

# Comparison of permanent $^{125}\text{I}$ seeds implants with two different techniques in 500 cases of prostate cancer

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## Abstract

**Purpose:** To perform a comparative study of 500 consecutive  $^{125}\text{I}$  seeds implants for intracapsular prostate carcinoma with two techniques differing in terms of both strand implantation and planning.

**Material and methods:** From 2002 to 2007 we performed 250 implants with fixed stranded seeds (RapidStrand™) and a preplanning system and from 2007 to 2010, 250 with real-time and ProLink™ system. Mean age was 68 and 66, respectively, median PSA (prostate-specific antigen) 7.3 and 7.2, stage T1-T2a in 98% and 94%, and Gleason  $\leq 6$  in 96% and 86%. Low risk cases were 81% and 71%. The prescribed dose was 145 Gy to the prostate volume, or 108 Gy plus EBRT 46 Gy in some intermediate risk cases. Hormonal treatment was given to 42% and 28%.

**Results:** Median follow-up was 48 and 47 months, respectively, 14 patients in the first group and 7 patients in the second developed biochemical failure (BF). Actuarial biochemical relapse-free survival (bRFS) at 5 years increased from 90.2% to 97.2% (low risk from 91.3% to 97.2%, intermediate risk from 84.2% to 97.1%). Biochemical failure was independent of hormone treatment. Rectal complications were G1-2 in 1.2% and 5.2%, respectively. A urinary catheter was necessary in 6.9% and 9.6%, and urethral resection in 1.9% and 4.4%. Genitourinary toxicity was G1-2 in 4.6% and 12%, G3-4 in 1.9% and 4.8%. An assessment of mean  $D_{90}$  in a sample of patients showed that the dosimetry in postoperative planning based on CT improved from a mean  $D_{90}$  of 143 Gy to 157 Gy.

**Conclusions:** The outcome of patients with low risk prostate carcinoma treated with  $^{125}\text{I}$  seed is very good with low complications rate. The real-time approach in our hands achieved a more precise seed implantation, better dosimetry, and a statistically non-significant better biochemical control. We have made this our standard technique.

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**Key words:** LDR brachytherapy, permanent, prostate cancer, real-time, seeds, technique.

## Purpose

Permanent low-dose-rate brachytherapy (LDR-BT) has become a standard treatment for localized prostate cancer, achieving ten-year biochemical relapse-free survival (bRFS) comparable to radical prostatectomy (RP) [1-4], and better than external beam radiation therapy (EBRT) [5]. Both, LDR-BT and RP are considered equivalent, while lacking randomized studies [6,7]. Excellent results with radioactive seeds at fifteen years of follow up have now been published [8,9].

The implant technique has evolved greatly [10], achieving good results with loose or stranded seeds, and different forms of seed placement, as described in the American [11] and European [12,13] recommendations. The use of

real-time systems has improved bRFS in some series [14]. In this paper we review the experience of a single center comparing 500 consecutive implants in localized prostate carcinoma, with two different techniques. The first 250 patients were treated with stranded seeds (RapidStrand™) according to a preplanning dosimetry system, and the other half with real-time planning and a quick system to prepare and decide seed positions with greater flexibility in seed distribution with different distances between them (Bard ProLink™). The Pro-Link system also uses linked seeds with the difference that spacers of different lengths can be used to prepare custom strands.

The aim of this study was to compare the two different techniques in a single center to know our own expe-

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rience, to evaluate whether the optimized technique can improve results and achieve high quality implants, and to know which changes we can do to get a better outcome.

