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The impact of dose and quality assurance in early prostate cancer treated with Low Dose Rate (LDR) brachytherapy as monotherapy.

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Abstract

Aims To examine the relationship between post-implant CT dosimetry and long term PSA relapse free survival in patients treated with Iodine 125 LDR prostate brachytherapy as monotherapy and secondly, to audit recent practice against RCR guidelines following the re-introduction of post-implant dosimetry for all patients in our centre.

Methods and Materials (A) Between March 1995 and September 2007, 2157 consecutive patients with localized prostate cancer underwent I-125 permanent prostate brachytherapy as monotherapy in a single UK centre. All patients were trans-rectal ultrasound (TRUS) planned delivering 145 Gy (TG 43) minimum peripheral dose. None received supplemental external beam radiotherapy. Post implant CT based dosimetry was undertaken between 4 to 6 weeks post-treatment and was available for 711 (33%). Outcomes were analysed in terms of relation of D90 to PSA relapse free survival (Nadir 2+ definition) and all patients had **a** minimum follow up of 5 years.

(B) For contemporary patients from 2011 quality metrics from post-implant CT as defined by RCR guidelines are presented.

Results (A) A mean D90 of 138.7 (SD 24.7) Gy was achieved for the historic cohort. Biochemical control at 10 years was 76% in patients with D90 > 140 Gy and 68% in those with D90 <140 Gy ($p < 0.01$). (B) In current practice, over the last 3 years the mean (SD) D90 has increased from 154 (15.3) Gy in 2011 to 164 (13.5) Gy in 2013. Similarly an increase in the mean (SD) V100 from 92 (4.4) % to 95 (3.2) % is noted over time. No difference between clinicians was noted.

Conclusion D90 values of less than 140Gy continue to be predictive of increased risk of recurrence of prostate cancer across risk groups with longer follow-up. Quality assurance can be used to ensure improved and consistent implant quality in a team with multiple clinicians.

Keywords: Brachytherapy, Dosimetry, Outcomes, Prostate Cancer, Quality Assurance.

Introduction

Permanent low dose rate brachytherapy is a well-established treatment option for early prostate cancer [1] with advantages over other options in terms of improved sexual, bowel and urinary function in the long term [2]. In early prostate cancer improved PSA control with radiation dose escalation has been demonstrated in randomised trials using external beam radiotherapy [3] and in multi-institutional series of cohorts treated with permanent prostate brachytherapy [4].

In permanent prostate brachytherapy, CT based post-implant dosimetry is used to quantify D90 (the minimum dose received by 90% of the prostate volume) and V100 (the percentage volume of the prostate receiving at least 100% of the prescribed dose) as measures of both the quality of an individual implant and also quality assurance (QA) for the prostate brachytherapy programme. Concerns about training and QA in the United States led the UK and Ireland Prostate Brachytherapy Group in conjunction with the RCR to develop and publish QA practice guidelines in 2012 [5].

An initial analysis by our group [6] demonstrated a dose response only in low risk patients and not in the entire group of patients treated with I-125 monotherapy, although with longer follow-up dose response for the entire group became apparent [7]. This work documents outcome in a larger cohort of patients all with at least 5 years follow-up and secondly audits our current post-implant dosimetry results against RCR guidelines.

Methods and materials

(A) Between March 1995 and September 2007, 2157 men (mean age 64 years, range 37-85) were treated with permanent prostate brachytherapy alone at a single

cancer centre. Clinical staging used the 1997 AJCC TNM system. Patients were stratified using the Memorial Sloan-Kettering (MSK) model, defining low risk as PSA ≤ 10ng/mL and Gleason 2-6 and cT1-T2 disease; intermediate risk as the presence of one factor of PSA >10ng/mL or Gleason >6 or T3 disease and high risk as two or three of the intermediate factors.

All patients were treated by implantation with ^{125}Iodine seeds as monotherapy using a pre-planning technique as described previously [7] with a prescribed dose of 145Gy (TG 43) to the prostate with a margin of 3mm.

