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Orignal Article

Impact of a dominant intraprostatic lesion (DIL) boost defined by sextant biopsy in permanent I-125 prostate implants on biochemical disease free survival (bDFS) and toxicity outcomes

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ABSTRACT

Background and purpose: To compare bDFS and toxicity outcomes in a population of intermediate risk prostate cancer patients treated using I-125 LDR brachytherapy with or without DIL boost based on multiple core biopsy maps.

Materials and methods: Between January 2005 and December 2013, all our intermediate risk prostate cancer patients treated with LDR I-125 brachytherapy were reviewed. All patients were given 144 Gy to the prostate. A pathologic DIL distribution (defined by sextant biopsy) was contoured prospectively prior to planning, to be covered by the 150% isodose line. Of the 165 patients treated, 55 received a DIL boost. Patients completed prospectively the IPSS questionnaire, a sexual and bowel function questionnaire. Gastro-intestinal toxicities were graded according to CTCAE v4.03. A patient was considered to have erectile dysfunction if he was unable to achieve erection to perform intercourse. BDFS was determined according to the Phoenix consensus definitions.

Results: The median follow-up was 78 months. The estimated 7-year bDFS rate was 96% (95% CI, 74–99%) in the DIL group versus 89% (95% CI, 79–94%) in the control group ($p = 0.188$). There was no difference between groups in urinary, gastro-intestinal or sexual toxicities up to 5 years of follow-up. There was no difference in urinary obstruction with catheterization between DIL versus control groups (3,6 vs 2,8 %, $p = 1.00$). Only 1 patient in the DIL group had ≥grade 3 toxicity (TURP) and none in the control group.

Conclusions: Boost to DIL defined by sextant biopsy with permanent seed prostate implant shows a trend toward improvement of biochemical control in intermediate risk prostate cancer patient without increasing toxicity.

Prostate cancer is the most common cancer in men. Even with its high cure rate, it's still the second leading cause of cancer death in men. Permanent seed prostate implant (PPI) under transrectal ultrasound (TRUS) is a standard of care for intermediate-risk prostate cancer [1] and it has been used since 1994 at *Centre Hospitalier Universitaire (CHU) de Québec, Canada* [2]. The technique has evolved over the last two decades, but standard radiation treatment still encompasses the whole gland, even if the disease is localized. It has been demonstrated that prostate cancer tends to recur in previously involved areas [3–5]. Prostate cancer has a dose–response curve that supports dose escalation [6–9], but tumor control is limited by adjacent organ at risk dose tolerance [10]. Keeping that in mind, it's desirable to increase dose escalation to the dominant intraprostatic lesion (DIL) while sparing surrounding normal tissues to improve biochemical control rates with similar or lesser side effects.

Because this type of cancer is known for its multifocal nature, the term DIL has been used to describe the area within the prostate containing the largest and/or highest grade of cancer lesion [11,12]. Several methods are being investigated as complementary tools to evaluate focal therapy strategies. The simplest is sextant prostate biopsy and it has a positive predictive value of 94–95% based on prostatectomy specimens [13,14]. The superiority of imaging studies over biopsy alone for defining areas of involvement has never been demonstrated. Areas with positive biopsy reliably correspond to areas of cancer involvement, justifying boost dosage based on sextant biopsy in brachytherapy planning.

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Several authors studied the feasibility of DIL boost technique [15–20]. A recent meta-analysis reported that a combination of external beam radiotherapy (EBRT) plus brachytherapy allows for dose escalation to the DIL and that, it is safe and effective with 5-years bDFS between 78 and 92% [21].

The principle of dose boost to DIL of the prostate is logical and has been applied to LDR brachytherapy alone. It was previously reported that planned boost to DIL up to 216 Gy can be delivered without increasing toxicity [22]. Few studies have evaluated long-term bDFS after DIL boost with LDR brachytherapy [23,24]. Their heterogeneous population with all NCCN risk groups and different radiation technique made it difficult to draw conclusions. In this context, the purpose of this study was to compare bDFS and toxicity outcomes in intermediate risk prostate cancer patients treated using I-125 LDR brachytherapy with or without DIL boost based on multiple core biopsy maps.

