Modern Prostate Brachy

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Prostate cancer remains the most common solid cancer and the second leading cause of cancer death among American men. Although there was an initial, rapid rise in the incidence of prostate cancer diagnoses in the early 1990s following the development of the Prostate Specific Antigen (PSA) screening test, this "harvesting" effect is over. The incidence rate for prostate cancer is now nearly back to its pre-PSA era level.[1,2]

One significant and lasting result of the widespread adoption of the PSA test was the dramatic increase in the proportion of treatable, early-stage cancers found at the time of diagnosis. Prior to the availability of PSA testing, a majority of patients were diagnosed with more advanced, difficult-to-treat malignancies. Today, almost 80 percent of newly diagnosed patients have early-stage disease, which has a much higher probability of biochemical relapse-free survival. The other major contribution of the PSA test is its usefulness as a post-treatment monitoring tool that can detect recurrent disease much sooner than had previously been possible, and also tells physicians whether they have successfully treated the entire tumor or left residual disease behind.

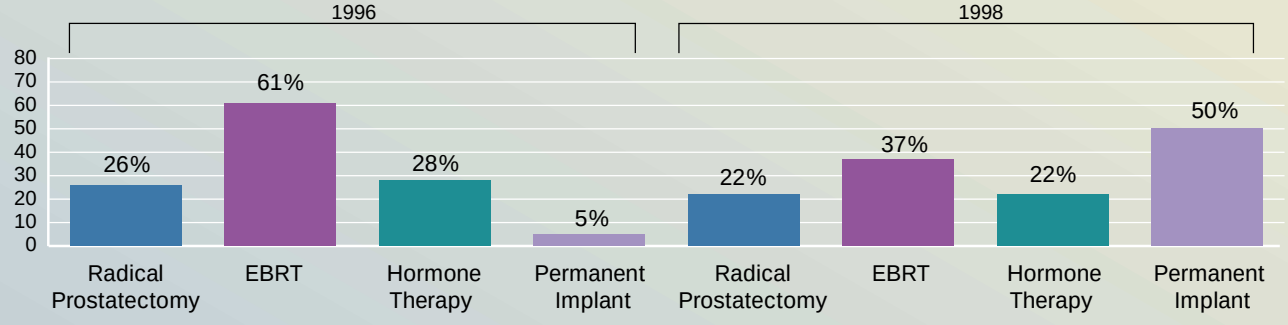
Early-stage cancers are usually amenable to treatment with conventional local therapies, radical prostatectomy, or external beam radiation therapy (EBRT) and, increasingly, with radioactive seed implantation, also known as transperineal interstitial permanent prostate brachytherapy (TIPPB). Over the past decade, the use of TIPPB has risen significantly for several reasons. First, research has clearly demonstrated that ultrasound-guided seed implantation, with its sophisticated instrumentation, treatment planning tools, and evaluation techniques, is as effective as other treatments in terms of long-term cancer control, and it has a low incidence of serious side effects and complications. In addition, the use of the PSA for follow-up evaluation has revealed that EBRT and radical prostatectomy are not as effective at eradicating prostate cancer as once thought.[3-6]

Another factor behind the rising interest in seed implantation has been the pressure of traditional market forces and, in particular, patient demand. Attracted by TIPPB's outpatient orientation, rapid recovery time, low complication rate (especially with regard to impotence and incontinence), and favorable long-term survival rates, men and their families have been actively seeking out brachytherapy treatment and the physicians who provide it. One recent evaluation estimated that almost 50 percent of the men treated for prostate cancer used TIPPB as part of their treatment course[1] (Figure 1).

The History of Brachytherapy

In 1903 Alexander Graham Bell first proposed the insertion of radioactive sources into the prostate as a treatment for prostate cancer. By 1922 Denning reported mixed results in a study of 100 prostate cancer patients treated with transurethral insertion of radium into the prostate.[7] In the early 1950s, Flocks was injecting radioactive liquid gold directly into the prostate.[2] In these early years, measuring the dose of radiation delivered to the prostate was not yet possible and patients usually presented with advanced disease. While some

Figure 1. Percentage of Prostate Cancer Patients Receiving Treatment Options as Any Part of Therapy*



* Percentages include patients who received the treatment modality as monotherapy and patients who received the treatment modality as part of combination therapy.

