

Brachytherapy for Prostate Cancer

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Introduction

Over 240,000 men will be diagnosed with prostate cancer in the United States in 1995. In this same period, more than 40,000 men will lose their lives to this disease, which is the second most common cause of cancer-related death among males.¹ Despite these statistics, the appropriate treatment for this disease remains controversial. Treatment recommendations have ranged from expectant observation to radical prostatectomy, external-beam radiation therapy, and brachytherapy. This review will focus on the use of brachytherapy for carcinoma of the prostate.

Brachytherapy is a form of radiation therapy in which radioactive sources are implanted directly into a malignant tumor. This approach offers the appealing

concept of delivering a high dose of radiation to a confined volume with relative sparing of adjacent normal tissue. Brachytherapy has a long and successful history in the treatment of many malignancies, such as carcinomas of the cervix, breast, endometrium, and head and neck.

The prostate is located adjacent to the critical structures of bladder and rectum and is therefore conceptually well suited to the confined radiation dose created by an implant. Brachytherapy can deliver more radiation to the prostate with less dose to the surrounding normal organs than conventional external-beam radiation therapy. This higher intraprostatic dose should theoretically result in more effective tumor sterilization with fewer complications. However, the use of brachytherapy for carcinoma of the prostate is controversial because of mixed results reported with older implant techniques and because of the large number of competing treatment methods available to the clinician.

Over the past 10 years, improvements in methods for prostate brachytherapy have been stimulated by advances in technology (including the introduction of new radioisotopes, innovative afterloading techniques, computer-based dosimetry analysis, and modern imaging modalities) and an improved understanding of the radiobiology asso-

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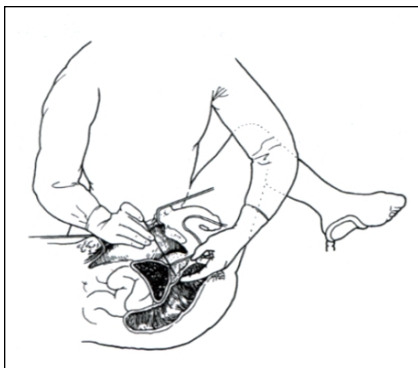


Fig. 1. Retropubic technique for prostate seed implantation.

ciated with different dose rates of radiation delivery. These advances promise to help brachytherapy for prostate cancer reemerge as an effective modality, which may be the least morbid and most cost-effective treatment for localized carcinoma of the prostate.

Historical Background

Brachytherapy represents one of the oldest techniques of radiation therapy for prostate cancer. In 1911 Pasteau² published the first report on brachytherapy treatment for prostate cancer, which involved the simple insertion of radium into the prostatic urethra via a catheter. In 1922 Denning published a series of 100 cases treated by this technique.³ Although short-term local control of the disease was surprisingly good for this crude method, the complications were significant, occurring in about 15 to 20 percent of patients.

Subsequently, other methods of treatment for prostate cancer were developed, such as radical prostatectomy and hormone manipulation by orchiectomy or estrogen administration. In 1956 megavoltage external-beam radiation therapy

was introduced and became the preferred radiotherapeutic management for localized prostate cancer.^{4,5}

In 1972 an open-surgical, retropubic brachytherapy method with permanent implants used for the radiation source was introduced by Whitmore et al⁶ at Memorial Sloan-Kettering using iodine 125 and by Carlton et al⁷ using gold 198 in combination with external-beam radiation therapy (Fig. 1). Although initial enthusiasm was high for these techniques, the limited technology of the time did not allow for accurate assessment of the quality of these implants. Modern methods of computer analysis have revealed frequent inhomogeneity of dose distribution with these manual techniques. The mixed clinical results of retropubic implantation and radiobiologic questions about low dose-rate sources caused these permanent implant methods to fall into disfavor. During this period, other workers introduced an open-surgical retropubic method for the temporary implantation of iridium 192.

In 1983 Holm et al⁸ introduced the era of closed transperineal implantation, incorporating several technologic advances to improve the accuracy and reproducibility of source placement and minimize patient morbidity. This approach has been further modified and refined by several workers (Fig. 2) and is currently being investigated with permanent and temporary implants. A large amount of experience and data has accumulated using these methods, and researchers are now much closer to defining their efficacy in treating prostate cancer.