Materials and methods

Patient selection

Between January 2005 and December 2013, all our intermediate risk (prostate-specific antigen [PSA] 10–20 ng/mL, clinical stage T2b-T2c, Gleason's score of 7, according to National Comprehensive Cancer Network (NCCN) guidelines [1]) prostate cancer patients treated with low dose rate I-125 brachytherapy were reviewed in a retrospective analysis. Of 204 patients initially included in the study, 165 patients were analyzed. Exclusion criteria were: prior pelvis irradiation (9), missing dosimetric data (11) and follow-up $\leq$4 years (19). 110 patients had low-dose rate brachytherapy alone and 55 patients had a boost to DIL with LDR brachytherapy. Patients not eligible for dose escalation to the DIL were those with diffuse disease without a zone with more aggressive lesion that can't be defined according to sextant biopsy or with lacked topographic prostate biopsy map. Initially, patients were distributed randomly between 3 radiation oncologists before consultation. The study was approved by the Ethics Committee of CHU de Québec.

Treatment technique

The biopsy pattern used was the double-sextant scheme with 12 cores as recommended by American Association of Urology and biopsies correlated with clinically palpable disease [25]. The transition zone and the anterior horn are not biopsied with this technic. Prostate anterior horn was biopsied in a second procedure, only if initial biopsies were negatives. Transition zone is not usually biopsied with this technic, but cancer is less common in this zone and boost to this region could impose a burden given to urethra dose tolerance. Patients had a TRUS prostate volumetric measure done by one of the 3 radiation oncologists before PPI. If their prostate size was more than 50 cc, they received cytoreductive hormonal therapy. For the procedure, patients were under general anesthesia and placed in a lithotomy position. Entire prostate image was acquired with TRUS three-dimensional digitization and integrated in SPOT Pro system from Nucletron. All contours were performed by a radiation oncologist. Plans were generated using an inverse plan simulated annealing algorithm (IPSA). PPI were implanted in prostate with interstitial needles inserted through perineal template under TRUS guidance. No seeds were planned outside the prostate capsule. All patients were given 144 Gy with I-125 (mean activity: 0.6 mCi) to the prostate plus a 3 mm PTV margin. Dose–volume objectives and constraints included the prostate D90 $\geq$ 185 Gy, V150 < 65% and V200 < 30%. The urethra V125 was planned to be zero and urethra D5 < 205 Gy. For those eligible, a pathologic DIL distribution defined by sextant biopsy was contoured prior to planning. The DIL was defined according to largest or highest grade lesion on sextant biopsy and based on a standard model that separate peripheral zone into base, midgland and apex, and again between right and left depending on anatomy [26]. If more than one sextant was involved, both sextants were contoured separately if they were non-contiguous for a maximum of two. They were incorporated in the same contour if they were contiguous. The contours extend to midline, exceeding midline only if the contralateral zone was part of the DIL and under the urethra. A 5 mm margin was given to the urethra. The aimed DIL dose was V150% > 95% ($\geq$216 Gy). A CT scan was performed 1 month after the implant to revaluate dosimetric parameters (prostate volume, prostate D90, prostate V100, prostate V150, prostate V200, rectum V100, bladder V100, bladder D5, urethra V150, urethra D5). These parameters were applied to both groups.

Clinical evaluation

Patients had a clinical evaluation pre-PPI as well as at 1, 3, 6, 9, 12, 24, 36, 48 months after procedure. It involved history, digital rectal exam and PSA. Patients completed prospectively the International Prostate Symptom Score (IPSS) questionnaire [27] and bowel function questionnaire used at our center (assessing tenesmus, diarrhea, anal irritation and rectal bleeding). The acute and late genitourinary (GU) and gastro-intestinal (GI) toxicities were graded according to Common Terminology Criteria for Adverse Events (CTCAE v4.03). Acute toxicity was defined as toxicity occurring within 6 months of implantation, and late toxicity occurring more than 6 months after implantation. A patient was considered to have erectile dysfunction, if he was unable to achieve erection to perform intercourse without PDE5 inhibitor. BDFS rate was determined according to the RTOG-ASTRO Phoenix consensus failure definition (PSA clinical nadir rise of 2 ng/mL) [28].

Statistical methods

Both groups were compared according to patient's baseline characteristics (age, hypertension, dyslipidemia, diabetes, cardiac disease, active smoking, IPSS pre-treatment and erectile dysfunction) and disease's characteristics (stage, Gleason's Score, initial PSA level, positive biopsy ratio, maximal invasion biopsy ratio and cytoreductive hormonal therapy). Multivariate analyses for specific characteristics were performed if there was a statistical difference between both groups in univariate analysis. Quantitative variables are described as median, first and third quartiles, and qualitative variables as frequencies and percentages. Nonparametric Wilcoxon–Mann–Whitney's test was used to compare continuous data by groups after normality verification; chi-squared or Exact tests were used for categorical data comparisons. BDFS was tested using Kaplan–Meier's survival estimator. Statistical analyses were performed using SAS Statistical Software v.9.2 (SAS Institute, Cary, NC, USA) with a two-sided significance level set at $p < 0.05$.

