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CLINICAL INVESTIGATION **Prostate**

PROSTATE BRACHYTHERAPY CAN BE PERFORMED IN SELECTED PATIENTS AFTER TRANSURETHRAL RESECTION OF THE PROSTATE

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Purpose: To evaluate urinary function and bother after prostate brachytherapy (PB) in patients who have had prior transurethral resection of the prostate (TURP).

Methods and Materials: A total of 171 patients with stage T1a-T2b prostate cancer, Gleason score ≤7 who underwent prior TURP received PB at a single institution. In January 2002, all 171 patients were mailed the University of California-Los Angeles Prostate Cancer Index and International Prostate Symptom Score sheet. One hundred patients (60%) returned completed surveys. Time of TURP before implant ranged from 2 to 300 months (median, 6.5 years). Mean patient age was 74 ± 5.2 years, follow-up time after implant ranged from 6.1 to 50.9 months (median, 25 months).

Results: The mean urinary function score and bother score for the entire study group was 83.5 ± 19.5 and 82.5 ± 23.7, respectively. Multivariate analysis revealed higher pretreatment International Prostate Symptom Scores to have significant negative impact ($p = 0.001$) on urinary function and bother scores.

Conclusion: With accurate ultrasound identification of the urethral defect and precise dosimetry, brachytherapy can be performed in selected patients who have had prior TURP with resultant low impact on urinary function and bother scores. © 2004 Elsevier Inc.

Prostate brachytherapy, Prostate cancer, Urinary incontinence, TURP.

INTRODUCTION

Developed in 1930, transurethral resection of the prostate (TURP) is a surgical procedure performed to remove the prostate parenchyma proximal to the verumontanum and distal to the bladder neck as a treatment for urinary obstruction. The surgeon removes as much tissue as necessary without penetrating the prostatic capsule to allow the patient to void (1). During the mid-1980s, TURP peaked with an incidence of approximately 350,000 cases per year (2). However, this past decade, with the advent of newer medications and procedures such as transurethral needle prostate tissue ablation and transurethral incision of the prostate, the occurrence of TURPs has decreased to less than 100,000 cases per year (2). The incontinence rate from TURP alone is low, ranging from 1% to 5% (3).

Since the mid 1980s, prostate brachytherapy (PB) using I_{125}/Pd_{103} has gained wide acceptance. This renewed enthusiasm was the result of the development of transrectal ultrasound allowing transperineal insertion of radioactive isotopes into the prostate gland (4). Today, there are various approaches and philosophies regarding optimal treatment planning for prostate brachytherapy. Although our institution follows the preplanned preloaded needle technique, we recognize that the real-time technique (intraoperative) using a Mick applicator is prevalent and doubt results between these two methods are significantly different. However, the question remains, is prior TURP a contraindication to PB?

METHODS AND MATERIALS

Between October 1997 and August 2001, 171 patients (1997 American Joint Commission on Cancer) Stage T1a-T2b, Gleason score ≤7 underwent prior TURP before receiving PB at a single institution. Although 175 patients with prior TURP presented to our institution, 4 patients (2.4%) did not receive PB because the residual prostate parenchyma did not meet the 1-cm margin criteria, which is described later in Materials and Methods. All patients were mailed the University of California-Los Angeles Prostate Cancer Index (UCLA PCI) and International Prostate Symptom Score (IPSS) index with a self-addressed, postage-paid return envelope. They were given 3 weeks to return their completed surveys. The UCLA PCI is a validated disease-specific quality of life instrument used to measure quality of life in men treated for early-stage prostate

