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Long-term outcomes and prognostic factors in patients treated with intraoperatively planned prostate brachytherapy

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ABSTRACT

PURPOSE: Evaluate outcomes and prognostic factors in men with localized prostate cancer.
METHODS AND MATERIALS: A total of 3760 patients have undergone prostate seed implantation at our institution. This review is of our initial 304 consecutive patients treated before January 30, 2001. A total of 124 patients were treated with ^{125}I implant monotherapy and 180 with ^{103}Pd implant combined with 45-Gy external beam radiation therapy.
RESULTS: The median followup was 10.3 years. A 10-year biochemical control for low risk (LR) was 98% , intermediate risk (IR) 94%, high risk (HR) 78%, and HR with one HR factor 88% ($p < 0.001$); cause-specific survival was 99%, 98%, and 84% for LR, IR, and HR, respectively ($p < 0.001$); No significant difference in outcome was seen for LR and IR patients ($p > 0.3$). On multivariate analysis, only pretreatment PSA, Gleason score, and T-stage were significant for biochemical control. Most biochemical failures occurred within 5 years (93%).
CONCLUSIONS: With a minimum followup of 10 years, results are excellent and do not differ for LR or IR prostate cancer patients. HR patients are a very heterogeneous group, and excellent results can still be achieved for HR patients with only one HR feature.

Keywords: External beam radiation therapy; Brachytherapy; Prostate-specific antigen; Biochemical control; Overall survival; Toxicity; Outcomes; Prostate cancer

Introduction

Randomized studies comparing different treatment modalities in the management of prostate cancer are limited. Most published experience with low-dose-rate (LDR) prostate brachytherapy relies on the retrospective analysis from select institutions (1−7). This is one of the largest brachytherapy series with a median followup longer than 10 years.

The purpose of this analysis was to analyze a single institution's long-term brachytherapy outcomes in patients treated a minimum of 10 years ago and further define prognostic risk factors for localized prostate cancer treated with intraoperative brachytherapy alone or combined with external beam radiation therapy (EBRT).

Methods and materials

A total of 3760 patients have undergone an intraoperative LDR prostate seed implant by a Florida Radiation Oncology Group physician at our institution. Patient and treatment data were prospectively collected in our institutional review board−approved database. Patients received brachytherapy with or without EBRT and/or androgen suppression (AS). Patients who had radiologic or pathologic evidence of metastatic or lymph node−positive diseases were not included in this database. For this analysis, only patients treated before January 10, 2001 were selected. Patients lost to followup ($n = 34$) or treated for

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salvage ($n = 17$) for local recurrence after prior EBRT were excluded. A total of 304 patients were available for review.

All patients were evaluated initially by a thorough history and physical examination (including digital rectal examination) followed by routine laboratory studies, including pelvic computed tomographic scans, bone scans, serum prostate-specific antigen (PSA) levels, and Gleason score (GS) determined by needle biopsy. All patients were restaged according to seventh edition of the American Joint Committee on Cancer Staging System. Patients were stratified further into low-risk (LR), intermediate-risk (IR), and high-risk (HR) groups as per National Comprehensive Cancer Network (NCCN) guidelines (8).

Treatment

All patients were implanted using an interactive ultrasound (US)-guided transperineal technique. Under general anesthesia, patients were placed in the dorsal lithotomy position. Foley catheter was placed and temporarily clamped. Under transrectal US guidance, the prostate position was determined on both transverse and sagittal views. The prostate was then contoured on successive 5-mm cuts, and the prostate volume was determined planimetrically. Two 18-gauge needles were placed in the center of the prostate to help immobilize the gland. Needles were then placed evenly spaced around the periphery of the gland at the largest transverse image. Needles were spaced approximately every 0.7−1 cm under real-time transverse and longitudinal US guidance. Special attention was given to avoid the rectum, bladder, and urethra. Images of the prostate gland were then entered into the Variseed (Varian Medical Systems, Inc., Palo Alto, CA) planning computer system at 5-mm intervals. All critical anatomies, including the prostate, rectum, urethra, and seminal vesicle, were contoured on each slice. All *actual* needle positions were then entered into the planning system as well. Position and shape of all structures were then reviewed compared with real-time US feed on both the axial and sagittal planes. Using real-time US guidance in the sagittal plane, radioactive seeds accounting for 75% of the activity were then placed through the needles with a Mick applicator. Central needles were then placed using both transverse and sagittal information, carefully evaluating the position of the urethra. Different seed arrangements were then evaluated to optimize the dosimetry. Once an ideal solution is found, the inner seeds are placed under US guidance. Intraoperative dosimetry report is complete as soon as the last seed is positioned. Prostate D_{90} 100% was 160 Gy for iodine implants alone and 100 Gy for palladium implants followed by EBRT. One month after implant, postoperative dosimetry is done. Three dimensional (3D)−based EBRT was done 8 weeks after the implant. EBRT was 3D based because they were treated before 2001 and subsequently the start of intensity-modulated radiation therapy at our institution.

