

INTERMEDIATE TERM BIOCHEMICAL-FREE PROGRESSION AND LOCAL CONTROL FOLLOWING ¹²⁵IODINE BRACHYTHERAPY FOR PROSTATE CANCER

NELSON N. STONE,^{*,†} RICHARD G. STOCK AND PAM UNGER

From the Departments of Urology (NNS), Radiation Oncology (RGS) and Pathology (PU), Mount Sinai School of Medicine, New York, New York

ABSTRACT

Purpose: We determined the 10-year biochemical and local control results for ¹²⁵I prostate brachytherapy in men followed a minimum of 4 years.

Materials and Methods: A total of 279 men with T1–T2 prostate cancer with a minimum followup of 4 years were implanted with ¹²⁵I from 1990 to 1998 using the real-time technique. Patients were treated with the implant alone (215 or 72.5%) or with the implant and 6 months of hormone therapy (64 or 27.6%). Of the men 185 (66.3%) agreed to ultrasound guided biopsy (6 to 12 cores) a minimum of 2 years after implantation. All patients with increasing prostate specific antigen (PSA), evidence of local recurrence or a prior positive biopsy underwent repeat biopsy yearly until biopsy became negative or there was clear evidence of biochemical (PSA) progression. The radiation dose delivered to 90% of the gland (D₉₀) was determined 30 days after implantation by computerized tomography based dosimetry. Biochemical failure was defined as 3 consecutive PSA increases. Survival curves were calculated by the Kaplan-Meier method. Cross tabulations were tested by Pearson chi-square analysis. The effect of multiple variables was tested by the log rank test (Cox regression).

Results: Median patient age was 67 years (range 42 to 82) and median followup was 6 years (range 4 to 12). Of the patients 49 (17.6%) experienced failure, for a 10-year freedom from failure (FFF) rate of 78%. Univariate analysis for 10-year FFF demonstrated that initial PSA (p = 0.001), stage (p = 0.002), risk group (p <0.001), hormone therapy (p = 0.013) and D₉₀ (p <0.001) were significant. Multivariate analysis demonstrated that D₉₀ (p <0.001) and risk group (p = 0.013) were the only significant variables. The RR of PSA failure was 3.0 (95% CI 2.0 to 4.4, p <0.001) and 5.6 (95% CI 3.1 to 10, p <0.001) for doses below 140 and 120 Gy, respectively. Of the 185 patients 166 (90%) had a negative post-implantation prostate biopsy. FFF was 85% vs 21% in those with a positive biopsy (p <0.001). Patients with a D₉₀ of at least 140 Gy had a positive biopsy rate of 4.8% compared to 20.5% in those with a lower dose (p <0.001). The RR for positive biopsy at doses less than 140 and 120 Gy was 2.6 (95% CI 1.6 to 4.4, p = 0.002) and 4.3 (95% CI 2.3 to 8.1, p <0.001), respectively.

Conclusions: These data demonstrate high biochemical and local control in men with T1–T2 prostate cancer treated with ¹²⁵I brachytherapy. The delivered radiation dose and risk category are important predictors of success. Patients receiving a dose of at least 140 Gy have a 90% chance of biochemical FFF and a 95.2% likelihood of local control.

KEY WORDS: prostate, prostatic neoplasms, brachytherapy, iodine, risk

The optimal treatment modality for localized prostate cancer is controversial. Radical prostatectomy, external beam radiation therapy and brachytherapy are viable options. The lack of randomized, prospective data has led physicians to rely on single institution, retrospective data to influence their recommendations. Skepticism about brachytherapy has mostly stemmed from the lack of long-term data to support the initial promising outcomes. This has been due to the fact that modern transperineal ultrasound guided prostate seed implantation began in the late 1980s and early 1990s. In addition, brachytherapy series have lacked the corresponding pathological information that is usually found in radical prostatectomy reports. This information is vital for shedding

light on the nature of biochemical failure and its relationship with local control. Although long-term data from the Seattle group have begun to emerge, there are few other sources available for examining the biochemical response after 5 years.^{1–3} In addition, to our knowledge there are no data available for comparing long-term biochemical outcomes following brachytherapy with systematic posttreatment biopsy results.

