

12-YEAR OUTCOMES FOLLOWING PERMANENT PROSTATE BRACHYTHERAPY IN PATIENTS WITH CLINICALLY LOCALIZED PROSTATE CANCER

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ABSTRACT

Purpose: We reviewed the outcomes in men treated with permanent prostate brachytherapy (PPB).

Material and Methods: A total of 1,449 consecutive patients with a mean age of 68 years treated with PPB between 1992 and 2000 and mean pretreatment prostate specific antigen (PSA) 10.1 ng/ml were included in this study. Of the patients 55% presented with Gleason 6 tumors and 28% had Gleason 7 disease. A total of 400 patients (27%) were treated with neoadjuvant hormones and 301 (20%) were treated in combination with external radiation plus PPB. Several biochemical freedom from recurrence (BFR) definitions were determined. Statistical analysis consisted of log rank testing, Kaplan-Meier estimates and Cox regression analysis.

Results: Median followup was 82 months with 39 patients at risk at for 144 months. Overall and disease specific survival at 12 years was 81% and 93%, respectively. The 12-year BFR was 81%, 78%, 74% and 77% according to the American Society for Therapeutic Radiology and Oncology (ASTRO), ASTRO-Kattan, ASTRO-Last Call and Houston definitions, respectively. The 12-year ASTRO-Kattan BFR using risk stratification was 89%, 78% and 63% in patients at low, intermediate and high risk, respectively ($p = 0.0001$). Multivariate analysis identified the dose that 90% of the target volume received ($p < 0.0001$), pretreatment PSA ($p = 0.001$), Gleason score ($p = 0.002$), the percent positive core biopsies ($p = 0.037$), clinical stage ($p = 0.689$), the addition of hormones ($p = 0.655$) and the addition of external radiation ($p = 0.724$) for predicting BFR-ASTRO. Five-year disease specific survival was 44% in patients with a PSA doubling time of less than 12 months vs 88% in those with a PSA doubling time of 12 months or greater ($p = 0.0001$).

Conclusions: PPB offers acceptable 12-year BFR in patients who present with clinically localized prostate cancer. Implant dosimetry continues as an important predictor for BFR, while the addition of adjuvant therapies such as hormones and external radiation are insignificant. In patients who experience biochemical failure it appears that PSA doubling time is an important predictor of survival.

KEY WORDS: prostate, prostatic neoplasms, brachytherapy, radiometry, prostate-specific antigen

Permanent prostate brachytherapy (PPB) has emerged as a definitive treatment option in men with clinically localized prostate cancer. Biochemical control rates in patients treated with transperineal PPB appear similar to those in patients treated with radical prostatectomy or external beam radiation.¹ Nonetheless, long-term data on PPB are only now becoming available since the technique was developed and perfected in the late 1980s and early 1990s. Despite favorable outcomes considerable controversy remains to define the role of adjuvant external beam radiation therapy (EBRT) or androgen ablation (AA). While some groups believe that all patients should receive adjuvant EBRT, it appears that those at low and intermediate risk may be treated successfully with an implant as monotherapy.² Randomized trials addressing the role of EBRT combined with brachytherapy are currently ongoing but the final analysis is still several years away. In the current study we reviewed the outcomes in a maturing data set of men undergoing prostate brachytherapy

by assessing various biochemical definitions of failure and we assessed factors that may impact disease specific survival.

MATERIALS AND METHODS

Patient selection. A total of 1,449 consecutively treated patients with clinically localized prostate cancer underwent PPB after informed consent was obtained between 1992 and 2000. All patients had biopsy proven adenocarcinoma and were staged with history and physical examination according to 1997 American Joint Committee on Cancer standards.³ Central pathological review was performed on all pathology specimens obtained elsewhere.

Treatment. All patients underwent transrectal ultrasound to assess prostate size. Those with glands greater than 60 cc received 3 to 4 months of AA therapy consisting of a luteinizing hormone releasing hormone agonist with or without an antiandrogen. Other patients were started on AA at the discretion of their urologist. Mean AA duration was 5.2 months (range 1 to 24). Treatment typically followed the standards suggested by the American Brachytherapy Society, in that patients presenting with prostate specific antigen (PSA) 10 ng/ml or less, Gleason score 2 to 6 and clinical stage

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T1 to T2a were considered at low risk and were treated with brachytherapy alone.⁴ Patients with PSA greater than 10 ng/ml, Gleason score 7 to 10 or clinical stage T2b were considered at higher risk and were offered a combination of EBRT and PPB. However, considerable overlap of combined therapy occurred based on physician or patient preference.

