**10-YEAR OUTCOMES USING LOW DOSE RATE BRACHYTHERAPY FOR LOCALISED
PROSTATE CANCER:**

AN UPDATE TO THE FIRST AUSTRALIAN EXPERIENCE

RUNNING HEAD: 10-YEAR LOW DOSE RATE BRACHYTHERAPY OUTCOMES

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Abstract:

Aim: To report long-term prostate specific antigen (PSA) and toxicity outcomes for patients with localized prostate cancer treated with Iodine-125 permanent implantation at a single Australian centre.

Methods and Materials: Between September 1994 and November 2007, 207 patients at Sir Charles Gairdner Hospital with localized prostate cancer were consecutively treated with Iodine-125 permanent interstitial implantation. Post therapy assessment was performed 3-monthly and included clinical review and biochemical (PSA) evaluation. PSA progression was evaluated using the Phoenix (nadir + 2.0) definition. Treatment related morbidity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 guidelines. The rate of biochemical failure was calculated by Kaplan-Meier plots. Univariate and multivariate analyses were performed to evaluate outcomes by pre-treatment clinical prognostic factors and radiation dosimetry.

Results: Median follow-up was 7.8 years. The 10-year biochemical disease free survival (bDFS) for the entire cohort was 89%. 10-year bDFS estimates by pre-treatment risk group were 96% for low-risk, 83% for intermediate-risk and 50% for high-risk disease. On multivariate analysis, pre-treatment PSA was an independent predictor of bDFS. D90 dose did not show a statistically significant effect on bDFS. The peak incidences of late grade 3 or higher urinary and rectal toxicities were 10.7% and 1.1% respectively.

Conclusion: Excellent long-term biochemical control was demonstrated with Iodine-125 permanent interstitial implantation in appropriately selected patients with prostate cancer. The results of our single centre experience are comparable with those of other single institutions.

Key words: biochemical control, brachytherapy, dosimetry, prostate cancer, toxicity

Introduction:

Carcinoma of the prostate is the most common form of cancer in Australian men, with over 20,000 new cases diagnosed in Australia each year¹. Low dose rate (LDR) prostate brachytherapy is a well-established and effective treatment modality for those patients with low risk, early stage prostate cancer². Iodine-125 seeds are inserted into the prostate via a transperineal approach and through slow decay (half-life 60 days) they release short-range 27 keV photons³. As such, LDR

brachytherapy results in adequate radiation dose to prostate cancer confined to the gland, whilst ideally sparing damage to the surrounding normal tissues.

Medium and long-term outcome data from single centre studies have reported excellent disease control rates utilising Iodine-125 LDR brachytherapy as monotherapy in cohorts of low and intermediate risk patients⁴⁻⁷. The relationship between dose delivered to the prostate and biochemical control has been well described with varying results. Optimal biochemical control has thus far not been consistently attributed to a specific D90 dose⁸⁻¹⁰. There are few published reports on long-term morbidity outcomes¹¹⁻¹².

The Sir Charles Gairdner Hospital was the first Australian centre to deliver Iodine-125 permanent interstitial prostate implants. The first performed implants were carried out on the 7th of September 1994 and it remains the sole provider of LDR brachytherapy in Western Australia. Reports on short-term biochemical outcomes at this centre have been previously reported¹³.

We review the long-term biochemical and toxicity outcomes for the first 207 consecutively treated patients at Sir Charles Gairdner Hospital using Iodine-125 therapy with up to 15 years follow-up. We also assess the relationship between biochemical control and prostate dosimetry.

To our knowledge this report represents the longest follow-up of Australian patients receiving LDR brachytherapy.

