



Original Article

Five Year Prostate-specific Antigen Outcomes after Caesium Prostate Brachytherapy

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Abstract

Aims: To report 5 year prostate-specific antigen outcomes in men undergoing prostate brachytherapy with caesium 131 at a single institution.**Materials and methods:** All patients who underwent prostate brachytherapy with caesium 131 at our institution and had at least 24 months of follow-up were included in this study. The results are reported by risk group (low, intermediate and high) as well as by treatment received (monotherapy, combination therapy or trimodal therapy). The Phoenix definition (absolute nadir plus 2 ng/ml) was used to define biochemical freedom from disease (BFD).**Results:** Four hundred and eighty-five patients underwent prostate brachytherapy with caesium 131 at our institution and 367 patients had at least 24 months of follow-up and were included in this analysis. Using the Phoenix criteria, 5 year actuarial BFD was 96.0% for patients in the low-risk category, 92.7% for patients in the intermediate-risk category and 82.9% for patients in the high-risk category. By treatment category, 95.7% of men treated with monotherapy had BFD, 84.9% of men treated with combination therapy had BFD and 92.0% of men treated with trimodal therapy had BFD.**Conclusions:** The present study showed that prostate brachytherapy with caesium 131 achieves excellent oncological outcomes at 5 years.

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Key words: Prostate brachytherapy; prostate cancer; PSA outcomes

Introduction

Prostate brachytherapy is now accepted as an effective treatment for men diagnosed with clinically localised prostate cancer [1]. Several centres carrying out large numbers of these procedures have published outcomes with long-term follow-up showing excellent cancer control [2–4]. Prostate brachytherapy has been shown to have equal outcomes in terms of cancer control when compared with radical prostatectomy and external beam radiotherapy [5,6]. Given the equivalent cancer control of these treatments, issues such as quality of life, time devoted to treatment and recovery time become important factors in the decision process of patients diagnosed with clinically localised prostate cancer. Patients who choose prostate brachytherapy are attracted in part to the minimally invasive nature of

the procedure, the quick return to full activity and the low risk of urinary incontinence.

However, virtually all men who undergo prostate brachytherapy will experience some degree of bothersome irritative and/or obstructive voiding symptoms. Most men who undergo prostate brachytherapy with implantation with the iodine 125 (¹²⁵I) isotope do not resume their baseline voiding pattern for at least 1 year after their procedure [7]. Although prostate brachytherapy is indeed minimally invasive and patients can usually return to full activity very quickly after their procedure, these lower urinary tract symptoms can become quite bothersome and can markedly affect quality of life [8–11].

A newer isotope, caesium 131 (¹³¹Cs), is now being used in prostate brachytherapy [12]. A major potential benefit of ¹³¹Cs is the possibility of a shorter duration of the bothersome voiding symptoms that accompany prostate brachytherapy [13,14]. For this reason our centre is now using this isotope in our prostate brachytherapy programme and our initial outcomes do support this contention [15]. Obviously, the primary goal when treating clinically localised prostate

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cancer is eradication of the disease. If ^{131}Cs does indeed provide for a shorter duration of the urinary morbidity associated with prostate brachytherapy, this improvement in morbidity is insignificant if it comes at the cost of inferior cancer control.

Given the general long natural history of clinically localised prostate cancer, long-term follow-up is required to definitively evaluate the oncological capability of any new treatment for this disease. However, as we await long-term results, it is important to provide short- and intermediate-term outcomes of new treatments to ensure that these treatments are on course to provide at least equivalent outcomes when compared with existing treatment options. Towards that end, the present study reports 5 year actuarial prostate-specific antigen (PSA) outcomes after ^{131}Cs prostate brachytherapy.

