Impact of Urethral Localization During Transrectal Ultrasonographically Guided Transperineal Prostate Brachytherapy

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The majority of acute toxicity following prostate brachytherapy is related to urethritis. To avoid implanting seeds in the vicinity of the urethra, several techniques have been proposed to better identify its course throughout the prostate during implantation. Our study compares the accuracy of sonographic urethral localization with and without an intraoperative urethrogram, as well as differences in genitourinary (GU) toxicity between two groups of patients who underwent prostate palladium-103 brachytherapy with and without an intraoperative urethrogram. Patients were placed in the dorso-lithotomy position, and the preplanning prostate ultrasound image was duplicated. The urethral position at the base, midgland, and apex was predicted. The distal urethra was catheterized, and 30 cc of an aerosolized Surgilube mixture was injected. Actual urethral positions were recorded and compared with the predicted ones. Acute toxicity for this group was compared with that of 50 patients implanted during the same period who did not receive a urethrogram. A total of 100 patients with organ-confined prostate cancer with prostate volumes ranging from 9 to 56 cc received ^{103}Pd prostatic seed implants. In 40% of patients, the actual urethral position was more lateral or anterior than predicted. Of these, 45% would have had seeds implanted into the urethra. Acute toxicity was found to be 35% for patients implanted with intraoperative urethrogram vs 66% for patients implanted without urethrogram. Careful intraoperative ultrasound delineation of the urethra will result in less acute GU toxicity and should be routinely performed.

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Treatment options for organ-confined prostate cancer include radical prostatectomy, external beam radiation therapy, and transperineal interstitial permanent brachytherapy.[1,2] Due to technological advances, such as improvements in transrectal ultrasonography and pre- and postimplant brachytherapy planning software, as well as recent data reporting durable prostate-specific antigen (PSA)-free survival rates in those treated with permanent radioactive seed implants,[3,4] there has been increased interest in ultrasound-guided transperineal in-

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terstitial brachytherapy. While severe urinary toxicity is rare, 50% to 80% of patients treated with brachytherapy will experience short-term grade 1-2 nocturia, dysuria, and increased daytime urinary frequency.[5-7] As the cause of these acute side effects is generally attributed to radiation-induced urethritis, one way to decrease their incidence is to avoid implanting seeds in the immediate vicinity of the urethra.

Most centers that use preplanning brachytherapy software rely on an algorithm that places the urethra in the midline, slightly anterior to the center of the gland at the base and positioned more centrally at the apex. In theory, urethral-sparing implants can be accomplished by implanting vertical coordinates 5 to 10 mm lateral to the midline. Due to the relationship between acute urinary morbidity and the periurethral dose, many brachytherapists have taken steps to more accurately delineate the urethral course. Some have used a Foley catheter to sonographically visualize the urethra during the implant; however, the sonographic shadowing of the catheter tends to overestimate the transverse diameter of the urethra. In addition, since the preplanning volumetric study is performed without a catheter, the variation in prostate positioning can lead to dosimetric discrepancies (Figure 1). Recently, several centers have advocated the use of contrast with aerosolized Surgilube during real-time intraoperative ultrasonography to better identify the urethra. Because of the paucity of published data demonstrating an advantage of one technique over the other, most physicians evaluate the urethral course with ultrasonography without contrast while others continue to rely on preplanning software and a theoretically centrally located urethral position.

The aim of this study was to evaluate the accuracy of urethral localization using real-time ultrasonography with or without contrast, the incidence of periurethral seed implantation when relying on preplanning software, and the impact on acute urinary toxicity.

Materials and Methods

A total of 100 patients with organ-confined prostate cancer were treated with 45 to 50.4 Gy of external beam radiotherapy in combination with a 90-Gy palladium-103 implant. Patients were staged clinically by history, physical exam, digital rectal examination, and serum PSA measurement. Additional studies, including computed tomography scan, bone scan, and endorectal magnetic resonance imaging, were

