ORIGINAL ARTICLE

Results of 125-iodine seed implant with preplanning system in 250 patients with prostate cancer

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Abstract

Introduction: We review the experience with prostate carcinoma patients treated with permanent implants of 125-I seeds and the outcome eight years after the beginning of this technique.

Material and methods: From 2002 to 2007 we have performed 250 implants with LDR brachytherapy with RapidStrand® and preplanning system. Mean age was 68 (49–78). Mean PSA was 7.32 (2.31–14.6). T1–T2a was the stage in 98%, and Gleason ≤ 6 in 96%. Low-risk cases were 81% and intermediate risk 19% (ten of them received 46 Gy EBRT). Hormonal treatment was used in 42%.

Results: With a mean follow-up of 48 months, 14 patients (5.7%) showed biochemical failure (BF). Eleven patients (4.5%) with theoretical BF were observed and PSA decreased without treatment. Actuarial PSA relapse-free survival at 5 years was 91% (92% low risk, 86% intermediate cases), and 92% vs. 81% with PSA <10 vs. >10 (p < 0.05). Rectum complications were G2 in 0.6%.

A urinary catheter was necessary in 6.5%. Sexual function was conserved in 60%. Mean V100 was 89% and D90 143 Gy.

Conclusion: The outcome of patients with low-risk prostate carcinoma treated with I-125 seed is very good with very low complications rate. Cases with PSA bounces should be controlled before starting a salvage treatment.

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PALABRAS CLAVE
Próstata; Semillas I-125; Braquiterapia; Tiempo real

Resultados de implante de semillas de iodo-125 con sistema de preplanificación en 250 pacientes con carcinoma de próstata

Resumen

Objetivo: Revisar la experiencia con implantes permanentes de semillas de I-125 en carcinoma de próstata y el resultado a los 8 años de comenzar la técnica.
Material y métodos  De 2002 a 2007 hemos realizado 250 implantes con brachi- terapia de baja tasa con RapidStrand® y sistema de preplanificación. La edad media fue 68 años (49-78). El PSA medio fue 7,32 (2,31-14,6), 98% T1-T2a, 96% Gleason ≤ 6, 81% de bajo riesgo y 19% de riesgo intermedio (10 de estos últimos recibieron 46 Gy de radioterapia externa). Un 42% recibieron hormonoterapia.

Resultados: Con seguimiento medio de 48 meses, 14 pacientes (5,7%) tuvieron recaída bioquímica (RB). En 11 pacientes (4,5%) con teórica RB el PSA descendió espontáneamente sin tratamiento. La supervivencia actuarial sin recaída bioquímica a 5 años fue del 91% (92% bajo riesgo, 86% riesgo intermedio); 92 vs 81% en pacientes con PSA < 10 vs > 10 (p < 0,05). Hubo complicaciones rectales G2 en el 0,6%, sondaje vesical en un 6,5%; el 60% conservaron la función sexual. El V100 medio fue del 89% y el D90 143 Gy.

Conclusión: El resultado en carcinoma de próstata de bajo riesgo mediante semillas de Iodo-125 es muy bueno con muy pocas complicaciones. Las elevaciones de PSA deberían ser controladas antes de dar tratamiento de rescate.

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Introduction

Currently, active treatment of prostate carcinoma in patients with localized disease and long life expectancy is recommended.1 Permanent brachytherapy (BT) with 125-I seed implant gets a PSA control 10 years higher than that reported with external radiotherapy (ERT), and comparable to radical prostatectomy (RPT).2-7 There are already publications with 15 years of monitoring.8 In Spain more than 30 centers have implemented this technique, but there are few published results.9-12 There is a perception that only large centers obtain satisfactory long-term results. Therefore, we will review our experience in 250 patients treated according to the American13 and European14 recommendations, with braided seeds or "strands" (RapidStrand®) according to a pre-planning dosimetry system, to know its own results and see; if we get adequate results, the technique can be improved or the indications of the BT should be adjusted further.

