SAFETY AND SHORT-TERM EFFICACY OF CHEMOHORMONAL THERAPY IN HORMONE SENSITIVE METASTATIC PROSTATE CANCER

THESIS

Submitted to

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Master of Chirurgiae (MCh)

Urology

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DECLARATION

I here by declare that this thesis titled **"Safety and short-term efficacy of chemohormonal therapy in hormone sensitive metastatic prostate cancer"** is a bonafide and original research work carried out in partial fulfilment of the requirements for the degree of Master of Chirurgiae (M.Ch.) in Urology under supervision and guidance, in the Department of Urology, All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled **"Safety and short-term efficacy of chemohormonal therapy in hormone sensitive metastatic prostate cancer"** is the bonafide work of **Dr Gaurav Baid** carried out under our guidance and supervision, in the department of Urology, All India Institute of Medical Sciences, Jodhpur.

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Date:

Place: **Dr Gaurav Baid**

DEDICATED

TO

MY

MOTHER

ABBREVIATIONS

QOL	Quality of life
ADT	Androgen deprivation therapy
mHNPC	Metastatic Hormone Naive prostate Cancer
mHSPC	Metastatic Hormone Sensitive Prostate Cancer
PSA	Prostate Specific Antigen
LHRH	Luteinizing Hormone Releasing Hormone
CRPC	Castration Resistant Prostate Cancer
PSMA	Prostate Specific Membrane Antigen
G-CSF	Granulocyte –Colony Stimulating Factor
RECIST	Response Evaluation Criteria in Solid Tumors
ECOG	Eastern Cooperative Oncology Group
PFS	Progression free survival
LUTS	Lower urinary tract symptoms
DRE	Digital rectal examination
TRUS	Trans rectal ultrasound
mpMRI	Multi parametric magnetic resonance imaging
DHT	Dihydrotestosterone
CHAARTED	Chemohormonal therapy versus androgen ablation randomized trial in extensive disease
STAMPEDE	Systemic therapy in advanced and metastatic prostate cancer evaluation of drug efficacy

SUMMARY

Study Design - Single center prospective study.

Objective - To assess toxicity and clinical, radiological & biochemical response of chemohormonal therapy in metastatic hormone sensitive prostate cancer.

Background - Prostate cells need androgen to survive. Decrease in androgen levels lead to apoptosis of prostate cancer cells. For many years this was the basis of treatment of metastatic prostate cancer in the form androgen deprivation therapy (ADT). The hypothesis that a subpopulation of prostate cancer cells may be AR-negative (Androgen Receptor), and thus resistant to ADT from the beginning, is the rationale for combining ADT with docetaxel in men with mHSPC (hormone-sensitive metastatic prostate cancer). So in this study we want to see how safe and efficacious chemohormonal therapy is, in mHSPC patients presenting to our center.

Method - 25 Biopsy proven metastatic prostate cancer patients fulfilling inclusion criteria are included in this study. Patients were subjected to Inj Docetaxel and ADT (medical/surgical). Total of 6 cycles of Inj Docetaxel have been given and adverse events & radiological, clinical, biochemical response have been recorded. In our study majority (36% each) of study population belong to 51-60 and 71-80 year age group. Most of the patients were of good performance score that is 84% were of ECOG 0. Most of the patients were of high grade group, 56% of the patients were of grade group 5, 24 % were of grade group 4. Median PSA at the presentation in our study was 100 ng/ml. In our study neutropenia, requiring G-CSF Inj Filgrastim, occurred in 4 patients (16%). Post-chemotherapy radiological response was partial in 12, stable disease in 7 and progressive disease in 2 patients according to the RECIST criteria. The number of patients achieving a nadir PSA value of less than 0.2 ng per millilitre was 6 in our study. 76.9% patients improved symptomatically.

Conclusion - Docetaxel chemotherapy with ADT was found to be safe with an adequate biochemical and clinical response in patients presenting first time with metastatic prostate cancer in our population. Radiological response was limited. Potential side effects aside the cost-benefit to patients as well as proven efficacy make it the first-line therapy alongside ADT in such patients.

INDEX

LIST OF FIGURES

LIST OF TABLES

LIST OF GRAPHS

INTRODUCTION

INTRODUCTION

Prostate cancer is the most common malignancy in older men. (1) If localized, complete surgical extirpation of the gland (radical prostatectomy), Radiotherapy and active surveillance are the options of treatment.(2) (3) Multiple drugs are available for patients with locally advanced, recurrent or metastatic tumours, which help in prolonging survival and the progression-free interval, while maintaining a good quality of life (QOL). (1)

For many years, androgen deprivation therapy in the form of medical or surgical castration has been the mainstay of therapy for metastatic prostate cancer. The basis of this treatment is the fact that prostate cells need androgen to survive. Decrease in androgen levels lead to apoptosis of prostate cancer cells. (4) (5) However, after several months, prostate cancer cells enter a "hormone refractory" state, where they stop responding to ADT (Androgen Deprivation Therapy) alone. (5) (6) This state, more correctly termed "castration resistant", is treated with chemotherapy or newer generation antiandrogen.

An initial RCT (Randomized controlled trial) published in 2004 evaluated the use of a chemohormonal therapy (estramustine phosphate plus ADT) for newly diagnosed patients with metastatic prostate cancer, and showed a longer cPFS (progression free survival) for the combined modality ($p = 0.03$), although there was no significant difference in the overall survival. (7)

A combination of docetaxel, a semi-synthetic second-generation taxane, with prednisone, was the first treatment that could significantly improve overall survival in men with metastatic castration-resistant disease. (8) (9)Many questions have been raised since then, as to whether administering chemotherapy to men with metastatic hormone-sensitive prostate cancer (mHSPC), before symptomatic disease progression after starting ADT, could improve the overall survival and the quality of life of the patients. (10)

The hypothesis that a subpopulation of prostate cancer cells may be AR-negative (Androgen Receptor), and thus resistant to ADT from the beginning, was the rationale for combining ADT with docetaxel in men with mHSPC (metastatic hormone-sensitive prostate cancer).
Some early clinical studies have shown that the addition of docetaxel to ADT significantly increased the clinical progression-free survival of patients with mHSPC. (11) However, the results for the overall survival remained controversial. In two different RCTs published in 2015, no differences were observed in the first RCT for the overall survival between the

groups studied (11) (12) (13) , while in the other (14) (15) the overall survival was 13.6 months longer for the group with a combination of Docetaxel (6 cycles) plus ADT (57.6 months vs. 44 months).

Prostate cancer is a heterogeneous disease with marked variability in treatment outcomes, depending on many factors including racial & geographical variations. These data are from west, this study aims to evaluate the effectiveness and safety of Docetaxel with standard ADT in the treatment of patients with mHSPC presenting to our center.

AIM & OBJECTIVES

AIM AND OBJECTIVES

The aim of the study is to assess safety and short-term efficacy of administration of Inj Docetaxel with androgen deprivation therapy in hormone sensitive metastatic prostate cancer at tertiary care center.

The objectives of this study are:

i) To assess toxicity (Hematological and Nonhematological adverse events) of Inj Docetaxel with androgen deprivation therapy in hormone sensitive metastatic prostate cancer
ii) To see Clinical and Biochemical response (PSA response) after 3 and 6 cycles of Inj Docetaxel with androgen deprivation therapy in hormone sensitive metastatic prostate cancer
iii) To see radiological response after 6 cycles of Inj Docetaxel with androgen deprivation therapy in hormone sensitive metastatic prostate cancer

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Epidemiology and Etiology

Prostate cancer is among the most common noncutaneous malignancies, second most common in men worldwide. (15) The incidence rate of prostate cancer was initially stable then it increased dramatically after the use of PSA screening and then it declined and came back to base line, then again it rose and ever since it is fluctuating year by year.

Incidence rate of prostate cancer increases with age, 1 in 350 under the age of 50 years, 1 in 52 men between the age of 50 to 59, and it is 60% over the age of 65 years. (16) A trend towards increasing incidence of prostate cancer worldwide has been observed. Increasing incidence in developing countries is likely due to increased ease of medical access and documentation of cases. The incidence rate has also increased in those regions where PSA screening is not routinely used, is likely due to westernization of life style, obesity, dietary factors, sedentary habits. (17)

The exact etiology of prostate cancer remains unclear, but some of well established risk factors are advanced age, family history, ethnicity and genetic factors. Some other factors contributing to prostate cancer are obesity, physical inactivity, hyperglycemia, diet (increase intake of animal fat, red meat, low intake of fruits, vegetable, vitamins), exposure to radiation and chemicals. (18)

The prevalence of prostate cancer varies considerably among different racial groups, it is highest in African- American men. (16) 20% of patients of prostate cancer have a positive family history, and 5% have genetically inherited background. (19) Different genes responsible for prostate cancer are HPC1 gene (1q24-25), HPC/ELAC2 (17p11), MSR1 (8p22), BRCA1, BRCA2. (20) (21)

Dietary variables may have an important role in the development of prostate cancer, as indicated by multiple studies on immigrants migrating from low-risk areas (developing world) to high-risk areas (developed world), which revealed how the transition to a "westernised" lifestyle resulted in an increase in prostate cancer incidence.

Most epidemiological studies have found no link between smoking and prostate cancer, although other cohort studies have found that smokers who smoke more than a pack a day had a 2 to 3 time higher risk than nonsmokers. (22)

Prostate cancer and inflammation have a close link, and Rudolf Virchow was the first to discover a high density of leukocytes in neoplastic samples in 1863, implying a link between inflammation and cancer. (23)

Pathophysiology of prostate cancer

Prostate cancer has a complicated molecular pathology: numerous genes are implicated in its pathogenesis, and other environmental variables such as nutrition and inflammation also play a role.

Prostate cancer can be separated into hereditary and sporadic types epidemiologically, but they cannot be discriminated molecularly, and unlike many other cancers, there are no highly penetrant inherited genes conferring the prostate cancer phenotype.

