The Evolving Role of Prostate Brachytherapy

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Background: The publication of several large studies with long-term results on the use of prostate brachytherapy has resulted in increased use of this option for patients with localized prostate cancer.

Methods: A historical review of brachytherapy as an approach to prostate cancer management is provided, as well as a general summary of the implant technique and the results to date according to patient risk. The effects of combination therapies for specific patient groups are also reviewed.

Results: A recent 12-year follow-up reported no failures after 10 years, and 75% of recurrences occurred within the first 5 years. Patients at low risk for failure based on stage, grade, and prostate-specific antigen (PSA) parameters are likely to have disease confined to the prostate. Those with more advanced disease are likely to have a lower probability of cure with brachytherapy as monotherapy. Complications involve primarily the urinary tract. Ideal candidates have a PSA of $\leq 10$, Gleason score of $\leq 7$, and low-volume/low-stage disease (stage T1c or T2a). Patients with more-advanced disease are candidates for brachytherapy combined with external-beam radiation therapy (EBRT). For high-risk men with multiple adverse prognostic features, consideration should be given to clinical trials investigating innovative treatment combinations (eg, the addition of androgen blockade, and EBRT).

Conclusions: The rarity of failures after 5 years and the absence of recurrence after 10 years suggest that brachytherapy for localized prostate cancer can provide durable disease control. Future improvements in pathologic tools may lead to selection of patients more likely to respond well to brachytherapy.

Introduction

Prostate cancer is a serious health concern, with approximately 180,000 new cases diagnosed each year in the United States and 396,000 reported worldwide. With the widespread use of prostate-specific antigen (PSA) screening over the past decade, patients are being seen with earlier-stage disease. Cure rates are
steadily improving, with 5-year survival rising from 67% in 1976 to 93% in 1994. At the same time, the number of therapeutic options available has increased. Permanent brachytherapy, commonly called "seed implantation," has become an accepted and standard means of therapy and is now a part of the therapeutic armamentarium available to radiation oncologists and urologists worldwide. In a patient care evaluation study conducted by the American College of Surgeons, brachytherapy accounted for only 1.5% of treatments in 1990. Mettlin et al reported a doubling of this rate to 3% by 1996. Significantly, by 1996, 5.8% of patients with T1c tumors (nonpalpable), which has accounted for a significant proportion of recent cancer diagnoses, received brachytherapy. Regional variations across the United States were also reported, with a higher probability of receiving brachytherapy in the East compared to the West and Midwest. Since 1996, the interest in brachytherapy has continued to grow exponentially as evidenced by the number of seeds sold, the plethora of publications, and the extensive meeting time devoted to this topic. When the statistics are compiled for 2000, brachytherapy will probably have reached the 19% predicted in the mid 1990s.

This article provides a summary of the current status for professionals involved in prostate brachytherapy, as well as a guide to the state of the art for other allied physicians who provide care and guidance for patients with prostate cancer.

History

Brachytherapy is the placement of radioactive sources in close proximity to any tumor. It takes advantage of the simplest physical properties of radiation. High doses of radiation are present in the vicinity of a radioactive material, and a rapid drop in dose occurs with increasing distance from the source. Brachytherapy has been in use worldwide since shortly after the introduction of radioactive materials. Intracavitary or surface applications are used in some human tumor types (e.g., cervix, skin, and bronchus), while interstitial insertions are useful in other situations (e.g., head and neck, gynecologic, prostate, and sarcoma).

Prostate brachytherapy has been performed over the years with a variety of approaches and with state-of-the-art technology during each era. Implantation techniques have evolved from intraurethral insertion of a temporary source in the early decades of last century, to permanent interstitial implantation using a retropubic approach, and eventually to the current ultrasound-guided transperineal techniques (Fig 1).

In 1965, radioactive iodine ($^{125}\text{I}$) was introduced to clinical practice for permanent implantation. With a half-life of just under 60 days and a relatively low energy radiation (average = 32 kV), it is well suited for permanent brachytherapy. During the 1970s and early 1980s, retropubic implants with $^{125}\text{I}$ were popular. As with many innovations in medicine, the initial enthusiasm was dampened by reports of poor source and dose distribution and high recurrence rates. The technique proved to be difficult to reproduce widely, and many implants were judged to be inadequate, even by the comparatively primitive imaging and dosimetry capabilities available at that time. Most practitioners abandoned this procedure; however, a few understood that with improvements in case selection and technique, the fundamentals remain sound.