Results

Patient characteristics

Both groups were similar according to pre-treatment age, hypertension, diabetes, heart disease, active smoking, IPSS pre-treatment and erectile dysfunction pre-treatment. More patients in the control group had dyslipidemia (40% vs 20,9%, $p = 0{,}015$), but multivariate analyses demonstrated no statistical difference on bDFS. Clinical stage according to NCCN, Gleason's score, initial PSA, positive biopsy ratio and maximal invasion biopsy ratio were similar for both groups. A median of 12 prostate biopsies was taken

on each patient at diagnostic and correlated with clinically palpable disease. 22% of patients in DIL group versus 7% ($p = 0,01$) of patients in control group were treated with cytoreductive hormonal therapy and no difference were reported with multivariate analyses on bDFS. Median hormonal therapy treatment time was 3 months. The median prostate volume pre-hormonal therapy was 56 cc and 40 cc post-cytoreductive homotherapy. The median follow-up was 78 months. Tables 1 and 2 summarize patient characteristics and disease characteristics by treatment groups.

Dosimetry parameters

Dose–volume histograms were used for analysis of dosimetry characteristics, as summarized in Table 3. Prostate volumes as well as live intraoperative dosimetry parameters related to prostate were similar no matter the treatment. Compared with control group, prostate V150 post-PPI in the DIL group was statistically higher with 60,5 % versus 57,8 % ($p = 0,03$). V200 post-PPI shows the same difference with 31,4% versus 29,4% ($p = 0,028$). Also, in post-PPI parameters, a statistically significant difference was seen for the urethra V150 (4,0% vs 0,2%, $p = 0,0001$) and the bladder D5 (94,3 Gy vs 86,17 Gy, $p = 0,04$), which were all higher in DIL group. Median DIL volume was 4,3 cc (range, 2,6–6,2). V100, V150 and V200 post-implants parameters were respectively 100% (range, 99,7–100), 91,2% (range, 83,2–94,3), and 55,6% (range, 47,2–69,8). DIL contours encompassed 41,8% right apex, 32,7% left apex, 40% right median lobe, 27,3% left median lobe, 34,5% right base and 32,7% left base. 6 patients had a second DIL contoured.

Biochemical disease-free survival

According to the Phoenix consensus definition (nadir + 2 ng/mL), the 7-year bDFS rate estimated in the DIL group was 96% (95% CI, 74–99%) versus 89% (95% CI, 79–94%) in the control group ($p = 0.188$) (Fig. 1). The PSA nadir was lower in the DIL group compared to the control group (0,03 vs 0,04, $p = 0,042$). The percentage of patients with a PSA over 0.4 ng/ml at 5 years was 8,9% in the DIL group and 18,1% in the control group ($p = 0,131$). The median PSA at last follow up was 0,06 vs 0,08 for the DIL and control group respectively ($p = 0,292$).

Toxicities

There was no statistically significant difference in the mean IPSS score at baseline and during follow-up at 1, 3, 6, 9, 12, 24, 36 and 48 months (Fig. 2). Tables 4 and 5 summarize toxicities for both groups up to 5-year follow-up. For GU toxicities in DIL group versus control group, grade 1 acute toxicities were reported in 51,9% versus 58,1% and grade 2 acute toxicities were 46,2% versus 33,3%, $p = 0,118$. For late outcomes, 60,4% versus 50,5% grade 1 toxicities and 37,7% versus 36,6% grade 2 toxicities were reported respectively, $p = 0,076$. Only 1 patient in the DIL group had a grade 3 urinary toxicity, requiring a RTUP 1-year post-treatment for obstructive urinary symptoms, and none in the control group. There was no urinary obstruction with catheterization difference between DIL versus control group (2 vs 3 patients, $p = 1.00$). There was 1 urethral stricture in the DIL group and 2 in the control group. Grade 1 acute GI toxicities occurred in patients 17,6% versus 13,2%, $p = 0,252$ respectively, whereas 11,5% versus 18,4%, $p = 0,194$ patients experienced grade 1 late GI toxicity. No grade ≥ 2 were noted in both groups. The same comparison for erectile dysfunction shows no difference statistically significant for acute (46,8% vs 50,9%, $p = 0,698$) and late toxicities (52% vs 60,7%, $p = 0,473$).