Hereditary prostate cancer

Although the ELAC2, RNASEL, MSR1, NSB1, and CHEK2 genes have been discovered as probable inherited prostate cancer susceptibility genes in some families, the proportion of instances of hereditary prostate cancer owing to germline mutations at these loci is minimal. These potential gene mutations have also been found in sporadic prostate cancer.

Because prostate cancer is so widespread, it's sometimes difficult to tell the difference between sporadic prostate cancer in families and real hereditary prostate cancer.

Table 1. Hereditary prostate cancer genes

Gene	Chromosomal locus	Putative function	Status in prostate cancer
ELAC 2	17p	Metal dependent hydrolase	Unknown
RNASEL	1q	Ribonuclease that degrades viral and cellular RNA and can produce apoptosis on viral infection	Deleted
MSR1	8p	Encodes a macrophage scanvenger receptor responsible for cellular uptake of molecules, including bacterial cell wall products	Deleted
NBSI	5p	Encodes a protein, nibrin, involved in processing/repair of DNA double strand breaks and in cell cycle checkpoints	Deleted
CHEK2	22q	Upstream regular of p53 in the DNA damage signaling pathway	Deleted

Sporadic prostate cancer

The vast majority of prostate cancers are sporadic.

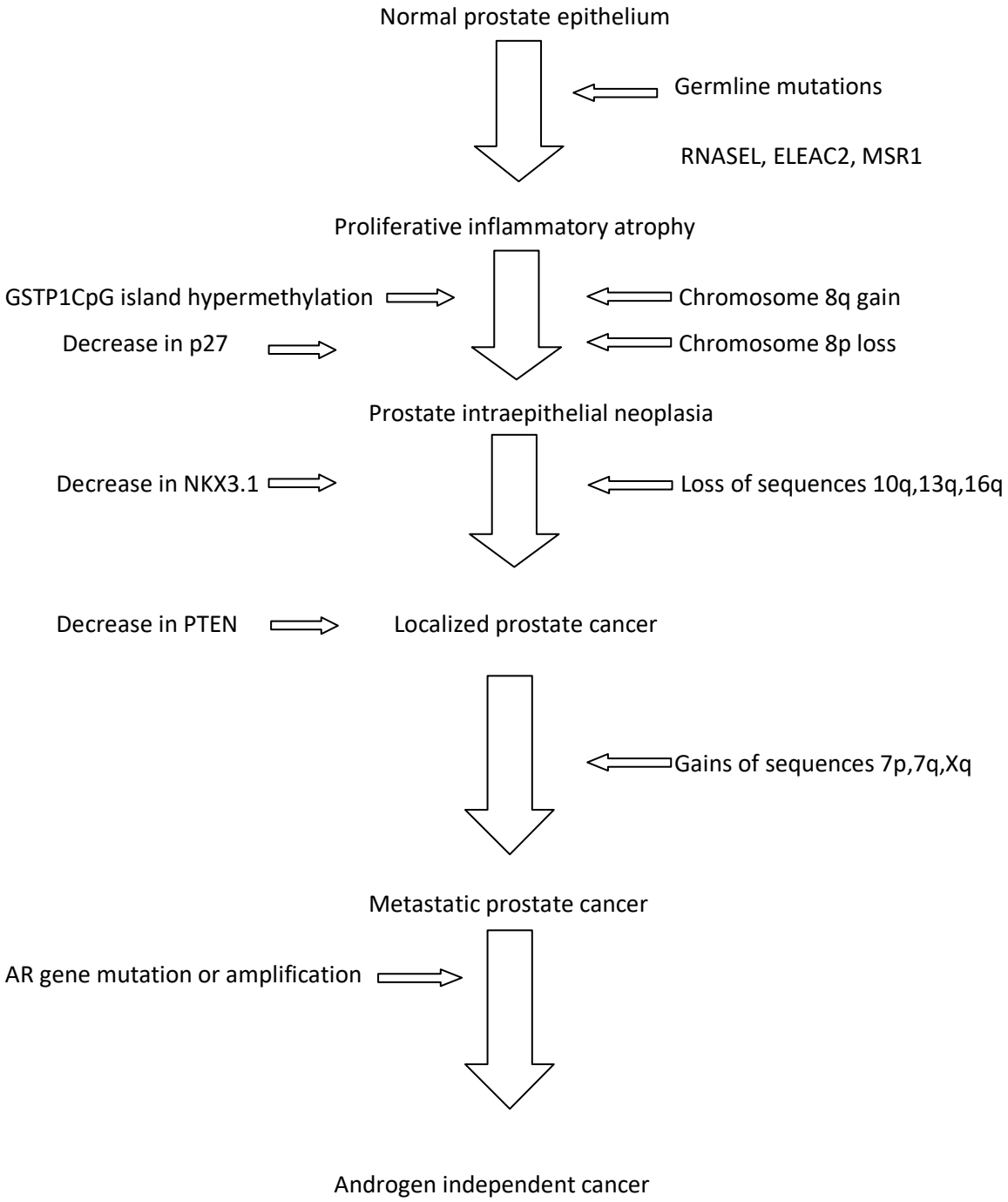


Figure 1. Pathophysiology of prostate cancer

Symptoms and signs

Prostate cancer has varied ways of presentation, in some countries, the widespread use of PSA as a prostate cancer screening test has resulted in more asymptomatic men being diagnosed. Men may present with LUTS or other genito-urinary symptoms. (24) Hematuria is a well-known high-risk symptom for urological malignancy, including prostate cancer. (25) Erectile dysfunction, another highly frequent complaint in males that increases in incidence with age, has also been linked to prostate cancer. (26) Weight loss, bone pain, generalized weakness, anasarca, pedal edema, renal failure etc. are features of advanced prostate cancer.

Diagnosis and staging

Prostate cancer (PCa) is diagnosed by digital rectal examination (DRE) and prostate-specific antigen (PSA) blood test, followed by prostate biopsy. Because prostate cancer is such a heterogeneous disease, ranging from small, indolent, low-grade tumours to large, aggressive, life-threatening tumours, the primary goal for urologists during prostate cancer baseline evaluation is to assess local and distant cancer extension, as well as the aggressiveness of the disease by staging.

DRE - According to the research, clinical staging errors are widespread, and inter observer variability of DRE can lead to misinterpretation of genuine staging but can more selectively detect more aggressive cancers. (27)

Imaging modalities

mpMRI- When clinical presentation and serum PSA suggestive of localized disease, mpMRI is advised for local staging, it may be performed prebiopsy or postbiopsy, however to minimise artefacts caused by biopsy it should be performed at least 6 weeks after biopsy.

CT Scan - Although nomograms can assist predict the probability of lymph node metastases, CT is conventional imaging modality for assessing lymph node extension in individuals with intermediate or high risk prostate cancer. CT Scan is recommended for high risk patients such as clinical stage T3 or more or >20% nomogram probability of lymph node metastasis.

PSMA PET - PSMA is a type II, 750-amino-acid integral membrane glycoprotein. PSMA (prostate-specific membrane antigen) is a potential and specific imaging target for prostate cancer. PSMA–PET imaging can contribute molecular information to multiparametric MRI and, consequently, designate suspicious lesions for targeted biopsies. PSMA–PET imaging

increases detection of metastatic lesions in biochemically recurring prostate cancer, even when serum PSA levels are low.

Bone Scan - Tc Bone scintigraphy remains the gold standard nuclear examination for high risk disease or symptomatic patients to diagnose bone metastasis, with a sensitivity of 0.79 (95 percent CI: 0.73–0.83) and a specificity of 0.82 (95 percent CI: 0.78–0.85). Despite its poor performance with PSA values less than 20 ng/mL, technetium scintigraphy remains the gold standard for detecting bone metastases with traditional technetium uptake at metastatic locations. (28) Men with clinical T1 disease and PSA >20 ng/mL, Gleason score 8, clinical T3 or T4 illness, or symptoms indicative of metastases should get a bone scan, according to the NCCN guidelines. (29)

Other PET Scan - The limited uptake of Fluorodeoxyglucose (FDG) by prostate cancer cells and high overlap with marker uptake by BPH limit the efficacy of PET Scanning with FDG in diagnosing prostate cancer. Another disadvantage is that normal urine FDG excretion causes excessive bladder activity, masking abnormal FDG uptake in the prostate. Bone metastasis in prostate cancer are sclerotic and they take up FDG less avidly so FDG PET is considered inferior to bone scan for prostate cancer. Carbon 11 labeled choline (^{11}C-choline), accumulates in prostatic cells and it is not excreted in urine like FDG and therefore does not influence visualization of prostate. In recurrence patients ^{11}C-choline-PET has a high positive predictive value.

Treatment

Treatment options for metastatic prostate cancer

Androgen deprivation therapy

Androgens are thought to be the source of energy for prostate cancer. (30) More than 90% of systemic androgen function is accounted for by testosterone, with dihydrotestosterone (DHT) being the most significant form (cytosolic). (31) Although DHT is a more potent androgen for structural and metabolic reasons, the AR binds to both testosterone and DHT with similar affinity. (32) The initial treatment for metastatic prostate cancer is androgen deprivation therapy (ADT), which can be done medically or surgically. ADT has quick and substantial therapeutic benefits in males with symptomatic metastatic prostate cancer. (33)

Surgical castration - Charles Huggins first showed that prostate cancer cells are inhibited by testosterone suppression. Initially testosterone suppression was achieved by surgical castration (orchidectomy). (34)

First generation antiandrogens - Veterans Administration Cooperative Urologic Research Group (VACURG) trial in the 1960's showed that oral estrogen (diethylstilbestrol) was as effective as surgical castration, which in turn led to further efforts at drug development for "medical castration". (35) In the 1970's, flutamide, an oral non-steroidal antiandrogen which blocks the androgen receptor was developed. (36)

Non-steroidal drugs (such as bicalutamide, nilutamide, and flutamide) and the steroidal drug cyproterone acetate were among the first anti-androgens. Many men will respond, and these drugs can help to delay disease progression and the requirement for newer drugs later on in the disease's progression.