Post implant dosimetry was performed by CT four to six weeks after implantation when the majority of oedema should have settled. The contouring was carried out by either experienced members of the medical physics team and/or experienced radiologists (BC and JS). Previous work from our centre has demonstrated that the radiologist is most consistent in accurate post-implant prostate contouring [8]. The number of seeds was identified from CT with an automated seed detection program and was also checked manually. Dosimetry was calculated using VariSeed™ (Varian Medical Systems, Palo Alto, CA). Dose was described in terms of D90.

Patients were followed up with 3-monthly PSA assays for the first 2 years and then 6-monthly. Biochemical relapse was defined using the Nadir+2 (plus 2mg/mL rise above post treatment nadir).

Actuarial survival curves were calculated by the Kaplan-Meier method [9] with the log-rank (Mantel-Cox) and Breslow (Generalized Wilcoxon) tests used to evaluate the difference in survival curves. The relationship between D90 and biochemical outcomes were analysed using a threshold of above and below 140Gy. Cox

proportional-hazards multivariate analysis was used to assess the influence of different co-variants on the results [10].

(B) RCR guidelines recommend clinicians treat 25 patients per year each with LDR and record a number of target related parameters (prostate D90, V100, and V150) and organ at risk doses (D10% and D30% urethra if possible, D 2cc and D 0.1cc rectum). It also recommends ensuring the post implant CT: planning US volume ratio is ≥ 0.9 to help with prostate capsule delineation on post implant CT. Implant quality is considered satisfactory if the prostate V100 is ≥ 80% and the D90 ≥ 90% of the prescription dose (130Gy for I-125 monotherapy).

From 2011 post-implant dosimetry for all patients was re-introduced in our centre. In the years prior to this only a random sample of approximately 20% of patients treated had routine post-implant CT. From 2011 we also made incremental changes in technique including always using both the transverse and sagittal US imaging for seed placement, with the final seed deposition guided using the sagittal image. For post-implant dosimetry we now use metrics to guide CT contouring (CT: US ratio, height, width and length from end of implant US) and review post-implant CT results as an MDT regularly.

For each yearly cohort up to and including 2013, target parameters are described in terms of mean (SD) value and the proportion of patients achieving the target thresholds. Rectal doses and the ratio of the post implant CT to the pre-implant TRUS volumes are also presented [Table 1]. Urethral dose volume statistics are not available as patients are not routinely catheterised for post-implant CT and the urethra is not visible on CT without a catheter. No change in I-125 seed strength or source energy used over time from 1995 was made. Similarly no change in V150prostate prescription was introduced.

Results

(A) Patients had a median follow up of 6.5 years (range 0.2 to 17.7 years). Post implant CT dosimetry was carried out in 711 patients (33% of total). With respect to risk groups in those with post-implant CT dosimetry, 348 (49%) were low risk, 292 (41%) intermediate risk and 71 (10%) were high risk as defined by MSK model. A mean D90 of 138.7 (SD 24.7) Gy was achieved for this historic cohort (Figure 1). The CT:US ratio mean for post-implant dosimetry was 1.0 (SD 0.25) but with a wide range of values (0.5-3.1). Only 79% of CT:US ratios were >0.9. Biochemical control at 10 years was significantly higher at 76% in patients with D90 > 140 Gy and 68% in those with D90 <140 Gy ($p<0.01$) (Figure 2). There was a trend to improved biochemical control with dose over 140Gy across all risk groups although not statistically significant on subgroup analysis.

(B) From 2011 at least 94% of patients undergo CT post-implant dosimetry, with a few patients missed due to administrative problems with out of region patients. We have noted reduced overall numbers treated over time and this likely reflects the increasing use of active surveillance and the more widespread availability of robotic prostatectomy as a treatment option. In the last two years, this reduction in overall numbers treated has made it difficult to ensure that all 3 clinical oncologists implant at least 25 patients each per year, with only 1 of 3 clinicians achieving this [Table1].