Implant technique. Preplanning for PPB used the prostate dimensions measured by transrectal ultrasound to determine the total isotope activity required. Briefly, patients were placed in the dorsal lithotomy position. A biplane ultrasound probe was used with needles placed based on a weighted peripheral loading and urethral sparing approach. Seeds were placed in the prostate with an interstitial gun applicator without fluoroscopy.

Dosimetry. The prescribed doses for patients implanted with ¹²⁵I or ¹⁰³Pd were 144 (Task Group [TG]43) and 136 Gy (National Institute of Standards and Technology-1999), respectively. The prescribed dose was changed during the treatment period to conform with updated TG-43 and National Institute of Standards and Technology-1999 standards.^{5,6} However, the delivered doses for ¹²⁵I and ¹⁰³Pd were kept constant. When EBRT was added, the prescribed implant doses for ¹²⁵I and ¹⁰³Pd were decreased to 108 Gy (TG-43) and 102 Gy, respectively. EBRT doses were 41.4 to 45 Gy at 1.8 Gy per fraction, typically administered before implant. Three-dimensional post-implantation software became available in 1996 and dosimetry was performed in 945 patients 3 weeks after brachytherapy.

Followup. Followup intervals were scheduled 5 weeks after implantation, every 3 to 4 months for 2 years and every 6 months thereafter. At each followup visit serum PSA was determined. A total of 51 patients were without a followup of greater than 12 months at the time that the study was performed. All actual followup PSA values were entered into our database to allow computer generated PSA failure across the entire cohort. We applied several definitions of outcomes. 1) We used the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of PSA relapse-free survival (PSA-RFS) following EBRT⁷ with failure marked at the midpoint in time between the posttreatment nadir and the first of 3 consecutive PSA increases. 2) We assessed the ASTRO definition with 2 modifications (ASTRO-Kattan definition).⁸ The requirement that the 3 increases had to be consecutive was relaxed and, in patients in whom the most recent PSA values were increasing at the last followup but in whom failure had not occurred, followup time was truncated at the PSA immediately before the first increase. 3) We assessed the outcome based on 3 consecutive PSA increases, calling failure on the date of the last increase (ASTRO-Last increase). 4) We assessed outcome based on the Houston definition, which identifies failure based on a PSA increase of 2 ng/ml from the nadir.⁹

Risk stratification. Patients were stratified by certain factors, including pretreatment PSA less than 10, or 10 ng/ml or greater, Gleason score less than 7, or 7 or greater and percent positive core biopsy specimens less than 50%, or 50% or greater. There was no significance on univariate analysis for clinical stage and, therefore, it was not used for risk stratification. Patients with 3 favorable factors were classified as being at low risk, those with 1 adverse factor were classified as being at intermediate risk and those with 2 or more adverse factors were classified as being at high risk.

Analysis. Multivariate analyses were performed by the Cox proportional square hazards model testing to evaluate several factors.¹⁰ Kaplan-Meier curves were constructed to demonstrate survival distributions.¹¹ The log rank test was used to compare PSA-RFS between the subsets of patients analyzed. Disease specific survival was assessed in patients who experienced BFR (ASTRO-Kattan definition).

RESULTS

Tables 1 and 2 list patient characteristics, followup and characteristics based on risk classification. Median followup was 82 months with 39 patients at risk at for 144 months. Overall and disease specific survival at 12 years was 81% and 93%, respectively. The 12-year BFR using the ASTRO-Kattan definition was 78% (fig. 1).

Table 3 shows BFR based on the examined definitions in the entire cohort and by risk stratification at 12 years. BFR using the ASTRO-Kattan definition was 89% in patients at low risk, 78% in those at intermediate risk and 63% in those at high risk ($p = 0.0001$, fig. 2).

Cox regression revealed that the dose that 90% of the target volume received (D90) ($p < 0.0001$), pretreatment PSA ($p = 0.001$), Gleason score ($p = 0.002$) and the percent of positive core biopsies ($p = 0.037$) were significant, while clinical stage ($p = 0.689$), the addition of hormones ($p = 0.655$) and the addition of external radiation ($p = 0.724$) were insignificant factors predicting BFR-ASTRO (table 4).