LHRH agonist and antagonists - After identifying the structure of luteinizing hormone-releasing hormone (LHRH) in 1980, intranasal buserelin in prostate cancer patient showed a significant decrease in serum testosterone. (37) The concern for possible disease flare was there due to transient rise in serum androgens. The combination of an antiandrogen (flutamide) with an LHRH agonist (LHRH ethylamide [HOE-766]) prevented this flare phenomenon, resulting in a decrease in prostatic acid phosphatase levels and symptomatic improvement in 9 of 10 patients. (38) After that, several generations of antiandrogens (nilutamide, bicalutamide) and LHRH agonists (leuprolide, goserelin, triptorelin) have been used to treat prostate cancer. After that Androgen suppression via LHRH agonists has become the backbone of therapy for metastatic hormone-sensitive disease.

Newer antiandrogens - The new anti-androgens go after different parts of the androgen synthesis pathway, which is important for tumour growth. Previously these drugs were used in men who were not fit for chemotherapy and whose disease has progressed on chemotherapy. Early introduction of medications previously designated for castrate-resistant disease can enhance overall survival in other patients with metastases, according to studies on the best therapy sequence.

Abiraterone acetate - Enzymes involved in testosterone production include cytochrome P450 17 alpha-hydrolase and C17, 20-lyase. They play a role in the transformation of pregnenolone-like steroids into androgens. Because abiraterone is an oral inhibitor of these

enzymes, it prevents the production of both extragonadal and testicular androgens. (39) Prednisone should be taken with abiraterone to reduce the abiraterone-induced decrease in blood cortisol and increase in mineralocorticoids. A meta-analysis from LATITUDE and STAMPEDE trials demonstrated improvement in survival associated with abiraterone in addition to ADT vs ADT alone in mHSPC. (40) Patients should be monitored for hypertension, hypokalemia, and peripheral oedema, as well as an increase in hepatic aminotransferases, which may necessitate a therapy interruption.

Enzalutamide - Enzalutamide is an androgen-receptor signalling inhibitor. Enzalutamide has activity both before and after chemotherapy. (41) Adverse effects include hypertension, fatigue, memory impairment, falls and, less commonly, seizures. Studies into upfront Enzalutamide are ongoing. ENZAMET (NCT02446405) is an international phase 3 trial in which men with mHSPC receive ADT with or without docetaxel, and are randomized to treatment with enzalutamide or placebo.

Apalutamide – Block the androgen receptor on cancer cells, blunting androgen's ability to fuel prostate cancer growth.The TITAN study (NCT02489318) is a international phase 3 trial randomizing men with mHSPC to treatment with ADT with or without apalutamide, a novel antiandrogen.

Chemotherapy

Prior to 2004 options were limited for progressing prostate cancers on AR targeted therapies so investigators tested chemotherapy for mCRPC (Metastatic Castration Resistant Prostate Cancer).

Clinical trials of cytotoxic chemotherapy (alkylating agents) in advanced prostate cancer began in the 1950s. As number of patients was less and meaningful endpoints were lacking, the results were difficult to interpret. (42) So many investigators suggested that prostate cancer was a chemotherapy-resistant disease. (42) (43) (44)

As survival benefit could not be perceived, chemotherapy trials were then designed to assess palliation endpoints. Based on symptomatic improvement mitoxantrone in combination with prednisone was the first FDA-approved chemotherapy for mCRPC. (45) Mitoxantrone is a topoisomerase II inhibitor given intravenously (12 mg/m^2) on a 3-week schedule. Side effects range from mild (nausea, alopecia) to more severe (dose-dependent cardiomyopathy).

Prostate-specific antigen (PSA) responses were low and no survival benefit was shown. (45) (46) (47) Until 2004 there was no chemotherapeutic agent that improved overall survival in prostate cancer.

Docetaxel and paclitaxel were developed in the early 1990s. (48) Estramustine and docetaxel showed a synergistic effect in Prostate Cancer. (49) The combination was found to be safe and clinically active against castration-resistant prostate cancer. (50) (51) (52) The 21-day cycle of docetaxel (60 mg/m^2 given on Day 2) with estramustine (280 mg three times daily on Days 1– 5) significantly increased the median overall survival by 1.9 months and included improved PSA and objective responses in SWOG9916, A randomized Phase III trial in mCRPC patients. (8) As estramustine causes thromboembolic events, docetaxel was studied as a single agent and shown to have activity in advanced prostate cancer. (53) (54)

A pivotal Phase III TAX327 trial (Tannock et al.), showed a 2.4-month increase in overall survival in the docetaxel (given every 3 weeks) + prednisone arm compared with mitoxantrone + prednisone, in mCRPC. (9) Docetaxel (75 mg/m^2) given every 3 weeks also had a significant survival advantage over weekly docetaxel (30 mg/m^2). Docetaxel caused significant reductions in pain and improved quality of life measures, although adverse events (peripheral edema, neuropathy, gastrointestinal toxicities) were more as compared to mitoxantron. In 2008, One hundred and fifty men with mCRPC were randomly assigned to docetaxel (35 mg/m^2 on Days 2 and 9 every 21 days) and prednisone (10 mg daily) with or without estramustine (280 mg on Days 1–5 and 8–12 every 21 days), which showed no difference in PSA response or overall survival, although docetaxel as a single agent was FDA approved in 2004. (55) SWOG9916 and TAX327 established that docetaxel to be given on a 3-week schedule as firstline chemotherapy in metastatic prostate cancer after developing disease progression on conventional hormonal therapy.

After FDA approval of docetaxel in 2004 and no other known life prolonging therapies at the time, a number of trials were launched investigating the combination of ADT with docetaxel in patients with newly metastatic disease. After invention of abiraterone and enzalutamide for mCRPC, these trials were easy to forget and almost rendered obsolete as the conventional thought was to incorporate these new agents at the time of castration resistance pushing chemotherapy further down in the lines of treatment. Chemotherapy would then be considered following the use of these drugs.

GETUG-AFU15, CHAARTED, and STAMPEDE, these three clinical trials assessed the effect of ADT with concurrent chemotherapy for metastatic hormone-naive disease. The thought was that in the latter stages of disease the performance status tends to be worse so chemotherapy may be better tolerated earlier in the disease course. And the cytotoxic effect of chemotherapy and ADT-mediated apoptosis results in synergistic cell kill.

CHAARTED and STAMPEDE (arm C) trials showed a survival benefit of chemohormonal therapy in metastasized hormone-sensitive prostate cancer (mHSPC). (56) (14) GETUG-AFU 15 trial also showed this, which previously had failed to demonstrate survival benefit itself. (57) (11) (58) Treatment-associated grade 3 to 5 toxicity among mHSPC study population was reported in 30% to 52% of patients. In particular, the rate of febrile neutropenia grade 3 to 5 was as high as 6% to 15%. So far, reported rates of grade 3 to 5 adverse events ranged between 34% and 40%. (59) (60) So toxicity is a hurdle in widely implementing upfront cytotoxic treatment, as docetaxel was associated with a lower toxicity rate in the mCRPC setting in the TAX 327 trial (26%). (9)

Real-life data might contribute to the understanding of a better patient stratification outside clinical trials.

PARP (Poly adenosine diphosphate ribose polymerase) inhibitor
Trials are going on to treat metastatic prostate cancer which has defects in DNA- repair genes, with PARP inhibitor Olaparib.

Local treatment of the prostate
Recent research suggests that even after the emergence of metastatic disease, the initial tumour has a role in disease progression.

Radiotherapy - prospective data from STAMPEDE demonstrates radiotherapy to the prostate is associated with prolonged survival for men with low volume mHSPC. (61)

Radical prostatectomy - Data regarding a potential benefit for cytoreductive radical prostatectomy for men with mHSPC remains limited to retrospective studies.

MATERIALS & METHODS

MATERIAL AND METHODS

Study setting: -

Following Confirmation of eligibility, all patients who admitted in department of Urology, AIIMS.

Study design: -

Single center prospective study.

Study Procedure: -

A clearance from ethical committee of institution was obtained prior to the investigation (Ethical clearance number AIIMS/IEC/2019-20/985).

Biopsy proven metastatic prostate cancer patients are included in this study, TNM staging has been done with relevant investigations i.e. Axial Imaging (CT or MRI Abdomen +Pelvis), Bone Scan or PSMA (Prostate Specific Membrane Antigen) PET Scan. Patients have been offered all the current standard of care treatment choices, written consent have been taken, who wanted to be part of study. After baseline hematological investigations *viz* (complete hemogram, blood urea, serum creatinine, liver function test), patients were subjected to Inj Docetaxel and ADT (medical/surgical). ADT was performed first, followed by first dose of Inj docetaxel within 90 days of ADT initiation, in the form of surgical castration or medical castration (LHRH agonist or antagonists).

In this study, we used premedication in the form of Tab Dexamethasone 8 mg 12 hr, 3 hr, and 1 hr before Inj Docetaxel (as used in CHAARTED trial). The patients have been given Inj Docetaxel 75 mg/m^2 IV in 500 cc NS (normal saline) over 1 hr (dose modifications have been done according to body surface area of patient and toxicity of Docetaxel, up to 55mg/m^2). Inj Pantoprazole 40mg IV and Inj Ondansetron 4 mg IV were given prophylactically before the Inj Docetaxel. Adverse events are classified according to the Common Terminology Criteria for Adverse Events (Version 4.0) of the National Cancer Institute. All adverse events of each administered cycle of Docetaxel and ADT are recorded. In case of neutropenia ≥ grade 2 (a count of 1000-1500) during the first or subsequent cycle, Granulocyte-colony stimulation factor (G-CSF) have been prescribed (Inj Filgrastim 300 mg subcutaneous single dose). Examination was performed at start of treatment, just before 4th cycle of Inj Docetaxel and

within 8 weeks of 6th cycle of Inj Docetaxel. Biochemical response (PSA level) was documented at the start of ADT then 3 weeks after 3rd cycle of docetaxel and then within 8 weeks of last cycle of docetaxel. Bone scan along with CT/MRI of abdomen and pelvis have been performed, within 8 weeks after last cycle of docetaxel. Radiological response has been reported using RECIST (Response Evaluation Criteria in Solid Tumors -Version 1.1) criteria. Patients were given 1000 mg of Calcium Carbonate and 800 IU vitamin D per day.

