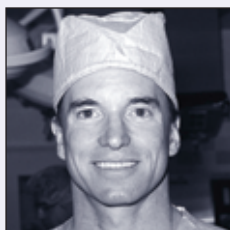


Prostate Brachytherapy for the Treatment of Prostate Cancer – Disease Control and Toxicity Outcomes

a report by

John Sylvester, MD

Director, Education and Training, Seattle Prostate Institute, Swedish Hospital



John Sylvester, MD, is the Director of Education and Training of the Seattle Prostate Institute at Swedish Hospital in Seattle Washington, which he co-founded with Dr Peter Grimm in 1997. Prior to this he was the initial Director of the Puget Sound Tumor Institute. As part of the original Seattle team that pioneered modern prostate brachytherapy he has performed thousands of transrectal ultrasound guided radioactive seed implants of the prostate since 1987. To date, several thousand physicians have been trained in implant techniques and selection criteria through this program. He has published numerous articles on prostate cancer in multiple medical journals as well as medical textbook chapters and (along with his partners Grimm and Blasko) *The Prostate Cancer Treatment Book*, a book on prostate cancer for the general public. He regularly lectures at national and international cancer conferences. He is a member of the American Brachytherapy Society, American Society of Therapeutic Radiation Oncology, American Medical Society and The American College of Radiology. He received his medical degree and specialty training as a radiation oncologist at UCLA.

Permanent radioactive seed implantation (I^{125} and Pd^{103} brachytherapy) is, in general, appropriate in most patients (who do not have severe obstructive urinary symptoms) with clinical stage T1c–T2c and Gleason grade 2–10 prostate cancer who have prostates that are not too large.⁹

At the Seattle Prostate Institute a patient will typically undergo an ultrasound volume study (precise measurement of the gland) and consultation with the physician, on day one. If deemed an appropriate candidate for brachytherapy, an implant date will be selected, a few days or weeks later. The radiation oncologist will approve the computerized pre-planned implant plan, which outlines the number and strength and type of radioactive seed to be used and the 3-dimensional (3-D) coordinates that the seeds are to be placed into. The entire prostate and a 5mm margin around the prostate receives 100% of the prescription dose (14,500cGy for I^{125} implants or 12,500cGy for Pd^{103} implants). The procedure is performed in an out-patient ambulatory surgical center in the hospital or physician's office under spinal or general anesthesia. The seeds are preloaded into 18 gauge needles by technical staff then inserted by the radiation oncologist and urologist into the prostate via the perineum under template grid and transrectal ultrasound guidance. Once the needle (containing 2–7 seeds) is in the correct x,y coordinate as visualized and agreed upon by both the radiation oncologist and urologist (working in a team approach), the depth (z axis) of the needle is verified again under direct visualization. The needle is then withdrawn over a central stylet leaving the strand of seeds behind in the prostate in the planned locations. This continues until all the seeds are distributed into the planned coordinates. The procedure typically takes 20 to 40 minutes and the patient is discharged a couple of hours later, without a catheter. The patient will typically return to work a few days later and undergo a post-implant CT scan to verify adequate coverage of the prostate. If a cold spot (an area without enough seeds) is seen, the patient can be scheduled to have more seeds placed into that area a few weeks later. With the technical advancements that have occurred, this is rarely needed.

Results

Patients are usually divided into risk groups based on their pre-treatment prostate-specific antigen (PSA), Gleason score and digital rectal examination (DRE) stage. Confusion can occur because there are different risk group classification systems. The D'Amico risk grouping system (DRG) classifies a patient as low risk if the PSA is less than 10.0ng/ml, Gleason score is two to six, and the DRE is cT1c–T2a. There is intermediate risk if the PSA is more than 10 but less than 20ng/ml, and/or a Gleason score of seven, and/or DRE stage is T2b. There is a high risk if the PSA is more than 20ng/ml and/or the Gleason score is eight to 10, and/or the stage is T2c.¹⁰ The Memorial Sloan Kettering Cancer Center risk grouping system (MRG 0) is somewhat different. In general, the system will have patients with a worse prognosis (and therefore worse disease control rates) in the intermediate and high-risk groups than the D'Amico system. The five-, 10- and 15-year disease control rates with I^{125} or Pd^{103} brachytherapy, with or without five weeks of moderate dose external beam irradiation therapy (EBRT) added, are at least as good as those at respected surgical and EBRT centers. While the five-year disease free survival results noted with 3-D high-dose conformal EBRT look good, the data does not hold up as well at 10 years. The EBRT failures may be due to the lower dose delivered with EBRT compared with brachytherapy – 7,560–8,100cGy with EBRT compared with 14,500cGy for I^{125} implants and 12,500cGy for Pd^{103} implants.

