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Prostate brachytherapy

# Patterns of failure after iodine-125 seed implantation for prostate cancer ☆

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ABSTRACT

*Purpose:* To determine the site of relapse when biochemical failure (BF) occurs after iodine-125 seed implantation for prostate cancer.
*Materials and methods:* From 2001–2009, 500 men underwent implantation in Wellington, New Zealand. Men who sustained BF were placed on relapse guidelines that delayed restaging and intervention until the prostate-specific antigen (PSA) was ⩾20 ng/mL.
*Results:* Most implants (86%) had a prostate D90 of ⩾90%, and multivariate analysis showed that this parameter was not a variable that affected the risk of BF. Of 21 BFs that occurred, the site of failure was discovered to be local in one case and distant in nine cases. Restaging failed to identify the site of relapse in two cases. In nine cases the trigger for restaging had not been reached.
*Conclusions:* If post-implant dosimetry is generally within the optimal range, distant rather than local failure appears to be the main cause of BF. Hormone treatment is therefore the most commonly indicated secondary treatment intervention (STI). Delaying the start of STI prevents the unnecessary treatment of men who undergo PSA 'bounce' and have PSA dynamics initially mimicking those of BF.
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Since low-dose-rate (LDR) brachytherapy using ultrasound-guided transperineal seed implantation was first reported as a treatment for early stage prostate cancer [1], a number of groups in North America and Europe have published the results of large series of men undergoing this treatment, confirming its effectiveness in achieving high rates of prostate-specific antigen (PSA) control [2–8].

Reports on two early series of men who underwent a post-implant CT scan for dosimetry purposes [9,10] showed that cases with a D90 value above a cut point had significantly better PSA control than cases below the cut point. This implied that there was a dose–response relationship for local control of the cancer within the prostate, and that local relapse was a major cause of biochemical failure (BF). An optimal range for D90 was therefore included as a key measure of the quality of an implant in American and European guidelines [11,12]. However, two more recently reported series have been unable to confirm a relationship between the D90 and PSA control [13,14].

In a series of 500 consecutive men treated with iodine-125 implantation, we set out to determine what PSA patterns post-implant permitted the call of BF to be made confidently, whether or not post-implant dosimetry was a variable influencing the risk of BF, and what was the most common site of failure when BF occurred.

## Materials and methods

Between 2001 and 2009, 500 men had their prostate cancers treated with iodine-125 seed implantation in Wellington, New Zealand. Men were considered suitable for this treatment if their cancer was Stage T1C or T2A, Gleason score ⩽7, and PSA <20 ng/mL, which meant they had low or intermediate-risk cancer using the risk algorithm proposed by D'Amico [15]. Men with prostate glands greater than 60 $cm^3$ first underwent hormone treatment to reduce the size of the gland. At the start of the programme, men with intermediate-risk prostate cancer received

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external beam radiotherapy (EBRT – 46.00 Gy in 23 daily fractions) before implantation.

A pre-plan for the implant was generated from a trans-rectal ultrasound volume study. The implant was subsequently performed using iodine-125 seeds in *Rapidstrand* (Oncura) placed in a modified uniform seed distribution. The prescribed dose for an implant was 145 Gy when performed as monotherapy, and 110 Gy when performed after EBRT. The individual seed strength for an implant varied between 0.32 and 0.42 U.

Four to six weeks after the implant, men underwent a pelvic CT scan, and from the images obtained dose parameters recommended in North American and European consensus guidelines [11,12] were calculated. These were the D90, V100 and V150 (expressed as percentages) for the prostate clinical target volume and the V100 (expressed as an absolute volume) for the rectum.

Every effort was made to follow up men for at least 5 years after the implant, with the PSA being measured every 6 months. The Phoenix definition of BF [16] was used, but because a PSA rise to more than 2 ng/mL above the post-treatment nadir is often caused by the treatment-related 'bounce' phenomenon [17], True BF was only considered to have occurred when there were two further rising PSA values after Phoenix BF, and the date of BF was taken as the date of the last of the three PSA values. A bounce was considered responsible for Phoenix BF if subsequent PSA values spontaneously fell to low levels. For the purposes of this study, those men who had fulfilled the Phoenix definition of BF at the close off date for analysis, and who had no subsequent PSA values to suggest a bounce was responsible, were considered to have sustained True BF.