Patients who experienced biochemical failure (ASTRO-Kattan definition) were analyzed based on additional treatment or outcomes (table 5). Figure 3 shows disease specific survival in this group of patients.

DISCUSSION

This study presents 12-year outcomes from a maturing data set of consecutively treated patients who have undergone ultrasound guided, transperineal prostate brachytherapy. Regardless of the definition used biochemical control continues to support brachytherapy as a successful treatment option in men presenting with clinically localized prostate cancer. Our results are similar to those of others who have presented 8 to 13-year biochemical control rates between 66% and 88%.^{12,13}

Permanent prostate brachytherapy is prescribed to deliver a high radiation dose to the prostate with a small margin. The concept of a dose response to assess implant quality was first reported by Stock et al, who identified a dose cutoff point at 140 Gy with PSA control rates at 68% in patients receiving a D90 of less than 140 Gy compared with 92% in those with a D90 of 140 Gy or greater ($p = 0.02$).¹⁴ We have reported results confirming the significance of D90 as an implant quality measure with a significant cutoff point identified at a D₉₀ dose of at or above 90% of the prescribed dose.¹⁵ The current study further confirms that dosimetry using D90 as a parameter for implant quality remains an important predictor of BFR, at least in our patient cohort. Since D90 is a reflection of a minimum dose to the prostate volume, it does not account for excess radiation within the gland and it may not be the best method to identify regions within the gland that are under dosed, of which each may have an equally important role in determining the outcome and toxicity risk. As a result, some groups have questioned the validity of D90 as the best parameter of implant

TABLE 1. Patient characteristics and followup

Age:	
Mean	68.05
Range	43.5–84.4
% D90:	
Mean	102
Range	57–188
No. clinical stage (%):	
T1b	9 (.6)
T1c	864 (60)
T2a	472 (33)
T2b	72 (5)
T2c	32 (2)
Followup PSA:	
No.	14,354
Mean (ng/ml)	7.2
Mean followup (mo)	82.3

TABLE 2. Patient classifications based on risk assessment

	Low	Intermediate	High	Totals
No. pts	481	554	418	1,449
No. adjuvant therapy addition:				
EBRT	11	62	107	180
Hormones	101	106	72	279
Hormones + EBRT	8	47	66	121
Isotope:				
¹²⁵ I	67	129	124	320
¹⁰³ Pd	414	425	290	1,129
No. % core biopsy pos:				
Less than 50%	481	222	105	808
50 or Greater		332	309	641
Mean pretreatment PSA (ng/ml)	6.3	9.4	15.3	10.1
Gleason score:				
2-6	481	374	110	965
7	0	163	249	412
8-9	0	13	59	72

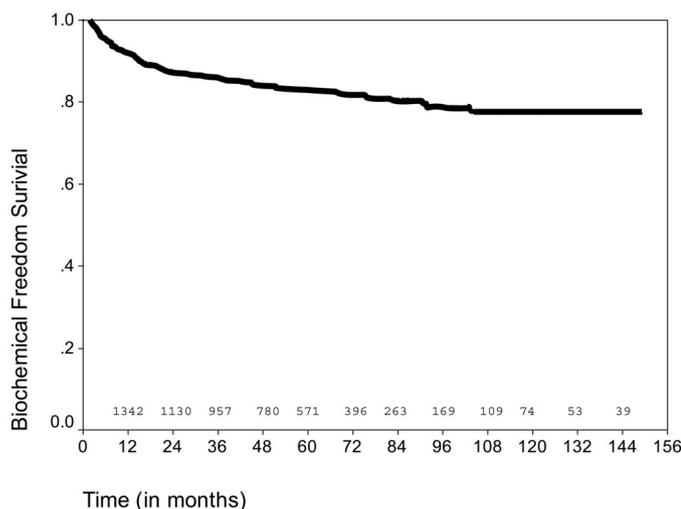


FIG. 1. ASTRO-Kattan biochemical freedom from failure in all 1,449 patients with those at risk labeled.

TABLE 3. Outcomes based on definitions of biochemical freedom from failure

	% ASTRO	% ASTRO-Kattan	% ASTRO-Last Call	% Houston
All pts	81	78	74	77
Low risk	91	89	85	88
Intermediate risk	80	78	74	76
High risk	66	63	59	62

quality. Using bioeffective modeling that measures regions of high or low radiation dose relative to cancer location may better assess implant quality.¹⁶ Nonetheless, clinical data and dose modeling standards for such techniques remain elusive at this time.

