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

Authors

S K Bhat1*, Nisar Ahmed Ansari2, P K Mishra3, Maham A4, C S Rawat5, Nikhil Mehrotra6, A K Roy7

1Associate Professor, Department of General Surgery, RML institute of Medical Sciences, Lucknow, India
2Associate Professor, Department of Surgery, Era Medical College, Lucknow
3Assistant Professor, Department of Health and bio statistics, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow
4Senior Resident, Department of Surgery, Era Lucknow Medical College and Hospital, Lucknow
5Associate Professor, Department of Surgery, Era Medical College, Lucknow
6Junior Resident, Department of Surgery, Era Lucknow Medical College and Hospital, Lucknow
7Professor, Department of Surgery, Era Medical College, Lucknow

*Corresponding Author
Dr Sanjay Kumar Bhat
Associate Professor, Department of General Surgery, RML institute of Medical Sciences, Lucknow, India

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 (orchietomy) 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)\(^8-10\). 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 seminal 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 differentiated, 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)

| Patient Characteristic | Total (N=14) | Surgical Castration | Medical Castration | P value |
|------------------------|-------------|---------------------|-------------------|---------|
| Age( years)            | 64.6±5.87   | 63.67±5.00          | 66.4±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   |
| 6 months    | 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%                    | >0.05   |
| 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

|               | Surgical castration | Medical castration | Overall |
|---------------|---------------------|--------------------|---------|
| Value         | 34.67               | 31.20              | 33.43   |
| 95% Confidence Interval | 19.21               | 27.54              | 28.33   |
| Median time   | 36.00               | 30.00              | 36.00   |
| 95% Confidence Interval | 18.47               | 4.24              | 25.11   |

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 GnRH 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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