Materials and Methods

All patients who underwent prostate brachytherapy with implantation of the ^{131}Cs isotope at our institution and had a minimum of 24 months of follow-up were included in the present study. Patients were stratified by risk category and treatment delivered. Low-risk patients were defined as having both a Gleason sum ≤ 6 , a PSA of < 10 ng/ml and a clinical stage of T1–T2. Intermediate risk was defined as Gleason sum 7 or a PSA ≥ 10 ng/ml with clinical stage T1–T2; high risk was defined as Gleason sum ≥ 8 or a PSA ≥ 20 ng/ml or clinical stage T3–T4. Patients were characterised as receiving monotherapy if they underwent either prostate brachytherapy alone or prostate brachytherapy combined with androgen deprivation therapy (ADT). Patients who received ADT + prostate brachytherapy were placed on ADT either before referral to our centre, to downsize the prostate before undergoing prostate brachytherapy or due to the presence of high-risk disease but with contraindications to radical prostatectomy and external beam radiotherapy. Combined radiotherapy consisted of external beam radiotherapy followed by prostate brachytherapy about 4 weeks after patients completed their external beam radiotherapy. Patients undergoing external beam radiotherapy received 45 Gy in 25 fractions to prostate and seminal vesicles \pm pelvic nodes. Patients undergoing trimodal therapy received ADT + external beam radiotherapy + prostate brachytherapy. In general, patients with low-risk disease were treated with prostate brachytherapy as monotherapy and patients with high-risk disease were treated with trimodal therapy. Patients with intermediate-risk disease and a Gleason score of $3 + 4 = 7$ underwent prostate brachytherapy as monotherapy, whereas patients with intermediate-risk disease with a Gleason score $4 + 3 = 7$ received combination therapy. However, patient preference occasionally led to deviation from these recommendations.

The technique of implantation at our centre has been previously described [15]. Patients undergoing prostate brachytherapy as monotherapy were treated with a prescribed dose of 115 Gy, whereas patients undergoing combination therapy were treated with a prescribed dose of

85 Gy. Targets for dosimetry were: D90 $> 110\%$, V100 $> 90\%$, V150 $< 50\%$ and V200 $< 20\%$. Computed tomography-based dosimetry was obtained on day 0.

Patients were asked to obtain a serum PSA every 3 months for the first year after the procedure; and then at 6 monthly intervals until year 5 and then annually. All patients included in this study had a minimum of 24 months of follow-up. Patients who died for reasons other than prostate cancer before 24 months after their procedure and had not failed were not included in the analysis. The Phoenix definition (absolute nadir plus 2 ng/ml dated at the event) was used to define biochemical freedom from disease (BFD) [16].

Statistical Analysis

IBM SPSS statistical software version 21 was used for the analysis. For BFD, the Kaplan–Meier method was used with the Log-rank test for evaluating the difference in BFD for different risk categories.

Results

Four hundred and eighty-five patients had undergone prostate brachytherapy with ^{131}Cs at our institution at the time this manuscript was prepared. Three hundred and sixty-seven patients had at least 24 months of follow-up and were, therefore, included in this study. One hundred and forty-five patients had low-risk disease, 193 patients had intermediate-risk disease and 29 patients had high-risk disease. Two hundred and sixty-one patients were treated with prostate brachytherapy as monotherapy, including 19 (7.3%) patients who received ADT in combination with their brachytherapy. Seventy-one patients received combination therapy and 35 patients received trimodal therapy. The clinical characteristics of the cohort can be found in Table 1. The mean follow-up was 56.2 months (range 24–84).

Sixteen patients in the cohort have died, making overall survival 95.6%. Two patients died of prostate cancer, which corresponds to a disease-specific survival of 99.5%. Patients in the monotherapy cohort who received ADT had a mean duration of ADT of 6.8 months. Men undergoing trimodal therapy received ADT for a mean duration of 18.1 months. No patients in the cohort remained on ADT 24 months after their procedure and therefore were not on ADT at the time of their first PSA obtained for this study. Dosimetry outcomes for the cohort can be found in Table 2. The mean D90 and mean V100 for the entire cohort were 106.6 and 93.0%, respectively. The target for D90 was 110%, but this target was achieved intraoperatively via ultrasound planning. Formal dosimetry was obtained by computed tomography, which probably explains the discrepancy between the D90 target and the D90 achieved. Although many patients in the cohort experienced a PSA bounce, no patients had a PSA increase of more than 2.0 ng/ml from their nadir and subsequently had their PSA decrease without treatment.