Methods

A wide variety of brachytherapy approaches have been used for prostate carcinoma. Methods of implantation involve either temporary implants, where the radioisotopes are left in the patient for a calculated time and then removed, or permanent implants, where the radioiso-

topes are permanently implanted into the patient and decay to an inert state over a predictable time. Temporary implants are often combined with external-beam radiation therapy, while permanent implants are usually used alone. Some work is being done using permanent implants as a boost following modest doses of external-beam irradiation.

In the past both permanent and temporary implants involved a surgical laparotomy in which needles or trocars were manually guided into the prostate retropubically or transperineally with or without the aid of a perineal template. For permanent implants this open-laparotomy retropubic approach has largely been abandoned in favor of a closed transperineal approach using a template and guidance by either high-resolution transrectal ultrasound (TRUS) or computed tomography (CT). Similarly, several workers have now incorporated this nonsurgical, transperineal route for temporary implants.

To appreciate the promise of the new techniques, it is useful to consider the technical shortcomings of earlier methods and compare them with new techniques that help to overcome them.

PERMANENT IMPLANTATION

Retropubic Technique

In the early 1970s, little was known about the radiobiology of permanently implanted radioisotopes with low dose rates. In addition, the frequency of extraprostatic extension of disease in advanced-stage and high-grade malignancies was not fully appreciated. As a result, surgical retropubic techniques were often unwittingly applied to advanced-stage and high-grade malignancies where the extent of disease was beyond the confined reach of a permanent implant.

The traditional retropubic implant technique consisted of a formal retropubic exploration through an extraperitoneal

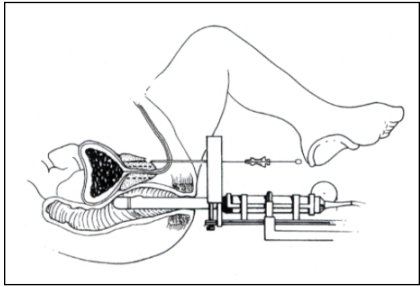


Fig. 2. Transperineal technique for prostate seed implantation.

lower-abdominal incision, a pelvic lymph-node sampling, and mobilization of the prostate from the surrounding tissues to allow access for the insertion of large-bore trocars. This approach was used for permanent implantation with radioisotopes such as iodine 125 and gold 198.

To achieve proper dose distributions of radiation, it was important that trocars were inserted parallel throughout the implant volume and that the sources were homogeneously distributed throughout the prostate volume. Iodine 125 seeds were deposited through the trocars into the prostate at uniform spacing using a variety of devices designed for this function. The surgical nature of the procedure required hospitalization and was responsible for many of the reported complications described in earlier series.⁹ The mobilization of the prostate often produced a bloody operative field where visualization of the gland was difficult.

Compounding this problem, patients with narrow or deep pelvises had a restricted retropubic space where access to the prostate was difficult. This cramped situation hampered uniform spacing of the trocars, often resulting in cone-shaped rather than parallel arrays. To minimize rectal injury, trocars had to be withdrawn about 1 cm from the rectum before insertion of the first seed in each

track. This was accomplished by palpating the needle tips through a rectal sheath and withdrawing the needle until it was no longer palpable. It was difficult to achieve consistent accuracy and reproducibility for this maneuver.

In the retropubic era, the ability to plan an ideal distribution of radiation for permanent implants was limited. The desired target dose was achieved by intraoperatively measuring the prostate and then determining the appropriate spacing of the sources and trocars by the use of a nomogram.¹⁰ This calculation yielded a "matched peripheral dose" for the prostate. This was defined as the dose for a computed contour volume that "matches" a mathematical ellipsoidal volume. Because of individual variability in prostate size and contour, this ideal condition was very difficult to achieve. Both well-distributed and poorly distributed implants could have the same value for matched peripheral dose.

Postoperative evaluation of the quality of these implants was restricted to simple orthogonal x-rays. This method did not allow for accurate assessment of the dose distribution relative to the actual prostate, and areas of underdosage were frequently unrecognized.