Source: Advisory Board, 2000.

therapy

Figure 2. Freehand Surgical Implants

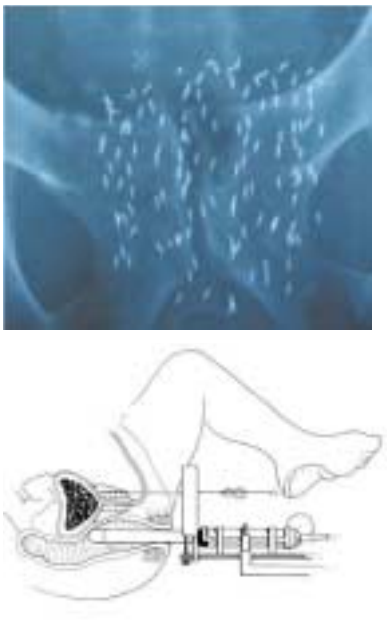


Figure 3. Ultrasound-guided Prostate Implant

patients were apparently cured using these procedures, others suffered local failures and/or complications related to radiation.

In the 1960s and 1970s there was heightened interest in prostate brachytherapy after Willet Whitmore, M.D., of New York's Sloan-Kettering Memorial Cancer Center and Peter Scardino, M.D., at Baylor Medical College in Houston pioneered the use of sealed, radioactive sources containing Gold-198 and Iodine-125.[8,9] These sealed sources, or seeds, were implanted using an open, retropubic surgical technique in which the prostate was exposed, allowing the physician to insert needles containing the seeds directly into the gland (Figure 2).[3] When the seeds were placed evenly throughout the prostate and provided uniform radiation exposure, these early, freehand surgical implants could achieve results in early-stage cancer patients that were comparable to those achieved with external beam therapy and radical surgery.[10-12] However, owing to various technical limitations of that era and the inability to produce uniform seed distribution on a consistent basis, the surgical seed implant technique did not gain wide acceptance within the medical community.

The development of transrectal ultrasound in the early 1980s brought renewed interest in radioactive seed implantation as a primary treatment for early-stage prostate cancer. Transrectal ultrasound gave physicians the ability to see inside the prostate in real time and, coupled with needle guidance instrumentation, allowed implant procedures to be planned and carried out with significantly greater consistency and precision than had been possible in the past. The same visualization and needle guidance capabilities also eliminated the need for open surgery. The seed-carrying needles could now be safely and accurately inserted into the prostate through the perineum (Figure 3).

In 1983 Hans Holm, M.D., of Denmark reported on the transrectal ultrasound-guided approach to prostate seed implantation.[4] Building on Holm's work, John Blasko, M.D., of Seattle, Wash., performed the first ultrasound-guided prostate implant in the United States in 1985. Over the last 17 years, the Seattle approach has resulted in consistent, high-quality implants with uniform seed placement and high rates of local control and long-term disease-free survival.[13-15] These favorable results are due to the use of ultrasound and improved patient selection in the PSA era, as well as the development of highly accurate, computerized treatment planning and evaluation tools.

Modern Brachytherapy Practice

The typical patient seen in the PSA era has stage II disease with a Gleason score of 5-7 and a PSA of less than 20 ng/ml. These patients have less advanced disease than those treated in the retropubic era. If microscopic disease extends beyond the prostate capsule, it is rare for the extension to exceed 3 mm.[16-19] These patients are good candidates for seed implantation if the technique used treats the prostate plus a margin of several millimeters.[20]

Patients are candidates for TIPPB if their pretreatment disease stage, technical, and tolerance factors are favorable. Patients with very large prostates (> 60 cc), those who have had a prior transurethral resection of the prostate (TURP), and those who have severe obstructive urinary symptoms, or stage T3 disease are *not* good candidates for implantation. Those patients with favorable prostate volumes, T1-T2c disease, and relatively mild urinary symptoms may be treated with TIPPB alone (monotherapy) or with a combination of EBRT plus implantation.