We retrospectively reviewed the records of patients treated with ¹²⁵I brachytherapy without the addition of external beam irradiation who were followed a minimum of 4 years to assess intermediate term biochemical control rates and determine posttreatment biopsy outcomes. In addition, factors affecting these results as well as the correlation of biopsy with prostate specific antigen (PSA) control were analyzed to shed light on the intricate relationship between local control and prostate cancer eradication.

MATERIALS AND METHODS

Patient demographics and evaluation. From June 28, 1990 to August 1, 1998, 637 men with T1–T3 prostate cancer

Submitted for publication June 8, 2004.

Presented at annual meeting of American Urological Association, Chicago, Illinois, April 26–May 1, 2003.

* Correspondence: 21 Timber Trail, Suffern, New York 10901 (telephone: 845-354-7565; FAX: 845-362-8561; e-mail: nelsonstone@optonline.net).

† Financial interest and/or other relationship with Praecis Pharmaceutical, Pfizer and Aventis.

underwent seed implantation with ¹²⁵I or ¹⁰³Pd without external beam irradiation. Of these men 279 with T1–T2 prostate cancer received ¹²⁵I brachytherapy with a minimum of 4 years of followup (median 6, range 4 to 12). All patients underwent routine evaluation, including bone scan and computerized tomography (CT) in most of them. Clinical staging was determined using 1992 American Joint Committee on Cancer recommendations. Those who presented with PSA greater than 10 ng/ml, Gleason score greater than 6, or stage T2b or greater underwent seminal vesicle biopsies (6 cores) and were excluded if results were positive.

Patients were treated with the implant alone (240 or 78.4%) or with the addition of 5 to 6 months of hormone therapy with a luteinizing hormone-releasing hormone analogue plus antiandrogen. Hormone therapy was given in 66 cases because of a prostate volume of greater than 50 cc (20) or because of initial PSA greater than 10 ng/ml, Gleason score 7 or greater, or stage greater than T2a (46 at high risk). It was administered 3 months prior to implantation and for 2 to 3 months after implantation.

Implantation technique. From the outset patients were treated with an implant technique developed at Mount Sinai Medical Center in 1990. The real-time method relied on intraoperative planning with axial imaging to place the needles and sagittal imaging to insert the seeds. This technique, which has been previously described, was developed because of concern about performing preplanned implantation in an organ that was subject to displacement and distortion by needle placement.⁴ The initial implants relied on uniform seed spacing and used the seed activity nomogram developed at Memorial Sloan-Kettering Cancer Center for the retropubic implant program.⁵ Based on post-implantation dosimetric analysis these 2 assumptions proved to be incorrect, resulting in a redistribution of sources to the periphery in a 75/25 arrangement and by increasing the amount of activity by 35% in a 4-year period.⁵ These changes, coupled with the introduction of linear ray, biplanar ultrasound technology, resulted in a steady increase in delivered doses.⁶

Post-implantation radiation doses were determined by CT at 1 month. Abutting 3 mm CT images were taken from the bladder base to just below the apex. An in-house 3-dimensional software program (1990 to 1996) or Pinnacle software (ADAC Laboratories, Milpitas, California) (1996 to 1998) was used to calculate a dose volume histogram for the prostate and surrounding normal structures. The implant dose was defined as the dose delivered to 90% of the gland (D₉₀). The D₉₀ value has been shown to be the best indicator of the risk for biochemical relapse.⁷ Dosimetry data were available on 239 patients (85.7%). No patients received supplemental external beam irradiation.

