ELSEVIER

BRACHYTHERAPY

JOHN C. BLASKO

Brachytherapy is a radiotherapeutic strategy in which radioisotopes are inserted directly into a cancer-bearing organ so that high doses of radiation are delivered to the malignancy with relative sparing of surrounding normal tissue. Although this approach has been a standard of care in gynecologic malignancies for decades, its accepted use in prostate carcinoma is recent. Similar to gynecologic cancer, prostate cancer is anatomically well suited for the characteristics of a brachytherapy approach. The prostate gland is accessible by a transperineal route, it is in close physical approximation to sensitive normal structures (rectum and bladder), and prostate cancer is often localized and slow to metastasize. These theoretical concepts have been recognized since 1911, when the first prostate brachytherapy procedure was attempted.[1] These historical efforts met with limited success and even less acceptance because the technology of the time did not enable accurate placement of radioisotopes. In the 1980s, the development of transrectal ultrasound, computed tomography, and advances in computer-based treatment planning permitted the accurate and reproducible placement of radioisotopes, which could be optimized to conform to the exact contours of the prostate.[2,3] The use of real-time transrectal ultrasound and a closed, perineal approach meant that the procedure could be performed on an outpatient basis as a single-setting, cost-effective treatment, with little inconvenience for the patient. It is these appealing advantages of brachytherapy, as well as the encouraging results reported, that have fueled the current surge in interest for this modality. Today, physicians can confidently offer this modality to appropriate patients with the promise of convenience, effectiveness, and excellent quality of life. However, there have been parallel advances in radical prostatectomy, external beam radiotherapy, and other novel treatment approaches to prostate cancer in the past decade. Faced with this myriad of effective treatment choices, why choose brachytherapy?

RESULTS

In this PSA era, outcomes of prostate treatment in general, and of brachytherapy in particular, are usually reported in terms of biochemical success. The prostate-specific antigen (PSA)-based results of four published series, stratified by initial PSA level are presented in Table I.[4–7] Although these are all retrospective, single-institution experiences, and the treatment approaches and end point definitions vary, the outcomes to 7 years for favorable patients presenting with an initial PSA less than 10 ng/mL have been uniformly excellent. For patients with a higher initial PSA, the variability in outcome is greater. Whether this is due to patient selection factors other than PSA level or to differences in implant technique is unknown. Ragde *et al.*[8] reported an average PSA level after brachytherapy of 0.18 ng/mL in 147 patients, with a median follow-up of 119 months. Sixty-six percent maintained an "immeasurable" level of less than 0.5 ng/mL at 10 years.

Figure 1 represents the overall Seattle brachytherapy experience in 634 consecutively treated patients using the widely accepted American Society for Therapeutic Radiology and Oncology (ASTRO) Consensus Conference[9] definition of PSA progression as the end point.[10] The patients in this series had clinical Stage T1-T2 tumors, with a risk profile similar to that of other modern series treated with either radical prostatectomy or conformal external beam radiotherapy. In this patient cohort, 20% had a Gleason score of 7 or greater, and the median PSA was 11.0 ng/mL. The biochemical outcomes of these patients after being stratified into risk groups by Gleason score, initial PSA, and clinical stage according to the method of Zelefsky *et al.*[11] are shown in Figure 2. These results appear to be equivalent to modern dose-escalated conformal external beam irradiation and radical prostatectomy. Accepting the drawbacks of single-institution, retrospective experience, brachytherapy

J. C. Blasko is a consultant to several sponsors involved with this technology.

From the Seattle Prostate Institute, Seattle, Washington

Reprint requests: John C. Blasko, M.D., Seattle Prostate Institute, 1101 Madison Street, Suite 1101, Seattle, WA 98104

Submitted: July 28, 1999, accepted (with revisions): October 5, 1999

UROLOGY 55: 306–308, 2000 • 0090-4295/00/$20.00
PII S0090-4295(99)00472-0

TABLE I. ***Biochemical disease-free rates after brachytherapy***

Series	n	Median Follow-up (mo)	PSA at Diagnosis* (ng/mL) 0–4	4–10	10–20	20+
Dattoli *et al.*[4]	102	38	82		85	70
Grado *et al.*[5]	490	47	88		72	57
Ragde *et al.*[6]	320	56	95	87	77	65
Wallner *et al.*[7]	92	36	100	80	45	39

KEY: PSA = prostate-specific antigen.
** Percentage of patients disease free at last follow-up for the respective series.*

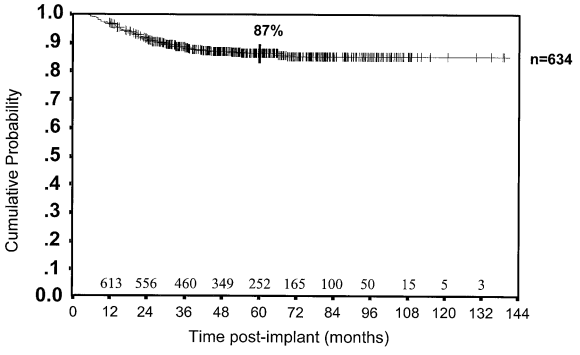

FIGURE 1. *PSA progression-free survival for 634 patients with clinically localized carcinoma of the prostate treated with implant (iodine 125 or palladium 103) with or without external beam radiotherapy.*

has demonstrated excellent results when performed at centers of excellence.