Over the last 3 years the mean (SD) D90 has increased from 154 (15.3) Gy in 2011 to 164 (13.5) Gy in 2013. The number of implants with a D90 > 140Gy has increased from 82% to 98%. Similarly an increase in the mean (SD) V100 from 92 (4.4) % to 95 (3.2) % is noted over time. The current average implant delivers more dose to the

prostate than the historic cohort (mean D90 138Gy) and also implants are more consistent with a lower SD (13.5Gy) across the population when compared to the historic series (SD 24Gy). We have also compared dosimetry between the three clinical oncologists and have found no difference between operators in terms of post-implant dosimetry [data not presented]. Dose to the rectum and CT: US ratios are presented in Table 1 with compliance to recommendations of over 90%. Of note, the modern post-implant dosimetry series has a CT:US ratio approaching 100% whereas the older cohort this was 79% suggesting with time contouring the post-implant CT has become more consistent.

Discussion

This institutional series demonstrates that D90 values of less than 140Gy continue to be predictive of increased risk of PSA recurrence across risk groups in a cohort of 711 men with at least 5 years follow-up. In our practice, the re-introduction of routine post-implant CT dosimetry has been associated with better and more consistent dosimetry between patients.

In the early years of permanent prostate brachytherapy, Stock and Stone were the first to demonstrate a dose response with a D90 cut off of 140Gy in 134 men with median follow up of 4 years and a mean D90 of 140.8Gy [11]. Higher D90 resulted in 92% disease free survival as compared to 62% in those with D90 lower than 140Gy. An initial learning curve was demonstrated and over time incremental improvements in outcomes associated with refinement of implantation technique. Subsequently,

Potters et al [12] also demonstrated a dose response in a larger cohort of 719 men with PSA improved in those with D90 greater than 90% of the prescribed dose.

An initial analysis by our group [6] demonstrated a dose response only in low risk patients and not the cohort as a whole. The impact of dose on PSA control has become more apparent in a larger cohort of patients with longer median follow-up [7]. The PSA control curves only divide after 3 years of follow-up as the use of neo-adjuvant hormone manipulation masks the impact of radiation dose on PSA control in the initial years. The British Colombia group provide an excellent example with a rigorous QA program and excellent implant quality across the province and multiple operators [13]. In over 2000 patients a median D90 of 150Gy is achieved with few low dose implants and excellent clinical outcomes. A dose response is less obvious perhaps because of the consistent high quality and the use of hormone manipulation in 58%.

The initial planning dosimetry for permanent prostate implants is undertaken using trans-rectal ultrasound as it provides excellent imaging of the prostate in an intra-operative setting. Post-implant dosimetry is generally undertaken using CT as seeds are much easier to see using x-ray imaging. There are a number of challenges and uncertainties in post implant dosimetry. In the immediate post-operative period the prostate is subject to swelling and distortion but immediate (Day 0) imaging has advantages in that there may be an opportunity to intervene and re-implant if there has been geographical miss. More commonly, post implant dosimetry is undertaken at 4-6 weeks allowing time for operative changes and swelling to settle.

Inter-observer variability in contouring the prostate causes the most significant uncertainty in post-implant dosimetry calculations as demonstrated in a recent multi-

centre planning study comparing observer variability in contouring, seed reconstruction and image fusion across multiple European centres [14]. MR-CT fusion has been recommended to help identify the prostate capsule and improve accuracy in post-implant dosimetry, but in this study the SD of CT and MR contoured volumes was noted to be 23% and 17% respectively, demonstrating only a small reduction in observer variability with the use of MR.

RCR guidelines [5] recommend minimum staffing levels of both two radiation oncologists and medical physicists in a prostate brachytherapy team. To minimise the learning curve effect, mentoring for the first ten cases with subsequent remote supervision by an experienced centre is advised. A case volume of at least 25 per year per oncologist is suggested to ensure that skills are maintained. With reduced numbers undergoing I-125 brachytherapy it is likely that the recommendation of 25 implants per year per clinical oncologist may be difficult to maintain. In centres such as our own, where we deliver both LDR and HDR brachytherapy, a pragmatic approach may be that the 25 per year may include LDR and HDR procedures combined, as long as a minimum number of LDR implants are performed, for example 15 per year, recognising that LDR is more technically challenging and operator dependent than HDR.