Of the 279 men 185 (66.3%) agreed to post-implantation prostate biopsy. All biopsies were performed without regard to disease status a minimum of 2 years after implantation and they were reviewed by 1 pathologist experienced with evaluating post-irradiation prostate tissue. Biopsies were performed under transrectal ultrasound guidance. A minimum of 6 cores was taken in all cases with up to 12 in cases of increasing PSA when initial biopsy was negative. Patients with an initial positive biopsy were offered yearly repeat biopsy until biopsy reverted to negative or there was clear evidence of biochemical progression. Patients with initial negative biopsy were offered repeat biopsies if biochemical progression was experienced. There were no differences in disease characteristics between the 185 patients who underwent prostate biopsy and those who did not.

Outcomes assessments. The pretreatment variables PSA, Gleason score, clinical stage, risk category (low—PSA 10 ng/ml or less, stage T2a or less and Gleason score 6 or less and high—all others), hormone therapy and patient age as well as the treatment variable D₉₀ were tested for their effect on PSA failure and local control. Biochemical progression

was defined as 3 consecutive PSA increases of at least 0.1 ng/ml above a nadir value.⁸ Statistical analyses were performed with SPSS software (SPSS, Chicago, Illinois). The effect of multiple variables was tested by the log rank test (Cox regression). Survival curves were calculated by the Kaplan-Meier method.

RESULTS

Median patient age was 67 years (range 42 to 82) and median PSA was 7 ng/ml. Gleason score was 6 or less in 272 men (97.5%), stage was T2a or less in 198 (71%) and risk was low in 146 (52.3%). Median followup was 6 years (range 4 to 12). Median post-implantation D₉₀ was 164 Gy (range 15 to 256) (table 1).

Biochemical control. Of the patients 49 (17.6%) experienced PSA failure, giving a 10-year freedom from failure (FFF) of 78% (fig. 1). Median PSA in nonfailures was less than 0.1 ng/ml (range 0 to 1.6). Of the patients PSA was 0.2 ng/ml or less in 197 (70.6%), 0.5 ng/ml or less in 245 (87.8%) and 1.0 ng/ml or less in 273 (97.8%). Univariate analysis for 10-year FFF demonstrated that initial PSA (p = 0.001), stage (p = 0.002), risk group (p < 0.001), hormone therapy (p = 0.013) and D₉₀ (p < 0.001) were significant (table 2, fig. 2). Multivariate analysis demonstrated that only D₉₀ (p < 0.0001) and risk group (p = 0.013) were significant (table 3). Mean freedom from progression time in the low dose group was 7.6 years (95% CI 6.5 to 8.7) compared to 9.6 years (95% CI 9.2 to 9.9, p < 0.001) in the higher dose group. The PSA failure RR was 3.0 (95% CI 2.0 to 4.4, p < 0.001) and 5.6 (95% CI 3.1 to 10, p < 0.001) for doses below 140 and 120 Gy, respectively. Subset analysis of low risk cases revealed that only D₉₀ was a significant predictor of PSA failure (p < 0.001). In the 133 patients at high risk hormone therapy (p = 0.017) and dose (p < 0.001) were significant (fig. 3).

Local control. A total of 234 biopsies (1 to 4 per patient) were performed in 185 patients, of whom 166 (90%) had a negative final prostate biopsy. Biopsies were performed once in 156 patients, twice in 18, 3 times in 10 and 4 times in 1. Based on final biopsy results the rate of freedom from biochemical failure was 85% vs 21% in those with negative vs positive biopsy (p < 0.001). Patients with a D₉₀ of at least 140 Gy had a positive biopsy rate of 4.8% compared to 20.5% in those with a lesser dose (p < 0.001, table 4). Patients receiv-

