BJUI SUPPLEMENTS

# High-dose rate brachytherapy compared with open radical prostatectomy for the treatment of high-risk prostate cancer: 10 year biochemical freedom from relapse

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## Abstract

### Objective

- To compare long-term biochemical control of high-risk prostate cancer in those men receiving high-dose rate brachytherapy (HDRB) and radical prostatectomy (RP).

### Patients and methods

- The 10-year biochemical freedom from relapse (BFR) was calculated for 243 patients who underwent either RP or combined therapy with HDRB + external beam radiotherapy + androgen deprivation between 1998 and 2000.
- Inclusion criteria: clinical stage ≥ T2b, or Gleason sum ≥ 8, or PSA level of > 20 ng/mL. Groups were appraised using the Kattan nomogram for surgery to calculate progression-free probability (PFP).

### Results

- For the RP group (153 patients) the median PSA level was 8.1 ng/mL and the median age was 62.2 years. The median 5- and 10-year predicted PFP for RP was 64% and 56 %, respectively. The 5- and 10-year BFR was 65.5% and 55.4%. There was no significant difference between the predicted and the actual PFP for the RP group ($P = 0.525$).
- For HDRB group (90 patients). The median PSA level was 14.2 ng/mL and the median age was 67.6 years. The median 5- and 10-year predicted PFP for HDRB was 46% and 35%, respectively. The 5- and 10-year BFR was 79.6% and 53.6%. There was a significant improvement between the actual and the predicted PFP for the HDRB group ($P = 0.002$).

### Conclusions

- Amongst a high-risk cohort, patients undergoing RP performed as predicted by the pre-treatment surgical nomogram, whereas the patients undergoing HDRB performed significantly better than was predicted by the surgical nomogram at 10 years.

### Keywords

high-risk prostate cancer, brachytherapy, high dose rate, radical prostatectomy, nomogram

## Introduction

The management of patients with high-risk localised prostate cancer remains controversial [1]. Prognostic models have been described incorporating various clinicopathological features [2]. One of the most widely used is the Kattan nomogram, which predicts the probability of freedom from progression after radical prostatectomy (RP), is based upon the preoperative PSA level, primary and secondary Gleason scores and Gleason sum, seminal vesicle involvement (SVI), surgical margin involvement, extracapsular extension (ECE), lymph node involvement, neoadjuvant treatment and year of surgery [2]. The multi-institutional validation study by Graefen *et al.* [3], including patients from this institution, assessed the predictive accuracy of the post-RP Kattan nomogram across different patient populations, and this model has been further validated for use in the Australian population [4].

The combination of high-dose rate brachytherapy (HDRB) and external beam radiotherapy (EBRT) has been previously shown by our group to be both technically and clinically feasible as definitive treatment for localised prostate cancer [5]. A recent retrospective analysis by Deutsch *et al.* [6]

suggests it is the most effective form of dose escalation. Surgical treatment in high-risk patients remains challenging; they have a high incidence of ECE and positive surgical margins (PSMs), with a resultant increase in the risk of biochemical recurrence after RP [7]. Even experienced surgeons report a PSM rate of 30–50% for higher risk disease [8]. Nevertheless, there is an increasing trend amongst surgeons towards RP for high-risk disease [9,10]. More recently a multimodality approach with adjuvant EBRT has gained favour after reports of benefit in patients with ECE, SVI or PSMs [11].

The two current options for high-risk patients are surgery-based multimodal therapy or combined radiotherapy (dose escalation *and* androgen deprivation). There is presently a lack of clinical data comparing the long-term outcomes for combined radiotherapy vs surgery. Hence, we aimed to compare the efficacy of both treatment methods in preventing PSA recurrence in high-risk patients. We present 10-year BFR in two groups treated within a single institution by either open RP + multimodal adjuvants (RP) or a combined therapy of HDRB as a boost to EBRT and finite androgen blockade. Due to the long natural history of prostate cancer, surrogate endpoints for prostate cancer-specific mortality after curative primary treatment are needed. PSA recurrence is one such surrogate that has been shown to predict clinical prostate cancer recurrence [12]. By ensuring a minimum of 10-years follow-up, we sought to mitigate the effects of adjuvant hormonal therapy.

Patients and methodsAll patients treated for adenocarcinoma of the prostate between 1 January 1998 and 31 December 2000 by the Urology unit of our tertiary referral centre were identified in a prospective database. The inclusion criteria for analysis in the present study were features of high-risk disease as defined by D'Amico *et al.* [1]. Thus, patients with clinical stage ≥ T2b (American Joint Committee on Cancer [AJCC] 1997), Gleason Sum ≥ 8, or PSA level of ≥ 20 ng/mL were included. Patients were stratified based upon treatment with either RP combination (153 patients) or HDRB combined therapy (90); those who underwent alternative primary treatment were excluded.

