First 100 cases at a low volume prostate brachytherapy institution: learning curve and the importance of continuous quality improvement

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Introduction: *We report the first 100 patients who underwent prostate brachytherapy as monotherapy with ^{125}I at an institution with moderate volume radical prostatectomy but low volume brachytherapy (< 2 cases per month). Learning curve and quality improvement was assessed by way of achieving prescription dose targets.*

Materials and methods: *From May 2002 to August 2006, 100 patients underwent prostate ^{125}I brachytherapy monotherapy via preplanned approach. Preoperative planned dose to 100% of prostate gland (D100) was 145 Gy and postoperative confirmed dose was assessed by computed tomography. The cohort was divided into quartiles and recurrence was assessed using Kaplan-Meier analysis.*

Results: *Patient quartiles were of similar age and Gleason grade, while PSA was slightly higher in the first group. Postoperative D90 increased after the first quartile ($p = < 0.0001$) reaching targeted values. Kaplan-Meier survival analysis revealed that 5 year recurrence-free survivals by Phoenix definition was 96%-100% in all groups while by ASTRO definition there was a decrease in recurrence for later cases.*

Conclusions: *At our low volume institution during the first 100 brachytherapy cases, a learning curve for radiation dosimetry was evident, which improved after 25 patients. Preplanned dose-volume parameters were adjusted, enabling the achievement of post-implant goals emphasizing the importance of continuous quality improvement. Although recurrence data is limited by sample size and moderate follow up, there was a discrepancy between the Phoenix and ASTRO definition when evaluating recurrence.*

Key Words: prostate cancer, brachytherapy, learning curves, disease-free survival

Introduction

While the most common treatment for localized prostate cancer remains radical prostatectomy, approximately one-fourth to one-third of patients undergo some form of radiation therapy.[1,2] However, randomized controlled studies on overall and biochemical disease-free survival rates for radical prostatectomy, external beam radiation, and interstitial brachytherapy (BT) are limited.

Early interstitial BT studies created varying opinions regarding oncologic outcomes compared to surgery for low grade disease.[3-5] Improved techniques and technology subsequently broadened its use. Five year disease-free survival for radical prostatectomy versus BT has shown equivocal results across risk groups[6] and, in a randomized prospective study, for low grade disease.[7] Biochemical failure rates have been shown to be similar for localized disease in general, when comparing surgery, external beam radiotherapy, and monotherapy BT.[8]

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Patients with intermediate and even high risk disease are now being effectively treated. Long term outcome data for clinically localized prostate cancer treated with permanent interstitial BT reported by Taira and colleagues showed excellent biochemical-free survival of 98.6%, 96.5%, and 90.5% for low, intermediate, and high risk disease, respectively. Median follow up was 7 years, but almost 50% of patients received supplemental external beam radiation therapy.[9] Zebentout and associates reported biochemical failure-free survival according to Phoenix criteria in intermediate risk patients at 60 and 96 months to be 87.1% and 81%, respectively.[10] Often, younger men are considered poor candidates for BT, though favorable outcomes have been reported when evaluating freedom from progression in patients under and over age 60 with low, intermediate, and high risk disease.[11]

The use of external beam radiotherapy has steadily declined, but BT use increased from 0.0% to 29.6% from 1973 to 2004 according to the Surveillance, Epidemiology, and End Results (SEER) registry.[12] Interestingly, BT outcomes were investigated to determine if a relationship existed between physician and institution volume. It was observed that men treated by higher volume physicians were at lower risk for recurrence and prostate cancer death, with a borderline decrease in total deaths. However, there was no clear relationship between provider volume and postoperative complications.[13] We reviewed our first 100 patients treated with ^{125}I BT to determine oncologic efficacy of a single low volume institution (< 2 cases per month) and to identify if and to what extent a learning curve is reached based on evaluation of dosimetric calculations and to assess if recurrence-free survival was effected by analyzing patient subsets in the form of quartiles. A secondary aim addressed the effectiveness and reliability of the Phoenix and ASTRO definitions for biochemical recurrence status post-implant.