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cancer (5). This self-administered 20-item questionnaire quantifies prostate cancer specific health-related quality of life in six domains: urinary function and bother, bowel function and bother, and sexual function and bother. Rectal injury and erectile dysfunction after PB in TURP patients have been described elsewhere (6). It is unclear as to the true risk of urinary morbidity in TURP patients implanted with current techniques. Therefore, for this study, only the urinary function and bother scores were assessed. The UCLA PCI quality of life scale ranges from 0 to 100, with higher scores representing better outcomes. The IPSS is a symptom problem index assessing one's quality of life as a result of urinary problems (7). The symptom index's seven questions measure frequency, nocturia, weak urinary stream, hesitancy, intermittence, incomplete emptying, and urgency. The IPSS symptom scale ranges from 0 to 35, with lower scores representing better outcomes. A total of 102 patients returned surveys by mail, for an overall response rate of 60%. Two respondents did not complete at least 80% of the UCLA PCI and were therefore excluded. Time of TURP before implant ranged from 2 to 300 months (median, 6.5 years; mean, 7.7 years) and 8 patients had more than one TURP before implant. The mean patient age for this group was 74 ± 5.2 years, whereas mean prostate target volume was 37.53 ± 14.4 cm^3. Patients had a mean pretreatment IPSS score of 7.75 ± 5.9. Time to follow-up after undergoing PB ranged from 6.1 to 50.9 months (median, 25 months). A total of 59% of patients received Amersham 6711 I_{125} implant (144 Gy TG-43), whereas 41% received Theragenics 200 Pd_{103} (132 Gy NIST 99). Thirty-one percent of patients had neoadjuvant total androgen blockade for downsizing, and no patients underwent external beam radiation therapy as part of their treatment. All dosimetry was completed using Rosses medical treatment planning systems.

Brachytherapy was performed using a three-dimensional volume reconstructed preplanned/preloaded needle technique. Our philosophy has been to implant TURP patients only if the TURP defect is less than 25% of the total prostate volume. This is because the ability to contour the defect while avoiding V150 (implant volume receiving 150% percent of the prescribed dose) on the defect is very difficult in small (<30 cm^3) glands. Furthermore, we do not implant TURP patients if the gland does not have at least a 1-cm margin around the posterior and lateral margins of the defect. Special care was taken in all cases to identify the urethral defect and avoid 150% of the prescribed matched peripheral dose to the TURP defect (Fig. 1).

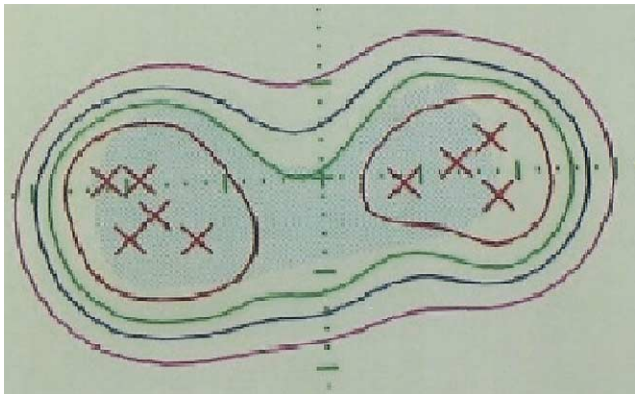

Fig. 1. Postplan with isodose lines. This postplan demonstrates the prostate gland remnant (light blue shaded area) with contoured isodose lines. The red, green, blue, and pink lines indicate 150%, 100%, 75%, and 50% isodose lines, respectively.

Table 1. UCLA Prostate Cancer Index, urinary function*

	No. Patients (%)
How often leaked urine	
Not at all	51 (51)
Less than once a week	17 (17)
About once a week	10 (10)
Every day	22 (22)
Best description of urinary control	
Total control	54 (54)
Occasional dribbling	45 (45)
Frequent dribbling	1 (1)
No control whatsoever	0 (0)
Pads or adult diapers used daily to control leakage	
Not needed	77 (77)
No pads	14 (14)
1–2 pads per day	9 (9)
3 or more pads per day	0 (0)
How big a problem is dripping urine or wetting pants	
No problem	57 (58)
Very small problem	23 (23)
Small problem	16 (16)
Moderate problem	2 (2)
Big problem	1 (1)
Missing response	1
How big a problem is urine leakage interfering with sexual activity	
No problem	78 (91)
Very small problem	5 (6)
Small problem	1 (1)
Moderate problem	0 (0)
Big problem	2 (2)
Missing response	14

* Percentage of each item may not equal 100% due to rounding. For items with missing responses, valid percentage is used.