In all cases, staging was carried out by one of five surgeons at our institution. This evaluation routinely includes history, DRE, PSA level measurement, an TRUS-guided biopsy of the prostate, bone scan and CTof the chest, abdomen and pelvis. A minimum of sextant biopsy was performed using an 18-G Tru-Cut needle via a transrectal approach. A specialist genitourinary pathologist reviewed the biopsy specimens for all patients undergoing surgery or HDRB using the Gleason histological grading system.

Surgical treatment consisted of an open retropubic RP and bilateral pelvic lymph node dissection. Open RP was performed via an infra-umbilical midline incision in a standardised fashion as previously described by Walsh *et al.* [13]. Incremental nerve sparing was performed selectively, depending upon the clinical extent of disease and the patient's preoperative erectile function. Treatment with adjuvant hormone and/or RT (≤3 months of surgery) was based upon pathological stage after multi-disciplinary discussions. Men with positive lymph nodes, SVI or persistently elevated PSA levels after surgery were treated as having silent metastatic disease and were not offered adjuvant RT. Rather it was given to younger men with higher pathological Gleason sum or where ECE or a PSM was present. Those men that received salvage RT (>3 months from surgery), were deemed to have failed in terms of the freedom from biochemical recurrence survival analysis.

HDRB combined treatment consisted of interstitial HDBR with three-dimensional conformal EBRT boost (using a treatment protocol described previously [5]) combined with androgen-deprivation therapy (ADT). Patients were treated uniformly with the following protocol. Patients received ADT synchronously with their combined RT. This consisted of bicalutamide (Cosudex) 50 mg orally for 28–56 days and either goserelin (Zoladex) or leuprorelin acetate (Lucrin) depot implant monthly for 12 months. HDRB delivered a minimal peripheral dose of 16.5 Gy in three fractions over a 24-h period. The maximum time interval between HDRB and EBRT was 2 weeks with EBRT consisting of a standard four-field box (conformal) technique encompassing the prostate, SVs, and proximal pelvic lymph nodes to a dose of 45 Gy in 25 daily fractions in all cases.

Insertion of interstitial transperineal brachytherapy catheters into the prostate was performed with ultrasound guidance using the technique described by the Seattle group [14], with some modification. The bases of the SVs were included in the field. In a typical implant, 18–20 6-F steel Speiser-type needles (20 cm long; Nucletron, Veenendaal, Netherlands) were used. Needles were implanted using a standard pattern that maximised density in the McNeal postero-lateral zones, sparing the central and anterior zones. Fiducial markers in the form of two gold seeds were deposited in the base and the apex of the prostate. These seeds referenced needle depth during placement and defined target volume length on subsequent CT dosimetry.

Clinicopathological data was prospectively collected. These data included details of clinical staging, PSA history, pathological staging where appropriate, and details of neoadjuvant and adjuvant treatment. Patients were followed-up at a minimum of 3-month intervals for the first year, 6-monthly for the second year, and then on an annual basis. At each follow-up serum PSA was collected before DRE.

A retrospective review of outcome data was undertaken for all patients. From the 243 patients identified, three (1.2%) had residual PSA level elevation after RP and six (2.5%) were lost to follow-up. Of the six lost to follow-up, three (3.3%) were from the HDRB group, and three (2%) were from the RP group. Patients were followed until 30 June 2008. The duration of follow-up was calculated from the date of treatment until their most recent PSA test or review. The median (range) follow-up for the HDRB group was 94.5 (10–126) months and for the RP group was 95 (3–126) months. A minimum follow-up of 36 months was achieved in (217/234) 92.7% of patients, whilst a minimum follow-up of 60 months was achieved for (192/234) 82.1% of patients.

