

A COMPARISON OF LEUPROLIDE ACETATE VERSUS BILATERAL ORCHIECTOMY FOR PATIENTS WITH METASTATIC PROSTATE CANCER

AISWARYA PURUSHOTHAMAN¹, GINIL KUMAR², GANGADHARAN P³, ROSHNI PR^{1*}

¹Department of Pharmacy Practice, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, AIMS Health Sciences Campus, Kochi, Kerala, India. ²Department of Urology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham University, AIMS Health Sciences Campus, Kochi, Kerala, India. ³Department of Cancer Registry, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham University, AIMS Health Sciences Campus, Kochi, Kerala, India. Email: roshnivipin@gmail.com

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ABSTRACT

Objective: Prostate cancer is the most common visceral malignancy and leading cause of cancer-related death in men. Androgen deprivation therapy is the established treatment of metastatic prostate cancer and has different approaches in the reduction of androgen activity including surgical castration (bilateral orchiectomy) and medical castration (luteinizing hormone-releasing hormone agonists/antagonists). Our purpose was to study the clinical profile, effectiveness, and outcome of South Indian patients with metastatic prostate cancer undergoing treatment with surgical and medical castration.

Methods: A total of 30 surgical and 30 medical castration patients diagnosed with metastatic prostate cancer between (2008 and 2009) were followed up to 5 years. Serum prostate specific antigen (PSA) levels at the time of the first diagnosis, post-treatment nadir PSA levels, time to nadir PSA, time to hormonal resistance between the study groups were assessed, retrospectively. The Kaplan–Meier method was used with log-rank test for survival rate calculations. Gleason score, PSA levels, skeletal-related events, and sites of metastasis of the study groups were studied.

Result: The average survival time after medical castration was 60 months and 42 months for surgical castration. No significant difference could be established between the groups. Bone was the most common site of metastasis and radiation was the major skeletal-related events in medical groups.

Conclusion: There were no statistical differences between the groups in terms of treatment modalities in metastatic prostate cancer.

Keywords: Skeletal related events, Orchiectomy, Prostate cancer.

INTRODUCTION

Prostate cancer is the most common visceral malignancy and leading cause of death in men. The aim of castration is to lower serum testosterone to < 50 ng/ml such that stimulation of prostate cancer cells is minimized [1]. Androgen deprivation therapy (ADT) is widely used to manage the symptoms of advanced prostate cancer and has shown to slow the progression of the disease. ADT is the established treatment of metastatic prostate cancer has different approaches in the reduction of androgen activity include surgical castration (bilateral orchiectomy) and medical castration (luteinizing hormone-releasing hormone [LHRH] agonists/antagonists) which are found to be equally effective. The surgical castration by bilateral orchiectomy is an effective method of rapidly decreasing testosterone levels. It is a relatively simple procedure with minor surgical risks and physical mobility; however, it has fallen out of favor given its physiological impact and the availability of viable medical alternatives for androgen deprivation. Additional benefits of surgical castration include rapid palliation of symptoms, the elimination of patient compliance issues, as well as the cost/benefit ratio [2,3].

Medical castration using the LHRH agonists, such as leuprolide and goserelin, is currently the most prevalent method of androgen deprivation. Treatment either these agents initially results in an elevation of LH and Follicle stimulating hormone from the hypothalamus in the first 1-2 weeks of the therapy, with the release of testosterone from the testes. It is for this reason that co-administration of androgen receptor antagonists used before and for the first 1-2 weeks of the therapy, with the release of testosterone from the testes. It is for this reason that co-administration of androgen receptor antagonists used before and for the first 2-4 weeks of the therapy is recommended in metastatic prostate cancer, preventing an associated “tumor flare” [3].