Considering the formidable drawbacks of the retropubic approach, it is not surprising that the clinical results from this era were mixed depending on the skill and experience of the individual brachytherapist and the case selection that was employed.

Transperineal Technique

In the early 1980s, several technologic developments were applied to prostate brachytherapy to address the physical shortcomings of the open-surgical retropubic implantation method. The goal was to improve outcome by increasing the uniformity of source distribution, customizing the dose distribution, accurately assessing the quality of the implant, and

reducing the morbidity of treatment.

The most important technologic advances were improvements in imaging ability created by TRUS and CT. TRUS in particular offered the brachytherapist an opportunity to intraoperatively visualize needle insertion into the prostate. This real-time visualization ability not only enhanced the accuracy of placement within the prostate but also allowed the operator to identify and correct for potential sources of error, such as prostate movement and internal tissue distortion that can occur during needle insertion. Unless corrected, these movements can perturb the desired placement of the seeds.

This improved imaging ability and a shift to the perineal route for needle insertion obviated the need for a laparotomy and thereby minimized surgical morbidity, permitting the procedure to be done on a cost-effective outpatient basis. Patient morbidity was further reduced by refinement of the implantation trocars from large-bore devices to thin-walled 17- or 18-gauge needles that penetrate tissue with minimum trauma.

As a further aid in accuracy of source placement and maintenance of parallel needle paths, a generation of rigid perineal templates was developed with a standardized design of parallel holes spaced in a symmetrical grid design. Software incorporated in commercial ultrasound units was developed that accurately displays the template coordinates superimposed over real-time images of the prostate, providing targets for the accurate placement of needles into the prostate.

These developments appear to have overcome many of the inaccuracies inherent with the open-surgical, retropubic method of seed insertion. Published series now document greater than 90 percent success in achieving a desired target dose with these methods.^{11,12}

In contrast to the retropubic method, contemporary transperineal approaches allow clinicians to preoperatively plan the

placement, activity, and number of sources to be implanted. This is done by a two-step process. First, preimplant studies are done with TRUS or CT to accurately determine the exact volume and contour of the prostate. Second, sophisticated, treatment-planning computer programs are used to customize dose distributions based on the measurements of target volume.

For the computer analysis, the contours of the prostate target volume, bladder neck, and rectum are entered into a computer program so that different arrangements of needles and source strengths can be considered. Three-dimensional dose distributions of radiation are calculated for the prostate, rectum, and bladder, and variables can be adjusted to optimize the dose to the prostate and minimize the dose to adjacent tissue. This method facilitates the creation of an idealized implant, customized to account for the wide range of individual prostate sizes and shapes.

Finally, postimplant evaluation by CT can be used to accurately assess implant quality referenced to the true prostate volume. This detailed information can be subjected to a wide variety of sophisticated analyses, such as the use of dose-volume histograms to determine the adequacy of the treatment dose or the amount of dose delivered to normal tissue.

TEMPORARY IMPLANTATION

Temporary implants have used iridium 192 almost exclusively. The vast majority of clinical studies involve implantation of iridium 192 with a low dose-rate placed in the patient for about three days and then removed.¹³⁻¹⁶ Some pioneering work has used high dose-rate iridium 192 sources applied for minutes rather than hours.¹⁷

Traditionally, temporary implants involve a laparotomy, pelvic-node sampling, and intraoperative guidance of transperineal needles into the prostate. Most of these approaches use a fixed-geometry perineal template to guide and

support the needles. Postoperatively, the needles and the attached template are left in place while iridium 192 sources are inserted for a calculated period of time, usually about 72 hours. X-rays of the needle arrangement are taken, and times of source insertion are adjusted to compensate for any irregularity of needle positioning.

Current refinements in this technique employ ultrasound guidance techniques so that open laparotomy is not required. The use of CT evaluation of needle placement relative to prostate volume allows greater accuracy in determining proper dose distributions and normal tissue doses. The development of modern afterloading devices results in greater optimization of dose distribution and radiation protection for medical workers. Although hospitalization is still required for these techniques, accuracy has been improved and patient morbidity should be reduced.

