

Biochemical (prostate-specific antigen) relapse-free survival and toxicity after ¹²⁵I low-dose-rate prostate brachytherapy

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Accepted for publication 24 July 2006

OBJECTIVE

To report our clinical experience and 5-year prostate-specific antigen (PSA) relapse-free survival rate for early-stage prostate cancer after ¹²⁵I low-dose-rate prostate brachytherapy.

PATIENTS AND METHODS

In all, 300 patients were treated between March 1999 and April 2003, and followed prospectively. Patients were stratified into low-, intermediate- and high-risk groups, and those receiving neoadjuvant androgen deprivation (NAAD) or not. Kaplan-Meier estimates of PSA relapse-free survival and PSA nadirs were obtained for all patients and for the risk groups. Toxicity, as urinary and erectile dysfunction (ED), were reported from a prospective database.

RESULTS

The median (range) follow-up was 45 (33–82) months. The actuarial PSA relapse-free survival was 93% at 5 years; 21 (7%) of patients had evidence of biochemical failure as defined by the American Society of Therapeutic Radiation Oncology criteria. There was no significant difference in actuarial survival for patients in the different risk groups, or between those receiving NAAD or not (low-risk 96%, intermediate 89%, high 93%, $P=0.12$; NAAD 92%, no NAAD 95%, $P=0.30$). Overall the 3-year median PSA level was 0.3 ng/mL (192 men). There was no significant difference in median 3-year PSA levels for different risk groups, or for those treated with or with no NAAD. The 3- and 4-year PSA nadir of <0.5 ng/mL was achieved by 71% and 86% of men, respectively. The acute urinary retention rate was 7%; 5.6% of men

developed urethral strictures requiring dilatation, while 2.7% required a transurethral resection of the prostate after implantation, for obstructive symptoms. Of patients with no ED before treatment, 62% had no ED at 2 years, and of these 60% used a phosphodiesterase inhibitor.

CONCLUSION

This prospective series confirms the excellent overall biochemical survival after ¹²⁵I brachytherapy; the treatment was tolerated well, with early and late urinary toxicity and ED similar to other published results.

KEYWORDS

prostate carcinoma, brachytherapy, survival, urinary toxicity, erectile dysfunction

INTRODUCTION

Recent guidelines from the UK National Institute of Clinical Excellence supporting the use of low-dose-rate (LDR) brachytherapy for localized prostate cancer call for continued audit and careful clinical governance. We here report our clinical experience and 5-year PSA relapse-free survival for this treatment. The accepted radical treatment options for early prostate cancer include radical prostatectomy, conformal external beam radiotherapy (EBRT) and transperineal interstitial LDR brachytherapy. The 5- and 10-year biochemical (PSA) relapse-free survival rates after brachytherapy, reported from the USA, have been shown to be equivalent to those from the best series of radical prostatectomy and conformal EBRT [1–5].

Prostate brachytherapy has been used at the authors' cancer centre since March 1999; to date >750 men presenting with early prostate cancer have been treated, and followed prospectively. We report our clinical experience and results from the first 300 consecutive patients treated, who have a follow-up of ≥ 33 months.

PATIENTS AND METHODS

All patients were assessed before treatment with a medical history, physical examination, TRUS, the IPSS and uroflowmetry. Baseline erectile function was evaluated using the International Index of Erectile Function-5 (IIEF-5). Clinical stage, PSA levels and Gleason score were documented, with pelvic MRI and bone scans used if clinically indicated.

Patients were classified as having low-, intermediate- or high-risk disease [6]; those with low-risk disease (stage $\leq T2b$, PSA level ≤ 10 ng/mL and Gleason sum ≤ 6) received brachytherapy alone, with intermediate-risk disease (one unfavourable factor of stage $\geq T2c$, PSA level >10 ng/mL or Gleason ≥ 7) 3 months of neoadjuvant androgen deprivation (NAAD) and brachytherapy, and those with high-risk disease (two unfavourable factors) a combination of NAAD, EBRT and brachytherapy. Patients whose treatment did not adhere to these guidelines were so treated as a result of individual factors such as multiple positive biopsies, perineural invasion on biopsy, young age (<60 years) or delay in treatment decision and waiting times. The prescribed dose for ¹²⁵I-monotherapy was 145 Gy and combined

with whole pelvic EBRT (45 Gy in 25 fractions) 110 Gy.