Using the Phoenix criteria, the Kaplan–Meier analysis demonstrated that BFD rates were 96.0% for the low-risk

Table 1
Clinical characteristics

	n	Mean age (range)	Mean pretreatment prostate-specific antigen (ng/ml; range)	Median Gleason sum	Percentage of patients with clinical stage T1C
Total cohort	367	65.9 (50–83)	6.6 (1.0–78.0)	7	74.9
Low risk	145	65.4 (50–80)	5.3 (1.0–9.7)	6	88.3
Intermediate risk	193	66.0 (50–83)	7.0 (2.0–20.0)	7	71.0
High risk	29	68.0 (50–83)	11.1 (1.7–78.0)	8	34.5
Monotherapy	261	65.8 (50–83)	5.9 (1.0–16.9)	6	81.6
Combination therapy	71	65.0 (50–78)	6.7 (1.7–15.2)	7	69.0
Trimodal therapy	35	68.3 (51–79)	11.7 (1.8–78.0)	8	37.1

category, 92.7% for men in the intermediate-risk category and 82.9% for men in the high-risk category ($P < 0.01$) (Figure 1a). By treatment category; 5 year BFD rates were 95.7% for the men treated with monotherapy, 84.9% for men treated with combination therapy and 92.0% for men treated with trimodal therapy (Figure 1b). At the time of the last PSA obtained, 40.2% of patients had an undetectable PSA, 57.8% patients had a PSA of ≤ 0.1 ng/ml, 72.2% of patients had a PSA of ≤ 0.2 ng/ml, 85.2% of patients had a PSA of ≤ 0.5 ng/ml, 92.6% of patients had a PSA of ≤ 1.0 ng/ml and 96.0% patients had a PSA of ≤ 1.5 ng/ml. The mean PSA at 24 months was 0.46 ng/ml, 0.2 ng/ml at 36 months, 0.1 ng/ml at 48 months and < 0.1 ng/ml at 60, 72 and 84 months.

Discussion

Given the general slow growth of prostate cancer and its usual chronic nature, long-term follow-up in the range of 15 years is thought necessary to definitively determine the oncological success of any treatment for clinically localised prostate cancer. However, until any modality has this length of follow-up, short-term and intermediate-term results should be reported to ensure that newer interventions are

on course to provide similar or perhaps improved cancer control when compared with existing treatment outcomes. If any new modality for the treatment of clinically localised prostate cancer cannot be utilised until 15 years of follow-up is obtained, very little progress will be made in improving the treatment of this disease. Although ^{131}Cs is the newest isotope being utilised for prostate brachytherapy, this isotope has now been in use since 2004 and it is important to know whether with at least intermediate-term follow-up ^{131}Cs is on course to provide cancer control on par with prostate brachytherapy using the established isotopes ^{125}I or palladium ^{103}Pd .

The primary potential benefit of ^{131}Cs prostate brachytherapy is the possibility of a shorter duration of the urinary morbidity associated with prostate brachytherapy. However, any improvement in the duration of urinary morbidity will be of minimal importance if oncological outcomes do not meet those achieved with ^{125}I or ^{103}Pd brachytherapy. The present study reported 5 year PSA outcomes in patients undergoing ^{131}Cs prostate brachytherapy at our institution. This longitudinal, single institution study showed that oncological outcomes are quite acceptable in patients undergoing prostate brachytherapy with ^{131}Cs as BFD rates were 96.0, 92.7 and 82.9% for low-risk, intermediate-risk

Table 2
Dosimetry outcomes, seeds placed and total activity delivered

	D90 (%)			V100 (%)		
	Mean	Median	Range	Mean	Median	Range
Total cohort	106.6	105.1	88.0–133.4	93.0	93.7	75.9–99.1
Low risk	104.6	103.7	89.7–126.8	92.1	92.7	76.7–98.8
Intermediate risk	107.0	106.2	88.0–133.4	93.3	93.8	75.9–99.1
High risk	110.8	109.6	96.9–130.7	94.8	95.1	88.0–98.7
Monotherapy	105.1	103.8	88.0–126.8	92.4	93.0	75.9–98.8
Combination therapy	109.6	107.6	96.9–133.4	94.2	94.4	88.0–99.1
Trimodal therapy	111.1	109.6	97.9–130.7	94.8	95.1	89.1–98.7
	Number of seeds placed			Total activity		
	Mean	Median	Range	Mean	Median	Range
Total cohort	91.3	90	47–159	168.6	165.6	32.04–316.41
Low risk	99.9	100	62–159	189.5	182.0	32.0–316.4
Intermediate risk	88.2	86	47–154	160.5	156.6	75.2–308.0
High risk	69.1	64	48–118	118.3	117.0	76.8–212.4
Monotherapy	98.8	98	61–159	186.6	181.0	32.0–316.4
Combination therapy	75.0	74	51–129	128.5	123.2	81.6–217.2
Trimodal therapy	68.6	66	47–118	115.8	108.0	75.2–212.4

