A prospective audit of the 10-year outcomes from low dose-rate brachytherapy for early stage prostate cancer

David S Lamb, Lynne Greig, Grant Russell, John N Nacey, Kim Broome, Mohua Jain, Judith Murray, Peter J Lamb, Lisa Woods

ABSTRACT

AIM: New Zealand men diagnosed with early stage prostate cancer need to know what outcomes to expect from management options.

METHODS: Between 2001 and 2016, 951 men were treated with low dose-rate brachytherapy (permanent iodine-125 seed implantation) by the Wellington Prostate Brachytherapy Group based at Southern Cross Hospital, Wellington. At follow up after treatment, men had their PSA measured and were scored for urinary, bowel and sexual side effects.

RESULTS: Median follow-up of men was 7.9 years (range 2.0–16.3 years). Ten-year PSA control was 95% for the 551 men with low-risk prostate cancer and 82% for the 400 men with intermediate-risk prostate cancer. Adverse effects were generally minor and short-term only. Temporary urinary obstruction developed soon after the implant in 2.6% men, and the 10-year cumulative risk of urethral stricture was 2.6%. Erectile dysfunction developed in 29% men, two-thirds of whom had a good response to a PDE5 inhibitor. Most men returned to a normal routine within four days of the implant.

CONCLUSION: LDR brachytherapy is a highly effective low-impact treatment option for New Zealand men with early stage prostate cancer.

PSA testing of asymptomatic men has led to prostate cancer becoming the most commonly diagnosed cancer in New Zealand men, with 3,068 new cases registered in 2015.1 Many men currently being diagnosed have early stage disease, making them eligible for a number of different management options.

Because PSA-detected cancers generally progress slowly over many years,2 some men will be offered Active Surveillance, a management option that involves withholding active treatment at the point of diagnosis, and only intervening when either the PSA rises more rapidly than anticipated, repeat biopsies show progression of the histological grade (Gleason score), or the man decides he wants his cancer treated. However, not all men feel comfortable about delaying treatment, and the ProtecT trial3 showed that major cancer progression occurred 2.4 times more frequently on Active Surveillance than after immediate surgery or external beam radiotherapy (EBRT).

Early stage cancers can be treated by surgery, EBRT or low dose-rate (LDR) brachytherapy. There is evidence that these three treatments achieve comparable results in terms of cancer control,4–6 so other factors become important for men selecting their preferred treatment. These include treatment convenience, the expected recovery time, and the risk of long-term sexual and urinary side effects.

LDR brachytherapy involves the permanent implantation of radioactive seeds into the prostate. Since the Seattle Prostate Institute published the 10-year outcomes it achieved with the treatment,7 many other centres in North America and Europe have reported their results.5,6,8–10

We report the 10-year outcomes from LDR prostate brachytherapy delivered in a New Zealand centre.
Methods

From 2001 to 2016, the Wellington Prostate Brachytherapy Group (WPBG) treated 951 men with permanent iodine-125 seed implants at Southern Cross Hospital, Wellington.

Men were eligible for an implant if they had low-risk or intermediate-risk prostate cancer as defined by D’Amico. Low-risk cancers were those that were less than 20mm in diameter clinically, had a Gleason pathological score of ≤6, and a presenting PSA <10mcg/L. Intermediate-risk cancers were those with a Gleason pathological score of 7 and/or a presenting PSA 10–20mcg/L, and in addition had low-volume cancers no more than 20mm in diameter clinically or on MRI scanning. If the volume of the prostate gland was more than 60cc, hormone treatment was used before the implant to reduce its size. At the start of the programme, men with intermediate-risk prostate cancer were first treated with 45Gy external beam radiotherapy (EBRT), a practice that ceased after four years when the implant team felt confident that an implant on its own consistently delivered sufficient radiation to the entire prostate.

Implants were performed using the same methods as originally described by the Seattle Prostate Institute. The implant team comprised a urologist, a radiation oncologist and a medical physicist, and implants were pre-planned in order to determine the precise number and position of seeds needed for the implant. For the majority of men in this series, pre-planning used ultrasound images collected at a separate procedure called a Volume Study, but the more latterly treated men were pre-planned using MRI images collected routinely at the same time as their diagnostic MRI scan. These men were able to proceed directly to an implant once they decided this was their preferred treatment option.

