

Long-Term Urinary, Sexual, and Rectal Morbidity in Patients Treated with Iodine-125 Prostate Brachytherapy Followed Up for a Minimum of 5 Years

Nelson N. Stone and Richard G. Stock

OBJECTIVES	To define the long-term morbidity in patients with prostate cancer who underwent iodine-125 brachytherapy.
METHODS	A total of 325 men with localized prostate cancer treated with iodine-125 brachytherapy had a median follow-up of 7 years (range 5 to 15). The American Urological Association symptom score, erectile function status, rectal bleeding incidence, and presence of urinary incontinence were collected prospectively before implantation and every 6 months thereafter. Comparisons were made between the pretreatment and treatment-related factors and their associations with quality-of-life changes. Associations were tested using the Student <i>t</i> , chi-square, and Wilcoxon signed rank tests.
RESULTS	The median prostate volume and maximal dose to 90% of the prostate was 36.6 cm ³ and 167 Gy, respectively. Of the 325 men, 15.7% experienced prostate-specific antigen failure and 4% started androgen deprivation therapy. The mean total symptom and bother scores increased from baseline ($P < 0.001$) to 6 months after implantation, steadily decreased, and were unchanged at the last follow-up visit ($P = 0.6$). There were no significant associations among patient age, race, hormonal therapy use, prostate size, radiation dose, and urinary morbidity. Incontinence occurred in 4 (1.2%) of the 325 patients at the last follow-up visit and was associated with transurethral resection of the prostate (odds ratio 8.8, 95% confidence interval 1.3 to 62, $P = 0.008$). Before implantation, 77.2% were able to have an erection adequate for intercourse and 50.6% were able to at the last follow-up visit. A significant correlation was found between potency preservation and age ($P < 0.001$). Rectal bleeding occurred in 78 men (24%) 1 to 3 years after implantation. Nine patients (2.8%) complained of minor bleeding beyond 5 years, which was associated with greater radiation doses ($P = 0.023$).
CONCLUSIONS	The preservation of urinary, sexual, and rectal quality of life is excellent at long follow-up for patients implanted with iodine-125. UROLOGY 69: 338–342, 2007. © 2007 Elsevier Inc.

Brachytherapy is a common procedure for localized prostate cancer.¹ Although several centers have reported 10-year biochemical (prostate-specific antigen [PSA]) failure-free data, few studies have evaluated the quality-of-life (QOL) changes that occur with longer follow-up.^{2,3} Because an iodine-125 (¹²⁵I) implant takes almost 1 year to deliver the radiation dose, several more years could lapse before morbidity becomes evident. Schellhammer and El-Mahdi⁴ reported that men treated with a retropubic implant were still developing side ef-

fects 5 years later. Talcott *et al.*⁵ found that patients with prior transurethral resection of the prostate (TURP) reported urinary leakage when evaluated 3 years afterward.

We initiated our brachytherapy program in 1990. Prospective data on urinary, erectile, and rectal morbidity have been collected since the outset. We report the QOL changes experienced by a cohort of patients implanted with ¹²⁵I and followed up for a minimum of 5 years.

MATERIAL AND METHODS

A total of 325 men with Stage T1-T2 prostate cancer were treated with ¹²⁵I brachytherapy from 1990 to 2000 (Table 1). The median patient age was 67 years (range 41 to 82), and the median follow-up was 7 years (range 5 to 15). Of the 325 patients, 75 (23.1%) received 5 to 6 months of hormonal

N. N. Stone is the owner of Prologics LLC, and R.G. Stock is a paid consultant/speaker for CR Bard.

From the Departments of Urology and Radiation Oncology, Mount Sinai School of Medicine, New York, New York

Reprint requests: Nelson N. Stone, M.D., Department of Urology, Mount Sinai School of Medicine, 1 Timber Trail, Suffern, NY 10901. E-mail: nelsonstone@optonline.net

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Table 1. Presenting and treatment disease characteristics

Variable	Patients (n)
PSA (ng/mL)	
≤4	38 (11.7)
>4–10	212 (65.2)
>10	75 (23.1)
Gleason score	
2–4	64 (19.7)
5–6	255 (78.5)
7–8	6 (1.8)
Clinical stage	
T1c	132 (41.2)
T2a	100 (30.8)
T2b	77 (23.7)
T2c	14 (4.3)
Race	
White	271 (83.4)
African American	34 (10.5)
Hispanic	16 (4.9)
Asian	3 (0.9)
Indian	1 (0.3)
HT	
No	250 (76.9)
Yes	75 (23.1)

PSA = prostate-specific antigen; HT = hormonal therapy.
Data in parentheses are percentages.

therapy (3 months before implantation), and 33 (10%) had undergone TURP.