Participants

Inclusion criteria-

All patients with metastatic hormone sensitive prostate cancer (diagnosed as per protocol mentioned in study design) with good performance status [ECOG (Eastern Cooperative Oncology Group) Performance status 0, 1 or 2] and who have provided written informed consent.

Exclusion criteria-

1) Poor performance status (ECOG 3 or 4)
2) Those who are unable to complete at least 3 cycles of Docetaxel
3) Those who have not consented this treatment protocol
4) Those with deranged liver function test, hematological abnormality or any other abnormality which preclude administration of ADT or Inj Docetaxel

Study duration: -

From January 2020 to August 2021

Sample size:-

The previous studies were multicentric trials (STAMPEDE and CHAARTED trial), large sample size was there and duration of follow up was long.

Since we are doing single center study, so those patients are studied which came between January 2020 to August 2021. Follow up has been done till December 2021.

Statistical Analysis

All data have been acquired in a specified format as in Performa and entered in SPSS (statistical package for the social science system) V 25/ MS-Excel software for analysis. Proportions have been calculated. To see correlation between events Pearson or Spearman correlation has been calculated.

Non-parametric tests of significance (Friedman test and Wilcoxon signed rank test) used for comparing data not normally distributed (PSA levels). Time to event is analyzed by Kaplan Meier curve. P value <0.05 has been considered as significant in all statistical evaluations.

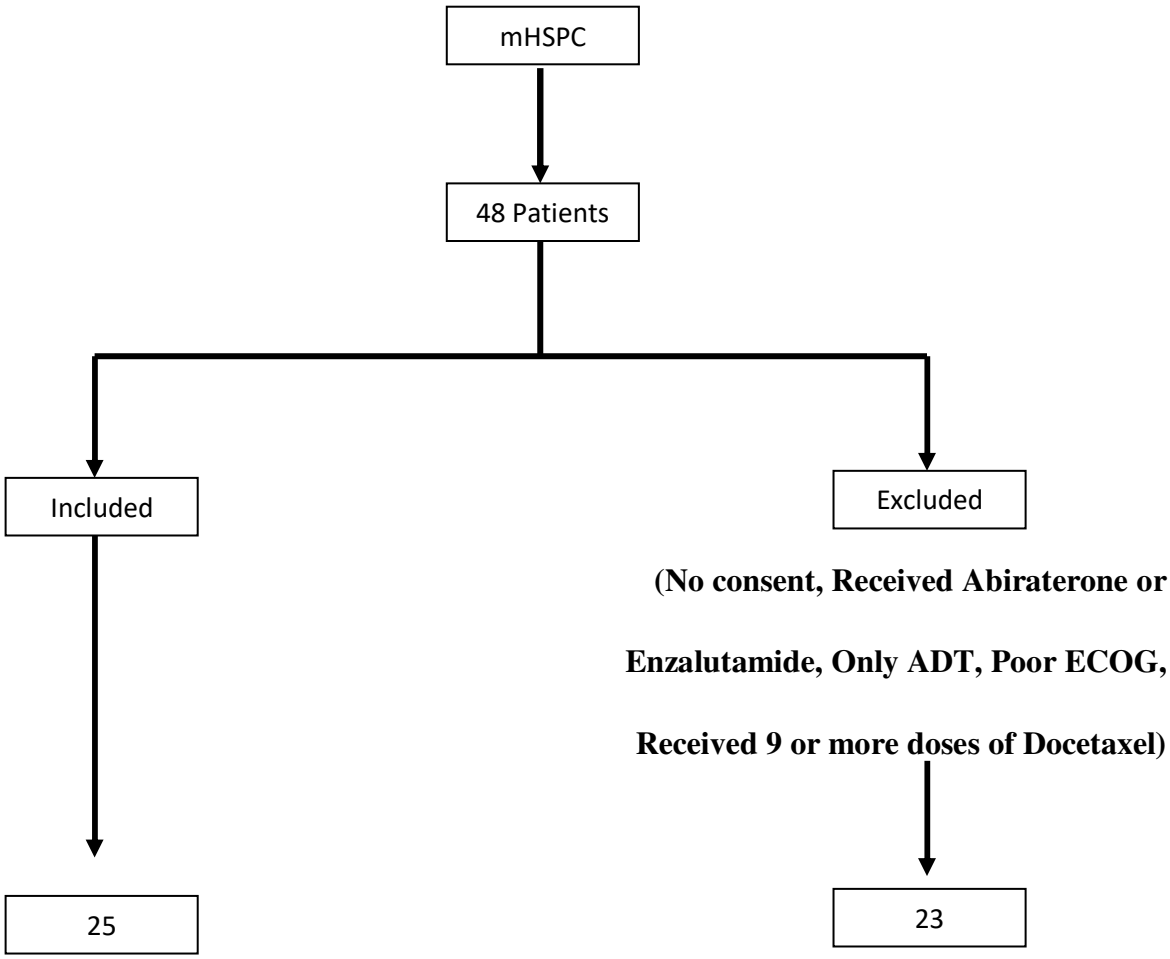
Ethical Considerations

All the patients enrolled in the study have received the standard care management, and the participation in the study has not lead to change in their usual diagnostic work up, follow up or management. All personal data collected during study are kept strictly confidential.

RESULTS

RESULTS

The present study has been conducted in Department of Urology, All India institute of medical sciences, Jodhpur, from January 2020 to December 2021. Total 48 patients presented with metastatic hormone sensitive prostate cancer out of which 25 patients met inclusion criteria and received ADT and Injection Docetaxel and were included in study, the results are as follows



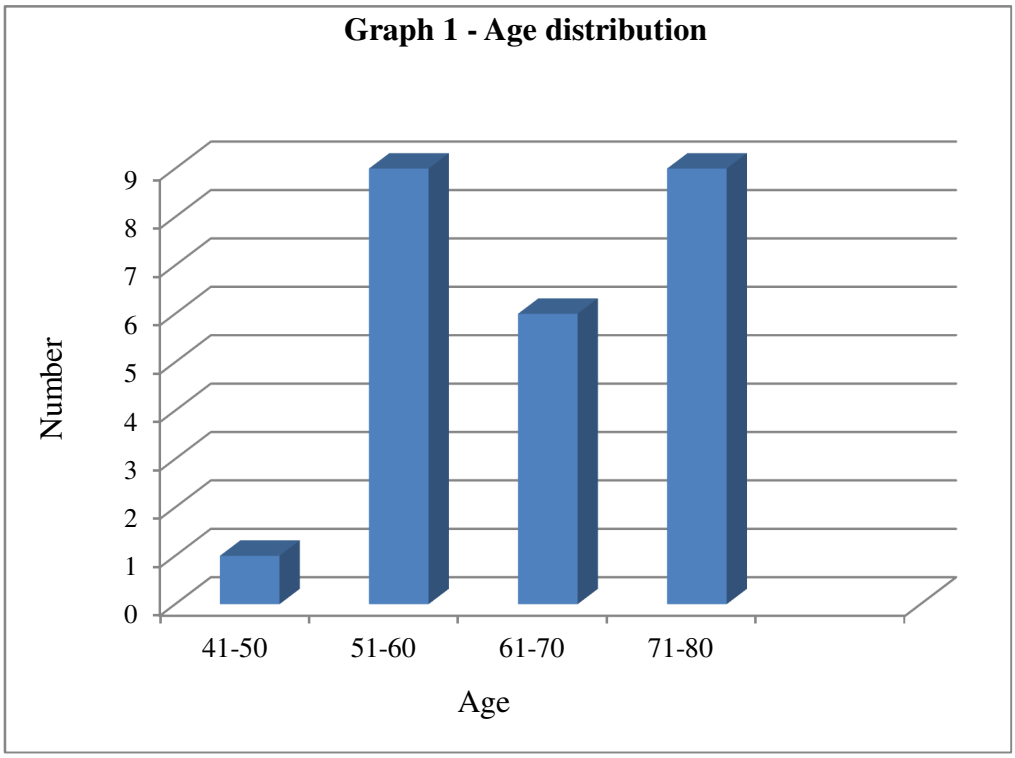
Patient characteristics

1. Distribution of study population according to age

Table 2. Distribution of population according to age

Age group	No.	%
41-50	1	4
51-60	9	36
61-70	6	24
71-80	9	36
Total	25	100.0

Mean age of the study population was 65.24 ± 8.86 (SD) years with youngest patient of 49 years and oldest of 80 years of age.