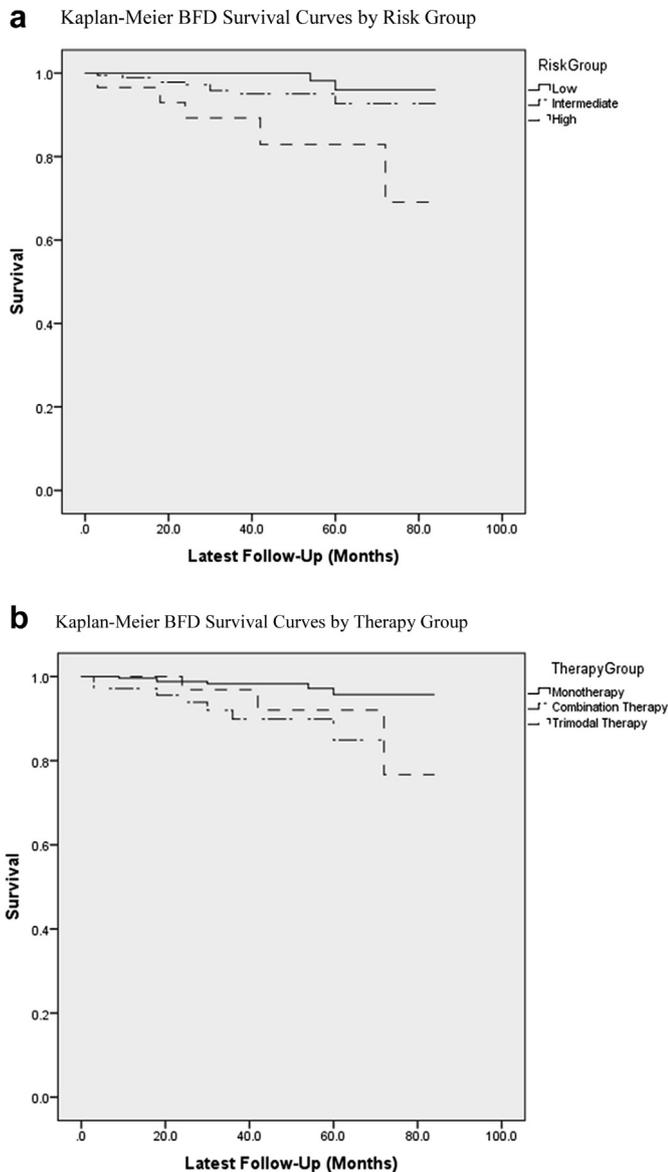


Fig 1. Kaplan–Meier biochemical freedom from disease (BFD) survival curves by (a) risk group; (b) therapy group.

and high-risk disease, respectively. Patients undergoing prostate brachytherapy with ^{125}I and ^{103}Pd have been reported to have long-term BFD rates of 88–97% if they presented with low-risk disease, 78–96% if they presented with intermediate-risk disease and 53–72% if they presented with high-risk disease [7].

Several centres have published their 5 year outcomes in men with clinically localised prostate cancer. Kubicek *et al.* [16] reported actuarial BFD rates of 85.4, 83.2 and 79.6% in men with low-, intermediate- and high-risk disease, respectively; although 71.3% of these patients received ADT. Dickinson *et al.* [17] reported 5 year actuarial PSA outcomes from three centres in the UK for men with low-risk disease of 94.2%. ADT was given to 22% of patients in this cohort. Vassil *et al.* [18] reported a 5 year actuarial BFD of 89.5% in men with intermediate-risk disease undergoing prostate brachytherapy. Zelefsky *et al.* [19] reported 5 year actuarial

BFD outcomes of 96% in men with low-risk disease and 89% in men with intermediate-risk disease.

Five years is certainly too early to definitively determine the efficacy of treatment for localised prostate cancer. Recurrences can occur many years after initial treatment, particularly local recurrences, which tend to present later than distant failures [17]. Additionally, PSA outcomes are only a surrogate outcome for the more important end points of metastases-free survival and prostate cancer-specific survival. However, 5 year outcomes do carry prognostic value [20].

If a single, fixed cut-off is set below which cure was highly likely and above which failure is likely to eventually occur, an earlier assessment of treatment efficacy will have been realised and an early interim analysis can be reliably carried out. Lo *et al.* [21] reported that men with a PSA ≤ 0.4 ng/ml 4 years after treatment had a $< 1\%$ risk of disease relapse at 8 years, whereas all patients in their study who had a PSA > 1.0 ng/ml 4 years after treatment relapsed. In our patients who had not failed, 97.9% of patients with low-risk disease, 96.7% of patients with intermediate-risk disease and 100% of high-risk disease had a PSA ≤ 0.4 ng/ml 4 years after their procedure.