**Material and methods**

From December 2002 to October 2007 we performed 250 implants with LDR <sup>125</sup>I seeds brachytherapy with RapidStrand™ and a preplanning system and from November 2007 to December 2010, 250 implants were performed with real-time planning and the Bard Pro-Link™ system. Nine patients were lost at the beginning of the follow-up and seven were excluded because they died of non-related diseases in the first two years and are not included in the analysis. Therefore, we compare 250 consecutive patients with the first system and 250 with the more recent technique. All cases were treated by the same clinical team. All patients had biopsy proven diagnostic

of adenocarcinoma. In each group, mean age was 68 and 66, respectively, median PSA (prostate-specific antigen) was 7.3 and 7.2 ng/dl and Gleason score was ≤ 6 in 96% and 86%. The tumour stage was T1-T2a in 98% and 94%. According to the D'Amico classification, modified with the recommendations of EORTC [13], low risk cases (PSA < 10, Gleason 2-6, T1-T2a stage) were 80.8% and 71.2%. Intermediate risk cases (PSA 10-20, Gleason 7, T2b-c stage) were 19.2% and 27.6%. No high risk cases (PSA > 20, Gleason 8-10, T3) were treated with the preplanning system and only 3 patients without extracapsular involvement with the real-time system. Patient characteristics are described in Table 1, showing that the second group treated with real-time technique had younger men, more intermediate risk patients, and T2b stage, higher Gleason, less hormonal treatment and more cases of combined treatment with EBRT. Other inclusion criteria were life expectancy of more than 5 years, International Pros-

**Table 1.** Patient characteristics

Factors	Preplanning system		Real-time system		p
	n	%	n	%	
Median age (range)	68 (49-78)		66 (48-78)		
< 60	22	8.8	40	16	0.008
60 < 70	123	49.2	132	52.8	n.s.
> 70	105	42	78	31.2	0.01
Clinical stage					
T1a-b	2	0.8	1	0.4	n.s.
T1c	155	62	164	65.6	n.s.
T2a	89	35.6	70	28	n.s.
T2b	1	0.4	7	2.8	0.03
T2c	3	1.2	8	3.2	n.s.
Gleason					
Unknown	4	1.6	0	0	0.04
G ≤ 6	236	94.4	214	85.6	0.001
G 7	10	4	35	14	0.000
G 8	0	0	1	0.4	n.s.
PSA					
Median PSA	7.32		7.2		
Range PSA	2.3-14.6		1.7-30.2		
PSA ≤ 10	217	86.8	214	85.6	n.s.
PSA > 10-20	33	13.2	33	13.2	n.s.
PSA > 20	0	-	3	1.2	n.s.
Risk group					
Low	202	80.8	178	71.2	0.01
Intermediate	48	19.2	69	27.6	0.02
High	0	0	3	1.2	n.s.
Treatment					
Exclusive BT	238	95.2	195	78%	0.000
EBRT + BT	12	4.8	55	22%	0.000
Hormonal treatment	105	42	70	28%	0.001
No hormonal treatment	145	48	180	72%	0.001

EBRT – external beam radiotherapy, BT – brachytherapy, n.s. – non significant

tate Symptoms Score (IPSS) < 20, and > 6 months from a transurethral resection of prostate (TURP). All patients signed a specific informed consent form.

The prescribed minimal peripheral dose was 145 Gy to the prostate volume. In some intermediate-risk cases, a combined approach with EBRT 46 Gy on the prostate and seminal vesicles, followed by 108 Gy peripheral dose by implant was used. More cases received this combined treatment in the real-time group (26% vs. 73%). Two cases of each group had technical complications during the implant and less seeds than planned were inserted, and additional EBRT was given.

Hormonal treatment (HT) was given to 42% and 28% in each group during 3-6 months; in only 10% of the whole population, the HT was given to reduce prostate volume in order to achieve a better distribution of the needles and avoid pubic arch interference. The other cases came to our department with HT prescribed by their urologists. Biochemical failure (BF) was defined according to the Phoenix criteria.

With the preplanning system, a volume study was performed and recorded 3-4 weeks before the implant date. A theoretical optimal distribution of the seeds was

calculated using the Variseed 7.0 planning system, to achieve  $V_{100} > 98\%$  and  $D_{90} > 145$  Gy ( $D_{90} > 108$  Gy when used as a boost combined with EBRT). Constraints were urethral  $V_{150} < 1\%$  and rectal  $V_{100} < 5\%$ . On the day of the implant, the position of the prostate at the time of the volume study was reproduced prior to needle insertion, which was undertaken with transrectal ultrasound guidance and fluoroscopy. Technical and dosimetric details have been previously described [15]. With the real-time and Bard Pro-Link™ system, a volume study was performed several weeks before the implant to confirm the suitability and volume of the prostate. We used the Variseed 8.0 planning system, to achieve the required dosimetric parameters. In both cases, if the volume was > 50 cc, HT was given and the volume study was repeated three months later. The seeds model was the same but the visibility of the seeds and spacers was better with the Pro-Link™ system.