RESULTS

UCLA PCI urinary function and bother scores for all 100 patients who responded with a complete survey were analyzed (Tables 1 and 2). The mean urinary function score and bother score for the entire study group was 83.5 ± 19.5 and

Table 2. UCLA Prostate Cancer Index, urinary bother

Overall urinary function bother	No. Patients (%)
No problem	55 (55)
Very small problem	28 (28)
Small problem	10 (10)
Moderate problem	6 (6)
Big problem	1 (1)

Table 3. Urinary function score analysis

Variables	Univariate *p*	Multivariate *p*
Pretreatment IPSS	0.001*	0.001*
Isotope	0.000*	0.065
Follow-up time	0.484	0.120
Pretreatment PSA	0.621	0.141
Age	0.466	0.611
Gleason score	0.310	0.716
Time from TURP to implant	0.949	0.729
Hormonal therapy	0.998	0.765
Total seed activity	0.002*	0.832

Abbreviations: IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; TURP = transurethral resection of the prostate.

* Significant.

82.5 ± 23.7, respectively. The majority of patients experienced little or no problem with urinary function. Specifically, 68% of men said they leaked urine less than once a week or not at all; 99% said they had total urinary control or had only occasional dribbling. Additionally, 91% said they did not use absorbent pads or did not need pads or diapers. Only 3% of patients reported a moderate or big problem with dripping urine and no patients reported having no urinary control whatsoever. With regard to urinary bother, the vast majority of patients, 93%, indicated they were bothered very little or not at all. Factors examined were pretreatment IPSS symptom score, isotope, time to follow-up, pretreatment prostate-specific antigen, age, Gleason score, time from TURP to implant, use of total androgen blockade, and total activity.

Univariate analysis demonstrated there to be less impact on urinary function and bother scores in patients who had a pretreatment IPSS score less than or equal to 8, those implanted with I_{125} and lower total seed activity. However, on multivariate analysis, pretreatment IPSS score was the only variable that showed a significant impact ($p = 0.001$) in both urinary function and urinary bother scores (Tables 3 and 4). All statistical tests were calculated using SPSS 11.5 software (SPSS Inc., Chicago, IL). Statistical significance was established with $p < 0.05$.

Table 4. Urinary bother score analysis

Variables	Univariate *p*	Multivariate *p*
Pretreatment IPSS	0.001*	0.001*
Total seed activity	0.011*	0.198
Pretreatment PSA	0.454	0.205
Gleason score	0.022*	0.280
Hormonal therapy	0.639	0.394
Time from TURP to implant	0.496	0.399
Isotope	0.007*	0.752
Age	0.837	0.826
Follow-up time	0.217	0.866

Abbreviations: IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen; TURP = transurethral resection of the prostate.

* Significant.

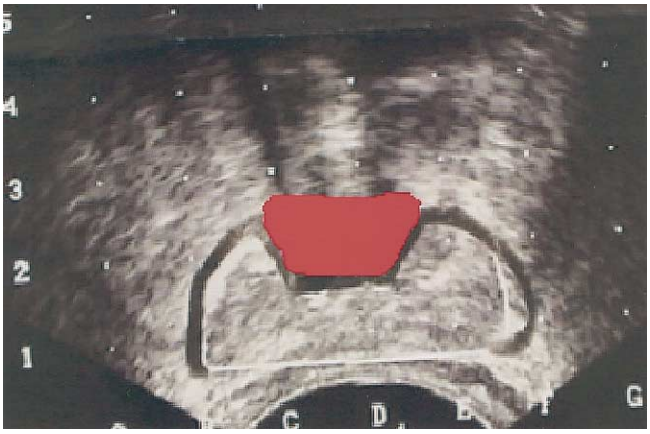

Fig. 2. Transurethral resection of the prostate defect identification on ultrasound. This picture demonstrates an ultrasound image of a prostate. The transurethral resection of the prostate defect is also identified in red.