Prostate brachytherapy came into the modern era with a preliminary report in 1983 by Holm et al, who described the use of transrectal ultrasonography to guide transperineal insertion of needles into the prostate to permanently deposit $^{125}\text{I}$ sources into the gland. This concept was studied by a number of investigators, but Blasko et al are generally credited for developing and popularizing the current techniques. With the passage of time and the publication of numerous large studies with long-term results, prostate brachytherapy is undergoing a worldwide renaissance, with more patients choosing this treatment each year.

Fig 1. — An AP radiograph of a typical $^{125}\text{I}$ implant. The sources can be seen as linear metallic "wires" within the pelvis. The extent of the prostate cannot be seen on such a film; however, the entire gland is treated and always confirmed on computed tomography.
Description of the Procedure

A variety of techniques have been developed and are in current practice for permanent prostate brachytherapy. It is beyond the scope of this review to catalog them all or to provide enough detail to perform any one technique. Nevertheless, a general understanding of the basic concepts is important to answer patient questions that may fall outside of a physician’s field. In addition, certain biologic constraints are imposed on brachytherapists that must be understood to better guide case selection.

Implantation is almost always performed as minor outpatient surgery under general or spinal anesthesia. An implant typically requires approximately 1 hour, and patients can return home after a brief recovery. A urinary catheter may be left in overnight or removed prior to discharge, depending on the individual. Most patients return to their normal routines within 1-2 days with minimal restrictions. Since the energy of the implanted sources is low, the radiation exposure surrounding the patient is low. This is measured postoperatively and compared to published radiation safety guidelines. Normal social interaction a few feet away should not be of concern, even for children and pregnant women who are generally considered to be more sensitive to the effects of radiation.

In an effort to achieve optimal geometry of the implanted sources, templates are now almost universally used, in contrast to the freehand approach commonly used with retropubic implants. With the patient in the lithotomy position, these templates are held rigidly in place over the perineum and act as guides for needle placement. This allows for control over the entire prostate target volume and specification of source placement at any point within the gland. If the prostate is imagined as a three-dimensional ellipsoid within the pelvis, then any point within the prostate can be given a unique set of coordinates using the grid on the template to define the X and Y coordinates and using the distance from the plane of the template at the perineum to define the Z coordinate. For every 5-mm increment or “step” from the “zero plane” at the base of the prostate to the apex, transrectal ultrasonography can be used to map the area of the gland onto this grid. This creates a series of 2-dimensional images that can be totaled to create a 3-dimensional target volume. For a number of reasons, the treated area is slightly larger than the actual organ boundaries. While no absolute margin is applied, a general consensus has developed that 3-5 mm is generally adequate and can be achieved9 (Fig 2).

Modern treatment planning computers can use this planning target volume to develop a pattern for radioactive source placement that will deliver the desired dose. The position of each source is defined based on the grid coordinate system that follows from the chosen template and its depth or distance from the template. Generally, each needle is used to place multiple sources in a line. Historically, they have been placed every 1 cm along the path of a given needle from base to apex. However, with improvements in planning capabilities, irregular spacing is now commonly used along a needle path. Planning may take place weeks in advance of the implant procedure or may be performed intraoperatively. While most practitioners utilize computer optimization for planning, others have successfully developed a nomogram for estimating source requirements and placement.10 Skill and experience are required with whichever approach is used.

It is generally agreed that postoperative dosimetry must be performed to assess the adequacy of implantation and to determine the actual dose received by the prostate and normal tissues.10 Historically, this dose calculation was performed using a pair of orthogonal radiographs. Even during the retropubic era, it was possible to identify those implants with significant dose inhomogeneity and recognize those patients at higher risk for treatment failure. Unfortunately, these plain

Fig 2. — A portion of a preimplant ultrasound plan for a single axial plane through the gland. The prostate has been outlined in white. Radionuclides deposited in this plane are shown as solid green dots, while needles to be used only in adjacent planes are shown as open circles. The resultant dose is calculated and displayed as isodose lines. Everything within the red isodose line will receive 145 Gy (100% of the dose). Note that this is placed 3-5 mm beyond the edge of the gland. (The grid points are 5 mm apart.) All tissue within the blue line will receive 150% of the prescription dose. The central zone containing the urethra (faintly visible as a white enhanced signal) is spared from this higher-dose region.
films fail to identify the prostate anatomy. With the more recent use of computed tomography scanning for dose calculation, it is now possible to calculate the dose received not only by the patient, but also by the prostate (Fig 3). Thus the planning and execution of the implant can be evaluated using 3-dimensional reconstruction of the prostate to optimally assess the dose coverage of the gland.

