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## **COMPARATIVE STUDY BETWEEN ORCHIDECTOMY ALONE AND ORCHIDECTOMY WITH HORMONAL THERAPY (COMBINED ANDROGEN BLOCKADE) FOR PATIENTS WITH ADVANCED CARCINOMA OF THE PROSTATE**

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### **Abstract**

Worldwide, prostate cancer incidence and mortality vary significantly between countries and regions and are highest in African American men. In the USA, prostate cancer is the most common visceral malignant neoplasm in men and the second leading cause of cancer-related deaths. Bilateral orchidectomy with or without hormonal therapy are the main treatment options for patients with advanced prostate carcinoma.

The objective of this study is to compare the efficacy of orchidectomy alone and orchidectomy plus flutamide in treating patients with advanced carcinoma of prostate.

The study was conducted from June 2006 to March 2010. Thirty six patients were included in the study. The inclusion criteria were histologically documented carcinoma prostate along with distant metastasis (stage D2). Following orchidectomy, the patients were stratified into two groups. Group I had patients treated with orchidectomy alone (17 patients) and Group II those treated with orchidectomy plus flutamide therapy (19 patients). Follow up of patients was done for the next two years following initiation of therapy.

The maximum percentage change in PSA was found in the first three months after orchidectomy. The mean percentage change at two years, in the two groups was 65% and 62% respectively. Based on the evaluation of response, there was no significant difference in response rate between the two treatment groups.

In conclusion, addition of antiandrogen like flutamide to orchidectomy has not given any significant benefit to effect the PSA changes as well the survival in advanced carcinoma of prostate. Hence, routine use of additional antiandrogen to orchidectomy is not advisable.

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### **Introduction**

Worldwide, prostate cancer incidence and mortality vary significantly between countries and regions and are highest in African American men. In the USA, prostate cancer is the most common visceral malignant neoplasm in men and the second leading cause of cancer-related deaths. PSA testing has induced a significant downward migration in age and stage (both clinical and pathological) at diagnosis. Both genetics and environment are important in the origin and evolution of prostate cancer<sup>1-3</sup>. Since Labrie et al<sup>4-6</sup> reported excellent results

with CAB in non randomized studies, during the last few years the interest regarding endocrine therapy for prostate cancer has been directed at complete androgen blockade (CAB). The impressive results shown by Labrie et al exalted many urologists to use maximum androgen blockade by using additional antiandrogens to block the adrenal derived circulating androgens. But others never achieved the excellent results obtained by Labrie and the results in subsequent studies have been conflicting making complete androgen blockade unresolving question. The aim of the

study is to compare the efficacy of orchidectomy alone to orchidectomy plus flutamide in the management of advanced carcinoma of prostate.

### Materials and Methods

The study was conducted from June 2006 to March 2010. Thirty six patients were included in the study. The patient's characteristics are given in (Table I). The inclusion criteria were histologically documented carcinoma of prostate along with distant metastasis (stage D2) or locally advanced disease.

Among these patients fourteen patients were diagnosed after they had TURP for symptomatic prostatic enlargement while twenty two patients were diagnosed on basis of prostatic biopsy for evaluation of high PSA value. All patients had a normal serum testosterone levels before treatment. Ten patients who underwent TURP had their PSA assessed before surgery. Three of them showed normal PSA values and seven showed elevated PSA values. Four patients had no pre-operative PSA assessment but they were discovered to have carcinoma of the prostate following resection of prostatic tissues. All 36 patients were thoroughly evaluated by complete physical examination and laboratory and imaging investigations. Laboratory investigations included performing complete blood film and assessment of blood urea nitrogen and serum creatinine levels. Imaging studies done included radiology of lumbar spines and sonography examination of the abdomen. Computed tomography scanning was performed for patients with suspected secondary deposits like in patients with abnormal sonography findings or abnormality of the spines on radiology. Out of thirty six patients, eight had evidence of secondary metastasis in the spine manifested as osteosclerotic lesions. Three patients presented with evidence of visceral metastasis involving the lungs and the liver. Twenty five patients presented

with evidence of locally advanced disease. All patients were prepared for bilateral orchidectomy. The orchidectomy was done via scrotal approach. Following surgery the patients were stratified into two groups. Group I had patients treated with orchidectomy alone (17 patients) and Group II those treated with orchidectomy plus flutamide therapy (19 patients).

