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Original research article

Impact of real-time, dose-escalated permanent seed implant brachytherapy in intermediate-risk prostate cancer

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ABSTRACT

Purpose: To retrospectively evaluate biochemical control and toxicity in patients who underwent 125I seed brachytherapy (BT) for intermediate-risk prostate cancer (PCa).
Materials and Methods: Between January 2004-December 2014, 395 patients with intermediate-risk PCa underwent 125I BT. Of these, 117 underwent preoperative planning (PP; 145 Gy) and 278 real-time intraoperative preplanning (IoP; 160 Gy). All patients were followed for ≥ 6 months (> 5 years in 48% of patients and > 7 years in 13%). Median follow-up was 59 months.
Results: Biochemical relapse-free survival (BRFS) rates at 5 and 8 years were, respectively, 91.7% and 82.1%. By treatment group, the corresponding BRFS rates were 93.5% and 90% for IoP and 89% and 76.8% for PP. The maximum dose to the urethra remained unchanged (217 Gy) despite the dose escalation (from 145 to 160 Gy), without any significant increase in treatment-related toxicity (p = 0.13). Overall toxicity outcomes in the series were excellent, with only 3 cases (0.76%) of grade 3 genitourinary toxicity.
Conclusion: The real-time intraoperative planning technique at 160 Gy yields better biochemical controls than the preoperative planning technique at 145 Gy. Dose escalation did not increase urinary toxicity. The excellent results obtained with the IoP BT technique support its use as the first treatment option in this patient population.

1. Introduction

Approximately 60 %–70 % of patients with prostate cancer (PCa) are diagnosed with organ-confined disease.[1,2] A wide range of treatments[3] are available for localized PCa. Studies have shown that permanent seed implant brachytherapy BT, prostatectomy, and external beam radiotherapy (EBRT) all yield similar survival outcomes in this population.[4]

Permanent seed, low-dose rate (LDR) BT is a well-established treatment option in patients with low-risk PCa.[3] However, in intermediate-risk disease, the role of BT monotherapy is less clear. The results of the NGR Oncology/RTOG-0232 trial[5,6] in 2018 showed that progression-free survival (PFS) in patients with intermediate-risk PCa treated with permanent seed BT alone were comparable to those obtained with EBRT combined with BT, but with less toxicity. The Seattle group[7] described their experience with BT alone in intermediate-risk patients, reporting a biochemical relapse-free survival (BRFS) of 79.9% at 15 years, a result that is in line with the 5-year BRFS (94%) reported by Zelefsky et al.[8] Although the evidence supporting the use of permanent seed BT as monotherapy in intermediate-risk PCa continues to grow, more data would be valuable.

In the present study, we evaluated treatment outcomes and toxicity in patients with intermediate-risk PCa who underwent permanent seed BT as monotherapy. We also compared the results based on the implantation technique and dose used, either preoperative planning (PP) at 145 Gy or real-time intraoperative planning (IoP) at 160 Gy.

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2. Methods and materials

2.1. Patients

We retrospectively evaluated 395 patients who had undergone permanent implant 125I seed BT as monotherapy between January 2004 and December 2014. All patients were intermediate-risk PCa according to the criteria of the National Comprehensive Cancer Network (NCCN).[3] All patients received luteinizing hormone-releasing hormone (LHRH) analogues for 6 months. The patient characteristics are detailed in Table 1.

2.2. Procedures

All treatments were performed in accordance with ABS[9] and GEC-ESTRO recommendations.[10] Due to changes in clinical practice over the 11-year study period, two different BT techniques were used. Between 2004–2007, the preoperative planning technique with 145 Gy was used. In October 2007, we switched to the real-time IoP technique with 160 Gy. Due to this change, we grouped and compared the patients according to the treatment technique and dose used (PP at 145 Gy vs. IoP at 160 Gy).

In accordance with ABS and GEC-ESTRO recommendations, the urethral dose constraint was 150% of the prescribed dose, which is typically 145 Gy (217 Gy). However, when a higher prescription dose was used (160 Gy), the urethral dose was maintained at 217 Gy (135% of the prescribed dose). In normal treatment planning, the aim is to ensure that the maximum dose to the urethra is as low as possible without compromising CTV coverage, but always below the maximum recommended dose (217 Gy, 135%). In most cases, the final dose administered is less than 135% of the maximum dose, although the specific value varies in each case. In summary, the goal is to deliver at least the minimum dose to the urethra, but this must always be less than 135% of the prescribed dose, which is often 130% but can be as low as 120% in patients with more favourable anatomy.