Discussion

In this report, we summarize our institutional experience using dose escalation to dominant intraprostatic regions delimited with sextant biopsy. This study presents the largest population with intermediate risk prostate cancer patient treated with DIL technique and low dose brachytherapy in the literature. Low risk prostate cancer patients were excluded from this present study, owing the very good prognostic in this category of patients. We believe that previous studies had difficulty to show a statistically significant improvement of bDFS with DIL technique, because the majority of patients are from this subgroup. Therefore, we hypothesized that a cohort of intermediate risk prostate cancer patients might be more appropriate to show the impact of a DIL boost on bDFS.

Both groups are similar for pre-treatment patient and disease characteristics, except for dyslipidemia and cytoreductive hormonal therapy. As a risk factor for erectile dysfunction, dyslipidemia has been analyzed in this study. There were more patients with dyslipidemia in the control group. A recent meta-analysis proposes that statin use can improve bDFS in prostate cancer [29], but the impact is still uncertain [30,31]. The statin use wasn't reported in this study, but there was no statistically significant difference on bDFS in known patients with or without dyslipidemia. Hormonal therapy is known to improve prostate cancer survival and outcomes in intermediate and advanced disease [32]. However, it's important to notice that androgen deprivation was used here in purposed of prostate volume reduction and for a median time of only 3 months. RTOG 98-04 trial [32], demonstrated that the use of short-term ADT for 4 months before and during radio-

Table 1
Patient baseline characteristics by group.

	LDR only		LDR + Boost DIL		*p* value
Patient characteristics	*n*	% (Range)	*n*	% (Range)	
Median age	64	(59–69)	66	(61–72)	
≤65	59	53,6	26	47,3	0,315
>65	51	46,4	29	52,7	0,510
Hypertension	47	42,7	19	34,5	0,400
Dyslipidemia	23	20,9	22	40	0,015*
Diabetes	14	12,7	7	12,7	1,00
Cardiac disease	19	17,3	9	16,4	1,00
Active smoking	18	16,4	6	10,9	0,483
IPSS pre-treatment					
Median	5	(2–9)	4	(1–8)	0,556
Erectile dysfunction					
Pre-treatment	39	38,2	13	24,5	0,107
Follow-up (month)	82	(60–100)	71	(60–92)	0,958

Abbreviation: LDR = Low Dose Rate brachytherapy, IPSS = International Prostate Symptom Score, Range = First Quartile and Third Quartile,
* =statistical difference.

Table 2
Disease baseline characteristics by group.

	LDR only		LDR + Boost		*p* value
Disease characteristics	*n*	% (Range)	*n*	% (Range)	
Stage (NCCN)					
T1c	61	56	28	51	
T2a	16	15	13	24	0,226
T2b	28	26	14	26	
T2c	5	5	0	0	
Gleason's score					
6	57	52	28	51	0,359
7 (3 + 4)	48	44	27	49	
7 (4 + 3)	4	4	0	0	
Initial PSA level					
Median	6,3	(3,2–10,1)	6,1	(4,1–11,0)	
<10	81	74	38	69	0,424
≥10	29	26	17	31	0,583
Positive biopsy ratio (%)	21	(14-38)	28	(17-33)	0,333
Maximal invasion biopsy ratio (%)	20	(10-45)	20	(10-40)	0,461
Cytoreductive hormotherapy	8	7	12	22	0,011*
Median	2,5	(1,5-3,0)	3,0	(3,0-6,0)	0,101

Abbreviation: LDR = Low Dose Rate brachytherapy, NCCN = National Comprehensive Cancer Network, PSA = Prostate-Specific Antigen, Range = First Quartile and Third Quartile,
* =statistical difference.

Table 3
Dosimetric parameters by group.

