

Original Article

Interstitial Low Dose Rate Brachytherapy for Prostate Cancer — A Focus on Intermediate- and High-risk Disease

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ABSTRACT:

Aims: To investigate the role of brachytherapy in intermediate- and high-risk prostate cancer. We report our results and a review of published studies.

Materials and methods: Between March 1999 and April 2003, 300 patients were treated with low dose rate I-125 interstitial prostate brachytherapy and followed prospectively. The patients were stratified into low-, intermediate- and high-risk groups and received brachytherapy alone or in combination with external beam radiotherapy (EBRT) and/or neoadjuvant androgen deprivation (NAAD). One hundred and forty-six patients were classified as low risk, 111 as intermediate risk and 43 as high risk. Biochemical freedom from disease and prostate-specific antigen (PSA) nadirs were analysed for risk groups and for treatment received in each risk group.

Results: The median follow-up was 45 months (range 33–82 months) with a mean age of 63 years. Actuarial 5-year biochemical relapse-free survival for the low-risk group was 96%, 89% for the intermediate-risk group and 93% for the high-risk group. When stratified by treatment group, low-risk patients had a 5-year actuarial biochemical relapse-free survival of 94% for brachytherapy alone ($n = 77$), 92% for NAAD and brachytherapy ($n = 66$) and 100% for NAAD, EBRT and brachytherapy ($n = 3$). In the intermediate-risk patients, biochemical relapse-free survival was 93% for brachytherapy alone ($n = 15$), 94% for NAAD and brachytherapy ($n = 67$), 75% for EBRT and brachytherapy ($n = 4$) and 92% for NAAD, EBRT and brachytherapy ($n = 25$). In the high-risk group, biochemical relapse-free survival was 100% for brachytherapy alone ($n = 2$), 88% for NAAD and brachytherapy ($n = 7$), 80% for EBRT and brachytherapy ($n = 5$) and 96% for NAAD, EBRT and brachytherapy ($n = 29$). Overall 3- and 4-year PSA = 0.5 ng/ml were achieved by 71 and 86%, respectively, and a 4-year PSA = 0.2 ng/ml was achieved by 63%.

Conclusion: Although the role of combination treatment with pelvic EBRT and androgen therapy is not clear, our early results show that many patients with intermediate- and high-risk disease have excellent results with brachytherapy. Khaksar, S. J. *et al.* (2006). *Clinical Oncology* 18, 513–518

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Key words: Intermediate- and high-risk disease, prostate brachytherapy, survival

Introduction

As a result of prostate-specific antigen (PSA) screening, men are presenting with prostate cancer at a younger age and with organ-confined disease. At the same time, the standardisation of histopathological analysis has led to an increase in patients with intermediate and high grade disease [1].

Radical treatments with curative intent include radical prostatectomy, interstitial brachytherapy and external beam radiotherapy (EBRT). The success of these treatments is dependent on the disease being truly localised. Certain techniques or combinations of treatments may be more suitable if there is a risk of more advanced disease.

Patients are commonly stratified into low-, intermediate- and high-risk disease on the basis of the statistical risk of

extracapsular spread, seminal vesicle and lymph node involvement. Factors known to be predictive of this are stage, grade and initial PSA. Other factors that may have an additional role are perineural invasion, multiple positive biopsies and bilateral disease. The three risk group classification systems predominantly used are: Memorial Sloane Kettering [2], Mount Sinai Risk Group and D'Amico Risk Group.

Interstitial low dose rate brachytherapy for prostate cancer as monotherapy has historically been used for low-risk early prostate cancer (stage < T2c, PSA < 10, Gleason score ≤ 6) with excellent results [3–5]. Indeed, the American Brachytherapy Association recommends brachytherapy alone for low-risk disease only, and combination treatment for intermediate- and high-risk disease [6]. However, with a histology review, many of the patients in

the original studies may be reclassified as intermediate risk [1]. Is combination treatment therefore necessary for intermediate-risk organ-confined disease and are these risk groups the optimum way of stratifying men?

From a prospective database of over 750 men treated with interstitial low dose rate brachytherapy for prostate cancer, we report on the first 300 consecutive patients with a minimum follow-up of 33 months.

Materials and Methods

Patient Selection and Treatment

Between March 1999 and April 2003, 300 consecutive patients underwent interstitial low dose rate prostate brachytherapy with I-125 seeds. All patients were assessed prospectively with a clinical history, physical examination, transrectal ultrasound scan, uroflometry and pre-treatment International Prostate Symptom Score. The clinical stage, PSA and Gleason score were documented. Pelvic magnetic resonance imaging and bone scans were carried out if clinically indicated.