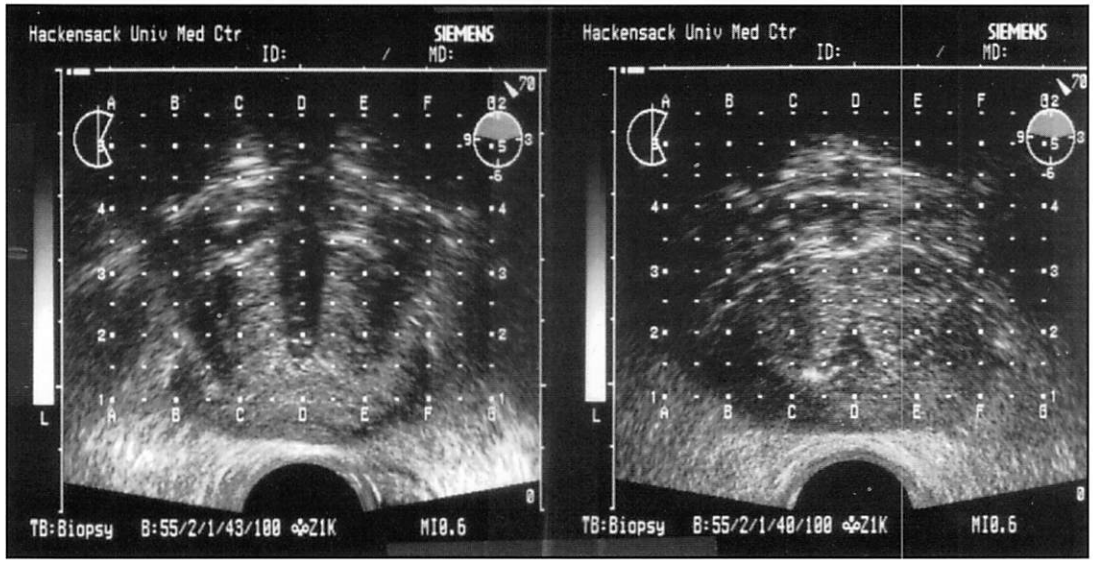

Figure 1. Shadowing from the Foley catheter (a) overestimates the urethral position and distorts the prostate position when compared with a urethrogram with aerosolized Surgilube (b).

obtained as clinically indicated. External beam radiotherapy was delivered to a limited field encompassing the prostate gland and seminal vesicles using a 1.8-Gy daily fractionation with 6- to 15-MV photons using either intensity-modulated radiation therapy or three-dimensional conformal techniques.

Brachytherapy preplanning software was used to plan a minimum prescription dose of 90 Gy to the prostate target volume using a modified peripheral loading technique to limit the planned urethral dose to less than 150% of the prescription dose. Two to three weeks before the scheduled implant, a volume study was performed using transrectal ultrasonography to define the prostate target volume, including the ultrasonically visualized prostate gland plus 2-mm anteroposterior and 5-mm lateral margins. On the day of the implant, anesthesia was induced, patients were placed in the dorso-lithotomy position, and transrectal biplanar ultrasonography was performed. The prostate was visualized in 5-mm increments from base to apex, and needles were placed into the template according to the preplanned coordinates. The distal ends of the needle were visualized in both the transverse and sagittal planes to avoid puncturing the bladder. The initial 50 patients (group 1) were implanted according to the preplan without urethral mapping and needle placement adjustment.

The subsequent 50 patients (group 2) underwent urethral mapping, and when necessary needle placement was adjusted to avoid implanting the periurethral area. A urologist visualized the prostate gland in 5-mm increments from base to apex and recorded the predicted urethral position. Aerosolized Surgilube was made by mixing 30 cc of Surgilube with 20 cc of saline in a 60-cc Toomey syringe. The distal urethra was then catheterized, 30 cc of this aerosolized mixture was slowly injected, ultrasonography was repeated, and the actual urethral position was recorded. The preplan was then reviewed and when the central needles required repositioning to avoid the urethra, the new coordinates were recorded. A Foley catheter was inserted at the conclusion of each implant and was removed within 24 hours. Acute toxicity was assessed every four weeks for the first three months and scored using a modified Radiation Therapy Oncology Group (RTOG) urinary morbidity grading system (Table 1).

Results

From January 1, 1999, to October 30, 1999, a total of 100 consecutive patients were implanted with ^{103}P seeds (Theraseed, Indigo Medical, Cincinatti, Ohio) using preplanned ultrasound techniques. The median patient age was 68 years (range, 55 to 84 years) and the median PSA level was 8 ng/mL (range, 2 to 46 ng/mL). The stage distribution was 53% T1c and 47% T2. Seventy- one percent had Gleason scores of 6 or less, and 29% Gleason scores of 7 or greater. The decision to pretreat with androgen deprivation was left to the individual urologist's judgment, and a total of 64% of patients were treated. The median prostate volume was 28 cc (range, 9 to 56 cc). A median of 20 needles (range, 15 to 28) were used to implant a median of 66 seeds (range, 39 to 97). Total implant activity ranged from 44 to 124 mCi, with a median seed activity of 1.15 mCi (range, 1.1 to 1.26 mCi). Comparison between groups 1 and 2 showed no difference in pretreatment characteristics (Table 2).