The seed supplier was a British company (BXT-Accelyon) that sourced the iodine-125 seeds from the US. The seeds were delivered preloaded into sterile needles as determined by the pre-plan, so were ready to be implanted without any additional processing.

The prescribed radiation dose for implants was 145Gy, or 110Gy if the implant was preceded by EBRT. Post-implant, men had a CT scan to allow the radiation dose distribution achieved to be calculated. The parameters D90 (percentage of prescribed radiation dose received by 90% of the prostate volume) and V150 (percentage of prostate volume receiving 150% of prescribed radiation dose) were calculated as measures of the implant quality.

The importance of long-term follow up by the WPBG was stressed to all treated men. At each follow-up appointment with a WPBG clinician (co-authors DSL, GR, JNN and KB), men had their PSA measured, and urinary and bowel side effects were scored using a scale 0–3 on which a score 3 meant that a medical intervention was undertaken for the side effect. Erectile dysfunction (ED) was scored as being a side effect of the implant if the man required a PDE5 inhibitor during the first three years after the implant, but not before. Direct follow up by a WPBG clinician continued for a minimum of five years, and often for 10 years or more, but those men whose PSA had fallen to low levels were permitted to continue their follow up with their general practitioner, who was instructed to refer the man back if the PSA rose by ≥2.0mcg/L or he developed troublesome urinary symptoms.

A small number of men whose place of domicile made it difficult to attend a clinic serviced by a WPBG clinician were followed up remotely by WPBG using clinic letters from supervising medical practitioners and email communications with the patient. Presenting cancer characteristics, post-implant dosimetry and follow-up data were entered onto a database which was established by the first author in the second year of the programme, and thereafter was updated and checked for completeness on an annual basis. In statistical analyses of the database, survival and cumulative probability of an event figures were derived using the Kaplan-Meier method.

Results

Table 1 shows the patient and tumour characteristics of the 951 treated men. The median age of treated men was 62.7 years, with a range 39.3–75.7 years.

The median follow up after treatment was 7.9 years, with a range 2.0–16.3 years. Follow up of 933 men was performed by a
WPBG clinician, and these men had full PSA and toxicity data collected. The remaining 18 men were unable to attend WPBG clinics for geographical reasons, and were followed up remotely.

The implant was preceded by hormone treatment in 128 men, and by EBRT in 48 men. Thirteen men had both hormone treatment and EBRT before their implant.

Post-implant radiation dosimetry demonstrated that the mean D90 for all treated men was 99% (desirable range for an implant 90–125%), and the mean V150 was 50% (desirable range 40–65%).

Biochemical failure (BF) occurred in 73 men. Eighteen BFs occurred in men with low-risk cancers (rate 3.3%), and 55 in men with intermediate-risk cancers (rate 13.7%). BF was called if there was a rise in PSA of $\geq 2.0$mcg/L above the post-treatment nadir PSA value$^{15}$ followed by two further rises in the PSA at six-monthly intervals, or alternatively if the PSA value never fell to low levels after the implant. One hundred and seventy-one men (18%) experienced a temporary spike in PSA of $\geq 2.0$mcg/L after their implant known as PSA ‘bounce’.16

Figure 1 shows that 10-year PSA control was 90% for all treated men, 95% for men with low-risk cancer and 82% for men with intermediate-risk cancer. Numbers of men at risk at 60, 120, and 180 months are provided.

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Table 1:

<table>
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<th>Patient age (years)</th>
<th>&lt;50</th>
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<td>546</td>
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<th>T2a</th>
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<table>
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<th>Tumour Gleason score</th>
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<th>&gt;6</th>
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<td>7</td>
<td>331</td>
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<table>
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<th>Presenting PSA (mcg/L)</th>
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<th>≥10</th>
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<td>833</td>
<td>118</td>
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</table>

<table>
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<th>Risk category</th>
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<tr>
<td>551</td>
<td>400</td>
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</tbody>
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Figure 1:
There were six deaths from prostate cancer, two in men with low-risk prostate cancer and four in men with intermediate-risk cancer.

Table 2 shows the acute urinary and bowel side effects, defined as those occurring within six months of the implant. No side effects or ones causing minor bother only were experienced by 96% men for urinary symptoms, and by 99% men for bowel symptoms. Twenty-five men (2.6%) developed a grade 3 acute urinary side effect (outflow obstruction requiring temporary catheterisation), and one man a grade 3 acute bowel side effect (rectal ulceration).