With earlier disease detection, due to patient and physician awareness and PSA and DRE screening, disease control rates continue to climb for all treatment modalities. While urologists have published results of laproscopic and robotic assisted prostatectomy, these newer surgical techniques still require that the prostate be removed and have not been shown to improve on disease control rates or to significantly and consistently reduce the rate of impotency and incontinence that exists with the modern open retropubic nerve-sparing prostatectomy.

Improvements in computer and radiologic imaging technology and understanding of radiation biology are

occurring at an increasingly rapid pace. Some of these advances are fundamental and paradigm shifting. These advances allow radiation oncologists using intensity modulated radiation therapy (IMRT) and brachytherapy to deliver higher doses more accurately, with less toxicity than was possible even a few years ago.

Toxicity of Brachytherapy

Immediately following implantation the patient will experience dysuria – this usually resolves within 24–36 hours. As the prostate swells in reaction to the radiation and trauma of needle insertion the patient will experience obstructive urinary symptoms.^{21,22} Alpha-blocker medications help to relieve these symptoms and are usually used for two to six months following the implant. Mild bruising and discomfort of the perineum lasts for two to three weeks, and fatigue for a few days. Bowel symptoms don't occur in most patients, but when they do they tend to be mild

The Radiation Therapy Oncology Group (RTOG) performed a prospective health-related quality of life study (HRQOL) on 98 patients treated with I¹²⁵ brachytherapy in 24 institutions across the US.²⁶ These patients also self-administered the standardized questionnaires, which included general, urinary and sexual functioning domains pre-treatment and every three months after treatment. The findings confirmed the previously mentioned reports. Urinary incontinence at one year was less than 1% and impotency (in those 'potent' prior to treatment) occurred in 16% of patients. Short-term increases in obstructive urinary symptoms were typical and patients were back to pre-treatment urinary functioning levels at one year post-treatment.

The most recent HRQOL report comes from Talcott and colleagues from Harvard University.²⁷ They tracked the pre- and post-treatment urinary, sexual and bowel functioning in patients treated at Mass General Hospital,

These advances allow radiation oncologists using intensity modulated radiation therapy (IMRT) and brachytherapy to deliver higher doses more accurately, with less toxicity than was possible even a few years ago.

and temporary. Fistula formation has been reported, but is very rare. Patients return to work within a few days, but are instructed to avoid strenuous physical exertion for a couple of weeks.

Late or permanent side effects are much less common. Most reports note a 1% risk of incontinence, and a 10% to 50% risk of impotency (strongly related to the patient's age, pre-treatment erection ability, smoking history and other health issues, such as diabetes). Davis and colleagues looked at the toxicity of EBRT, surgery and brachytherapy at a single institution.²⁴ The strengths of this study included that the patients documented the answers to the questionnaires themselves – this has been shown to be a more accurate indicator of toxicity results than physician documented data.²⁵ They used five different previously verified standard questionnaires. Moreover, they checked on the patients two-and-a-half-year status post-treatment, to gain a more accurate picture of permanent (rather than temporary) side effects. They found that brachytherapy resulted in superior urinary and sexual functioning than surgery (despite the fact that the surgical patients were younger and healthier pre-treatment). They also noted that bowel functioning and fear of recurrence was worst in the EBRT patients.

Dana Farber and the Joint Centers of Radiation Therapy in the northeast. They also noted that surgery resulted in a significantly higher rate of incontinence and impotency than brachytherapy, again despite the fact that the brachytherapy patients were older. Surgery improved pre-existing obstructive urinary symptoms in patients with these symptoms pre-treatment.