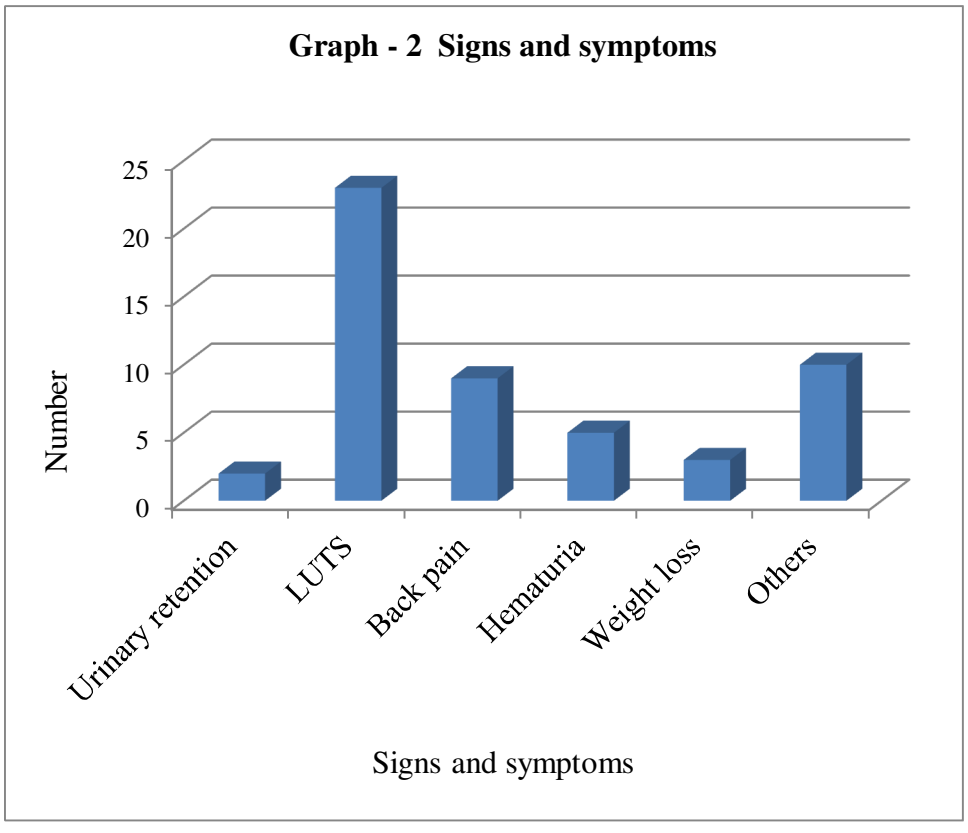


2. Distribution of population according to signs and symptoms

Table 3. Distribution of population according to signs and symptoms

S. No.	Signs and symptoms	No.	%
1.	LUTS	23	92
2.	Back pain	9	36
3.	Hematuria	5	20
4.	Weight loss	3	12
5.	Urinary retention	2	8
6.	Others	10	40

Most of the patients presented with multiple symptoms. 92% of patients presented with lower urinary tract symptoms while symptoms due to metastasis like back pain and weight loss were reported in 36% and 12% of patients respectively. 10 patients were having other symptoms like abdominal pain, hip joint pain, and generalized body ache.



3. Distribution of population according to Addiction

Table 4. Distribution of population according to Addiction

S. No.	Addiction	No.	%
1.	Smoking	6	24
2.	Tobacco chewing	4	16
3.	Alcohol	3	12

6 (24%) patients were smoking, 4 (16%) were having habit of tobacco chewing, and 3 (12%) patients were taking alcohol.

4. Distribution of population according to comorbidity

Table 5. Distribution of population according to comorbidity

S. No.	Comorbidity	No.	%
1.	HTN	4	16
2.	CAD	3	12
3.	DM	2	8
4.	Others	3	12

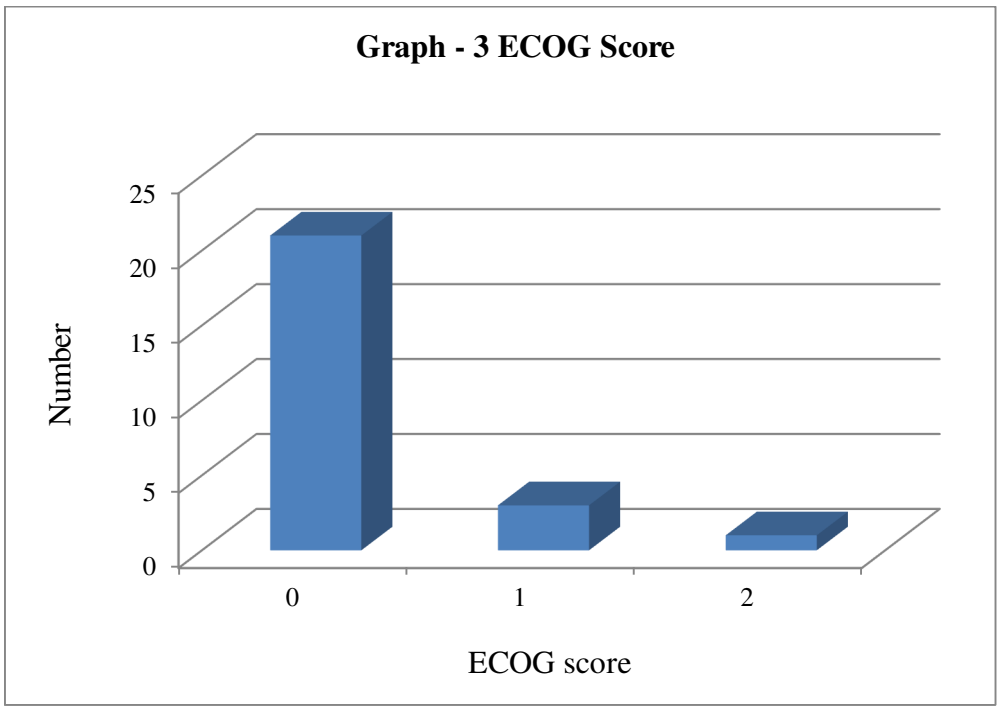
4 patients had HTN, 3 had CAD, 2 were diabetic, and 3 had other comorbidities (like ulcerative colitis, Recurring depressive disorder with hypothyroidism and Parkinsonism).

5. Distribution of population according to ECOG score

Table 6. Distribution of population according to ECOG score

S. No.	ECOG	No.	%
1.	0	21	84
2.	1	3	12
3.	2	1	4

Most patients were of good performance status (ECOG score was 0 in 84% of patients and 1 in 12% of patients and 2 in 4% of patients).

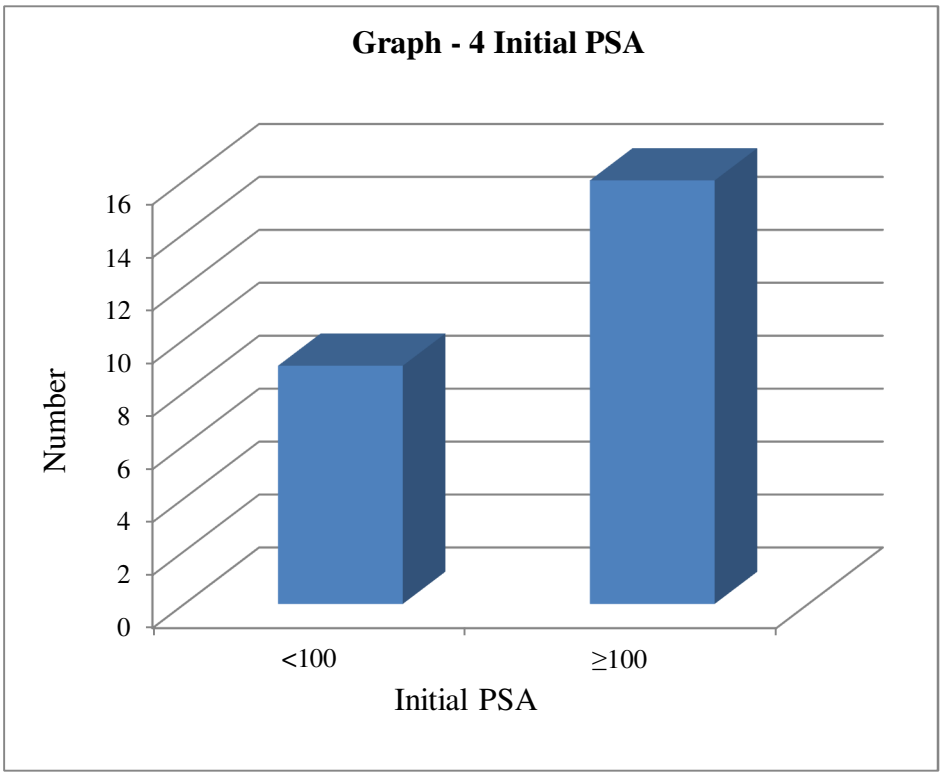


6. Distribution of population according to initial PSA

Table 7. Distribution of population according to initial PSA

S. No.	Initial PSA (ng/ml)	No.	%
1.	<100	09	36
2.	≥100	16	64

12 (48%) patients had >100 ng/ml initial PSA and 9 (36%) had <100 ng/ml and 4 (16%) had 100 ng/ml. The median initial PSA was 100 ng/ml. Ranged from 14.65 to 747 ng/ml.

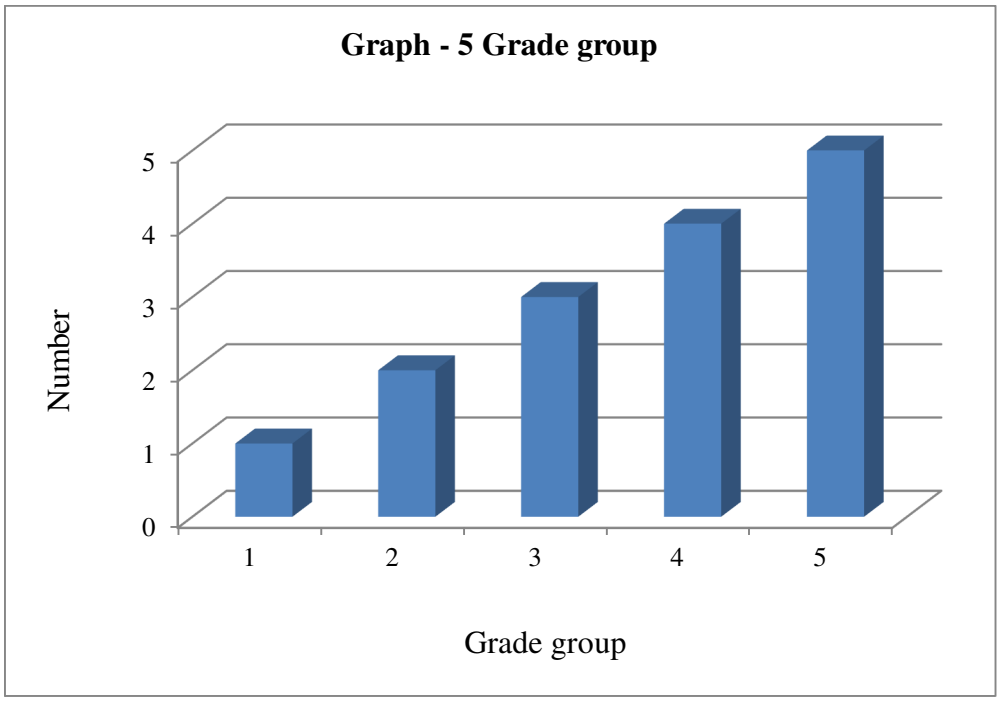


7. TRUS guided biopsy- Grade group

Table 8. TRUS guided biopsy- Grade group

S. No.	Grade group	No.	%
1.	1	1	4
2.	2	2	8
3.	3	3	12
4.	4	6	24
5.	5	14	56

56% of the patients were of grade group 5, 24 % were of grade group 4, 12% were of grade group 3, 8% were of grade group 2 and 4% of grade group 1.