While combining EBRT and brachytherapy remains a popular method for treating some patients, the current study does not support the effectiveness of EBRT for predicting BFR. Unfortunately randomized trials to address the role of adding EBRT to PPB require accrual and maturity before the answer is appropriately addressed. Of note, only 20% of our patients received combined PPB and EBRT. While there was clearly a trend toward the addition of EBRT in patients at higher risk (table 2), the addition of EBRT was not an independent predictor for BFR (table 4). Furthermore, the EBRT technique during most of this study would qualify as a minipelvic, 4 field arrangement using 10 × 10 cm field sizes. Based on Radiation Therapy Oncology Group external beam data suggesting the role for whole pelvic radiation in patients

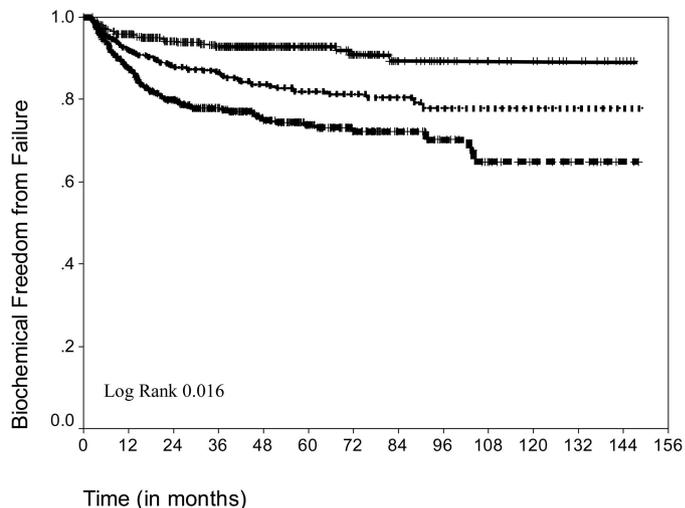


FIG. 2. ASTRO-Kattan biochemical freedom from failure based on risk classification of low, intermediate and high.

TABLE 4. Multivariate analysis to predict ASTRO-Kattan freedom from biochemical recurrence

	p Value	Exp(B)	Exp(B) 95% CI	
			Lower	Upper
% D90	0.000	1.021	1.014	1.028
Pretreatment PSA	0.001	1.023	1.009	1.037
Gleason score	0.002	1.47	1.156	1.869
Pos biopsy core	0.037	1.492	1.024	2.173
Hormone addition	0.655	0.912	0.608	1.368
Clinical stage	0.689	0.94	0.694	1.273
EBRT addition	0.724	0.925	0.599	1.427

TABLE 5. Patient outcomes stratified by PSA doubling time

	No. Doubling Time (%)	
	Less Than 12 Mos	12 Mos or Greater
Overall	51 (43)	69 (57)
Hormone therapy	11 (22)	29 (42)
Metastasis	3 (6)	1 (1)
Death:		
Disease	13 (25)	5 (7)
Other	8 (16)	6 (9)
Alive, no treatment	8 (16)	6 (23)

at high risk, it is not clear that our field size and technique may have been suitable to impact BFR in those at high risk.¹⁷ Our current treatment philosophy is to use the addition of EBRT in patients at high risk using a treatment technique similar to current Radiation Therapy Oncology Group high risk protocols. Interestingly we have reported that in patients receiving combined radiation and brachytherapy D90 is not a significant predictor of BFR and, therefore, when patients receive combined modalities, implant quality is less important.¹⁵ Therefore, the addition of EBRT may mask a poor dosimetric implant, albeit with added expense and toxicity.

