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Radioactive sources embedded in suture are associated with improved postimplant dosimetry in men treated with prostate brachytherapy

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Abstract

Background and purpose: Reports using the retropubic and transperineal technique of prostate brachytherapy suggest that adequate radiation doses are required for good clinical results with I-125. After 3 years of using loose sources (LS), radioactive sources embedded in suture (SES) were introduced into our prostate brachytherapy technique. The purpose of the present report is to determine whether dosimetric quantifiers of implant adequacy were affected by the use of SES.

Materials and methods: Between September 1999 and April 2000, 20 patients were treated with prostate brachytherapy alone with a preplanned, preloaded needle technique using LS. Between May 2000 and February 2001, 20 patients were treated with prostate brachytherapy alone with a preplanned, preloaded needle technique using SES. Dosimetric quantifiers (DQ) of implant adequacy were calculated using a computed tomography scan performed 1 month following prostate brachytherapy. DQ were compared between patients treated with LS and patients treated with SES.

Results: The demographic characteristics were similar for each group. Men treated with SES had slightly smaller prostate glands compared to men treated with LS. The mean total activity and activity per seed were similar for each group but the activity per unit volume was slightly higher for the SES group. Patients treated with SES were found to have significantly improved DQ compared to patients treated with LS. The mean V100 for patients treated with SES was 94.10% compared to 86.54% in those patients treated with LS ($P < 0.001$).

Conclusions: In our experience using preplanning and preloaded needles, the use of SES is associated with improved postimplant DQ. © 2002 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Prostate cancer; Interstitial brachytherapy; Iodine 125

1. Introduction

Prostate cancer is the most commonly diagnosed solid tumor in American men. In 2001, approximately 198 100 new cases will be diagnosed [10]. A majority of these cases will be clinically organ confined at the time of diagnosis [10]. The management of organ-confined adenocarcinoma of the prostate remains one of the most controversial areas in all of oncology. Treatment options include expectant management, radical prostatectomy, external beam radiation therapy, and interstitial brachytherapy [2]. In the absence of prospective randomized trials, proponents of each technique continue to aver that one therapy is superior to all others.

Prostate brachytherapy (PB) has been used for many decades with heterogeneous results [6,8,15,22]. Improvements in technology have allowed the development of a

transperineal approach in which radioactive sources can be placed accurately within the prostate gland using real time ultrasound guidance [6]. Excellent results have been reported with the use of brachytherapy alone in men with favorable risk disease, and brachytherapy combined with external beam radiation therapy in men with intermediate risk prostate cancer [6,7,8,15].

With the development of sophisticated treatment planning systems, it is now possible to obtain three-dimensional dosimetric evaluations soon after PB is completed [5,13]. The American Brachytherapy Society has recommended that all patients treated with PB undergo some form of dosimetric analysis following treatment [13]. This is most commonly achieved with a pelvic computed tomography (CT) scan performed within weeks after prostate brachytherapy. A number of dosimetric quantifiers (DQ) have been studied and reported. The two DQ that have been most closely studied include V100 and D90 [13,18–20]. V100 represents the percentage of the prostate volume

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that receives 100% of the prescription dose. D90 is the maximum dose received by 90% of the prostate gland.

A seminal report from the largest reported series using retropubic seed placement observed that the prescription dose often was not achieved because of inaccurate seed placement [9]. Importantly in this report, lower prostate doses were associated with inferior outcomes, especially local relapse. The few patients that received homogeneous high doses to the prostate gland achieved excellent local control rates.

A recent report of patients treated with a modern transperineal ultrasound-guided technique also reports a dose response relationship [20]. In this series all patients underwent postimplant dosimetric analysis using CT scans obtained approximately 1 month following prostate brachytherapy. Those patients found to have a D90 of greater than 140 Gy experienced improved disease-free survival when compared to patients found to have a D90 of less than 140 Gy. This data with modern technique supports the notion that disease control is associated with dosimetric parameters that can be easily measured. A technique that increases the likelihood of achieving adequate radiation dose of the prostate gland should result in improved disease control.

Although many different techniques are utilized during prostate brachytherapy, most patients are treated with loose sources (LS). A unique medical device that consists of loose seeds embedded in stiffened suture has been developed (RAPIDStrand™, Nycomed Amersham, United Kingdom). This formulation allows for the placement of sources outside of the prostate gland without the concern of seed migration that has been documented with loose seeds [21]. The fixed geometric distribution of seeds embedded in suture (SES) reduces spacing errors and may allow for improved dose delivery [16].

After approximately 3 years of performing prostate brachytherapy at Wake Forest University using LS, we incorporated SES into the prostate brachytherapy procedure. The purpose of this analysis is to determine if the use of SES is associated with improved DQ compared to the use of LS.