A patient who has a prostate volume that is too large

but otherwise is a good candidate for TIPPB can frequently downsize his prostate with several months of androgen ablation (hormone) therapy that can reduce the prostate volume by as much as 40 percent.[21]

TIPPB can be performed with either Iodine-125 or Palladium-103 radioactive sources (seeds) since there is no clinical evidence that either isotope is superior in terms of disease control or toxicity. In the Seattle series, approximately two-thirds of the patients seen are treated with TIPPB monotherapy (seeds alone) and one-third with a combination of EBRT and TIPPB.

The TIPPB Process

The first step in the TIPPB process is a transrectal ultrasound prostate volume study, which takes 15-30 minutes and determines the prostate's total volume, contour, and length. The evaluation can be done as a hospital outpatient procedure or in the radiation oncologist's or urologist's clinic. The transrectal ultrasound verifies that the prostate volume is appropriate, and that the prostate "map" the procedure produces is used to determine the number, activity, and precise coordinates of each seed's placement in three dimensions. The radiation oncologist uses the volume study images to specify a "target volume," the area to be covered by radiation from implanted seeds. To protect against the possibility of cancer cells outside the prostate, the target volume is greater than the actual prostate volume, especially at the base and apex (Figure 4). Next, the seeds are ordered from the seed distributor by the radiation oncology department's dosimetrist or physicist, or the nuclear medicine department's technologist. The radiation oncology department's nurse arranges the OR schedule so that the urologist, radiation oncologist, patient, and seeds of proper activity arrive in the OR at the same time. (This coordination effort is so complex that it has its own billing code.)

The procedure is usually performed with a urologist and a radiation oncologist working together as a team. Spinal anesthesia is used for most procedures, but occasionally a patient needs a general anesthetic. With the patient in an extended lithotomy position, the stabilization apparatus, stepper, template grid, and ultrasound probe are arranged in the same position they were in at the time of the ultrasound volume study. Once the patient and all the implant apparatus are positioned, the needles containing the radioactive seeds are inserted through the template grid and perineal skin into the prostate and visualized on the ultrasound monitor (Figure 5). Once the needles are in the proper position, each needle is slowly withdrawn over its stationary "stylet", so that a row of radioactive seeds and absorbable vycryl spacers are left behind in a relatively straight line as per the pretreatment dosimetric plan (Figure 6). This process continues, needle after needle, until all the seeds are placed.[20] Fluoroscopy is then used to evaluate the quality of the implant (Figure 7). If any gaps in the seed distribution ("cold spots") are identified, extra seeds can be implanted to fill the gap. The seeds remain in the prostate permanently, but slowly lose their radioactivity over the next few months until they become inert (the half-lives of I-125 and Pd-103 are 60 days and 17 days, respectively).

The procedure takes approximately 45 minutes to perform and the patient is discharged to home in a few hours. He is able to perform most normal activities almost immediately and usually returns to work a few days later.

Side Effects

Mild prostate edema develops after the implant procedure is performed. This edema, combined with irritation of the urethra, bladder neck, and prostate by the slow release of radioactivity, results in temporary lower urinary tract symptoms. Virtually all patients experience some degree of urinary frequency and urgency for two to six months following an implant. Most patients respond well to alpha-blocker medications, such as Flomax® and nonsteriodal anti-inflammatories (NSAIDS). Rectal side effects are uncommon. If they occur at all, they tend to be transient and mild.

The risk of long-term complications, such as urinary incontinence and impotence, is low after TIPPB. If the patient has not previously undergone a TURP, most

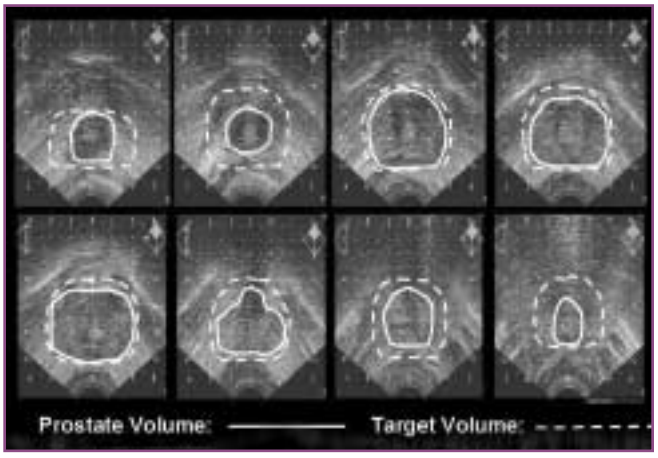


Figure 4. A Transrectal Ultrasound Prostate Volume Study. The prostate "map" is used to determine the number, activity, and precise coordinates of each seed's placement.