Material and methods

In December 2002, we started the treatment of prostate carcinoma with radioactive I-125 seeds. Until October 2007, we performed 250 implants with RapidStrand® and preplanning system. Two patients were lost at the start of follow-up and three were excluded because they died of intercurrent disease within two years. Therefore, this review is of 245 consecutive low- and intermediate-risk patients, according to the classification of D’Amico15 modified according to the recommendations of the EORTC14: low risk with PSA < 10, Gleason 2–6, stage T1–T2a; intermediate risk with PSA 10–20, Gleason score 7, stage T2b–c (T2c was included as intermediate risk according to the EORTC criteria). No high-risk cases (PSA > 20, Gleason 8–10, T3) or with three intermediate-risk factors were included. Other exclusion criteria were: life expectancy <5 years, compromised urinary function (International Prostate Symptoms Score: IPSS > 20), and transurethral resection (TUR) in the last 6 months. All patients signed a specific informed consent.

The mean age was 68 years (49–78 years). The PSA level before BT was 7.32 ng/ml (2.31–14.6), 87% <10 and 13% >10. Clinical stage was T1–T2a in 98.4% and T2b–c in 1.6%. All patients were diagnosed with adenocarcinoma through ultrasound-guided biopsy. The Gleason score was ≤6 in 96% and 7 in 4%. Low-risk cases were 81% and intermediate-risk 19% (Table 1). (Only one patient presented two intermediate-risk factors.) Hormone therapy (HT) was used in 105 patients (42%), in most cases scheduled at another center, with an average of 6 months of treatment,

Table 1 Characteristics of the 250 patients.

<table>
<thead>
<tr>
<th></th>
<th>Patients</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Age &lt; 55</td>
<td>6</td>
<td>2.4%</td>
</tr>
<tr>
<td>Age 55–59</td>
<td>16</td>
<td>6.4%</td>
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<tr>
<td>Age 60–64</td>
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<td>0.8%</td>
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<tr>
<td>Age 65–69</td>
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<td>Age 70–74</td>
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<tr>
<td>Age ≥75</td>
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<td>10.4%</td>
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<tr>
<td>Clinical stage</td>
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<td></td>
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<tr>
<td>T1a–b</td>
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</tr>
<tr>
<td>T1c</td>
<td>155</td>
<td>62%</td>
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<tr>
<td>T2a</td>
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<tr>
<td>T2b</td>
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<td>0.4%</td>
</tr>
<tr>
<td>T2c</td>
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<tr>
<td>Gleason</td>
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<td></td>
</tr>
<tr>
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<td>1.6%</td>
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<tr>
<td>G2</td>
<td>15</td>
<td>6%</td>
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<tr>
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<td>14</td>
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<td>G4</td>
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<td>PSA 4–10</td>
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<td>83.6%</td>
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<td>PSA &gt; 10</td>
<td>33</td>
<td>13.2%</td>
</tr>
</tbody>
</table>
Results of $\text{125-}$iodine seed implant with preplanning system

Figure 1 Radioscopic vision of the seeds at the end of the implant in the operating room with RapidStrand®.

and it was suspended on the day of the volumetry. Only in 25 cases (10%) HT was indicated to reduce prostate volume $>50 \text{ cm}^3$ (bicalutamide for a month and LH–RH analogue for three months).

The prescribed minimum peripheral dose for prostate was 145 Gy (monotherapy). Ten intermediate-risk cases (4%) were treated with ERT and seed implant with less activity (combined treatment). ERT was used on prostate and seminal vesicles formed with 7 fields, 10–15 MV photons at 2 Gy/day up to 46 Gy in 5 weeks. From two to four weeks later, an implant was performed by administering 108 Gy. In two patients, fewer seeds were implanted because of technical problems and ERT was added later.

The volumetry for pre-planning was performed between three and four weeks before the implant using transrectal ultrasound. If the volume was greater than 50 cm$^3$, hormonal treatment was offered and repeated at three months. A few days after the volumetry, the distribution of the seeds was calculated using the Variseed 7.0 planning system to achieve the following constraints: $V_{100} > 98\%$ (prostate volume receiving 100% dose); $D_{90} > 145 \text{ Gy}$ (dose that 90% of the prostate receives) or $D_{90} > 108 \text{ Gy}$ when ERT is associated; $V_{150}$ urethra $< 1\%$ (volume of the urethra receiving 150% dose), and rectal $V_{100} < 5\%$ (volume of the rectum that receives 100% dose). Technical aspects and other dosimetric parameters have been described previously.\textsuperscript{16}

The needles were prepared in the operating room by cutting the number of seeds required per needle. The median seed activity was 0.42 mCi (millicuries) per seed for 145 Gy and 0.35 mCi for 108 Gy. The needle insertion was performed under ultrasound control, checking the position of the seeds by radioscopy (Fig. 1). The patients were discharged the following day. They were given an appointment a month after the implant for RX (Fig. 2) and CT definitive dosimetry.