Most LR patients were treated with brachytherapy alone, and all IR and HR patients received brachytherapy and external radiation. When used, EBRT was done based on 3D planning to the prostate and seminal vesicles alone. Total EBRT dose was 45 Gy in 1.8-Gy fractions.

Data analysis

All dosimetric calculations were done on the date of implant and at 1 month after the implantation. Dates for all events were recorded based on the date of the finding by PSA, imaging, or physical examination. All possible attempts were made to determine the cause of death. This information was available for most cases. If the cause of death was not available, patients with known metastatic disease were considered to have died of prostate cancer. Biochemical failure was based on current nadir plus 2 ng/mL definition, start of AS regardless of PSA, or a clinical failure. Distant metastases were based on imaging findings with or without biopsy. Kaplan−Meier curves and Cox univariate and multivariate analyses (MVA) were used for all statistical calculations using Systat Software Inc., Chicago, IL, and a two-sided p-value lower than 0.05 was considered significant.

Results

A total of 3760 patients have been treated with low-dose prostate brachytherapy in our program since 1997. Our initial 355 consecutive patients, all treated before January 10, 2001, were included. Of these 355 patients, 17 patients treated with brachytherapy for salvage and 34 patients lost to followup were excluded. A total of 304 patients were used for the current analysis. The median followup for our patient population was 10.3 years (range, 6 months−14 years). Patient characteristics are described in Table 1. AS was used because of the urologist preference or gland downsizing. Most patients had AS for 3 months or for shorter duration. As per our guidelines, HR patients were kept on AS for 9−12 months. Only 16 patients of the 247 treated with AS received it for more than 1 year.

Outcomes by risk group

Outcomes were stratified by risk groups using the NCCN stratification. The results for overall survival (OS), cause-specific survival (CSS), freedom from distant metastasis (FDM), and biochemical control (BC) are summarized in Table 2.

Interestingly, for the LR and IR patients, no difference was seen in survival ($p = 0.8$), CSS ($p = 0.3$), FDM ($p = 0.6$), or BC ($p = 0.5$).

Analysis of risk factors

In univariate analysis, GS, T-stage, and PSA were significant for OS, CSS, FDM, and BC ($p < 0.002$). Although perineural invasion (PNI) was significant for FDM and

Table 1
Patient's characteristics

Parameters	% of N ($N = 304$)
T-stage	
T1	62.4
T2	32.9
T3	4.7
PSA (ng/mL)	
<10	72.6
10–20	20.1
>20	7.3
Gleason score	
≤6	74.7
7	15.1
8–10	10.2
Risk groups	
Low	45.7
Intermediate	25.3
High	29.0
Low	22
High	7
Perineural invasion	17.1
Percent core involvement	
Median	33
≥50	35.2
Androgen suppression	81
Median (mo)	3
Range (mo)	1–24
Median age (y)	67

PSA = prostate-specific antigen.

Table 2
Outcomes for all patients by risk group

Risk group	10-Year outcome
Overall survival (SE)	
Low risk, %	83 (3.4)
Intermediate risk, %	81 (4.7)
High risk, %	62 (5.3)
p-Value	<0.001
Cause-specific survival (SE)	
Low risk, %	98 (0.9)
Intermediate risk, %	94 (2.1)
High risk, %	84.1 (4.2)
p-Value	<0.001
Freedom from distant metastasis (SE)	
Low risk, %	98 (1.2)
Intermediate risk, %	97 (2.1)
High risk, %	80 (4.7)
p-Value	<0.001
Biochemical control (SE)	
Low risk, %	98 (1.4)
Intermediate risk, %	94 (2.7)
High risk all, %	78 (4.5)
High risk—low, %	88 (4.9)
High risk—high, %	44 (11.2)
p-Value	<0.001

BC, it was not significant for OS or CSS. Percent biopsy core involvement and >50% core involved were significant for CSS, DM, and BC but not for OS.