Critz *et al.* [22] reported that in men who reached a PSA nadir of ≤ 0.2 ng/ml, 92% had a non-rising PSA 10 years after treatment. To date, 72.1% of men in our cohort have achieved a PSA nadir ≤ 0.2 ng/ml. The percentage of men reaching a nadir ≤ 0.2 ng/ml in the present study at 2, 3, 4, 5, 6 and 7 years is 43.5, 74.3, 98.3, 100, 100, and 100, respectively.

Although ^{131}Cs is a relatively new isotope for prostate brachytherapy and therefore long-term outcomes are not known, as long as the proper dose of radiation is delivered to the target volume one would expect oncological outcomes to be similar to those achieved with ^{125}I and ^{103}Pd . No difference in oncological outcomes has been shown between ^{125}I and ^{103}Pd despite their different dose rates [23]. It is therefore likely that as long as the dosimetry achieved is acceptable, oncological outcomes will be similar when comparing ^{131}Cs , ^{103}Pd and ^{125}I . Our dosimetry results are very acceptable and should portend excellent long-term cancer control [24]. It had long been postulated that the higher dose rate of ^{103}Pd could lead to better cancer control when compared with ^{125}I , but a difference in cancer control has never been shown between these two isotopes. It has also been theorised that with the combination of a dose rate similar to ^{103}Pd and an energy level similar to ^{125}I , ^{131}Cs will achieve cancer control better than ^{103}Pd and ^{125}I [25]. However, only longer term outcomes will address this question and this issue cannot be definitively determined without a prospective, randomised, controlled trial.

This study had limitations. Most importantly, the follow-up was not adequate to definitively determine the oncological control associated with ^{131}Cs . The intermediate-term follow-up of these patients is more likely to overestimate outcomes in men with low-risk disease when compared with patients with intermediate- and high-risk disease. Patients with low-risk disease are very likely to have clinically localised disease and at least some of the patients in the cohort were not followed for long enough for failure to occur [26]. By contrast, men with high-risk disease are more

likely to have microscopic metastatic disease at the time of diagnosis and PSA recurrence will probably occur earlier in these men compared with patients with low-risk disease. An exception is in men with high-risk disease treated with androgen deprivation. If these patients remain on ADT for 2–3 years, shorter-term follow-up may overestimate disease control as these patients' PSA may still be suppressed by their hormonal therapy.

Additionally, enthusiasm for new treatments for prostate cancer may not be warranted based on early PSA outcomes. This cohort will continue to be closely followed and outcomes will be reported as follow-up of the cohort matures. It must also be noted that these results are from a single centre and therefore their transferability is uncertain. Results from other institutions may vary depending on patient selection and the treatment techniques used.

Conclusion

Patients undergoing prostate brachytherapy with ^{131}Cs have excellent oncological outcomes at 5 years. Although more years of follow-up are required to assess the true cancer control ability of prostate brachytherapy with ^{131}Cs , these intermediate-term outcomes show that there is no reason at this time to suspect that ^{131}Cs will not provide oncological outcomes at least on par with those of ^{125}I and ^{103}Pd . As follow-up of this patient cohort matures, we will continue to publish our results to show the long-term oncological outcome of ^{131}Cs prostate brachytherapy.