The PSA control was performed every three months the first year, every four the second, every 6 months up to 5 years and annually thereafter. Biochemical relapse (BR) was considered according to the Phoenix criterion:

$\text{PSA nadir} + 2 \text{ ng/ml.}^{17}$ Toxicity was measured with the RTOG/EORTC scale and urinary function also with IPSS. Sexual function was measured by the scale of the National Cancer Institute. For biochemical control statistical analysis, the Kaplan–Meier test was performed.

**Results**

The mean follow-up was 48 months (24–84), maximum 7 years and at least two years. Twenty-five patients had PSA elevations with risk of biochemical relapse. Eleven patients (4.5%) with theoretical BR remained untreated because the PSA remained at levels below the diagnostic ones and below 10, with negative extension studies and/or negative biopsy, and in them PSA declined spontaneously. Therefore, only 14 patients actually had BR (5.7%). Seven of them had a positive prostate biopsy and were treated with HT (one with cryotherapy and another one with ERT rescue). In 5 cases the biopsy was negative, and patients remain untreated because the PSA is $< 10 \text{ ng/ml}$. Two cases were not biopsied due to advanced age and starting HT at another hospital. The mean age of the 14 cases with BR was 66 years (59–73).

The actuarial survival free of BR at 5 years was 91%. In cases of low and intermediate risk it was 92% and 86%, respectively (Fig. 3). There were no differences according to Gleason or T stage. Patients with PSA $>10$ had a BR-free survival of 81%, compared to 92% with PSA $<10$ ($p < 0.05$). To determine whether hormone treatment was associated with greater control, we studied the BR-free survival at 5 years in cases with HT, which was 88%, while in patients without HT it was 92% ($p = \text{ns}$). In fact, 8 of the 14 cases with real BR had received HT, and 6 of the 11 with false BR. Time until BR was between 9 and 84 months (mean 41 months). The 11 cases of false BR occurred between 12 and 36 months (mean 24 months). Transient PSA elevations were studied in a subgroup of 80 patients with over 6 months follow-up. An increase of $>0.1 \text{ ng/ml}$ was detected in 49% (28% without HT, 79% with HT). When an increase of $>0.4 \text{ ng/ml}$ was considered, the transient elevations were 14% (8.5% without HT, 21% with HT).

Figure 2 Simple XR at a month of performing the implant.
Rectal acute complications are related to endorectal probe, G2: 0.6%, G1: 17%. Rectal late toxicity was minimal with only three cases of rectal bleeding (1.2%) (G2:1, G1:2). Hematuria occurred in some cases during the first and second day. No case of long-term incontinence or hematuria has been detected (G0). Mean IPSS before the implant was 8 (0-18) and mean time for full recovery was 5.5 months (range 0–16 months). We had to probe 6.5% patients due to acute urinary retention, which resolved within two months on average. Only 1.9% had to maintain the urinary probe for more than 6 months and underwent TUR.

Sexual function was collected in the first 160 patients, and discarding previous cases of impotence, it was preserved in 60% of the patients. Analyzing only the cases that did not receive HT, 12% had prior impotence, and those with some degree of power, one year after implantation, 76% of the patients had regained the same level of prior sexual power.

Regarding the CT dosimetric data at one month of the implant, a mean V100 of 89% and D90 of 143 Gy was obtained, checking a learning curve in the first 20 cases with significantly lower figures (V100 75% and D90 111 Gy). Mean prostate size was 30 cm³ (11–54 cm³).