The *actual urethral position* (defined by the sonographic appearance of the urethra with injected aerosolized Surgilube) was more lateral or anterior to the *predicted urethral position* (defined by sonography without contrast) in 40% of group 2 patients. The difference in location ranged from 5 to 10 mm in all cases. We attempted to correlate the inability of accurate urethral prediction with the stage of disease, the use of androgen ablation, prostate volume, body habitus, and urologist's experience but could not demonstrate any associations. Without needle repositioning (based on actual urethral position), seeds would have inadvertently been placed in the urethra in 17% of cases. Dose-volume histogram (DVH) analysis showed that for those patients whose actual urethral location deviated from the predicted one, the 150% dose limitation to the urethra was often exceeded (as much as 10% of the urethral volume could receive more than 200% of the prescription dose).

Table 1. Acute Toxicity Scores Using the Modified Radiation Therapy Oncology Group (RTOG) Grading System

Grade	RTOG Definition	Supplemental Description for Acute Urinary Morbidity
0	No treatment-related symptoms	No change from pretreatment voiding habits.
1	Minor symptoms requiring no intervention	Frequency/nocturia up to twice the pretreatment habit and not requiring medication. Dysuria/urgency not requiring medication.
2	Moderate symptoms responding to outpatient management	Frequency/nocturia greater than twice the pretreatment habit but less than hourly. Dysuria/urgency or frequency/ nocturia requiring non-narcotic medication.
3	Major/distressing symptoms	Hourly nocturia. Frequency with urgency. Dysuria requiring regular frequent narcotic use. Gross hematuria. Urinary retention requiring catheterization.
4	Symptoms requiring surgical intervention or prolonged hospitalization	Hematuria requiring transfusions.
5	Fatal complications	...

Fewer cases of urinary morbidity were found in those patients undergoing urethral mapping and needle repositioning (Figure 2). The incidence of grade 1-2 acute toxicity was 35% for those in group 2 and 66% for those in group 1. Most urinary symptoms developed within two weeks of implant and included frequency, nocturia, dysuria, and urgency. The severity and duration of urinary symptoms were less severe for those patients undergoing urethral mapping. While no patient in group 2 experienced grade 3 toxicity, a 7% incidence was noted in group 1.

Discussion

Since the beginning of the past century, brachytherapy—the insertion of sealed radioactive sources into a tumor—has been used in the treatment of prostate cancer. The initial technique, performed by inserting a radium source into the urethra, resulted in severe urethritis and necrosis.[8] Since its introduction, interest in prostate brachytherapy has waxed and waned as new techniques and new low-energy radionucleides were developed. Despite their early promise of success, these techniques were invariably associated with high recurrence rates due to poor seed distribution and the resultant inadequate dosimetric coverage of the prostate gland. Dose distribution around a brachytherapy source is a complex function of the radioactive source geometry, emitted radiation, and surrounding media. Because of the inverse square law, dose

Table 2. Patient Characteristics

Parameter	Without Urethrogram	With Urethrogram	Statistical Comparison
Median age (yrs)	72 (60-81)	68 (55-84)	NS
Stage			
T1c	24 (48%)	29 (58%)	NS
T2	26 (52%)	21 (42%)	NS
PSA level (ng/mL)			
0-4	5 (10%)	6 (12%)	NS
>4-10	34 (68%)	24 (48%)	NS
>10-20	8 (16%)	18 (36%)	NS
>20	3 (6%)	2 (4%)	NS
Gleason score			
2-6	37 (74%)	34 (68%)	NS
7-10	13 (26%)	16 (32%)	NS
Prostate volume (cc)	28 (14-48)	31 (9-56)	NS
Androgen ablation	62%	68%	NS
EBRT before palladium	88%	92%	NS

*PSA indicates prostate-specific antigen; EBRT, external beam radiation therapy; and NS, not significant.

from a single radioactive seed reduces nearly 75% by increasing the distance from 1 to 2 cm from the brachytherapy source.[9] While brachytherapy is effective if the prescribed dose covers

