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URINARY AND RECTAL TOXICITIES EVALUATION IN FIRST 3 MONTHS AFTER PERMANENT IMPLANT WITH I-125 IN LOCALIZED PROSTATE CANCER

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RESUME

Commençant par l'octobre 2006, en Roumanie a été effectué les premiers implants permanents avec I-125 pour le cancer de prostate localisé, brachytherapy avec l'implant permanent devenant la troisième option thérapeutique possible également dans notre pays. L'évaluation urinaire et rectale de toxicité dans les trois premières bouches, pour les 32 premiers patients présentant le cancer de prostate localisé, traitées avec l'implant permanent avec I-125 et la recherche correspond entre la catégorie de la toxicité urinaire et les cliniques et les paramètres de dosimètres que nous avions suivis. Entre les octobre 2006 et mars 2007, a été traité 32 patients avec l'implant permanent avec I-125, prof. Dr. Alexandru Trestioreanu, Bucarest et institut Fundeni, Bucarest dans d'oncologie institut le « de clinique. L'âge patient moyen était de 66.7 ans. Pour brachytherapy comme monothérapie, étaient seulement les patients inclus avec l'adénocarcinome de prostate, l'étape T1c-T2b, PSA< ; 10ng/ml, et < de points de Gleason ; 7, < de volume de prostate ; 60 cc, sans implantation antérieure de TUR-P, se conforment consensus d'ESTRO et d'EORTC. Pour brachytherapy en tant que thérapie combinée, étaient les patients inclus présentant des valeurs de PSA entre 10 et 20 ng/ml, étape T2b-T2c ou points de Gleason = 7. sources d'Interstrand avec l'activité moyenne de 0.708 MCI/graine ont été employées. Prescrivez la dose était 145 GY en cas de 30 patients et 110 GY pour 2 patients qui ont reçu la radiothérapie de thérapie, brachytherapy et externe combinée de faisceau (EBRT), avec la dose totale des 45 GY, 6 semaines de post implant. la thérapie hormonale de Néo--adjuvant pour trois bouches, en cas de 16 patients a été employée et elle n'a pas été continuée après l'implant. Tous les patients ont reçu l'alpha - traitement de blocus - tamsulosin, pour 2 bouches après implant. Les symptômes urinaires et rectaux étaient éventuels analysés utilisant la balance de RTOG, à 1 bouche et à 3 bouches après implant. Les paramètres de dosimètres étudiés étaient volume de prostate à l'heure de l'implantation, D90, nombre des aiguilles utilisées, D1 pour l'urètre. Résultats Le volume moyen de prostate à l'heure de l'implantation était de 35.44 cc ; le nombre moyen des aiguilles utilisées était 16.66 (des aiguilles de gamme 10-30) ; le nombre moyen des graines utilisées était 43.44 (des graines de gamme 22-75). Des procédures d'implant ont été faites sous l'anesthésie générale, elle prend entre 2 et 4 heures, sans problèmes et patients a été mis dans l'hôpital entre 24 et 72 heures. 46.8% patients se sont présentés à 1 catégorie urinaire 1 de toxicité de bouche, 21.8% patients ont présenté la catégorie urinaire 2 de toxicité et 12.5% patients ont présenté la catégorie urinaire 2 de toxicité, à 3 bouches. Aucun patient n'a présenté la conservation urinaire aiguë. 2 patients ont présenté le saignement mineur au moment de l'élimination urinaire de cathéter. On n'a pas observé la toxicité rectale à 1 et 3 bouches post implant. Concernant le volume de prostate au moment de l'implant, les patients qui ont eu la catégorie 2 de toxicité ont eu également une valeur moyenne du volume de prostate 47.33 cc, qui est plus grand en

comparaison des patients qui ont présenté la catégorie 0 de toxicité et 1, dans laquelle les cas signifient volume de prostate était 30.61cc et de 32.83 cc, respective. La valeur D90 était 199.3 que la GY pour des patients présentant la toxicité évaluent 2 en comparaison de 177.69 GY pour les patients qui ont eu la catégorie 0 de toxicité. La valeur moyenne de D1 à l'urètre a varié de 227.8 GY, pour des patients sans toxicité urinaire à 252.9 GY pour des patients présentant la catégorie urinaire 2. de toxicité. Brachytherapy avec l'implant permanent utilisant les graines I-125 radioactives représentent une alternative pour le prostatectomie radical, dans le traitement du cancer de prostate localisé ; c'est un traitement bien toléré par des patients, présentant une basse morbidité urinaire, dans la plupart de cas, étant à la catégorie 1 et 2, la morbidité corrélés avec le volume de prostate au moment de l'implant et avec la dose fournie à l'urètre. On n'a pas observé la conservation urinaire aiguë et la toxicité aiguë rectale.