8. Number of metastasis

Table 9. Number of metastasis

S. No.	Characteristic	No.	%
1.	Bone		
	Nil	4	16
	1	2	8
	2	1	4
	4	1	4
	>4	17	68
2.	Liver	3	12
3.	Pulmonary	3	12

18 patients (72%) had a high volume of disease (defined as >4 bony lesions and at least one lesion outside the spine or pelvis or the presence of visceral metastasis). 3 patients each had metastasis to liver, lungs, and non regional lymphnodes.

Treatment characteristics

9. ADT

Medical ADT was the most common form of primary androgen deprivation therapy used in 16 (64%) patients. Surgical ADT in the form of bilateral simple orchidectomy was done in 9 (36%) patients.

10. Time to chemotherapy after ADT

Chemotherapy was started on an average 27.44 ± 8.51 days after starting androgen deprivation. Earliest was 14 days gap and maximum was 42 days.

11. Dose of Injection Docetaxel

Table 10. Dose of Injection Docetaxel

S. No.	Dose of Injection Docetaxel	No.	%
1.	100 mg	23	92
2.	< 100 mg	1	4
3.	> 100 mg	1	4

A total of 6 cycles of docetaxel were administered. 23 patients received 100 mg Inj.Docetaxel in each cycle. In one patient we gave 110 mg Inj. Docetaxel. Dose modification was required in one patient, from initial dose of 100 mg later on to 90 mg.

Safety

12. Adverse events of Docetaxel

Table 11. Adverse events of Docetaxel

S. No.	Characteristic	No.	%
1.	Fatigue	11	44
2.	Neutropenia	4	16
	2000-1500	2	8
	1500-1000	0	0
	1000-500	1	4
	<500	1	4
3.	Anemia	3	12
4.	Neuropathy	3	12
5.	Thrombocytopenia	2	8
6.	Febrile neutropenia	1	4
7.	Diarrhoea	1	4
8.	Brittle nails	1	4

Complete hemogram was done one day prior and 3-5 days after each cycle of Inj Docetaxel. Adverse events were classified according to the Common Terminology Criteria for Adverse Events (Version 4.0) of the National Cancer Institute and the grades of neutropenia were defined as-

Grade 1- 1500-2000/mm^3

Grade 2 - 1000-1500/mm^3

Grade 3 - 500-1000/mm^3

Grade 4 - <500/mm^3

The major haematological adverse events reported were severe anaemia requiring blood transfusion in 1 patient (4%) while neutropenia requiring Inj Filgrastim in 4 patients (16%). Out of these one patient (4%) had febrile neutropenia. Furthermore, the grade of neutropenia was 1 in 2 (8%) patients, 3 in 1 (4%) patient and 4 in 1 (4%) patient.

Gastrointestinal toxicity (diarrhoea) severe enough to require admission was seen in one patient (4%). One patient had brittle nails after chemotherapy. None of the patients had allergic reaction. No patient had any incidence of thromboembolism.

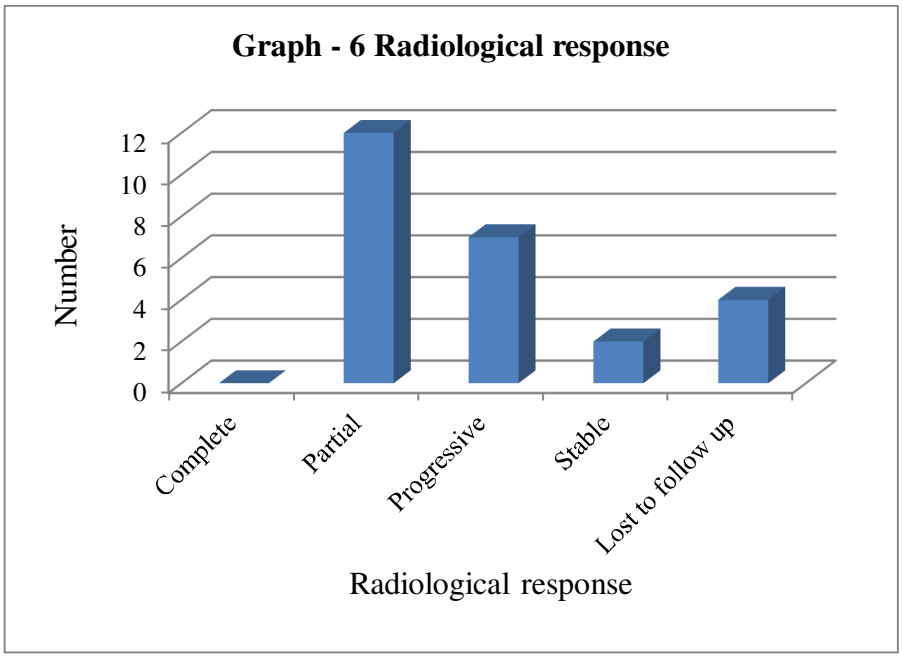
Efficacy

13. Radiological response (according to RECIST criteria) after 6 cycles of chemotherapy

Table 12. Radiological response (according to RECIST criteria) after 6 cycles of chemotherapy

S. No.	Characteristic	No.
1.	Complete	0
2.	Partial	12
3.	Progressive	7
4.	Stable	2
5.	Lost to follow up after 3 cycles of Injection Docetaxel	4

Post 6 cycles of chemotherapy, all patients were subjected to CT/PET/Bone Scan/MRI alone or in combination to assess the radiological response. The RECIST criteria were used for radiological grading. Overall, 2 patients had stable disease, while a partial response was seen in 12 patients. 7 patients had progressive disease. And 4 patients got lost to follow up after 3 cycles of Inj. docetaxel.



14. Biochemical response

The PSA levels were assessed for normality by using Shapiro-Wilk's test of normality. The data was found to be not normally distributed ($p<0.05$). Hence non-parametric tests of significance (Friedman test) used for comparing PSA levels at 3 time points. For comparing PSA levels between 2 time points Wilcoxon signed rank test was used.

Table 13. Biochemical response

	Baseline	**After 3 cycles**	**After 6 cycles**
Median PSA (ng/ml)	100	3.83	1.35

Reduction in PSA level found to be significant ($P <0.000$).

S. No.	**Reduction in PSA**	**P value**
1.	Baseline and after 3 cycles	<0.000
2.	After 3 cycles and after 6 cycles	0.131
3.	Baseline and after 6 cycles	0.001

PSA values were significantly lower at the end of 3 cycles compared to baseline. PSA values were significantly lower at the end of 6 cycles as compared to baseline but not significantly lower as compared to after 3 cycles.

After 3 cycles 7 patients achieved a PSA of ≤2 ng/ml. And after 6 cycles of chemotherapy 12 patients achieved a serum PSA less than 2 ng/ml, while in 9 patients the PSA remained above 2 ng/ml and 4 patients got lost to follow up after 3 cycles of chemotherapy.

6 patients achieved PSA value of <0.2 ng/ml.

15. Clinical Response (symptomatic improvement)

Table 14. Clinical Response (symptomatic improvement)

S. No.	Characteristic	No.	%
1.	After 3 cycles	16 (n=25)	64
2.	After 6 cycles	16 (n=21)	76.19

64% patients after 3 cycles and 76.9% patients after 6 cycles of chemotherapy improved symptomatically.

Follow up

Post chemotherapy 19 patients are stable and are on regular follow up. 4 patients were lost to follow up after 3 cycles of chemotherapy. 2 patients died during the follow up.

DISCUSSION

DISCUSSION

This is a prospective observational study conducted in department of Urology, All India institute of medical sciences, Jodhpur. In the department of Radiation Oncology patients received 9 or more doses of docetaxel hence patients could not be included in the analysis. The study period was from January 2020 to December 2021. In this we set upon to study the toxicity and clinical, biochemical, and radiological response of 6 cycles of Injection Docetaxel with androgen deprivation therapy in hormone sensitive metastatic prostate cancer.

Three major trials GETUG-AFU-15, CHAARTED and STAMPEDE, including an altogether total of nearly 2951 patients have reinforced the concept of early administration of docetaxel along with androgen deprivation in metastatic prostate cancer and radically changed the treatment of metastatic patients in hormone naive setting.

All our patients were metastatic at presentation unlike the GETUG-AFU 15 trial, which had 71 % and the CHAARTED-E3805 trial, which had 73 % of patients who were proven metastatic at the time of diagnosis.

In our study majority (36% each) of study population belong to 51-60 and 71-80 year age group, followed by 61-70 (24%). Minimum (4%) number of participants were of age group 41-50 year. Mean age of the population was 65.24 ± 8.86 (SD) years. Most of the patients were of good performance score that is 84% were of ECOG 0, 12% were of ECOG 1 and 4% were of ECOG 2.