A two-stage brachytherapy technique was used [7]; the prostate volume was assessed using TRUS with the patient in the extended lithotomy position. The prostate volume was measured, the pubic arch assessed and a series of transverse images taken 5 mm apart from base to apex. A 3–5 mm margin was added to create the planning target volume for which the dose was prescribed. The images were digitized into the planning computer and the seed distribution created. The patient returned for treatment up to 4 weeks later. Under general anaesthesia, in the extended lithotomy position, needles pre-loaded with stranded seeds (RapidStrand™, Oncura, Plymouth Meeting, PA, USA) were inserted transperineally. CT was used 30 days after implantation, for dosimetry.

A prospective database for the follow-up was designed and implemented. Patients were followed 3–6 monthly, data collected prospectively and entered onto the database. The follow-up was determined from the date of implant and not the date of biopsy or start of NAAD. The PSA response and toxicity were recorded. Toxicity was assessed using the IPSS and the IIEF-5 questionnaires, the latter, with the full IIEF, being designed for assessing erectile dysfunction (ED) in clinical settings and research trials. Both have been well validated in patients who are in active heterosexual relationships [8–10]. The IIEF-5 has a maximum score of 25, with values of <12 associated with moderate, and <8 with severe ED; scores of 12–16 reflect mild-to-moderate ED, 17–21 mild ED and >22 no ED. Using the IIEF, men who are able to obtain a satisfactory erection, but who are not sexually active, are classified as having ED. In the present study men who were free from moderate-to-severe ED were defined as potent and as such a threshold of 12 was used; this is supported by published data [11–13]. Phosphodiesterase-5 (PDE-5) inhibitor use was routinely encouraged to promote nocturnal erections and thereby optimize erectile function [14,15].

Biochemical failure was defined as three consecutive rises in PSA level each ≥ 3 months apart. The time to failure was defined as the midpoint between the lowest serum PSA level and the first increase; this corresponds with the American Society for Therapeutic Radiology and Oncology (ASTRO) definition of

biochemical failure [16]. Patients whose PSA level subsequently decreased and continued to do so, suggesting a prolonged PSA 'bounce' were not classified as having biochemical failure. Clinical failure was defined as biopsy-confirmed local recurrence or radiologically confirmed distant relapse.

Survival analysis methods were used to analyse the time to biochemical failure; the Kaplan–Meier product limit method was used to construct survival curves where survival was considered as the duration that a patient was PSA relapse-free, with each patient represented as a failure, censored observation or PSA relapse-free at the latest follow-up. The log-rank test was used to compare the survival curves for different groups.

The possible effects of several other variables, including PSA level, Gleason score, stage, NAAD, EBRT and the dose in Gy received by 90% of the prostate (D90) on PSA relapse-free survival were investigated using ANOVA and *t*-tests on the occurrence or otherwise of a biochemical failure, and a Cox proportional hazard model using the time to failure information. Categorical data (proportions) were analysed using Pearson's chi-square test.

RESULTS

The first 300 patients were treated between March 1999 and April 2003; the patients' characteristics and treatment received are summarized in Table 1; the median (range) follow-up was 45 (33–82) months. In all, 197 patients (66%) received NAAD, either bicalutamide monotherapy (55.5%), LHRH analogue (43%), total androgen blockade (1%) or cyproterone acetate monotherapy (0.5%). The primary indications were volume reduction if the prostate volume was >50 mL with pubic arch interference, and therapeutic benefit in patients deemed to be at higher risk of micrometastatic disease. Secondary indications included delayed treatment funding and decision making. In all, 69 of 146 low-risk patients received NAAD, of whom 20 required volume reduction. The remaining 49 patients (34%) were commenced on NAAD due to concerns about delayed treatment (Table 1).

There were two deaths from prostate cancer and seven from unrelated causes (three cardiovascular, one from carcinoma of the sigmoid colon, two from carcinoma of the lung and one from a primary brain tumour).

One patient with intermediate-risk disease and the other with high-risk disease after histological review, died from prostate cancer. The first presented with a stage T2b tumour, Gleason sum 8, a PSA level of 9.4 ng/mL, and was treated with a combination of NAAD, EBRT and brachytherapy. The treatment failed at 27 months, the patient having bone metastases, and he died at 37 months from complications of spinal cord compression. The second patient presented with a T2c tumour, a PSA level of 6 ng/mL, Gleason sum 5 (reviewed as Gleason sum 7) and was treated with brachytherapy alone; at 15 months he had bone metastases and died at 26 months from meningeal disease.

