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A CLINICAL STUDY OF CARCINOMA PROSTATE CASES WITH SPECIAL REFERENCE TO SERUM PSA LEVEL IN PRE AND POST ORCHIDECTOMY / ANTIANDROGEN THERAPY

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ABSTRACT

INTRODUCTION: Carcinoma of prostate is the most common malignant tumour in men over the age of 65 yrs. The lifetime risk of 50 year old man for latent carcinoma prostate is 40%, clinically apparent carcinoma prostate 9.5%, and death from carcinoma prostate 2.9%. We evaluated the serum PSA level in carcinoma prostate patient managed by the endocrine treatment (orchidectomy) or antiandrogen therapy), pre and post treatment (less than and more than 3 month).

MATERIAL AND METHODS: This study was conducted in 35 patients of carcinoma prostate by hormonal treatment (Orchidectomy and/or Antiandrogen therapy). All patients were scored before operation (using the AUA score). Serum PSA level of all the 35 patients was measured before orchidectomy and/or anti androgen therapy. It was planned to measure PSA level in all cases of post orchidectomy and/or anti androgen therapy but only 25 patients came in follow-up, whose PSA levels were taken.

RESULT : In our study, most of the cases of carcinoma prostate patient were in the age group 50-60 yrs i.e. 34.28% followed by 71-80 years i.e. 31.42%. All the cases of carcinoma prostate had complaint of sensation of incomplete emptying of bladder, weak urinary stream and hesitancy. PSA level was found >100 ng/ml in 16 cases i.e. 45.71%. 97% or greater decrement in PSA within 6 months of initiating therapy.

CONCLUSION: Serial PSA level estimation distinguishes favourable from non-favourable responders early within the course of therapy and greatly assist in the monitoring for progression.

KEYWORDS

PSA Level, Carcinoma Prostate, Orchidectomy, Antiandrogen

INTRODUCTION

Carcinoma of prostate is the most common malignant tumour in men over the age of 65 yrs. About 10-15% of younger men who develop prostate cancer have a positive family history of disease but the aetiology is unclear. Carcinoma prostate usually originates in the peripheral zone of prostate. Prostate cancer is the most common cancer diagnosed and is the second leading cause of cancer death in American men. Incidence of carcinoma prostate continues to increase with advancing age. Prostate cancer is predominantly a disease of elderly man with more than 75% of new prostate cancer being diagnosed in men older than 65 year. The lifetime risk of 50 year old man for latent carcinoma prostate is 40%, clinically apparent carcinoma prostate 9.5%, and death from carcinoma prostate 2.9%.

The probability of carcinoma prostate developing in a man under the age of 40 is 1 in 10,000, for men 40-59 it is 1 in 103 and for men 60-79 it in 1 in 8.

The following types of prostate cancer occur:

- Microscopic latent cancer found on autopsy or at cystoprostatec tomy.
- Tumours found incidentally during TURP [T_{1a} and T_{1b}] or following screening by PSA measurement [T_{1c}]
- Early, localised prostate cancer [T_2]
- Advanced local prostate cancer [$T_3 - T_4$]
- Metastatic disease which may arise from a clinically evident tumour [T_2, T_3, or T_4] or which may arise from an apparently benign gland [T_0, T_1] i.e. occult prostate cancer.

A positive family history of carcinoma prostate also increases the relative risk for carcinoma prostate. Several risk factors for prostate cancer have been identified. If the age of onset is 70, the relative risk is increased 4 fold. If age of onset is 60, the relative risk is increased 5-fold. If age of onset is 50, the relative risk is increased 7- fold. High dietary fat intake increases the relative risk for carcinoma prostate by almost a twice. Another exposer that may increase the risk for carcinoma prostate involves cadmium, which is found in cigarette smoke, alkaline batteries and in the welding industry.

Screening

The cancer detection rate, using measurement of PSA is between 2-4% and approximately 30% of men with elevated PSA will have prostate cancer confirmed by biopsy. 20% of men with clinically significant prostate cancer will have PSA value with the normal range (Russell et al, 2004)[1].