With the increase in life -expectancy, adoption of newer lifestyles and screening using prostate specific antigen (PSA), the incidence of prostate cancer is on the rise [1]. In practice, PSA is an invaluable tool for detection, diagnosis, management, and monitoring of patients with prostate cancer. Levels of PSA are used for monitoring disease recurrence after initial treatments and for evaluating response to cancer treatments [4,5]. Gleason grading system for prostatic carcinoma is the dominant method in research, and daily practice is based on the histopathology of cancer cells [5]. Digital rectal examination (DRE) is physical exam done by a urologist to check the growth or enlargement of the prostate gland to examine for the presence of a hard lump [4,6]. About 70-80% of patients with metastatic prostate cancer have increased the risk of skeletal-related events of pathological fractures, spinal cord compression, and severe pain, on radiotherapy or surgery for bone lesions. SRE results in significant complications and may affect the quality of life. SREs can lead to severe pain, increased risk of death, increased health care costs, and reduced quality of life [7].

MATERIALS AND METHODS

A total of 60 patients were enrolled for the study. A total of 30 surgical and 30 medical castration patients diagnosed with metastatic prostate cancer (between 2008 and 2009) and were followed up to 5 years. All the patients were confirmed as primary prostate cancer by pathological diagnosis and were diagnosed with metastatic disease through radioisotope and magnetic resonance imaging.

All newly diagnosed male patients with metastatic prostate cancer and who had undergone bilateral orchiectomy and medical castration were included for the study. Patients with the age group of 50-80 years and with proper biopsy reports were only included for the study. All Patients

with incomplete data and having any other pre-existing malignancies were excluded from the study.

Patients age at diagnosis, Gleason Score, DRE status at the initial diagnosis, treatment modalities administered, sites of metastasis, Lab values, skeletal-related events, and survival status were retrospectively collected and reviewed. The serum PSA values were determined from the hospital laboratory using ELISA method. The normal range of PSA was ≤ 4 ng/ml. The PSA values of the patients were characterized as 0-4 ng/ml, 4-20 ng/ml, and ≥ 20 ng/ml. The Gleason score of patients was characterized into >6 , 7, and 8-10. The survival time of patients was calculated from the date of initial diagnosis to the date of death or last follow-up. The statistical analysis was performed using SPSS 20.0 software. The Kaplan–Meier method was used with a log-rank test for survival rate calculations. The Chi-squared test was used for comparison between the groups. $p < 0.05$ was considered as statistically significant. The study was approved by the Institutional and ethics committee of Amrita Institute of Medical Sciences, Kerala, India.

RESULTS

Case records of 60 metastatic prostate cancer patients who visited Uro-oncology and Oncology Department of a tertiary care hospital during the year 2008-2009 were enrolled for the study and were followed up to a period of 5 years. The average age of the patients at the time of initial diagnosis was 68.63 ± 6.531 (mean \pm standard deviation [SD]) for surgical castration and 66.17 ± 6.052 (mean \pm SD) for medical castration.

The mean PSA values (ng/ml) for surgical and medical castration before treatment were 468.95 and 120, respectively ($p > 0.05$). The Gleason score of all age groups were 7 ($p > 0.05$). The Nadir PSA (ng/ml) after treatment was 16.52 and 27.32, respectively ($p > 0.05$), whereas the time to the nadir PSA (months) was 5.1 and 3.5 months, respectively ($p < 0.05$). The time to hormonal resistance (months) was 20.78 and 19.71, respectively ($p > 0.05$). The average survival after medical castration was 60 months and 42 months for surgical castration. A significant difference could not be established between these prognostic factors except for the time (months) to the nadir PSA ($p < 0.05$). Based on the site of metastasis in patient's undergone surgical and medical castration for bone, liver, brain, and lymph nodes was (93% vs. 100%), (13% vs. 20%), (3% vs. 3%), and (13% vs. 10%), respectively ($p > 0.05$). Based on the skeletal-related events associated with surgical versus medical castration for radiation, pathological fracture, spinal cord compression, and surgery was (65% vs. 35%), (83% vs. 17%), (100% vs. 0%), and (75% vs. 25%), respectively. No statically significant difference was found between the skeletal-related events ($p > 0.05$) except for the radiation ($p < 0.05$) (Table 1, Figs. 1 and 2).