Analyses of cutoff values were based on the relative changes of the selected variables in relation to BC. The best cutoff for T-stage in our patient population was T2b, with little variation among the curves for T1c and T2a disease. As can be seen in the curves (Fig. 1), significant differences were seen among T1–T2a, T2b, and T2c–T3 ($p = 0.008$). However, no difference was seen in the curves between T2b and T2c–T3 disease ($p = 0.98$). Ten-year BC was excellent for different risk factors. For T1c–T2a, T2b, and T2c–T3 patients, 10-year BC was 98% (SE, 1.5%), 87% (SE, 4.8%), and 86% (SE, 3.1%), respectively.

Regarding GS, the best separation among the curves was seen based on maximum Gleason, including either the primary or secondary grade, as can be seen in Fig. 2. The separation between the curves was better than that for GS divided in the traditional three-tier system of GS ≤6, 7, and 8–10. As this was a population treated more than 10 years ago, there was a strong selection bias for patients with aggressive disease to be treated with radiation rather than surgery; the results by maximum GS are still favorable. Ten-year BCs were for maximum Gleason Grade 3, 96%; Gleason Grade 4, 72%; and Gleason Grade 5, 33% ($p < 0.0001$).

Pretreatment PSA was found to be a strong discriminant for poor outcomes largely because of its ability to segregate patients with a high potential for metastatic disease. When all patients were included, or divided into three groups, pretreatment PSA as a continuous variable was significant for OS, CSS, FDM, and BC. However, if pretreatment PSA level of ≥40 ng/mL is used as an exclusion criteria based on the high likelihood of the presence of microscopic metastatic disease, pretreatment PSA is less valuable to divide the patient population in different risk groups. Ten-year BC for PSA levels of <10, 10–20, and ≥20 and <40 ng/mL was 94% (SE, 1.7%), 86% (SE, 4.6%),

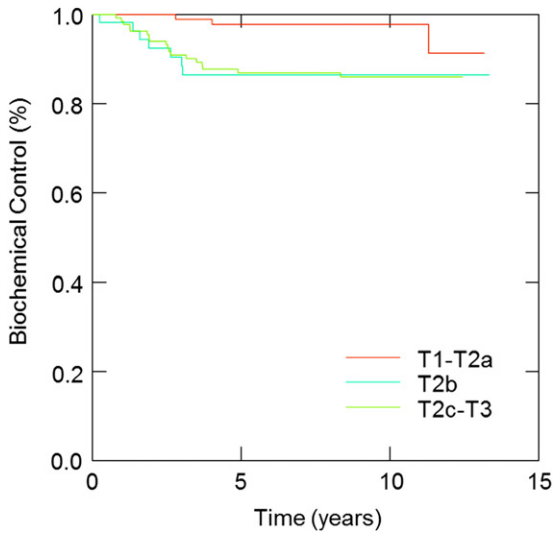

Fig. 1. Biochemical control by tumor stage for all cases.

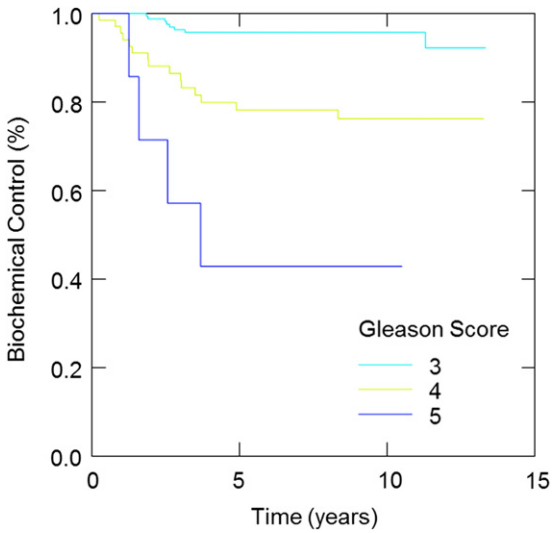

Fig. 2. Biochemical control by Gleason score for all cases.

and 84% (SE, 10%), respectively and were not significantly different ($p = 0.1$).

Multivariate analysis

MVA revealed that only PSA, GS, and T-stage were significant for BC as seen in Table 3. Interestingly, pretreatment PSA was not significant when limited to patients with a PSA level of <40 ng/mL. However, GS and T-stage remained significant. PNI or percent core involvement was not significant in MVA for all cases or excluding patients with a PSA level of >40 ng/mL.