External QA review procedures are now accepted as an essential component in radiotherapy trials to ensure that treatment effects are not masked by the delivery of poor quality radiation [15-16]. RCR guidelines also recommend external peer review every 2 years of a random selection of LDR cases to ensure quality is maintained and reduce the bias associated with reviewing one’s own cases. This has not yet been implemented and the prostate brachytherapy community will need to develop clear and transparent methods to undertake this. It will be challenging as clinician

auditors should have performed 100 cases in the last 3 years and physics auditors be the physics lead in 100 cases in the last 3 years.

Post implant dosimetry is a useful internal QA tool in seed brachytherapy programmes but it is important to remember for individual patients there is uncertainty associated with the dose calculations. We have found its routine re-introduction helps us reflect on our practice as a multi-disciplinary team. This has resulted in improved seed placement and more consistent post-implant CT contouring with improvements in implant quality for the population overall.

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Figure legends

Figure 1: Frequency distribution for historic cohort of 711 patients with post-implant CT dosimetry and minimum follow up of 5 years.

Figure 2: Overall actuarial PSA relapse-free survival (Nadir+2) using a D90 threshold of 140Gy as calculated from CT post implant dosimetry (P=<0.01) in cohort of 711 historic patients with post-implant dosimetry and minimum follow up of 5 years.

Table 1: Prostate LDR implants in yearly cohorts from 2011 onwards described in terms of RCR guidelines 2012.

Figure 1: Frequency distribution for historic cohort of 711 patients with post-implant CT dosimetry and minimum follow up of 5 years.