Materials and methods

Following Institutional Review Board approval, we performed a detailed chart review of the first 100 patients who underwent ^{125}I brachytherapy monotherapy for prostate cancer from May 2002 to August 2006 at the University of Iowa. Patients were excluded from analysis if they received external beam radiation therapy or salvage prostatectomy. All patients were treated by a single urologist, one physicist, and two radiation oncologists.

Demographic and patient characteristics collected included age, preoperative and postoperative prostate-specific antigen (PSA), Gleason grade, PSA nadir, time to nadir, use of androgen deprivation and duration, as well as various pre- and post-therapy dosimetry calculations. PSAs were reviewed and biochemical recurrence identified according to the American Society for Therapeutic Radiology and Oncology (ASTRO) (3 consecutive rises in PSA) and Phoenix (PSA nadir + 2) definitions.

Statistics

Patients were divided into quartiles and data was reviewed retrospectively. Pre- and post-implant dose-volume parameter values were compared for each quartile. Statistical analysis including 5 year recurrence-free survival based on the Phoenix and ASTRO definitions was conducted using SAS 9 (Cary, NC, USA). Kaplan-Meier survival analysis was performed for the first and fourth quartiles.

Brachytherapy preplanned approach

After thorough counseling, patients who wish to proceed with brachytherapy for localized prostate cancer undergo a transrectal ultrasound (TRUS) prostate volume study. This is used to construct the three-dimensional seed distribution necessary to achieve the planned dose to 100% of prostate gland volume (D100) of 145 Gy as well as the planned dose to 90% of the gland volume (D90) of 160 Gy-190 Gy while maintaining the maximum planned dose to the urethra below 217.5 Gy (150%). Intraoperatively, the perineal template is configured to match the preplanned TRUS volume study. The patient is placed in the dorsal lithotomy position and an indwelling Foley catheter is placed. The bladder is filled with ~200 cc of contrast and saline (1:1) and the balloon is inflated with contrast to provide adequate orientation and localization of the bladder and bladder neck when fluoroscopy is used. Hollow needles are placed according to the template and ^{125}I seeds deposited. Each needle is marked after placement to ensure that displacement does not occur during seed administration. Fluoroscopy and TRUS are used to monitor needle placement depth. Cystoscopy is performed to ensure no seeds are located within the bladder. The catheter is removed and the patient is discharged with 3 days of antibiotics as well as 1 month of an alpha-blocker. All patients undergo a post-implant CT of the pelvis approximately 1 month after treatment in order to evaluate the post-implant dose-volume parameters including D90. Planned pre-implant D90 values for the first 25 patients ranged from 160 Gy-170 Gy, but as post-implant D90 objectives were not being achieved, a pre-implant D90 value of 180 Gy-190 Gy was used for all remaining patients.

TABLE 1. **Demographics and clinical responses per quartile of brachytherapy treatment course**

	Brachytherapy treatment quartile					
	1st	2nd	3rd	4th	p value	
Pretreatment						
Mean age (years)	65.7	66	64.4	65.3	0.57	ANOVA
Mean PSA	7.28	6.17	5.4	6.29	0.04	ANOVA
Gleason ≥ 7	4%	4%	4%	16%	0.25	Chi-square
Treatment assessment						
Median postop D90 (Gy)	114.6	145.4	158.4	151.4		
Increase per quartile		26.8%	8.9%	-4.4%		
Confirmed dose > 140 Gy	8%	50%	88%	83%	< 0.0001	Chi-square
Median preop D90 (Gy)	168.7	183.3	186.2	186.6		
Follow up						
Median follow up (months)	84	73	63	41		
PSA nadir < 0.5 ng/dL	72%	92%	88%	84%	0.24	Chi-square

Results

There was no difference in patient age when assessing demographics (p = 0.57). Gleason grade was similar between each cohort (p = 0.25), but there was a slight difference in preoperative PSA (p = 0.04) with the first quartile having the highest mean PSA (7.28 ng/mL [5.40 ng/mL-7.28 ng/mL]), Table 1. Of those patients receiving androgen deprivation therapy (ADT), 81.4% (22/27) received only 3 months of therapy, while one patient received 10 months of therapy.