References

- Cesaretti JA, Stone NN, Skouteris VM, et al. Brachytherapy for the treatment of prostate cancer. *Cancer J* 2007;13:302–312.
- Stock RG, Cesaretti JA, Stone NN. Disease-specific survival following the brachytherapy management of prostate cancer. *Int J Radiat Oncol Biol Phys* 2006;64:810–816.
- Potters L, Morgenstern C, Calugaru E, et al. 12-year outcomes following permanent prostate brachytherapy in patients with clinically localized prostate cancer. *J Urol* 2008;179(Suppl. 5): S20–S24.
- Dattoli M, Wallner K, True L, et al. Long-term outcomes after treatment with brachytherapy and supplemental conformal radiation for prostate cancer patients having intermediate and high-risk features. *Cancer* 2007;110:551–555.
- Grimm PD, Blasko JC, Sylvester JE, et al. 10-year biochemical (prostate-specific antigen) control of prostate cancer with (125)I brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;51: 31–40.
- Zelevsky MJ, Hollister T, Baben A, et al. Five-year biochemical outcome and toxicity with transperineal CT-planned permanent I-125 prostate implantation for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;47: 1261–1266.
- Stock RG, Stone NN. Current topics in the treatment of prostate cancer with low-dose-rate brachytherapy. *Urol Clin N Am* 2010;37:83–96.
- Ash D, Bottomley D, Al-Qaisieh B, Carey B, Gould K, Henry A. A prospective analysis of long-term quality of life after permanent I-125 brachytherapy for localised prostate cancer. *Radiother Oncol* 2007;84:135–139.
- Van Gellekom MP, Moerland MA, Van Vulpen M, Wijrdeman HK, Battermann JJ. Quality of life of patients after permanent prostate brachytherapy in relation to dosimetry. *Int J Radiat Oncol Biol Phys* 2005;63:772–780.
- Feigenberg SJ, Lee WR, Desilvio ML, et al. Health-related quality of life in men receiving prostate brachytherapy on RTOG 98-05. *Int J Radiat Oncol Biol Phys* 2005;62:956–964.
- Lee WR, McQuellon RP, Harris-Henderson K, Case LD, McCullough DL. A preliminary analysis of health-related quality of life in the first year after permanent source interstitial brachytherapy (PIB) for clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2000;46:77–81.
- Isoray Medical, Inc. CS-1 ^{131}Cs product information sheet and company web site. Available at: www.isoray.com.
- Kinsey RR. The NuDat program for nuclear data on the web. National Nuclear Data Center, Brookhaven National Laboratory. Available at: www.nndc.bnl.gov/nndc/nudat.
- Nath R, Anderson LL, Luxton G, et al. Dosimetry of interstitial brachytherapy sources: recommendation of the AAPM Radiation Therapy Committee Task Group No. 43. *Med Phys* 1995; 22:209–234.
- Jacobs BL, Smith RP, Beriwal S, Benoit RM. Acute lower urinary tract symptoms after prostate brachytherapy with cesium-131. *Urology* 2010;76:1143–1147.
- Kubicek GJ, Naguib M, Redfield S, Grayback N, Brown SI. Combined transperineal implant and external beam radiation for the treatment of prostate cancer: a large patient cohort in the community setting. *Brachytherapy* 2011;10:449–453.
- Dickinson P, Malik J, Mandall P, et al. Five year outcomes following I-125 seed brachytherapy for low risk prostate cancer at three United Kingdom cancer centres. *BJU Int* 2014;113:748–753.
- Vassil AD, Murphy ES, Reddy CA, et al. Five year biochemical recurrence free survival for intermediate risk prostate cancer after radical prostatectomy, external beam radiation therapy or permanent seed implantation. *Urology* 2010;76:1251–1257.
- Zelevsky MJ, Yamada Y, Cohen GN, et al. Five-year outcome of intraoperative conformal permanent I-125 interstitial implantation for patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2007;67:65–70.
- Zelevsky MJ, Shi W, Yamada Y, et al. Postradiotherapy 2-year prostate-specific antigen nadir as a predictor of long-term prostate cancer mortality. *Int J Radiat Oncol Biol Phys* 2009; 75:1350–1356.
- Lo AC, Morris WJ, Lapointe V, et al. Prostate-specific antigen at 4 to 5 years after low-dose-rate prostate brachytherapy is a strong predictor of disease-free survival. *Int J Radiat Oncol Biol Phys* 2014;88:87–93.
- Critz FA, Williams WH, Holladay CT, et al. Post-treatment PSA < or = 0.2 ng/mL defines disease freedom after radiotherapy for prostate cancer using modern techniques. *Urology* 1999; 54:968–971.
- Heysek RV. Modern brachytherapy for treatment of prostate cancer. *Cancer Control* 2007;14:238–243.
- Stock RG, Stone NN, Tabert A, et al. A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41: 101–108.
- Bice WS, Prestidge BR, Kurtzman SM, et al. Cesium Advisory Group. Recommendations for permanent prostate brachytherapy with (131)Cs: a consensus report from the Cesium Advisory Group. *Brachytherapy* 2008;7:290–296.
- Stock RG, Cesaretti JA, Unger P, et al. Distant and local recurrence in patients with biochemical failure after prostate brachytherapy. *Brachytherapy* 2008;7:217–222.