Methods and Materials:

Patient selection

Between September 1994 and November 2007, a total of 207 consecutively treated patients with clinically localized prostate cancer received a permanent implant of Iodine-125 seeds as outpatients. The study cut-off date was chosen to allow a minimum follow-up of 5 years. All patients had biopsy proven adenocarcinoma. Baseline evaluation included a complete history and physical examination, trans-rectal ultrasound for prostate volume determination and a serum PSA level. Local tumour (T) stage was determined by digital rectal examination performed by a Urologist or Radiation Oncologist and was described using the American Joint Committee on Cancer system. Where indicated staging was completed with whole body bone scan and computed tomography (CT) of the abdomen and pelvis.

Patient selection evolved over the course of our LDR brachytherapy program. Initially, patients were only required to have $<T3N0M0$ disease and PSA $<20\text{ng/mL}$. More recently eligible patients were those with $T1c\text{-}T2cN0M0$, Gleason 6 or 7 and PSA up to 10ng/mL . Patients with a prostate volume of $>60\text{cc}$, previous TURP procedure or significant obstructive symptoms were deemed unsuitable for LDR brachytherapy.

We classified patients into three risk groups as per the National Comprehensive Cancer Network (NCCN). Consequently, low-risk disease was classified as T1-T2a, low-grade (Gleason 6 or less), and PSA <10ng/mL. Intermediate risk disease was defined by T2b-T2c, intermediate grade (Gleason = 7), or PSA 10 -20ng/mL. High-risk disease was defined by stage T3, high grade (Gleason 8 or higher) or PSA > 20ng/mL.

Treatment

Neo-adjuvant hormonal therapy was administered to patients with a large prostate volume to downsize the gland and improve volume coverage. It was delivered for 3-6 months using either single-agent leutinising hormone-releasing hormone (LHRH) agonist, or LHRH agonist combined with an anti-androgen.

Implant technique, pre- implant planning and post-implant dosimetry

A pre-planning approach was used for all patients. 6 weeks before the scheduled implant date, the urologist performed a trans-rectal ultrasound volume study with the patient in the modified lithotomy position. Transverse images in 5 mm increments, typically from 5 mm superior of the prostate base to 10 mm inferior of the apex, were recorded for pre-implant treatment planning. The radiation oncologist outlined the required treatment volume on the ultrasound images and a physicist used in-house treatment planning software to manually optimise the number of radioactive I-125 seeds, their source strength (0.31mCi – 0.37mCi), and locations, to achieve the prescribed radiation dose of 144 Gy (using the TG43 formalism) to the prescribed volume with a 0 – 5 mm margin around the contoured prostate. The urethra was visualized on the pre-implant volume study using an inserted catheter as guidance. The reported dose to the urethra was the average of point doses recorded at the centre of the marked urethra on each slice of the prostate volume study, from the prostate base to the apex. The recorded dose to the rectum was defined by the point dose 10mm below to the posterior

edge of the prostate, outlined on the middle slice of the ultrasound volume study image set.

For the first 20 patients treated, no attempt was made to limit dose to the urethra. For all subsequent patients a urethral sparing technique was used. In doing so, no seeds were placed along the central column of template holes, avoiding direct implantation into the urethra. Planned seed placement was adjusted to produce a maximum dose in the center of the prostate to no more than 150% of the prescribed dose.

On the scheduled implant date, a transperineal implantation technique guided by trans-rectal ultrasound and fluoroscopy was used for all patients, as described by Kaye et al¹⁴. Patients were under general anaesthesia and were placed in the lithotomy position. All seeds were implanted by a urologist with guidance from the radiation oncologist. A physicist managed the manually pre-loaded sterilised seeds and assisted with dosimetry advice if required. All patients were implanted with loose I-125 seeds (Model 6711, Oncura, Amersham Health), manually pre-loaded into a mean of 31 (range 23-45) needles. A mean of 103 (range 42 – 156) seeds were implanted, with a mean total activity of 1.25 GBq (range 0.63 GBq - 1.81 GBq). During the procedure a urinary catheter was inserted and the inferior extent of the inflated balloon was used to assist determination of the prostate base. The orientation of a trans-rectal ultrasound transducer was then adjusted until the live images matched those acquired at the planning volume study. A needle template was fixed onto the transducer and two stabilisation needles were introduced into the prostate, with tips located at the prostate base. The pre-loaded seeds were then inserted at pre-planned locations.