Within the gland, some dose inhomogeneity is always created. Areas and structures in immediate proximity to a source will often receive more than the stated dose. As a result, the dose is generally defined to a volume rather than at some fixed point. In years past, this was termed the “matched peripheral dose.” Some practitioners have used the term “minimum peripheral dose” to indicate the lowest dose received within the prostate volume. More recently, a variety of dose measures have been recognized, such as the D90 (dose received by 90% of the prostate volume) or V100 (percent volume of the prostate receiving the prescription dose). These dose parameters are of increasing importance as a quality indicator for the brachytherapist and as a prognostic indicator for the patient. While controversy continues regarding many technical details, such as when to perform the computed tomography scan and how to define the prostate contour, there is general agreement that these parameters predict for outcomes. Stock et al\(^{11}\) described a dose response curve for D90. Patients who achieved a dose of 140 Gy to at least 90% of the prostate using \(^{125}\text{I}\) achieved a higher PSA-based tumor control rate than those with lower D90.

Physicians have a variety of options in the choice of isotope. Radium, radon, cesium, and colloidal gold are interesting historical footnotes but are not of value to today’s brachytherapists. Gold seeds remain available but are rarely used today. Iridium is often employed for temporary insertion at either low or high dose rates. For permanent implantation, \(^{125}\text{I}\) has been in use for 35 years, and palladium (\(^{103}\text{Pd}\)) has been available for more than a decade. Despite differences in the half-lives and energies of these two isotopes, no differences have been established in clinical outcomes (eg, effectiveness or complications). As a result, both isotopes continue to be used for prostate brachytherapy with no clear consensus or rational schema for choosing one over the other. Studies often report mixed groups, since stratification by isotope has not shown any difference. No attempt has been made in this review to separate studies by the choice of source.

To achieve equivalent biologic results when using the two isotopes, the prescribed doses must be different due to differences in the basic physics. Over the years, several advancements in physics and dose calculation have occurred. As a result, the initial dose specification of 160 Gy for \(^{125}\text{I}\) from the early literature has been updated to 145 Gy as the most common current prescription (attempting to consistently achieve a dose of >140 Gy to 90% of the gland). For \(^{103}\text{Pd}\), the historical dose of 115-120 Gy developed in the late 1980s has been updated to 125 Gy.\(^{12}\) For both isotopes, the prescribed dose is reduced when combined with external-beam radiation (EBRT): 110 Gy for \(^{125}\text{I}\) and 100 Gy for \(^{103}\text{Pd}\).

**Results**

Prostate cancer, with its long natural history and variable biology, is not well suited for evaluation using simple survival or local control endpoints. Many untreated patients with prostate cancer do not die of their disease for many years or even decades. Consequently, control of the prostate-specific antigen, or PSA, has become the surrogate endpoint used to evaluate treatments. While there are pitfalls with this strategy, better standard endpoints have not yet been developed, and all the studies reviewed in this article have used some form of this PSA endpoint. It is generally accepted that the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of PSA failure (ie, three consecutive rising intervals) is suitable for brachytherapy as well as EBRT.\(^{13}\) Much of the pub-
lished literature that predated the ASTRO consensus statement used a variety of PSA cutoff points. Also, case selection has varied among institutions, making strict comparisons difficult. With these caveats, much can be learned from a review of the published results.

In a large and well-documented report in 1995, Blasko et al.14 noted that the PSA normalized in 98% of treated patients. They also showed that long follow-up is required; at 2 years, only 82% had achieved a PSA nadir of <1.0, whereas 97% had done so by 4 years. These initial excellent results have been updated and carefully analyzed. In 1998, Radge et al.15 observed 10-year brachytherapy results in the treatment of 152 consecutive patients with clinically organ-confined prostate carcinoma. Ten-year disease-free survival was reported at 70% for the entire cohort, which compared favorably with surgical results. In a 2000 update,16 no failures were seen after 10 years, and 75% of recurrences occurred within the first 5 years. Numerous other studies report 5-year results and have documented flattening of the survival curves. The rarity of failures after 5 years, which is demonstrated both in the biochemical “no evidence of disease” (bNED) plots in Fig 4 and in the absence of recurrence after 10 years, suggests a true and durable cure from prostate brachytherapy.

Nine-year follow-up for monotherapy using $^{103}$Pd was separately reported by Blasko et al.17 In 230 patients selected for implantation alone, 5-year PSA-based NED rates ranged from 65% to 94%, depending on the presence or absence of high-risk features. Risk groups have typically been developed depending on the presence of PSA at $\geq 10$ or a Gleason score of $\geq 7$. For the purposes of this study, low-risk patients had neither feature, while high-risk patients showed both. The presence of a single adverse feature was associated with an intermediate risk (82% NED).