DISCUSSION

Since the early 1990s, more sophisticated treatment planning systems for the purpose of PB have dramatically evolved to our present-day three-dimensional technology. This technology accommodates either a preplanned or real-time (intraoperative) philosophy. Furthermore, ultrasound image quality has improved drastically in addition to allowing both sagittal and axial viewing. With newer technology and superior ultrasound imaging, one is able to accurately identify the TURP defect and the prostate gland remnant (Fig. 2). Isodose distributions can then be created and customized to the desired target volumes (Fig. 3). Careful adherence to these principles allows one to adequately cover

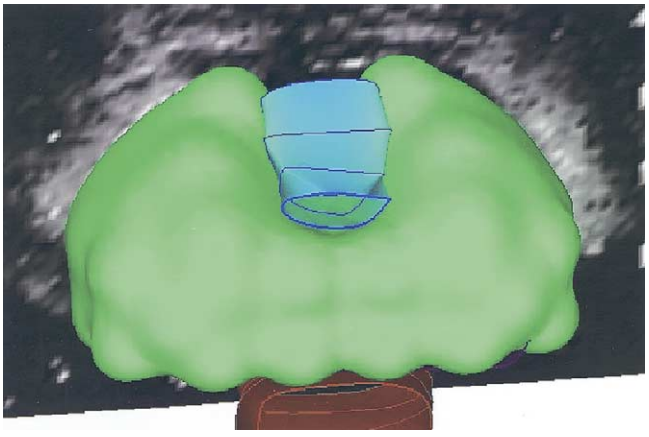

Fig. 3. Isodose cloud contouring transurethral resection of the prostate defect. This picture demonstrates a three-dimensional isodose cloud covering the prostate gland. The defect is also identified; note how radiation dose or isodose cloud conforms to the defect (blue area). The brown structure is the rectum.

Table 5. UCLA PCI urinary score comparison

	Healthy controls $n = 134$	Radical prostatectomy $n = 74$	Brachytherapy (non-TURP) $n = 48$	Brachytherapy (TURP/CPCC) $n = 100$
Urinary function	92 ± 13	71 ± 25	80 ± 22	84 ± 20
Urinary bother	86 ± 23	74 ± 29	65 ± 32	82 ± 25

Abbreviations: PCI = Prostate Cancer Index; TURP = transurethral resection of the prostate; CPCC = Chicago Prostate Cancer Center.
Source: Brandeis et al. (11)

residual prostate gland with the prescribed dose while not exposing the urethral defect to unnecessary high-dose radiation and risking the development of suburethral necrosis.

Significant toxicity, primarily urinary incontinence, was observed in implant patients who had undergone prior TURP. However, there are few data on this subject and the data do not assess large patient samples. The Seattle group initially reported their experience with brachytherapy performed on patients who had undergone prior TURP in 1991, describing a 17% risk of incontinence in TURP patients (8). Side effects and complications related to PB were acceptable; however, TURP was considered to be a contraindication (9). However, much of these data originated from patients treated with early dosimetry planning systems and homogeneous loading of the radioactive isotopes. Later, Wallner *et al.* emphasized a peripheral loaded urethral-sparing technique and reported a 6% incontinence rate in a TURP patient group (6). Stone *et al.* suggest that brachytherapy can be safely performed with a low risk of urinary incontinence if a real-time method combined with peripheral loading is used. Furthermore, they point out that other techniques of seed implantation may result in a higher risk of urinary incontinence (10). With extensive experience and improved techniques, there is little doubt that the incontinence rates for all these groups have considerably decreased. This is the first reported series using a preloaded/preplanned needle technique that does not suggest an increased risk of urinary incontinence. As a result, we believe that brachytherapy can be performed with a low risk of urinary incontinence in patients who have had prior TURPs. This is possible regardless of the technique used whether preloaded preplanned needles or real time intraoperative planning is used, provided a peripheral loading philosophy is exercised.