Patients with pubic arch interference preventing anterior needle placement due to volumes greater than 50 ml were offered cytoreductive androgen deprivation or alternative treatment.

Men were stratified into low-, intermediate- or high-risk disease using the Memorial Sloane Kettering Prognostic Index [2]. The treatment received was brachytherapy alone (145 Gy I-125), combination treatment with neoadjuvant androgen deprivation and EBRT, or NAAD, EBRT and brachytherapy (whole pelvis 45 Gy in 25 fractions + 110 Gy I-125). The length of NAAD was 4–12 months. Men who received greater than 6 months of NAAD were as a result of delayed treatment funding or decision making. No patient received adjuvant androgen deprivation.

A two-stage brachytherapy technique was used. Under anaesthesia, pre-loaded needles were inserted transperineally and stranded seeds implanted (RapidStrand™, Nycomed Amersham). After implantation, computed tomography was carried out for dosimetry.

Follow-up

Data were collected prospectively and entered into a bespoke prostate brachytherapy database. Patients were followed up 3–6 monthly for the first 5 years and yearly thereafter. Follow-up was determined from the date of implant and not the start of NAAD.

Analysis

Biochemical relapse-free survival was defined as three consecutive increases in PSA and the time to failure was defined as the midpoint between the lowest serum PSA and the first increase, corresponding with the American Society for Therapeutic Radiology and Oncology (ASTRO) definition [7]. Men whose PSA subsequently fell were

considered as having a prolonged PSA bounce and not as a failure.

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

The possible effects of a number of other variables, including PSA, Gleason score, stage, androgen deprivation, RBRT and D90, on PSA relapse-free survival were investigated using analysis of variance and *t*-tests on the occurrence or otherwise of a biochemical failure and Cox's proportional hazard model using the time to failure information. Categorical data (proportions) were analysed using Pearson's chi-squared test. Analyses were carried out using Minitab version 14 and STATA version 8 packages.

Accepting that follow-up is relatively short, PSA nadirs were examined as a surrogate end point for biochemical relapse-free survival.

Toxicity data have been reported previously [8].

Three hundred consecutive patients with a minimum follow-up of 33 months were treated between March 1999 and April 2003. Of these, 146 were low risk, 111 intermediate risk and 43 high risk. The median follow-up was 45 months (range 33–82 months) and the mean age of all patients was 63 years. The characteristics of the risk groups and the treatment received are shown in Tables 1 and 2.

Table 1 – Patient characteristics

	Low risk	Intermediate risk	High risk
Number of patients	146	111	43
Mean age (range)	63 (44–77)	64 (49–75)	62 (48–76)
PSA (ng/ml)			
0–4	6 (4%)	3 (3%)	6 (14%)
4.1–10	140 (96%)	59 (53%)	4 (9%)
10.1–20	0 (0%)	48 (43%)	31 (72%)
≥ 20	0 (0%)	1 (1%)	2 (5%)
Gleason score			
2–4	36 (25%)	0 (0%)	2 (5%)
5–6	110 (75%)	88 (79%)	12 (28%)
7–10	0 (0%)	23 (21%)	29 (67%)
Stage			
T1c	78 (53%)	31 (28%)	5 (12%)
T2a/b	68 (47%)	45 (41%)	7 (16%)
T2c	0 (0%)	31 (28%)	26 (60%)
T3a	0 (0%)	4 (4%)	5 (12%)
% Positive cores			
< 34	70%	50%	67%
34–50	23%	25%	14%
> 50	7%	25%	19%

PSA, prostate-specific antigen.

Table 2 – Treatment received

	BXT	NAAD + BXT	EBRT + BXT	NAAD, EBRT + BXT
Low risk (n = 146)	77 (53%)	66 (45%)	0	3 (2%)
Intermediate risk (n = 111)	15 (14%)	67 (60%)	4 (3%)	25 (23%)
High risk (n = 43)	2 (5%)	7 (16%)	5 (12%)	29 (67%)

BXT, brachytherapy; NAAD, neoadjuvant androgen deprivation; EBRT, external beam radiotherapy.