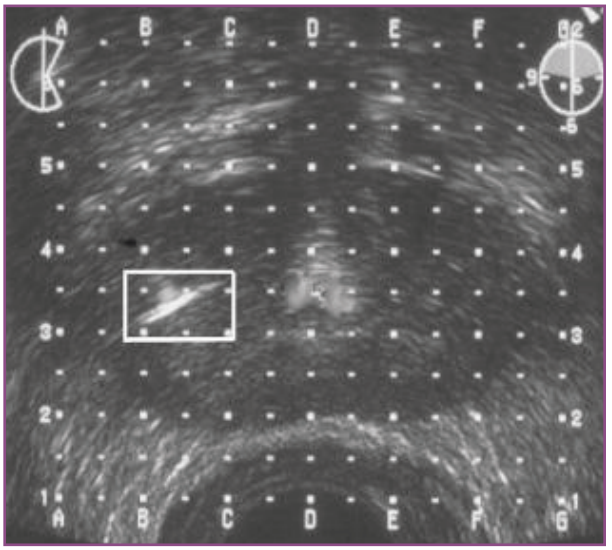


Figure 5. Seed Insertion. Needles containing the radioactive seeds are inserted through the template grid and perineal skin into the prostate and visualized on the ultrasound monitor.

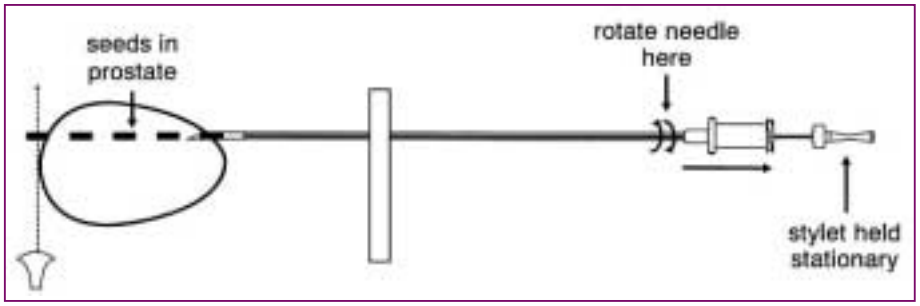


Figure 6. Placing the Seeds per the Dosimetric Plan. Each needle is slowly withdrawn over its stationary stylet, leaving behind a row of radioactive seeds and absorbable spacers.

series report a less than 1 percent incidence of incontinence, including stress incontinence. The incidence of impotence is age related. The Seattle data, based on a self-administered patient questionnaire, reveal a 10 percent risk of impotence in men in their 50s, a 15 percent risk for men in their 60s, and a 25 percent risk for men up to 70 years old.

Davis and colleagues[22] compared the late toxicity of radical prostatectomy, TIPPB, and 3-D conformal radiation. Using five different patient-reported, self-administrated, validated quality-of-life questionnaires, they noted that patients treated with TIPPB suffered significantly less urinary and sexual dysfunction and less sexual bother than surgical patients. (Sexual bother is a measurement of how much a man's sexual impairment "bothers" him, as opposed to sexual function, which measures how well he can physically function sexually.) The TIPPB patients also suffered less rectal dysfunction and bother and had a lower fear of cancer recurrence than the EBRT patients.[22]

Quantitative Implant Quality Analysis

Postoperative CT scan-based dosimetry is performed between days 0 and 30. To compensate for postoperative edema and its gradual resolution, each center should perform the dosimetry on a consistent postoperative day of its choice.[23] Dose volume histogram (DVH) analysis determines how much of the prostate volume has received 100, 150, and 200 percent of the prescription dose (V100, V150, and V200, respectively). It also measures the dose delivered to 90 percent of the prostate (D90) and produces isodose curves for more detailed anatomical dose-distribution analysis.

