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A comparison of medical castration versus surgical castration for patients with advanced prostatic carcinoma

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Abstract
Background: *The introduction of androgen deprivation therapies in the treatment paradigm for advanced prostate cancer have shown excellent survival benefits .However there seems controversies revolving around with the optimal timing , duration and most importantly the serious side effects especially higher incidences of peripheral vascular diseases and diabetes. The present study tried to compare the survival benefits, recurrence free survival and side effects between the medical and surgical treatment in advanced carcinoma prostate.*
Material and Methods: *This is a hospital based retrospective study from January 2012 to January 2017 was conducted in medical college in north part of India. All patients diagnosed with advanced prostate carcinoma were included who received either GnRHa or orchiectomy as primary cancer therapy within 12 months of diagnosis. Associations between clinical outcomes and prognosis were compared between the two modalities; the impact on the prostate-specific antigen (PSA) normalization rate, the rebound rate and the disease-free survival rate were evaluated. The median follow-up was 22.3 months*
Results: *Despite similar results in normalization of the PSA score between two groups in initial time intervals beyond 18 months the response in the surgical group was higher as compared to medical group though not reaching statistical significance. At the end of the study, normalization was sustained in surgical group (20%) while in the medical group, sustained proportions was Nil (0%). Among the surgical group, recurrence free survival was higher especially in late time intervals indicating sustainable effect.*
Conclusion: *Advanced prostate carcinoma patients, surgical castration group do better in terms of better PSA rebound rates and overall survival in comparison to the medical treatment*
Keywords: *Advanced carcinoma prostate, medical castration, surgical castration, recurrence free survival.*

Introduction

Prostate carcinoma is the most common nonskin malignancy among men and the 6th leading cause of death among men worldwide[1]. Though age is identified as one of the essential risk factors yet its incidence is growing over the years with the expected to be around 1.7 million new cases and 499000 new deaths by 2030[1]. Increased serum level of androgen receptor target Prostate-specific antigen (PSA) is being used as screening modality as this unique cancer seems to be driven by the hormonally responsive transcription factor androgen receptor (AR)[2]

Localized and low-risk prostate cancer is actively monitored or treated with radical prostatectomy (RP), brachytherapy, or external beam radiation therapy (EBRT)[3,4]. Yet a small but significant proportion of prostatic cancers are locally advanced at the initial diagnosis whose management seems quite challenging with use of a combination of 'long-term' (24–36 months) androgen deprivation therapy (ADT) and EBRT.

Androgen deprivation therapy (ADT) has since long been established treatment modality for advanced and metastatic prostate carcinoma, which began with Huggins's observations on advanced and metastatic prostate carcinoma[5]

The advantage of this therapy is survival benefit with, biochemical recurrence after ADT being a serious long term problem. ADT can be achieved either surgically (orchiectomy) or pharmacologically with gonadotropin-releasing hormone (GnRH) analogues. High cost of LHRH agonist and poor availability of medical reimbursement system results in option of surgical castration however over the years surgical castration was largely replaced by medical castration GnRH agonists (GnRHa) due to its ease of administration, the psychological impact of orchiectomy and reversibility[6,7]. Recently a number of observational studies have indicated an increase in risk of fractures, diabetes mellitus (DM),peripheral arterial disease (PAD), venous thromboembolism (VTE), and cardiovascular disease (CVD).[8-10] though this is not substantiated by any randomized clinical trials (RCTs). However these nerving data did prompt the US Food and Drug Administration to mandate changes to GnRHa labeling to include a warning of the increased risk of DM and CVD.

The point revolves around that though ADT remains the treatment modality in advanced and metastatic prostatic carcinoma yet the valuable question arises that can it cause less harm in this population.

Looking back in literature prior studies did show lower risk of adverse events with orchiectomy yet no definitive conclusions could be drawn as there were no direct comparisons available between the two available modalities. Recent study by Sun et al reported a lower risk of fractures, peripheral arterial disease and cardiac-related complication among surgical group versus the medical therapy group though no statistical differences were noted between the treatment arms in term of risk of DM and cognitive disorders[11].