An increasing amount of data is linking side effects of treatment to quality of implant and post-implant dosimetry. As previously noted, following treatment, patients undergo a CT scan that documents the position of each radioactive seed and the structure it is in and near to. Several studies demonstrate a direct relationship to post-operative dosimetry findings and the risk of developing side effects. The risk of radiation proctitis (rectal bleeding) is low and is related to the volume of rectum receiving high doses of radiation.²⁸ Proctitis rates might be lowered even further by using IMRT techniques in patients treated with combined EBRT and brachytherapy, and by using sagittal imaging to verify the posterior row needles containing the I¹²⁵ or Pd¹⁰³ radioactive seeds are within the prostate (anterior to the rectum). By avoiding high doses to the penile bulb we may further reduce the risk of impotency following brachytherapy.²⁹ Impotency drugs

such as sildenafil seem to be particularly effective at treating radiation-induced impotency.³⁰

Conclusion

Population demographics resulting in a growing number of men being diagnosed with prostate cancer combined with a greater than ever awareness among medical personnel and the lay public alike about the effectiveness and relatively low toxicity of prostate brachytherapy continues to boost the number of brachytherapy

treatments performed each year. The long-term disease-free survival results from the Seattle Prostate Institute and other centers prove (as much as is possible without a randomized trial) that brachytherapy is at least as effective as radical prostatectomy in eradicating disease. The additional advantages of brachytherapy include the one-day out-patient treatment, a short convalescence and a significantly lower risk of impotency and incontinence. Advances in technology drive the radiation oncology field and should continue to improve disease control and toxicity profiles. ■

References

1. Aronowitz J N, "Dawn of prostate brachytherapy 1915–1930", *Int. J. Radiat. Oncol. Biol. Phys.* (2003);54: pp. 712–718.
2. Whitmore W F Jr, Hilaris B, Grabstald H, "Retropubic implantation to iodine 125 in the treatment of prostatic cancer", *J. Urol.* (1972);108: pp. 918–920.
3. Fuks Z, Leibel S A, Wallner K E et al., "The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation", *Int. J. Radiat. Oncol. Biol. Phys.* (1991);21: pp. 537–547.
4. Holm H H, Juul N, Pedersen J F, Hansen H, Stroyer I, "Transperineal 125-iodine seed implantation in prostatic cancer guided by transrectal ultrasonography", *J. Urol.* (1983);130: pp. 283–286.
5. Blasko J C, Radge H, Schumacher D, "Transperineal Percutaneous Iodine-125 Implantation For Prostatic Carcinoma Using Transrectal Ultrasound and Template Guidance", *Endocuriether. Hypertherm. Oncol.* (1987);3: pp. 131–139.
6. Sylvester J, Blasko J C, Grimm P, Ragde H, "Interstitial implantation techniques in prostate cancer", *J. Surg. Oncol.* (1997);66: pp. 65–75.
7. Grimm P D, Luce R A, Stern E M et al., "The effect of income on prostate cancer patient's satisfaction, awareness and discussion levels of treatment options", *Int. J. Radiat. Oncol. Biol. Phys.* (2004);60: S566–567, abstract.
8. "Prostate Cancer Brachytherapy: Clinical and Financial Imperatives for Permanent Implantation", in the *Oncology Roundtable Annual Meeting, Washington DC, The Advisory Board Co.* (2000); p. 15.
9. Sylvester J E, Blasko J, Grimm P, "Brachytherapy as Monotherapy", in *Prostate Cancer: Principles and Practice*, Kantoff P, Carroll P C, D'Amico A V, (eds), Philadelphia, Lippincot Williams & Wilkins (2001); pp. 336–357.
10. D'Amico A V, Whittington R, Malkowicz S B et al., "Clinical utility of the percentage of positive prostate biopsies in defining biochemical outcome after radical prostatectomy for patients with clinically localized prostate cancer", *J. Clin. Oncol.* (2000); 18: pp. 1,164–1,172.
11. Carroll P R, "Radical Prostatectomy at the University of California at San Francisco-Rationale, Technique and Outcomes", presented at the *Swedish Hospital Prostate Cancer Conference, Seattle WA (April 2004)*.
12. Zelefsky M J, Fuks Z, Hunt M et al., "High dose radiation delivered by intensity modulated conformal radiotherapy improves the outcome of localized prostate cancer", *J. Urol.* (2001);166: pp. 876–881.
13. Blasko J C, Grimm P D, Sylvester J E, Badiozamani K R, Hoak D, Cavanaugh W, "Palladium-103 brachytherapy for prostate carcinoma", *Int. J. Radiat. Oncol. Biol. Phys.* (2000);46: pp. 839–850.
14. Zelefsky M, Fuks Z, Chan H, "Ten-year results of dose escalation with 3-dimensional conformal radiotherapy for patients with clinically localized prostate cancer", *Int. J. Radiat. Oncol. Biol. Phys.* 57(2);150, abstract.
15. Grimm P, Blasko J, Sylvester J E, Meier R M, Cavanagh W, "10-year biochemical (prostate-specific antigen 0 control of prostate cancer with 125-I brachytherapy", *Int. J. Radiat. Oncol. Biol. Phys.* (2001);51: pp. 31–40.
16. Sylvester J E, Blasko J C, Grimm P D et al., "15-year follow-up of the first cohort of localized prostate cancer patients treated with brachytherapy", abstract, *J. Clin. Oncol.* (June 2004), presented ASCO (2004).
17. McMullen, deGuzman, McCullough, Lee, "Cancer control after low-dose-rate prostate brachytherapy performed by a multidisciplinary team with no prior prostate brachytherapy experience", *Urol.* (June 2004);63(6): pp. 1,128–1,131.
18. Beyer D C, Priestley J B Jr, "Biochemical disease-free survival following 125-I prostate implantation", *Int. J. Radiat. Oncol. Biol. Phys.* (1997);37: pp. 559–563.
19. Merrick G S, Butler W M, Galbreath R W, Lief J H, "Five-year biochemical outcome following permanent interstitial brachytherapy for clinical T1-T3 prostate cancer", *Int. J. Radiat. Oncol. Biol. Phys.* (2001);51: pp. 41–48.
20. Sylvester J E, Blasko J C, Grimm P G, Millar J, Meier R, Ore P, Heaney C, Malmgren J, "10 year biochemical relapse free survival functions following brachytherapy with external beam radiotherapy for patients with localized prostate cancer: the Seattle experience", *Int. J. Radiat. Oncol. Biol. Phys.* (November 2004).
21. Grier D, "Complications of permanent seed implantation", *J. Brachytherapy Int.* (2001);17: pp. 205–210.