Likewise the role of AA therapy remains controversial. The classic role of AA in patients undergoing PPB remains that of prostate reduction. However, this approach may carry the unfortunate risk of higher urinary retention rates. Since there are data indicating that prostate size should not be a contraindication to PPB, size reduction may be unnecessary.¹⁸ As adjuvant therapy, there are no randomized studies using AA with PPB and until such studies are reported the potential advantage of AA remains speculative.¹⁹ In the cur-

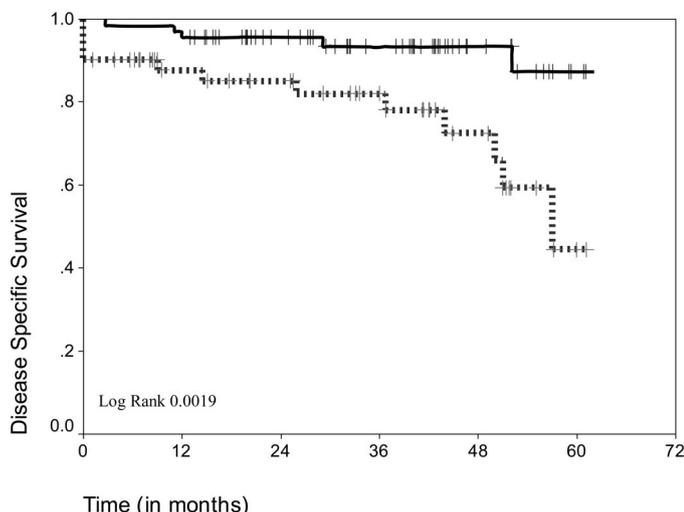


FIG. 3. Disease specific survival based on PSA doubling time (less than 12 months and 12 months or greater).

rent study the addition of AA was not an independent predictor for BFR, although its use was not closely controlled for and many urologists administered hormones at their discretion regardless of prostate size.

Debate continues on the acceptance of an appropriate biochemical definition to serve as a surrogate for disease specific survival. To that end the ASTRO definition based on 3 consecutive PSA increases remains the standard definition, if for no other reason than to compare results with those of already published studies. Similar to others who have addressed this issue, there is no considerable difference in the current study between the biochemical definitions examined despite the suggestion that the sensitivity and specificity of the Houston definition may have the best sensitivity/specificity and be most appropriate (table 3). While a biochemical outcome definition may allow earlier outcome assessment of surgery or radiation therapy, the better use of such a PSA based outcome definition should be to identify the need for and aggressiveness of salvage therapy. To delineate better clinical outcomes with the biochemical definition we identified that PSA doubling time greater or less than 12 months is highly significant for predicting disease specific survival. This observation identifies a group of patients that likely require aggressive salvage therapy. This result is similar to that presented by D'Amico et al, who reported that the PSA doubling time in men treated with external radiation therapy predicted disease specific survival.²⁰ Interestingly in the current study patients who experienced biochemical failure (ASTRO-Kattan definition) with PSA doubling time greater than 12 months had 89% 5-year disease specific survival. Perhaps, then, the most common biochemical definitions used following radiation therapy significantly overestimate patients at risk for disease progression and those who need salvage therapy. This dichotomous outcome between a PSA surrogate definition and disease specific survival is also seen in radical prostatectomy series. The Johns Hopkins group reported their 15 year outcomes using a PSA definition of 0.2 ng/ml.²¹ Overall 10 and 15-year biochemical recurrence-free survival rates were 72% and 61%, respectively. The overall metastasis-free survival rates at 10 and 15 years were 90% and 82%, respectively and the overall cancer specific survival rates at 10 and 15 years were 96% and 90%, respectively. While it is not clear that the difference between BFR survival and metastasis-free survival was based on salvage therapy, there appears to be a group of patients with biochemical recurrence that may do well without salvage treatment. Unfortunately until there is additional information that exam-

ines the role of surrogate definitions relative to salvage therapy, using standard biochemical definitions to identify men who require aggressive salvage therapy remains controversial. Perhaps, then, PSA doubling time may offer additional information when deciding on salvage therapy.

CONCLUSIONS

The 12-year outcomes following PPB continue to remain acceptable. We continue to identify a direct relationship between implant quality, as measured by D90 and outcomes. Adjuvant therapies, such as the addition of EBRT or AA, remain questionable pending randomized data. When PSA doubling time is less than 12 months in men who experience biochemical failure, aggressive salvage therapy may be required.