TABLE 1. Pretreatment and dosimetry values in 279 men implanted with ¹²⁵I

Variable	No. Pts (%)
PSA (ng/ml):	
4 or Less	28 (10.1)
Greater than 4–10	174 (62.2)
Greater than 10	77 (27.7)
Gleason:	
2–4	61 (21.9)
5–6	212 (75.9)
7	6 (2.2)
Clinical stage:	
T1c	110 (39.9)
T2a	80 (29)
T2b	64 (25)
T2c	17 (6.2)
Hormone therapy:	
No	215 (77.2)
Yes	64 (22.8)
Risk group:	
Low	146 (52.3)
High	133 (47.7)
D ₉₀ (Gy):	
Less than 100	25 (10.5)
Greater than 100–120	10 (3.7)
Greater than 120–140	25 (10.5)
Greater than 140–160	48 (20.1)
Greater than 160–180	69 (28.8)
Greater than 180	63 (26.4)

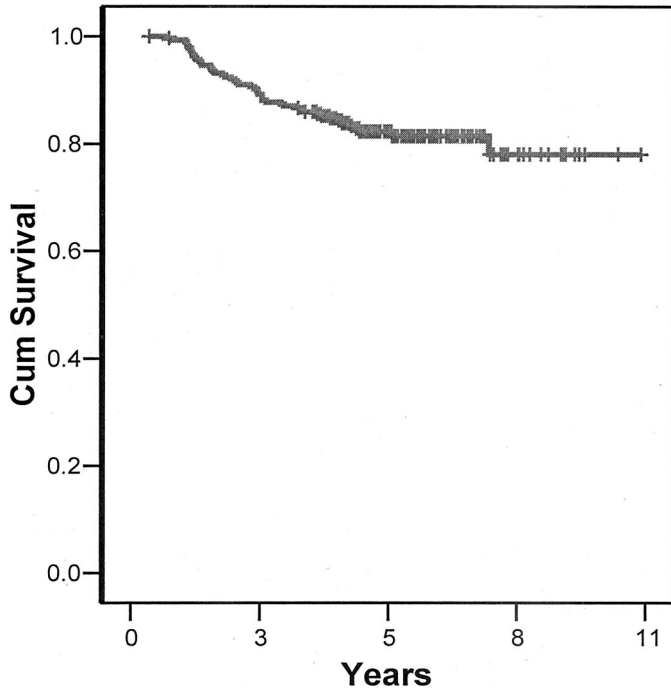


FIG. 1. Biochemical freedom from PSA failure (American Society for Therapeutic Radiation and Oncology [ASTRO]) in 279 men treated with ¹²⁵I prostate brachytherapy. *Cum*, cumulative.

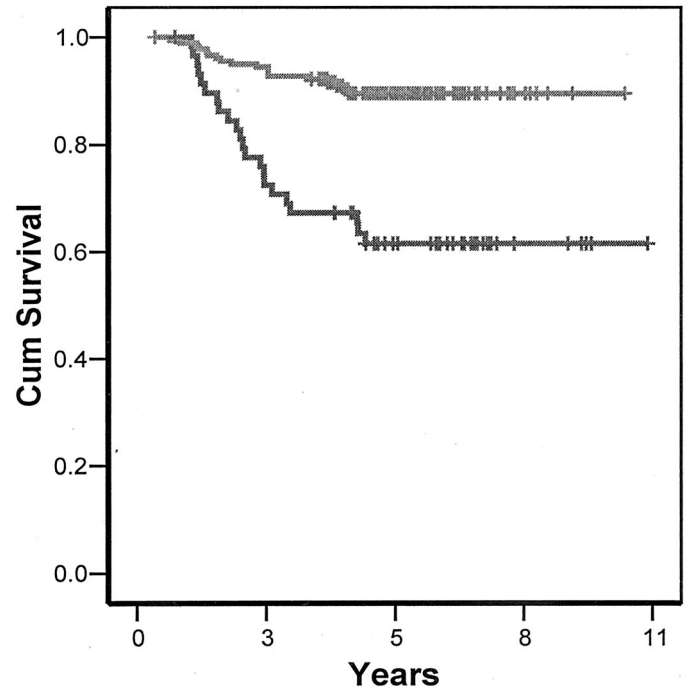


FIG. 2. Biochemical freedom from PSA failure (ASTRO) in 239 men treated with ¹²⁵I prostate brachytherapy by D₉₀ less than 140 Gy, or 140 Gy or greater. Ten-year FFF was 61.5% vs 90% (p < 0.0001). *Cum*, cumulative.