Post-implant dosimetry was performed within 24 hours of implantation using in-house software that used seed positions determined via a stereo-shift film technique, as described by Smith et al¹⁵. A mean of 102 (range 42 – 154) seeds were detected and used in the post-implant dose calculation. The ultrasound-defined prostate volume was used for post-implant dosimetry, according to the

method of Haworth *et al.*¹⁶. Implant quality was assessed using parameters recommended by the American Brachytherapy Society¹⁷ and the American Association of Physicists in Medicine¹⁸, including the maximum dose delivered to 90% of the prostate volume (D90).

Follow-up

Patients were reviewed in clinic every three months, for the first 2 years, by both their Urologist and Radiation Oncologist. They were subsequently reviewed every 6 months thereafter. Follow-up assessments included PSA analysis and symptom assessment, including a LENT-SOMA late effects questionnaire on a regular basis up until 2007. LENT-SOMA outcomes were entered into a database at the time of review. Patient data for this study was collected retrospectively through review of clinical notes and pathology reports. The LENT-SOMA database was used to assist in the retrospective reporting of late toxicity outcomes. Dosimetry data, including dose to urethra and rectum, as well as D90 dose values were recorded at the time of treatment.

Biochemical failure was defined by the 'nadir + 2' definition¹⁹. It was measured from the date of implant. Late urinary and rectal toxicities were graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Patients were excluded from the analysis for several reasons and are represented in Figure 1. Sixteen patients were lost to follow-up within one-year post implant. A further 10 patients were deceased at the time of data collection and their details were not available for inclusion in the cohort. Five patients had received external beam radiotherapy (45 Gy in 25 fractions), prior to an Iodine-125 brachytherapy boost and were also excluded from the analysis.

Analysis

Time to biochemical failure as well as associations between pretreatment risk and subsequent biochemical outcomes were displayed using Kaplan-Meier curves. Uni- and multivariate analyses were performed using cox proportional hazards models to determine the effect of pre-treatment tumour characteristics and dosimetry on bDFS. The tumour variables included PSA at diagnosis, T stage, Gleason score and risk group. Dosimetry effect was analysed by comparing biochemical outcomes of patients with a D90 of <140 Gy, to those with a D90 of greater than or equal to 140 Gy. Model 1 of the multivariate analysis included the risk group of the individual, age and whether hormone therapy was used. Model 2 removes the risk group and introduces its components that include PSA at diagnosis, T stage and Gleason score, allowing analyses of their effect individually. A sub-group multivariate analysis was performed on the intermediate-risk patients, comparing the effect of favourable to unfavourable on bDFS. Favourable intermediate-risk was defined as primary Gleason 3 pattern, with no more than one intermediate risk factor. Unfavourable was defined as primary Gleason 4 pattern, or 2 or more intermediate risk factors. No analysis was made to correlate late morbidity with target dose. All analyses were performed in R Version 3.1.2 (R Development Core Team 2014), with Kaplan-Meier curves and Cox proportional hazards models being fit using the survival (T. M. Therneau 2014) package.

The Sir Charles Gairdner Hospital Quality Improvement committee approved this study.

End points

The primary end-point was biochemical disease free survival (bDFS) defined by 'PSA nadir + 2'. The secondary end-point was peak incidence of late urinary and rectal toxicity.

Results:

One hundred and seventy-six patients were included in the analysis with a median follow-up of 7.8 years. The median age at treatment was 65.4 years and the median PSA at time of treatment was 7.8 ng/mL.

Ninety (51.1%) patients were stratified as low-risk, 84 (47.7%) as intermediate-risk and 2 (1.1%) as high risk. 102 (58.0%) patients received neo-adjuvant ADT including 47 (52.2%) low-risk, 53 (63.1%) intermediate-risk and 2 (100%) high-risk patients.