The day after the implant, the patient was discharged and one month later a planning CT was done for the definitive dosimetry. A PSA blood test was taken every three months during the first year, every four months in the second year, and every six months until the fifth year of follow-up, and yearly afterwards. Toxicity was graded according to the RTOG/EORTC scales and sexual function with the National Cancer Institute scale. The Kaplan-Meier method was used to evaluate bRFS.

**Table 2.** Five-year biochemical relapse-free survival comparing both groups of treatment

Factors	Preplanning	Real-time
Median follow-up	48 months	47 months
Total	90.2%	97.2%
Clinical stage		
T1a-b	–	100%
T1c	98.5%	98.1%
T2a	89.7%	94.3%
T2b	100%	100%
T2c	100%	100%
Gleason		
Unknown	100%	–
G ≤ 6	90.1%	96.7%
G 7	100%	100%
G 8	–	100%
PSA, median		
PSA ≤ 10	91.6%	97.6%
PSA > 10-20	79.9%	93.8%
PSA > 20	–	100%
Risk group		
Low	91.3%	97.2%
Intermediate	84.2%	97.1%
High	–	100%
Treatment		
Exclusive BT	90.4%	96.4%
EBRT + BT	90.9%	100%
Hormonal treatment	88.3%	97.1%
No hormonal treatment	91.7%	97.2%

EBRT – external beam radiotherapy, BT – brachytherapy

## Results

The median follow-up for the first group of patients was 48 months (range 24-84) and 14 cases (5.7%) had biochemical failure (BF), seven with a positive prostate biopsy, five with a negative biopsy, and two treated with HT without biopsy. Mean age in these cases was 66 (range 59-73). Mean time to relapse was 41 months (range 9-84). Biochemical relapse-free survival at 5 years was 90.2%, in low risk cases this was 91.3% and in intermediate risk cases 84.2%. No differences according to Gleason or T stage were seen but when presenting PSA was ≤ 10, bRFS was 91.6% compared with 79.9% in cases with PSA > 10 ( $p = 0.08$ ) (Table 2).

The median follow-up for the second group of patients treated with real-time was 47 months (32-70) and 7 cases (2.8%) had BF, three with distant metastasis, two with a negative prostate biopsy, and two without biopsy, treated with HT. Mean age in these cases was 71 (range 64-74). Biochemical relapse-free survival at 5 years was 97.2% (low-risk cases: 97.2%, intermediate-risk cases 97.1%). No differences according to Gleason, T stage or PSA were detected.

When comparing both groups, bRFS was always superior in the group of real-time technique but with the Kaplan-Meier method, no statistical significant (n.s.) differences were achieved at five years. Considering the whole group of 500 patients, no statistical differences were seen comparing Gleason 6 versus 7, T1 stage versus T2, PSA until 10 ng/dl or over 10, hormonal treatment versus no blockade, and exclusive brachytherapy versus combined treatment using EBRT. The only variable that achieved a significant difference ( $p < 0.05$ ) was in cases treated with

exclusive brachytherapy comparing PSA until 10 ng/dl (bRFS: 97.6%) versus cases with PSA over 10 ng/dl (bRFS: 84.8%), suggesting that these last cases should be better managed with a combined treatment (bRFS: 94.7%).

Spikes of PSA over nadir plus 2 ng/dl (false relapses or PSA bounces) were seen in 11 of the first group and 5 of the second group, at a median time of 24 months, which went down to low levels without further treatment. Median time to true relapses in the first group was 41 months and in the second group 24 months.