Isotopes

The decision to use either a temporary or a permanent method of implantation is largely determined by the choice of isotope. A variety of isotopes exists for clinical use, and each has unique characteristics of energy and half-life. It is these physical characteristics that determine if a source will be used as a temporary or as a permanent implant. Controversy exists about the various merits and demerits of one isotope versus another. This section describes some of the scientific underpinnings that characterize the wide variety of isotopes used in brachytherapy for prostate cancer.

Radioactive isotopes are characterized by their energy and their half-life. The radiation of higher energy sources, such as iridium 192 and gold 198, penetrates further into tissue, so the position of individual sources is less critical to the achievement of a homogeneous dose. However, the greater depth of radiation penetration

Table 1
Radioisotopes Used for Prostate Brachytherapy

	Energy (keV)	Half-Life (days)	Half Value Layer (HVL) in mm of lead	Initial Dose Rate (cGy/hr)	Dose to Infinity (Gy)
Permanent					
Iodine 125	27	60	1/40	8	160
Palladium 103	21	17	1/100	20	120
Gold 198	412	2.7	4	64	60
Ytterbium 169	93	32	1/2	13	140
Temporary					
Iridium 192	340	70	3	High, variable	Variable (30-40)

results in less sparing of surrounding normal tissue, potentially causing greater complications or limiting the dose that can be given to the target volume.

The radiation of low to moderate energy sources, such as iodine 125, palladium 103, and ytterbium 169, delivers a more confined dose to the prostate but must be placed with great precision to avoid areas of underdosage (cold spots) due to the limited penetration of the low-energy radiation.

The initial dose rate of a given isotope is dependent on its half-life and the total dose prescribed. Dose rate is an important determinant of the biologic effectiveness of the emitted radiation. For a given unit of radiation, a high dose rate will result in greater biologic damage to both normal and malignant tissue than will a low dose rate. Because normal tissue tolerance is the limiting factor for radiation dose, higher dose-rate sources are usually prescribed to a lower total dose to avoid complications. Because the relationship between dose rate and cell cycle time of a malignancy is thought to have

significance for tumor control, the issue of source selection may be important. The characteristics of commonly employed isotopes are detailed in Table 1.

IODINE 125

Most experience with brachytherapy for prostate cancer involves the use of iodine 125 as a permanent implant.¹⁸⁻²² Iodine 125 has a low energy (27 keV) and a half-life of 60 days. The advantage of low energy is the ease of radioprotection for medical workers and the confined volume of radiation dose from the implant that minimizes the dose to surrounding normal tissue. These same characteristics can create disadvantages that must be recognized when considering the use of this source. At this energy level, tissue absorption becomes an important factor. Meticulous attention must be given to the accurate placement of iodine 125 sources. Otherwise inhomogeneities within the implant area may easily occur, leading to areas of underdosage and tumor sparing.²³ Further, although the confined dose

may spare adjacent normal tissue, any significant extraprostatic extension of disease will not be adequately treated.

The relatively long half-life results in an initial peripheral dose rate of 8 to 10 cGy/hr when a total dose of 160 Gy is prescribed. This low dose rate has raised concerns about the effectiveness of iodine 125 for rapidly dividing malignancies. Laboratory experiments have demonstrated that in rapidly dividing tumors with short half-lives, tumor proliferation may occur during the course of an iodine implant, potentially reducing the degree of cell kill.²⁴ Ling has applied mathematical models to the question of degrees of cell kill relative to tumor doubling times for several permanent isotopes (unpublished data, 1995). This model predicts less effective cell destruction with iodine 125 compared to higher dose-rate isotopes in rapidly dividing tumor systems.

equivalence to the results achieved with external-beam radiation therapy and even surgery.²⁶

Although the relevance of these laboratory and mathematical models to prostate cancer in man is uncertain, it would appear prudent to avoid the use of iodine 125 as a stand-alone treatment for patients with bulky stage B2 or C disease or poorly differentiated histology. However, the patient with stage B1 or low-volume stage B2 disease and well-differentiated or moderately differentiated histology may be well served by this source.

PALLADIUM 103

Palladium 103 was introduced in 1986 as a new, permanently implantable radioisotope for use in brachytherapy. The physical dimensions of palladium 103 are iden-

***Brachytherapy is a form of radiation therapy
in which radioactive sources are implanted directly
into a malignant tumor.***

Conversely, this model also describes excellent effectiveness in slowly dividing malignancies.