The implant was performed using the real-time transperineal method.^{6–8} The radiation doses were determined 30 days after implantation using computed tomography-based dosimetric analysis.⁹ The dose was defined as the maximal dose to 90% of the prostate (D_{90}).

QOL data were collected prospectively starting before implantation and every 6 months thereafter. Patients completed an American Urological Association (AUA) symptom score form before seeing the physician. Erectile function was determined using the Mount Sinai Erectile Sexual Function Score (MSEFS): 0, no erection; 1, erection inadequate for penetration; 2, erection adequate for penetration but suboptimal; and 3, normal erection.¹⁰ More recently, patients completed the International Index of Erectile Function questionnaire. Erectile function (EF) assessments were made with patients taking phosphodiesterase-5 (PDE-5) medication.

Rectal bleeding was determined by interview, and the presence of an ulcer was determined by digital rectal examination or colonoscopy and graded according to the Radiation Therapy Oncology Group scale. Patients were considered incontinent of urine if any protective pad was required, regardless of the cause.

Statistical Analysis

Comparisons were made between the pretreatment and post-treatment factors and their associations with QOL changes. Baseline and follow-up scores were compared. Not all patients completed the forms at each visit. The last follow-up visit was considered the last encounter with the patient. For the AUA score analysis, 213 (65.5%) of 325 had data available for analysis. For ED analysis, 300 (92.3%) of 325 had data available, and all data were available for incontinence and rectal bleeding assessment. The associations between the differences in the preimplant scores and follow-up scores, hormonal therapy (HT), age, length of follow-up, and prostate dose were analyzed.

Table 2. Comparison of preimplant and postimplant urinary symptoms as measured by AUA symptom score

Time	n	Preimplant Score	SD	P Value (Compared with Baseline)
Baseline	325	7.1	6.3	
6 mo	156	12.5	7.4	<0.001
1 yr	145	9.1	6.5	<0.001
2 yr	165	9.5	7.0	0.012
3 yr	161	8.1	6.6	0.381
4 yr	164	7.3	6.0	0.199
5 yr	176	7.3	6	0.615
Last follow-up	213	7.1	5.8	0.610

AUA = American Urological Association.

Numbers represent mean on scale of 0–35; postimplant scores at average of 7 years after implantation.

Table 3. Comparison of preimplant and postimplant urinary bother scores as measured by AUA symptom score

Time	n	Preimplant Score	SD	P Value (Compared with Baseline)
Baseline	325	1.5	1.4	
6 mo	158	2.6	1.5	<0.001
1 yr	142	2	1.4	<0.001
2 yr	163	1.9	1.4	<0.001
3 yr	158	1.6	1.3	0.279
4 yr	166	1.6	1.3	0.406
5 yr	178	1.6	1.2	0.380
Last follow-up	214	1.5	1.2	0.591

AUA = American Urological Association.

Numbers represent means on a scale of 0–6; postimplant scores at median of 7 years after implantation.

A cross-tabulation was determined for age, follow-up time, and multiple D_{90} cutpoints. Associations were tested using the Student *t*, chi-square, and Wilcoxon tests. Correlations were computed using the Pearson and Spearman rho. Biochemical failure was defined as three rises in the PSA level greater than the nadir (American Society for Therapeutic Radiology and Oncology definition). Survival function was determined by Kaplan-Meier analysis.

RESULTS

The median implant prostate volume was 36.6 cm³ (range 11.5 to 107). The median D_{90} was 167 Gy (25th to 75th percentile 147 to 187). Of the 325 patients, 271 were available for evaluation at 5 years after implantation and 24 had died (2 of prostate cancer). Of the 325 patients, 51 (15.7%) experienced PSA failure and 13 (4%) started HT. The 11-year biochemical freedom from failure rate was 81% (free of three consecutive PSA elevations greater than the nadir).

Urinary Morbidity

The mean total AUA score increased from 7.1 to 12.5 ($P < 0.001$) by 6 months after implantation, steadily decreased, and was 7.1 at the last follow-up visit ($P = 0.6$; Table 2). The mean bother score increased from 1.5 to

Table 4. Relationship between age and postimplant potency preservation in patients with initial potency score of 2 or 3 (Spearman rho $r = 0.375$, $P < 0.001$)

Age (yr)	Erectile Function Score (n)				Total
	0	1	2	3	
40–50	0	0	1 (12.5)	7 (87.5)	8
51–60	3 (6.3)	6 (12.5)	12 (25.5)	27 (56.3)	48
61–70	20 (16.1)	29 (23.4)	29 (23.4)	46 (37.1)	124
>70	16 (28.6)	17 (30.4)	11 (19.6)	12 (21.4)	56
Total	39 (16.5)	52 (22)	53 (22.5)	92 (39)	236

Scores from mean of 7.2 year after implantation.
Data in parentheses are percentages.