A further 19 patients had a biochemical failure as defined previously, and of these, 10 clinically relapsed; the characteristics of these patients and salvage treatments received are shown in Table 2. Two patients had a salvage prostatectomy, one laparoscopically and the other retropubically. The first failed biochemically whilst the latter patient had an undetectable PSA level at 4 years after surgery.

In all, 36% of patients had a PSA 'bounce' where the PSA increased by >0.1 ng/mL before declining. Three patients in whom treatment failed according to the ASTRO definition of three consecutive PSA increases subsequently had decreases in their PSA level and were reclassified as having a 'rebound'. There were recent proposals to use the 'Houston + 2' definition of failure, defined as an increase of 2 ng/mL above the PSA nadir [17]. With this definition only one of these three patients would have been classified as a biochemical failure.

The actuarial PSA relapse-free survival for all patients was 93% at 5 years (Fig. 1). There was no statistical difference in actuarial survival for patients in different risk groups (low 96%, intermediate 89%, high 93%; $P = 0.12$), or between hormone-naïve (95%) and hormone-treated (92%) patients ($P = 0.30$).

The 3-year median PSA level for all 192 patients was 0.3 ng/mL, and there was no significant difference in the median 3-year PSA level for the different risk groups, or for those treated with or without NAAD (Table 3). At 3 years 71% (192) of patients had a PSA level of ≤ 0.5 ng/mL and at 4 years 86% (92) had a PSA level of ≤ 0.5 ng/mL. Of the 21 patients in whom the treatment failed, 16 had received NAAD; of these, three reached a PSA

Variable	Value	TABLE 1 <i>The patients' characteristics at baseline, and the treatment received</i>
Mean (range) age, years	64 (44–76)	
N (%):		
Stage		
T1c	117 (39)	
T2a/b	117 (39)	
T2c	57 (19)	
T3a	9 (3)	
PSA level, ng/mL		
0–4	10 (3)	
4.1–10	208 (69)	
10.1–20	79 (26)	
>20	3 (1)	
Gleason sum		
0–4	55 (18)	
5–6	194 (65)	
7–10	51 (17)	
% of positive biopsy cores		
<34	186 (62)	
34–50	68 (23)	
>50	46 (15)	
unknown		
Risk group		
low	146 (49)	
intermediate	111 (37)	
high	43 (14)	
NAAD		
Yes	197 (66)	
No	103 (34)	
Treatment received		
brachytherapy alone	95 (32)	
NAAD + brachytherapy	139 (46)	
EBRT + brachytherapy	9 (3)	
NAAD, EBRT + brachytherapy	57 (19)	
NAAD use		
N (%) patients on NAAD [N requiring NAAD for volume reduction]		
low-risk	69 (47) [20]	
intermediate-risk	92 (83) [19]	
high-risk	36 (84) [4]	

Variable	Value	TABLE 2 <i>The characteristics of the 21 patients in whom the treatment failed</i>
N (%):		
Risk group		
low	7 (34)	
intermediate	11 (52)	
high	3 (14)	
Treatment		
brachytherapy alone	5 (24)	
NAAD + brachytherapy	11 (52)	
NAAD, EBRT + brachytherapy	5 (24)	
PSA nadirs (no NAAD)		
≤0.2	0	
>0.2 to ≤0.5	0	
>0.5 to ≤1	0	
>1 to ≤6	5	
Salvage treatment		
prostatectomy	2 (9.5)	
hormones	5 (24)	
chemotherapy	2 (9.5)	
cryotherapy	1 (5)	
surveillance	11 (52)	

nadir of ≤0.2 ng/mL, and of the five who did not receive NAAD none reached a nadir of ≤0.5 ng/mL.

There was no evidence that PSA, Gleason score, stage, NAAD or EBRT showed any significant difference between the men with biochemical failure and those who were still PSA relapse-free at their latest follow-up. None of these variables showed any relationship with biochemical relapse-free survival, considering duration in the Cox proportional hazard analysis.