On deeper evaluation it seemed that use of bone antiresorptive agent's corticosteroids and diethyilstilboestrol could have impacted the risk of fractures, DM, and VTE in metastatic advanced cancer. Thus caution must also be exercised while interpreting these studies. There seems variability in terms of association with CVD, some studies have shown that GnRHa, but not orchiectomy was associated with excess CVD[10,12]) while a recent metaanalysis of observational studies have found an increased risk of CVD with both GnRHa and orchiectomy.[13] Besides the risk of fracture have been though not more but with similar frequency between the group treatment modalities.[14]

Whether there exists any true difference between orchiectomy and GnRH agonists needs prospective trials as they a results from observational studies.

In this study, we compared the clinical effectiveness of surgical and medical castration with respect to recurrence free survival and side effects. We also tried to compare the biochemical failures between the two treatment modalities.

Study Design: Retrospective Cohort study

Material and Methods

Patient Selection

This was a hospital based retrospective study conducted in the Department of Surgery, Era Lucknow Medical College and Hospital, Lucknow after obtaining an institutional review board approval. Medical records were reviewed from January 2012 to January 2017 and identified all patients who had advanced prostate carcinoma. We included those patients who received either GnRHa or orchiectomy as primary cancer therapy within 12 months of metastatic prostatic carcinoma. Diagnosis excluded patients on radiotherapy, chemotherapy or a combination of both GnRHa and orchiectomy. The informed consent was obtained for experimentation with human subjects. The privacy rights of human subjects was observed. The work was carried out in accordance with The Code of Ethics of the World Medical Association.

The exclusion criteria for this study were concurrent malignancy, Previous surgical, radiotherapy or hormonal therapy for prostate carcinoma, poor renal and hepatic function, and a life expectancy of less than 3 months.

All of the patients who were included in the study had a baseline PSA Gleason scoring, ultrasonography, CT Scan & Pelvic magnetic resonance imaging findings, whole-body bone scans and a chest X-ray film.

All of the prostate tumors were pathologically staged according to the 1997 TNM classification.

Definition of advanced prostate carcinoma (defined as stage III or Stage IV carcinoma)

Stage III prostate cancer occurs when conditions are T3, N0, M0, any G

T3 tumor

Cancer spread to the connective tissue near the prostate (T3a) or to the s eminal vesicles as well(T3b)

Stage IV is T4, N0, M0, any G; any T, N1, M0, any G; or any T, any N, M1, Any G.

T4 -

Cancer spread within the pelvis to tissue next to the prostate such as the bladder's sphincter, the rectum, or the wall of the pelvis.

N1-Prostate cancer spread into the regional lymph nodes of the pelvis

M- Prostate cancer metastasized outside the pelvis in distant lymph nodes (M1a), bone (M1b) or organs such as the liver or the brain (M1c). Pain, weight loss, and fatigue often accompany the M1 stage.

The grade of the tumor (G) was assessed during the biopsy.

Graded- G1, G2, and G3, indicating the tumor is well, moderately, or poorly differ rentiated, respectively.

Maximal androgen blockade (MAB)-Classification

- All advanced prostate carcinoma (defined as stage III or stage IV carcinoma) with complete medical records.
- Surgical castration plus antiandrogens therapy with cyproterone (100 mg twice daily), Flutamide (250 mg three times per day), or bicalutamide (50 mg daily)
- Medical castration - LHRH agonist hormone therapy (Goserelin 3.6 mg monthly or leuprorelin 14 mg monthly) plus antiandrogens therapy.
- The patients who received medical castration received antiandrogens 2 weeks in advance for testosterone flare-up prevention

All patients were divided into two groups

Group 1-Surgical castration

Group2-Medical castration

They were evaluated and assessed for association with subsequent disease progression and treatment patterns. After initiating the hormone therapy, patients were monitored regularly with a PSA checkup every 3 months

Statistical Analysis

Statistical Package for Social Sciences, version 23 (SPSS-23) was used for data analysis

Categorical data were presented in frequency and percentage. Comparison in Proportions of normal/abnormal biochemical parameters between two treatments modality at different time intervals was done using Fisher exact test. Mann Whitney U test was used to compare the distributions

between two groups. Kaplan Meier Method with below test was used to compare the recurrence free survival time between two treatments. Survival time was presented in mean /median with 95% confidence interval. A p value < 0.05 considered as statistically significant.