The relationship of dose rate, cell cycling, tumor grade, and local control has been described in clinical studies as well as in the laboratory. Kuban et al²⁵ have demonstrated that in patients with stage B2 and C poorly differentiated tumors, external-beam radiation therapy may be superior to implants with iodine 125. It is unknown whether this result was due to a true dose-rate effect related to cell-cycling issues; advanced disease beyond the effective range of iodine 125 implants; or, simply, poor geometry from the retropubic technique used. Conversely, the long-term, clinical results in small-volume, low- to moderate-grade prostate cancers (e.g., stage B1 disease) have shown clear

tical to those of iodine 125, and therefore implantation devices designed for iodine 125 can be used for palladium 103 as well. Its photon energy is also similar to iodine 125 at 21 keV, but its shorter half-life (17 days) yields a higher initial dose rate of about 20 cGy/hr as compared with 8 cGy/hr with iodine 125.

Because of its low energy, palladium 103 demonstrates the advantages of radioprotection and confined dose and the potential disadvantage of a rapid decrease in dose similar to the characteristics of iodine 125. Although the amount of clinical data reported for this new source is small, its primary theoretical advantage lies in its higher dose rate. It is hoped that this higher dose rate will address some of the radiobiologic concerns raised by the low dose rate of iodine 125

and will result in the successful treatment of poorly differentiated malignancies.

GOLD 198

Gold 198 has been used as a permanent implant either alone or as an adjunct to external-beam radiation therapy.^{27,28} Flocks et al²⁹ began using this isotope when they developed the technique of injecting the colloidal form of radioactive gold directly into prostate tumors. However, this technique is extremely difficult, and gold seeds developed later offered the advantages of simpler handling and easier placement. Gold 198 has a short half-life (2.7 days) and a maximum energy of 1.2 MeV. The theoretical advantage of a gold 198 implant is rapid delivery of radiation at a very high dose rate, thus potentially avoiding some of the radiobiologic problems associated with iodine. The higher energy of the source, however, results in less sparing of adjacent normal tissue, thereby limiting the dose that can be prescribed to the prostate without complications occurring.

An additional disadvantage of this isotope is the risk of radiation exposure to staff performing the implantation. Carlton reported that a radiation oncologist in his center, after performing more than 100 gold seed implants in a year, received 6,300 millirem to the hands and 340 millirem whole body.³⁰ While these figures are below the permissible dose levels accepted for radiation exposure, this does not comply with the ALARA principle in which the dose received should be as low as reasonably achievable.³¹ Because of this radiation protection problem, gold 198 implantation has fallen into disfavor at many centers.

YTTERBIUM 169

Ytterbium 169 is another source that has been proposed as a replacement for iodine 125 in permanent implant brachytherapy. It has a slightly higher initial dose

rate of 12.5 cGy/hr and also a higher energy of 93 keV, thus allowing more favorable dose distributions and negligible tissue self-attenuation compared with both palladium and iodine implants. Its disadvantage as a permanent implant material is the presence of a small (less than three percent) photon peak at 300 keV that significantly affects the radiation protection requirements required for its use.³²

Offsetting that disadvantage is its high specific activity, which translates into the possibility of developing physically small, high-activity sources as a replacement for iridium 192 in temporary brachytherapy.

IRIDIUM 192

Iridium 192 is a gamma emitter with a mean energy of 400 keV and a half-life of 72 days. It has primarily been used as a temporary implant, usually combined with external-beam radiation therapy as part of a "shrinking field" technique.^{13-15,33,34}

Some of the disadvantages inherent with permanent implant sources do not occur with this isotope because of its physical characteristics. The higher energy, for example, is less susceptible to tissue attenuation and penetrates a greater distance, reducing the chance of cold spots. The temporary and removable nature of the implant means that application times can be varied to compensate for irregularities in needle placement. Finally, the higher dose rate is reassuring to those concerned about the relationship of radiation dose rate to cell cycle times.