DISCUSSION

Bone was the most common site of metastasis in prostate cancer patients. In the current study, the various sites of metastasis in patients underwent surgical versus medical castration for bone, liver, brain was (93% vs. 100%), (13% vs. 20%), and (3% vs. 3%),

respectively ($p > 0.05$). Similar to others studies, the current study also showed, the degree of bone metastasis in prostate cancer patients was higher compared other visceral sites. This may be due to the spread of malignant cells from the prostate to bones in the hip, spine, and pelvis and once relocated the cells begin to grow at rapid pace. Giorgio *et al.* and Andrew *et al.* in their observation found that bone was the most common site of metastasis in prostate cancer and individuals with visceral metastasis experience a shorter survival rate compared to patients with exclusive bone involvement.

In the current study, mean PSA values (ng/ml) for surgical and medical castration before treatment were 468.95 and 120, respectively ($p > 0.05$). This was not statistically significant. The mean Gleason score of both surgical and medical castration patients at the

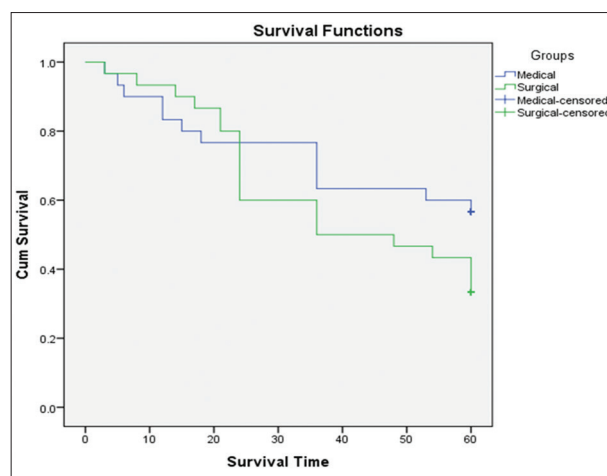


Fig. 1: Overall Survival rate of the study groups

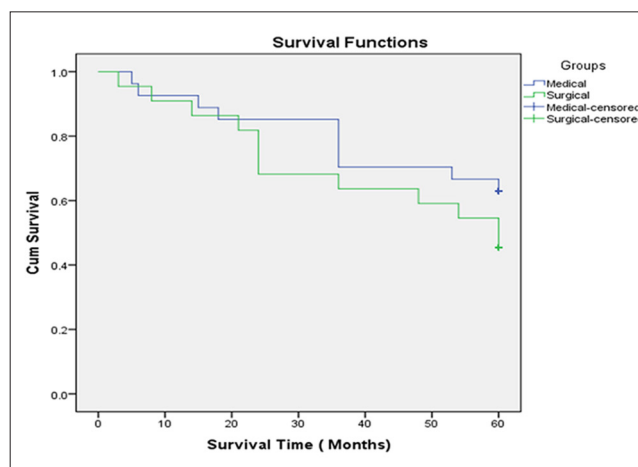


Fig. 2: Cancer-specific survival of the study groups

Table 1: The summary of the results of each treatment group

| Parameters | Medical | | Surgical | | p value |
|--|---------|--------|----------|-------|---------|
| | Median | Mean | Median | Mean | |
| PSA value (ng/ml) before treatment | 93.40 | 468.95 | 120 | 93.40 | >0.05 |
| Gleason score | 7 | 7.23 | 7 | 7.15 | >0.05 |
| The nadir PSA (ng/ml) after treatment | 1.98 | 16.52 | 2.51 | 27.32 | >0.05 |
| The time to nadir PSA (months) | 3 | 5.1 | 3 | 3.5 | <0.05 |
| The time to hormonal resistance (months) | 18 | 20.78 | 18 | 19.71 | >0.05 |
| Survival (months) | 44.93 | 60 | 40.60 | 42 | >0.05 |

PSA: Prostate specific antigen

diagnosis of metastatic prostate cancer was 7 which indicates the cancer cells are moderately differentiated.