MORBIDITY

To date, brachytherapy morbidity and complications have been reported as physician-observed events.[12–15] In the acute postimplant period, it is self-evident that patients experience significant irritative lower urinary tract symptoms, and short-term retention may occur in 5% to 10%.[12–14] However, these side effects are self-limited and correspond to the radioactive life of the isotope used. Late complications, either urinary or rectal, have been reported as infrequent in most series. The rate of incontinence has been reported at 1%, provided that transurethral resection of the prostate or other surgical intervention has not been performed.[13,14,16,17] Radiation Therapy Oncology Group (RTOG) grade 3 rectal complications occurred in 1% to 3% of patients when implants were used as monotherapy and in 6% to 9% if brachytherapy was used in conjunction with external beam irradiation.[13–16] Potency maintenance has been reported as 75% to 90% in the first few years after an implant, but few data exist regarding long-term potency maintenance.[13–15,17] Brachytherapy

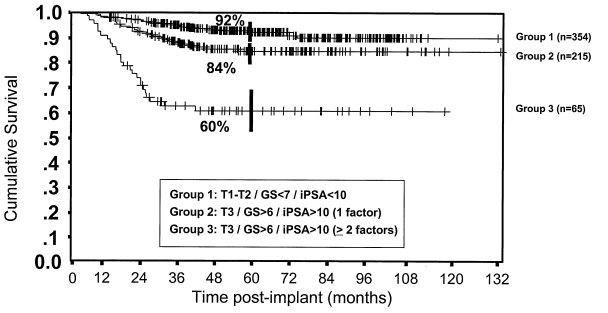

FIGURE 2. *PSA progression-free survival by risk group.*

has yet to be exposed to the rigors of prospective, patient-oriented, quality-of-life studies. These studies are underway and will be important to define the eventual place of brachytherapy in the therapeutic armamentarium. Arterbery *et al.*[18] has published a small quality-of-life study of 51 patients treated with brachytherapy and reported that none had incontinence, 3% had rectal bleeding, 93% resumed work, and 98% would choose brachytherapy again as a treatment option. Although short-term side effects can be significant with brachytherapy, the apparent lack of long-term morbidity and high patient acceptance are additional factors that account for the appeal of this modality.

COMMENT

The benefits of prostate brachytherapy are clear. Excellent clinical results in a substantial number of patients at 4 to 10 years after treatment have been reported from several institutions. The single-setting, outpatient basis with a rapid return to normal activities inherent when using brachytherapy as a stand-alone treatment is appealing for patients and attractive from a cost standpoint. Because brachytherapy is performed jointly between urology and radiation oncology, it provides a forum for multidiscipline collaboration between specialties. Given these advantages, it is not surprising that the number of patients treated with brachytherapy has increased dramatically in the past few years.

Early reports of ultrasound-guided brachytherapy were limited to low-risk, favorable patient cohorts. Hence, brachytherapists today confidently offer brachytherapy as monotherapy for low-risk patients (usually defined as those with Stage T1-T2, Gleason score less than 7, and PSA less than 10 ng/mL).[19] It is with this use of brachytherapy that the strongest advantages of patient convenience and cost-effectiveness exist. A second use of brachytherapy is in combination with external beam irradiation. The rationale for this approach

postulates that patients with higher risk disease are more likely to have extracapsular extension that can be beyond the reach of the confined doses of an implant. The addition of external beam theoretically addresses this possibility. In this scenario, brachytherapy provides a substantial boost to the intraprostatic portions of the tumor and external beam treats the periprostatic tissues. When this combination therapy is performed, brachytherapy loses some of the advantages of convenience and cost effectiveness, and morbidity may be higher. However, if dose matters for the higher risk patient, there is no more effective method of dose escalation than brachytherapy. Evidence is mounting that higher risk patients benefit from higher doses of radiation.[20] If you are serious about dose escalation, why not use brachytherapy?