Age adjusted reference range for PSA

Value for	
Age (Years)	PSA Normal Ranges (ng/ml)
40-49	0-2.5
50-59	0-3.5
60-69	0-4.5
70-79	0-6.5

PSA is single-chain glycoprotein that contains 93% amino acid and 7% carbohydrate (Chu et al 1989)[2]. Normally, PSA is secreted into the lumina of prostatic ducts and is present in seminal plasma at rather high concentration. In seminal fluid PSA is involved directly in liquefaction of seminal coagulation that is formed at ejaculation (Lilja et al 1985)[3].

It may be that a longer period is necessary for effect of the prostatic examination to have its true influence on serum PSA concentrations, 1.92 fold increases in post-rectal examination serum PSA level (Stamey et al 1989)[4].

Cystoscopic examination was observed to cause a 4-fold increase in serum PSA level, and needle core biopsy of prostate produced a 57-fold elevation in PSA level over the pre-biopsy value (Stamey et al 1987)[5]. Transrectal USG alone have a minimal effect on serum PSA value.

Transurethral resection of prostate (TURP) for benign disease causes a 53-fold increase in the immediate postoperative serum PSA level (Stamey et al 1989)[4].

Exact effect of urethral catheterization or ejaculation on serum concentration has not been investigated. It is ideal to wait approximately 2 weeks before attempting to measure reliable serum level.

The two most commonly used assays in the United States are

Tandem - R PSA
Pros – Check - PSA assay

Both assays are reliable and accurate for determining the concentration of PSA in human serum.

Tandem - EPSA Assay - Like its isotopic counterpart Tandem–R PSA, Tandem–EPSA is solid phase, 2 – site immunometric assay that uses the same 2 mussive monoclonal antibodies. Instead of using a radioactive – labelled antibody, Tandem-EPSA has an enzyme, alkaline phosphatase, attached to the unbound antibody that is used to measure the serum PSA concentration.

PSA bound to -1 antichyrotryesin may have 3 of its 5 epitoxes masked. Prostate cancer patient demonstrate a lower % of free PSA than do patient with benign disease. Men with a normal digital rectal examination (DRE) and total PSA level between 4 – 10 ng/ml, a 25% free PSA cut off would detect 95% of cancer while avoiding 20% of unnecessary biopsies.

Treatment:-

Small volume, stage T_{1C} who are good candidate for conservative management i.e. watchful waiting (Carter et al, 1997)[6]. Yearly surveillance biopsies and twice-yearly DRE and PSA screening performed. Patient with local but clinically significant disease (i.e. high grade or large volume disease) require intervention as long as they have life expectancies of greater than 10 years. The two conventional mode of therapy are radiation and surgery. Radiation therapy – external beam radiation most commonly used (Horwitz & Hanlon et al, 1998)[7].

Surgical treatment of local prostate cancer is most commonly performed as an anatomical radical retropublic prostatectomy (Walsh et al, 1994)[8].

Neoadjuvant therapy with hormonal ablation has been gaining widespread use in both radiation therapy and surgical therapy. Success with conventional external beam conformal radiation may be augmented by pre-treatment with hormone based therapy.

In locally advanced disease (T_3) adjuvant therapy with external beam radiation may also play a role in preventing or delaying biochemical progression and cancer progression (Cheng et al, 1993)[9].

Suppression of testicular androgen has been cornerstone of treatment for advanced prostatic cancer. It has been achieved with surgical castration (orchiectomy), estrogen and leuteinizing hormone releasing hormone agonists.

Surgical or chemical adrenalectomy as a second line treatment in relapsing castrated patients, has been used to obtain total androgen ablation. The simultaneous removal of all active androgen through combination of an antiandrogen with surgical or chemical castration as first hormonal treatment of advanced prostatic cancer.

The first double-blind trial of orchiectomy plus a nonsteroidal antiandrogen versus orchiectomy plus a placebo showed a significant beneficial effect of the combination treatment as judged by best objective response (Janknegt and Abbou et al, 1993)[10].

Bilateral surgical orchiectomy replaced daily administration of subcutaneous leuprolide acetate. Recently, bilateral total orchiectomy (BTO) has seldom been selected because of patients' aversion to an empty scrotum (Melton et al, 2001)[11].