TABLE 2. Univariate analysis of FFF in 279 patients implanted with ¹²⁵I

Variable	No. Pts	% FFF	p Value
PSA (ng/ml):			
10 or Less	201	86.4	
Greater than 10	78	61.5	0.001
Stage:			
T2a or less	198	88	
Greater than T2a	89	61.4	0.0002
Hormone therapy:			
Yes	64	94	
No	215	75	0.013
Risk:			
Low	146	91.3	
High	133	66.1	<0.001
D ₉₀ (Gy):			
Less than 140	59	61.5	
140 or Greater	180	90	<0.001

Low risk group—PSA less than 10 ng/ml, Gleason score less than 7 and stage less than T2b, D₉₀ dose less than 140 Gy vs 140 Gy or greater and hormone therapy was used for 5 to 6 months.

ing a dose less than 120 Gy had a 30% likelihood of a positive biopsy result. The RR for positive biopsy at doses less than 140 and 120 Gy was 2.6 (95% CI 1.6 to 4.4, p = 0.002) and 4.3 (95% CI 2.3 to 8.1, p < 0.001), respectively. Subset analysis in the 85 patients at low risk revealed that only D₉₀ was a significant predictor of local failure (p = 0.05). In the 84 patients at high risk hormone therapy (p = 0.02) and dose (p = 0.006) were significant.

DISCUSSION

As permanent brachytherapy has developed into a viable treatment option for localized prostate cancer, questions about appropriate patient selection, hormone therapy use and the durability of results have arisen. Since most brachytherapy series have short followup, it is difficult to derive meaningful conclusions about these issues. This is especially true in patients at low risk, in whom the long natural history of prostate cancer requires greater followup. Several recent studies in low risk cases treated with radical prostatectomy

or external beam irradiation demonstrated infrequent failures after 7 years and they may represent a more realistic long-term prediction of actual cure.^{9,10}

The Seattle group reported the longest term prostate brachytherapy results performed exclusively with ¹²⁵I monotherapy.^{9,11} Some groups have claimed that these results are inferior to those of radical prostatectomy and they have used this as a rationale for dissuading patients from electing brachytherapy as a treatment.¹² Ragde et al reported that the overall 10-year biochemical freedom from failure rate was 66% in their T1–T2 cases.¹¹ This series included patients from their early experience with this treatment. Grimm et al reported an 87% FFF in patients at low risk treated with ¹²⁵I after 1988 and 67% prior to that date.⁹ While no dosimetry data were available on these patients, one can postulate that the implants performed during the learning curve were of poorer quality than the later implants and it is this difference that accounts for the difference in biochemical control rates.

Our data demonstrate a 10-year biochemical progression-free rate of 78% in the entire cohort of T1–T2 cases. Men who presented with low risk disease had a 91.3% likelihood of being free from failure. These results are comparable to the best reported data on prostatectomy or beam irradiation.^{13,14} Because these data are not prospective or randomized, it is not possible to claim the superiority of 1 treatment over others but, given the long followup in this study (median 6 years), it is reasonable to claim that biochemical outcomes are similar.

