears to be no difference in bNED survival between isotopes based on retrospective studies.³²⁻³⁶ The toxicity profiles of these two isotopes are slightly different with ¹⁰³Pd side effects resolving more quickly.³⁷

A new isotope is emerging in the brachytherapy arena. In March 2003, radioactive Cesium-131 (IsoRay Medical Inc, Richland, Wash) was approved for use in the treatment of prostate cancer.³⁸ Cesium-131 has a

half-life of 9.7 days with an energy of 29 KeV and delivers 90% of its therapeutic dose within 1 month. The potential advantages of this new isotope are a more expedient resolution of brachytherapy-related side effects and an improvement in coverage of the prostate area with the higher energy photon emission. However, significant concerns relate to the efficacy of treatment in which 50% of the therapeutic dose is delivered in only 9 days, at a time when the periprostatic edema is just beginning to resolve. Moderate underdosing of the prostate gland during the time in which significant prostatic edema is present immediately after the seeds are placed is a potential problem. In addition, no long-term studies exist for Cesium-131 as they do for palladium or iodine. It remains to be determined if radioactive Cesium-131 can produce the same high rates of bNED survival at 10 to 15 years and with equivalent low toxicity that has been achieved with ¹²⁵I and ¹⁰³Pd seed implantation.

Prostate-Specific Antigen Failure

In 1996, the American Society of Therapeutic Radiation Oncologists (ASTRO) established a uniform definition that has been accepted worldwide for prostate-specific antigen (PSA)-defined failure following treatment with radiation for prostate cancer. This definition states that three consecutive rises must be documented after a nadir is reached and then the failure date is backdated halfway between the nadir and the first rise. This definition, although well accepted, was cumbersome. In January 2005, the RTOG and ASTRO convened a consensus conference to establish a new definition for PSA failure after radiation treatment. A rise by 2 ng/mL or more above the nadir PSA was established as the new standard definition for biochemical failure after radiation treatment with or without the use of androgen blockade.³⁹ This definition has recently been validated for biochemical failure after brachytherapy.⁴⁰ It is hoped that this new definition will assist centers in comparing results and providing consistency in patient management.

Conclusions

Radioactive prostate seed implantation, used either alone or combined with supplemental external-beam radiation, is an excellent treatment alternative for all risk groups of prostate cancer. It is a safe, highly effective treatment that can be performed on an outpatient basis. It has stood the test of time, with 15-year data now available showing excellent cure rates. Although many advances in brachytherapy have emerged over the years, it is important to note that the most important aspect of producing a high-quality implant is the experience of

the brachytherapist. High-volume institutions or centers of excellence will continue to achieve the highest success rates and the least morbidity in the arena of minimally invasive, high-technology procedures.

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