The presenting characteristics of the study cohort are shown in Table 1.

The Kaplan-Meier estimate of bDFS for the entire cohort is 93% at 7 years and 89% at 10 years. There were a total of 18 failures (10.2%). Figure 2 depicts

Kaplan-Meier estimates of bDFS stratified by pre-treatment risk group. The Kaplan-Meier estimates of bDFS at 10 years were 96%, 83% and 50% for low, intermediate and high-risk respectively.

Table 2 shows the clinical status of the cohort at last follow-up.

Univariate and multivariate analysis was performed based on pre-treatment age, PSA, clinical stage, Gleason score, risk group and D90 value. These are represented in Table 3. On univariate analysis, PSA at diagnosis showed a hazard ratio of 1.12 ($p=0.014$), indicating an increase in one unit of the PSA at diagnosis, leads to a 1.12 times increase in the risk of failure. Gleason score 7 ($p=0.051$) and intermediate risk disease ($p=0.055$) were shown to be strong negative predictors for bDFS, however were not statistically significant. High-risk disease significantly reduced bDFS ($p=0.002$). On multivariate analysis, PSA at diagnosis again showed a statistically significant effect on bDFS ($p=0.030$). High-risk disease was also shown to significantly impact bDFS ($p=0.008$). Gleason grade 7 ($p=0.094$) and intermediate-risk disease ($p=0.130$) were again predictive of failure however were not statistically significant.

The 10-year estimate of bDFS for the intermediate-risk patients was 91% for favourable-risk and 74% for unfavourable-risk. On sub-group multivariate analysis of the intermediate-risk patients, unfavourable-risk was not predictive of poorer bDFS.

The median D90 dose was 150.1Gy (range 64.4 to 201.0). 66.3% of patients received a D90 of 140 Gy or higher. On uni- and multivariate analysis a D90 of greater than or equal to 140 Gy failed to show a statistically significant effect on bDFS.

Figure 3 shows a graphical representation of the co-efficients and 50/95% confidence intervals for Model 2 of the multivariate analysis.

Table 4 shows the late urinary and rectal toxicities for this cohort based on the CTCAE version 3.0 criteria. The overall incidence of Grade 3 and higher toxicity was 10.7 % for urinary effects and 1.1% for rectal effects. There were 12 (6.8%) grade 3 urethral strictures, all requiring intermittent catheterization or dilatation. There was 1 (0.6%) reported incidence of grade 3 urinary incontinence and 2 (1.1%) reports of grade 3 hemorrhagic cystitis requiring cauterization. There were 4 (2.2%) grade 4 urethral strictures requiring a transurethral resection of prostate (TURP). There were 2 (1.1%) reported incidences of grade 3 or higher late rectal effects, both of which were radiation proctitis requiring cauterization.

Discussion:

This article reports the long-term bDFS and late toxicity outcomes for the first Australian patients treated with Iodine-125 brachytherapy for localized prostate cancer. Our study provides a reference for biochemical outcomes following Iodine-125 treatment, having successfully achieved long-term biochemical follow-up in a moderate sized cohort of consecutively treated patients. Due to frequent clinical review and extensive documentation on both the presence and absence of all

relevant genitourinary and gastrointestinal outcomes, we report an estimate of late urinary and rectal effects following LDR brachytherapy.

Patient selection and treatment techniques have evolved over the course of our LDR brachytherapy program. Initially, patients were required only to have <T3 disease and PSA <20ng/mL to be eligible for treatment. As such, many of the cohort's earlier patients would be deemed inappropriate for treatment today. Despite this we report an excellent 10-year overall bDFS rate of 89%.

Our 10-year bDFS of 96% for low-risk disease is consistent with published literature. Grimm et al² performed a comparative analysis of bDFS based on treatment modality and risk stratification on all published data on localized prostate cancer from 2000 to 2011. In patients treated with LDR brachytherapy for low-risk disease, the 10-year bDFS ranged between 88 and 98%.