MOTS CLES*:* *cancer de prostate localisé, implant permanent avec I-125, toxicité aiguë rectale.*

1. Introduction

Prostate cancer represents a problem of public health, frequently occurred in men from European Union and USA. The incidence of prostate cancer also increased before the PSA screening and will continue to do so once the screening spreads in most of the countries and the life expectancy increases [3]. In localized prostate cancer, for low risk group, brachytherapy with transperineal permanent implant with I-125 sources, has become the third therapeutic option, together with the radical prostatectomy and conformal external radiotherapy. The 5 year biochemical control is equivalent, to the three therapeutic methods, but brachytherapy is associated with a better quality of life, in comparison with the other treatments [3,8]. This method was also accepted in Romania and beginning with October 2006 in the Oncology Institute “Prof. Dr. Alexandru Trestioreanu”, Bucharest and later in the Clinic Institute Fundeni, Bucharest, the first implant procedures were performed.

The implant advantages are: a shorter period of hospitalization of the patients speedy recovery of the patient with a relatively low toxicity [4,21].

Even if our study includes a small number of patients (32), with a short follow up period, 3 months only, we consider that it is worth presenting the first results regarding urinary and rectal morbidity, trying to establish correlation with some dosimetric and clinic parameters.

2. Materials and Methods

Our study includes 32 patients who have performed permanent implant with I-125, from October 2006 until March 2007, in the Oncology Institute “Prof. Dr. Alexandru Trestioreanu”, Bucharest and the Clinic Institute Fundeni, Bucharest.

For brachytherapy as monotherapy, was included only patients with prostate adenocarcinoma, stage T1c-T2b, PSA< 10ng/ml, and Gleason Score < 7, prostate volume < 60 cc, without TUR-P prior implantation, conform ESTRO and EORTC consensus [1,7].

For brachytherapy as combined therapy, was included patients with PSA values between 10 and 20 ng/ml, stage T2b-T2c or Gleason score = 7.

The exclusion criteria were, conform ESTRO and EORTC guidelines: locally advanced cancer or metastatic disease, prostate volume > 60 cc, contraindications for general anesthesia, recently TUR-P (under 6 mouths), hope of life lower than 5 years [1,7]

A bone scan was performed for all patients and it tested negative for secondary lesions in all cases. 16 patients (50%) have been given neo-adjuvant hormonal therapy, for 2-3 mouths, in order to reduce

the prostate volume but it hasn't been continued once the implant was done.

The implant was performed under general anesthesia; the patient placed in the lithotomy position, and under transrectal ultrasound control. A soft dosimetry program, PSID, was used for the implant; the dosimetry was made in real time and the working team was composed by an urologist, a radiation oncologist and a medical physicist. Interstrand sources, with mean activity 0.708 mCi/seed (range 0.612 – 0.729 mCi/seed) were used [6].

Implant procedures take between 2 and 4 hours, without problems and the patients were hospitalized between 24 and 72 hours.

In the first 5 to 7 days from the implant procedures, all patients received therapy with antibiotics - chinollones and alpha-blockers – tamsulosin, at least 2 months after implant.

The prescribed dose was 145 Gy for 30 patients, who undergo monotherapy, and 110 Gy for 2 patients who received combined therapy. For these 2 patients, external radiotherapy was performed in the Oncology Institute "Prof. Dr. Alexandru Trestioreanu", Bucharest, 6 weeks post-implant, the prescribed dose was 45 Gy, with 180 cGy/fr.

Patient characteristics

Mean age was 66.7 years (range 52 – 75 years). In our group, most of the patients were in stage T2a, representing 81.25%, in stage T2b and T2c, representing 3.13%, each stage. 93.75 % had Gleason score between 5 and 7; the PSA values between 5 – 10 ng/ml were recorded at 78.13% patients, and PSA values between 11 and 20 ng/ml were recorded at only 9.37% patients; clinical characteristics are indicated in table 1.

Table 1. *Clinical characteristics for implanted patients*

Variable	Number of patients
Disease stage	
T1c	4 (12.5)
T2a	26 (81.25)
T2b	1 (3.13)
T2c	1 (3.13)
Gleason score	
0 – 4	2 (6.25.)
5 – 7	30 (93.75)
8 – 10	0 (0)
PSA (ng/ml)	
0 - 4	4 (12.5)
5 -10	25 (78.13)
11 – 20	3 (9.37)
HT	16 (50)

Values in parentheses represent the percentages.

For each patient, the following parameters have been recorded: the prostate volume (established with transrectal ultrasound), the number of implanted sources, the number of needles used and the following values: D90 (minimum dose covering 90% of the prostate volume), V 100 (percent volume of prostate receiving at least 100% of the prescribed minimum peripheral dose), V 150 (percent volume of prostate receiving at lest 150% of the prescribed minimum peripheral dose), V 200 (percent volume of prostate receiving at lest 200% of the prescribed minimum peripheral dose), D1 to urethra (dose covering 1% from prostate urethra), D1 to rectal mucous (dose covering 1% from rectal mucous).