The nadir PSA (ng/ml) after treatment for medical and surgically castrated patients in the current study were 16.52 and 27.32, respectively, and the time to the nadir PSA (months) was 5.1 and 3.5 months, respectively. These prognostic factors failed to show a statistically significant difference between the study groups except for the time to nadir PSA ($p < 0.05$). This was against the reports of western studies. More patients are required to confirm these findings. Tomioka *et al.* Sasaki *et al.* in their study results found that lower nadir PSA and longer time nadir PSA were evaluated as predictors of survival in patients with bone metastasis. Survival was longer in patients with lower PSA nadir. Grivas *et al.* in his work suggest that patients with longer time to PSA nadir > 9 months had longer survival in both lower and higher PSA nadir subgroups. In our study, even though patients with medical castration had a longer time to nadir PSA compared to surgical castration, the time to nadir was not greater than 9 months showing no correlation with the study of Grivas *et al.*

In the current study, the overall survival time of patients after medical castration was 45 months and 41 months for surgical castration ($p > 0.05$). The cancer-specific survival rate of patients between the study groups was 49 months and 44 months, respectively ($p > 0.05$), and the present study found that surgical and medical castration are equal in their clinical effectiveness which was similar to the previous evidence suggested by western studies. Batto *et al.* conducted a comparative study on the cancer-specific survival rate of metastatic prostate cancer patients, who received LHRH agonist and surgical castration and found the mean survival of patients with surgical castration, was 37.5 ± 3 months and 33 ± 3 months for medical castration and at 3 years no significant difference was found in survival rate. Cheng *et al.* reported that 1, 2, 3, 4, and the 5-year survival rate of patients after the diagnosis of diseases was 95.5%, 77.5%, 68.5%, and 3.7%, respectively, and the median survival time of 55.6 (range 8.0-175) months. Aslan *et al.* found that average survival time for bilateral orchiectomy and LHRH + anti-androgen were 45 and 42.5 months. Kaisary *et al.* found that both treatments were equally effective in lowering the serum testosterone concentrations to within the surgically castrate range. At a median follow-up of 2 years, there was no difference in overall survival, confirming that medical castration is an effective alternative to orchiectomy in patients with metastatic disease. Oleg *et al.* conducted a single-center retrospective study on patients with osseous metastasized prostate cancer and found overall survival time was 29 months, after bilateral subcapsular orchiectomy. Due to an effective and persistent oncological effectiveness, less morbidity, and absence of psychological implications, bilateral subcapsular orchiectomy seems to be a practicable and advisable alternative in the first-line therapy of metastasized PCA. These studies show no statistically significant difference between the study groups and showing they are equally effective.

The time to hormonal resistance (months) was in our study groups were 20.78 and 19.71, respectively ($p > 0.05$), showing no significant difference between the study groups. This was similar to the study reports of Aslan *et al.* showing the mean time of hormonal resistance between the bilateral orchiectomy and LHRH + AA as 32.77 and 26.48, respectively. In our study, the number of patients undergone castration-resistant prostate cancer was more in medically castrated groups (11) compared to surgically castrated groups (4) with a statistically significant difference ($p < 0.05$). This shows that surgical castration can be an effective alternative for medical castration in metastatic prostate cancer patients.

The morbidity from bone metastasis is referred to as skeletal-related events, which includes fractures, cord compression, radiation to bone and surgery to bone leads to impaired quality of life and significant costs [16]. In our study, the skeletal-related events associated with

surgical versus medical castration for radiation, pathological fracture, spinal cord compression, and surgery was (65% vs. 35%), (83% vs. 17%), (100% vs. 0%), and (75% vs. 25%), respectively. No statically significant difference was found between the skeletal-related events (>0.05) except for the radiation ($p < 0.05$). We found that probability of getting radiation in medical castration was higher compared with surgical castration with SRE, this may be due to poor compliance, delayed treatment, more concern, financial assistance and quality of medicine, resulting from ending up with SRE. Broder *et al.* in his studies showed that patients with SREs had more pain and less survival time compared to patients with no SRE.

CONCLUSION

No significant difference in survival time between the treatment groups shows that medical and surgical castration are equally effective in metastatic prostate cancer. Among the various known prognostic factors studied, we found that time to nadir was better with surgically managed patients. The chance to get a radiation treatment because of disease progression was less with surgical castration patients compared to medically castrated patients. Even though both study groups had similar survival time, considering the nadir PSA level, better quality of life, patient compliance and adherence, reduced hospital visit and decreased the cost of treatment, the surgical castration may be a better treatment option for metastatic prostate cancer patients, especially in developing countries.

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