Results

Five-year actuarial biochemical relapse-free survival was 96% for the low-risk group, 89% for the intermediate-risk group and 93% for the high-risk group. When stratified by treatment group, low-risk patients had a 5-year actuarial biochemical relapse-free survival of 94% for brachytherapy alone (n = 77), 92% for NAAD and brachytherapy (n = 66) and 100% for NAAD, EBRT and brachytherapy (n = 3). In the intermediate-risk group, biochemical relapse-free survival was 93% for brachytherapy alone (n = 15), 94% for NAAD and brachytherapy (n = 67), 75% for EBRT and brachytherapy (n = 4) and 92% for NAAD, EBRT and brachytherapy (n = 25). High-risk patients had a biochemical relapse-free survival of 100% for brachytherapy alone (n = 2), 88% for NAAD and brachytherapy (n = 7), 80% for EBRT and brachytherapy (n = 5) and 96% for NAAD, EBRT and brachytherapy (n = 29) (Table 3, Fig. 1).

A number of men received individualised treatment due to tumour and patient factors. Kaplan–Meier estimates of biochemical relapse-free survival are unlikely to be valid for groups of less than 10 patients.

At 3 years after treatment, 71% (n = 192) of all men had a PSA ≤ 0.5 ng/ml and at 4 years 86% (n = 97) had a PSA ≤ 0.5 ng/ml. Sixty-three per cent of men achieved a 4-year PSA ≤ 0.2 ng/ml.

In the intermediate-risk group, 70% (n = 74) had a PSA ≤ 0.5 at 3 years, and in the high-risk group, 83% (n = 30) had a PSA ≤ 0.5 at 3 years (Table 4).

Of the 34% of men who did not receive androgen deprivation, 71% (n = 53) achieved a PSA ≤ 0.5 ng/ml at 3

Table 3 – Five-year actuarial biochemical-free survival

	Low risk	Intermediate risk	High risk
BXT alone (n = 94)	94% (n = 77)	93% (n = 15)	100% (n = 2)
NAAD + BXT (n = 140)	92% (n = 66)	94% (n = 67)	88% (n = 7)
EBRT + BXT (n = 9)	na	75% (n = 4)	80% (n = 5)
NAAD, BXT + EBRT (n = 57)	100% (n = 3)	92% (n = 25)	96% (n = 29)

BXT, brachytherapy; NAAD, neoadjuvant androgen deprivation; EBRT, external beam radiotherapy.

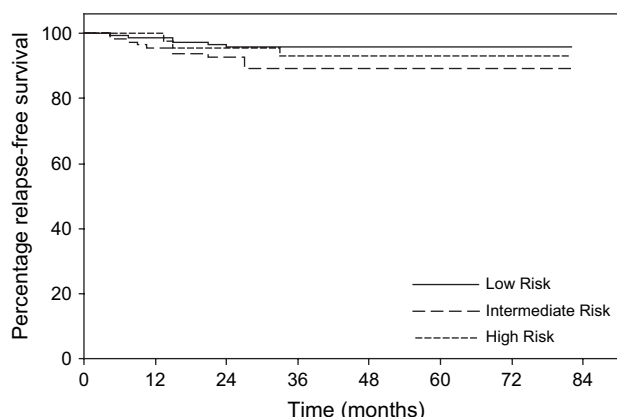


Fig. 1 – Kaplan–Meier graph of biochemical relapse-free survival stratified by risk group.

years (Table 5). There was no significant difference in the proportion of men with a PSA ≤ 0.5 treated with or without androgen deprivation.

Twenty-one men failed by ASTRO criteria, of these five were treated with brachytherapy alone, 11 with NAAD and brachytherapy and five with NAAD, EBRT and brachytherapy. None of the five who did not receive NAAD reached a nadir PSA ≤ 0.5.

There was no evidence that the initial PSA, Gleason score, stage, androgen deprivation, or the use of EBRT was predictive of PSA relapse-free survival using analysis of variance and *t*-tests and none showed any relationship with biochemical relapse-free survival, taking into account the length of time in the Cox proportional hazard analysis (Table 4).

To assess the value of D90 in predicting biochemical failure, as suggested by Stock *et al.* [9], we analysed men treated with brachytherapy monotherapy and combined with pelvic EBRT. After treatment, D90 was expressed as a percentage of the prescribed dose, that is 145 Gy for monotherapy and 110 Gy for combination therapy. There was no significant difference in the D90 of men who were PSA relapse free and those who had biochemically failed.

It has been suggested that the addition of EBRT to brachytherapy can compensate for a poor-quality implant. In combination treatment, the prostate receives 45 Gy from whole pelvis EBRT, which may offset areas of the gland underdosed by the implant. On assessing the D90 of men treated with brachytherapy monotherapy, men who were PSA relapse free did have a statistically significantly higher D90 than those who failed (success 145 Gy [standard deviation 21.9] vs failure 133 Gy [standard deviation 16.2]; 95% confidence interval for difference 1.5–20.9; *t* = 2.44; *P* = 0.026).