2. Materials and methods

2.1. Brachytherapy technique

Transperineal prostate brachytherapy at Wake Forest University began in September 1997. The technique has been previously described by Blasko and Grimm [6]. This technique relies on preplanning using an ultrasound volume study of the prostate gland. Based on the preplan sources are ordered and preloaded into brachytherapy needles using catgut spacers to ensure adequate spacing between sources. From September 1997 until April 2000, all men were treated with LS. In May of 2000, SES were

incorporated into the brachytherapy procedure. The needles containing SES were confined to the periphery of the prostate gland. LS were utilized in the center of the prostate gland. On average for a SES implant, 70–80% of the sources were SES. This technique differs from that of Batterman and others where SES are used throughout the gland [4]. All patients were treated with I-125 alone and the prescription dose was 144 Gy.

2.2. Dosimetric evaluation

According to a uniform institutional protocol, 1 month following prostate brachytherapy, all men underwent a CT scan of the pelvis and prostate. Three millimeter thick images were obtained at 3 mm scan intervals from 2 cm above the most superior seed to 2 cm below the most inferior seeds. The images were then transferred by local area network to the Treatment Planning System. Prostate volumes were outlined by single radiation oncologist (WRL). A single physicist localized each individual seed on the CT scan, and isodose volumes were calculated. Dose volume histograms were calculated with 0.5 mm pixel spacing, the voxel size was 1.25 cc and the dose bins were 5 Gy. A variety of DQ were examined to allow comparison between the patients treated with LS and those treated with SES. At the recommendation of the American Brachytherapy Society, we have reported the V100 and D90 [13]. The rate of seed migration was determined by a KUB film and chest X-ray taken 1 month following the implant procedure.

2.3. Statistical analysis

Descriptive analyzes were performed using PCSAS Version 6.12. Comparison of categorical variables relied on the chi-square test and continuous variables were compared using the *t*-test. The assumptions of these tests were met and no transformations were required. All *P* values are two-sided.

3. Results

The patient and treatment characteristics for the entire study population are listed in Table 1. The characteristics are also sorted according to implant technique (LS versus SES). None of the demographic characteristics are significantly different between the LS and SES groups. Men treated with SES did have slightly smaller prostate glands on average than men treated with LS (SES 33.74 cc, LS 39.55 cc; *P* = 0.0474). The treatment parameters were similar for each group although the SES group did have a significantly higher activity per unit volume of prostate (LS 0.92 mCi/cc, SES 1.02 mCi/cc, *P* = 0.0091). Seed migration was observed in two (10%) patients treated with LS. Seed migration was not seen in any patients treated with SES.

Table 2 lists the dosimetric quantifiers of implant

Table 1
Patient and treatment characteristics of the overall study population ($n = 40$) and stratified by implant technique^a

Variable	Overall ($n = 40$)	LS group ($n = 20$)	SES group ($n = 20$)	<i>P</i> -value
Mean age (SD)	65.8 (5.4)	66.65 (5.3)	65 (5.6)	NS
T1 (%)	29 (72)	14 (70)	15 (75)	NS
T2 (%)	11 (28)	6 (30)	5 (25)	
Mean pPSA (ng/ml)	6.44	6.43	6.44	NS
Gleason 2–6 (%)	37 (92)	18 (90)	19 (95)	NS
Gleason 7 (%)	3 (8)	2 (10)	1 (5)	
Mean (SD) prostate volume (cc)	36.6 (9.3)	39.55 (10.7)	33.74 (6.9)	0.0474
Mean (SD) activity/source (mCi)	0.36 (0.03)	0.35 (0.02)	0.36 (0.03)	NS
Mean (SD) total activity (mCi)	34.77 (6.0)	35.16 (5.88)	34.39 (6.3)	NS
Mean (SD) activity/volume (mCi/cc)	0.97 (0.14)	0.92 (0.14)	1.02 (0.11)	0.0091

^a SD, standard deviation; NS, not significant; and $P > 0.05$.

adequacy for the entire group and stratified by implant technique. By any measure, those patients treated with SES were found to have significantly improved dosimetric coverage of the prostate gland. The mean V100 for those patients treated with SES was 94.10 versus 86.54% in those patients treated with LS ($P < 0.001$).

4. Discussion

As the utilization of PB increases in the United States, there is accumulating evidence that treatment success is dependent on the accurate delivery of an adequate radiation dose to the prostate gland. The wide availability of robust treatment planning systems should allow most practitioners to obtain measures of implant quality in a timely fashion. This information should allow clinicians to modify their technique, if needed, resulting in improved dosimetric outcomes. We have used a rigorous dosimetric analysis to examine whether the incorporation of SES into our technique improves postimplant DQ. Our results indicate that the use of SES is associated with improved DQ as defined by CT scan 1 month following PB. Based on this analysis, we have moved to using SES for all subsequent implants.