Clinical opinion is divided on whether LDR monotherapy is suitable for intermediate-risk disease. In total, 84 patients with intermediate-risk disease were treated in our series, with a 10-year bDFS of 83%. Our results are consistent with other published series that included large numbers of intermediate-risk patients⁵. On further stratifying the intermediate-risk patients into favourable and unfavourable, we found a trend towards improved 10-year bDFS in the favourable group (91% vs 74%). On multivariate analyses this was not shown to be a statistically significant predictor of improved bDFS, however our study was likely underpowered to show such an effect. Our results support the use of LDR brachytherapy as a standard treatment option in selected patients with intermediate risk prostate cancer.

Neo-adjuvant ADT was administered to 58% of our cohort solely on the basis of prostate size, regardless of tumour characteristics, to downsize the gland and improve volume coverage. The impact of neo-adjuvant ADT on biochemical outcomes for such patients is unclear, with conflicting results from published series^{20, 21}. It is, however, recognised that the use of ADT has no impact on

outcomes in low-risk disease²². Whilst the use of ADT may have impacted on our results in the longer term, it was not shown on uni- and multivariate analyses to predict for improved bDFS.

Delineation of dosimetry parameters that are predictive of bDFS would assist in identifying those patients that may require supplemental treatment if such parameters are not achieved. To evaluate the effect of D90 dose on bDFS we selected a D90 cut-off value of 140 Gy. This was based on several published series that have shown a relationship between this value and bDFS⁸⁻⁹. The ability of our series to identify such a relationship was impaired by our sample size and number of events. Other single centre series have also failed to show an effect. Morris et al.¹⁰ reviewed 2000 patients treated with Iodine-125 monotherapy with a median follow-up of 5 years. They failed to identify a statistically significant D90 dose-response relationship despite analyzing cut-off points of 130, 140, 150, 160, 170 and 180 Gy. Whilst a longer-term follow-up may demonstrate a correlation between bDFS and D90 dose, it has been suggested that the D90 is not the most appropriate surrogate for prediction of clinical outcome due to the lack of spatial information associated with this parameter²³.

The incidence of late urinary and rectal toxicity in our series is consistent with other published data, acknowledging the evolution of our technique over time to include urethral sparing. Keyes et al.¹¹ reported late urinary toxicity in 2709 patients treated between 1998 and 2009 with Iodine-125 LDR brachytherapy with a median follow-up of 54.5 months. Toxicity was scored using the RTOG grading system. The actuarial rate of grade 3 or higher toxicity was 10% at 9-13 years. Ragde et al.¹² bears the closest resemblance to our series in terms of cohort size and follow-up time. Their series followed 118 patients following Iodine-125 monotherapy with a median follow-up of 69.3 months. Using the CTCAE criteria, the reported incidence of late grade 3 urinary effects was 12%. All of which were urethral strictures and all were treated with urethral dilation. They reported a 4.2% incidence of late grade 4 urinary effects, all of which were strictures requiring TURP.

We acknowledge several limitations in this study. A number of patients in our series were treated from inter-state and subsequently lost to follow-up. We are subsequently unable to reflect their biochemical outcomes, although they represent a small percentage of our cohort. Furthermore, several patients had been deceased for more than 10 years at the time of data collection. As such, their records were unavailable for inclusion in the analysis. Their inclusion would potentially alter our results given the possibility that a proportion may have died of metastatic prostate cancer. Following strong initial compliance, LENT-SOMA assessments were only performed sporadically. Although toxicity outcomes were comprehensively documented in patient records, sustained prospective data collection through patient and clinician questionnaire may have provided more accurate data than our retrospective review of patient files.

Conclusion:

Excellent 10-year biochemical control rates were achieved at the first Australian centre using Iodine-125 brachytherapy for patients with clinically localized, low-risk prostate cancer. Despite the modifications in patient selection and implant technique since the commencement of our program, our biochemical and toxicity outcomes are consistent with other published studies producing similar results.