In CHAARTED trial median age was 64 years (range, 36 to 88) in the combination group and 63 years (range, 39 to 91) in the ADT-alone group. 70% patients had an ECOG performance score of 0. (14)

Six (24%) patients were chronic smoker, 4 (16%) were tobacco chewer and 3 (12%) were chronic alcoholic. Four (16%) patients were hypertensive, three (12%) were known case of CAD, two (8%) were diabetic.

Most of the patients presented with multiple symptoms. The most common symptoms were LUTS (found in 92% of patients) followed by back pain (found in 36% of patients), hematuria (20%), weight loss (12%) and urinary retention (8%).

In our study most (44%) of the patients were of high Gleason score that is 5+4, followed by 4+4 (24%), 5+5 (12%), 4+3 (8%), 3+4 (8%), least number of patients were in the 3+3 (4%)

group and mean gleason score was 8.44 ± 1.04 ng/ml. 56% of the patients were of grade group 5, 24 % were of grade group 4, 12% were of grade group 3, 8% were of grade group 2 and 4% of grade group 1. In 84% of patients perineural invasion was present. This aggressive presentation also reflects in the three trials in which the mean gleason score was greater than 8 in nearly 70% of patients.

Most (84%) of the patients were of T4 disease, 16% were of T3, 92% were N1, 72% were of M1b disease and 20% were of M1c and 8% were of M1a. High volume metastatic disease in our study was 72%, which was 48% in the GETUG-AFU 15 trial and 65% in the CHAARTED-E3805.

Median PSA at the presentation in our study was 100 ng/ml which was higher than that reported for the GETUG and CHAARTED trial which was 26 and 52 ng/ml respectively and 70 for the STAMPEDE trial results. This again points to extremely aggressive disease at the start.

Maximum patients chose medical castration that is 64%, and 36% patient were surgically castrated.

ADT was in the form of orchidectomy or LHRH analogues or antagonist as was in all the three trials. Chemotherapy was administered within 27.44 days (mean) (range was 14-42days) in our study similar to the CHAARTED study (1 month). In comparison, the meantime to chemotherapy in GETUG-AFU 15 trial was 15 days and two months (8.6 weeks) in STAMPEDE trial. An early introduction of chemotherapy post castration (less than 20 days) has been determined to increase the risk of febrile neutropenia in comparison to those who start chemotherapy 80 days after commencing ADT. (60) The risk is nine times higher and the cause is still unclear. Multiple explanations have been offered including the decreased docetaxel clearance in non-castrate men, possibly due to alteration in the number and function of docetaxel transporters in the liver, (61) or significant bone marrow infiltration by the tumour or even the effect of ADT on neutrophil development and maturation. Studies in mice have pointed out that the androgen receptor is essential for neutrophil production (62) but these have not been validated in humans.

Most (92%) of the patients received 100 mg dose of Injection docetaxel, one patient (4%) received <100 mg and one patient (4%) received >100 mg.

In our study neutropenia, requiring G-CSF Inj Filgrastim, occurred in 4 patients (16%) which was higher as compared to 8%, 6%, and 12% in the GETUG-AFU 15, CHAARTED-E3805, and STAMPEDE trials. In 1 of our patient, the neutropenia requiring G -CSF occurred in the first cycle while in other two patients, it was during the second cycle and in another patient it was during third cycle. None of the patients had allergic reaction. No patient had any incidence of thromboembolism. There was no death during chemotherapy.

Although the total number of docetaxel cycles to be administered is still open to question in most studies, including ours, the median number of docetaxel cycles is six as in the CHAARTED, and the STAMPEDE trial. However, in the GETUG – AFU trial, the median number of cycles administered was 9. An appropriate balance between patient compliance and the oncological outcome may influence the number of cycles, as the proportion of patients completing the planned number of cycles was 48% in the GETUG-AFU 15 trial (nine planned cycles), 86% in the CHAARTED-E3805 trial and 76% in the STAMPEDE trial (six planned cycles). And 84% in our study.

Post-chemotherapy radiological response was partial in 12 patients, stable disease in 7 and progressive disease in 2 patients according to the RECIST classification. Although there is no adequate literature available for radiological response of ADT alone.

PSA values were significantly lower at the end of 3 cycles (P <0.000) and 6 cycles (P 0.001) compared to baseline. The median time to nadir PSA in our study was six months. This compares to the study by Rulach et al. which showed that the time to nadir PSA was around 7 months in both the combination and ADT alone group. The number of patients achieving a nadir PSA value of less than 0.2 ng per millilitre on two consecutive measurements at least four weeks apart which denoted a complete serologic response was 24% (6 patients) in our study while it was 26.2% in the Rulach study. (60) The CHAARTED study had 32% patients achieving that level of PSA at 6 months and 27.7% at 12 months in combination group while in ADT alone group it was 19.6% at 6 months and 16.8% at 12 months. (14) Lower PSA nadir and longer time to PSA nadir (TTN) were formerly thought to be risk factors for a faster development to CRPC. Recent studies, on the other hand, have found that a lower PSA nadir and a longer TTN are related with a longer time to CRPC. (63)

Whether a 6 cycle chemohormonal therapy has an inadequate radiological response as compared to a more florid PSA response is something to be considered.

In the GETUG-AFU 15 study, four treatment-related deaths were reported compared with the CHAARTED-E3805 trial where only one treatment-related death occurred in the combination arm. In our series, there were no treatment-related deaths, although 2 patients died in the follow up. Although these numbers, considered overall, are quite reassuring, it is well known that patients enrolled in clinical trials are selected compared with all patients treated in daily clinical practice in terms of age, performance status, and comorbidities. (64)

SARS CoV 2 affects every gender, age, ethnicity but it tends to cause more morbidity and mortality in men of older age group and prostate cancer diagnosis in this age group increases the lethality of this disease. (65) Due to gender differences, age, and a higher tendency for risk factors, (eg, respiratory disease, obesity, hypertension, and smoking status) epidemiological research suggests that Prostate cancer patients have a higher incidence and death from SARS-CoV-2 infection. (66) COVID 19 pandemic did affect the sample size of our study, fortunately there was no mortality due to COVID in our study cohort.

Our study presents real-world data on docetaxel administration in Indian patients presenting to our center in the hormone-sensitive metastatic prostate cancer setting.

Limitations

Our study is limited by the small number of patients as it is a single center study. While the biochemical response is adequate, the limited radiological response requires greater appraisement. A longer follow up is needed to conclude regarding progression free and overall survival. A larger study would comprehensively reveal the docetaxel efficacy and adverse events necessitating a dose modification in mHSPC if any.

CONCLUSION

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In conclusion, docetaxel chemotherapy with ADT is safe to administer in patients presenting first time with metastatic prostate cancer in our population. We found an adequate biochemical and clinical response after 3 cycles and 6 cycles of docetaxel chemotherapy, but the radiological response was found to be limited. Potential side effects aside the cost-benefit to patients as well as proven efficacy make it the first-line therapy alongside ADT in such patients. However larger population and longer follow up would be needed to comment upon progression free and overall survival.

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ANNEXURES

ANNEXURE – I

ETHICAL CLEARANCE CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/2035 Date: 01/01/2020

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/985**

Project title: **"Safety and short-term efficacy of chemohormonal therapy in hormone sensitive metastatic prostate cancer"**

Nature of Project:	**Research Project**
Submitted as:	**M.Ch. Dissertation**
Student Name:	**Dr. Gaurav Baid**
Guide:	**Dr.Gautam Ram Choudhary**
Co-Guide:	**Dr. Vijay Kumar Sarma Madduri, Dr.Puneet Pareek, Dr. Arvind Sinha, Dr. Mahendra Singh & Dr. Himanshu Pandey**

This is to inform that members of Institutional Ethics Committee (Annexure attached) met on **23-12-2019** and after through consideration accorded its approval on above project. Further, should any other methodology be used, would require separate authorization.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Enclose:
1. Annexure 1

Page 1 of 2

ANNEXURE – II A

GOVERNMENT OF INDIA

ALL INDIA INSTITUTE OF MEDICAL SCIENCES,

JODHPUR- 342005, INDIA

INFORMED CONSENT FORM (in English)

Participant identification number for this trial: _____

Title of project: **SAFETY AND SHORT-TERM EFFICACY OF CHEMOHORMONAL THERAPY IN HORMONE SENSITIVE METASTATIC PROSTATE CANCER**

Name of Principal Investigator: Dr Gaurav Baid Tel. No (s). 9928754869

The contents of the information sheet dated …….. That was provided have been read carefully by me / explained in detail to me, in a language that I comprehend, and I have fully understood the contents. I confirm that I have had the opportunity to ask questions.

The nature and purpose of the study and its potential risks / benefits and expected duration of the study, and other relevant details of the study have been explained to me in detail. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal right being affected. I understand that the information collected about me from my participation in this research and sections of any of my medical notes may be looked at by responsible individuals from AIIMS. I give permission for these individuals to have access to my records.

I agree to take part in the above study.

---------- Date:

(Signature / Left Thumb Impression) Place:

Name of the Participant: _____

Son / Daughter / Spouse of: _____

Complete postal address: _____

This is to certify that the above consent has been obtained in my presence.