Various surgical procedure have been designed to preserve palpable testes. These have included subcapsular orchiectomy, subcapsular orchiectomy with eversion of tunica albuginea about the epididymis, implantation of testicular prostheses, subepididymal orchiectomy and orchiectomy in combination with a fibrofatty graft to tunica vaginalis (Glenn et al 1990[12], Kihara and Oshima 1998[13]).

In SCOT (subcapsular orchiectomy) I procedure, the TVG (tunica vaginalis pedicle graft) was secured to inner wall of the turnica albuginea.

In SCOT II procedure, the TVG was folded and secured to the external wall of turnica albuginea. The SCOT I & II procedure preserved 43-63% of preoperative testicular area, achieved castrate level of total testosterone and maintained life satisfaction.

Serum PSA is the most useful tumour marker in clinical practice for diagnosis, staging and monitoring of prostate cancer. Prostate cancer initiation and progression are influenced by androgen. Prostate tumours are exquisitely sensitive to androgen and regress after medical or surgical castration.

Various definition of nadirs under endocrine treatment after 3 to 6 months and various definitions of PSA progression have been used to evaluate the role of PSA as a predictor of outcome.

Surgical castration is considered the "gold standard" of endocrine treatment of advanced prostate cancer and is an efficient and low cost treatment.

In this clinical study we are evaluating the serum PSA level in carcinoma prostate patient managed by the endocrine treatment (orchidectomy) or antiandrogen therapy), pre and post treatment (less than and more than 3 month).

AIMS AND OBJECTIVES

- To assess the pretreatment PSA level in carcinoma prostate patients.
- To assess the effectiveness of endocrine treatment i.e. orchidectomy and/ or antiandrogen therapy on the serum PSA level in carcinoma prostate patients and thereby distinguish favourable from non favourable responders and thus monitoring the progression of disease.

MATERIAL AND METHODS

This study was conducted in 35 patients of carcinoma prostate admitted in various surgical wards of M.B. General Hospital, Udaipur and managed by Hormonal treatment (Orchidectomy and/or Antiandrogen therapy). The cases included in this study were on antiandrogen therapy and/or orchidectomy was done previously. The antiandrogen therapy was given in the form of flutamide 250 mg thrice a day in all cases except two cases out of them, one case tablet Honvan 120mg thrice a day was given and in the remaining case tablet Bicalutamide 50mg once a day was given.

Patients were evaluated by taking detailed clinical history, with special reference to the age of patients and duration of symptoms and particularly related to urinary tract, physical and local examination was done as per the proforma.

Special Investigations

PSA (prostate specific antigen)-

- pre operative (b/l orchidectomy)/pre drug therapy
- less than 1 month (b/l orchidectomy)/post drug therapy
- 1 to 3 month (b/l orchidectomy)/post drug therapy
- more than 3 month (b/l orchidectomy)/post drug therapy

All patients were scored before operation (using the AUA score). Serum PSA level of all the 35 patients was measured before orchidectomy and/or anti androgen therapy. It was planned to measure PSA level in all cases of post orchidectomy and/or anti androgen therapy but only 25 patients came in follow-up, whose PSA levels were taken.

RESULTS

Table I AGE Group in Cases of Carcinoma Prostate

Age in Years	No. of Patient (N=35)	Percentage
< 50	Nil	0
50-60	12	34.28
61-70	7	20
71-80	11	31.42
>80	5	14.28

Most of the case were between 50-60 years age group followed by 71-80, 61-70 & >80 years respectively.

Table 2: Showing Complaints Of the Patients of Carcinoma Prostate

S. No.	Complaints	No.	%	Duration					
				<1 Month		1-2 Month		>2 Month	
				No.	%	No.	%	No.	%

1	Sensation of incomplete emptying of urinary bladder	35	100	2	5.71	18	51.42	15	42.85
2	Frequency	33	94.29	8	24.24	21	63.64	5	15.15
3	Intermittency	33	94.29	2	6.06	21	63.64	9	27.27
4	Urgency	32	91.43	8	25.00	21	65.63	3	9.38
5	Weak urinary stream	35	100	3	8.57	22	62.86	9	25.71
6	Hesitancy	35	100	3	8.57	22	62.86	10	28.57
7	Nocturia	33	94.29	8	24.24	23	69.70	2	6.06
8	Other symptoms Hematuria	6	17.14	2	33.33		0.00	4	66.67
9	Dysuria	29	82.86	7	24.14	14	48.28	8	27.59
10	Burning micturition	20	57.14	5	25.00	11	55.00	4	20.00
11	Retention of urine	8	22.86	7	87.50	1	12.50	0	0.00

All the case of carcinoma prostate had complaint of sensation of incomplete bladder. Freq. and intermittency and nocturia were present in 94.29 of uses. These symptoms were followed by urgency (91.43%), Dysuria (82.86%) burning micturition (57.14%), retention of urine (22.86%) and hematuria in 17.14 case.

Table 3: AUA Score In Case Of Carcinoma Prostate

S.N.	Urinary Symptoms (Symptom score criteria)	AUA Score											
		Not at a11 0		<1 time in 5 1		less than half a time 2		about half a time 3		>half the time 4		almost always 5	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
1	Sensation of incomplete emptying of urinary bladder	Nil	0	Nil	0	2	5.71	6	17.14	10	28.57	17	48.57
2	Frequency	2	5.71	2	5.71	13	37.14	7	20	8	22.85	2	5.71
3	Intermittency	2	5.71	1	2.85	1	2.85	6	17.14	4	11.42	21	60
4	Urgency	3	8	Nil	0	8	22.85	5	14.28	5	14.28	14	40
5	Weak urinary stream	Nil	0	Nil	0	1	2.85	5	14.28	6	17.14	23	65.71
6	Hesitancy/ Straining	Nil	0	Nil	0	3	8.57	5	14.28	6	17.14	21	60
		None		1 time		2 times		3 times		4 times		≥5 times	
		0		1		2		3		4		5	
7	Nocturia	Nil	5.71	Nil	0	2	5.71	2	5.71	11	31.42	18	51.42

Table 4: PSA level in cases of carcinoma prostate [Before surgery or Antiandrogen]

S.N.	PSA level [ng/ml]	No. of patient	Percentage
1	0-4	2	5.71%
2	4-20	5	14.29%
3	21-40	3	8.57%
4	41-60	3	8.57%
5	61-80	4	11.43%
6	81-100	2	5.71%
7	>100	16	45.71%

PSA level was found normal in only 2 cases i.e. 5.7% cases. PSA level was found >100 ng/ml in 16 case i.e. 45.71% cases.

Table 5: PSA level in cases of carcinoma prostate in whom more than two estimation of PSA was done

S.N.	Cases No.	PSA level [mg/ml] before Antiandrogen therapy / orchidectomy	PSA level (ng/ml)					
			<1 mth		1-3 mth		>3 mth	
			No.	%	No.	%	No.	%
1	4	>100					30.95	70
	4	>100					63	40
2	6	>100	>100	Nil	0.778	99	0.365	99.5
3	7	67.46	55.59	17.7	4.61	94	1.04	98.4
4	8	100	90	10			5.68	95
	8	100					0.648	99
5	9	99.82	75.16	25			0.461	98
6	15	>100			5.29	98	2.041	98
7	16	>100	>100	Nil			5.02	95
	16	>100					4.91	95
8	26	26.67					15.23	42
	26	26.67					0.37	99
9	31	14					9.57	31.64
	31	14					2.22	84.28

Table 6: Analysis of serum PSA level [ng/ml] in cases of carcinoma prostate >3 months duration antiandrogen therapy/orchidectomy

(Total No. of Patients-17)

S. N.	Case No.	3-6 M		6-12 M		12-24 M		24-36 M		>36 M	
		PSA level (ng/ ml)	% of ↓in PSA	PSA level (ng/ ml)	% of ↓in PSA	PSA level (ng/ ml)	% of ↓in PSA	PSA level (ng/ ml)	% of ↓in PSA	PSA level (ng/ ml)	% of ↓in PSA
1	1					11.86	87.4				
2	2	9.29	90								
3	4			30.95	70	63	40				
4	5					24.10	80				
5	6	0.36	99.9								
6	7			1.04	98						
7	8	5.68	95	0.64	99						
8	9	0.46	98								
9	10	25.97	75								
10	15	2.041	98								
11	16									5.02	94.08
	16									4.91	95.09
12	17			0.41	99						
13	18							0.259	99		
14	19	5.41	90								
15	26			15.23	42.8	0.37	99				
16	31			9.57	31.6	2.22	84.2				
17	35									1.58	85.1

DISCUSSION

In our study, most of the cases of carcinoma prostate patient were in the age group 50-60 yrs i.e. 34.28% followed by 71-80 years i.e. 31.42%. Subsequently 61-70 i.e. 20% and more than 80 years i.e. 14.28. According to Presti et al[14] (2004), the probability of carcinoma prostate in a man under the age of 40 is 1 in 10,000, for men 40-59 it is 1 in 103 and for men 60-79 it is 1 in 8. If the age of onset is 70 years, the relative risk is increased 4-fold, if 60 years the relative risk is increased 5-fold and if 50 years the relative risk is increased 7-fold. According to Reiter et al[15] (2002) the incidence of prostate cancer in men 50-59 years has increased substantially, since 1970's.

All the cases of carcinoma prostate had complaint of sensation of incomplete emptying of bladder, weak urinary stream and hesitancy. Frequency and intermittency and nocturia were present in 94.29% of cases. These symptoms were followed by urgency (91.43%), dysuria (82.86%), burning micturition (57.14%), retention of urine (22.86%) and haematuria in 17.14% cases. According to Carter et al[16] (2002) prostate cancer rarely causes symptoms early in the course of disease because the majority of adenocarcinomas arise in the periphery of gland distant from the urethra. The presence of symptoms suggests locally advanced or metastatic disease. Growth of prostate cancer into urethra or bladder neck results in obstructive voiding symptoms i.e. hesitancy, decreased force of urinary stream, intermittency and irritative symptoms i.e. frequency, nocturia, urgency, urge incontinence.

AUA symptom score is sum of question A_1 to A_7 i.e.
A1: Incomplete emptying: over the past month, how often have you

had a sensation of not emptying your bladder completely after you finished urinating?
A2: Frequency: Over the past month, how often have you had to urinate again less than two hours after you finished urinating?
A3: Intermittency: Over the past month, how often have you found you stopped and started again several times when you urinate?
A4: Urgency: Over the past month, how often have you found it difficult to postpone urination?
A5: Weak stream: Over the past month, how often have you had a weak urinary stream?
A6: Straining/ Hesitancy: Over the past month, how often have you had to push or strain to begin urination?
A7: Nocturia: Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?

from the time you went to bed at night until the time you got-up in the morning?

In our study urinary symptoms - Almost always present - In A1 was 48.57%, A2 was 5.71%, A3 was 60%, A4 was 40%, A5 was 65.71%, A6 was 60%, A7 was 51.42%.

More than half the time – In A1 was 28.57%, A2 was 22.85%, A3 was 11.42%, A4 was 14.28%, A5 was 17.14%, A6 was 17.14%, A7 was 31.42%.

About half the time – In A1 was 17.14%, A2 was 20%, A3 was 17.14%, A4 was 14.28%, A5 was 14.28%, A6 was 14.28%, A7 was 5.71%.

Less than half the time – In A1 was 5.71%, A2 was 37.14%, A3 was 2.85%, A4 was 22.85%, A5 was 2.85%, A6 was 8.57%, A7 was 5.71%.

Less than 1 time in 5 – In A1 was 0%, A2 was 5.71%, A3 was 2.85%, A4 was 0%, A5 was 0%, A6 was 0%, A7 was 0%.

Not at all – In A1 was 0%, A2 was 5.71%, A3 was 5.71%, A4 was 8%, A5 was 0%, A6 was 0%, A7 was 5.71%.