2.3. Preoperative planning

This study starting in January 2004 and continued until September 30, 2007 (n = 117) underwent PP. Ultrasound (US)-guided dosimetry was performed 2 weeks before implantation in all but 35 (30%) cases, in which the dosimetric evaluation was performed immediately prior to the intervention, thus resulting in more accurate patient positioning. Dosimetry was planned using the SIMUPLAN planning system. The total dose was 145 Gy. Stranded seeds (IsoCord from Bebig, Germany) were inserted.

2.4. Real-time intraoperative planning

Starting in October 2007, we switched to real-time IoP at 160 Gy. A total of 278 patients were treated. Stranded seeds (IsoCord from Bebig, Germany) were used in 81% of cases, with loose seeds in the finale 54 patients (19%) treated. The Spot (Elekta/Nucletron) and SeedSelectron treatment planning systems (TPS) were used.

In both techniques, volume definition was performed according to ICRU Report 58 criteria and ESTRO/EAU/EORTC recommendations.[11] Since the GTV can only be defined for tumors higher than stage T1c, we did not contour the GTV in these cases; rather, we used the clinical target volumen (CTV), which includes the entire gland. Since the planning target volume (PTV) is a geometric concept designed to compensate for set-up errors (which are not relevant in BT), we assumed that the CTV = PTV.

Post-implant computed tomography (CT) scan on Day 0 was performed to early identification of dosimetric problems. At one month after implantation, the patients underwent thoracoabdominal x-ray (seed migration), CT, and T2-MRI (post-planning). In contrast to the majority studies, we maintained the dose constraint (<217 Gy) to the urethra after transitioning to the higher-dose IoP technique. This implies a more restrictive dose constraint for IoP (135% of 160 Gy vs. 150% of 145 Gy).

2.5. Follow-up

All patients were treated with alpha blockers for ≥ one month after permanent implant. Follow-up was in our center. According to protocol, PSA and testosterone values were measured. Phoenix definition of biochemical relapse was used. To confirm the type of recurrence,[12] the appropriate clinical tests were administered: biochemical (serum PSA), local (biopsy/MRI), nodal (CT), or distant (CT/bone scan/position-emission tomography [PET]).

Toxicity scales were provided by the Radiotherapy Oncology Group (RTOG)[13] and the Common Terminology Criteria for Adverse Effects (CTCAE, v. 3.0).[14]

2.6. Statistical analysis

To know and define the characteristics of prostate cancer patients, the variables of interest were summarized by means (standard deviation; SD) or medians (interquartile range; IQR) for continuous variables, and absolute and relative frequencies for categorical variables. The results are presented in tables and figures obtained from the statistical software R (v. 3.2.3).[15]

For the between-group comparisons, statistical significance was set at p = 0.05. Kaplan Meier curves were compared using the log-rank test. The Chi-square test was used to compare qualitative variables.

3. Results

3.1. Disease Control

At a median follow-up of 59 (38,96) months, no PCa-specific deaths were observed. Overall survival (OS) in the whole series (n = 395) at 5, 8 and 10 years was 93.1% 83.2% and 78.5%, respectively. The corresponding BRFS rates were 91.7%, 82.1% and 67%. Among the 40 patients (10.2%) in whom biochemical recurrence was detected, 19 cases (4.8% of the sample) were due to local relapse in year 1 (confirmed by biopsy or MRI). In 6 other cases (1.5%), the biopsy was negative and thus the relapse was considered biochemical only. Seven patients (1.8%) were diagnosed with recurrent disease based on PSA determination, but CT and bone scans were also performed to rule out nodal and metastatic disease; however, biopsy was not performed in these patients due to their age (>80 years). The remaining 8 recurrences (Table 2) included 6 cases (1.5%) of regional failure and 2 cases (0.5%) of metastatic disease. Table 2 shows the distribution of the recurrences according to treatment technique. Biochemical and local recurrences were significantly (p < 0.05) more common in the PP group. No significant between-group differences were observed with regard to nodal and metastatic recurrences, probably due to the relatively rarity of these recurrences in our cohort. The median time to recurrence was longer in the IoP group (65 vs. 37 months). The median initial PSA in the patients who developed recurrent disease was 9.16 [IQR: 7.03–11.48].