2.6 ($P < 0.001$) by 6 months after implantation and decreased to 1.5 ($P = 0.591$) at the last follow-up visit (Table 3). The mean difference between the preimplant and postimplant scores for each period was 5.6 at 6 months, 2.2 at 1 year, 2 at 2 years, 0.58 at 3 years, 0.41 at 4 and 5 years, and 0.8 at the last follow-up visit. A large prostate size did not predict for increased urinary symptoms (total score change at 6 months 5.9 for prostate volume less than 50 cm³ and 4.9 for a prostate volume of 50 cm³ or larger, $P > 0.05$). At 1 year, HT had reduced the risk of increased total urinary symptoms (odds ratio [OR] 0.495, 95% confidence interval [CI] 0.240 to 1.019, $P = 0.05$), and D₉₀ greater than 160 Gy had increased this risk (OR 2.38, 95% CI 1.125 to 5.03, $P = 0.022$). These associations were no longer significant by 2 years after implantation and thereafter. For both scores, the difference was 1.3 at 6 months, 0.47 at 1 year, 0.34 at 2 years, 0.04 at 3 years, 0.15 at 4 years, and 0.11 at 5 years and the last follow-up visit. At 1 year after implantation, HT, race, and dose were associated with bother score changes. By 2 years, these associations were also no longer significant.

Of the 325 patients, 27 (8%) reported TURP before implantation and 6 (1.8%) reported undergoing TURP after implantation. Incontinence occurred in 4 (1.2%) of 325 men and was minor in all patients (one pad daily) and was associated with TURP (2 [6.1%] of 33 versus 2 [0.7%] of 292, OR 8.8, 95% CI 1.3 to 62, $P = 0.008$).

Erectile Function

Of the 325 patients, 307 (94.5%) reported potency scores before implantation, of whom 188 (61.2%) and 49 (16%) had a score of 3 or 2, respectively. At the last follow-up visit, 320 (98.5%) of 325 reported their EF status, with 50.6% claiming adequate EF (99 [30.9%] had a score of 3 and 63 [19.7%] of score of 2). Sixty-eight patients (22.1%) reported using PDE-5 inhibitors at the last follow-up visit. Of the 236 with an initial EF score of 2 or 3, 145 (61.5%) maintained adequate EF. Age correlated highly with EF preservation (Spearman rho [r] = 0.375, $P < 0.001$; Table 4). No associations were found between potency preservation and preimplantation HT, D₉₀, or TURP. At last follow-up, 160 patients had completed the IIEF questionnaire. The results correlated highly with the MSEFS (Pearson $r = 0.728$, $P < 0.001$).

Rectal Morbidity

Rectal bleeding had occurred in 78 men (24%) 1 to 3 years after implantation. Of the 78 patients, 9 (2.8%) complained of minor bleeding (grade 1 or 2) for longer than 5 years. The incidence of late rectal bleeding was associated with greater prostate radiation doses (Spearman $r = 0.129$, $P = 0.023$). Late rectal bleeding increased from 1.4% to 5.8% in patients with a D₉₀ of less than 179 Gy versus 180 Gy or greater (OR 2.0, 95% CI 1.3 to 3.4, $P = 0.032$). No cases of rectal ulcers (grade 3) or fistula (grade 4) injuries were reported. One patient required cauterization.

COMMENT

Late complications after brachytherapy affect urinary, sexual, and bowel function. In the first postimplant year, most patients develop increased urinary bother, which returns to baseline within 12 to 18 months after implantation.¹¹ About one third of patients also develop a temporary exacerbation of their symptoms 2 to 3 years after implantation.¹² We noted a significant increase in total and urinary bother scores that peaked at 6 months and persisted for 2 to 3 years after implantation. However, the total and bother scores had returned to baseline by year 3 and remained unchanged at 7 years of follow-up. These results compare favorably with those Merrick *et al.*¹³ reported on 205 patients followed up for a median of 64 months. They found no significant differences for urinary leakage or bother between patients undergoing implantation and controls. Van Gellekom *et al.*¹⁴ prospectively studied 127 patients undergoing implantation using the RAND-36, European Organization for Research and Treatment of Cancer prostate cancer module, and AUA score. Although the overall urinary QOL was not different by 2 years after implantation, the AUA symptom score was still slightly elevated (10.4 versus 7.3, $P < 0.0001$).

