Brahiterapia Low Dose Rate cu I-125 în cancerul de prostată localizat. Analiza morbidității acute urinare şi rectale

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Abstract

Background and aims: The evaluation of the urinary and rectal toxicity after iodine –125 permanent implant, establishing any correlations between urinary and rectal toxicities and clinical and dosimetrical parameters.

Methods: This prospective study analyses the data from 83 patients with localized prostate cancer who performed permanent implant with I-125 brachytherapy (BT), between October 5th 2006 and February 15th 2007, at The Oncology Institute, Bucharest and at The Fundeni Clinical Institute. The mean age was 65.96 years old. The uniform modified implant technique, was used for the implantation of seeds; 75 and 8 patients performed monotherapy and concomitant treatment, brachytherapy and external beam radiotherapy, respective. Because of the difficulty in establishing the biological equivalent doses, in a comparative way, for the patients treated with permanent implant as monotherapy, and for the patients treated with simultaneous therapy, we evaluated separately the patients who performed monotherapy and combined therapy. The following parameters have been analyzed, pre-implant prostate volume, number of implanted seeds, number of used needles, D90, V100, V150, V200, D1 at urethra, D1 at rectal mucous, in order to identify the predictive factors for urinary toxicity.

Results: The average follow up was at 19 months (range 12-28 months). The prevalent symptomatology was urinary, the most important clinic features were: nocturia, dysuria, and urgency. None patient presented urinary incontinence. In the firsts three months, 50.66% of patients presented grade 1 urinary toxicity, 37.33% of patients presented grade 2 urinary toxicity and acute urinary retention occurred at 2 patients (2.67%). Grade 1 rectal toxicity, in the first 3 months, presented 4 monotherapy patients and 5 combined therapy patients. One patient presented rectal toxicity either in monotherapy group and combined therapy group. Univariate and multivariate analysis showed one single predictive factor for grade 2 urinary morbidity being preimplant prostate volume ($p<0.05$). Conclusions: In our study, acute urinary toxicities were mild/moderate with maximum intensity in the firsts 3 months and with a greater incidence of rectal morbidity in combined therapy group.

Key words: predictive factors, prostate brachytherapy, urinary morbidity

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Introduction

Scope. The aim of the study is to make an analysis of urinary and rectal toxicities after iodine – 125 permanent implant, to evaluate the risk factors for acute urinary retention (AUR) and to find if there are any correlations between urinary and rectal toxicities and clinical and dosimetrical parametrics.

From October 2006, in Romania, in Oncological Institute Bucharest and after wards in Clinical Institute Fundeni, had been made permanents implants using iodine – 125 seeds, for localized prostate cancer. In this prospective study we analyze the urinary and rectal toxicity for the first 83 patients who were treated using this therapeutically method and we are searching for identification of predictive factors, also for the association between independent risk factors and acute urinary retention and rectal toxicity.

Patients and methods

This study analyzes the prospective data of 83 patients with localized prostate cancer who performed permanent implant with I-125 brachytherapy (BT) between 05.10.2006 and 15.02.2007, at the "Prof. Dr. Alexandru Trestioreanu" Oncology Institute, Bucharest and the Fundeni Clinical Institute Bucharest. Because the definition of the biological equivalent doses is difficult, in a comparative way, for the patients treated with permanent implant as monotherapy, and for the patients treated with concomitant therapy (BT and external beam radiotherapy, EBRT), we evaluated in a separate mode the patients who performed monotherapy and combined.

The pretreatment investigations were: histopathological diagnosis, Gleason score, PSA, the status of the lymph nodes evaluated in a computer topography examination, bone scan, IPSS, transrectal ultrasound for prostate volume measurement.

According to the ESTRO and EORTC recommendations (1), for brachytherapy (BT) with I-125, as monotherapy, the inclusion criteria were: patients with prostate adenocarcinoma, stage T1c-T2a, PSA≤10ng/ml and Gleason Score≤6, prostate volume < 60cc, without TUR-P prior implantation in the last 6 months.

The prescribed dose was 145 Gy for 75 patients (90.36%) who performed monotherapy and 110 Gy for 8 patients (9.64%) who had combined treatment (BT + EBRT).

In the combined treatment, the EBRT was initiated at one month post implant, and the prescribed dose for EBRT was 45 Gy/25-27 fr., 1.8-2 Gy/fr. with 6 MV photons beam.