Late urinary and bowel side effects were defined as those occurring more than six months after the implant. For both systems, all men scored 0 or 1 except for the 23 men who developed a score 3 late side effect. Seventeen men developed a urethral stricture, and the cumulative risk of this complication was 2.6% at 10 years. Five men developed rectal bleeding and one man rectal ulceration.

Two hundred and seventy-six men (29.0%) required a PDE5 inhibitor after their implant, but not before. Of these, two-thirds (192 men) reported that the PDE5 inhibitor restored satisfactory sexual function.

### Discussion

The most important measure of any cancer treatment is its ability to permanently control (or cure) the cancer. For prostate cancers suitable for LDR brachytherapy, 10-year PSA control rates are considered to equate to cure rates because PSA relapse after 10 years is very uncommon, and our results are supportive of this.

The 10-year PSA control rates we achieved are similar to those reported by LDR centres in North America and Europe treating large numbers of cases, and at least match control rates achieved by other treatments for similar prostate cancers. The high PSA control rates achieved by the WPBG can be attributed in part to the routine measurement of the implant D90 and V150.

### Table 2:

<table>
<thead>
<tr>
<th>Acute side effect score</th>
<th>Urinary</th>
<th>Bowel</th>
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<tbody>
<tr>
<td>0 (none)</td>
<td>567 (59.62%)</td>
<td>856 (90.01%)</td>
</tr>
<tr>
<td>1 (minor bother)</td>
<td>346 (36.38%)</td>
<td>87 (9.15%)</td>
</tr>
<tr>
<td>2 (major bother)</td>
<td>13 (1.37%)</td>
<td>7 (0.74%)</td>
</tr>
<tr>
<td>3 (intervention required)</td>
<td>25 (2.63%)</td>
<td>1 (0.11%)</td>
</tr>
</tbody>
</table>

The 10-year PSA control rates we achieved are almost identical to those recently reported on a series of 207 men treated with LDR brachytherapy in Western Australia. This provides additional evidence that groups in New Zealand and Australia can produce results equal to those achieved in the Northern Hemisphere.

Analysis of the PSA changes occurring after implants demonstrated that the Phoenix definition of BF after EBRT, a rise in PSA of ≥2.0mcg/L above the post-treatment nadir value, overstates BF after LDR brachytherapy. We found that a PSA bounce occurred in 18% men after their implant, and that this non-prognostic rise in PSA due to radiation effects on the normal prostate could only be distinguished from BF by the PSA falling again within 12 months rather than continuing to rise.
Factors such as convenience, time off work and possible side effects are also important to men making decisions about how they wish to be treated. LDR brachytherapy delivered by the WPBG was easy for men to schedule into their lives, especially once men needed to put aside only a single day for the treatment. Nearly all men were able to return to work or to a normal routine within four days of the implant. Adverse effects were generally minor and short-term only, with the main exceptions being ED, temporary urinary obstruction soon after the implant, and late onset of urethral stricture.

ED is a difficult side effect to quantify after any treatment for prostate cancer because a degree of dysfunction is common as part of the normal aging process in men passing through the seventh decade of life, and not all men are sexually active when treated. Also, ED is variable in severity, with some cases responding better to a PDE5 inhibitor than others. Our 29% rate of ED was similar to the 25% rate in a recently reported series of men aged 60 years or younger.19 Our results suggest that approximately two-thirds of men experiencing ED as a side effect of an implant will have a good response to medication.

The 2.6% rate of men requiring temporary catheterisation after their implant is similar to the 3.2% rate reported in another large series,20 when the risk of catheterisation was found to be higher in men with bigger prostates and more baseline lower urinary tract symptoms. We found that catheterisation was less often required as the implant team became more adept at correctly positioning needles in the prostate at the first attempt, and later men in our series rarely needed this intervention.

The 2.6% cumulative risk of a urethral stricture at 10 years is similar to the 3.2% absolute rate recently reported in another large series.20 Both these rates are considerably lower than the 15.7% risk of a serious urinary adverse event reported in a recent overview of nearly 13,000 LDR brachytherapy cases,21 in which a serious urinary adverse event included urethral stricture, urinary incontinence and radiation cystitis. These latter two side effects were not seen in men we treated.

Conclusion

LDR brachytherapy is a highly effective low-impact treatment option for New Zealand men with early stage prostate cancer.

Competing interests:
Nil.

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REFERENCES: