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THE PSA KINETICS ANALYSIS AFTER PERMANENT IMPLANT FOR PATIENTS WITH LOCALISED PROSTATE CANCER

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ABSTRACT

The PSA kinetics is different after radical prostatectomy and after external beam radiotherapy in the folowing way: following radical prostatectomy, PSA should fall to an undetectable level, reaching the PSA nadir in a few weeks; after external beam radiotherapy and after brachytherapy, the PSA values had a constant and gradual decrease during few months even years until the nadir is reached. This study analyse the PSA kinetics for 129 patients with localised prostate cancer treated with I-125 permanent interstitial implantation between October 2006 and January 2010, in the Institute "Prof. Dr. A. Trestioreanu" and Clinical Institute Fundeni, Bucharest. The median follow up was 32 month (range: 18-45 months); we analysed the PSA decreasing, the bounce phenomenon and the biochemical failure. In this study we consider the ASTRO consensual definition for the biochemical relapse: three consecutive rises of the PSA value with at least 3 months between determinations.

KEYWORDS*: brachytherapy low dose rate, prostate cancer, kinetincs PSA, PSA bounce, biochemical control.*

1.Introduction

The aim of the study is to analyse the PSA dynamic after I-125 permanent implant in localised prostate cancer.

2. Materials and methods

Between October 2006 and January 2010, 129 patients with biopsy-proven adenocarcinoma of the prostate were treated with I-125 permanent interstitial implantation using a transrectal ultrasound-guided approach in Institute "Prof. Dr. A. Trestioreanu" and Clinical Institute Fundeni, Bucharest. Patients underwent prostate implantation using a real-time intraoperative-planned approach.

From those 129 patients, 110 (85.27%) effectuated brachytherapy as monotherapy and 19 (9.43%) performed combined treatment (brachytherapy and external beam radiotherapy, BT+EBRT). EBRT was made at 4-6 weeks postimplant at the Oncological Institute "Prof. Dr. A. Trestioreanu", with linear accelerator with 15 MeV photons, using the „box" technique on target volume

which involves the prostate and the seminal vesicals. The prescribed dose was 45Gy/25 fr./5 weeks, dose/fraction = 180cGy. The patient characteristics are shown in Table 1. Prostate volume measurements referred to in this report were made at the time of the implantation procedure.

The mean age at implantation was 64.89 years (range 46-83 years). PSA<10ng/ml had 84.5% of patients, only one patient had PSA>20ng/ml, 6.2% of patients had PSA between 11 and 20ng/ml. 88.18% of monotherapy patients and 63.16% of combined therapy patients had PSA<10ng/ml.

Table 1. *Clinical characteristics*

	Patient's total number n=129	**Monoterapy patients n=110 (85.27%)**	**Combined therapy patients n=19 (9.43%)**
Mean age (years) (range)	64,89 (46-83)	66,19 (49-83)	64,31 (46-78)
PSA (ng/ml)			
<10	109 (84,5%)	97 (88,18%)	12 (63,16%)
=10	11 (8,5%)	8 (7,27%)	3 (15,79%)
11÷20	8 (6,2%)	5 (4,55%)	3 (15,79%)
>20	1 (0,78%)	0	1 (5,26%)
T-stage			
T1c	48 (37,2%)	45 (40,91%)	3 (15,79%)
T2a	79 (61,24%)	65 (59,09%)	14 (73,64%)
T2b	1 (0,78%)	0	1 (5,26%)
T2c	1 (0,78%)	0	1 (5,26%)
Gleason score			
2-6	120 (93%)	104 (94,55%)	16 (84,21%)
7	7 (5,4%)	5 (4,55%)	2 (10,53%)
8-9	2 (1,6%)	1 (0,91%)	1 (5,26%)
Mean prostate volume (cc) (range)	29,4 (10,1-63,07)	33,93 (10,1-63,07)	32,53 (17,29-50)