A number of other investigators have utilized postimplant DQ to examine whether changes in technique or equipment result in improved dosimetric outcomes [3,18,23]. These modifications in technique or equipment run the gamut from the simple to the complex. Baird et al. observed that placing two marker seeds prior to PB (one at the base and another at the apex) resulted in better D90 values [3]. Stock

et al. found that the use of a dual-phase ultrasound probe resulted in fewer patients with low D90 values compared to the use of a mechanical sector probe [18]. Zelefsky et al. at Memorial Hospital in New York have found that intraoperative computer-optimized conformal planning is associated with improved dosimetric outcomes [23]. It is the authors' opinion that SES is a treatment improvement device which, like the other examples listed above, can lead to better post-implant dosimetry.

This association between SES and improved implant dosimetry is quite plausible. In two large reports examining the spatial distribution of dose with the prostate gland, the region of the prostate most likely to receive a lower dose is the anterior base [14,17]. This region is close to the dorsal vein complex and sources placed near the anterior base could be more prone to embolize through the venous system. There is evidence that the use of SES results in lower rates of source embolization [21]. In this small sample the rate of seed embolization was lower with SES but the sample size is quite small and this difference was not statistically significant. We are presently examining the rate of source migration in a larger group of patients. Since the base is at the periphery of the implanted volume the migration of a few sources can result in significant unintended underdosage. One possible explanation of our results could be that SES allows for less source embolization, which is particularly important at the base, resulting in improved target coverage. It is important to point out that the use of loose seeds in the central portion of the prostate gland does not appear to result in seed embolization (no embolization seen in 20 patients treated with SES). Unlike the reports of

Table 2
Dosimetric quantifiers for the overall study population ($n = 40$) and stratified by implant technique

Variable	Overall ($n = 40$)	LS ($n = 20$)	SES ($n = 20$)	<i>P</i> -value
Mean (SD) V100 (%)	90.32 (5.1)	86.54 (3.7)	94.10 (2.9)	< 0.001
Mean (SD) V90 (%)	93.53 (4.2)	90.43 (3.2)	96.63 (2.2)	< 0.001
Mean (SD) V80 (%)	96.31 (3.0)	94.12 (2.6)	98.50 (1.3)	< 0.001
Mean (SD) D90 (Gy)	148.17 (21.9)	132.13 (11.6)	164.2 (17.3)	< 0.001
D90 >140 Gy (%)	27 (67)	7 (35)	20 (100)	< 0.001

others, we did not systematically identify the regions that were underdosed. We are in the process of performing sector analysis in a larger group of patients. At present it is our opinion that in the majority of cases the base region is more likely to be underdosed.

At least three criticisms of this analysis deserve mention. First, this is a non-randomized retrospective comparison. All patients in this report were treated by the same PB team including a single radiation oncologist and a single urologist. Other than changing the type of source used for the procedure all other variables have remained the same. We chose to compare the SES group with the most recent 20 LS cases rather than the entire LS experience because we have documented a steep learning curve for this procedure and we were seeking to minimize any temporal trends [11]. There are small differences in the prostate size and the activity per unit volume implanted between the SES and LS groups. It is possible that a 10% increase in activity will improve the V100 and D90 by 2–3% but the magnitude of improvement we observed was larger than this. These variables were included in the multivariate analysis and the source type continued to be the only independent predictor of implant quality. As much as the investigators have attempted to keep all variables constant, the potential for residual confounding exists.

Secondly, one may question the use of an intermediate endpoint such as V100 or D90. As has been previously mentioned, limited information does suggest that measures of implant adequacy can be correlated with disease-free survival. The authors hasten to point out, however, that no measure of implant adequacy has been associated with overall survival or prostate cancer specific survival. The correlation between some measure of radiation dose to the prostate gland and survival (if one exists) can only be examined in large cohorts of patients with long follow-up. In the meantime, there is evidence that the DQ used in this report are reliable [5,18]. The authors believe that DQ can provide clinicians with important information that can be utilized as part of a continuous quality improvement process to maximize the likelihood of an adequate prostate implant.

Finally the DQ used in this report rely on prostate delineation on the postimplant CT scans. There are two reports that indicate that there is a large amount of disagreement between reviewers when different reviewers are asked to outline the prostate on identical images [1,12]. In this report, the prostate was outlined by a single reviewer (WRL) so interobserver reliability was not a factor in prostate delineation. The single reviewer was not aware of the technique used (LS versus SES) in each case.

5. Conclusions

This non-randomized retrospective comparison of transperineal preplanned prostate brachytherapy indicates that

the use of SES results in improved postimplant dosimetry compared to the use of LS.