After orchidectomy in both groups first PSA estimation and serum testosterone value were obtained at first month and three months thereafter. The evaluation of efficacy was based primarily on findings of bone radiology and the serum PSA and testosterone values on follow-up. A complete response (CR) was defined as normalization of bone radiology and serum PSA returning to normal ( $< 4$  ng/ml) with castration level of serum testosterone ( $< 50$  ng/dl). A partial response (PR) was defined as ( $\geq 50\%$ ) reduction in metastasis mass as compared to the initial study or decrease in PSA level and serum testosterone level ( $\geq 50\%$ ) of initial values. Progressive disease (PD) was defined as development of any new lesions on bone radiology or any increase in previously existing PSA or serum testosterone levels by 25%. Percentage change in PSA and serum testosterone values was also calculated each time as compared to the pretreatment value in both groups in order to compare the efficacy of the two treatment arms. A (p-value) of  $< 0.05$  was considered as statistically significant. Chi-square distribution was used to analyze the results.

### Results

In the study a total of thirty six patients were included. The maximum percentage change in PSA was found in the first three months after orchidectomy (Table II). The mean percentage change in PSA at two years, in the two groups was 65% and 62% respectively (Table III). It was not statistically significant (p-

value =0.95). The mean percentage change in testosterone level at two years, in the two groups was 64% and 62% respectively (Table IV). It was not statistically significant (p-value = 0.92). Based on the evaluation of response as defined in the protocol, there was no significant difference in response rate between the two treatment groups (Table V). There was no statistical difference in two groups ( p-value > 0.05).It is evident that additional flutamide therapy did not significantly improve the outcome of patients undergoing bilateral orchidectomy for metastatic carcinoma of the prostate.

## **Discussion**

It is well known that prostate gland is androgen dependent and controlled by circulating testosterone, which is synthesized and secreted from the testes up to 90-95%. Removal of trophic androgen by medical or surgical castration has been the standard therapy for prostate carcinoma for more than fifty years. In the normal prostate, androgen ablation induces within days profound morphological changes including apoptotic cell death<sup>7</sup> and the initial positive effect of castration therapy in prostate cancer is attributed to apoptotic depletion of androgen dependent tumor cells<sup>8</sup>. Prostate tumor may respond in a variety of ways to castration therapy including apoptosis and decrease in cell proliferation. The androgens, especially those formed in the adrenal cortex, are thought to be very important when there are low levels of circulating testosterone, there is still a continuous stimulation of the prostate whose receptors are 'hungry' for androgen<sup>9</sup>. Orchidectomy over the decade has been the most effective tool for lowering the circulating testosterone. The procedure provides symptomatic relief for up to 70-80% of patients<sup>10,11</sup>. The endocrine response of carcinoma prostate (CAP) depends upon the

presence of androgen sensitive cells. The incidence of primary androgen independent prostate carcinoma is approximately 20%<sup>12</sup>. It has been postulated that inactivation of oncogenes like P53 and expression of Bcl-2 can block the process of apoptosis<sup>13</sup>. There is no definitive way to predict which patient will respond to orchidectomy. Some experimental studies have suggested that study of apoptosis related oncoproteins like P53, Bcl-2 and C-myc might help in predicting which patient will respond to castration and which will not<sup>14,15</sup>.

PSA has been used as the clinical marker to monitor the disease both in surgical as well as nonsurgical mode of treatments. In a study on human prostates, a 7-fold increase in apoptosis in normal human prostatic tissue was seen at 7 days after castration. It is therefore likely that a major castration induced changes in apoptosis index in human prostate tumors would be detected at this time<sup>15</sup>. In the present study, the changes in PSA level after orchidectomy were recorded and it was evident that maximum percentage changes in PSA is seen in the first three months after orchidectomy. This can be explained to some extent by the degree of apoptosis, which is maximum within the initial 7 days<sup>15</sup>. PSA has got a prognostic importance in endocrine therapy in carcinoma prostate. The multinational nilutamide study and INT-0105 study provided interesting observations about the PSA changes in endocrine therapy of carcinoma prostate. In the former trial after three months of treatment serum PSA level normalized in 121 patients in both arms, which predicted a longer survival time and time to progression. The percent of patients with serum PSA less than 4 ng/ml at three months was significantly higher in complete androgen blockade group. Whilst, in INT-0105 there was a difference in PSA normalization between complete androgen blockade

and monotherapy (74% versus 61%)<sup>16</sup>. In the present study there was no statistical difference in percentage change in PSA and testosterone in both the treatment groups.

Labrie et al reported a 96% response rate and long term survival in advanced carcinoma prostate<sup>4</sup>. But similar excellent results were never achieved in the hands of others. Several randomized studies in the early nineties demonstrated better results with combined androgen blockade<sup>16,17</sup>. A multicentre study in United States (National Cancer Institute), compared LHRH agonist plus flutamide with a LHRH agonist and a placebo control and found that results of combined androgen blockade were better than LHRH agonist alone. The results were more evident in patients with low volume disease<sup>18</sup>. Till date combined androgen blockade in metastatic carcinoma prostate remains controversial. Studies done before the nineties showed minor to major advantages of complete androgen blockade over orchidectomy. Further with the time, more controlled studies failed to show any substantial advantage of complete androgen blockade over orchidectomy alone. In the mid nineties the concept of complete androgen blockade further contracted as a few studies showed that it is only effective in patients with good performance status and a low volume disease<sup>19,20</sup>. The complete androgen blockade policy further suffered a blow when the EORTC phase three prospective trial study comparing orchidectomy to orchidectomy plus cyproterone acetate and diethyl stillbestrol (DES) showed that there was no difference in progression and survival in all three arms<sup>20</sup>. In an open, multicenter, randomized study it was concluded that both short term or continuous addition of cyproterone acetate to buserline, a LHRH agonist, did not improve treatment results compared to