To assess the value of D90 in predicting biochemical failure, as suggested by Stock

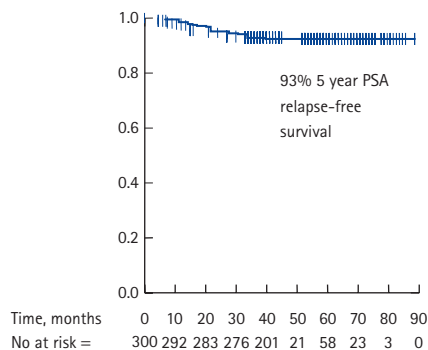
and Stone [18], we analysed patients treated with both brachytherapy monotherapy and combined with pelvic EBRT. The D90 after treatment was expressed as a percentage of the prescribed dose, i.e. 145 Gy for monotherapy and 110 Gy for combined therapy. There was no significant difference in the D90 of patients who were PSA relapse-free and those who had biochemical failure. However, it was suggested that adding EBRT to brachytherapy can compensate for a poor-quality implant. In the combined treatment the prostate receives 45 Gy from the whole pelvic EBRT, which might offset areas underdosed by the implant. On assessing the D90 of patients treated with brachytherapy alone,

those who remained PSA relapse-free had a statistically significantly higher mean (SD) D90 than those who failed, i.e. success 145 (21.9) Gy vs failure 133 (16.2) Gy (95% CI of the difference 1.5–20.9; *P* = 0.026).

Of the 300 patients treated, 65 required clean intermittent self-catheterization (CISC) after implantation; 22 (7%) for acute urinary retention (AUR) and 43 (14.3%) for bothersome LUTS. Eight patients (2.7%) required a TURP for obstructive symptoms after implantation. In all, 17 patients (5.6%) developed membranous urethral strictures requiring dilatation, and one had temporary urinary leakage after the procedure. The median (range) time to stricture was 30 (10–54) months.

Of 300 patients, 205 completed the baseline and more than one IIEF-5 questionnaire after implantation; 104 (51%) were potent at baseline, and at 2 years 62% of these remained potent, with 60% using a PDE-5 inhibitor to maximize their potency. Of the patients who tried a PDE-5 inhibitor, 56% found it to be of benefit. Age (>60 years), the addition of NAAD or EBRT and the degree of pre-existing potency were investigated as possible predictive factors for maintaining potency (Table 4). Potency was significantly

FIG. 1. PSA relapse-free survival for the first 300 patients treated.



less in patients aged >60 years than in those ≤60 years (chi-square, $P = 0.038$).

Changes in patient and treatment selection with time were examined by comparing the fifth group of 100 patients treated with the first 300. The proportions of low-, intermediate- and high-risk patients treated essentially remained the same. The most obvious difference was the change in the use of NAAD, which decreased considerably, from 66% to 26%, as more patients were treated with brachytherapy alone rather than NAAD and brachytherapy. The proportion treated in combination with EBRT was unchanged, reflecting a change in practice for the intermediate-risk group. Patients in this group with features considered favourable, e.g. Gleason score 3 + 4 rather than Gleason score 4 + 3 [19], absence of perineural invasion [20] and fewer than half the biopsy cores positive [21] now receive brachytherapy alone, whilst those with unfavourable features are treated with combined NAAD, EBRT and brachytherapy. Improved funding reducing the waiting times for treatment and advances in the understanding of the natural history of prostate cancer have also led to a reduction in the use of NAAD by referring clinicians with patients in the low-risk group. The urological selection practice for pretreatment IPSS and maximum flow rates was unchanged. However, the number of patients using CISC for bothersome symptoms after implantation decreased substantially between the third and fifth 100 patients treated (10% to 3%). This cannot be explained by selection (as the pretreatment IPSS was unchanged), nor by the duration of follow-up bias, as the first 500 patients have had a follow-up of >1 year. During this period the percentage of patients receiving NAAD decreased from 66% to 26%,

Group (n)	3-year median (range) PSA, ng/mL	% patients with PSA ≤0.5 at 3 years
Risk		
low (88)	0.3 (0.02–10.3)	68
intermediate (74)	0.24 (0.06–66)	70
high (30)	0.1 (0.05–2.6)	83
NAAD (139)	0.3 (0.02–66)	72
No NAAD (53)	0.3 (0.05–53)	71

TABLE 3
The 3-year median PSA levels and PSA nadirs

Group (n)	% potent after brachytherapy
Age	
≤60 (33)	70
>60 (71)	48
Treatment received	
brachytherapy alone (43)	51
brachytherapy + NAAD (38)	68
EBRT + brachytherapy (5)	3/5
NAAD, EBRT + brachytherapy (18)	33
Pre-treatment IIEF score	
12–16; mild-moderate ED (16)	50
17–21; mild ED (28)	50
22–25; no ED (60)	58

TABLE 4
Potency after brachytherapy, classified as patients with an IIEF-5 of ≥12

and it was previously suggested that NAAD increases acute urinary toxicity [22], although this might be a reflection of larger prostate volumes in these patients who commonly had NAAD to reduce gland size. However, there was no difference in the median prostate volume with time in the present series. Notably, all patients received an α -blocker after treatment; this was changed from alfuzosin hydrochloride to tamsulosin hydrochloride during this period.