After RP a sustained PSA level rise of ≥0.2 ng/mL was deemed indicative of prostate cancer recurrence [15]. To maintain uniformity with current literature, all RT patients were analysed using the 'Phoenix' definition of biochemical recurrence, a rise

*Table 1 Pretreatment clinicopathological characteristics and median follow-up times*

| Variable | HDRB | RP | P |
|---|---|---|---|
| Number of patients | 90 | 153 | |
| Treatment Period | 1998–2000 | 1998–2000 | |
| Median (range): | | | |
| Follow-up, months | 94.5 (10–128) | 95.3 (6–130) | 0.786 |
| Age, years | 67.6 | 62.2 | <0.001 |
| PSA level, ng/mL | 14.5 | 8.1 | <0.001 |
| N (%): | | | |
| PSA level (ng/mL): | | | |
| <4 | 2 (2.2) | 15 (9.9) | |
| 4–10 | 20 (22.2) | 83 (54.6) | |
| 10–20 | 33 (36.7) | 41 (27.0) | |
| >20 | 35 (38.9) | 12 (7.9) | |
| Gleason sum: | | | 0.122 |
| <7 | 12 (14.1) | 47 (30.7) | |
| 7 | 35 (41.2) | 56 (36.6) | |
| 8 | 21 (24 .7) | 30 (19.6) | |
| 9 | 13 (15.3) | 15 (9.8) | |
| Median (range): | | | |
| Primary Gleason score | 4 (1–5) | 3 (3–5) | |
| Secondary Gleason score | 4 (2–5) | 4 (2–5) | |
| Percentage positive biopsies | 51 (8–100) | 59 (16–100) | |
| N (%): | | | |
| Clinical stage: | | | <0.001 |
| T1 | 10 (11.9) | 20 (13.3) | |
| T2 | 53 (63.1) | 120 (80) | |
| T3 | 21 (25.0) | 10 (6.7) | |
| Adjuvant treatment: | | | <0.001 |
| hormones alone | 90 (100) | 10 (6.7) | |
| radiotherapy alone | n/a | 9 (6.0) | |
| both | n/a | 14 (9.3) | |

*n/a, not applicable.*

*Table 2 Pathological characteristics of RP specimens in the RP cohort (n = 153)*

| Characteristic | N (%) |
|---|---|
| Gleason score: | |
| missing | 2 (1.3) |
| ≤6 | 32 (20.9) |
| 7 | 84 (54.9) |
| ≥8 | 35 (22.9) |
| ECE: | |
| missing | 2 (1.3) |
| positive | 77 (50.3) |
| negative | 74 (48.4) |
| SVI: | |
| missing | 1 (0. 7) |
| positive | 21 (13.7) |
| negative | 131 (85.6) |
| Margin status: | |
| missing | 2 (1.3) |
| positive | 75 (49.0) |
| negative | 77 (50.3) |
| P-stage: | |
| missing | 2 (1.3) |
| pT2 | 72 (47.1) |
| pT3 | 75 (49.0) |
| pT4 | 4 (2.6) |
| Nodes: | |
| missing | 3 (1.9) |
| positive | 3 (1.9) |
| negative | 147 (96.2) |

in PSA level of 2 ng/mL above the after treatment nadir [15].

The groups were compared for their baseline clinicopathological characteristics. Categorical data were compared using Pearson's chi-squared test. Two-sample independent *t*-tests were used to analyse differences in means. All patients had their *predicted* progression-free probability (PFP) calculated using the Kattan *et al.* [16] preoperative nomogram for surgery. The *historical* model (1998) was used, as this was relevant to patients treated in this era. It provides a probability of PSA recurrence at up to 10 years after treatment with RP. As there is no nomogram for HDRB, both treatment groups were compared with the same surgical pretreatment nomogram. Kaplan–Meier survival analysis was used to compute BFR for each treatment group [17]. The method described by Heller *et al.* [18] was used to evaluate the differences between predicted and observed PFPs.

## Results

Pre-treatment characteristics are shown in Table 1. Patients undergoing RP generally had more favourable disease characteristics than those in the HDRB group. The RP cohort had a lower median age than those who underwent HDRB (62.2 vs 67.6 years, $P < 0.001$). Furthermore, there was a higher PSA level and clinical stage (both $P < 0.001$) in the HDRB group. As per the HDRB protocol, ADT was used for all patients, and thus there was a statistically significant difference from the RP group ($P < 0.001$). There was no significant difference in Gleason score ($P = 0.122$). Follow-up extended to 10 years in both cohorts, with a median follow-up of ≈ 95 months for each arm.