According to McConnell et al (1994), the self administered questionnaire developed by the American Urological Association (AUA) is both valid and reliable in identifying the need to treat patient and in monitoring their response to therapy.

Serum PSA level was found normal in only 2 cases i.e. 5.71% cases. PSA level was found >100 ng/ml in 16 cases i.e. 45.71%. Serum PSA level between 4-20 ng/ml, 61-80 ng/ml was found in 14.29% and 11.43% respectively. It was found between 21-40 ng/ml and 41-60 ng/ml in 8.57% cases each. Two cases (5.71%) had PSA level 81-100 ng/ml. According to Partin et al (1990, 1993), as general guidelines, the majority of men (70-80%) with PSA values less than 4.0 ng/ml have pathologically organ-confined disease, more than 50% of men with PSA levels greater than 10.0 ng/ml already have established capsular penetration and most men (75%) with serum PSA levels greater than 50 ng/ml have positive pelvic lymphnode.

Carter et al[16] (2002), because of the significant risk of prostate cancer, prostate biopsy is recommended for all men who have digital rectal examination abnormalities, regardless of the PSA level, because 25% of men with cancer have PSA level less than 4.0 ng/ml. Comparing to it, in our study, the PSA level of less than 4 ng/ml was found in 5.71% cases.

In our study in >36 months post orchidectomy and/or antiandrogen therapy, one had 95% decrease and another one had 85.12% decrease serum PSA level.

According to Stamey et al[4] (1989) the PSA level decreased to undetectable level approximately 6 week later, as did pain. PSA remained undetectable at 8 and 14 month after orchidectomy. Even one patient required 11 months to reach the nadir PSA had a decrease from 2,435 to 2.1 ng/ml. Of these 45 patients 36 (80%) had serial PSA value after initiation of antiandrogen therapy, the pattern of change was observed in relation to interval after therapy. Only 1 patient showed an increasing PSA level within the first 3 months and only 3 had increase within 6 months, however the majority of patient (21 of 30) showed a steadily increasing PSA at a mean rate of 147 ng/ml per month. Only 3 patient continued to have decreasing levels beyond 6 months after starting anti-androgen therapy and no patient showed a decreasing PSA beyond 2 year.

The decrease in PSA after initiating antiandrogen confirm the exquisite sensitivity of this enzyme to withdrawal of androgens. Out of 11 patients, 10 had a 97 percent or greater decrement in PSA within 6 months of initiating therapy.

In our study whose PSA level were taken in more than 3 Month duration of antiandrogen therapy and/or orchidectomy, out of 17 cases 7 had a fall in PSA level within 6 months of initiating therapy. In these 7 cases, one case had fall in 99.9% decrease in serum PSA level, 2 cases had 98% decrease, one cases had 95% decrease, 2 cases had 90% decrease and one case had 75% decrease in serum PSA level.

Another 7 cases had fall in PSA level in 6-12 months after initiating therapy. In these 2 cases had fall in 99% decrease in serum PSA level, one case had 98% decrease, one case had 80% decrease, one case had 70% decrease, and another 2 case had 42.8 and 31.6% decrease respectively in serum PSA level.

One case had decrease in 99% in serum PSA level in 24-36 month duration. Two case came in >36 month duration of treatment. In that one of these case, in orchidectomy plus antiandrogen therapy was given whose PSA decreased 94.08% level in 5 year, 5 months, 14 days and this same case had 95.09% decrease in serum PSA level in 5 year 10 month and 18 days duration. Another case had 85% decrease in serum PSA level in 4 year, 4 month duration of treatment in which only antiandrogen was given. Both these cases suggest that hormonal therapy in the form of antiandrogen therapy plus orchidectomy as well as only antiandrogen therapy were effective.

CONCLUSION

We conclude from our study that serum PSA level in carcinoma prostate cases is increased in around 95% cases. When serum PSA levels were taken after antiandrogen therapy and/or orchiectomy, it was found that PSA level decreased to around 90% in 90% cases. The remaining cases, in whom decrease was not so significant had partial response. Thus serial PSA level estimation distinguishes favourable from non-favourable responders early within the course of therapy and greatly assist in the monitoring for progression.

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