Hormone therapy has become more popular with patients receiving radiation therapy. Several randomized, external beam trials showed advantages with the addition of short course androgen deprivation to external beam irradiation.¹⁵ Although to our knowledge there are no randomized studies of patients receiving brachytherapy, hormone therapy has found its way into clinical practice in men receiving implantation. The data in this study failed to demonstrate an advantage of 6 months of androgen deprivation in patients at low risk treated with ¹²⁵I brachytherapy. On the other hand, patients with high risk status (PSA greater than 10 ng/ml,

TABLE 3. Multivariate analysis of presenting and treatment variables

Variable	Significance	Exp (B)	For Exp (B) 95% CI	
			Lower	Upper
Hormone therapy	0.162	2.44	0.699	8.534
Risk group	0.013	0.330	0.137	0.792
PSA	0.140	1.106	0.995	1.037
Gleason score	0.877	0.972	0.683	1.384
Stage	0.099	0.692	0.447	1.072
D ₉₀	<0.0001	1.000	1.000	1.000

Hormone therapy and risk group were categorical variables, while PSA, Gleason score, stage and D₉₀ were continuous variables.

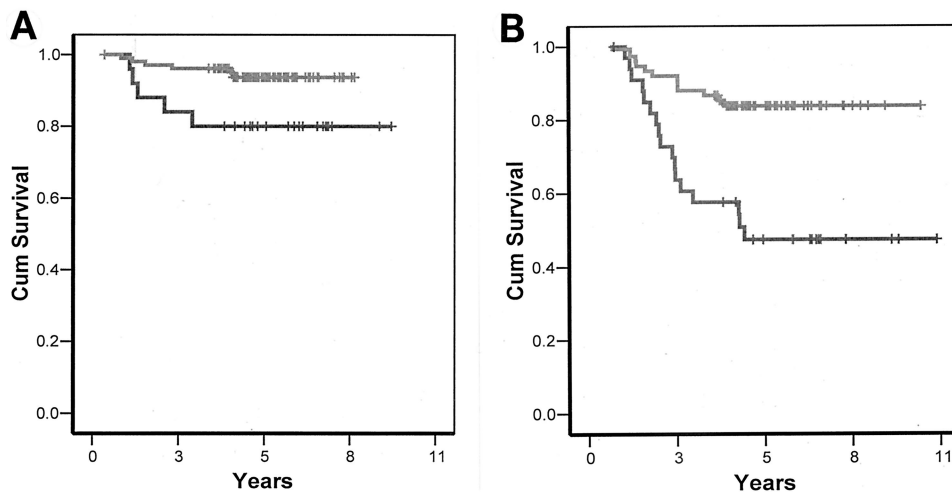


FIG. 3. Biochemical freedom from PSA failure (ASTRO) D₉₀ less than 140 Gy, or 140 Gy or greater. 10-year FFF was 80% vs 94% (p = 0.022). A, in 130 patients at low risk. B, in 109 patients at high risk. 10-year FFF was 47.4% vs 84% (p = 0.0001). Cum, cumulative.

TABLE 4. Univariate analysis in 185 patients implanted with ¹²⁵I who underwent prostate biopsy 2 years after implantation

Variable	No. Pts	% Pos Biopsy	p Value
PSA (ng/ml):			
10 or Less	122	7.6	0.06
Greater than 10	44	17	
Stage:			
T2a or less	109	6	0.014
Greater than T2a	57	17.4	
Hormone therapy:			
Yes	42	2.4	0.06
No	143	12.6	
Risk:			
Low	89	4.5	0.013
High	96	15.6	
D ₉₀ (Gy):			
Less than 140	44	20.5	0.002
140 or Greater	124	4.8	

Low risk group—PSA less than 10 ng/ml, Gleason score less than 7 and stage less than T2b, D₉₀ less than 140 Gy vs 140 Gy or greater and hormone therapy was used for 5 to 6 months.

stage greater than T2a or Gleason greater than 6) benefitted from the addition of 6 months of luteinizing hormone-releasing hormone analogue plus antiandrogen (94% vs 64%, p = 0.013).