Pathological characteristics of prostatectomy specimens are shown in Table 2. This shows an upstaging of Gleason sum from biopsy to specimen consistent with standard rates. A high rate of SVI (13.7%), ECE (50.3%) and positive surgical margins (49%) commensurate with high risk disease. Patient outcomes are shown in Table 3. Of the 87 HDRB patients, 79 were alive at the time of last follow-up. Although there were no prostate cancer-related deaths, five died from other causes (6.0%). During the follow-up period, 49 men (58.3%) showed no evidence of relapse. However, 18 men (21.4%) had a PSA relapse alone; a further 12 men (14.3%) had a clinical relapse (local, bony or visceral metastasis). From the 150 RP patients, 128 were alive at the time of

*Table 3 Biochemical and clinical outcomes*

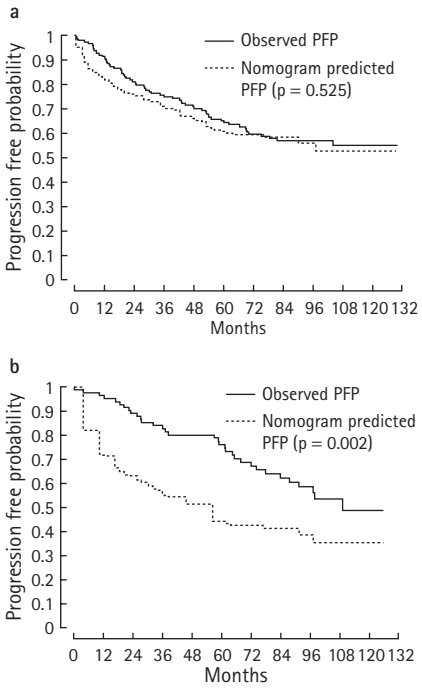
| | Outcome | | | | | |
|---|---|---|---|---|---|---|
| Treatment | No relapse | PSA relapse | PSA + clinical | Death – prostate cancer | Death – other | Total |
| N (%): | | | | | | |
| HDRB | 49 (58.3) | 18 (21.4) | 12 (14.3) | 0 | 5 (6.0) | 84 (100) |
| RP | 86 (56.2) | 43 (28.1) | 2 (1.3) | 5 (3.2) | 17 (11.1) | 153 (100) |

*PSA + clinical, includes: local recurrence, distant visceral metastases, and bone metastases. Death – prostate cancer, were deaths directly attributable to prostate cancer. Death – other, includes other cancer deaths, unrelated deaths, and deaths of unknown cause.*

*Table 4 Predicted PFP and actuarial BFR for the HDRB and RP groups.*

| | Actual PFP, % | | Nomogram predicted PFP, % | |
|---|---|---|---|---|
| Treatment | Estimate (95%CI) | | Estimate (95%CI) | |
| Group | 5 year | 10 year | 5 year | 10 year |
| HDRB | 80 (69–87) | 54 (38–67) | 45 (41–51) | 35 (30–41) |
| RP | 66 (57–73) | 55 (46–64) | 64 (62–67) | 56 (52–59) |

*Figure 1. Kaplan–Meier survival curves for BFR vs nomogram. A, Observed vs predicted survival curves for RP group (P = 0.525). B, Observed vs predicted survival curves for HDRB combined therapy group (P = 0.002)*




last follow-up, with 88 of these men (58.7%) showing no evidence of relapse. There were five prostate cancer deaths (3.3%) and 17 deaths from other causes (11.3%). There were 43 men (28.7%) with a PSA relapse alone, whilst a further two men (1.3%) had clinical relapse.

Predicted PFP, generated by the Kattan preoperative nomogram [16], was calculated for each treatment group. PFP results are shown in Table 4, alongside actuarial data using the Kaplan–Meier method for PFP. The HDRB group had a median *predicted* PFP at 5- and 10-years of 45% and 35%, respectively. The actuarial data shows the 5- and 10-year actual PFP were 79.6% and 53.6%, respectively. Across the same periods, the RP group had median *predicted* PFPs of 64.4% and 56 %, with actual PFPs of 65.5% and 55.4. This is represented graphically in Figure 1 and shows a significantly better survival curve for the HDRB group than predicted ($P = 0.002$).

## Discussion

Given the selection bias before administration of treatment, the absence of difference in rate of recurrence recorded between the RP and HDRB groups was unexpected. Clinicians assigned patients to treatment groups according to clinical features, which in turn were used to forecast prognosis; as a consequence the HDRB group had statistically worse pre-treatment stage and pathological indicators. Despite this selection bias leading to poorer pre-treatment clinical characteristics, those patients receiving the combined therapy of HDRB with EBRT boost and ADT had similar 10-year BFR outcomes to those patients who underwent primary RP. These HDRB patients surpassed initial expectations, performing better than was predicted by the Kattan pre-treatment nomogram.

Patients were included in the study based on their high risk pre-treatment features conforming with the D'Amico criteria described in his original article in 1998 [1]. The patients in that study were collected between 1989 and 1997, during which time the 1992 AJCC staging system was used. As the present our cohort was diagnosed and treated between 1998 and 2000, we applied the AJCC 1997 staging system, which had reverted to a two-tier clinical T2 stage. That is, T2a one lobe involved, T2b both lobes involved. Thus, ≥T2b as our inclusion criteria was most comparable with the D'Amico *et al.* [1] T2c. The D'Amico *et al.* [1] high-risk group was predicted to have a >50% chance of PSA recurrence at 5 years, and this was proved true in the present cohort also.