27 patients (42.86%) have been given neo-adjuvant hormonal therapy with LH-RH agonists, for 3-4 months, in order to reduce the prostate volume.

The implant was performed under general anesthesia, with the patient in lithothomy position, and also under transrectal ultrasound control. The treatment had the following steps: pre-planning, the implant itself and the implant evaluation (post-planning). In the first step, ultrasound images of the patient's prostate are taken with 5-mm step. These images were taken by the soft who make the treatment planning – Soft PSID from Ibt Germany. The uniformed modified technique, described by Blasko and Radge [1], was used for the implantation of seeds. This method has the advantage of the decrease urethral dose and, consecutive the decrease of urinary morbidity. The implant procedures took between 1.5 and 3 hours, without any problems, the urethral catheter was maintained until next day and the patients were hospitalized between 24 and 48 hours.

The patient's characteristics are presented in table 1. The mean age was 65.96 years (range 46-82 years); 63.82% of cases had T2a disease stage and 33.73% in T1c. The Gleason score was < 6 in 89.16% of cases and 2 patients had Gleason score 8. the IPSS score was≤8 for 80% of patients.

A mean number of 16.18 needles (range 10-30) and 42.47 seeds (range 22-75) were used.

The permanent implant with I-125 was performed observing the following values of the dosimetric parameters:

- D90 ≥ 180Gy,
- V100 > 98% - 100%,
- V150 < 30%,
- D1 at rectal mucous = 145Gy.
- D1 at urethra: max 230Gy (monotherapy);
- D1 / D10 at urethra: < 216Gy /210Gy

For performing the postimplant dosimetric analysis a 1-month after implant CT scan was made. The dosimetric parameters reviewed were V100, V150, V200, D90. Also D1 at urethra and D1 at rectal mucous were evaluated. The dosimetric characteristics of the implanted patients are summarized in table 2.

Table 1. Clinical characteristics of the implanted patients

Variables	Number of total patients, n=83	Number of mono-therapy patients, n=75
Mean age (years)	65.96 (46-82)	65.79 (46-82)
PSA (ng/ml)		
≤ 10	74 (89.16%)	63 (84%)
11-20	8 (9.64%)	12 (16%)
>20	1 (1.2%)	0
Disease stage		
T1c	28 (33.73%)	28 (37.33%)
T2a	53 (63.86%)	46 (61.33%)
T2b	1 (1.2%)	1 (1.33%)
T2c	1 (1.2%)	0
Gleason score		
2-6	74 (89.16%)	73 (96%)
7	7 (8.43%)	3 (4%)
8-9	2 (2.41%)	0
Mean prostate volume (cc) at implantation	39.65 (17.7-60.4)	34.34 (17.7-60.4)
IPSS		
≤ 8	66 (80 %)	65 (87%)
8-12	12 (14%)	7 (9.33%)
>12	5 (6%)	3 (4%)
Neoadjuvant hormonal therapy	27 (32.53%)	24 (32%)
Mean number of neadles	16.18 (10-30)	16.09 (10-30)
Mean number of seeds	42.47 (22-75)	42.07 (22-75)
Total activity of seeds (mCi)	31.19 (15.68-49.01)	30.9 (11.52-36)

Table 2. Real-time dosimetric characteristics for implanted patients

Parameters followed	Mean values for the patients who effectuated BT as mono-therapy (n=75)	Mean values for the patients who effectuated combi-ned therapy: BT+RTE (n=8)
V100 (%)	99.4 (range 96.3-100)	96.95 (range 94.3-100)
V150 (%)	76.21 (range 57.8- 94.6)	70.55 (range 54.5-94.6)
V200 (%)	41.41 (range 19.2- 67.9)	40.91 (range 23.3-71)
D90 (Gy)	192.80 (range 167- 234)	160.71 (range 137-180.9)
D1 at urethra (Gy)	237.5 (range196.8 –309.8)	208.07 (range 173-259.5)
D1 at rectal mucous (Gy)	109.71 (range 43 - 209)	106.9 (range 59.9-142.2)

Patient's follow-up began in first day from implant and the patients were clinical evaluated at 1 month, 3, 6, 9 and 12 months. Alpha-blockers treatment was given 6 months after implant**.** The 1-month postimplant CT did not show migrated seeds at distance.

Urinary and rectal toxicity was scored according to the RTOG modified morbidity scale (table 3 and 4), and the informations were recorded with questionnaires, by e-mail, and by phone [2].