These optimistic results are mirrored in studies from other institutions. Our series of 1,463 implanted patients was recently updated.18 With median follow-up of 61 months, 345 favorable-risk patients treated with implantation alone had 5-year bNED rates of 85%. With shorter median follow-up, Stokes et al.19 reported 5-year bNED rates of 100% and 86% for patients with initial PSA level $\leq 4$ and 4.1-10, respectively. Grade et al.20 with almost a 4-year median follow-up, described a bNED rate of 88% overall for men presenting with a PSA $< 10$. Dattoli21 presents similar results of 93% for low-risk patients.

Two studies have evaluated outcomes when different treatments are used. Brachman et al.22 compared a series of 695 brachytherapy patients with 1,527 treated with conventional (nonconformal) EBRT at our institution. Low-risk patients (PSA $< 10$, Gleason score $< 7$) have a 5-year bNED of 89% regardless of the treatment method. D’Amico et al.23 report similar results of 85%-90% when comparing brachytherapy, radical prostatectomy, and EBRT in several related institutions. These data also suggest that high-risk patients presenting with bulky disease, high initial PSA, or high Gleason score fare poorly (<50% bNED) when managed with brachytherapy alone. In both series, either EBRT or surgery was superior to implant as monotherapy.

Zelefsky et al.24 retrospectively stratified 248 patients with a median of 48 months of follow-up into favorable, unfavorable, and intermediate strata using PSA of $\leq 10$, Gleason score of $\leq 6$, and stage $\leq T2a$. As in all similar studies, favorable-risk patients fared well with 88% NED at 5 years (Table).17,18,23-26 Unfavorable-risk patients (showing 2 or more of these poor prognostic features) had roughly 50% PSA control at 5 years, while the intermediate group (a single adverse feature) was consistently in between.

These high-risk patients are the same ones predicted by the Partin Tables27 to have a high-risk of established capsular penetration and other indications of

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Adapted from Zelefsky et al.24
Combination Therapies

Brachytherapy has been combined with modest doses of EBRT for these high-risk subgroups in several reports. Some advocate combination therapy for all patients, while most suggest the addition of EBRT for high-risk patients only. This remains controversial since no prospective studies have been designed to test this hypothesis. Retrospectively, Ragde et al reported improved 12-year disease-free survival from 66% to 79% in those patients receiving EBRT. However, Grado et al suggest no benefit with the addition of EBRT (80% in those patients receiving EBRT vs 72%). However, both reports contain confounding variables that limit the value of the conclusions.

Grimm et al reported on 232 high-risk patients treated with 45 Gy EBRT followed by a reduced-dose implant showing 76% bNED at 7 years. Dattoli published similar results for 102 high-risk patients, with 79% bNED at 5 years using EBRT followed by a 103Pd implant. Critz et al describe results for 1,020 patients treated with combination therapy, albeit with a much shorter median follow-up. All patients, including those with favorable prognostic features, received EBRT, and many of these early patients were treated with open retropubic implant techniques. While these series may not be truly comparable, 72% of patients at 10 years remain as bNED.

Hormonal therapies have been used in conjunction with prostate radiation therapy with increasing frequency over the past few years. Total androgen blockade has been used to downsize the prostate prior to brachytherapy, thus allowing for implantation of glands that might otherwise be too large for the technique and also to improve the therapeutic ratio with improved geometry. No long-term results have been reported to support its use based on survival or PSA endpoints. The use of total androgen blockade with EBRT has been established for high-risk patients based on just such

It is important to recognize that using these same risk groupings, equivalent PSA relapse rates are obtained with brachytherapy as with conformal EBRT or surgery. Stage for stage and grade for grade, all therapies show increasing failures with increasing risk. It is often impossible to select one therapy over another based only on cure rates. Consequently, patient decisions are often guided by issues relating to quality of life and individual value judgments.

Complications

Early side effects and complications involve primarily the urinary tract. Irritative and obstructive lower urinary tract symptoms develop immediately as a result of implant trauma and over the first weeks as a result of the radiation. While some practitioners routinely choose to leave a urinary catheter in place overnight, retention may require more prolonged catheterization in 5%-22% of cases. Recent work suggests that it is possible to predict those patients at greatest risk of retention based on their response to a standardized survey of urinary symptoms (frequency, urgency, hesitancy, etc) and on their International Prostate Symptom Score (IPSS).