Discussion

Permanent TB in low-risk cases gets biochemical control at 10 years between 87% and 96%, and in intermediate-risk ones between 63% and 86%. Our study at 5 years (92% low risk, 86% intermediate) confirms the same results. In 33 patients with PSA >10 ng/ml it dropped to 81%, but only 4 had received ERT. For three years, all intermediate-risk cases have received combination treatment. Many clinical factors have been described that influence the result, PSA level, Gleason, T stage, percentage of positive biopsy cylinders, but in our study only the PSA level was significant.

A high percentage of cases in our study received HT (42%), but it did not improve the results. In the series of Mount Sinai School of Medicine, and Leeds, the HT did not influence the BR significantly. It is queried whether permanent implants are suitable for young men. In our study, of 22 patients <60 years, only one suffered a relapse, and all preserved sexual power. A study by the Mount Sinai School of Medicine confirms that men up to 60 years old achieve an excellent biochemical control at 8 years, comparable to older ones.

Transient PSA elevations are another datum to be studied. They are defined as an elevation of the PSA above the initial nadir, which later declines without any treatment. However, different definitions of the BR lead to false positives while transient elevations last. In our work, 11 of 25 cases with theoretical BR were monitored without treatment and the PSA declined. Mean time to the onset of the PSA elevation is a useful indicator. In our series, the real BR occurred at an average of 41 months and the false ones at 24 months. A study in Toronto with 292 patients showed that the median time to the PSA elevation indicative of the BR was 30 months, and concluded that caution is advised in interpreting an early increase in the PSA level in the first 30 months. The time to the first PSA elevation is the most valuable factor to distinguish between a transient increase and a BR, considering that transient elevations are more common in young men and that these cases have a better prognosis, as demonstrated in a study of 820 patients: control rate at 5 years in patients with elevation ≥0.2 was 97.7% vs. 91% in those who did not have transient PSA elevation.

Performing a post-implant dosimetry in patients undergoing permanent prostate BT is essential to know the D90 and V100, which correlate with the result. Doses higher or lower than 150 Gy were the only prognostic factor in 558 patients at intermediate risk at Memorial Sloan Kettering Cancer Center. With D90 >140 Gy control reached 93% at 10 years. At the Mount Sinai School of Medicine, in 243 patients on monotherapy, a group of optimal dose (≥140 Gy D90) was distinguished with control at 8 years of 82% and suboptimal (D90 <140 Gy) of 68%. In low-risk cases, this difference was 94% vs. 75%. The Leeds experience was similar, significant only in low-risk cases.

Intraoperative dosimetry is a new advance that for allows the immediate calculation of each seed when inserted into the prostate gland. The dose distribution for the implant is calculated in "real time" in the operating room, and new seeds can be inserted if cold areas are detected. When the implant is finished, the dosimetry reflects the dose distribution in agreement with the position in which the seeds have remained, properly identified with ultrasound images, which makes possible to get a better D90 and V100. Although there are slight differences between the results of intraoperative dosimetry and that performed monthly by CT, the intraoperative implant dosimetric system allows for a good approximation to the real administered dose. In November 2007, we changed from preplanning dosimetry to real-time dosimetry, and from seed construction system, using the Bard Pro-Link® system, which makes possible to place the seeds with a fixed gap of one centimeter, as with RapidStrand®, but at any multiple of 5 mm distance. We compared both methods and dosimetry improved clearly. In the group of patients treated with RapidStrand® and preplanning, monthly CT dosimetry presented a V100 of 89% and D90 of 143 Gy. These figures improved up to a V100 of 93.1% and a D90 of 157 Gy in the real-time treated patients and Pro-Link® system. When it was performed right at the end of the implant, in the operating room and under
ultrasound control, the V100 reached 97% and the D90 171 Gy. Planning based on real-time ultrasound does not accurately reflect dosimetry based on postoperative CT, although the prostate edges are better defined by ultrasound than by CT.

In a study of 2,693 patients from 11 institutions treated with permanent BT monotherapy, the only controllable factor with long-term impact was the D90, which reflects the quality of the implant. The impact of these changes will lead to better results, obtained through a closer integration of planning processes with the actual implant and the way to place the seeds.

In conclusion, the result of the treatment with 125-I seeds in patients with low-risk carcinoma is very good and with few complications. The hormone treatment did not affect the results. The PSA elevations must be controlled and, thus, a premature salvage therapy avoided.

Conflict of interest
The authors declare that they have no conflict of interest.

References