Analysis by group stratification

Based on the results of the MVA, groups defined by GS, T-stage, and PSA were created as seen. Because PSA, GS, and T-stage may define a heterogeneous population in which one single risk factor or multiple risk factors may define an individual patients risk, we analyzed long-term BC based on different combinations of this risk factors to more accurately define different patient populations as seen in Table 3.

The IR patients did not behave differently from LR patients ($p > 0.8$). All LR and IR patients, regardless of PNI or percent cores involved, had a 10-year BC of 96% (SE, 1.5%). Even HR patients with only one HR feature of GS of 8−10, PSA level of >20 ng/mL, or >T2c had a 10-year BC of 88% (SE, 3.9%), whereas patients with multiple HR features had a BC of 44% (SE, 11.2%), $p <$ 0.001. Figure 3 shows BC curves for all patients by a number of risk factors.

Toxicity in our study was low. Only 3% (10/304) of the patients treated presented with rectal Grade 2 or higher adverse events, 0.3% Grade 3. Grade 2 or higher genitourinary adverse events were seen in 10.9% (33/304) of patients. Of them, 6.9% (21/304) of patients required a temporary urinary catheter after treatment. Only 1 patient (0.3%) had Grade 4 genitourinary and gastrointestinal toxicities. No Grade 5 complications were seen.

Table 3
Multivariate analysis for biochemical control for all cases

Variables	*p*-Value
All cases	
Pretreatment PSA	0.02
T-stage	<0.001
GS	0.002
Pretreatment PSA	0.013
T-stage	0.001
GS	0.005
PNI	0.3
Pretreatment PSA	0.03
T-stage	0.003
GS	0.002
Cores (+), %	0.97
Pretreatment PSA	0.03
T-stage	0.001
GS	0.002
Cores >50%	0.93
PSA <40 ng/mL	
Pretreatment PSA	0.4
T-stage	0.002
GS	0.005

PSA = prostate-specific antigen; GS = Gleason score; PNI = perineural invasion.

Our prescription dose was 160 Gy for iodine and 100 Gy for palladium, and our median intraoperative dose to 90% of the prostate (PD_{90}) was 111%. The median PD_{90} at 1 month was 108%. The median rectum V_{100} was 0 cc, and only 1.2% had a rectal $V_{100} \geq 1.0$ cc.

Discussion

In our study, we analyzed diverse criteria to identify prognostic factors affecting long-term prognosis in patients

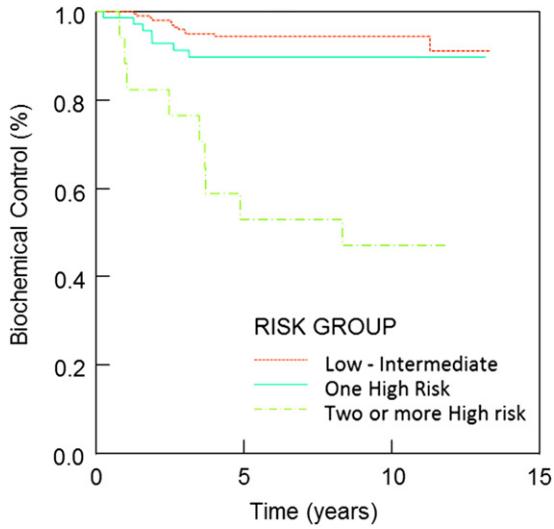

Fig. 3. Biochemical control by risk group for all cases.

treated with prostate brachytherapy with or without supplemental EBRT. Excellent long-term outcomes were found in all patient groups with the exception of very HR patients with multiple HR features.

Although LR patients were treated with seeds alone and IR patients had combined treatment, in our series, the 10-year BC rates for LR (98%) and IR patients (94%) were similar. This similarity in outcome differs from that typically reported in surgical series or randomized EBRT trials (9–14). With surgery or external radiation alone, it is possible to find differences in outcomes among subpopulations of LR or IR patients because of the lower BC rates seen with these modalities, allowing far more events and stratifications in the population.