When evaluating treatment quality, post-implant dose-volume parameters were calculated. Only 8% of patients in the first quartile received a post-implant D90 objective of at least 140 Gy. Preplanned D90 values were increased from 160 Gy-170 Gy to 180 Gy-190 Gy over the first 25 patients. Post-implant D90 of at least 140 Gy increased to 50% of patients within the second quartile with a mean dose 145.4 Gy. In the third quartile, 88% of patients achieved a post-implant D90 of at least 140 Gy with a mean dose of 158.4 Gy. The fourth quartile showed similar results with 83% of patients achieving a post-implant D90 of at least 140 Gy with a mean dose of 151.4 Gy. Post-implant CT confirmed dose reached statistical significance when comparing all quartiles (p = 0.001). The median preplanned D90 values increased from 168.7 Gy for the first quartile to 183.3 Gy for the second quartile. The median preplanned D90 remained stable for the third and fourth quartiles at 186.2 Gy and 186.6 Gy, respectively, Table 1.

PSA nadir did not reach statistical significance (p = 0.24), but did show improvement after 25 cases, Table 1. The median PSA nadir for patients who met biochemical failure according to the ASTRO and Phoenix definitions were 0.43 ng/mL and 0.75 ng/mL, respectively. The median PSA nadir for those who were free from failure was 0.05 ng/mL. Median time to recurrence was 26 and 81 months for the ASTRO and Phoenix definitions, respectively. All patients who met biochemical failure according to the Phoenix definition also met biochemical failure according the ASTRO consensus. This was not reciprocal.

Biochemical recurrence was assessed using both the ASTRO and Phoenix definitions for each quartile. Five year recurrence-free survival (RFS) according to the ASTRO definition for the first through fourth quartiles were 69%, 88%, 87%, and 89%, respectively, Figure 1. Regarding the Phoenix definition, the 5 year RFS for the four quartiles were 100%, 96%, 96%, and 100%, respectively, Figure 2. Neither definition

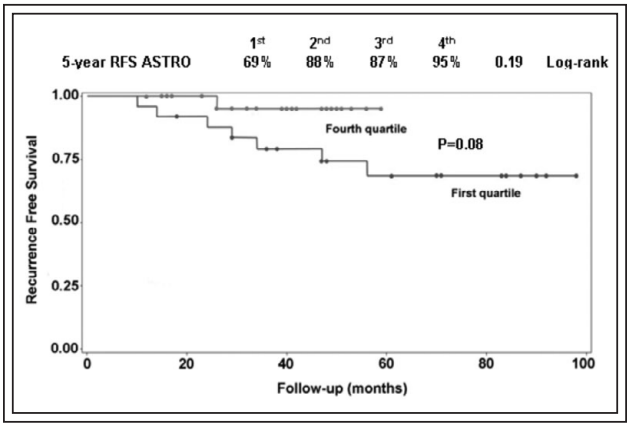

Figure 1. Biochemical failure (ASTRO).

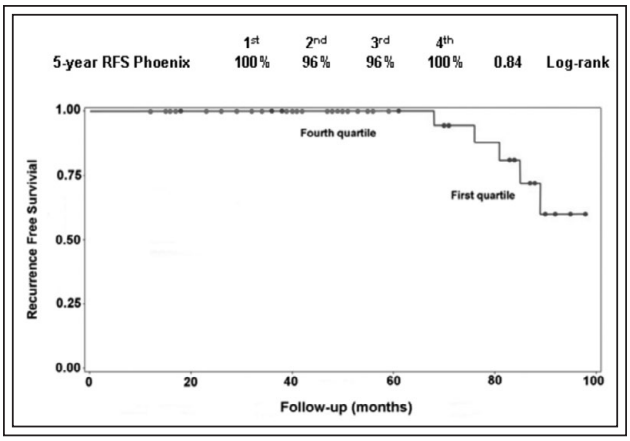

Figure 2. Biochemical failure (Phoenix).

reached statistical significance (p = 0.84 and p = 0.19, respectively), but for the ASTRO definition, statistical significance was approached, especially when comparing the first and fourth quartiles (p = 0.08).