Discussion

Radical treatments for early organ-confined prostate cancer with curative intent include radical prostatectomy, interstitial brachytherapy and EBRT. There is currently no convincing evidence that any one modality is better than

Table 4 – Multivariate Cox proportional hazard modelling analysis

Covariate	Parameter estimate (B)	Hazard ratio	95% confidence interval	z	P value
Risk group	0.28	1.32	0.58–3.01	0.66	0.51
Initial PSA	–0.01	0.99	0.87–1.12	–0.08	0.85
Gleason score	–0.17	0.84	0.55–1.29	–0.78	0.44
Androgen deprivation	0.42	1.53	0.91–2.56	1.61	0.11
Use of EBRT	0.24	1.29	0.36–4.59	0.38	0.71
D90 (all patients)	–0.02	0.99	0.95–1.01	–1.28	0.20
D90 (no EBRT)	0.01	0.98	0.95–1.00	–1.82	0.069

PSA, prostate-specific antigen; EBRT, external beam radiotherapy.

the others. Retrospective series of patients with organ-confined disease treated with radical prostatectomy, EBRT and interstitial brachytherapy have shown no difference in biochemical relapse-free survival [10–13].

This prospective series of 300 men has shown the excellent results achievable with brachytherapy, with overall actuarial 5-year biochemical-free survival of 93%; 96, 89 and 93% when stratified for low, intermediate and high risk, respectively. Direct comparisons with published US series are hampered by differences in selection criteria, treatment combinations and the length of the follow-up. Published 5-year PSA progression-free rates from the USA are in the order of 85–93%, with Zelefsky *et al.* [3] reporting 5-year biochemical-free survival from a series of 248 patients of 88, 77 and 35% in favourable-, intermediate- and unfavourable-risk patients, respectively, and Potters and Freeman [14] reporting biochemical-free survival of 93% in the favourable-risk group and 77 and 62% in the intermediate- and high-risk groups, respectively, from a series of 717 patients. Updated 12-year results from Potters *et al.* [15] show a biochemical-free survival of 89% in low-risk, 78% in intermediate-risk and 63% in high-risk groups, with iPSA, Gleason score, percentage positive core biopsies and D90 significant predictive factors of biochemical-free survival. The use of androgen deprivation and EBRT was not predictive of biochemical-free survival.

We acknowledge that a significant number of men (66%) received hormones. With a short follow-up, this will influence PSA relapse-free survival. We attempted to account for this by examining 3-year median PSA and PSA nadirs, as none of our patients received adjuvant hormones. These were encouraging, with a 3-year median PSA = 0.24 in intermediate disease and 0.1 in high-risk disease, whereas 70 and 83% of intermediate- and high-risk patients, respectively, achieved PSA ≤ 0.5 ng/ml at 3 years. The differences in 3-year median PSA and nadirs between the three risk groups were not statistically significant. The results for high-risk disease were, however, better than expected and can perhaps be explained by the small number of patients at 3 years, that all except one received neoadjuvant hormones and selection. The Memorial Sloane Kettering risk group stratification was used, which defines high-risk patients as having two risk factors from a PSA > 10, Gleason score > 6 and stage > T2b. Some men defined here as high risk may, therefore, be considered as having relatively favourable disease compared with other series. On further examination of the data, only two high-risk patients had initial PSA > 20 and four had Gleason score > 7.

Examining patients who did not receive androgen deprivation, 71% reached a PSA ≤ 0.5 ng/ml at 3 years. PSA nadirs have been shown to be of predictive value for biochemical freedom from disease after EBRT and brachytherapy, with PSA nadirs ≤ 0.5 ng/ml associated with a 5-year biochemical relapse-free survival of 93% [16]. PSA levels fall for at least 48 months, and in some cases up to 7 years after brachytherapy (with no hormones) [4].

These results for intermediate- and high-risk disease support the continued use of brachytherapy. However, determining which patients should receive what combination of treatment is not clear. There is currently a lack of randomised evidence resulting in extrapolation from the external beam data. This is briefly discussed below.