Hormonal treatment had no influence on PSA control in both arms. In the first group, bRFS was 88.3% with hormonal blockade and 91.7% without HT (n.s.), and in the second group were 97.1% and 97.2%, respectively. We have compared hormonal blockade in all low risk cases versus intermediate risk cases and no differences were achieved. In cases with intermediate risk, 74 without hormonal treatment had a 5-year bRFS of 96.7% and 40 with hormonal blockade 85.8% (n.s.).

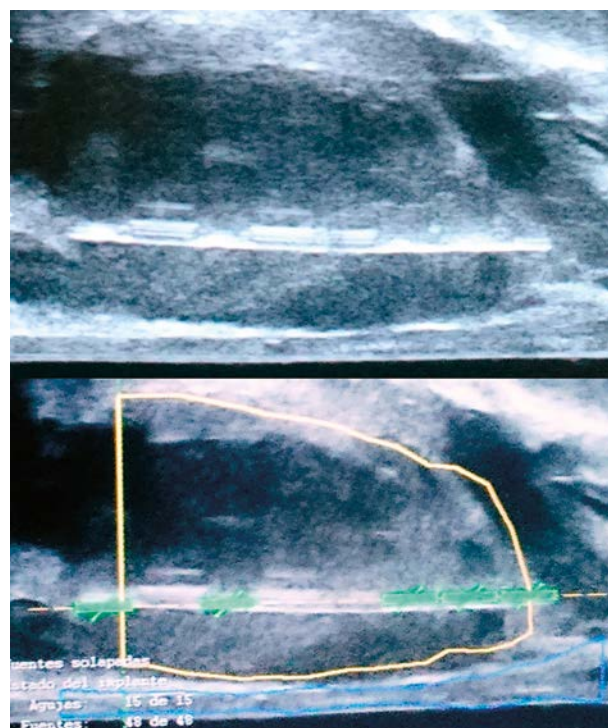
Late rectal toxicity was G1-2 rectal bleeding in 3.6% of the first group and 5.6% of the second group, there was no G3-4 toxicity. Genitourinary toxicity was G1-2 in 4.6% of the first group and 12% in the second group, and G3-4 in 1.9% and 4.8%, respectively. This was mainly related to urinary retention requiring catheter in 6.5% of patients in the first group and 9.6% in the second one. Only 1.9% and 4.4% required TURP respectively. Self-limiting grade 1-2 urinary bleeding was recorded in 4.8% and incontinence in 2% of the second group but none of the first group, and one case of G4 toxicity was registered resulting in a salvage cystectomy five years after the implant, because of bladder contraction with poor functional effects. The rate of complications was doubled when a combined treatment with EBRT plus BT was used compared with exclusive BT. In the second group, 195 patients received exclusive brachytherapy and the rate of rectal bleeding was 3.6%, urinary bleeding 3.6% and incontinence 1.5%. The 55 patients treated with a combined approach, EBRT plus BT, had a rate of 12.7%, 7.2%, and 3.6%, respectively. The rate of patients that required urinary catheter or TURP was not influenced by EBRT. Sexual function in previously active patients was preserved in around 60% of both groups.

Regarding dosimetric data, calculated in a representative group of 80 patients based on the planning CT one month after the implant, the median volume of the prostate receiving the 100% of the dose ( $V_{100}$ ) increased from 89% to 93% with preplanning and real-time technique. The median dose to the 90% of the prostate ( $D_{90}$ ) was 143 Gy and 157 Gy, respectively. When calculated from the ultrasound at the end of the implant in the operating room,  $V_{100}$  was 97% and  $D_{90}$  was 171 Gy for patients receiving brachytherapy alone using the real-time technique. This discrepancy can be due to the difficulty to draw the real size of the prostate in the CT images, usually larger than the size using the ultrasound.