However, disadvantages do exist. Because of the greater penetration ability of the higher energy, a larger volume of normal tissue is encompassed within the high dose volume, resulting in a greater risk of complications. Several series do confirm a relatively high rectal complication rate, particularly in earlier series.¹⁴⁻¹⁶ As a temporary implant, the isotope is introduced into the patient for a period of

time, usually via 10 to 15 indwelling transperineal needles. For the duration of the implant, the patient is hospitalized and bed-bound, requiring analgesia. There are also radioprotection problems for medical personnel administering post-operative care.

Clinical Results

IODINE 125 RETROPUBIC METHOD

Several thousand patients have been treated with retropubic iodine 125 brachytherapy from 1970 to the early 1980s. Because of the significant technical shortcomings of the retropubic technique as outlined previously, it is controversial whether the results reported from this era represent a true evaluation of the efficacy of iodine 125. Comparisons of published series are further handicapped by other factors as well, including nonuniformity of endpoints, variable patient selection, wide range of follow-up times, addition of hormonal manipulation, and lack of post-implant dosimetry.

Criteria for success in these retropubic series were usually limited to overall survival and disease-free survival. Disease-free survival was defined as either distant failure with a positive bone scan or local failure defined as a palpable abnormality or obstruction by tumor requiring surgical intervention.

Overall survival ranges from 83 to 92 percent in series with mean follow-up times of three to seven years.^{19,21,35-38} In those series that retrospectively compared iodine 125 with external-beam radiation therapy, overall survival results appeared equivalent at least to five years.^{18,19,21,25,39,40} Longer follow-up is available in a few series with 10-year results of 50 percent¹⁹ and 15-year actuarial survival of 37 percent.⁴¹ In the Hilaris series,⁴¹ a subgroup of patients judged to have been candidates for radical prostatectomy were identified based on pathologically negative pelvic lymph nodes and

solitary prostate nodules of 1.5 cm or less. These patients demonstrated a 15-year survival of 70 percent. Thus, overall survival for patients treated with iodine 125 did not differ significantly from survival results with external-beam radiation therapy or radical prostatectomy, at least among stage A and B patients.^{18,19,39,40,42-45}

The reported five-year survival with no evidence of disease (NED) for clinical stage A and B patients ranges from 75 to 90 percent, and five-year local control ranges from 83 to 95 percent. These figures appear equivalent to results for stage A and B patients treated with external-beam radiation therapy in a study of patterns of care that reported a five-year NED rate of 63 to 92 percent and a local control rate of 80 to 97 percent.⁴⁵ In those series that report a 10-year follow-up for iodine 125 treated stage A and early stage B patients, local control ranges from 85 to 90 percent.

For stage C patients, the five-year NED survival results reported for iodine 125 range from 28 to 38 percent. This appears inferior to the five-year NED rate of 50 to 70 percent reported for stage C patients who received external-beam treatment in the patterns-of-care study.⁴⁵ For stage C patients treated by iodine 125 implants, local control at 10 and 15 years is 56 percent and 18 percent, respectively. In the Hilaris series,⁴¹ the local control rate for patients with advanced stage B3 lesions (palpable disease involving both prostate lobes) was 18 percent at 15 years. These results for iodine 125 implants are inferior to the local control rates of 60 to 80 percent reported for stage C patients treated with external-beam radiation therapy.^{19,25,45}

It should be noted, however, that Fuks et al¹⁸ have demonstrated a clear relationship between an adequate implant dose and the probability of local control in a series of 679 relatively advanced stage B/N0 and C/N0 patients. In this series, patients who received a matched peripheral dose of 140 Gy or more achieved

a 10-year local control rate of 60 percent, while those with a matched peripheral dose of less than 140 Gy had a local control rate of only 20 percent at 10 years.¹⁸ These data reinforce the importance of a quality implant with adequate dose.

The question remains whether the poor results reported in other series^{35,39} were due to intrinsic characteristics of iodine 125 or to poor-quality, inhomogeneous implants. Given the uncertainties of the data, it appears that the five- and 10-year clinical results of retropubic implantation in the hands of skilled and experienced operators were comparable to standard external-beam radiation therapy for stage A and early stage B tumors. Stage C and, possibly, bulky stage B patients, however, often had inferior results by this method. Similar conclusions have been reached by other authors who reviewed their results with iodine 125 and retrospectively compared them to patients treated with external-beam radiation therapy at their own institutions.^{19,25,45}

Some series have attempted to evaluate the success of therapy by obtaining postimplant biopsies to determine histologic sterilization. The relevance of these histologic findings to the eventual clinical outcome is controversial as well.