Patients with LR disease in our series were typically treated with seed implant monotherapy. The excellent outcomes obtained may be because of the very high biologic equivalent doses (BEDs) delivered with brachytherapy, effectively ablating local disease within the prostate (15). Because patients with IR disease have a higher risk of extracapsular disease, although still nonmetastatic, treatment typically consisted of combined brachytherapy and low-dose EBRT. This regimen effectively eradicates both diseases in the prostate and occult disease in the periprostatic tissues, rendering a high BC rate that did not differ from that seen in LR patients. However, we have to emphasize that a combination of treatment results in higher total intraprostatic biologic dose and larger treatment margins than brachytherapy alone, likely resulting in the excellent results seen for IR patients and the lack of difference with LR patients. A large number of patients had short-term AS, and it was used mainly for downsizing or at the discretion of the treating urologists. It is unlikely that the use of AS was responsible for the excellent BC rates seen in this series given its short duration; most LR and IR patients had AS for up to 3 months if used. However, a randomized trial for IR patients with high-dose radiation with and without AS is necessary. Currently, the Radiation Therapy Oncology Group (RTOG) 0815 is open, and we have an in-house Phase III protocol open at our institution.

Along the same lines, volume of the disease as defined by percent core involvement was not significant on MVA (16). One may conclude that with ablative radiation doses, larger volumes of disease will be eradicated similarly as smaller volumes. Thus, traditional staging and prognostic factors proved useful to define treatment (brachytherapy alone or combined with EBRT) rather than outcome for LR and IR patients. In this regard, brachytherapy is unique among other modalities for the treatment of localized prostate cancer.

Multiple classifications, including the American Joint Committee on Cancer, the NCCN, and Harvard among others, have been commonly used to prognosticate for prostate cancer (17, 18). Although useful for patients treated with surgery or external radiation, their prognostic ability seems to be minimized in patients treated with brachytherapy in our series. As such, in our study, it is likely that the lack of difference in outcomes between LR and IR, or selected HR patients, is a result of much higher BED delivered, eradicating disease within the prostate, proximal seminal vesicles, and periprostatic tissue (15). Even in dose-escalation trials of external radiation, the BED is not likely to be similar to brachytherapy-based treatments (12–14).

Interestingly, in our patient population, the BC remained high in HR patients with only one risk factor (GS, 8–10; PSA, >20 ng/mL; or >T2c). This suggests that HR patients with only one HR factor will have predominantly localized disease, and aggressive local treatment will cure most long-term disease. However, when two or more HR factors were seen, the probability of long-term BC decreased likely as a result of distant disease present at the time of treatment. The fact that most failures in HR patients occurred within 5 years also suggests that distant microscopic disease at the time of diagnosis accounted for this failure. However, the HR population is still very heterogeneous and treatment should be tailored accordingly.

Contrary to other treatment modalities, almost all failures occurred within 5 years (19). This emphasizes the importance of aggressive local therapy to eradicate apparent and occult disease, preventing delayed cancer failures. BC in our series was excellent compared with modern surgical series (9–11). The difference between surgery and radiation is more striking when distant metastasis rates are compared. Bill *et al.* (20) found 15% rate of distant metastasis at 10 years with surgery (20, 21). For LR and IR patients, the failure rates were less than 3% in our series. Although not randomized, comparison with surgical historical controls suggests an advantage for high-dose radiation as used at our institution.

The BCs for LR and IR patients are higher in our series than those seen in randomized trials, in which surgery has been followed by adjuvant radiation (20–24). Because radiation needs oxygen to induce lasting DNA damage, postsurgical changes may impact unfavorable radiation results. Lower doses are also used after surgery in part to limit doses to the bladder as is pulled down into the prostate fossa. As such, Swanson *et al.* (22) published a 10-year BC of only 72% for adjuvant radiation, lower than the results seen in LR, IR, and HR patients in our study.

Interestingly, the BC after surgery, even for organ-confined disease with negative margins, differs for LR and IR patients (10). Furthermore, with surgery, the BC curves do not plateau as seen with LDR brachytherapy with or without EBRT, and events are seen throughout the followup period (9, 10). After surgery, it is likely that subclinical disease remains in the periprostatic tissue, nerve bundles, or remaining seminal vesicles accounting for late failures after surgery (22). In our series, only two biochemical events occurred beyond 5 years. This emphasizes the importance of optimizing local control as is possible with intraoperatively planned brachytherapy alone or with EBRT to achieve high long-term prostate cancer control.

Conclusion

Intraoperative brachytherapy alone or with external radiation is an excellent treatment for localized prostate cancer. Results for LR, IR, and selected HR patients are very good and almost undistinguishable from each other. HR patients remain a very heterogeneous population and better stratification is necessary to tailor treatments accordingly.