Finally, of the aforementioned 19 cases with locally-recurrent disease, 10 were salvaged by a second brachytherapy implant, with disease control achieved in 6 of these 10 salvage cases; the other 4 cases developed a progressive disease.

The median PSA nadir was 0.10 (range, <0.04–0.36), reached at a median of 28.7 months. A Cox regression model was performed to

Table 1
Patient characteristics.

Factors	Total	pre-planning 145 Gy	Intraoperative planning 160 Gy
Patients, n	395	117(29.6 %)	278(70.4 %)
Mean age, years	67	68	67
<55	14(3.5%)	2(1.7%)	12(4.3%)
55–65	143(36.2%)	36(30.8%)	107(38.5%)
>65	238(60.2%)	79(67.5%)	159(57.2%)
T stage			
T1–2a	185(45.8%)	90(76.9%)	95(34.1%)
T2b	138(34.9%)	19(16.2%)	119(42.8%)
T2c	72(18.2%)	8(6.8%)	64(23%)
median PSA (1 st - 3rd quartiles)	8.5(6–11.6)	10.2(6.5–11.7)	8(6–10.8)
Gleason score			
≤6	259(69%)	65(55.6%)	214(77%)
7	116(31%)	52(44.4%)	64(23%)
3 + 4	83(71.5)	33(63.4%)	50(78%)
4 + 3	30(25.8)	17(32.6)	13(20%)
Prior transurethral resection	25(6.4%)	5(4.3%)	20(7.2%)
Median pre-treatment IPSS	3	3	3
Median prostate volume (1 st - 3rd quartiles)	34(26–45)	35(24–46)	34(27–45)
Median number of seeds (1 st - 3rd quartiles)	58(50–72)	68(55–86)	57(49–66)
Follow up			
Median (months) (1 st - 3rd quartiles)	59 (33–82)	85(64–112)	46(28–70)

Abbreviations. PSA indicates prostate-specific antigen; IPSS, International Prostate Symptom Score.

Table 2
Recurrences.

Technique	Recurrence type			
	Biochemical	Local	Nodal	Metastatic
Pre-planning (145 Gy)	27/117 (23,07%)	13/117(11,1%)	3/117(2,5%)	1/117(0,8%)
IoP (160 Gy)	13/278 (4,67%)	6/278 (2,1%)	3/278 (1,0%)	1/278 (0,3%)
P value	<0.001	<0.001	0.36	0.50

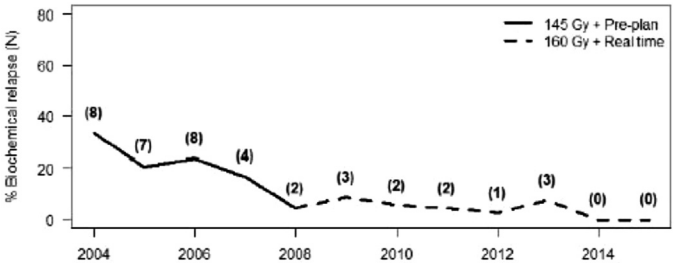

Fig. 1. Percentage of patients who developed recurrent disease.

evaluate the association between PSA nadir and time to biochemical relapse, revealing a significant association (p value < 0.001) between these two variables: the higher the PSA nadir, the greater the risk of biochemical recurrence. By contrast, neither prostate volume nor the number of seeds implanted was significantly associated with it.

Fig. 1 shows the percentage of patients (with absolute numbers in parentheses) who developed recurrent disease during each study year. As that figure shows, there was an initial peak followed by a progressive decrease over time, possibly reflecting the learning curve for the treatment team.

As Fig. 1 shows, the BRFS curve was higher for the IoP technique versus the PP technique.

We were unable to statistically compare the number of recurrences associated with stranded vs. loose seeds due to the limited sample size (n = 54) in the IoP group that received stranded seeds versus 117 patients (100%) in the PP group.

BRFS was better in patients with Gleason <7 versus = 7 and in patients with GS 3 + 4 versus GS 4 + 3. BRFS and OS were both better in the IoP group (versus PP) for both the GS 3 + 4 and GS 4 + 3 groups. Similarly, BRFS was significantly better (p = 0.05) in patients with stage T1–2a disease versus stage T2b. Note that, due to the short follow up period, patients with stage T2c disease were not evaluable. See Fig. 2.

TOXICITY The toxicity grade (G) in both groups (PP and IoP) in most patients was G0-G1. Fig. 3 shows the acute and late toxicity rates in the two groups.