Results

We identified 14 patients who received GnRHa or orchiectomy as primary cancer therapy with complete medical records. There were 9 patients in group 1 (surgical castration) and 5 Patients in group 2 (medical castration).

Table 1 shows the patient distribution and prostate carcinoma characteristics (initial PSA, Gleason score, tumor staging, and metastasis)

Age of the study patients was 64.6 years with range of 57-75 years. 63.7 years in Surgical castration and 66.4 years in medical castration with insignificant difference (p>0.05). LUTS was most common presentation in both the groups (55% vs. 80%, p>0.05). Similarly proportions of NAD (GPE findings) was maximum in both the groups (67% vs. 80%, p>0.05). PSA Baseline, USG_Weight and Gleason Sum was almost equal between two groups (p>0.05)

Table-1 Patient characteristics of the advanced prostate cancer

Patient Characteristics	Total (N=14)	Surgical Castration	Medical Castration	P value
Age(years)	64.64±5.87	63.67±5.00	66.40±7.47	0.547
# Clinical presentation (Pain/LUTS/Others)	9/2/3	5/2/2	4/0/1	0.748
#GPE Findings (NAD/PB/Others)	10/2/2	6/1/2	4/1/0	0.760
PSA Base line	142.1±142.5	163.3±172.2	103.8±62.6	0.841
USG_Weight_gm	71.2±14.5	69.1±13.2	75.0±17.6	0.547
Gleason score	7.8±0.89	7.7±0.9	8.0±1.0	0.514
Data presented in Mean± Standard deviation				
Mann Whitney U test / #Fisher exact test used to compare between two				

PSA normalization rate

The PSA normalization rates by study group are shown in **Table 2.**

We defined the PSA normalization rate as the percentage of patients with a PSA level returning to normal (<4 ng/mL) and staying normal.

Normalization of the PSA score between two groups was almost similar in initial time intervals. After 18 months, in surgical group, normalization proportions was higher as compared to medical groups, although proportions were not statistically significantly different between the groups (p>0.05). At the end of the study, normalization was sustained in surgical group (20%) while in the medical group, sustained proportions was nil (0%).

Table-2 Match comparison of patients undergoing ADT at PSA normalization rate

PSA (Normal)	Surgical castration (n=9)	Medical castration (n=5)	p value
1 months	88.9%	80.0%	>0.05
3 months	88.9%	100.0%	>0.05
6months	88.9%	100.0%	>0.05
12 months	88.9%	100.0%	>0.05
18 month	77.8%	60.0%	0.580
24 month	66.7%	50.0%	>0.05
30 month	75.0%	40.0%	0.293
36 month	66.7%	50.0%	>0.05
42 month	60.0%	33.3%	>0.05
48 month	20.0%	0.0%	>0.05

Recurrence free survival – (table-3 and Figure-1)

Mean recurrence free survival time (months) was higher in the surgical group as compared to the medical group (34.67 vs. 31.20)

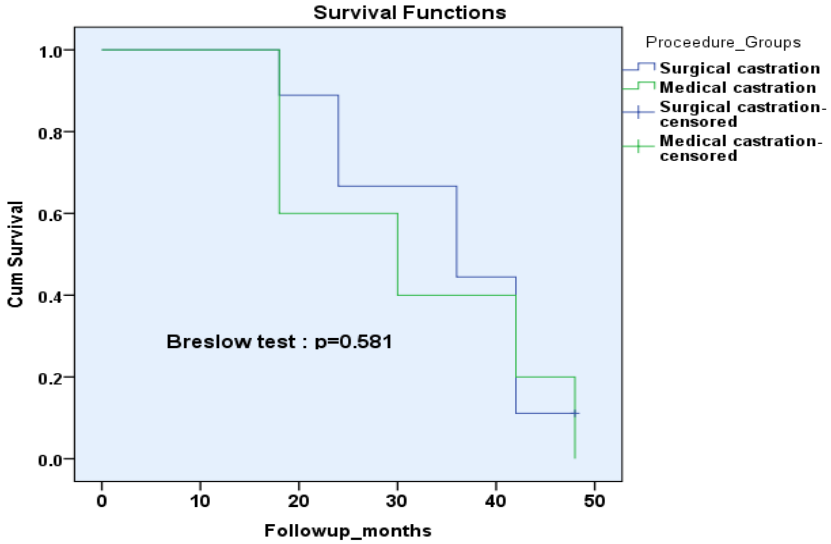
Similarly Median recurrence free survival time (months) was higher in the surgical group as compared to the medical group (36.00 vs. 30.00). The probability of the recurrence free survival between two groups was statistically insignificant (p=0.581). Overall surgical RFS was higher as compared to medical group especially in late time intervals which indicate that for sustainable effect, surgical process is better than medical therapy.