The most significant aspect of this study is the importance of the delivered radiation dose. Groups at most centers plan to deliver 144 Gy to the prostate. Our group plans a higher dose, that is 160 Gy, in the operating room. One of the reasons for the higher dose is that the planned doses are not always delivered when post-implantation dosimetry is performed.¹⁶ We have previously reported that D₉₀ is highly predictive of biochemical freedom from failure.⁷ By prescribing to a slightly higher dose the minimum required dose is more likely to be delivered. This study demonstrates that at

longer followup a D₉₀ of 140 Gy or greater is a durable predictor of biochemical control in patients at low and high risk. Indeed, after the group at our center finished refining the real-time implant in 1995, our group has consistently achieved this goal.⁶ In the last 5 years 693 ¹²⁵I implantation has been performed and 689 cases (99.4%) have received a minimum of 140 Gy.

A requirement for biochemical control is local control. Advocates for prostatectomy argue that gland removal is the only sure way to achieve this. Earlier external beam irradiation and brachytherapy data demonstrated higher local failure rates when prostate biopsies were performed (19% to 93%).^{17,18} Zelefsky and Whitmore reported local relapse in 639 of 1,087 retropubic implants (59%) performed during 17 years.¹⁷ Lee et al performed a biopsy study in a group with open ¹²⁵I implants and found persistent disease in 81%.¹⁸

While modern brachytherapy studies show more favorable 2-year biopsy results, questions about durability and sampling error contribute to the continued controversy. In the current study we followed a cohort of men a minimum of 4 years with repeat biopsies yearly if initial biopsies were positive or if PSA increased. All biopsies were performed under transrectal ultrasound with a minimum of 6 cores and in cases of increasing PSA, usually 8 to 12 cores. While it is possible that a small focus of cancer could have been missed, it is unlikely that cases of increasing PSA and multiple biopsy episodes would have been incorrectly classified as negative. These data demonstrate several key findings. It can take longer than 2 years after implantation for prostate biopsies to become negative. The negative biopsy rate was 82.2% at 2 years compared to 92.4% at 8 years. The implications of these data are 2-fold. 1) The interpretation of a positive biopsy result 2 years or earlier after implantation may be unreliable, a fact that Reed et al recently reported in a small number of patients.¹⁹ 2) At longer followup the local failure rate for T1–T2 prostate cancer

(7.6%) compares favorably to that of radical prostatectomy and external beam irradiation.

The significance of a positive prostate biopsy following brachytherapy has also been questioned. Our data demonstrate that patients in whom a positive biopsy persists have a high biochemical progression rate (79%). Taken together the low PSA progression rates along with the high negative prostate biopsy results indicate that ¹²⁵I brachytherapy can cure most men with low risk prostate cancer (8.7% PSA failure rate and 4.5% local failure rate) as long as an adequate dose is delivered.

CONCLUSIONS

These data substantiate the positive outcomes of ¹²⁵I prostate brachytherapy for T1–T2 prostate cancer. Patients at low risk treated with the implant alone have excellent local control and biochemical progression-free survival rates (95.5% and 91.3%, respectively). Patients at high risk may benefit from the addition of 6 months of androgen deprivation. The most important factor to recognize as contributing to these excellent outcomes is that patients should receive at least 140 Gy to 90% of the gland. Patients who receive less irradiation are more likely to experience failure.