Before implantation, the patients didn't experience severe micturition problems.

Table 2 . *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. Dysuria, 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 hospitalisations or major surgery. Heamaturia requiring transfusion s. acute urinary retention not secundary to the pasage of clots. Necrosis or ulceration of the urethra.
Grade 5 – Fatal complicatins.

Table 3. *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 pain 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.

The follow up period lasted 3 mouths, the mean prostate volume was 35.44 cc (range 22 – 66 cc.), an average of 44 seeds (range 22 - 75) were implanted, an average of 17 needles (range 10 -30) were used. The total mean activity was 30.77 mCi.

The implant protocol

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

- D90 ≥ 180Gy ;
- V100 = 100% ;
- V150 < 30% ;
- D1 urethra: max. 216Gy ;
- D1 urethra < 230Gy (mono-therapy);
- D1 urethra <175Gy (combined therapy);
- D1 at rectal mucous = 145Gy.

3. Results

The urinary acute toxicity was scored according to the RTOG scale (table 2) and the rectal toxicity monitored the presence or absence of the rectal bleeding, rectal tenesmus and diarrhea [1] (table 3).

The information on rectal and urinary morbidity were recorded at the moment of the CT post implant, performed 6 weeks after procedure and

afterwards 3 months postimplant and with questionnaires. The 2 patients 6.25%, (from 32), presented small urinary bleeding when removing the catheter, no severe urinary bleeding was notice. No patient presented acute urinary retention after the bladder catheter removal that would require a suprapubic catheterization.

The 2 patients who received a combined therapy presented 2nd grade bowel toxicity, (nausea, diarrhea), solved with medication.

1 month post-implant, 46.88 % (15/32 patients) presented 1st grade urinary toxicity and 21.88% (7/32 patients) presented 2nd grade urinary toxicity (table 4).

3 months a decreasing of the 2nd grade urinary toxicity has been recorded from 21.88% to 12.5% (4/32 patients); these patients continued treatment with tamsulosin. No patient did record 3rd, 4th or 5th grade urinary toxicity (table 4).

We tried to establish a correlation between the urinary and rectal toxicity grade and the monitored dozimetric and clinic parameters: prostate volume, D90, needles number, D1 to urethra, D1 to rectal mucous (table 5, 6).

Regarding the prostate volume before implantation, patients who presented 2nd grade toxicity had a mean volume of 47.3 cc, a prostate volume greater in comparison with patients who presented 0 and 1st grade toxicity, who had a mean prostate volume 30.61 cc and 32.83 cc, respective, statistic significant correlated only for 2nd grade urinary toxicity, $p<0.05$, (table 5).

The monitored dozimetric parameter, D90 had in a mean value of 185.83 Gy, recording an increase urinary toxicity with D90 value > 180Gy.

Mean value D90 was 199.33 Gy ($p<0.05$) for patients with 2nd grade urinary toxicity in comparison with mean value D90 = 177.69 Gy ($p=0.32$) recorded for patients with urinary toxicity grade 0, and mean value D90 = 180.47 ($p=0.45$) for patients with 1st grade urinary toxicity. In our study, significant statistic correlation, $p< 0.05$, we found for 2nd grade urinary toxicity with mean D90 value, and no significant statistic correlation for 1st grade urinary toxicity with mean D90 value (table 5).

Another dozimetric parameter which we monitored was D1 to urethra and we observed a mean value D1 = 227.8 Gy for patients without urinary toxicity, D1 = 238 Gy for patients with 1st grade urinary toxicity and a mean value D1 = 252.94 Gy for patients who presented 2nd grade urinary toxicity, the increase of urinary toxicity being correlated with the dose delivered to urethra.

The calculation of the p values was based on bilateral significance test, for statistically significance, $p < 0.05$.

4. Discussions

The most important predictive factors for urinary toxicity are the prostate volume, prior-implant, the dose delivered to urethra, the presence of urinary obstructive symptoms secondary to the prostate benign hypertrophy, D90, TURP prior - brachytherapy and the rectal toxicity is correlated with the proportion of rectal mucous which receives a greater dose than 145 Gy [4,8,9,10].

In our study, we found that at one month, it is predominant a 1st grade urinary toxicity, in 46.88 % of cases (15 / 32), while a 2nd grade urinary toxicity has been recorded in 21.88% of cases. At three months we observed a decrease of 2nd grade urinary toxicity, at 12.5% of patients, results being almost the same with those published in studies on this subject [10].

Among the first data on acute and late toxicity after the I-125 implant, is the study of Grimm et al. [14] published in 1996.