	LDR only		LDR + Boost		*p* value
	Median	Range	Median	Range	
Prostate volume (cc)	32,6	(26,1–40,0)	35,5	(28,2–41,6)	0,142
No. of seeds	48,5	(43–56)	50	(45–56)	0,514
Prostate					
D90live (Gy)	186,7	(181,0–191,6)	187,4	(182–192,4)	0,426
V100live (%)	99,4	(99,7–99,8)	99,2	(98,5–99,8)	0,434
D90post (Gy)	154.2	(142,5–165,9)	155,8	(142,4–167,6)	0,645
V100post (%)	92,7	(88,8–95,7)	93,2	(89,6–95,6)	0,515
V150post (%)	57,8	(49,1–65,9)	60,8	(53,6–70,1)	0,030*
V200post (%)	29,4	(23,1–35,0)	31,4	(27,4–36,9)	0,027*
Rectum					
V100post (cc)	0,2	(0,02–0,87)	0,2	(0,01–0,85)	0,650
Bladder					
D5post (Gy)	86,1	(73,0–104,0)	94,3	(80,7–113,5)	0,040*
V100 post (%)	0,55	(0,09–1,53)	0,73	(0,11–1,87)	0,750
Urethra					
V150post (%)	0,2	(0–1,7)	4,0	(0–21,4)	<0,001*
D5post (Gy)	227,5	(204,0–253,1)	219,5	(199,4–232,3)	0,090
DIL					
Volume (cc)	–	–	4,4	(2,9–6,0)	
V100post (%)	–	–	100	(99,7–100)	
V150post (%)	–	–	91,2	(83,2–94,3)	
V200post (%)	–	–	55,6	(47,2–69,8)	
2nd DIL (*n*)	–	–	6		

Abbreviation: LDR = Low Dose Rate brachytherapy, DIL = Dominant Intraprostatic lesion, post = 1 month after PPI, live = during planning, Range = First Quartile and Third Quartile,
* =statistical difference.

therapy was associated with significantly decreased disease-specific mortality in intermediate risk prostate cancer patients. No literature has yet demonstrated an impact on bDFS using less than 4 months of ADT in this risk group. Accordingly, this study reveals no statistically significant difference on bDFS for patients with or without cytoreductive hormonal therapy. The Phoenix failure consensus definition recommends reporting median follow-up of at least 24 months for prostate cancer [28]. This article respects widely this recommendation with 48 months of minimal follow-up and 78 months of median follow-up.

In the present article, boost to DIL with I-125 PPI shows a 7-year bDFS rate of 96% compared to 89% in the control group. The bDFS in the control group is similar to what our institution previously reported [33]. Compared to literature, bDFS in the DIL group seems higher. Ellis et al. published 7-year bDFS and 10-year bDFS rate at 87% and 78,7%, but their population included patients treated with EBRT and low dose brachytherapy [23,34]. According to the recent data from ASCENDE-RT randomized trial [35], patients with intermediate and high-risk prostate cancer treated with LDR boost were twice likely to be free of biochemical failure at 6,5 years compared with those treated with EBRT boost. That can explain the difference between our results and Ellis et al. results. We previously presented our results at *World Congress of Brachytherapy* in 2012 and the 5-year bDFS was estimated at 97,9% for low and intermediate prostate cancer treated with boost [36]. King et al. reported 10-year bDFS rate at 98% for 48 low and intermediate risk cancer

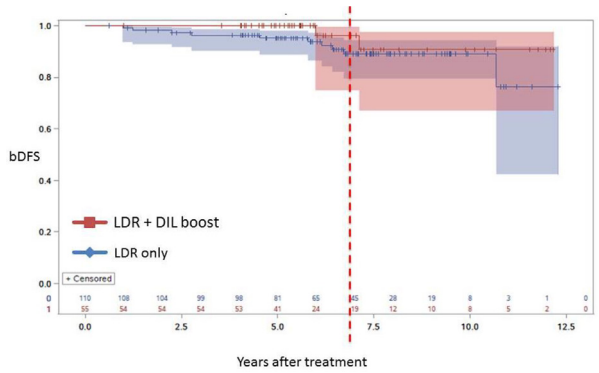

Fig. 1. Seven-year biochemical failure-free survival (7-year BFFS) curve.

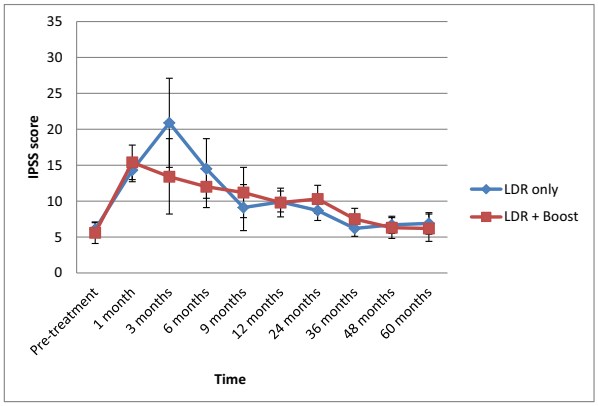

Fig. 2. Mean IPSS score during follow-up by group Abbreviation: LDR = Low Dose Rate brachytherapy, IPSS = International Prostate Symptom Score.