References

[1] Forsythe K, Burri R, Stone N, *et al*. Predictors of metastatic disease after prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2012;83: 645−652.

[2] Martinez AA, Gonzalez J, Ye H, *et al*. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. *J Radiat Oncol Biol Phys* 2011;79:363−370.

[3] Sylvester JE, Grimm PD, Blasko JC, *et al*. 15-Year biochemical relapse free survival in clinical Stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007;67:57−64.

[4] Sylvester JE, Grimm PD, Wong J, *et al*. Fifteen-year biochemical relapse-free survival, cause-specific survival, and overall survival following I(125) prostate brachytherapy in clinically localized prostate cancer: Seattle experience. *Int J Radiat Oncol Biol Phys* 2011; 81:376−381.

[5] Zelefsky MJ, Kuban DA, Levy LB, *et al*. Multi-institutional analysis of long-term outcome for stages T1-T2 prostate cancer treated with permanent seed implantation. *Int J Radiat Oncol Biol Phys* 2007; 67:327−333.

[6] Martinez AA, Demanes J, Vargas C, *et al*. High-dose-rate prostate brachytherapy: An excellent accelerated-hypofractionated treatment for favorable prostate cancer. *Am J Clin Oncol* 2010;33:481−488.

[7] Vargas CE, Martinez AA, Boike TP, *et al*. High-dose irradiation for prostate cancer via a high-dose-rate brachytherapy boost: Results of a phase I to II study. *Int J Radiat Oncol Biol Phys* 2006;66:416−423.

[8] National Comprehensive Cancer Network. 2012. Available at: https://subscriptions.nccn.org/gl_login.aspx?ReturnURL=http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed August 13, 2012.

[9] Hull GW, Rabbani F, Abbas F, *et al*. Cancer control with radical prostatectomy alone in 1,000 consecutive patients. *J Urol* 2002;167: 528−534.

[10] Menon M, Bhandari M, Gupta N, *et al*. Biochemical recurrence following robot-assisted radical prostatectomy: Analysis of 1384 patients with a median 5-year follow-up. *Eur Urol* 2010;58: 838−846.

[11] Suardi N, Ficarra V, Willemsen P, *et al*. Long-term biochemical recurrence rates after robot-assisted radical prostatectomy: Analysis of a single-center series of patients with a minimum follow-up of 5 years. *Urology* 2012;79:133−138.

[12] Dearnaley DP, Sydes MR, Graham JD, *et al*. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: First results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; 8:475−487.

[13] Kuban DA, Tucker SL, Dong L, *et al*. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67−74.

[14] Zietman AL, Bae K, Slater JD, *et al*. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: Long-term results from Proton Radiation Oncology Group/American College of Radiology 95-09. *J Clin Oncol* 2010;28:1106−1111.

[15] Stone NN, Potters L, Davis BJ, *et al*. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason score 7-10 prostate cancer treated with permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;73:341−346.

[16] Huang J, Vicini FA, Williams SG, *et al*. Percentage of positive biopsy cores: A better risk stratification model for prostate cancer? *Int J Radiat Oncol Biol Phys* 2012;83:1141−1180.

[17] Edge SB, Byrd DR, Compton CC, *et al*. *AJCC cancer staging manual*. 7th ed. New York, NY: Springer-Verlag; 2009.

[18] D'Amico AV, Moul J, Carroll PR, *et al*. Cancer-specific mortality after surgery or radiation for patients with clinically localized prostate cancer managed during the prostate-specific antigen era. *J Clin Oncol* 2003;21:2163−2172.

[19] Pound CR, Partin AW, Eisenberger MA, *et al*. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999;281:1591−1607.

[20] Bill AA, Holmberg L, Ruutu M, *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2011;364: 1708−1717.

[21] Bill AA, Holmberg L, Ruutu M, *et al*. Radical prostatectomy versus watchful waiting in early prostate cancer. *N Engl J Med* 2005;352: 1977−1984.

[22] Swanson GP, Hussey MA, Tangen CM, *et al*. Predominant treatment failure in postprostatectomy patients is local: Analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol* 2007;25: 2225−2229.

[23] Bolla M, Van PH, Collette L, *et al*. Postoperative radiotherapy after radical prostatectomy: A randomised controlled trial (EORTC trial 22911). *Lancet* 2005;366:572−580.

[24] Wiegel T, Bottke D, Steiner U, *et al*. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009;27:2924−2930.