In terms of gastrointestinal toxicity (GI), the results of the two techniques were similar. With regard to genitourinary toxicity (GU), there were only three cases (0.8%) of G3 chronic toxicity (dysuria, urethral stenosis and/or hematuria), all in the PP group. Somehow it must be considered that we are not including here patients with acute toxicity who required urinary catheterization but resolved within the first month post-implant. The toxicity is collected by different professionals over time and, although following the recommended scale, there is a part of subjective assessment.

The mean time elapsed from implant until maximum toxicity was 10.4 months.

Sexual function in patients who were sexually active prior to treatment remained unchanged in most (85.3%) cases.

Patients in both groups (PP vs. IoP) with loose or stranded seeds were compared to check toxicity outcomes. However, the propor-

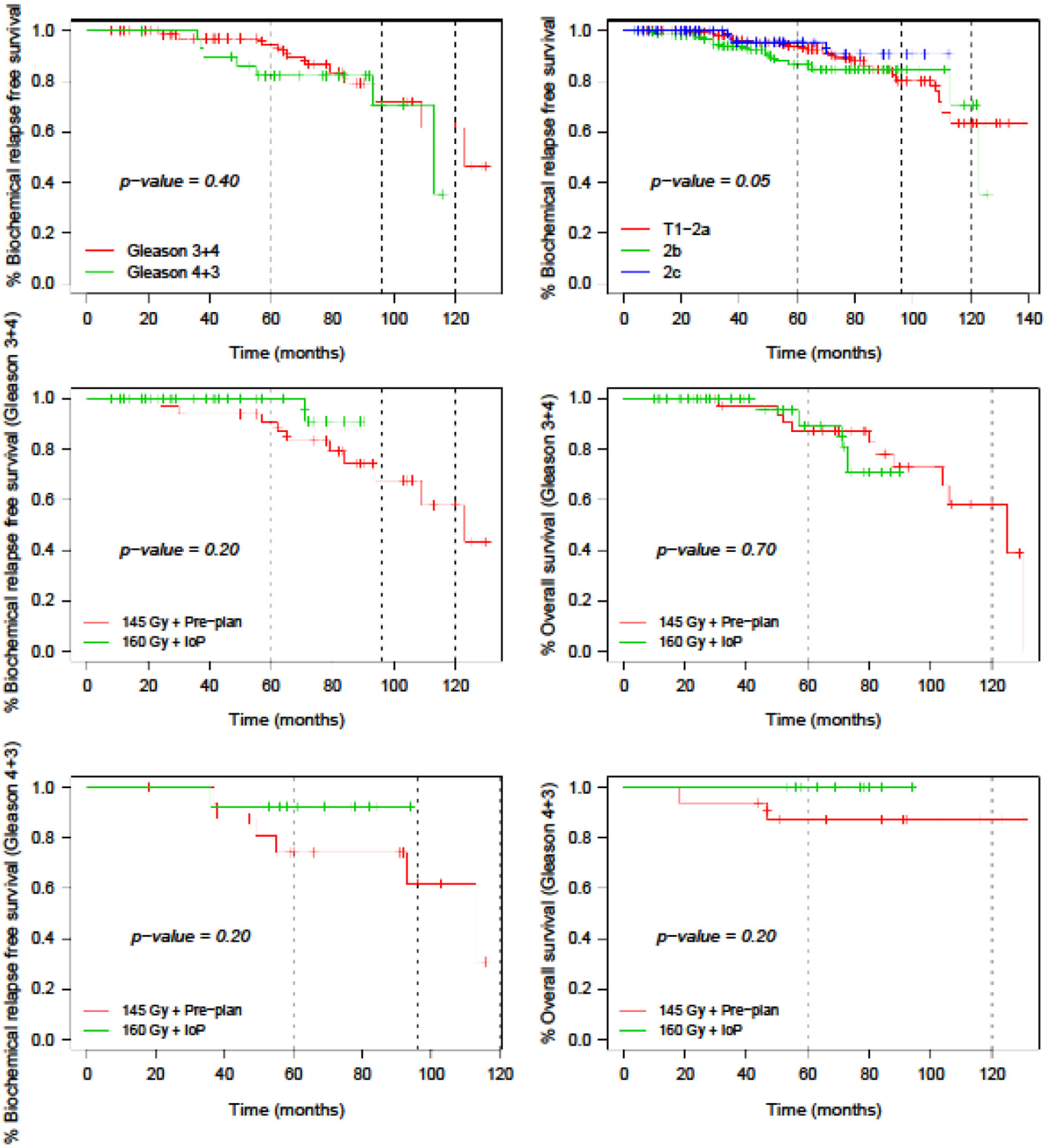

Fig. 2. BRFS and OS curves.

tion of patients in both groups who developed toxicity was similar for all toxicity grades. This lack of difference does not allow us to calculate p values. Additionally, the PP group had only 117 patients versus 278 in the IoP.