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REFERENCES

- Blasko, J. C., Mate, T., Sylvester, J. E., Grimm, P. D. and Cavanagh, W.: Brachytherapy for carcinoma of the prostate: techniques, patient selection, and clinical outcomes. *Semin Radiat Oncol*, **12**: 81, 2002
- Potters, L., Fearn, P. and Kattan, M. W.: External radiotherapy and permanent prostate brachytherapy in patients with localized prostate cancer. *Brachytherapy*, **1**: 36, 2002
- Fleming, I., Cooper, J. S., Henson, D. E., Huttler, R. V. P., Kennedy, B. J., Murphy, G. P. et al: *AJCC Cancer Staging Manual*, 5th ed. Philadelphia: Lippincott-Raven, 1997
- Nag, S., Beyer, D., Friedland, J., Grimm, P. and Nath, R.: American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys*, **44**: 789, 1999
- Beyer, D., Nath, R., Butler, W., Merrick, G., Blasko, J., Nag, S. et al: American Brachytherapy Society recommendations for clinical implementation of NIST-1999 standards for (103)palladium brachytherapy. The clinical research committee of the American Brachytherapy Society. *Int J Radiat Oncol Biol Phys*, **47**: 273, 2000
- Nath, R., Anderson, L. L., Luxton, G., Weaver, K. A., Williamson, J. F. and Meigooni, A. S. et al: Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group No. 43. American Association of Physicists in Medicine. *Med Phys*, **22**: 209, 1995
- Consensus statement: Guidelines for PSA following radiation therapy. American Society for Therapeutic Radiology and Oncology Consensus Panel. *Int J Radiat Oncol Biol Phys*, **37**: 1035, 1997
- Kattan, M. W., Fearn, P. A., Leibel, S. and Potters, L.: The definition of biochemical failure in patients treated with definitive radiotherapy. *Int J Radiat Oncol Biol Phys*, **48**: 1469, 2000
- Thames, H., Kuban, D., Levy, L., Horwitz, E. M., Kupelian, P., Martinez, A. et al: Comparison of alternative biochemical failure definitions based on clinical outcome in 4839 prostate cancer patients treated by external beam radiotherapy between 1986 and 1995. *Int J Radiat Oncol Biol Phys*, **57**: 929, 2003
- Cox, D. R. and Abadir, R.: Regression models and life tables. *J Roy Statist Soc*, **34**: 187, 1972
- Kaplan, E. L. and Meier, P.: Nonparametric estimation from incomplete observations. *J Cancer Res Clin Oncol*, **53**: 457, 1958
- Grimm, P. D., Blasko, J. C., Sylvester, J. E., Meier, R. M. and Cavanagh, W.: 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys*, **51**: 31, 2001
- Ragde, H., Grado, G. L. and Nadir, B. S.: Brachytherapy for clinically localized prostate cancer: thirteen-year disease-free survival of 769 consecutive prostate cancer patients treated with permanent implants alone. *Arch Esp Urol*, **54**: 739, 2001
- Stock, R. G., Stone, N. N., Tabert, A., Iannuzzi, C. and De Wyngaert, J. K.: A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys*, **41**: 101, 1998

15. Potters, L., Cao, Y., Calugaru, E., Torre, T., Fearn, P. and Wang, X. H. et al: A comprehensive review of CT-based dosimetry parameters and biochemical control in patients treated with permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys*, **50**: 605, 2001
16. Waterman, F. M. and Dicker, A. P.: Impact of postimplant edema on V(100) and D(90) in prostate brachytherapy: can implant quality be predicted on day 0? *Int J Radiat Oncol Biol Phys*, **53**: 610, 2002
17. Roach, M., 3rd, DeSilvio, M., Lawton, C., Uhl, V., Machtay, M., Seider, M. J. et al: Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol*, **21**: 1904, 2003
18. Sylvester, J., Blasko, J. C., Grimm, P. D., Meier, R. and Cavanagh, W.: Short-course androgen ablation combined with external-beam radiation therapy and low-dose-rate permanent brachytherapy in early-stage prostate cancer: a matched subset analysis. *Mol Urol*, **4**: 155, 2000
19. Roach, M., 3rd, Lu, J., Pilepich, M. V., Asbell, S. O., Mohiuddin, M., Terry, R. et al: Predicting long-term survival, and the need for hormonal therapy: a meta-analysis of RTOG prostate cancer trials. *Int J Radiat Oncol Biol Phys*, **47**: 617, 2000
20. D'Amico, A. V., Cote, K., Loffredo, M., Renshaw, A. A. and Schultz, D.: Determinants of prostate cancer-specific survival after radiation therapy for patients with clinically localized prostate cancer. *J Clin Oncol*, **20**: 4567, 2002
21. Han, M., Partin, A. W., Pound, C. R., Epstein, J. I. and Walsh, P. C.: Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am*, **28**: 555, 2001