Table 4
Genitourinary toxicities by group according to CTCAE v.4.03.

Toxicity	Grade	LDR only	LDR + Boost	*P* value
Acute (%)	1	58,1	51,9	0,118
	2	33,3	46,2	
	≥3	0	0	
Late (%)	1	50,5	60,4	0,076
	2	36,6	37,7	
	≥3	0	0,2	
Catheterism (*n*)		3	2	1,00

Abbreviation: LDR = Low Dose Rate brachytherapy, CTCAE = Common Terminology Criteria for Adverse Events.

Table 5
Gastro-intestinal toxicities by group according to CTCAE v.4.03.

Toxicity	Grade	LDR only	LDR + Boost	*p* value
Acute (%)	1	13,2	17,6	0,252
	2	0	0	
	≥3	0	0	
Late (%)	1	18,4	11,5	0,194
	2	0	0	
	≥3	0	0	

Abbreviation: LDR = Low Dose Rate brachytherapy, CTCAE = Common Terminology Criteria for Adverse Events.

prostate patients treated with LDR brachytherapy with DIL boost determined by MRI [24]. Only 12 of these patients were intermediate risk and their bDFS rate was estimated at 89%. This small number of intermediate risk patients makes it difficult to compare results. Also, the PSA nadir was a little lower in the DIL group. This supports the idea that using dose escalation to a biopsy positive segment is effective.

Compared to the control group, prostate V150 and V200 in the DIL group were statistically higher, which is explained by a geographic rearrangement of high doses to the DIL area. However, this increment is minimal and respectively of 3% and 2%. This isodose redistribution had no clinical impact on toxicities. Despite efforts to balance intraprostatic dose escalation with surrounding normal tissue constraints, post-PPI dosimetry revealed higher dose than expected to urethra and bladder. Even with these higher dosimetric parameters, there were no statistically significant differences in GU, GI or sexual toxicities in both groups. Our data support the non-inferiority study published by Gaudet et al. [22], which demonstrated no increased toxicity with DIL boost technique in LDR brachytherapy. The only patient with grade 3 GU toxicity had V150 and D5 to urethra higher than median, 19,9% compared to 4,0% and 239 Gy compared to 219 Gy respectively. Compared to King et al. [24], the present study shows less grade 3 late toxicities. Even if this study used the same CTCAE grading scale, differences can be explained because late toxicities were defined if it occurred within 12 months. In this study, 6 months is used for the cut off between acute and late toxicity. We chose this cut off to facilitate comparison with previous studies published from our center. However, because of the low dose rate of Iode-125, the 12-month cut off would have been adequate. CTCAE grading scale has been used to compare results with previous study from our center. However LENT grading scale is more severe, especially for urethral stenosis and comparison with other studies using this scale should be done wisely. This study reports similar urethral stenosis compare with a recent meta-analysis [37].

A key limitation of this study is its retrospective aspect. However, all data were collected prospectively with standard questionnaires and regular follow-up. Selective bias could have happened because physicians were not blinded. However, patients were distributed randomly between radiation oncologists before consultation and it is important to notice that both groups were similar according to Gleason, stage, initial PSA level, maximal invasion biopsy ratio and positive biopsy ratio. According to this, patients that could been boosted, seem to have an evenly distributed localized disease in both groups.

This study used double-sextant biopsies and TRUS to identify DIL. This technique can be easily exported in other centers, even if advanced technology is not readily available in their department. As mention in the method section, this technique can't identify if there is disease in the transition zone. However, it is important to notice that DIL contour encompasses the transition zone till midline. A systematic review reported that biopsy-confirmed imaging may address the uncertainty associated with the planning of boost therapies base on random systematic biopsies of the prostate alone [38]. New ASTRO ACROP consensus guidelines in 2018 suggest performing MRI if dose escalation on the DIL is considered [39]. This present study reported patients treated between 2005 and 2013, when imaging wasn't readily available in our department and commonly used for DIL identification. This aspect is important to notice according to the choice of DIL delineation done at the moment. Also, soft tissue contrast is inherently better in MRI, but access in a socialized health system is sometimes restrictive and comes with an increased cost. A better availability of MRI to contour DIL could increase bDFS and decrease toxicities in prostate cancer.

In conclusion, boost to DIL defined by sextant biopsy with permanent seed prostate implant shows a trend toward improvement of biochemical control in intermediate risk cancer patient without increasing toxicity. These results need to be validated in a larger prospective study with balanced distribution of patients.

Conflict of interest

None declared.

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