Table 2. Real – time dozimetric parameters

Parameter	**Patient's total number n=129**	**Monoterapy patients n=110 (85.27%)**	**Combined therapy patients n=19 (9.43%)**	p
V100 (%)	99,27 (94,3-100)	99,42 (95,4-100)	98,19 (94,3-100)	<0,001
V150 (%)	74,29 (43-96,4)	74,31 (43-96.4)	74,12 (54,5-94,6)	0,93
V200 (%)	39,04 (16,7-71)	38,64 (16,7-69,1)	41,86 (23,3-71)	0,28
D90 (Gy)	187,81 (137-234)	189,91 (142,1-234)	172,43 (137-206,4)	<0,001
DU1 (Gy)	228,44 (156-309,8)	230,26 (174-309,8)	214,79 (156-264)	0,02
DU3 (Gy)	220,03 (138,3-289,4)	221,62 (138,3-289,4)	208,17 (153,5-258)	0,04
DU10 (Gy)	159,68 (84,97-237,12)	161,85 (89,57-237,12)	144,37 (84,97-202,9)	0,035
DU30 (Gy)	163,68 (102,75-254,9)	166,24 (107,35-254,9)	145,63 (102,75-179,9)	0,002
DU50 (Gy)	135,98 (61,27-213,42)	138,09 (65,87-213,42)	121,08 (61,27-182,7)	0,04
D1MR (Gy)	109,15 (33,7-209)	109,32 (43-209)	107,93 (33,7-192)	0,87
D3MR (Gy)	104,85 (41-197)	103,93 (41-197)	111,31 (41-185,6)	0,302

Where: **V100** = percent of prostate volume who receive 100% of prescribe dose, **V150** = percent of prostate volume who receive 150% of prescribe dose, **V200** = percent of prostate volume who receive 200% of prescribe dose, **D90** = dose who recover 90% of prostate volume, **DU1** = dose recovering 1% of urethra volume, **DU3** = dose recovering 3% of urethra volume, **DU10** = dose recovering 10% of urethra volume, **DU30** = dose recovering 30% of urethra volume, **DU50** = dose recovering 50% of urethra volume, **DMR1** = dose recovering 1% of rectal mucous, **DMR3** = dose recovering 3% of rectal mucous

Regarding T-stage, 37.2% of cases were in T1c, 61.24% in T2aN0M0. In T2b and T2c, respectivley was one patient each, who made combined therapy. Gleason score < 6 had 93% of cases, 2 patients had Gleason score > 8, and 5.4% had Gleason 7. The mean prostate volume was 29.4cc; in the monotherapy and combined therapy subgroup, respectivley, the mean prostate volume was 33.93 cc and 32.53cc, respectivley.

3. Results

The median follow up was 32 month (range: 18-45 months).

In accordance with ASTRO (American Society for Therapeutic Radiology and Oncology) 1997 definition [1] the biochemical failure consists of three consecutive rises of the PSA value with at least 3 months between determinations. We don’t consider as having biochemical relapse the patients with bounce phenomenon (defined as a temporary rise of PSA followed by a consecutive decrease at the same or below the nadir PSA value recorded before the bounce phenomenon [2]. The date of the failure being considered the midst of the interval between the last PSA value and the first PSA value increase. In this study we consider the ASTRO consensual definition for the biochemical relapse.

Repeating the prostate biopsy after irradiation is not recommended and it is not necessary as a standard procedure after implant [3].

The clinical relapse is defined also as distance recurrence manifested with the presence of bone metastasis or local failure defined with postive biopsy or digital rectal examination, also positive.

The PSA monitoring after permanent treatment increases the early detection of the treatment failure.

In order to ASTRO definition being more an accurate in the local control representation is need for a long follow-up period, for the nadir indentification for each case and, also, to make the differences between PSA bounce and biochemical failure.

In our study, the PSA value was recorded at each 3 months, in the first year and at 6 months afterwards. We observed a continuosly deacrease of PSA values.

The mean preimplant PSA values were 8,4 ng/ml and respective 9,68 ng/ml for monotherapy and combined therapy patients, respective.

The PSA decrease at 3 months was by 79,76% and respective by 79,96% of initial preimplant PSA value, for monotherapy and combined therapy patients, respective. The PSA values were 1,7ng/ml in monotherapy group and 1.94 ng/ml in combined therapy group.

At 6,9 and 12 months, the PSA values for monotherapy patients were 1.09, 0.92 and respective 1.2ng/ml. We observed the same gradual decrease also for the BT+RTE patients recording 1,26, 1,06 și 1,31 ng/ml at 6, 9 and respective 12 months.

The PSA kinetics was comparable for the both of sublots of patients, at 12 months, recording a deacrease of 85.71% vs. 86.47% for monotherapy group vs. combined therapy, for the patients who manifested the bounce PSA phenomenon.

For the patients who did not manifested the bounce PSA phenomenon, the PSA value, at 12 months decreases with 90,9% and 89% at monotherapy gruop vs. combined therapy group.

The bounce phenomenon was recorded at 15 patients (11.63%), 9 patients (7.44%) with ages < 65 years (mean 59 years) and 6 patients (4.96%) from age groupe >65 years (mean 67 years). The PSA bounce has been manifested begining with 12 months postimplant, recording for monotherapy patients, the following mean values of PSA: 1.2, 1.4, 1.5, 1.57, 1,47 and respective 1,09 ng/ml at 12, 18, 24, 30, 36 and respective, 40 months postimplant. The highest PSA value during the bounce was 6ng/ml.

For combined therapy patients who manifested the bounce phenomenon, the mean PSA values at 12, 18, 24, 30, 36 and respective 40 months postimplant were 1.31, 1.36, 1.53, 1.55, 1.49 and respective 1,1 ng/ml. The mean bounce magnitude was 1.09ng/ml being ranging between 0.2-6ng/ml. The mean period of time of the bounce phenomenon was 18 luni postimplant. One patient presented the bounce phenomenon, at the time of this study (it is posibil to be bounce or relapse).

The mean PSA value at 12 months, for monotherapy patients who had bounce was 0,76ng/ml. For the patients who did not manifested the PSA bounce from combined therapy sublot, the mean PSA value was 0.87ng/ml.

The mean PSA values at 18, 24, 30, 36 and respective 40 months postimplant for the monotherapy patients and who did not manifested the PSA bounce, were 0.63, 0.57, 0.5, 0.36 şi respectiv 0.3 ng/ml. For the patients who did not manifested the PSA bounce from combined therapy sublot, the mean PSA values were 0.8, 0.7, 0.6, 0.39, respective 0.31ng/ml at 18, 24, 30, 36 and respective 40 months postimplant (table 3). In our study the PSA nadir 0.2ng/ml was reached for 61% of cases. The patients with a follow-up period smaller than 5 years and who did not reach the PSA nadir value of 0.2ng/ml, were considered free of disease even if they did not reach the nadir of 0.2 ng/ml, but they did not presented more than two rises of PSA values from the last monitoring.

Table 3. *The PSA dinamics*

	The moment of monitoring PSA	**Mean PSA (ng/ml) BT-monotherapy**		**Mean PSA (ng/ml) BT+RTE**	
		with bounce	without bounce	with bounce	without bounce
	Preimplant	8,4	8,3	9,68	9,69
Post implant	3 months	1,7	1,7	1,96	1,94
	6 months	1,09	1,09	1,26	1,28
	9 months	0,92	0,92	1,06	1,06
	12 months	1,2	0,76	1,31	0,87
	18 months	1,4	*0,63*	1,36	*0,8*
	24 months	1,5	*0,57*	1,53	*0,7*
	30 months	1,57	*0,5*	1,55	*0,6*
	36 months	1,47	*0,36*	1,49	*0,39*
	40 months	1,09	*0,3*	1,1	*0,31*

Table 4. *The clinical and dosimetrical postplan characteristics for biochemical relapse patients*

	The treatment effectuated	**Initial PSA (ng/ml)**	**PSA at the biochemical relapse (ng/ml)**	**Gleason Score**	**Stage**	**Postplan D90 (Gy)**	**The moment of relapse (months postimplant)**
Patient no. 1	BT - monotherapy	10	8.9	6	T2a	172,9	30
Patient no 2.	BT - monotherapy	10	9.05	6	T2a	157,6	24
Patient no. 3	BT - monotherapy	8	5.8	7	T2a	160,6	26
Patient no. 4	BT +RTE	12,68	11.7	9	T2a	154,6	15

We had recorded 4 cases (3.1%) of biochemical failure at 15, 24, 26 and 30 luni postimplant. Three patients were from monotherapy group and 1 patient from combined therapy group.

Regarding group of risk, 2 patients with biochemical relapse were in low risk group, 1 patient in intermediary risk and 1 patient in high risk group.

The PSA values for biochemical relapsing patients were between 5,8 and 11,7 ng/ml.

ll patients with biochemical relapse had CT abdomino-pelvin, NMR or bone-scan; this investigations did not evidenced local or distance relapse.

Repeating the prostate biopsy to confirm the local recurrence was put in discussion for 2 patients (patient no.1 and no.2), but they refused it.

The 4th case with biochemical failure belongs to high risk groupe and performed combined therapy, because of high PSA of 11,7ng/ml (table 4), having a PSA doubling time < 12 months, meaning unfavorable risk factors for distance disease recurence; for this case, the Oncological Committee decided the initiation of the hormonal treatment with LH-RH analogs; even if at that moment we were't able to indicate the recurence's situs, the imagistic tests were in normal limits.

The Oncological Committee decided the beginning of the hormonal treatment with LH-RH analogs also for the other 2 patients.

