

# Brachytherapy for prostate cancer

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Radioactive prostate seed implantation (brachytherapy) can be effectively used as monotherapy for early-stage prostate cancer. The technique is also efficacious in the salvage treatment of locally recurrent prostate cancer previously treated with external radiation. In properly selected patients, up to 70% of men are rendered disease free following treatment. Long-term side effects are minimal.

**A**pproximately 230,000 men will be diagnosed with prostate cancer this year, making it the most common cancer in the United States.<sup>1</sup> With increased early detection and recent advances in nonsurgical treatment, most men can now be cured of this disease and still maintain an excellent quality of life.

Prostate seed implantation is based upon the use of tiny radioactive seeds, each smaller than a grain of rice (Figure 1). The seeds are made of titanium and contain a small amount of either radioactive palladium-103 or iodine-125. After placement, the seeds emit an intense amount of radiation to the prostate over several months. Because of the low energy of the seeds (typically 21–28 keV), using modern implant techniques, the amount of radiation received by areas outside the prostate, such as the bladder and rectum, can be minimized. Gradually the radioactivity of the seeds decays over time and becomes clinically insignificant. Cancer cells can be selectively killed because they are much more sensitive to radiation than are normal cells.

Prostate brachytherapy has been performed in the United States for more than 30 years. Initial techniques involved the retropubic exposure of the prostate followed by free-hand implantation of the seeds.<sup>2</sup> The transperineal approach began in the 1980s with the advent of improved transrectal ultrasound imaging and seed-delivery devices.<sup>3</sup> Later advances in computer technology led to the real-time intraoperative dosimetry technique favored by many centers today.<sup>4</sup>

## Seed implant techniques

Prostate implantation is a simple outpatient procedure that typically takes less than 1 hour to perform and allows men to return to their normal activities within 1–2 days. Most men undergo general anesthesia, although spinal anesthesia is possible. When transrectal ultrasonography is utilized, a live picture of the prostate is obtained, and 18-gauge needles can be in-

serted through the perineum into the prostate. The radioactive seeds are then inserted through the hollow needles into the prostate (Figure 2).

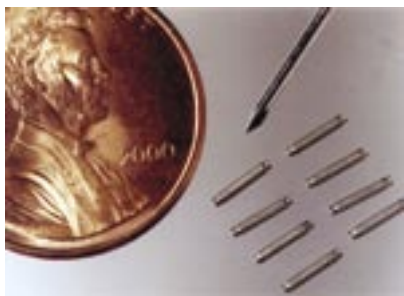
Several different implant techniques exist to determine the number and distribution of the radioactive seeds needed for the procedure. The older “pre-plan” technique involves mapping out the prostate by ultrasonography prior to the actual implant procedure. With these images, calculations are made to determine the future needle and seed position. Then, at a later time, the patient is brought back to the operating room and the initial ultrasonograph is used to determine where to place the needles and seeds in the prostate. However, the pre-plan technique may not take into account the differences in the size, shape, or position of the prostate at the actual time of surgery. Subtle changes in patient positioning, the degree of bladder filling, and the shape of the prostate after the needles are inserted can affect efforts to reproduce the pre-plan.

In contrast, with the “real-time” or “dynamic intraoperative” technique, the needle and seed positions are determined intraoperatively in a single session. Any motion of the prostate or change in its size or shape during the procedure can be immediately taken into account, ensuring accurate seed placement. Throughout the procedure, a computer is connected to the ultrasound machine to obtain and analyze live images of the prostate gland and surrounding anatomy. As the seeds are implanted, the computer can provide instant feedback of the doses of radiation received by the various anatomic structures. Hence, there is minimal risk of underdosing the prostate or overdosing the rectum or urethra with radiation. Several recent studies have shown that the radiation doses calculated intraopera-

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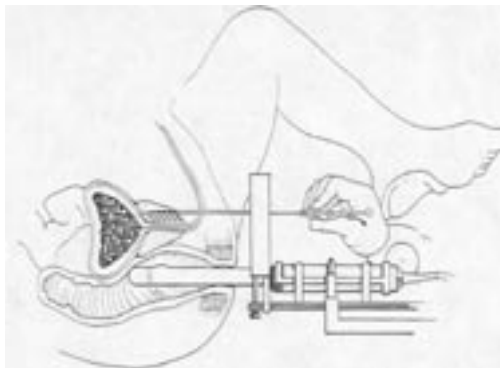
**FIGURE 1** Radioactive seeds and implant needle.

tively closely matched those calculated on a 1-month postoperative CT scan, where the final actual seed position could be verified.<sup>5-7</sup> With the advent of this technology, the real-time technique is considered by many to be an improvement over older pre-planned techniques, where the amount of radiation received by the prostate could not be determined until after implantation.