**Discussion**

Permanent LDR brachytherapy for prostate carcinoma achieves a ten-year bRFS of 87-96% in low risk

cases and 63-86% in intermediate cases. In a study on 1313 patients, 48% of them with EBRT, 7-year bRFS was 98% in low risk and 93% in intermediate cases [16]. The 20-year experience at Mount Sinai Medical Center, on 2495 patients treated for localized prostate cancer with brachytherapy or combined treatment with EBRT, resulted in 12-year bRFS of 90%, 84%, and 64% in low, intermediate, and high risk cases [17]. A selection of 1656 cases with high-quality brachytherapy treated in the University of Washington, Seattle, achieved excellent long-term outcomes, with 12-year bRFS of 98.6%, 96.5%, and 90.5%, respectively, results that compare favorably to alternative treatment modalities including prostatectomy [18]. We have compared two different techniques in 500 consecutive patients treated at a single institution by the same team. Median follow up is 4 years, it is a short term experience to draw conclusions but bRFS is always favoring the second technique, even if the differences are not statistically significant. With the first technique using RapidStrand™ and a preplanning system, we achieved five-year bRFS of 92% in low risk cases and 86% in intermediate cases. With the second technique using a real-time technique and the ProLink™ system, we achieved over 97% in both groups. Of course, the learning curve could have some influence in the outcome of the first group but the results of the second group are good enough, comparing other published papers, especially in intermediate risk cases. EBRT was used in intermediate cases in one quarter of the first group and three quarters of the second group. The dosimetric results are better using the real-time technique, which enables calculation of

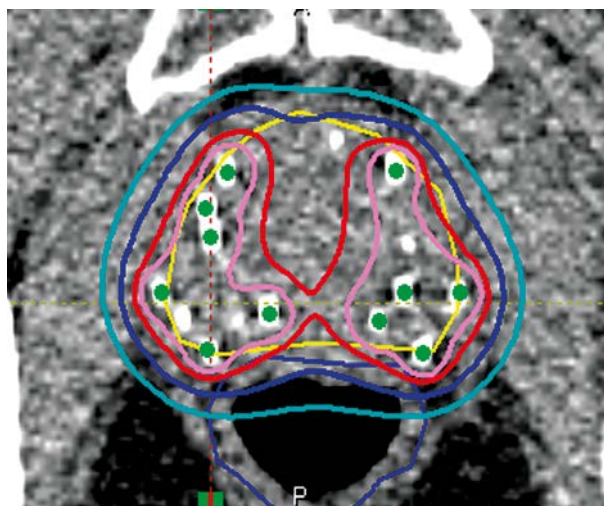


**Fig. 1.** Ultrasound image with real-time technique and Bard Pro-Link™ system. The distance between seeds is maintained by spacers, which are visible even clearly than seeds





**Fig. 2.** X-ray one month after the implant, with no displacement of seeds using Pro-Link system™ and real-time procedure



**Fig. 3.** Definitive dosimetry in a CT planning one month after the implant; extra seeds can be added during the procedure to assure an excellent coverage of the prostate

the actual dose during the implant and allows for insertion of extra seeds when needed. The ProLink™ system is very flexible allowing the use of consecutive or separated linked seeds with a rigid fixation (Figure 1), stable for at least six months, achieving better dosimetric isodose curves during the calculation in the operating room, and one month later in the CT, when less movement and misplacement of seeds was observed, remaining in place (Figure 2 and 3). A one-stage prostate brachytherapy technique (4D brachytherapy) using a combination of stranded and loose seeds showed significantly improved dosimetry [19]. With this technique, dosimetry at the end of the implant is excellent and we consider this is the reason for the improvement in the bRFS equivalent to the best published series [20]. Longer follow up will be required to confirm long term outcome.

Good dosimetric parameters in the definitive dosimetry done one month after the implant are related to better prognosis. At the Memorial Sloan Kettering Cancer Center, a  $D_{90} > 140$  Gy was the only predictive factor in 558 intermediate-risk patients who achieved a ten-year bRFS of 93% [21]. At the Mount Sinai School of Medicine in low-risk cases, eight-year bRFS was 94% with  $D_{90} \geq 140$  Gy compared to 75% with  $D_{90} < 140$  Gy [22], and in Leeds, the experience was similar [23]. Other studies point to a dose-response above and below 150 Gy [24]. In our study we have improved the  $D_{90}$  from 143 Gy to 157 Gy with the new technique [25] and the outcome shows the importance of these high doses for local control. In fact, the first group had suboptimal implants with 50% having less than the prescription dose. A review of 2693 patients from eleven centers reported that the  $D_{90}$  was the best way to define a good quality implant [26]. On this basis we expect our better results at five years of follow-up with real time implant dosimetry to be maintained long term. If post-implant dosimetry is within the optimal range, distant rather than local failure appears to be the main cause of BF [27], and that is our own experience.