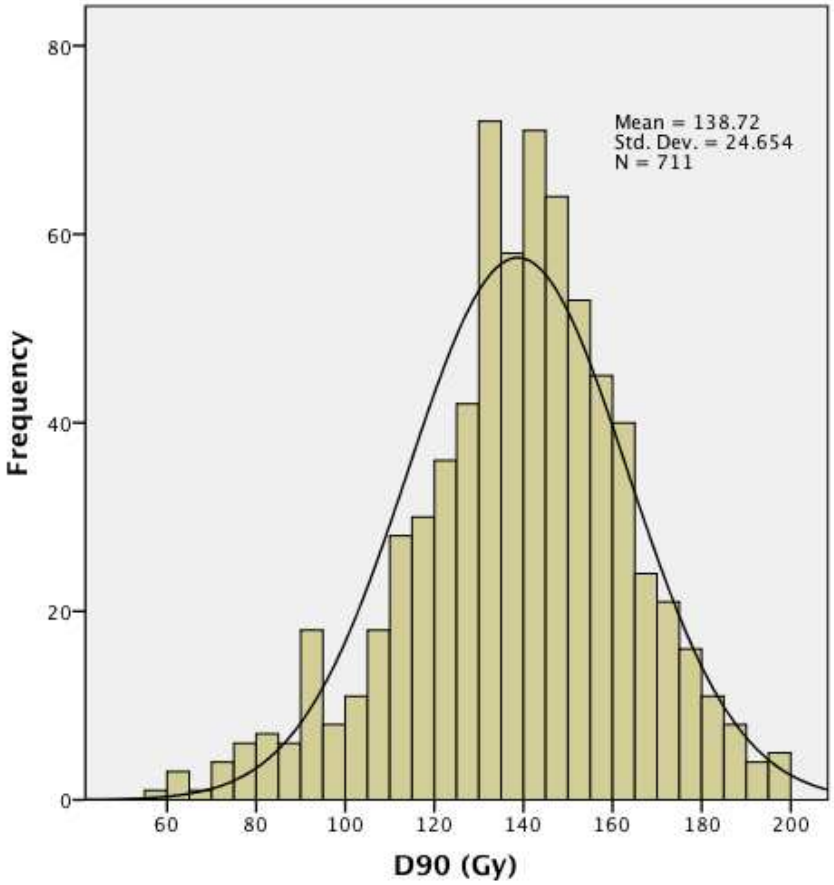
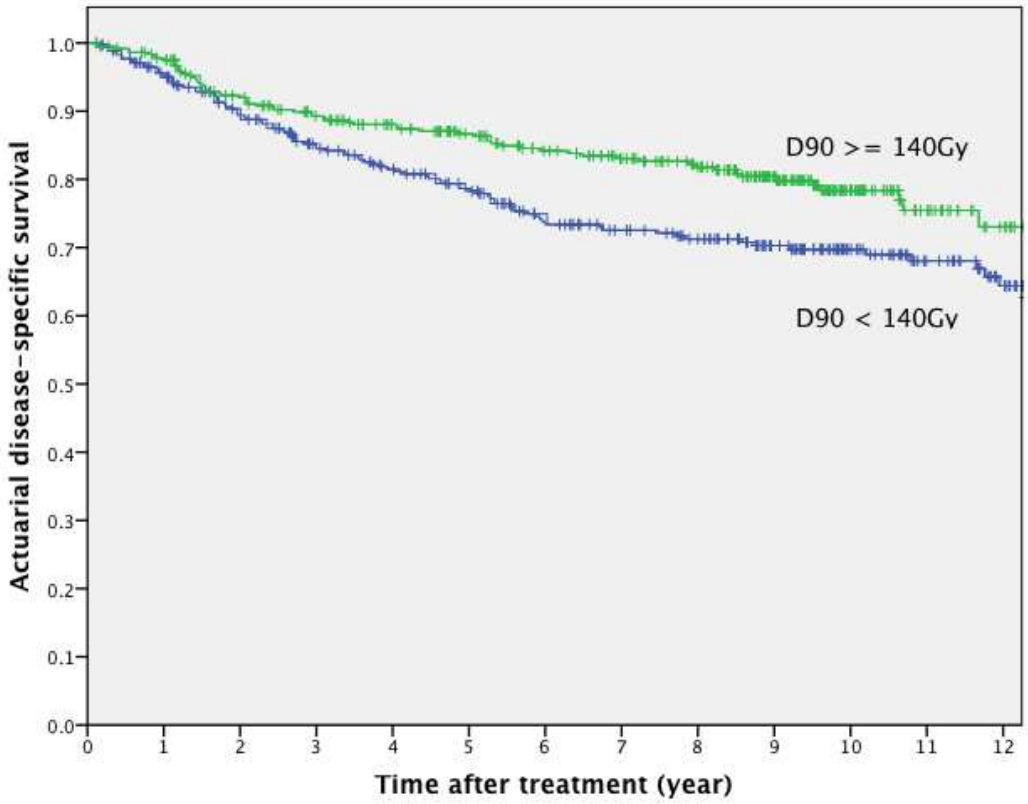


Figure 2a: Overall actuarial PSA relapse-free survival (Nadir+2) using a D90 threshold of 140Gy as calculated from CT post implant dosimetry (P=<0.01) in cohort of 711 historic patients with post-implant dosimetry and minimum follow up of 5 years.



Numbers at risk at entry into each year

Year	0	1	2	3	4	5	6	7	8	9	10	11	12
>140Gy	365	348	313	290	269	247	227	212	191	144	81	45	27
<140Gy	346	317	284	255	235	218	189	174	162	132	94	68	48

Table 1: Prostate LDR implants in yearly cohorts from 2011 onwards described in terms of RCR guidelines 2012.

Year	Total number of patients	Number with post implant CT (%)	Cases per clinical oncologist per year	Mean V100 prostate (SD) %	% with V100 > 80%	Mean D90 (SD) Gy	% with D90 > 130Gy	% with D90 >140Gy	% d_{2cc} rectum < 145Gy	% with CT:US ratio ≥ 0.9
2011	125	120 (96%)	50 40 30	92.0 (4.4)	98.3%	153.9 (15.3)	93%	82%	98.3%	96.7%
2012	121	119 (98%)	53 32 33	95.0 (3.6)	99.2%	165.7 (14.3)	98%	97%	94.1%	98.3%
2013	96	90 (94%)	49 22 19	94.5 (3.2)	100%	163.6 (13.5)	99%	98%	92.2%	98.9%