REFERENCES

1. Stone, N. N. and Stock, R. G.: Permanent seed implantation for localized adenocarcinoma of the prostate. *Curr Urol Rep*, **3**: 201, 2002
2. Blasko, J. C., Wallner, K., Grimm, P. D. and Ragde, H.: Prostate specific antigen based disease control following ultrasound guided ¹²⁵I iodine implantation for stage T1/T2 prostatic carcinoma. *J Urol*, **154**: 1096, 1995
3. Critz, F. A., Tarlton, R. S. and Holladay, D. A.: Prostate specific antigen-monitored combination radiotherapy for patients with prostate cancer: I-125 implant followed by external-beam radiation. *Cancer*, **75**: 2383, 1995
4. Stock, R. G., Stone, N. N., Wesson, M. F. and DeWyngaert, J. K.: A modified technique allowing interactive ultrasound-guided three-dimensional transperineal prostate implantation. *Int J Radiat Oncol Biol Phys*, **32**: 219, 1995
5. Stone, N. N., Stock, R. G., DeWyngaert, J. K. and Tabert, A.: Prostate brachytherapy: improvements in prostate volume measurements and dose distribution using interactive ultrasound guided implantation and three-dimensional dosimetry. *Radiat Oncol Investig*, **3**: 185, 1995
6. Stock, R. G., Stone, N. N., Lo, Y. C., Malhado, N., Kao, J. and DeWyngaert, J. K.: Postimplant dosimetry for ¹²⁵I prostate implants: definitions and factors affecting outcome. *Int J Radiat Oncol Biol Phys*, **48**: 899, 2000
7. Stock, R. G., Stone, N. N., Tabert, A., Iannuzzi, C. and DeWyngaert, J. K.: A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys*, **41**: 101, 1998
8. Consensus statement: guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys*, **37**: 1035, 1997
9. Grimm, P. D., Blasko, J. C., Sylvester, J. E., Meier, R. M. and Cavanagh, W.: 10-year biochemical (prostate-specific antigen) control of prostate cancer with ¹²⁵I brachytherapy. *Int J Radiat Oncol Biol Phys*, **51**: 31, 2001
10. Kollmeier, M. A., Stock, R. G. and Stone, N. N.: Biochemical outcome after prostate brachytherapy with 5-year minimal follow-up: importance of patient selection and implant quality. *Int J Radiat Oncol Biol Phys*, **57**: 645, 2003
11. Ragde, H., Elgamal, A. A., Snow, P. B., Brandt, J., Bartolucci, A. A., Nadir, B. S. 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, 1998
12. Ramos, C. G., Carvalhal, G. F., Smith, D. S., Mager, D. E. and Catalona, W.: Retrospective comparison of radical retropubic prostatectomy and ¹²⁵I iodine brachytherapy for localized prostate cancer. *J Urol*, **161**: 1212, 1999
13. Hanks, G. E., Hanlon, A. L., Epstein, B. and Horwitz, E. M.: Dose response in prostate cancer with 8–12 years' follow-up. *Int J Radiat Oncol Biol Phys*, **54**: 427, 2002
14. Freedland, S. J., Partin, A. W., Epstein, J. I. and Walsh, P. C.: Biochemical failure after radical prostatectomy in men with pathologic organ-confined disease: pT2a versus pT2b. *Cancer*, **100**: 1646, 2004
15. Pilepich, M. V., Winter, K., John, M. J., Mesic, J. B., Sause, W., Rubin, P. et al: Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*, **50**: 1243, 2001
16. Bice, W. S., Prestidge, B. R., Grimm, P. D., Friedland, J. L., Feygelman, V., Roach, M., 3rd et al: Centralized multiinstitutional postimplant analysis for interstitial prostate brachytherapy. *Int J Radiat Oncol Biol Phys*, **41**: 921, 1998
17. Zelefsky, M. J. and Whitmore, W. F.: Long-term results of retropubic permanent ¹²⁵I iodine implantation of the prostate for clinically localized prostatic cancer. *J Urol*, **158**: 23, 1997
18. Lee, F., Torp-Pedersen, S., Meiselman, L., Siders, D. B., Littrup, P., Door, R. P. et al: Transrectal ultrasound in the diagnosis and staging of local disease after I125 seed implantation for prostate cancer. *Int J Radiat Oncol Biol Phys*, **15**: 1453, 1988
19. Reed, D., Wallner, K., Merrick, G., Buskirk, S. and True, L.: Clinical correlates to PSA spikes and positive repeat biopsies after prostate brachytherapy. *Urology*, **62**: 683, 2003