## Indications and contraindications for seed implantation

### Indications

Most men with nonmetastatic prostate cancer are eligible for seed implantation. Proper patient selection is vital to obtain the best results. The primary prognostic factors for prostate cancer therapies include prostate-specific antigen (PSA), biopsy Gleason score, and clinical stage. Typical staging studies after the diagnosis of prostate cancer might include pelvic CT and bone



**FIGURE 2** Transperineal needle placement.

scans. Additional imaging studies such as positron emission tomography (PET) are under investigation.

Men with early-stage disease typically have a small likelihood of occult microscopic disease beyond the prostate and are thus good candidates for seed implantation alone as monotherapy. This group typically includes men with a PSA level < 10 ng/mL, a Gleason score < 7, and a clinical stage of disease < T2b (nodule on digital rectal examination confined to less than half of one lobe of the prostate).<sup>8</sup>

In men with more advanced or aggressive forms of prostate cancer, there is a higher risk of microscopic cancer spread beyond the confines of the prostate gland. These men typically have a PSA level  $\geq$  10 ng/mL, a Gleason score > 6, or a clinical stage of disease  $\geq$  T2b.<sup>8</sup> For any form of treatment to be effective in these patients, it must be directed at both the prostate and the surrounding areas potentially harboring microscopic cancer cells. A prostate seed implant is typically combined with a few weeks of external radiation treatment to the prostate and periprostatic tissues. In addition, the seed implant may also be combined with a few months of a luteinizing hormone-releasing hormone (LHRH) agonist, which lowers the serum testosterone level. Some studies have shown a clinical benefit to this combination approach.<sup>9,10</sup>

Only recently have men with locally recurrent prostate cancer following prior treatment with external-beam radiation therapy been considered eligible for implantation. In past years, treatment options for these men were somewhat limited and included potentially morbid salvage prostatectomy or prolonged hormonal therapy. To be considered candidates for salvage seed implantation, men must have biopsy-proven recurrent disease in the prostate without evidence of disease spread beyond the prostate. Men with documented grade 3/4 toxicities from previous external radiation treatment should be considered at higher risk of future morbidity.

### Contraindications

Relatively few contraindications exist for the use of brachytherapy for nonmetastatic prostate disease. Patients must be medically able to tolerate general or spinal anesthesia. Potential issues include patients with a large prostate (> 60 cc in volume) due to the possibility of pubic arch interference preventing adequate needle and seed placement. In most instances, however, several months of neoadjuvant hormonal therapy will adequately downsize the prostate to a smaller, more optimally implantable size. Men with small prostates (< 15 cc) are considered by some to be at increased risk of urethral morbidity with seed implantation, although with modern dynamic intraoperative implant techniques, this should not be a significant issue.<sup>6</sup> Men with large prior transurethral resections of the prostate (TURP) defects are often not optimal seed implant candidates due to the resultant architectural distortion and lack of adequate prostate tissue in which to distribute the seeds appropriately. Of note, men with small prior TURP defects are typically good implant candidates, with a minimal increased risk of complications.<sup>11</sup> Patients with severe connective tissue disorders might be at a greater risk of side effects with any type of radiation therapy, although studies are few and often inconclusive.<sup>12</sup>

### Outcomes

Optimal results with seed implantation depend on both proper patient selection and an adequate radiation dosage being received by the prostate (implant dosimetry).<sup>13</sup> Since the widespread availability of PSA measurement in the early 1990s, the outcomes following treatment of prostate cancer are typically measured biochemically with PSA assessment rather than clinically or radiographically.

In low-risk disease, most studies show that at 10 years following seed implantation, approximately 85%–90% of men overall are biochemically free of disease.<sup>9,14-16</sup> Upon further subgroup

analysis of those men receiving high prostate radiation doses in excess of 140–160 Gy on postimplant dosimetry, biochemical control rates greater than 93% can be achieved.<sup>13</sup> This finding lends further support to the importance of an optimal seed implant technique. Retrospective studies comparing the effectiveness of prostate brachytherapy with more invasive and radical surgery or time-consuming external radiation therapy have shown similar long-term outcomes in low-risk or early-stage patients.<sup>8</sup> In the United States, the largest proton experience reported to date stated that the 5-year biochemical outcome was only 73% for localized prostate cancer.<sup>17</sup> At the present time, these results appear to be inferior to outcomes with seed implantation, although the patient population in this study was somewhat heterogeneous and older proton irradiation techniques were used. Unfortunately, there are limited studies available utilizing proton therapy, and no direct randomized comparisons exist.