The risk of complication associated with treatment was not different between the two modalities. The risk of fractures (surgical -1, medical-1), cardiac related issues (surgical-1, medical-2), diabetes (surgical-1, medical-3), cognitive dysfunction (surgical-1, medical-3) were comparable.

Table-3 Recurrence free survival between the two modalities of treatment

Means and Medians for Survival Time (Recurrence free Survival)						
	Median time			Median time		
	Value	95% Confidence Interval Lower Bound	Upper Bound		95% Confidence Interval Lower Bound	Upper Bound
Surgical castration	34.67	19.21	43.19	36.00	18.47	53.53
Medical castration	31.20	27.54	39.32	30.00	4.24	55.77
Overall	33.43	28.33	41.01	36.00	25.11	46.89
Kaplan Meier Method : Breslow test : p value =0.581						

Figure-1 Recurrence free survival between the two modalities of treatment



Discussion

Treatment modalities for advanced prostatic carcinomas over the years have been between orchiectomy and oestrogens. The valuable contribution from the Huggin's observation in early 1940[5] revolutionarised the treatment protocols. Since then medical management has become the backbone for treatment in advanced metastatic prostatic carcinomas. Initial treatment focused on bilateral orchiectomy, estrogen therapy, or both. However each modality had its own negative impact both on quality of life and serious lethal cardiac events[15,16]. With the advent of usage of synthetic luteinizing hormone–releasing hormone agonists, there was a significant reduction in the cardiac toxicity and

the other side effects of androgen deprivation therapy. The path breaking trial of LHRH analogue in combination with oral antiandrogens showed a significant improvement not only in terms of survival but also cosmetic side effects[17,18] and since then LHRH agonist therapy became more popular than surgical castration[19,20].

However over the years trials have shown benefits of medical therapy even in advanced and metastatic disease[21,22]. Despite its advantages it poised a huge financial burden with serious medical side-effects forcing the physicians to rethink about its usage and thus surgical intervention became still more popular[10,11]. The risk of serious complications like cardiac dysfunction, peripheral arterial diseases and diabetes mellitus with medical therapy prompted the US Food and Drug administration to mandate changes to GnRHa labeling to include a warning of the increased risk of DM and CVD. The present study suggests a superiority of surgical treatment over medical therapy in patients with advanced carcinoma prostate better

mean recurrence free survival time (months) especially in late time intervals indicating its sustainable effect though the probability of the recurrence free survival between two groups was statistically insignificant. The probable explanation could be substantiated by Mergenthaler's saturation model, where in prostate carcinoma requires a fairly low testosterone concentration for the carcinoma to flourish[23] and sustainability of testosterone suppression[24]. And remarkable studies have shown that LHRH therapy could not achieve as low of a testosterone level as done with bilateral orchiectomy which is known to cease the production of testosterone all together[25]. The study showed survival advantage with sustained normalization scores for PSA in surgical compared to medical therapy group which was 20% versus 0% at the end of study.

Thus the present study highlights the survival advantages among surgical group in advanced prostatic carcinoma group with comparable side effects between the 2 groups

Limitation of the study was a small study population and need to substantiate these results with randomized trials to test the efficacy and sustainability of the two modalities of treatment comparing the side effect profile as well.

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