Kandzari et al⁴⁶ have reported one-year and two-year biopsy data on patients with stage B2 and C tumors treated with iodine 125 implants as primary therapy. The doses delivered ranged from 140 to 160 Gy. Positive biopsy rates one year after iodine implantation were 35 percent (n=37) for stage B tumors and 60 percent (n=11) for stage C tumors. After two years these figures were 38 percent (n=21) and 67 percent (n=6), respectively. Schellhammer et al⁴⁷ reported positive biopsy rates of 30 percent (n=40) for patients with stage B tumors and 43 percent (n=20) for patients with stage C tumors. The authors commented that grade was unpredictable in determining outcome in terms of postoperative biopsy results.

This was also observed in the Kandzari series.⁴⁶ Lytton et al⁴⁸ reported positive biopsies in 50 percent (n=22) of patients one year after implantation.

TRANSPERINEAL TECHNIQUES

Iodine 125 and Palladium 103

Although the numerous technical improvements that characterize the transperineal approaches are promising, no long-term data exist to confirm improved results. All authors have employed the technology and principles of modern transperineal implantation as previously discussed. However, technical variations are common, particularly in the relative use of TRUS, CT, and fluoroscopy. Because of the brevity of follow-up, most authors have relied on prostate-specific antigen response as an indicator of success. Histologic evaluation by postimplant biopsy of these transperineal techniques has not yet been published. Clinical and prostate-specific antigen responses for five studies using either iodine 125 or palladium 103 are referenced in Table 2.⁴⁹⁻⁵³ Although the relationship of early prostate-specific antigen normalization to long-term clinical cure is uncertain, these early results appear favorable. Allowing for selection of patients suitable for iodine implantation (i.e., the smaller stage B tumors), these results appear at least equivalent to what has been obtained with external-beam radiation therapy or radical prostatectomy.

Complications of transperineal iodine 125 brachytherapy have been low to date. Blasko et al⁵⁴ report late proctitis in one percent of the iodine group. Impotence data is not yet widely available for this treatment approach, and impotence may occur in a later time frame than other complications. Preliminary data on a group of 38 patients by Wallner et al⁵² suggest that potency can be maintained in 81 percent at three years. Kaye et al⁵¹ report a potency rate of 75 percent in 44 pa-

Table 2
Clinical and Prostate-Specific Antigen Response
Following Transperineal Brachytherapy

Reference	No. of Patients	Stages	Isotope	Clinical Disease Free (percent)	PSA Control (percent)	Follow-up (years)
Blasko et al ⁴⁹	197	T1b-T2b	125I	95	93*	5
Blasko et al ⁵⁰	97	T1b-T2b	103Pd	95	86*	4
Kaye et al ⁵¹	45	T1-T2	125I	—	98†	2
Wallner et al ⁵²	62	T1b-T2b	125I	90	83‡	3
Blasko et al ⁵³	99	T2a-T3	XRT+ ¹⁰³ Pd	84	64*	5
Kaye et al ⁵¹	31	T1-T2	XRT+ ¹²⁵ I	—	95†	2

*Defined as PSA <1.0 ng/ml.
†Defined as PSA <4.0 ng/ml.
‡Defined as a lack of PSA progression, regardless of level.
XRT = external-beam radiation therapy.

tients at one year. Longer follow-up time is clearly needed to assess the true incidence of impotence.

Clinical data using palladium 103 as an implant source are limited. Blasko et al report using palladium 103 with a target dose of 115 Gy in 34 patients treated with a median follow-up of 22 months. No patients has failed at this point. In 28 patients, a palladium boost was used in combination with external-beam radiation therapy, and the median follow-up is 24 months. Of these patients 26 (93 percent) have been controlled locally, and only two (seven percent) have had distant failure at this early time.⁵⁵

Gold 198

In most cases, gold 198 has been used in combination with external-beam radiation therapy in the treatment of prostate cancer. Carlton and Scardino reviewed

the data on patients treated at Baylor College of Medicine with gold seed implantation followed by external-beam radiation therapy. They found that after treatment 39 percent (n=12) of patients with stage B tumors were positive for tumor and 59 percent (n=23) of patients with stage C disease were positive following treatment.