As quality of life issues become more crucial in the treatment decision process for early-stage prostate cancer, use of validated instruments is paramount. The UCLA PCI has been implemented to assess outcomes for various therapeutic modalities. This survey is patient-friendly and practical for subsequent analysis. As reported by Brandeis *et al.*,the UCLA PCI urinary function and urinary bother scores after either radical prostatectomy or brachytherapy without prior TURP and healthy control groups are listed in Table 5 (11). In our experience, TURP patients had less urinary function symptoms and bother symptoms when presenting with an IPSS score of less than or equal to 8. Because urinary symptoms tend to be the most common irritative side effect of seed implants, one may expect that the less urinary dysfunction one has before implant, the better the outcomes after the procedure will be. Table 5 demonstrates that our group of TURP patients that underwent brachytherapy scored higher than both treatment groups and approached scores the cohort of healthy controls reported. Interestingly, the indication for TURP was to improve their urinary function and bother scores. Therefore, it is not surprising that when compared with non-TURP patients who had brachytherapy, the TURP patients' bother and function scores would be better, as seen Table 5. In summary, we expect those who have undergone preimplant TURP to have better voiding symptoms overall than those brachytherapy patients who never had a prior TURP.

Despite conflicting reports describing the impact that external beam radiation may have in patients who have had a TURP before treatment (12, 13), there has been a fervent belief that prior TURP is an absolute contraindication to PB. With a median follow-up of 25 months, our experience does not support this commonly held notion. In summary, adherence to the following guidelines can offer brachytherapy as a treatment option. Time interval from TURP to implant should be a minimum of 2 months; this will allow adequate time for reepithelialization of the TURP defect. Furthermore, a volume study should be performed to assess the residual prostate gland shape and size. The TURP defect must be satisfactorily visualized as well as the apex of the gland, which will approximate the location of the caudally adjacent lower external sphincter. Forethought using peripherally loaded dosimetry is essential, because high-dose regions ($\geq$V150) must be avoided in the vicinities of the urethra, rectum, and apex near the lower external sphincter. Dose minimization to these vulnerable regions needs to be considered while achieving the prescribed dose to the periphery of the gland. Dosimetry is most challenging if either the total prostate volume is <30 cm^3 or if the TURP defect is $\geq$25% of the total prostate volume, regardless of size. Even under ideal circumstances, while using a preplanned technique, the TURP defect may appear slightly different at the time of implant because of minimal setup differences of the ultrasound probe at the time of volume study and implant. Therefore, a conscious effort needs to be made during the implant procedure, avoiding needle placement and resultant seed deposition along the surface of the TURP defect. We also recommend a 1-cm margin of residual

prostate tissue that surrounds the TURP defect laterally and posteriorly, whereas anteriorly, there is no residual prostate tissue, especially at the base of the gland, because this was resected during the TURP. The concept of residual prostate margin was initially proposed by Blasko *et al.* (8) and later endorsed by Wallner *et al.* (6). Furthermore, the anterior margin of a TURP defect does not exist because this is the area that opens up into the urinary bladder. This is what we would expect with today's standard of practice regarding TURPs. This philosophy also allows adequate tissue for seed placement and dose falloff. Every effort should be made to minimize the dose to the epithelium covering the TURP defect. This can be done with either a preplanned preloaded needle technique or the real time (intraoperative) Mick technique. Although the cohort described in this article was treated using a preplanned technique, we believe there is no significant difference with regard to outcome if patients are treated with a real-time technique using Mick applicator.

Provided patients meet recommended selection criteria, we propose PB can be safely offered without significant urinary dysfunction to patients who previously underwent TURP. Not only is urinary function known to decrease as men age (14), this may be why patients who underwent TURP did so because of preexisting urinary dysfunction. When these issues are considered, our study group reported most favorably. Urinary function and bother scores in this group of patients are most acceptable when compared with patients treated with either radical prostatectomy, brachytherapy without prior TURP, or healthy controls. In conclusion, our experience suggests that patients who have undergone prior TURP can be implanted using either I_{125} or Pd_{103} with resultant low impact on urinary function and bother scores. As treatment planning systems and implant techniques continue to improve, it is likely that additional reports of brachytherapy on patients with prior TURP will emerge. It is our belief that, similarly, their results will be comparable.

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