Dose escalation to doses greater than 70 Gy results in improved biochemical relapse-free survival [2,17]. This was shown in the intermediate-risk group. Interstitial brachytherapy can provide high doses of radiation to the prostate with limited toxicity to the normal tissues and improved implant techniques can also encompass possible microscopic extraprostatic disease. The use of stranded seeds

Table 5 – Three- and 4-year median prostate-specific antigen (PSA) and nadirs (ng/ml)

	3-year median PSA (range)	% Patients with PSA ≤ 0.5 at 3 years	4-year median PSA (range)	% Patients with PSA ≤ 0.5 at 4 years	% Patients with PSA ≤ 0.2 at 4 years
All patients	0.3 (0.004–66); n = 192	71	0.1 (0.05–5.3); n = 97	86	63
Low risk	0.3 (0.02–10.3); n = 88	68	0.2 (0.05–2.2); n = 41	85	54
Intermediate risk	0.24 (0.06–66); n = 74	70	0.18 (0.05–5.3); n = 36	78	61
High risk	0.1 (0.05–2.6); n = 30	83	0.1 (0.05–0.5); n = 20	100	90
NAAD	0.3 (0.04–66); n = 139	72	0.1 (0.05–2.6); n = 64	83	63
No NAAD	0.3 (0.05–53); n = 53	71	0.18 (0.1–5.3); n = 33	91	64

NAAD, neoadjuvant androgen deprivation.

has also allowed a greater margin to be placed around the prostate without the risk of seed migration [18,19].

Men with intermediate- and high-risk disease have an increased risk of lymph node micrometastases. Intermediate-risk patients with a Gleason score of 8–10 have a 16% and high-risk patients a 17–30% probability of microscopic lymph node metastases [20]. This would suggest a possible benefit for whole pelvis EBRT. A retrospective series from Blasko *et al.* [21], however, showed no statistically significant benefit in biochemical survival with combined treatment for either the intermediate- or high-risk groups. These results may have been due to selection or the retrospective nature of the study [21]. RTOG 9413, a randomised trial comparing combined androgen therapy (neoadjuvant and concurrent or adjuvant), whole pelvis radiotherapy plus conformal boost to the prostate with combined androgen therapy and prostate-only radiotherapy in patients with a 15% risk of positive lymph nodes, recently showed an improved 4-year progression-free survival in patients treated with whole pelvis plus conformal boost to the prostate compared with prostate-only radiotherapy (54% vs 47%; $P=0.002$) [22]. Updated results of this trial were presented at the 2005 meeting of ASTRO, showing a continued, but reduced, statistically significant benefit only in patients receiving neoadjuvant and concurrent androgen therapy plus whole pelvis and prostate boost radiotherapy compared with the other three arms. When treating the pelvic lymph nodes it is, however, difficult to deliver a dose of greater than 70 Gy to the prostate using a conformal boost due to the increased rectal dose and associated risk of proctitis and fistulae. A higher local dose can be achieved with intensity-modulated radiotherapy or a brachytherapy boost. Combination therapy does, however, still increase rectal and bladder toxicity.

The role of androgen deprivation has also been questioned. In the neoadjuvant setting, its role is to reduce tumour bulk, so increasing local control with radiotherapy, whereas concomitant androgen deprivation is believed to improve radiation cell kill through enhanced apoptosis and its adjuvant role is in the treatment of micrometastatic disease. Used with EBRT, long-term (>2 years) adjuvant androgen deprivation has been shown to provide a survival benefit in locally advanced [23,24] and high-grade disease (Gleason 8–10) [25]. Recently, a benefit has been shown in intermediate-risk group short-term (6 months) androgen suppression (88% vs 78% 5-year biochemical relapse-free survival) [26].

The heterogeneity of the intermediate-risk group has been well recognised and methods to identify patients with favourable or unfavourable disease sought. D'Amico *et al.* [27,28] have shown that intermediate-risk patients with greater than 50% positive biopsy cores have an increased chance of biochemical failure, suggesting that this can be used to stratify patients and shape clinical decisions. Merrick *et al.* [29], however, suggested that there is a minimal absolute difference in biochemical outcome. Perineural invasion has also been associated with an increased risk of relapse in low-risk disease after EBRT [30].

The role of pelvic EBRT in addition to brachytherapy in intermediate-risk patients is now being addressed in a randomised setting with RTOG 0232. Eligible patients receive either brachytherapy monotherapy or 45 Gy EBRT to the pelvis and a brachytherapy boost. The primary end point is overall survival, with secondary end points including biochemical relapse-free survival, quality of life and cost-effectiveness. We eagerly await the results.

Conclusion

Our early results suggest that selected intermediate- and high-risk organ-confined prostate cancer may be treated with brachytherapy. Although the role of combination treatment with pelvic EBRT and androgen therapy is not clear, our results show that many patients had excellent results with brachytherapy.

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