22. Henderson A, Ismail A K, Cunningham M et al., "Toxicity and early biochemical outcomes from 125-Iodine prostate brachytherapy in the UK. A prospective study", *Clin. Oncol. (R. Coll. Radiol.)* (April 2004);16(2): pp. 95–104.
 23. Vicini F, "Structured literature review of morbidity following prostate brachytherapy", presented at the Annual American Brachytherapy Society Conference (May 2001).
 24. Davis, Kuban, Lynch, Schellhammer, "Quality of life after treatment for localized prostate cancer: differences based on treatment modality", *J. Urol.* (2001);166: pp. 947–952.
 25. Talcott J A, Rieker P, Clark J A et al., "Patient-reported symptoms after primary therapy for early prostate cancer: results of a prospective cohort study", *J. Clin. Oncol.* (1998);16: pp. 275–283.
 26. Lee W R, Hall M C, McQuellon R P et al., "A prospective quality-of-life study in men with clinically localized prostate carcinoma treated with radical prostatectomy, external beam radiotherapy, or interstitial brachytherapy", *Int. J. Radiat. Oncol. Biol. Phys.* (2001);51: pp. 614–623.
 27. Talcott J A, Manola J, Clark J A et al., "Time course and predictors of symptoms after primary prostate cancer therapy", *J. Clin. Oncol.* (2003);21: pp. 3,979–3,986.
 28. Snyder K M, Stock R G, Hong S M et al., "Defining the risk of developing proctitis following 125I prostate brachytherapy using a rectal dose-volume histogram analysis", *Int. J. Radiat. Oncol. Biol. Phys.* (2001);50: pp. 335–341.
 29. Merrick G S, Wallner K, Butler W M et al., "A Comparison of radiation dose to the bulb of the penis in men with and without prostate brachytherapy induced erectile dysfunction", *Int. J. Radiat. Oncol. Biol. Phys.* (2001);50: pp. 597–604.
 30. Merrick G S, Butler W M, Leif J H et al., "Efficacy of sildenafil citrate in prostate brachytherapy patients with erectile dysfunction", *Urol.* (1999);53: pp. 1,112–1,116.
-