Less dramatic urinary symptoms are commonly managed with nonsteroidal anti-inflammatory drugs and alpha blockers. Merrick et al reported that 85% of men required alpha blockers at 26 weeks, with 56% still using them at 50 weeks. Late grade 3 urinary complications (ie, requiring surgical intervention or altering functional status) may occur in approximately 2%-5% of patients, with stricture reported in 2%-3% of patients.

Management of the occasional patient with significant or prolonged urinary symptoms requires patience. While incontinence following brachytherapy alone is rare (<1%), it occurs to some degree in 25%-48% of men who have a transurethral resection of the prostate (TURP) after implantation. Spontaneous relief of obstruction may occur many months after implant, with complete symptom relief occasionally occurring as long as 1 year away. Thus, early surgical intervention (eg, TURP) after an implant should be avoided. Whether TURP performed prior to implantation poses a significant risk of incontinence remains controversial. The
current consensus is that it probably does not so long as healing has been adequate and sufficient tissue remains for good implant geometry.38

Late rectal complications, including proctitis with diarrhea, tenesmus, or rectal bleeding, may occur in 2%-19% of patients.39 There have been isolated reports of rectal fistula formations, particularly during the early years, with older implant techniques. Many of these were temporally correlated with aggressive rectal biopsies or laser therapies for minor bleeding. Conservative management of rectal radiation reactions is indicated with rectal steroids and other rectal preparations. Biopsy and laser rectal treatments should be used judiciously.

Compared with other standard treatments, permanent brachytherapy has been reported to offer prostate cancer patients their best chance of preservation of potency. Radiation-induced erectile dysfunction develops over time, and strict comparisons among various reported rates are difficult. Stock et al40 report impotence in 2.5% at 1 year and 6% at 2 years. However, 39% report some decrease in sexual function. In our own series of 706 evaluable patients, 76% report preservation of potency at 5 years (actuarial rate).

Quality-of-life issues have played a significant role in the emergence of prostate brachytherapy over the past decade. Recent work by Lee et al41 addresses this question using the FACT-G and FACT-P questionnaires combined with the commonly used IPSS. Thirty-one patients were evaluated prior to treatment and at 1 month, 3 months, 6 months, and 1 year following treatment. Patients experienced a minor decrease in the general quality-of-life measure (FACT-G) that, while statistically significant, is clinically trivial. The instruments more specific for lower urinary tract symptoms, such as the IPSS and FACT-P, revealed a clinically significant increase in patient-reported symptoms within the first month. For the IPSS, there is more than a twofold increase from a baseline median of 8 to 18, suggesting moderate to severe lower urinary tract symptoms. Longitudinal measurements show that this decrease in health-related quality of life is transient; by the end of the first year, scores are indistinguishable from baseline measurements. Continued quality-of-life analysis is needed for all therapeutically equivalent cancer treatments.

Case Selection

Current recommendations for case selection generally require a clinically localized prostate cancer in a man with a reasonable life expectancy, suitable gland size (generally <60 cc), and limited underlying obstructive urinary symptoms. Ideal candidates have a low risk of significant extraprostatic extension beyond the first few millimeters from the capsule. The most favorable patients, and those often considered suitable for brachytherapy as monotherapy, are those with a PSA of ≤10, Gleason score of ≤7, and low-volume/low-stage disease (typically stage T1c or T2a). Patients with more-advanced disease are candidates for brachytherapy in conjunction with a limited course of EBRT. For high-risk men with multiple adverse prognostic features, consideration should be given to clinical trials investigating innovative treatment combinations (eg, the addition of androgen blockade, EBRT) or new treatments, since results with standard therapy offer no better than a 50% of PSA control at 5 years.

Future Prospects

As the available pathologic tools improve, other factors such as DNA ploidy, number or percent of involved cores, perineural invasion, or newer blood markers may eventually play a role in selecting patients likely to respond well to brachytherapy. Better delineation of risk groups should help to determine the optimal use of adjuvant treatments such as EBRT or androgen deprivation. Advances in imaging technology are currently being exploited. Innovative uses of computed tomography and magnetic resonance imaging scanning with prostate brachytherapy are being studied to perform brachytherapy as well as to determine diagnostic staging. New devices to assist in implantation and to improve dose distribution and accuracy are being developed and should help to enhance the quality and consistency of implants.

Brachytherapy is a rapidly evolving treatment option. Innovations are introduced on an ongoing basis as more practitioners devote time and energy to creating better ways to evaluate patients and execute implants. At all times, the basic underlying principle remains: to deliver more radiation dose to the tumor and less to the surrounding normal tissues in an ongoing effort to improve the therapeutic ratio in the battle against prostate cancer.

References