The 3rd case with biochemical failure belongs to intermediary risk group and at the end of the study had to repeat the prostate biopsy; this patient is still in follow-up without the treatment initiation until the establishment of the recurrence site.

Recording the biochemical relapse even at low risk patients can be explained with a low quality of implant but we consider that our implants had a good quality, taking in to consideration the postimplant D90 values >140Gy; or the biochemical relapse can be explained, conform Partin's tables who note that, even for the favorable risk patients, it is a very low risk to be affected seminal vesicals or limfnodes, risk which is estimated to be at 2 and respectiv 1%.

The most important predictive factors for biochemical control are Gleason score, initial PSA, T-stage and D90 value.

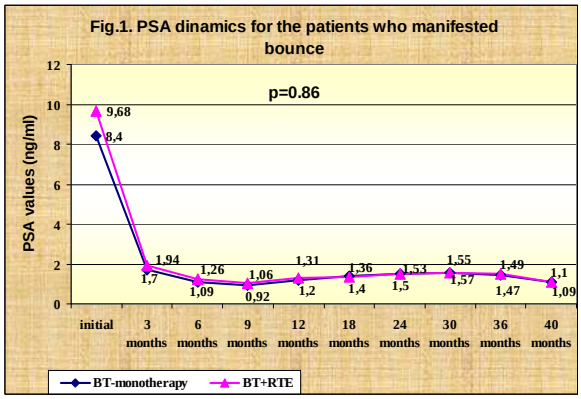

Figure 1. *PSA dinamics for the patients who manifested bounce*

The PSA dynamic was comparable for the both sublots, monotherapy vs. combined therapy, the statistical analyses did not indentify significant differences, p=0.86 (figure1)

We analysed in comparative mode, the PSA dinamic for the patients who manifested bounce vs. patients who did not manifested bounce and we observed that until the moment of bounce phenomenon beginning, the PSA decrease was similar, with out significant differences in the monotherapy lot and also in the combined therapy group (p=0,99 respective p=0,99), (figures 2 and 3).

Once the PSA bounce phenomenon was instaled and were recorded the higher PSA values, the differences in PSA dinamics were evident and statistic significant for the patients who manifested this phenomenon and vs. patients who did not manifest PSA bounce (p<0.0001), (figures 2 and 3).

If, for the patients without PSA bounce, the PSA values had a continous decrease, for the patients who manifest this phenomenon, the PSA values

presented a temporary increase and after that decreased at comparable values with those from 9 or 6 months postimplant.

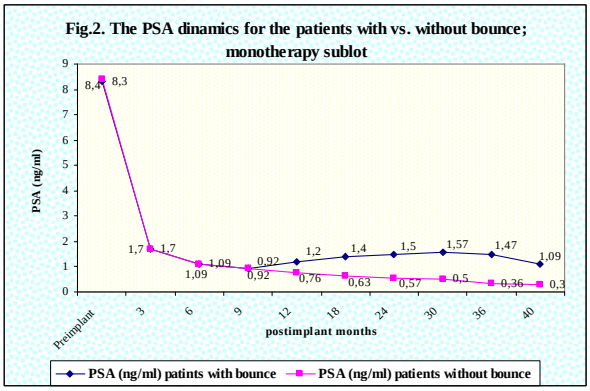

Figure 2. *The PSA dinamics for the patients with vs without bounce monotherapy sublot.*

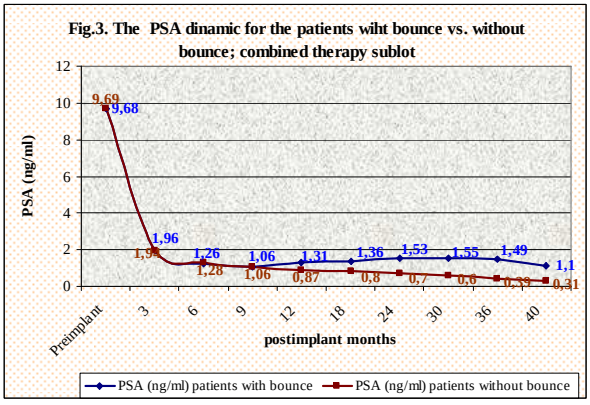

Figure 3. *The PSA dinamics for the patients with vs without bounce ; combined therapy sublot.*

4. Discussion

The PSA kinetics is different after radical prostatectomy and after external beam radiotherapy in the following way: after radical prostatectomy, PSA should fall to an undetectable level, reaching the PSA nadir in a few weeks; after external beam radiotherapy and after brachytherapy, the PSA values had a constant and gradual decrease during few months even years until the nadir is reached.