References

- [1] Al-Qaisieh B, Ash D, Bottomley DM, Carey BM. Impact of prostate volume evaluation by different observers on CT-based post-implant dosimetry. *Radiother Oncol* 2002;62:267–273.
- [2] Bahnson RR, Hanks GE, Huben RP, et al. NCCN Practice Guidelines for Prostate Cancer. *Oncology (Huntingt)* 2000;14:111–119.
- [3] Baird MC, Holt RW, Selby TL. Improvement of transperineal implant dosimetry by intraoperative cystoscopic confirmation of prostate anatomy. *J Urol* 2000;164:406–410.
- [4] Battermann JJ. I-125 implantation for localized prostate cancer: the Utrecht University experience. *Radiother Oncol* 2000;57:269–272.
- [5] Bice Jr WS, Prestidge BR, Grimm PD, et al. Centralized multiinstitutional postimplant analysis for interstitial prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998;41:921–927.
- [6] Blasko JC, Grimm PD, Ragde H. Brachytherapy and organ preservation in the management of carcinoma of the prostate. *Semin Radiat Oncol* 1993;3:240–249.
- [7] Blasko JC, Grimm PD, Sylvester JE, Badiozamani KR, Hoak D, Cavanagh W. Palladium-103 brachytherapy for prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2000;46:839–850.
- [8] Critz FA, Levinson AK, Williams WH, Holladay CT, Griffin VD, Holladay DA. Simultaneous radiotherapy for prostate cancer: 125I prostate implant followed by external-beam radiation [see comments]. *Cancer J Sci Am* 1998;4:359–363.
- [9] Fuks Z, Leibel SA, Wallner KE, et al. The effect of local control on metastatic dissemination in carcinoma of the prostate: long-term results in patients treated with 125I implantation. *Int J Radiat Oncol Biol Phys* 1991;21:537–547.
- [10] Greenlee RT, Hill-Harmon MB, Murray T, Thun M. Cancer statistics, 2001. *CA Cancer J Clin* 2001;51:15–36.
- [11] Lee WR, deGuzman AF, Bare RL, Marshall MG, McCullough DL. Postimplant analysis of transperineal interstitial permanent prostate brachytherapy: evidence for a learning curve in the first year at a single institution. *Int J Radiat Oncol Biol Phys* 2000;46:83–88.
- [12] Lee WR, Roach M, Michalski J, Moran B, Beyer D. Inter-observer variability leads to significant differences in quantifiers of prostate implant adequacy. *Int J Radiat Oncol Biol Phys* 2002;54(2):457–461.
- [13] Nag S, Bice W, DeWyngaert K, Prestidge B, Stock R, Yu Y. The American Brachytherapy Society recommendations for permanent prostate brachytherapy postimplant dosimetric analysis. *Int J Radiat Oncol Biol Phys* 2000;46:221–230.
- [14] Prestidge BR, Bice WS, Walker ES, Sarosdy MF. Spatial dose-mapping following transperineal interstitial permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2000;48:148.
- [15] Ragde H, Korb LJ, Elgamil AA, Grado GL, Nadir BS. Modern prostate brachytherapy. *Cancer* 2000;89:135–141.
- [16] Roberson PL, Narayana V, McShan DL, Winfield RJ, McLaughlin PW. Source placement error for permanent implant of the prostate. *Med Phys* 1997;24:251–257.
- [17] Sidhu S, Morris WJ, Spadinger I, et al. Prostate brachytherapy post-implant dosimetry: a comparison of prostate quadrants. *Int J Radiat Oncol Biol Phys* 2002;52:544–552.
- [18] Stock RG, Stone NN, Kao J, Iannuzzi C, Unger P. The effect of disease and treatment-related factors on biopsy results after prostate brachytherapy: implications for treatment optimization. *Cancer* 2000;89:1829–1834.
- [19] Stock RG, Stone NN, Lo YC, Malhado N, Kao J, DeWyngaert JK. Postimplant dosimetry for (125I) prostate implants: definitions and factors affecting outcome. *Int J Radiat Oncol Biol Phys* 2000;48:899–906.

- [20] Stock RG, Stone NN, Tabert A, Iannuzzi C, DeWyngaert JK. A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101–108.
- [21] Tapen EM, Blasko JC, Grimm PD, et al. Reduction of radioactive seed embolization to the lung following prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 1998;42:1063–1067.
- [22] Zelefsky MJ, Whitmore Jr WF. Long-term results of retropubic permanent 125iodine implantation of the prostate for clinically localized prostatic cancer. *J Urol* 1997;158:23–29 discussion 29–30.
- [23] Zelefsky MJ, Yamada Y, Cohen G, et al. Postimplantation dosimetric analysis of permanent transperineal prostate implantation: improved dose distributions with an intraoperative computer-optimized conformal planning technique. *Int J Radiat Oncol Biol Phys* 2000;48:601–608.