It has been our practice since 1991 to perform a peripheral weighted implantation, in which more seeds are placed under the prostatic capsule rather than uniformly distributed throughout the gland.⁷ This distribution has been shown to yield high peripheral doses without substantially increasing the urethral dose.^{7,8} We also treat patients to a greater dose (160 Gy versus 144 Gy) and

initially reported a relationship between greater doses and early (less than 2 years) urinary complaints.¹¹ We have again demonstrated that greater doses increase urinary symptoms for up to 2 years after implantation; however, with longer follow-up, these changes did not persist (Table 4). The prostate size also did not seem to influence the occurrence of urinary symptoms; thus, men with large glands need not be excluded from brachytherapy because of the fear of increased urinary morbidity.

The dose distributions from permanent prostate brachytherapy are typically markedly heterogeneous. The radiation dose delivered to the prostate and urethra, as well as the contiguous tissues (rectum and neurovascular bundles), is highly dependent on the final position of the seeds. Placing too many seeds inside the prostate can increase the urethral dose and increase the risk of urinary incontinence. TURP performed either before or after implantation may increase incontinence. In a review of brachytherapy complications, Stone and Stock¹⁵ reported incontinence rates of 0% to 19% without associated TURP and 0% to 85% with TURP. Most of these studies had short follow-up and differing methods of assessing incontinence. The patients in the present study had long follow-up and a standardized incontinence assessment method (pad use) was used. With long follow-up, the overall risk of incontinence was 0.7% for patients without associated TURP and 6.1% with TURP. Merrick *et al.*¹⁶ analyzed 26 implant patients who had undergone either preimplant ($n = 13$) or postimplant ($n = 13$) TURP and noted worse urinary QOL. The long-term risk of incontinence is eight times greater for men who have undergone TURP, but the overall risk at 6.1% may not be great enough to exclude these patients from implantation.

Potency was preserved in 50.6% of the patients. The men who were potent before treatment were more likely to maintain EF (61.5%). Stock *et al.*¹⁰ previously reported a 6-year actuarial (mean follow-up of 2.6 years) potency preservation rate of 59%. The present data, with much longer follow-up, have suggested that men with good initial EF preserve that function. Merrick *et al.*¹⁷ also analyzed the EF of 425 patients using the IIEF and MSEFS and reported similar findings. With a median follow-up of 40 months, they noted preservation of EF in 39%, with significant correlations to pretreatment function and patient age. Our own analysis of the utility of the MSEFS was confirmed by its close correlation ($r = 0.728$, $P < 0.001$) to the IIEF scores.

Radiation proctitis occurs with varying frequency and severity after brachytherapy. We reported a rectal bleeding rate of 24% within the first 3 years after implantation. Hu and Wallner¹⁸ found that 19% had rectal bleeding after ¹²⁵I brachytherapy that spontaneously resolved in one third. Gelblum and Potter¹⁹ analyzed 823 men after implantation for rectal bleeding and noted a 16% incidence that had resolved in most by 3.5 years. Merrick *et al.*²⁰ noted minor rectal bleeding in 21.4% of 187

postimplant patients. The low incidence of late rectal bleeding and other complications can be explained several ways. Strict attention was paid to seed placement posterior to the prostate. Dosing constraints were set so that the volume of the anterior rectum receiving the prescription dose (160 Gy) was less than 1.3 cm³.¹⁵ Despite these precautions, a patient who had received a greater prostate dose was two times more likely to have persistent rectal bleeding longer than 5 years after implantation.

This work represents the experience of a brachytherapy team that had performed seed implants for 15 years. In addition, the type of implant performed by our group (real-time) is different from that practiced by others. Without the benefit of a multicenter study, these data might not be applicable to all brachytherapy experiences. The instruments used to assess the patient's QOL in this study were not the standard instruments used today. Our study began in 1990, and we used the tools available at the time to assess urinary morbidity in a prospective manner. The power of this study is that all patients completed the AUA questionnaire before implantation. An assessment of EF was also not commonly done before treatment of localized prostate cancer by brachytherapy in 1990. The IIEF had not yet been developed and was not put into practice until almost 10 years later. We developed a four-point scoring system that we and others have published.^{10,17} Merrick *et al.*¹⁷ found a close relationship between the IIEF and MSEFS, as did we in this study (Pearson correlation 0.728, $P < 0.001$).

CONCLUSIONS

Brachytherapy is an effective means of treating localized prostate cancer. The high radiation doses delivered did not appear to put patients at substantial risk of long-term urinary morbidity. With a minimum of 5 years of follow-up, 61.5% of men with good EF before implantation were able to maintain erections sufficient for intercourse. With precise control of the radiation doses to the rectum, the risk of long-term bleeding was also low.

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