The Kattan nomogram has been previously validated in the Australian population [4]. As there is no validated nomogram for HDRB, both of the treatment groups had a predicted PFP calculated using the pre-treatment surgical nomogram. The surgical group performed as was predicted by the Kattan nomogram, with no statistical discord ($P = 0.525$). Hypothesising that the HDRB cohort were to have undergone RP, the median predicted PFP from the nomogram at 5 and 10 years was 45% and 38%, respectively. However, using the actuarial data shown in Table 4, the HDRB group recorded 5- and 10-year BFR rates of 80% and 54%, respectively. There was a statistically significant discord between the observed and predicted results for HDRB ($P = 0.002$), with the HDRB group performing better than was predicted by the Kattan nomogram.

ADT contributes to the elimination of occult systemic disease whilst also potentiating the effect of external and brachytherapy irradiation. This supra-additive mechanism of action is postulated to be due to the induction of apoptosis [19,20]. However, the effect on PSA relapse cannot be explained simply through this mechanism, as the addition of ADT neoadjuvantly to RP improves stage but not overall survival [21].

The addition of RT to ADT provides an important effect on overall and disease-specific mortality [22]. The Scandinavian Prostate Cancer Group reported in a prospective trial (SPCG-7/SFUO-3) that the addition of local RT to ADT halves the 10-year prostate cancer-specific mortality, whilst giving a three-fold decrease in PSA recurrence [23]. In comparison to RP, RT is able to treat a greater volume of tissue, especially if the four-field box is used. This additional benefit derived from RT may be due to its reduction in local progression, the reduction in pool of clonal cells with metastatic potential, or a combination thereof.

A limitation in the comparison of PFP data is the use of ADT in HDRB patients but not the RP patients. ADT was continued for 1 year after treatment and rendered the patients castrate. It has previously been shown that ADT as sole therapy extends BFR, but not overall survival [21]. Once ADT is ceased testosterone levels will usually return to pre-treatment levels, although the time for this is variable. A small proportion of men (<10%) have a persistent decrease in hormone. Given that ADT alone does not impact upon overall survival, the effect in the present cohort should be negligible by 10 years, although this cannot be absolutely quantified.

Given the present study involved retrospective analysis of prospective data, the selection of patients to each study arm was not randomised. Following on from this, is the asymmetrical size of each arm, with relatively fewer patients undergoing HDRB. Other limitations include the lack of morbidity/quality of life outcome data for these cohorts, so a comparison of treatment effects is limited to biochemical recurrence. There was also the potential for under-utilisation and under-dosing of adjuvant RT after RP. The results from the European Organisation for the Research and Treatment of Cancer (EORTC) trial 22911 did not mature until 2007 [24], and thus the treatment indications and regimes for PSMs differ between 1998 and today. Outcomes from RP were shown by Cagiannos *et al.* [25] to improve with time from 1980 to 2000. Whilst there was a levelling off in the late 1990s, more recent patients might do better still [9], and thus outcomes from 1998–2000 are not necessarily representative of outcomes to be expected today.

A major strength of the present study is the inclusion of all high-risk patients from the 1998–2000. All outcome data was collected prospectively. Whilst there was a selection bias towards treatment type, outcomes from all interventions are reported here. Lastly, the 10-year follow-up should mitigate the effect of ADT, whilst give sufficient time for differences in primary treatment to develop. Despite the limitations, the present study suggests that amongst a high-risk cohort, HDRB may offer potentially better durability and treatment efficacy than RP.

In conclusion, amongst a high-risk cohort, we found HDRB has both durability and the potential for high treatment efficacy. At 10 years, patients undergoing RP performed as predicted by the pre-treatment surgical nomogram, whereas the patients undergoing HDRB performed better than was predicted. The results of the present study may provide evidence to patients and clinicians considering treatment options for high-risk prostate cancer.

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Abbreviations: **ADT**, androgen-deprivation therapy; **AJCC**, American Joint Committee on Cancer; **BFR**, biochemical freedom from relapse; **(EB)RT**, (external beam) radiotherapy; **ECE**, extracapsular extension; **HDRB**, high-dose rate brachytherapy; **PFP**, progression-free probability; **PSM**, positive surgical margins; **RP**, radical prostatectomy; **SV(I)**, seminal vesicle (involvement).