Hormonal blockade, most times prescribed by an urologist previously to the implant, has shown no usefulness as described in other studies like series of the Mount Sinai School of Medicine [22] or Leeds [28]. Results of a cohort of 200 hormone-naïve patients had a bRFS of 95.6% at five years [29], in our study over 97% is achieved without HT, therefore, we consider that it is no longer required except in order to decrease a big prostate volume, over 50-60 cc.

Several factors can influence the outcome [12], and in the first group using the pre-planning system, PSA  $> 10$  ng/dl was a negative prognostic factor but using the real-time technique this was not a predictive, although, in this group most of the cases were treated with a combined approach with EBRT. A young age is considered an indication for radical prostatectomy in some centers. In our study, only one out of 22 patients younger than 60 years old relapsed in the first group and none of the 40 cases of the second group; furthermore, most of these have their sexual potency preserved. The Mount Sinai Medical Center confirmed in a study in men aged 60 or less that permanent LDR implants offer an excellent biochemical control at 8 years of follow-up, comparable to older men [30], with potency preservation [31,32].

Prostate-specific antigen bounces over nadir  $+2$  ng/dl, considered as "false relapses", were seen at a median of two years after the implant in 3.2% of the total population; the median time to true relapses was 41 months in the first group but only 24 months in the second group. This difference may be explained by predominance of distant metastatic relapse in the second group with no proven local recurrences. It would be expected that local recurrences will require more time to develop, and since no local recurrences occurred with the real-time technique, the median time to relapse is shorter. A study from Toronto showed that in 292 patients the median time to biochemical control was 30 months, and therefore, any PSA bounce during the first two years should be observed without starting treatment [33].

The complication rate both rectal and genitourinary was increased in the second group. This may be explained by higher median dose to the prostate and the larger number of patients treated with EBRT. Nevertheless, the 4.8% incidence of G3-4 late complications is considered acceptable when balanced against the very high rate of biochemical control, which is comparable to the best published series [34]. The addition of EBRT in intermediate-risk cases was possibly responsible for the higher rate of G1-2 urinary and rectal bleeding. It is probable that some cases of intermediate risk disease can be managed with exclusive brachytherapy [35], because the  $D_{90}$  is almost always higher than 145 Gy, and the implants with real time technique have an excellent dosimetry. It is important to point at the fact that the  $D_{90}$  is 115-120% of the planned prescription dose with the real time technique, and maybe this increase of dose is necessary to achieve an appropriate final  $D_{90}$ . A higher dose, over 170 Gy covering a 3 mm margin can be a good option to be considered. And this approach may decrease complications in the future, avoiding EBRT. In fact, we have decided to treat intermediate-low risk cases as Gleason 3+4 with exclusive brachytherapy.

Therefore, a better outcome in prostate LDR-BT can be expected if a good dosimetry with high  $D_{90}$  can be achieved, and probably, in this situation, a hormonal blockade could not be necessary. Every center should know the own results and try to find the best technique and practice without increasing the complications rate. In our experience, the real-time implantation and a good system to build the linked seeds offers excellent bRFS in prostate carcinoma.

## Conclusions

The outcome of patients with low risk prostate carcinoma treated with <sup>125</sup>I seeds is very good with a low complication rate. Hormonal treatment has no impact on the outcome and is not indicated. The real-time approach in our hands achieved a more precise seed implantation, better dosimetry, and a statistically non-significant better biochemical control at the price of an increased toxicity. We have made this our standard technique. In the intermediate risk group a combined treatment approach of EBRT and brachytherapy may be necessary to give the best outcome.

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## Disclosure

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