Table 3. Urinary toxicity: modified grading of the RTOG

Grade 0 – Absence of urinary symptoms.
Grade 1 – Minor symptoms not requiring treatment. Twice the frequency of micturition or nocturia than before the treatment / dysuria not requiring treatment.
Grade 2 – Symptoms requiring treatment. Frequency of micturition or nocturia < 1 h. dysuria or bladder spasms requiring treatment.
Grade 3 – Hospitalisations for diagnosis or minor surgery. Frequent micturition and nocturia every hour or more. Disuria, pelvic pain or bladder spasm requiring analgesics. Clinical haematuria with or without clots. Urinary retention requiring a urethral catheter or the insertion of a supra-pubic catheter.
Grade 4 – Prolonged hospitalizations or major surgery. Heamaturia requiring transfusion s. acute urinary retention not secondary to the passage of clots. Necrosis or ulceration of the urethra.
Grade 5 – Fatal complications.

Table 4. Rectal toxicity: modified grading of the RTOG

Grade 0 – Absence of rectal symptoms.
Grade 1 – Minor symptoms not requiring treatment. Increasing in frequency of evacuation, not requiring treatment.
Grade 2 – Symptoms requiring treatment. Diarrhea requiring treatment, rectal tenesmus, abdominal pains requiring analgesics.
Grade 3 – Diarrhea requiring paraentheral treatment. Severe mucousites or rectal bleeding
Grade 4 – Acute or subacute obstruction, fistula or gastric – bowel perforations, rectal bleeding requiring transfusions.
Grade 5 – Fatal complication.

Univariate and multivariate statistical analysis (t-test, χ^2-test, regression coefficient Pearson, and multiple linear regression) were made for assessing the correlation between clinical and real time dosimetric parameters with urinary and rectal toxicity. The following parameters have been analyzed: preimplant prostate volume, number of implanted seeds, number of used needles, and real-time dosimetrical parameters (D90, V100, V150, V200, D1 at urethra, D1 at rectal mucous).

The statistical analysis were not made for postplanning dosimetrical parameters neither for postimplant

prostate volume because at the moment of this study this data were not available for all patients.

Results

Median follow-up was 19 months (range 12-28 months). The prevalent symptomatology was urinary, the most important clinic features were nocturia, disuria, and urgency. 90% of patients presented temporary urinary symptoms damage, with maximum of toxicity in firsts 2 months.

From monotherapy patients, in first 3 months, 55.66% of patients had grade 1 urinary morbidity, 37.33%, grade 2 urinary morbidity, and only 2.67% of cases developed acute urinary retention (grade 3 urinary toxicity), which occurs at 2 respective 5 days postimplant and was necessary suprapubic catheterisation; the catheter was maintained 10 respective 14 days; one of the two patients had made TURP previously, 11 months before implant, more than 6 months before implantation. 9.33% of patients did not presented urinary toxicity. At 6 months postimplant, 73.33% of cases did not manifested urinary symptoms, 17.33% still presented grade 1 symptomatology and only 9,33% grade 2 morbidity (table 5).

Table 5. Postimplant urinary morbidity

Grade of toxicity	**3 months** No of patients (%)	**6 months** No of patients (%)	**12 months** No of patients (%)
Grade 0	**7 (9.3%)**	**55 (73.33%)**	**61 (81.33%)**
Grade 1	**38 (50.66%)**	**13 (17.33%)**	**11 (14.67%)**
Grade 2	**28 (37.33%)**	**7 (9.3%)**	**3 (4%)**
Grade 3	**2 (2.67 %)**	**0%**	**0%**

At 12 months, 14.76% and 4% of patients still presented grade 1 and, respective grade 2 urinary symptoms (table 5). One patient manifested urethral stricture at 18 months postimplant for who was effectuated optical internal urethrotomy.

We tried to establish the correlations between grade 2 urinary morbidity and clinical and dosimetrical, respective prostate volume, number of needles, D90, D1 at urethra, V100, V150, V200 at 3, 6 and 12 months.

Regarding grade 3 urinary morbidity, in firsts 3 months, because of the small patients number (n=2), we did not find significant statistical correlations between studied parameters and acute urinary retention. Also, because the small number of patients with grade 2 urinary toxicity at 12 months (n=3) we didn't were able to establish any correlations between the analyzed parameters and urinary morbidity.