When True BF occurred, the biochemical relapse guidelines used in the two Trans-Tasman Radiation Oncology Group (TROG) prostate cancer trials [18,19] were implemented. The guidelines stipulate that, providing a man has no symptoms referable to his prostate cancer, the investigator should wait until the PSA is $\geqslant$20 ng/mL before restaging and initiating a secondary treatment intervention (STI). The guidelines were introduced by the TROG 96.01 Trial Management Committee in 1999, three years after the start of recruitment, when it became clear that a STI was often being commenced on the early cases of BF before the site of failure could be established. The figure of $\geqslant$20 ng/ml as the trigger for restaging was agreed by consensus of the committee members, and led to satisfactory data being available on all endpoints when 10-year reporting on the trial took place in 2010 [18]. Restaging of men in this study was performed with a separate isotope bone scan and CT scan prior to 2010, and thereafter with a sodium fluoride PET-CT bone scan. The status of disease in the prostate was assessed clinically. Unless local recurrence was suspected clinically, re-biopsy of the prostate was not encouraged because of the difficulties in assessing the biopsy material taken from an irradiated prostate [20] and concerns about possible complications when trans-rectal biopsies are taken through irradiated rectal mucosa [21].

The close-off date for analysis of all 500 men in this series was October 2012, but additional follow up data on the BF subgroup were collected after this date with the objective of either determining the site of cancer relapse or confirming that BF had been correctly called.

Statistical analysis was undertaken using SPSS version 21. Univariate analysis of survival data was undertaken using the Kaplan–Meier method. Multivariate analysis using Cox regression modelling was employed to assess risk factors for BF.

## Results

The median age of the 500 men at implantation was 63 years, with a range 42–74 years. Brachytherapy was performed as monotherapy in 457 men, and was combined with EBRT in 43 men. Hormone treatment was used prior to implantation in 102 men, of which 58 men were treated with a luteinizing hormone releasing hormone (LHRH) analogue, and 44 with an anti-androgen medication. The duration of hormone treatment varied from 3 to 6 months, depending on how much volume reduction of the prostate gland was thought to be necessary before implantation.

At the time of analysis in October 2012 the median follow up was 30 months, with a range 0–115 months. The projected BF rate at 3 and 5 years was 2.6% and 4.3% for the 325 men with low-risk cancers, and 8.2% and 11.3% for the 175 men with intermediate-risk cancers ($p = 0.014$, Fig. 1).

In the 457 men undergoing monotherapy, Cox regression modelling showed that men with a PSA of $\geqslant$10 ng/mL had a hazard ratio for BF of 4.31 (confidence interval 1.64–6.98) compared to men with a PSA <10 ng/mL. Men with Gleason score seven tumours had a hazard ratio for BF of 4.12 (confidence interval 1.47–6.77) compared to men with Gleason score five or six tumours. The other variables put into the model, prostate D90 and whether or not hormone treatment was given prior to the implant, showed no association with the risk of BF.

The Phoenix definition of BF was satisfied in 54 men (11%), and was due to True BF in 21 men (4%) and PSA bounce in 33 men (7%). The median duration from implant to the call of True BF was 27 months (range 3–84 months).

In the 21 men with True BF, only one man had clinically detectable local recurrence. Restaging has been performed in twelve of the men, and was positive for metastatic disease in nine and negative in the other three, of which one was the man with local failure. Nine men have not been restaged because the PSA has yet to reach 20 ng/mL, and six of these were men called as having True BF on the basis of Phoenix BF alone at the close-off date for analysis. Of these six men, three subsequently experienced a sharp fall in the PSA value indicating bounce was responsible for the initial rise, and the other three have not yet posted three consecutive rising PSA values.

There were two deaths from prostate cancer. Both men underwent BF soon after their implant with very short PSA doubling

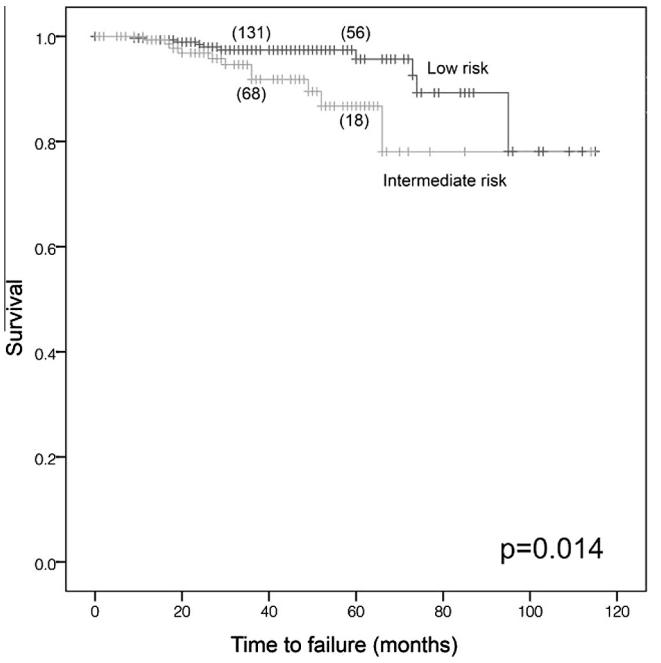


**Fig. 1.** Biochemical failure-free survival for 325 low-risk and 175 intermediate-risk cancers. (Figures in brackets are numbers at risk at 36 and 60 months.)