Postoperative DVH analyses correlate well with biochemical relapse-free survival rates and the rates of rectal and urinary toxicities and erectile dysfunction.[24-27] This ability to quantitatively evaluate the quality of the treatment is a unique feature of brachytherapy. If an underdosed region is found in a clinically significant area of the prostate, additional seeds can be placed or the patient can be treated with supplemental EBRT or high-dose brachytherapy before biochemical or clinical failure takes place.

Quantitative DVH analysis also allows physicians to compare the quality of their treatment with that of other physicians in an unbiased manner.

Results

Due to the long natural history of prostate cancer and the delay between diagnosis, the appearance of bony metastasis, and death, the effectiveness of prostate cancer therapy is usually measured by biochemical relapse-free survival. The pretreatment PSA level, the Gleason score of the biopsy sample, and the initial clinical stage by digital rectal exam (DRE) are all independent prognostic factors. In the PSA era, the vast majority of patients are diagnosed with stage II disease, so centers have recently been subdividing these patients into low, intermediate, and high-risk groups based on these prognostic factors.

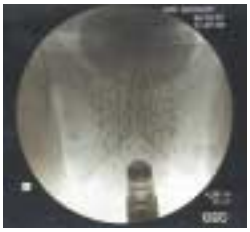


Figure 7. Fluoroscopy to Evaluate Implant Quality

The Memorial Sloan-Kettering Cancer Center and the Seattle Prostate Institute (SPI) define low-risk patients as those presenting with PSA values less than or equal to 10 ng/ml, Gleason scores between 2 and 6 and T1-T2b disease. These are good prognostic factors. Intermediate-risk patients have at least one poor prognostic factor (a PSA greater than 10 ng/ml, Gleason scores of 7 to 10, and/or a minimum of T2c disease), and high-risk patients have two or three of these poor factors. Several centers have achieved excellent five-year biochemical relapse-free survival results with implant monotherapy (seeds alone) in low-risk patients (Table 1),[28-30] and some have also reported that intermediate-risk patients had excellent five-year biochemical relapse-free survival results after the same treatment or a combination of TIPPB and EBRT.[13,14,31,32]

Surgical results based on risk-group analysis have been reported from the Hospital of the University of Pennsylvania (HUP), Brigham and Women's Hospital (B&W), and the Cleveland Clinic (CC) by D'Amico and Kupelian.[5,6] Five-year biochemical relapse-free survival with 3-D conformal EBRT using doses greater than or equal to 75 Gy have recently been reported by Zelefsky.[33] The five-year biochemical relapse-free survival of TIPPB appears to compare favorably with radical prostatectomy and 3-D conformal EBRT reports.

The Seattle Prostate Institute has published nine- and 10-year results with 103-Pd and 125-I TIPPB monotherapy, respectively.[13,14] The long-term biochemical relapse-free survival results from Seattle (with and without EBRT) were recently reported at the 2001 Annual Dutch Urological Association conference and the 2001 American Society for Therapeutic Radiology and Oncology conference. These 10-year results compare favorably to the five-year results from the surgical studies (Table 2).

It should be noted that EBRT, surgery, and TIPPB are all local therapies aimed at controlling local disease. The high doses of radiation delivered by TIPPB result in extremely high local control rates. In Grimm's 10-year 125-I study,[14] a 97 percent local control rate (as determined by DRE and postimplant biopsies) was

achieved. These patients were all treated between 1988 and 1990, when the quality of those implants was not as high as the quality that can be realized with current TIPPB techniques. In the last five years, less than 1 percent of patients treated by the Seattle Prostate Institute's physicians have suffered local failure. Clearly TIPPB, when performed properly, results in extremely high control of local disease.