Univariate analysis indicated contrary results: using χ^2 test we found statistically significant correlations for prostate volume, D90 and D1 at urethra. On the other hand, the t-Student test, put in evidence the statistically significant correlations only with prostate volume (table 6). Because of these different results, we used multiple linear regression, and the final result was that the preimplant prostate volume was the only significant predictive factor for grade 2 urinary morbidity (table 6.1).

Table 5.1. Postimplant rectal morbidity

Grade of toxicity	No of patients at 3 months	No of patients at 12 months
Grade 0	**71**	**74**
Grade 1	**4**	**0**
Grade 2	**0**	**1**
Grade 3	**0**	**0**

Table 6. Correlation between urinary toxicity grade and clinic and dosimetric parameters

Parameters	No. total patients **n= 75**	**Toxicity grade 0 at 3 months, n=7**	**Toxicity grade 2 at 3 months, n=28**	**Toxicity grade 2 at 6 months, n=7**
Mean prostate volume (cc)	34.47 95% CI =31.77-37.17	28.69 **p=0.02** 95% CI = 20.58-37.12	34.93 **p = 0.03** 95% CI = 22.93-46.93	38.18 **p=0.002** 95% CI = 24.75-51.61
Mean needles number	16.09 95% CI =15.31-16.88	14.5 **p=0.68** 95% CI =12.85-17.65	15.22 **p = 0.17** 95% CI = 12.04-18.4	16.57 **p=0.35** 95% CI =13.28-19.86
D90 (Gy)	192.8 95% CI =188.1-194.3	183.0 **p=0.324** 95% CI =177.33-196.87	188 **p = 0.507** 95% CI =180.26-196.22	185 **p=0,45** 95% CI =177.61-203.61
D1 at urethra (Gy)	236,5 95% CI =228,24-237,68	240,862 **p=0.37** 95% CI = 226,4-255,3	221,2 **p = 0.16** 95% CI = 213,72-228,68	222 **p=0,29** 95% CI =211.36-249.42
V100 (%)	99.45 95% CI =99.27-99.63	99.9 **p=0.86** 95% CI = 99.1-100.4	99.5 **p = 0.94** 95% CI =98.9-99.9	99.6 **p =0.83** 95% CI = 98.71-100.09
V150 (%)	76.43 95% CI =74.68-78.18	62.47 **p=0.07** 95% CI =53.69-71.31	73.6 **p = 0.67** 95% CI =68.7-76.5	73.47 **p=0.92** 95% CI =64.8-82.14
V200 (%)	41.32 95% CI =38.93-43,71	29.2 **p=0.15** 95% CI =17.54-40.76	36.95 **p=0.4** 95% CI = 30.9-49.96	37.45 **p=0.5** 95% CI =30.49-47.52

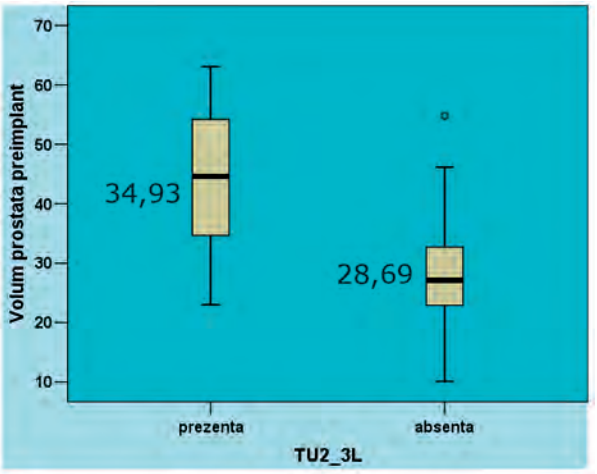


Fig.1. Preimplant prostate volume distribution for patients with or without urinary toxicity grade 2 at 3 months postimplant

Table. 6.1 Urinary morbidity analysis

Variables		*p*	
	Toxicity grade 0 at 3 months n=7	Toxicity grade 2 at 3 months n=28	Toxicity grade 2 at 6 months n=7
No. of needles	0.68[a]	0.17[a]	0.35[a]
Pre –implant prostate volume	0.02[a,b] 0.03[d]	0.03[a,c] 0.035[d]	0.002[a,b] 0.003[d]
D90	0.324[a] 0,008[b]	0,507[a] 0.00005[b] 0,587[d]	0,45[a] 0.009[b] 0.892[d]
D 1 at urethra	0,37[a] 0.0002[b]	0,16[a] 0.00004[b] 0,286[d]	0,29[a] 0.002[b] 0.376[d]
Neoadjuvant hormonotherapy		0.337[d]	
IPSS		0.55[b] 0.229[d]	