Crusinberry et al⁵⁵ described the treatment of prostate cancer with gold 198 seeds alone. They used a permanent implant technique described by Holm et al,⁸ to deliver doses of 9,000 to 15,000 cGy. Patients demonstrated a rapid decrease in prostate size within six months of treatment. This rate of change in prostate volume was correlated to the dose delivered. In patients who received 15,000 cGy as the maximum cumulative radiation dose, a significantly greater rate of tumor reduction was obtained than in patients receiving 9,000 cGy. Seven pa-

tients underwent prostate biopsy within 12 to 18 months following treatment. Six of these patients had positive biopsies, and two patients subsequently developed local recurrence.

Iridium 192 Brachytherapy

Several authors have now reported on the results of iridium 192 brachytherapy in combination with external-beam radiation therapy. Puthawala et al¹⁵ have demonstrated a negative biopsy rate of 85 percent in patients with stage B and C bulky tumors of the prostate. Martinez et al¹⁴ have also described a negative biopsy rate of 80 percent, using the multiple-site perineal applicator (MUPIT) technique in patients with tumors measuring between 5 and 6 cm in diameter. Porter et al have reported a negative biopsy rate of 75 percent for 75 patients with stage B or C prostate cancer biopsied 18 months after an iridium 192 temporary implant.^{13,16} Klein et al¹³ had similar results for 35 patients, of whom 15 were biopsied.

Martinez et al¹⁷ report a five-year survival rate of 82 percent for stage C carcinoma treated with a MUPIT implant technique, which exceeds rates reported for conventional external-beam radiation therapy. However, it is recognized that comparisons of data in this way are not necessarily valid, and phase III trials are necessary to confirm whether survival benefit does really exist.

However, while high rates of histologic local control have been achieved with these techniques, complications have been significant. In several series¹⁴⁻¹⁶ rates for severe complications between 10 and 20 percent have been reported. Pulmonary emboli may arise as a result of general surgery; lymph node dissections can lead to lymphedema and lymphocele; and complications may arise as a result of previous aggressive transurethral resection of the prostate. In addition radiation therapy may lead to complications due to implantation of needles perforat-

ing the rectum or delivery of dose rates in excess of 90 cGy/hr.

Donnelly et al¹⁶ report that use of computerized dosimetry as well as subcutaneous low-dose heparinization has helped to significantly reduce complication rates for iridium 192 brachytherapy in patients treated with dose rates below 70 cGy/hr.

Conclusions

It is too early to definitely determine whether prostate brachytherapy is the most effective modality in the treatment of prostate cancer and at which stages its use is appropriate. In brachytherapy series published to date, variability exists in patient selection and technical methods. In addition, there is a lack of phase III trials incorporating brachytherapy. Similarly, there are few if any widely accepted phase III trials that have rigorously tested any competing modalities of treatment against each other, whether it is surgery, external-beam radiation therapy, brachytherapy, or expectant management. All of this makes brachytherapy results difficult to compare against external-beam radiation therapy or radical surgery.

However, there is a degree of consistency among clinical results for brachytherapy showing improvement in histologic local control and greater understanding of the biology and physics underpinning this modality. There are now suggestions from the prostate cancer literature that improved local control can translate into improved survival as well as a reduction in the morbidity of local recurrence.

The potential for brachytherapy lies in two areas. First, brachytherapy may be able to offer the patient with an early, confined lesion the possibility of a single, cost-effective, low-morbidity outpatient treatment by the permanent transperineal implantation of radioisotopes with cure rates equivalent to conventional external-beam radiation therapy or radical

prostatectomy. Second, brachytherapy may be used as a boost following moderate doses of external-beam irradiation in locally advanced disease. In this setting, the question may be whether brachytherapy is the choice of radiation therapy to

achieve improved local control in bulky prostate cancer. Whether recent technological advances in brachytherapy can deliver on these promises will become clear in the next few years as ongoing studies mature. **CA**

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