4. Discussion

Several studies[14–20] have previously confirmed the excellent clinical control obtained with LDR permanent seed BT in patients with intermediate-risk PCa. In this regard, an important aim of the present study was to provide additional data to support this technique, whose use has declined in the last decade. Our results confirm the excellent BRFS in our cohort of intermediate-risk patients, findings that are consistent with previous reports (Table 3). The present series includes patients treated whit two different BT techniques (IoP at 160 Gy and PP at 145 Gy). At a median follow-up of 59 months, our data indicate that the IoP technique appears to yield better BRFS outcomes. However, due to the numerous differences in variables (technique, dose, and seed type), it is difficult to directly compare these two techniques. Nevertheless, our results suggest a trend (p = 0.05) towards better outcomes for

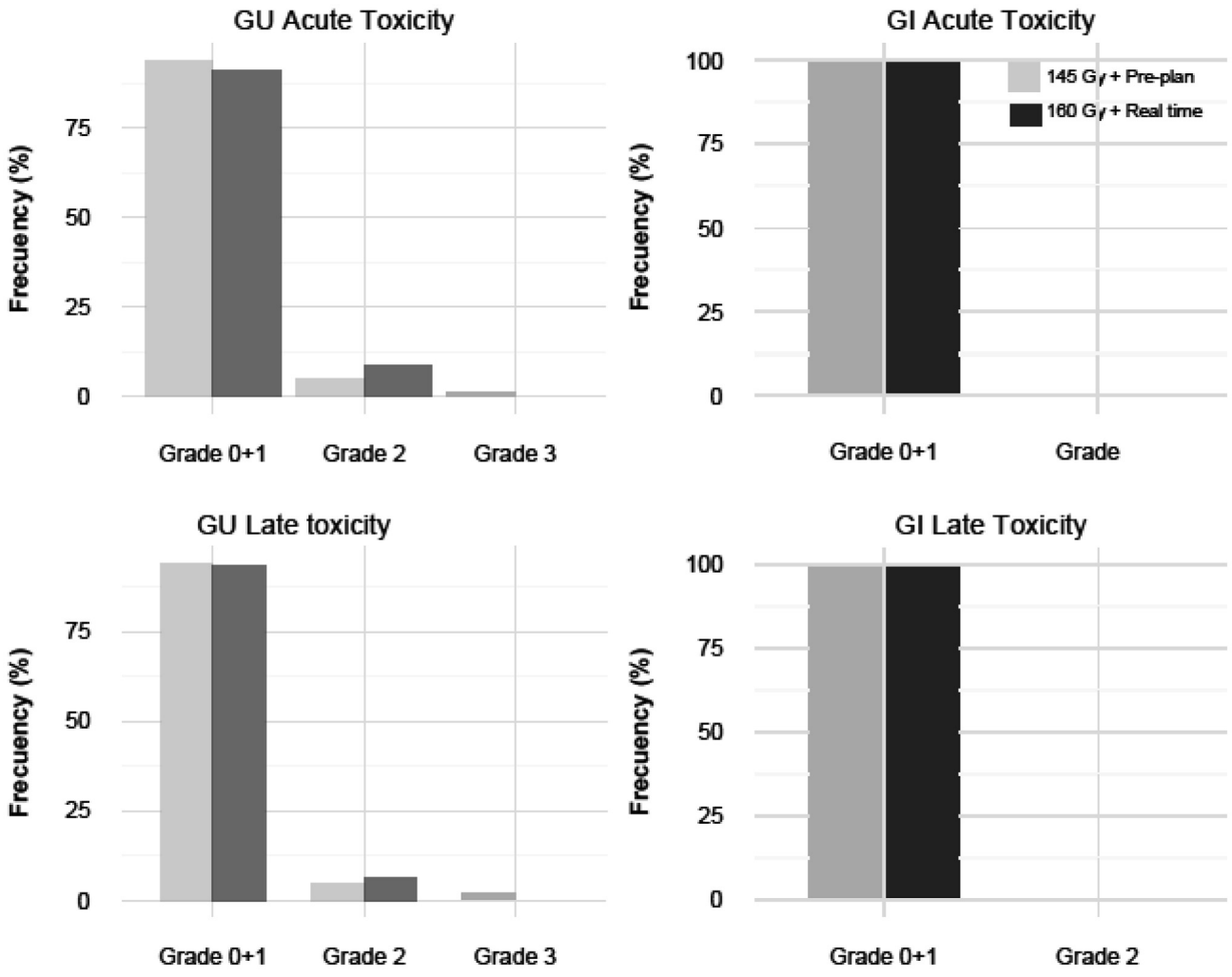

Fig. 3. Acute and late toxicity.

Table 3
Summary of studies evaluating patients with intermediate-risk prostate cancer treated with LDR brachytherapy.

Author (yr)	Patients, n (% intermediate risk)	BRFS, intermediate risk patients
Blasko et al. 2000[16]	230(46%)	79% (9 yr)
Zelefsky et al. 2007[17]	2693 (40%)	70% (8 yr)
Taira et al. 2011[18]	1656 (37%)	97% (12 yr)
Marshall et al. 20014[19]	2495 (39%)	84% (12 yr)
Funk et al. 2015[20]	966 (29%)	74% (10 yr)
Kittel et al. 2015[21]	1989 (30%)	79% (10 yr)
Fellin et al. 2016[22]	2237 (26%)	78% (7 yr)
Current series	117 (100%) PP 278 (100%) IoP	88% (5 yr), 76% (7 yr) 94% (5 yr), 91% (7 yr)

patients in the IoP group, despite the shorter follow-up in that group.

As our results show, patients with GS 3 + 4 had better BRFS than those with GS 4 + 3. In addition, both of these subgroups had better outcomes with the IoP technique. By tumour stage, BRFS was better in patients with stage T1c disease. Considered together, these findings suggest the existence of two biologically different types of intermediate-risk PCa: favourable risk vs. unfavourable risk disease. Given these differences in risk levels, LDR seed BT may be more appropriate in patients with favourable prognostic factors (Gleason 6 or 3 + 4, stage T1c, PSA < 10). When we decided this treatment option for the intermediate risk group, it was for patients who could have Gleason 4 + 3 but as the only risk factor. We did not count on HDR-BT technique at that moment, so we treated