Discussion

Numerous reports address learning curves for radical prostatectomy via an open or laparoscopic approach, with anywhere from 25 up to 1500 cases required to achieve this "learning curve" when analyzing factors such as surgical margin, operative time, biochemical recurrence, and potency.[14-17] In contrast, few reports address such learning curves for radiation treatments, whether brachytherapy or external beam. Further, while there are no established definitions of low or high volume centers for BT, we consider ourselves a lower volume institution, performing 100 cases in just over 4 years (1.9 cases per month). While surgical success can be measured by pathologic outcomes, brachytherapy implant quality is typically assessed in the form of post-implant dosimetry such as the D90 ≥ 140 Gy. Initially, Stone and Stock demonstrated that by achieving a post-implant D90 of >140 Gy, recurrence-free survival could be positively impacted.[18] Ash and colleagues demonstrated that a dose response for post-implant D90 of > 140 Gy can predict PSA failure for low grade disease only, a category into which the majority of our patients fall.[19] Nevertheless, the post-implant D90 > 140 Gy is utilized as a marker of achievement when completing outcome studies.[18-20] We observed drastic improvement when comparing the first and second quartile, with an increase from 8% to 50% of patients reaching a post-implant D90 dose goal of at least 140 Gy. It should be noted that as post-implant D90 objectives were not being achieved, preplanned D90 dosimetric values were adjusted from 160 Gy-170 Gy to 180 Gy-190 Gy within the first 25 patients, Table 1. Preplanned D100 remained consistent at 145 Gy. Post-implant dose-volume parameter improvement continued into the third quartile as well, as 88% of patients received a D90 of > 140Gy. It is difficult to attribute post-implant dose-volume parameter success to physician and/or oncologist/physicist learning curve, but with modifications in the preplanning process within the first quartile of patients, post-implant dose-volume objectives were achieved rather quickly. Thus, based on post-implant dosimetry, continuous quality improvement through evaluation of post-implant D90 in relation to planned pre-implant D90 for a low volume brachytherapy team at our institution resulted in implant quality goals being met after approximately 50 cases, which corresponded to 22 months. Lee et al assessed the dosimetric quality for the first 63 patients treated with brachytherapy alone and found that implant adequacy improved for all measured parameters when comparing the latest 33 patients to the first 30 patients, supporting a learning curve.[21] A post-implant D90 dose goal of at least 140 Gy was achieved in 88% of our patients after 50 cases were performed over a 2 year period. A quicker learning curve and may have been demonstrated in the second quartile of patients if procedure volume was greater at our institution.

Liu et al completed a retrospective review designed to identify whether a learning curve existed for the administration of BT in patients with small and large prostates.[22] A post-implant D90 > 140 Gy was used as the standard, and the learning curve was impacted by the size of the prostate, as well as the experience of the BT team. Chen and associates published a cohort of prostate cancer patients over age 65 who underwent BT according to Medicare claims in SEER surveillance areas.[13] They analyzed recurrence rate and prostate cancer death outcomes based on physician and institution volume from 1991-1999. They found that patients under the care of higher volume physicians (106-357 total cases) had lower recurrence rates (HR 0.89/100 cases, p = 0.01) and prostate cancer deaths (HR 0.80/100 cases, p = 0.03). This was not true for hospital volume.