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Figure Legends:

Figure 1. Patients excluded from analysis

Figure 2. 12-year Kaplan Meier curves for freedom from biochemical failure stratified by risk group

Figure 3. Estimates and confidence intervals for hazard ratios from the multivariable model.

Table 1. Patient characteristics and dosimetry

Variable	N=176 (%)	Median [Q1, Q3] †
Age at treatment (years)		65.4 [58.7, 69.3]
PSA at diagnosis (ng/mL)		7.8 [5.7, 9.9]

Prostate volume (cc's)		30.8 [25.2, 36.7]
Follow-up length (years)		7.8 [5.9, 9.8]
Hormone therapy (yes)	102 (58.0%)	
Prostate dose ≥ 140 Gy	116 (65.9%)	
D90 of prostate (Gy)		150.1 [136.3, 158.2]
Rectal dose (Gy)		69.2 [52.8, 88.0]
Urethral dose (Gy)		207.0 [179.7, 233.5]
Stage		
T1c	51 (29.0%)	
T2a	83 (47.2%)	
T2b	23 (13.1%)	
T2c	19 (10.8%)	
Gleason score		
≤ 6	153 (86.9%)	
7	23 (13.1%)	
Risk group		
Low	90 (51.1%)	
Intermediate	84 (47.7%)	
High	2 (1.1%)	

† Data shown as *median [Q1, Q3]* where Q1 represents the value below which the first quartile of the cohort exist and Q3 represents the value above which the fourth quartile of the cohort exist.

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Table 2. Clinical status at last follow-up

	N=176 (%)
Biochemical progression free survival	158 (88.75%)
PSA progression only	11 (6.88%)
Local disease	1 (0.62%)
Distant disease	2 (1.25%)
Deceased due to prostate cancer	4 (2.50%)

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654 **Table 3.** Uni- and Multivariate analysis for biochemical relapse

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Variable	Univariable	Univariable	Model 1	Model 1	Model 2	Model 2
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Age (treatment)	1.05 (0.97, 1.13)	0.202	1.03 (0.95, 1.11)	0.451	1.02 (0.94, 1.10)	0.690
PSA (diagnosis)	1.12 (1.02, 1.24)	0.014			1.13 (1.01, 1.25)	0.030
Stage (c.f. T1c)						
StageT2a	0.60 (0.18, 1.98)	0.401			0.49 (0.14, 1.65)	0.249
StageT2b	0.69 (0.14, 3.41)	0.646			0.56 (0.10, 3.01)	0.501
StageT2c	1.79 (0.50, 6.33)	0.370			0.68 (0.13, 3.57)	0.645
Gleason ≥ 7	2.84 (1.00, 8.11)	0.051			2.91 (0.83, 10.15)	0.094
Hormone therapy (yes)	1.75 (0.61, 4.97)	0.295	1.30 (0.44, 3.89)	0.634	1.42 (0.46, 4.40)	0.542
Risk group (c.f. low)						
Risk group, intermediate	3.05 (0.98, 9.52)	0.055	2.47 (0.76, 7.99)	0.130		
Risk group, high	36.58 (3.87, 345.68)	0.002	25.61 (2.31, 284.32)	0.008		

D90 $\geq$ 140 Gy	0.59 (0.22, 1.59)	0.299	0.82 (0.26, 2.34)	0.711	0.79 (0.28, 2.20)	0.646
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HR, hazard ration, CI, confidence interval, PSA, prostate specific antigen, D90, dose received by at least 90% of the prostate

Table 4. Incidence of CTCAE late urinary and rectal toxicity

	Grade 1-2	Grade 3	Grade 4
Genitourinary			
Frequency	31 (17.6%)	0	0
Cystitis	7 (4.0%)	2 (1.1%)	0
Stricture	9 (5.1%)	12 (6.8%)	4 (2.2%)
Incontinence	5 (2.8%)	1 (0.6%)	0
Gastrointestinal			
Radiation proctitis	5 (2.8%)	2 (1.1%)	0

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