In men with more locally advanced disease, as previously described, monotherapy with an implant alone typically yields suboptimal results.<sup>8</sup> Similarly, success rates with radical prostatectomy in this group of patients typically are only between 30% and 50%.<sup>8,18,19</sup> The most likely explanation for the poor results seen with surgery is that this population of patients possesses a high likelihood of extracapsular disease, which cannot be adequately resected. In contrast, the combination of a seed implant and a short course of external radiation therapy to the prostate and periprostatic tissues has yielded between 10- and 13-year success rates of approximately 80% in multiple studies.<sup>20,21</sup> Unlike surgery, the external radiation therapy component typically addresses the periprostatic tissues, a likely area of occult microscopic cancer cells. Treatment generally consists of 5 weeks of external radiation therapy for a few minutes each day.

With this strategy, the timing between seed implantation and external radiation therapy is particularly impor-

tant if the implant is performed first. In our practice, palladium 103, with a half-life of 17.5 days, is the isotope used in combination therapy. External radiation therapy typically begins 8 weeks after the implant, to allow for sufficient radioactive decay of the seeds. Trimodality therapy, with short courses of hormonal therapy, seed implantation, and external radiation therapy, might potentially offer the greatest long-term results in these high-risk patients.<sup>10</sup>

There are increasing data available for the use of prostate brachytherapy for salvage of local failures following prior external beam radiation therapy. Ideal candidates are men with a PSA level < 10 ng/mL, hormone-sensitive disease, and slower PSA doubling times > 6 months.<sup>22–24</sup> Treatment typically involves 3 months of hormonal therapy, followed by a palladium-103 seed implant, and an additional 3 months of hormonal therapy. Reports have shown success rates as high as 71%.<sup>22</sup>

### Morbidity

Morbidity following prostate brachytherapy is generally low and compares favorably with that of other treatment modalities. The implant procedure is typically performed in an outpatient setting, with most men returning to their normal activities within 24–48 hours.

The most common symptoms following treatment are prostatitis-like in nature and short-lived. Men typically report varying degrees of increased urinary frequency, urgency, and a weakened urinary stream. Dysuria and an increased frequency of bowel movements are also possible. Most studies show urinary incontinence rates following prostate brachytherapy of less than 1%.<sup>11,25,26</sup> Prolonged urinary retention, defined as the need for a Foley catheter for more than 24 hours, is typically seen in only 4% of men. Men with a high degree of pre-treatment urinary symptoms are at highest risk. Most instances of post-implant urinary retention occur within the first 2 weeks after the procedure. Half of these cases resolve spontaneously in

the subsequent few weeks. Up to 2% of patients might require a future TURP or other intervention for unresolved urinary retention. Incontinence rates in men requiring post-implant TURP are higher than normal, with rates up to 18% reported.<sup>11,26</sup> Acute urinary side effects typically last for 2–6 months post treatment. Obstructive urinary symptoms are usually managed with selective alpha-blockers such as tamsulosin (Flomax), and irritative symptoms are treated with antispasmodics and nonsteroidal anti-inflammatory agents.

Grade 3/4 proctitis (rectal bleeding) is rare and generally seen in less than 5% of men.<sup>27</sup> Risk factors for proctitis or rectal fistula following treatment are typically inappropriate use of transrectal cautery for mild bleeding or unusually high radiation doses to the rectum.<sup>27,28</sup> If the volume of rectum receiving the full dose of radiation is minimized, rates of proctitis less than 1% can be achieved.<sup>27</sup> Management of proctitis typically involves the use of local anti-inflammatory agents, such as pramoxine-HCl or steroid enemas, and fiber-bulking agents as well. Rectal cautery and unnecessary rectal biopsies should be avoided following brachytherapy.

Sexual potency after prostate brachytherapy is dependent on the degree of pre-treatment erectile function. In those men who are fully potent and able to obtain erections sufficient for intercourse, 50%–75% retain that ability after seed implant treatment. The potency preservation rate drops in men who are already experiencing some degree of erectile dysfunction prior to seed implantation and tends to decrease with longer follow-up.<sup>29,30</sup> Management of erectile dysfunction in the post-radiation setting is often successful, with 50% of men responding to sildenafil (Viagra) or similar drugs.<sup>31</sup>

### Cost-effectiveness

Prostate brachytherapy is an extremely cost-effective treatment. The procedure is performed in an outpatient setting, with typical anesthesia

times of less than 1 hour. Most patients are discharged home 2–3 hours after the procedure. With severe long-term morbidity being rare, post-treatment management expenses remain minimal as well. In contrast, for patients with early-stage disease, treatment with 8 weeks of external radiation or proton therapy is substantially more expensive and time-consuming than a single-session outpatient seed implant. Likewise, patients undergoing radical prostatectomy typically require 2–3 days of hospitalization and 2–3 weeks of an indwelling Foley catheter and are out of work longer, thus incurring higher expenses.<sup>32,33</sup>

## Conclusion

Prostate brachytherapy has been demonstrated to be a safe, efficacious, and cost-effective treatment for early-stage prostate cancer. Randomized studies are needed to gain more information by comparing it directly with other available treatment modalities.

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