orchidectomy only<sup>21</sup>. Another multicentre, randomized trial comparing zoladex with zoladex plus flutamide in advanced carcinoma prostate showed no statistical differences in objective response between the two groups, 67% in zoladex group and 65% in combination group. Also there was no difference in time to treatment failure and time to progression between the two treatment groups<sup>22</sup>. In a recent study the Agency for Health Care Policy and Research published the results of a comprehensive meta-analysis based on all 27 published complete androgen blockade studies. The meta-analysis detected no difference in 2-year survival rates. Only 10 of the 27 studies reported 5-year survival figures, and reported only minimal survival differences in favor of combined androgen blockade<sup>23</sup>. In a most recent review based on 27 clinical trials using various combinations of androgen deprivation data does not support routine use of antiandrogens in combination with medical or surgical castration as first line hormonal therapy in patients with metastatic prostatic carcinoma. It was also evident that quality of life-benefit resulting from orchidectomy in patients with metastatic prostate carcinoma appeared to be offset by the addition of flutamide, primarily because of an increased incidence of adverse effects<sup>24</sup>.

## **Conclusion**

In regard to hormonal therapy of advanced carcinoma prostate maximum percentage change (decrease) in serum PSA is seen in first three months after orchidectomy. Addition of antiandrogen like flutamide to orchidectomy has not given any significant benefit to effect the PSA changes as well the survival in advanced carcinoma of prostate. Hence, routine use of additional antiandrogen to orchidectomy is not advisable. Large randomized trials comparing the efficacy of orchidectomy alone and combined

androgen blockade are urgently warranted to guide the clinician in planning the appropriate treatment in

order to save both money as well as guard the patient against the unwanted effects of the antiandrogens.

**Table I: characteristics of the patients (pre- treatment)**

	Orchidectomy alone (Group I)		Orchidectomy plus Flutamide (Group II)	
Number of Patients	17		19	
Age (yrs )	55-72		56-70	
PSA (ng/ml)	10-35		8-32	
(Mean)	(18.6)		(18.2)	
Bone Pain	Number	Percentage	Number	Percentage
Nil	12	70.5 %	16	84.2%
Mild	2	11.7 %	2	10.5%
Moderate	2	11.7%	1	5.3%
Severe	1		0	
Intractable	0		0	

**Table II: Changes in the PSA level in the two groups before and after therapy**

Group	Pre-treatment PSA (ng/ml) range & (Mean)	1 mo	3 mo	6 mo	12 mo	18 mo	24 mo
I	10-35	6-20	3-12	4-15	4.5-13	5.5-13	5-12
	(18.6)	(7.5)	(5)	(5.7)	(6.1)	(7)	(6.5)
II	8-32	6.3-22	3.7-12.5	4- 13	4-12	5.1-12	5.1-13
	(18.2)	(7.4)	(5.2)	(5.6)	(5.9)	(7.2)	(6.9)

**Table III: Mean percentage change in PSA level in the two treatment groups after therapy**

Group		1 mo	3 mo	6 mo	12 mo	18 mo	24 mo
I	Mean percentage change	59.7 %	73.1 %	69.3 %	67.2 %	62.3 %	65 %
II	Mean percentage change	59.3 %	71.4 %	69.2 %	67.5 %	60.4 %	62 %

**Table IV: Mean percentage change in Testosterone level in the two treatment groups after therapy**

Group		1 mo	3 mo	6 mo	12 mo	18 mo	24 mo
I	Mean percentage change	57.7 %	71.1 %	68.4 %	66.2 %	61.3 %	64 %
II	Mean percentage change	57.3 %	70.4 %	68.2 %	66.3 %	60.8 %	62 %

**Table V: Clinical response in the two treatment groups after therapy**

Response	Group I		Group II	
	Number	Percentage	Number	Percentage
<b>Complete Response (CR)</b>	<b>3</b>	<b>17.6 %</b>	<b>3</b>	<b>15.7 %</b>
<b>Partial Response (PR)</b>	<b>12</b>	<b>70.6 %</b>	<b>13</b>	<b>68.4 %</b>
<b>Progressive Disease (PD)</b>	<b>2</b>	<b>11.7 %</b>	<b>3</b>	<b>15.8 %</b>

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