[a] – t-Student test, [b] – χ^2 test,
[c]- Pearson regression coefficient, [d] – multiple linear regression

The preimplant IPSS score wasn't a predictor significant statistical factor for urinary morbidity grade 2 at 3 months, both in univariate analysis and in multivariate analysis. But in the simple linear regression proved significant statistical correlations between preimplant IPSS value and 1 month postimplant IPSS and 3 months postimplant values, respective (p = 0.001 and p = 0.0007, respective).

We considered acute reaction, the reactions which was recorded in the firsts 12 months postimplant, considering that the whole radiation dose received by permanent implant is released in the first year, even if we found in the literature different views about the timing of the acute reactions, some investigators fitting the acute reactions in the firsts 6 months, late reactions after 6 months postimplant [2]. Most of the authors fitted acute reactions in the firsts 12 months postimplant, and late reactions those occurred after 12 months postimplant [3].

Regarding urinary morbidity manifested at patients who performed combined therapy, 4 patients had grade 1 toxicity, 3 patients had urinary toxicity grade 2, in the firsts 3 months and at 12 months postimplant one single patients presented urinary morbidity grade 1. Because of the small patients number we did not find correlations significant statistical.

Regarding rectal toxicity, in the monotherapy group, in the firsts 3 months 4 (5%) patients presented rectal tenesmus, diarrhea, mucus, which we fitted in grade 1 toxicity, conform RTOG modified scale (table 5.1), and in combined therapy group, 5 patients had rectal tenesma and mucus in the firsts 6 months. At 10 months one patients presented self-limiting rectal bleeding in monotherapy group, considered rectal toxicity grade 2, taken into account the colonoscopy who highlighted rectal mucous erithema and one combined therapy patient had rectal toxicity grade 1 at 12 months. None of patients, who performed combined therapy manifested gastro-intestinal toxicity, grade 2, 3, 4.

Discussions

Brachytherapy is characterized by more urinary morbidity comparative with external radiotherapy or radical prostatectomy. Acute urinary toxicity occurs in general in the second week postimplant and achieve his maximal intensity in 2 months postimplant; these because of the fact that half of the prescribed dose is released in this period; after 3 months this effects tends to regress and disappear [4], also in our study. Even if postimplant urinary sympthomatology tends to regress after 6 months, at some patients urinary morbidity can maintains until 1-year postiradiation. Different author's studies mention at more that one-year, in 20% of cases urinary morbidity persistent, in Kleinberg experince and in 22% of cases, in Brown experince [5,6]. Of course, the most unpleasant is reaction is acute urinary retention (AUR) and represents the most important acute toxicity. Postimplant acute urinary toxicity varies in literature between 2 and 33% [7]. Different authors tried to identify the predictive factors for postimplant urinary retention. Almost in all studies a great

prostate volume was described being one of the most important variables occurring in development of the postimplant urinary retention. Another specified factors are the preimplant IPSS values, androgen therapy before implant, urinary flow, prostate transition zone volume, number of the implanted needles [7,8]. In Crook's et al. study [7], the acute urinary retention rate is 13%, and the predictive independent factors of acute urinary retention was found to be prostate volume and androgen therapy before implant. In Terk's study on 251 implanted patients [9] with I-125 or Pd-103, at 5,6% of cases installed acute urinary retention and the same study showed that the preimplant IPSS score represented the most important predictive factor for postimplant urinary retention. Other study which highlights that preimplant IPSS score represents a predictive factor for urinary morbidity is the Hendersen and Cunningham's study [10], but they did not found any significant correlation between D10, D25 and D50, D90, V100 and V150 and AUR. In this study acute urinary retention occurred at 9.3% of patients. Ohashi et al. [11] in a 227 patients cohort, find acute urinary retention requiring catheterization in 5.3% of cases, and the predictive factors of acute urinary retention are neoadjuvant hormonal treatment (p=0.025) and number of implanted needles (p=0.02), the catheterization risk being for more than 24 implanted needles. In literature are contrary data regarding the possible correlations between preimplant hormonal therapy and AUR. One important study is Merrick's study on 760 patients, who find the neoadjuvant hormonal therapy a predictive factor for AUR [12].