DISCUSSION

This prospective series further shows the excellent biochemical-free survival achieved with transperineal LDR prostate brachytherapy in men with localized prostate cancer. Direct comparisons with published series from the USA are difficult due to differences in selection criteria, treatment combinations and length of follow-up.

We acknowledge that a significant number of patients received NAAD and with a relatively short follow-up this will influence PSA relapse-free survival. However, the 5-year actuarial biochemical relapse-free survival of 93%, with 96% for low-, 89% for

intermediate- and 93% for high-risk patients, are encouraging. The results for high-risk disease are better than would be expected, possibly explained by three factors; the few high-risk patients, combined treatment, and selection. Combined treatment might have been effective in preventing recurrence, or it might have simply delayed recurrence, which will become apparent as the data matures. The Memorial Sloan-Kettering risk group stratification was used, which defines high-risk patients as having two risk factors from a PSA level of >10 ng/mL, a Gleason sum of >6 and a stage of >T2b. Some patients defined here as high-risk might therefore be considered as having relatively favourable disease compared to other series. On further examination of the data only two high-risk patients had an initial PSA level of >20 ng/mL and five had a Gleason sum of >7.

Accepting that the follow-up is relatively short (which tends to underestimate recurrence using the ASTRO criteria), PSA nadirs were assessed, as these have been shown to be of predictive value for biochemical freedom from disease after EBRT and brachytherapy, with nadirs of <0.5 ng/mL associated with a 5-year biochemical relapse-

free survival of 93% [23]. NAAD will certainly affect PSA levels for the first year after treatment and possibly longer, but at 3 years 71% (192) and at 4 years 86% (97) patients had a PSA level of ≤ 0.5 ng/mL, with no difference between those treated with or without NAAD, suggesting that the present results might be durable.

Dosimetry after implantation is recommended by the American Brachytherapy Society as a measure of implant quality [24]. The D90 is associated with PSA relapse-free survival, with a D90 of ≥ 140 Gy correlated with improved PSA control [18]; these data illustrate the value of assessing the D90.

AUR and irritative and obstructive LUTS are the most significant acute toxicities after interstitial brachytherapy. In the present series, AUR occurred in 7% of patients, which is consistent with published rates of 5–15% [25–27]. The use of CISC in our patients was closely linked to the pre-implant IPSS, baseline prostate volume and urodynamic status [28]. Of the present patients, 5.6% developed urethral strictures, which responded well to dilatation followed by weekly CISC to prevent recurrence. Available data support rates of up to 5.3% with a median time of development of 26 months [29].

In all, 62% of patients maintained potency after brachytherapy, and of these 60% used a PDE-5 inhibitor at some time to maximize their potency. Detailed patient use of PDE-5 inhibitors was not separately coded for in our prospective database. We encourage the use of PDE-5 inhibitors to maximize potency and several patients do not use a PDE-5 inhibitor regularly, and some would be considered fully potent or as having mild ED with no medication. It is also important that the IIEF-5 questionnaire is only valid in men who are sexually active; several patients recorded as impotent might simply have been abstinent.

Studies suggested that poor pre-implant potency, being older (>60 years), the use of NAAD and EBRT are detrimental to maintaining potency [11,12], and our results support age as a significant factor in maintaining potency.

In conclusion, this is the largest prospective series from the UK and confirms the excellent overall biochemical survival rate after ¹²⁵I LDR interstitial prostate brachytherapy.

Brachytherapy is tolerated well, with early and late urinary toxicity and ED rates similar to those in series published from the USA.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **LDR**, low-dose-rate; **EBRT**, external beam radiotherapy; **IIEF**, International Index of Erectile Function; **NAAD**, neoadjuvant androgen deprivation; **ED**, erectile dysfunction; **PDE-5**, phosphodiesterase-5; **ASTRO**, American Society for Therapeutic Radiology and Oncology; **D90**, dose in Gy received by 90% of the prostate; **CISC**, clean intermittent self-catheterization; **AUR**, acute urinary retention.