This study mentions that, from a group of 310 patients, 90% presented 1st and 2nd grade urinary morbidity in the firsts 12 months after procedure; 3rd grade toxicity was observed in 8% of patients and a 4th grade toxicity occurred in 1.5 % of cases. The authors, also, reported an incontinence rate varying between 6 and 48 % of cases, among patients with TUR-P prior brachytherapy [14].

Table 4. *Urinary toxicity grade according with RTOG scale*

	1 month toxicity	**3 months toxicity**
Urinary toxicity grade (according to RTOG scale)	**No. of patients**	**No. of patients**
Grade 0	10 (31.25)	19 (59.38)
Grade 1	15 (46.88)	9 (28.13)
Grade 2	7 (21.88)	4 (12.5)
Grade 3	0 (0)	0 (0)

Table 5. *Correlation between urinary toxicity grade and clinic and dosimetric parameters*

Parameters	**No. total patients n= 32**	**Toxicity grade 0 n=10**	**Toxicity grade 1 n=15**	**Toxicity grade 2 n=7**
Mean age at the moment of implant	66.7	67.2	67.47	64.64
Mean prostate volume(cc)	36.91	30.61 p=0.25 (95% CI = 21.6-40.04)	32.83 p=0.79 (95% CI = 26.78-42.2)	47.30 p=0.02 (95% CI = 36.02-58.57)
Mean needles number	16.85	14.4 p=0.94 (95% CI = 11.61-17.19)	17 p=0.38 (95% CI = 14.72-19.28)	19.14 p=0.07 (95% CI = 15.8-22.48)
D90 (Gy)	185.83	177.69 p=0.32 (95% CI = 165.14-190.24)	180.47 p=0.45 (95% CI = 170.22-190.72)	199.33 p=0.01 (95% CI = 184.33-214.33)
D1 urethra (Gy)	238.13	227.88 p=0.31 (95% CI = 205.33-250.43)	238.07 p=0.99 (95% CI = 219.65-256.49)	252.94 p=0.2 (95% CI = 225.98-279.9)

Table 6 . *Correlation between rectal toxicity grade and dosimetric parameters*

Parameters	**No. total patients n= 32**	**Toxicity grade 0 n=10**	**Toxicity grade 1 n=15**	**Toxicity grade 2 n=7**
D1 rectal mucous (Gy)	124.88	126.96 p= 0.98; (95% CI = 103.7-150.19)	131.58 p= 0.61; (95% CI = 112.59-150.57)	116.09 p= 0.38; (95% CI =89.01-143.17)

Also regarding the acute urinary toxicity, Zelefski et. al [20] find a 2nd and 3rd grade toxicity in 40% and 9% of cases, respective. Stokes et. al [19] in 19% and respective 4% of cases and Blasko in 15% and respective 17 % of patients [15]. Urinary symptoms occur in the IInd – IIIrd week after the seeds implant and reach the maximum intensity between first and second month post-implant, according some authors, and after three – four mouths post – implant, according to the other studies [21].

Another study published in 2000 by Brown et. al, effectuated on a 87 patient group, the maximum intensity occurs at 3-4 months post-implant with a gradual decrease of the urinary symptoms during first 12 mouths [16], yet Klienberg et. al mentioned that urinary toxicity can maintain even longer than one year post-implant [12].

We interpret the absence of acute urinary retention by reducing the implanted prostate volume with neo-adjuvant hormonal – therapy, and with a careful selection of patients and also with a continuos developing and improvement of the dozimetric and implantation techniques [5,7,11,13].

The rate of urinary retention is mentioned in studies having values between 4 and 13%, and the risk of developing it is strongly correlated with pre-implant prostate volume and with the number of implanted needles.

Another predictive factor of urinary morbidity, especially for late morbidity, is the dose delivered near urethra, Stokes et. al, [19] showing a decrease of the 2nd grade urinary toxicity, from 42% to 19% cases, by reducing the peri-urethra dose, which can be done by putting seeds with half of activity around the urethra [18].

The presence of 2nd grade rectal toxicity, to the only 2 patients who underwent combined treatment, brachytherapy + external beam therapy, can be interpreted by respecting of rectal mucous dose [2].

5.Conclusions

Brachytherapy by I-125 permanent implant represents an alternative to external radiotherapy and to radical prostatectomy, in localized prostate cancer; it is a well tolerated treatment by patients, with a low urinary morbidity, in most of the 1st and 2nd grade cases correlated with the prostate volume before the implant's moment, with the number of needles, and dose delivered to the urethra [10,16,17]. Because in permanent implant with I-125 it is necessary one year for delivering total dose, it is necessary a long follow up period for urinary and rectal toxicity recording, knowing that this kind of morbidity can occur at many years post-implant [4].

Following studies at 6, 9, 12, 18 months will bring more information regarding this procedure.

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