A learning curve for brachytherapy could be established on the basis of dosimetry, but also cancer outcomes such as recurrence-free survival or biochemical recurrence, cancer-specific or overall survival, or complications. Improved cancer outcomes have been demonstrated with a post-implant D90 of ≥ 140 Gy for patients with low and intermediate risk disease.[10,18-20,22-24] However, conflicting data exists

questioning the validity of such a dose response, especially for intermediate and high risk disease.[19,25,26] Despite conflicting data, a post-implant D90 of ≥ 140 Gy was used as a benchmark, and recurrence-free survival was assessed using two available definitions for biochemical recurrence following radiation therapy to the prostate for localized disease: ASTRO (3 consecutive rises in PSA following BT) and Phoenix definitions (PSA nadir + 2). Our post-implant dosimetry objectives greatly improved with each of the first 3 quartiles in this study. We achieved an 88% post-implant D90 of > 140 Gy within 51-75 patients, up from only 8% for the first quartile verifying that post-implant dose-volume objectives can be reached shortly after the initiation of this procedure. Granted, refinements occur with the implant procedure as well as with defining dose-volume parameters values in the preplanning process, making it difficult to pinpoint the main contributor to improvement in achieving post-implant dose-volume goals. Nevertheless, with a consistent brachytherapy team, post-implant dose-volume objectives can be achieved quickly while maintaining a willingness to adjust preplanned dosimetric parameters if post-implant goals are not being realized.

We observed a discrepancy for the 5 year RFS in our data when employing each biochemical recurrence definition. The Phoenix definition 5 year RFS was excellent for each quartile, while a learning curve was suggested when utilizing the ASTRO definition. However, further analysis of the 5 year RFS Kaplan-Meier curve according to the Phoenix definition comparing the first and fourth quartiles, Figure 1 clearly showed that patients in the first quartile who recurred did so beyond 5 years, while no recurrence was detected for patients in the fourth quartile. This could be a reflection of short follow up versus improved treatment. If a patient was going to recur according to ASTRO, they typically did so relatively quickly, with a median time to recurrence of 26 months. This emphasizes that patients treated with brachytherapy necessitate extensive follow-up with knowledge of each definition's limitations. Long term retrospective studies have shown a similar recurrence-free survival for the two definitions with trends toward a gradual decrease in biochemical freedom from failure.[24] The reason for the discrepancy between the two definitions in our data is unknown.

PSA nadir has been viewed as a prognostic tool following brachytherapy and nadirs ranging from < 0.5 ng/mL to < 1.0 ng/mL have been reported.[27,28] The median PSA nadirs for patients who experienced failure under both definitions were < 1 ng/mL (0.43 ng/mL and 0.75 ng/mL for ASTRO and Phoenix definition, respectively) while the median PSA nadir for all patients free from failure was quite low, at 0.05 ng/mL. However, we observed two patients with a PSA nadir > 1 ng/mL who remained free from biochemical failure and 61.5% (8/13) of patients who met failure according to ASTRO had a PSA nadir < 0.5 ng/mL. This creates difficulty when counseling patients postoperatively regarding their prognosis based on their PSA values. Further, in a series published by Thompson and associates reviewing over 1000 BT patients with low grade to low-tier intermediate risk disease, 44% who met the Phoenix definition for biochemical failure were actually classified as a PSA bounce.[29] Consequently, recurrences identified by either definition may represent a PSA bounce, further complicating patient management.

There are several limitations to our study including the retrospective nature and the moderate length of follow up. The very nature of dividing the cohort into quartiles results in follow up variance. There is also an inherent error when calculating dosimetry with the use of postoperative imaging. Lastly, the exact length of androgen deprivation therapy was not taken into account when calculating biochemical recurrence and refuting evidence exists for its role in the use of brachytherapy, especially when its use is not directed toward merely reducing prostatic volume.[30]

Conclusions

Brachytherapy for the treatment of localized prostate cancer can be successfully administered at a low volume institution. Target dosimetry values can be achieved after approximately 50 patients, with a sharp improvement noted after only 25 patients, emphasizing the importance of continuous quality improvement The Phoenix definition for biochemical failure following brachytherapy appears to be insensitive, particularly when patients are not followed beyond 5 years. PSA nadir can be helpful at predicting recurrence-free survival when the value is quite low. □

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