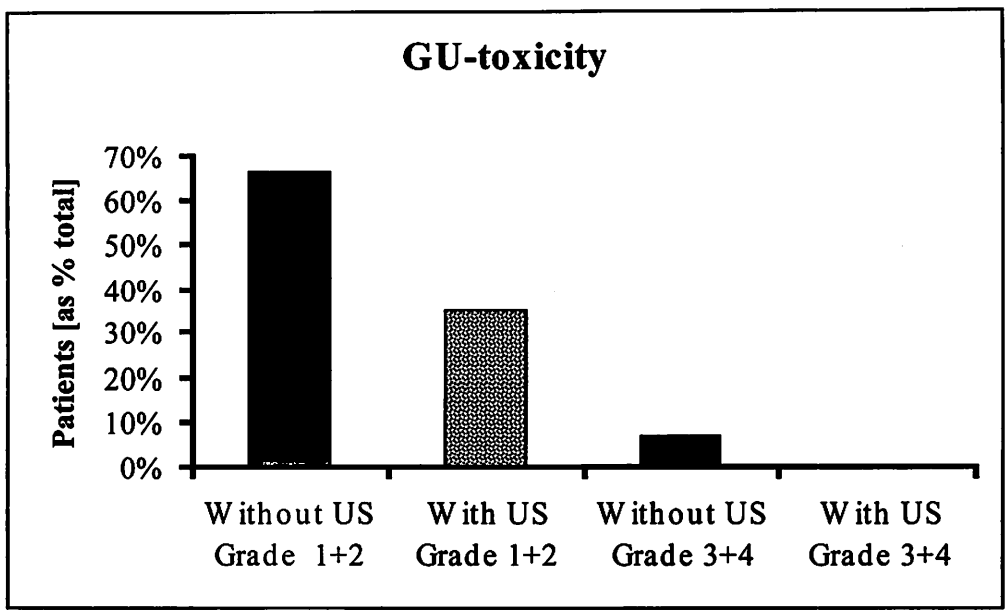

Figure 2. Postimplant acute genitourinary toxicity. (US indicates ultrasound; GU, genitourinary.)

the entire tumor volume, its sharp falloff will result in underdosing of the tumor if the implant does not adequately cover the tumor volume. Thus accurate and reproducible prostate imaging and seed placement is critical to the success of a brachytherapy procedure. During the past decade, important advancements in transrectal ultrasound imaging technology and treatment planning software have led to renewed enthusiasm for transperineal intersitial prostate brachytherapy.

Despite the public perception that brachytherapy represents treatment without toxicity, most patients experience some degree of urinary irritative/obstructive symptoms and some series have reported urinary retention rates greater than 20%.[10] Kleinberg et al[5] reported that within the first year after transperineal prostate implant, 70% of patients developed grade 1-2 acute urinary toxicity and 13% developed grade 3 symptoms. Symptoms usually subsided within six months; however, persistent frequency (48% of patients) and dysuria (20% of patients) were noted one year after implantation. Similarly, Nag et al[6] reported that with a median follow-up of 20 months, 88% of patients experienced some degree of dysuria, frequency, or obstruction. While most symptoms were transient and of a mild nature, 18% had grade 3-4 toxicity.[6]

Various patient- and treatment-related factors have been correlated with the risk of urinary morbidity. Wallner et al proposed both a maximal urethral dose greater than 400 Gy and large prostate gland size as independent risk factors for urinary morbidity.[11] Terk et al[12] correlated the preimplant international prostate symptom score (IPSS) with the risk of urinary retention, noting a 29% rate for those with IPSS greater than 20. Stokes et al[13] reported less urinary morbidity by reducing the individual source activity and percentage of sources in the periurethral region. Different loading patterns have an impact on the central urethral dose. Uniform source placement produces a nonuniform dose distribution resulting in higher urethral doses and frequent acute and chronic urinary morbidity.[14] While peripheral source loading diminishes high urethral doses and may decrease the likelihood of urinary morbidity, its utility is limited by the potential to underdose the prostate target volume with even minute degrees of seed misplacement.[6,15] A modified peripheral loading pattern is commonly used, and avoiding seed implantation into the periurethral area can reduce the incidence of urinary morbidity.[16] This can only be accomplished by accurate urethral localization.

Ultrasound imaging relies on the pulse echo principle in which images are formed based on calculations from echoes that are produced as a result of ultrasound interacting with tissue. Echoes are produced when the ultrasound encounters an interface between structures of differing density. In soft-tissue interfaces, the differences are small and only a small proportion of the ultrasound pulse is reflected back to the transducer. When the prostatic urethra is empty, the anterior and posterior walls are in contact, the anterolateral walls are folded longitudinally,[17] and ultrasound results in a nonechogenic signal. Because of the acoustic impedance achieved when aerosolized Surgilube dilates the prostatic urethra, a more intense echo is seen allowing for more accurate delineation.

While many centers that use preplanning brachytherapy software rely on implanting vertical coordinates away from the midline to avoid implanting seeds directly into the urethra, our results demonstrate the deficiency of relying on the predicted urethral location. Even when evaluating the prostate with real-time sonography without aerosolized Surgilube contrast, the predicted urethral location was incorrect 40% of the time. Had the central needles not been repositioned, 17% of patients would have had at least one seed implanted into the urethra. We attempted to correlate the inability of accurate urethral prediction with the stage of disease, the use of androgen ablation, prostate volume, and body habitus but could not demonstrate any associations. We believe that the reduction in grade 1-2 acute morbidity from 66% to 35% as well as the absence of grade 3 toxicity with accurate urethral mapping and needle repositioning is likely to be due to the improved urethral sparing achieved by better localization.

Conclusion

Sonographic urethral localization without contrast was incorrect in 40% of cases leading to inadvertent periurethral implantation 17% of the time. Sonographic urethral mapping with aerosolized Surgilube is more accurate than relying on central location and results in less acute urinary morbidity.

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