this group with either LDR or EBRT + LDR 108 Gy boost. Among the 145 Gy group, we observed that 77.6% were T1−2a (by MRI, not by biopsy), so one of the other two factors might be of intermediate risk (PSA / Gleason), that is why there are more patients with one of these higher factors in this group compared to the 160 Gy group, where 66% of the cases are T2b-c and present lower PSA and Gleason values. Nevertheless, we have to take into account that we are facing a retrospective study and we can find this type of bias. Our findings regarding the association between PSA nadir and risk of recurrence—a higher PSA nadir was associated with greater risk of recurrence—should also be considered when selecting the optimal treatment approach. Unfortunately, it is not possible to establish a specific cut-off point for PSA nadir due to the continuous nature of this variable and because recurrence is a multifactorial process (PSA is only one variable among many). Our findings show that, in addition to the known predictors of recurrence (Gleason and PSA), the PSA nadir value is associated with biochemical control, with lower values associated with better disease control.

In terms of overall toxicity, more than 95% of treatment-related toxicities were low grade (G0-G1). The mean time elapsed from seed implant until maximum toxicity was > 10 months (range, 4–13), which was shorter than the minimum follow-up in this series. Three patients—treated with PP at 145 Gy—developed chronic G3 GU toxicity. Although this limited number of cases of G3 toxicity does not allow us to draw any conclusions as to which technique is less toxic, the few cases with severe toxicity underscore that treatment was well-tolerated in most patients.

Several factors may explain the better results (BRFS) achieved with the higher dose IoP technique. First, due to technological advances in recent decades[23]—particularly the development of real-time volumetry—clinicians can better optimize the dosimetric values, thus allowing for dose escalation to 160 Gy with the consequent improvement in clinical and biochemical control. In addition, follow-up was longer in the PP group, thus increasing the likelihood of more relapses. However, other factors may have negatively impacted the results in the IoP group. Some studies[24] have found that Gleason scores were undergraded in the early years of the IoP technique, and this could have increased the relapse rate in that patient subgroup. In addition, as occurs with all new techniques, there is a learning period during which error rates may be higher, which could lead to a greater number of relapses among the cohort of patients who first underwent the new treatment approach.