Conclusions

TIPPB (radioactive seed implantation) continues to grow rapidly as a treatment approach for patients diagnosed with prostate cancer in the modern PSA era. Five-year data from multiple centers and long-term data (10-plus years) from the Seattle Prostate Institute show that TIPPB can achieve local control and biochemical relapse-free survival results that are at least equal to the best that surgery and EBRT can offer, with less risk of long-term urinary incontinence, rectal toxicity, and impotence. TIPPB has the additional advantage of usually being performed as a one-day, outpatient procedure. Finally, the use of postoperative DVH analysis allows physicians to continually monitor the quality of implants, identifying opportunities for improvement and, when necessary, taking corrective action.

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Table 1. Low-Risk Patients: 5-Year PSA-Based Outcome

Tx	Series (Yr)	N	PSA Failure Definition	FU	bNED*
Seeds	Blasko[34]	276	> 1.0 absolute	5 yr	88%
	Stock[35]	34	> 1.0 & 2 rises	5 yr	89%
	Beyer[36]	320	> 1.0 absolute	5 yr	79%
	Wallner[37]	50	> 1.0 & rising	5 yr	83%
Seeds + EBRT	Blasko[34]	73	> 1.0 absolute	5 yr	84%
	Dattoli[38]	41	> 1.0 & rising	3 yr	85%
	Critz[32]	210	2-3 rises > nadir	5 yr	82%

*No evidence of disease (through biochemical tests)

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Table 2. 5-Year Biochemical PSA NED* by Risk Group

Risk Group	RP D'Amico[5] (HUP)	RP D'Amico[5] (B&W)	RP Kupelian[6] (Cleveland)	3D-CRT Zelefsky[33] (5-Yr FU)	Seeds Blasko[13] (Seattle)	Seeds ± EBRT Sylvester[39] (10 Yr)
Low	85%	83%	81%	90%	94%	87%
Intermediate	65%	50%	40%	70%	82%	79%
High	32%	28%	-	47%	65%	51%

*No evidence of disease

Brachytherapy Reimbursement Update

The Centers for Medicare and Medicaid Servces (CMS) delayed until April 1, 2002, implementation of its 2002 ambulatory payment classification (APC) rates and the pass-through payment cut. April has come and gone and here is where we stand with regard to brachytherapy. In brief, there are significant changes from November 2001 to April 2002 for brachytherapy reimbursement.

The pass-through code payment for brachytherapy procedures will be reduced by 75 percent, partly because 75 percent of the cost of devices, needles, and seeds was added, or bundled, into the payment for the procedures. CMS will then reduce that reduced amount by 36.4 percent, which is the pass-through reduction. Thus, the payment you receive when you bill for needles and seeds will be reduced twice.

If that seems a bit confusing, here is an example. Suppose your hospital charges $2,000 for brachytherapy seeds. CMS says your cost is $1,000, but will reduce that by 75 percent to $250. CMS then reduces that amount by 63.6 percent, so CMS will pay 36.4 percent of what is left for each seed, or about $40 for each seed. You will be reimbursed for the number of seeds you use and the number of needles for which you charge.

As written in the *Federal Register*, CMS believes that payments for radioelement application (intracavitary and interstitial codes, 77761–77778) and for HDR (codes 77781–77784) may be too low. "However," notes CMS, "there were insufficient data to make any recommendations." Therefore, continues CMS, it proposes to make no changes to APCs 0312 and 0313 but will address radiation oncology issues at a 2002 meeting. APC code 0313 has been changed by bundling some of the cost of the seeds and needles into the procedure codes for the implants.

Devices have been added to procedure codes, so the pass-through portion will be reduced. However, devices can still be billed with the procedure. Oncology procedures with device additions include radioelement application codes 77761–77778 and brachytherapy codes 77781–77784 and 77799.

It should be noted the RVU changes for procedures 77761–77778 went from 4.09 in 2001 to 124.64 in 2002. The payment rate in 2001 was 205.49 with a payment rate increase in 2002 to 6344.67. For procedures 77781–77799 the RVU in 2001 was 7.89 and in 2002 the RVU is 35.74. The payment rate in 2001 was 396.40 and the payment rate in 2002 in 1819.31. Devices have been added to the procedures codes, so the pass-through portion will be reduced. However, devices can still be billed with the procedures.

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