In our study AUR occurred in 2 cases (2.4%), which represent a good result comparative with literature data, but because of the small number of patients we weren't able to find significant statistical correlations between AUR and any predictive factors.

Rectal morbidity is described after permanent implant, literature data reports different rates in symptomatology frequency and severity, between 1-12% [11]. In the immediately period after implant, the brachytherapy patient could manifest rectal minor discomfort and rectal bleeding as result of ultrasound maneuver during procedure [13]. The proctitti's mechanism is related with edema and colon mucous fibrosis, as the fibrosis is instaled, the mucous become more brittle and it's clinical manifestation is rectal bleeding [14, 15]. If the rate of proctittis is 12%, after Wallner et al. [6], represent the earlier experience of the implants, today, because of the accumulated experience the proctittis rate decreases at 4-6%. Wallner notes a correlation between grade 1 and 2 toxicity and rectal surface which receives a radiation dose greater than 100 Gy, but he did not identify any relation ship between rectal toxicity and implanted total activity, minimal allowed dose or seed activity [16].

Referring us about the Stone and Stock study [17] on 325 patients, this mentions 24% patients who presented rectal bleeding at 1-3 years from implantation. From this 2.8% presented rectal bleeding grade 1 and 2 at more than 5 years from treatment. Late rectal bleeding was correlated, Stone's work with D90 values, the rectal bleeding incidence for a D90 values less than 179 Gy was 1.4%, comparative with 5.8% for patients who have a D90 values greater than 180 Gy.

Blasok's study is another important report [18] that mentions a self-limiting proctittis rate post-brachytherapy by 2.6%, and suggests a increase of late proctittis incidence after combined treatment (BT and EBRT), comparative with BT alone, respective 6% vs. 1% [16]. But the Gelblum' study doesn't notes significant difference in proctitis incidence for patients with monotherapy vs. patients with combined therapy [18]. A meaningfully study is those of Potters and Gelblum [18] on 825 patients with 48 months median follow-up, notes the maximum of the rectal toxicity at 10 months, 9.6% of patients presenting toxicity grade 1 and 2. Rectal ulcerations evidenced by colonoscopy, were recorded as grade 3 side effects at 0.5% of patients and were not recorded before 12 months postimplant. Because the risk of fistula the biopsy is not indicated.

Even if 2 of the 4 patients with grade 3 proctittis performed biopsy at the moment of the colonoscopy, they did not developed fistula.

Another analyzed issue is the relation ship between delivered dose and rectal volume. An important contribution we have from Synder' study [19] et al. who conclude that the risk of the proctittis is volume dependent of delivered dose and notes that the proctittis development risk at 5 years was 5% if 1.3cc or less of rectal volume who received a prescribed dose of 160 Gy and by 17% for a rectal volume greater than 1.3 cc for the same dose.

For now, 4 patients presented proctittis grade 1 and one patient was recorded with rectal toxicity grade 2 at 12 months postimplant; we did not find rectal toxicity grade 3 and 4.

Table 7. Predictive factors for acute urinary retention – literature data:

Authors	Prostate volume	IPSS	Transition zone volume	Nr. needles	D90	D1 urethra	HT	V100
Crook [4]	+						+	
Terk [6]		+						
Hedersen [9]		+			-	-		-
Ohashi [7]				+			+	
Merrick [8]	+		+				-	
Potters and Gelblum [16]	+							

+: significant statistical correlations;
- : without significant statistical correlations

Table 8. Predictive factors for acute urinary retention – literature data:

Authors	Rectal surface receiving a dose >100Gy	Total implanted activity	Minimal permitted dose	Activity /seed	D90
Wallner [13]	+	-	-	-	
Stone and Stock [14]					+

+: significant statistical correlations;
-: without significant statistical correlations

Conclusions

The irritative and obstructive urinary sympthomatology is frequently find after permanent implant. In our study, brachytherapy was well tolerated recording low and moderate urinary morbidity, with a maximum intensity in the firsts 2-3 months.

The preimplant prostate volume was the only significant factor for urinary morbidity grade 2 at 3 months and 6 months. For no another studied parameter, wasn't find statistical significant correlations with urinary morbidity. Rectal morbidity was low.

The patient's continuous follow-up will bring more informations regarding recorded late toxicity.

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