Several studies have compared the treatment options for intermediate-risk PCa. The RTOG 0232 trial[25] compared LDR-BT (I-125 145 Gy or Pd-103 125 Gy) to EBRT + BT (45 Gy EBRT followed by I-125 145 Gy or Pd-103 100 Gy), finding similar PFS outcomes, but a greater late toxicity, mostly GU, in the combined treatment group. Importantly, however, that study did not stratify by risk subgroups and most patients had favourable intermediate-risk PCa (89% had GS $\leq$ 7, and 67% were T1c), which suggests that some patients with favourable prognostic factors (GS $\leq$ 7, stage T1c, PSA < 10) may have been overdosed. Another trial (RTOG 0019)[26] compared: LDR-BT vs. EBRT + BT vs. EBRT. That study found similar biochemical control rates at 8 years among the three groups, but greater toxicity in the EBRT + BT group. A comparative study conducted by Smith et al.[27] found better PFS in the LDR-BT group compared to EBRT alone (p value 0.001) but no differences in OS. Schlussel et al.[28] compared LDR-BT to EBRT + BT, finding no between-group differences in local or distant control; however, those authors suggested that the addition of EBRT to BT could prevent recurrences in higher risk subgroups. In the same study, patients receiving combination therapy were more likely to experience higher urinary toxicity. The excellent review by Grimm et al.[29] found that the combination of EBRT + BT yielded similar PFS outcomes to those achieved with BT, and both of these treatment schemes were superior to EBRT and surgery.

As the results of the present study demonstrate, permanent seed LDR-BT provides excellent BRFS and toxicity outcomes in patients with intermediate-risk PCa. Moreover, LDR-BT has a better toxicity profile than EBRT, despite the higher dose to the prostate. Compared to prostatectomy, LDR-BT can be performed more quickly, it is less aggressive, and it has a lower risk of operative complications. In addition, the IoP technique, which allows for dose escalation to 160 Gy, improves disease control without increasing urethral toxicity as the same dose constraint for the urethra is maintained (Dmax <217 Gy).

Despite the evidence in favour of LDR-BT, this technique is slowly falling into disuse, for several different reasons. First, the development of advanced radiotherapy techniques, such as intensity modulate radiotherapy (IMRT), stereotactic body radiotherapy (SBRT), and proton therapy, have all partially displaced LDR-BT. Second, the emergence of robotic surgery has increased the number of surgical interventions, to the detriment of BT. Third, brachytherapy requires well-trained, highly experienced clinicians and the reality is that this technique is available only at a limited number of hospitals, thus reducing the number of new physicians trained in this technique. Maybe, more professionals need to be trained in this technique.

Frank et al.[30] compared the costs and clinical outcomes of BT, IMRT, and proton therapy, concluding that BT is the best option for localized PCa. Hayes et al.[31] performed a cost-effectiveness analysis to compare observation to initial treatment, including an assessment of quality-adjusted life expectancy (QALE). That study found that active surveillance (AS) in men over the age of 65 was more effective in terms of QALE than any other treatment (BT, EBRT, prostatectomy). Those authors also underscored the lower cost of BT versus AS. While they found that IMRT is comparable to BT in terms of QALE, it is also more expensive. Prostatectomy was associated with worse QALE and also more expensive than BT. Based on their findings, the authors concluded that, compared with the other options, LDR-BT is the most cost-effective initial therapeutic option.

5. Conclusions

The findings of the present study suggest that 125I seed brachytherapy delivered with the real-time IoP technique at a dose of 160 Gy provides better BRFS outcomes than the lower dose (145 Gy) pre-planning technique.

There were lower rates of chronic toxicity in the patients treated with IoP. One of the strengths of the IoP technique is that the dose constraint to the urethra (Dmax <217 Gy) is maintained despite the increase in dose from 145 to 160 Gy, thus improving disease control without increasing toxicity.

The excellent results obtained with LDR-BT in localized PCa support the use of permanent seed BT as the primary treatment option in these patients.

Conflict of interest

None.

Financial disclosure

None.

Compliance with ethical standards

The present study has obtained the favourable opinion of the Ethical Committee of Biomedical Research of the Hospital Universitari I Politécnic La Fe (Valencia, Spain).

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