In our study, we observed that in the first 3 months after procedure it was recorded the most important PSA decrease being of 79,76% and respective 79,96% of initial preimplant PSA value for the monotherapy and combined therapy group, respective.

Even if the initial PSA mean value was higher in combined treatment lot, the PSA kinetics was comparable in the both groups, at 12 months PSA had a level of 90,9% and 89% of initial value, for montherapy and respectiv, combined treatment patients.

After treatment, the PSA value fall very rapid in the first 3 months after implant and gradual until 24 months, 51% of patients reaching the nadir of 0.5 ng/ml or less. Critz et al. [4] indicate that 77% of patients having combined therapy, reached the PSA 0,5ng/ml or less, in the first 5 years from implant. This observation is sustained by Stone and Stock's studies [5], which note that are necessary almost 4-5 years for reaching the PSA nadir.

In our study the PSA bounce was presented at 11,63% of patients, a smaller procent comparative to literature data, which can be explained by the medium follow-up period of our patients. This phenomenon was recorded between 12 and 36 months postimplant. The moment of PSA bounce is correlated with the moment of proctitis and erectile disfunction development. The PSA bounce is decribed in Critz's studies having a frequency of 45%, occurs between 12 and 24 months postimplant but was mentioned even at 1% of patients at 5 years after implantation. Darren et al. [6] mention in a study that this phenomenon can occurs even from 1,7 months postimplant until 40,6 months, mean of 14 months, and can last 12 months. The timing of PSA bounce apparition is different from the moment of biochemical relapse; in general the bounce phenomenon occurs at a mean of 14 months postimplant compared with a mean of 20,8 months

and 28 months for ASTRO Phoenix biochemical failure definition.

In this study, 9 and respective 6 of patients who manifested PSA bounce, had mean age of 59 years and respective 67 years. The PSA bounce phenomenon can produce confusions in patient’s gruping with bounce or with biochemical failure [6].

The PSA recurrence definition after radiotherapy was highly debated and in 1997 ASTRO combined a Committee for the recurence PSA postradiotheapy criteria establishment.

The Committee agreed that the biochemical failure is not equivalent with clinical failure and does not represent a reason for the treatmnet initiation.

Conform ASTRO and the PSA followup guide after radiotherapy, these does not recomand repeating prostate biopsy as standard after radiotherapy, and the absence of PSA growing after treatment is the best indicator of local control after treatment [7].

The clinical significance of biochemical recurence is not very obvious, some patients can develop local or distance recurrence and other patients can live many years without any significant risk of local recurrence. This phenomenon show us that the natural history of biochemical recurence is hard to predict. Much more, it was demonstrated that can pass 8 years from the increasing of PSA until we can clinicaly detect the metastatic disease [8]. Some times is difficult to identify the site of disease recurrence for patients with high levels of PSA after radiotherapy. The local recurrence is define as an increased PSA level in conjunction with a positive biopsy made at least at 18 months after the end of EBRT [9].

The patients with biochemical relapse may not present rapid progression of disease. The identification of high risk patients can allow a specific therapeutically decision. The PSA doubling time (PSA-DT), the PSA kinetics can allow the identification of recurrence site and so, the optimal therapeutically strategy.

The PSA dynamic, more precisely, the PSA doubling time define the tumor’s behavior. PSA-DT can predict the prostate cancer diagnosis with few years before and also the prostate cancer death after biochemical failure, after curative treatment. PSA-DT short, <12 months, represents the most important predictive factor of prostate cancer death. PSA-DT < 12 months in conjunction with PSA nadir >2ng/m can be used as an indication for the moment of androgenic deprivation therapy initiation.

Taking into consideration the literature data, we decide for the patient with PSA=11,7ng/ml and PSA-DT< 12 months, to initiate early hormonal therapy

5. Conclusions

The PSA kinetics is different after radical prostatectomy and after external beam radiotherapy.

In our study the PSA kinetics was comparable for the both of sublots of patients. The most evident decrease of PSA values was in the firsts 3 months postimplant, followed by a gradual and constant decrease. The PSA nadir 0.2ng/ml was reached for 61% of cases. The PSA bounce phnomenon was recorded at 11.63% of patients, in a smaller percent regarding literature data. 3.1% of patients manifested biochemical failure.

This is a study with a median follow-up period has limits especially in the PSA nadir follow-up, taking into consideration that, after some authors, are necessary 4-5 years for the nadir PSA being reached. The further studies will bring more information about the reaching of PSA nadir, and also about the PSA relapse free survival and disease specific survival (DSS) at 5 and at 10 years after permanent implant.

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