Brachytherapy, like all other treatment modalities, continues to evolve. In its present form, prostate brachytherapy is technically difficult and requires a substantial learning curve to master. Whether community-based practices can reproduce the results demonstrated from centers of excellence is unknown but is under investigation by the American College of Radiology Patterns of Care Study. Further technical innovations are being developed that will make the procedure easier in the future. Unanswered questions remain about this modality in terms of patient selection, the value of combining brachytherapy with external beam irradiation, the use of neoadjuvant/adjuvant androgen deprivation, and morbidity issues. Prospective trials incorporating brachytherapy have begun at several institutions and within cooperative groups but will require several years to mature. Nevertheless, the strength of the evidence that has accumulated to date validates brachytherapy alone as an appealing option for patients with early-stage prostate cancer. For patients with more advanced disease, brachytherapy may be important as an effective method of dose escalation.

REFERENCES

1. Pasteau O, and Degrais P: The radium treatment of cancer of the prostate. Rev Malad Nutr 363–367, 1911.

2. Holm HH, Juul N, Pedersen JF, *et al:* Transperineal 125-iodine seed implantation in prostatic cancer guided by transrectal ultrasonography. J Urol **130:** 283–286, 1983.

3. Grimm PD, Blasko JC, and Ragde H: Ultrasound-guided transperineal implantation of iodine-125 and palladium-103 for the treatment of early-stage prostate cancer: technical concepts in planning, operative technique, and evaluation, in Schellhammer PF (Ed): *New Techniques in Prostate Surgery*. Philadelphia, WB Saunders, 1994, pp 113–126.

4. Dattoli M, Wallner K, Sorace R, *et al:* Pd-103 brachytherapy and external beam irradiation for clinically localized, high-risk prostatic carcinoma. Int J Radiat Oncol Biol Phys **35:** 875–879, 1996.

5. Grado GL, Larson TR, Balch CS, *et al:* Actuarial disease-free survival after prostate cancer brachytherapy using interactive techniques with biplane ultrasound and fluoroscopic guidance. Int J Radiat Oncol Biol Phys **42:** 289–298, 1998.

6. Ragde H, Blasko J, Grimm P, *et al:* Brachytherapy for clinically localized prostate cancer: results at 7 and 8-year follow-up. Semin Surg Oncol **13:** 438–443, 1997.

7. Wallner K, Roy J, and Harrison L: Tumor control and morbidity following transperineal iodine 125 implantation for stage T1/T2 prostatic carcinoma. J Clin Oncol **14:** 449–453, 1996.

8. Ragde H, Elgamal A, Snow P, *et al:* Ten-year disease free survival after transperineal sonography-guided iodine-125 brachytherapy with or without 45-gray external beam irradiation in the treatment of patients with clinically localized, low to high Gleason grade prostate carcinoma. Cancer **83:** 989–1001, 1998.

9. Cox J, Grignon D, Kaplan R, *et al:* Consensus statement: guidelines for PSA following radiation therapy. Int J Radiat Oncol Biol Phys **37:** 1035–1041, 1997.

10. Blasko JC, Grimm PD, Sylvester JE, *et al:* The role of external beam radiotherapy with I-125/Pd-103 brachytherapy. Radiother Oncol (in press).

11. Zelefsky MJ, Leibel SA, Gaudin PB, *et al:* Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys **41:** 491–500, 1998.

12. Beyer DC, and Priestley JB Jr: Biochemical disease-free survival following ^{125}I prostate implantation. Int J Radiat Oncol Biol Phys **37:** 559–563, 1997.

13. Blasko JC, Ragde H, and Grimm PD: Transperineal ultrasound-guided implantation of the prostate: morbidity and complications. Scand J Urol Nephrol Suppl **137:** 113–118, 1991.

14. Kaye KW, Olson DJ, and Payne JT: Detailed preliminary analysis of 125 iodine implantation for localized prostate cancer using percutaneous approach. J Urol **153:** 1020–1025, 1995.

15. Stock RG, Stone NN, and Iannuzi C: Sexual potency following interactive ultrasound-guided brachytherapy for prostate cancer. Int J Radiat Oncol Biol Phys **35:** 267–272, 1996.

16. Beyer DC, and Priestley JB: Biochemical and disease-free survival following I-125 prostate implantation. Int J Radiat Oncol Biol Phys **37:** 559–563, 1997.

17. Wallner K, Roy J, Zelefsky M, *et al:* Short-term freedom from disease progression after I-125 prostate implantation. Int J Radiat Oncol Biol Phys **30:** 405–409, 1994.

18. Arterbery VE, Frazier A, Dalmia P, *et al:* Quality of life after permanent prostate implant. Semin Surg Oncol **13:** 461–464, 1997.

19. Blasko JC, Ragde H, Luse RW, *et al:* Should brachytherapy be considered a therapeutic option in localized prostate cancer? Urol Clin North Am **23:** 633–649, 1996.

20. Hanks GE, Hanlon AL, Schultheiss TE, *et al:* Dose escalation with 3D conformal treatment: five year outcomes, treatment optimization, and future directions. Int J Radiat Oncol Biol Phys **41:** 501–510, 1998.