Signature of the Principal Investigator Date:

Place:

1) Witness – 1

Signature

Name:

Address:

2) Witness – 2

Signature

Name:

Address:

ANNEXURE – II B

GOVERNMENT OF INDIA

ALL INDIA INSTITUTE OF MEDICAL SCIENCES,

JODHPUR- 342005, INDIA

सूचित सहमति प्रपत्र (in Hindi)

इस जाँच के लिए सहभागी पहचान नंबर_____

अनुसन्धान शीर्षक : SAFETY AND SHORT-TERM EFFICACY OF CHEMOHORMONAL THERAPY IN HORMONE SENSITIVE METASTATIC PROSTATE CANCER

मुख्य अन्वेषक का नाम : Dr Gaurav Baid **फोन नंबर: 9928754869**

मैंने दिनांक_____ के सूचना पत्र में दिये गए सभी तथ्यो को पढ़ लिया हैं| मुझे समझ आने वालीं भाषा में विस्तारपूर्वक बत्ता दिया है और मैनें तथ्यो को भली भांति समझ लिया है| मैं पुष्टि करता हूँ कि मुझे प्रश्न पूछने का अवसर दिया गया है|

मुझे अध्ययन की प्रकृति, उद्देश्य और इसके सम्भावित लाभ/जोखिमों और अध्ययन की सम्भावित अवधि अन्य प्रासंगिक जानकारी के बारे में विस्तार पूर्वक समझा दिया गया है | मैं समझता हूँ कि इस अध्ययन में मेरी भागीदारी स्वेछिक है और इस अध्ययन से किसी भी समय बिना कोई कारण बताए, बिना मेरी चिकित्सा देखभाल या कानूनी अधिकारों के प्रभावित हुए अपना नाम वापिस ले सकता हूँ | मैं समझता हूँ कि इस अनुसन्धान में मेरी सहभागिता से मेरे बारे में एकत्र जानकारी और चिकित्सीय नोटों को एम्स अस्पताल के जिम्मेदार लोगो द्वारा देखा जायेगा| मैं इन व्यक्तियों को अपने रिकोर्ड देखने की अनुमति प्रदान करता हूँ |

मैं उपर्युक्त अध्ययन में भाग लेने के लिए अपनी सहमति प्रदान करता हूँ |

सहभागी के हस्ताक्षर / बाएं अंगूठे का निशान दिनांक: स्थान:

सहभागी का नाम

पिता/पति का नाम

पूरा पता

यह प्रमाणित किया जाता है कि उपर्युक्त सहमति मेरी उपस्थितिमें ली गईं हैं |

मुख्य अन्वेषक के हस्ताक्षर **दिनाक:** **स्थान:**

१) गवाह के हस्ताक्षर **२) गवाह के हस्ताक्षर**

नाम **नाम**

पता **पता**

ANNEXURE – III A

PATIENT INFORMATION SHEET (in English)

Title: **SAFETY AND SHORT-TERM EFFICACY OF CHEMOHORMONAL THERAPY IN HORMONE SENSITIVE METASTATIC PROSTATE CANCER**

Name of Participant: .....

You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

You are being asked to participate in this study being conducted in AIIMS, Jodhpur because you satisfy our eligibility criteria.

What is the purpose of research?

This study aims to assess safety and short-term efficacy of administration of modified fixed dose of Inj Docetaxel (100 mg) or according to body surface area with androgen deprivation therapy in hormone sensitive metastatic prostate cancer in the Indian population presenting to our center. We have obtained permission from the Institutional Ethics Committee for conducting this study.

The study design

The study will be a single center prospective observational study and patients will be recruited from Department of Urology and department of Radiation therapy of AIIMS, Jodhpur.

Study Procedures

You will be counselled about the entire treatment plan. You will be given ADT (medical/surgical) and modified dose of Inj Docetaxel 100 mg or according to body surface area of patient intravenous infusion with all the prophylactic measures taken before giving chemotherapy, all the required blood investigations will be done before giving chemotherapy and you will be given Inj Pantoprazole and Inj Ondansetron prophylactically. All the events will be recorded.

Possible risks to you.

There is no added risk other than the risk involved due to chemohormonal therapy and the disease.

Possible benefits to you

It is seen that chemotherapy with the hormonal therapy increases the overall survival in metastatic prostate cancer.

Compensation

Nil

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

The alternatives you have

If you do not wish to participate, you still will get the standard treatment for your condition.

Reimbursement

You will not be paid to participate in this research study.

What should you do in case of injury or a medical problem during this research study?

Your safety is the prime concern of the research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form. You will be provided the required care/treatment.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, institutional ethics committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The results of clinical tests and therapy performed as part of this research may be included in your medical record.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons.

Can the investigator take you off the study?

You may be taken off the study without your consent if you do not follow instructions of the investigators or the research team or if the investigator thinks that further participation may cause you harm.

Right to new information

If the research team gets any new information during this research study that may affect your decision to continue participating in the study, or may raise some doubts, you will be told about that information.

Contact persons

For further information / questions, you can contact us at the following address:

Principal Investigator:
Dr Gaurav Baid
Senior Resident — Ph: 9928754869
Department of Urology — email: grv.baid7@gmail.com

Principal guide and Co-Investigator
Dr Gautam Ram Choudhary
Associate professor — Ph: 9414294982
Department of Urology — email: gautamoshu@gmail.com

ANNEXURE – III B

PATIENT INFORMATION SHEET (in Hindi)

भागीदारों के लिए सूचना

शीर्षक: SAFETY AND SHORT-TERM EFFICACY OF CHEMOHORMONAL THERAPY IN HORMONE SENSITIVE METASTATIC PROSTATE CANCER

प्रतिभागी का नाम: .....

आपको इस शोध □ ध्ययन में भाग लेने के लिए आमंत्रित किया जाता है। इस दस्तावेज़ में दी गई जानकारी यह तय करने में आपकी सहायता करने के लिए है कि भाग लेना है या नहीं। कृपया पूछें कि क्या आपके पास कोई प्रश्न या चिंता है या नहीं।

आपको एम्स, जोधपुर में आयोजित इस □ ध्ययन में भाग लेने के लिए कहा जा रहा है क्योंकि आप हमारे योग्यता मानदंडों को पूरा करते हैं।

शोध का उद्देश्य क्या है?

यह □ ध्ययन हार्मोन नाइव मेटास्टेटिक प्रोस्टेट कैंसर के भारतीय मरीजों में डोसीटेक्सल की संशोधित निर्धारित खुराक और ऐड्रोजन डेप्रिवेशन थेरेपी की □ ल्पकालिक सुरक्षा और प्रभावकारिता का □ ध्ययन करता है। हमने इस □ ध्ययन के संचालन के लिए संस्थागत नैतिकता समिति से □ नुमति प्राप्त की है.

अध्ययन डिजाइन

□ ध्ययन एक एकल केंद्र संभावित □ वलोकन □ ध्ययन होगा और रोगियों को यूरोलॉजी विभाग से भर्ती कराया जाएगा।

अध्ययन प्रक्रियाएं

आपको पूरी उपचार योजना के बारे में बताया जायेगा । आपको सभी रोगनिरोधी मापदंडो के साथ ऐड्रोजन डेप्रिवेशन थेरेपी और डोसीटेक्सल की संशोधित निर्धारित खुराक दी जायेगी। कीमोथेरेपी देने से पहले सभी जरुरी खून की झाँच की जायेगी। आपको रोगनिरोधक मापदंड के तहत इंजेक्शन पेंटोप्राजोल और इंजेक्शन ओडानसेट्रोन दिया जाएगा। सभी घटनाओं को रिकॉर्ड किया जाएगा।

आपके लिए संभावित जोखिम

कीमोथेरपी, ऐड्रोजन डेप्रिवेशन थेरेपी (मेडिकल/ सर्जिकल) और बीमारी के कारण जोखिम के □ लावा कोई □ तिरिक्त जोखिम नहीं है।

आपके लिए संभावित लाभ

यह देखा गया है की हार्मोन थेरेपी के साथ कीमोथेरपी देने से समग्र उत्तरजीविता बढ़ती है।

नुकसान भरपाई- शून्य

अन्य लोगों के लिए संभावित लाभ

शोध के नतीजे भविष्य के मरीजों को चिकित्सा ज्ञान और / या चिकित्सकीय लाभ के उन्नयन के मामले में समाज को लाभ प्रदान कर सकते हैं।

आपके पास विकल्प हैं

यदि आप भाग लेना नहीं चाहते हैं, तो भी आपको □पनी हालत के लिए मानक उपचार मिलेगा।

अदायगी

इस शोध □ध्ययन में भाग लेने के लिए आपको भुगतान नहीं किया जाएगा।

इस शोध अध्ययन के दौरान चोट या चिकित्सा समस्या के मामले में आपको क्या करना चाहिए?

आपकी सुरक्षा □नुसंधान की प्रमुख चिंता है। यदि आप इस □ध्ययन में होने के परिणामस्वरूप घायल हो गए हैं या चिकित्सा समस्या है, तो आपको सहमति फॉर्म के □ंत में सूचीबद्ध लोगों में से एक से संपर्क करना चाहिए। आपको आवश्यक देखभाल /उपचार प्रदान किया जाएगा।

आप से प्राप्त जानकारी की गोपनीयता

आपको □पनी चिकित्सा जानकारी (व्यक्तिगत विवरण, शारीरिक परीक्षाओं के परिणाम, जांच, और आपके चिकित्सा इतिहास) कीगोपनीयता के संबंध में गोपनीयता का □धिकार है। इस दस्तावेज़ पर हस्ताक्षर करके, आप □नुसंधान टीम जांचकर्ताओं, □न्य □ध्ययन कर्मियों, प्रायोजकों, संस्थागत नैतिकता समिति और कानून के □नुसार आवश्यक किसी भी व्यक्ति या एजेंसी को भारत केड्रग कंट्रोलर जनरल की आवश्यकता होगी, यदि आवश्यक हो तो आपका डेटा देखने के लिए। इस शोध के हिस्से के रूप में किए गए नैदानिक परीक्षण और चिकित्सा के परिणाम आपके मेडिकल रिकॉर्ड में शामिल किए जा सकते हैं। इस □ध्ययन की जानकारी, यदिवैज्ञानिक पत्रिकाओं में प्रकाशित या वैज्ञानिक बैठकों में प्रस्तुत की गई है, तो आपकी पहचान प्रकट नहीं होगी।

अध्ययन में भाग लेने का आपका निर्णय आपको कैसे प्रभावित करेगा?

इस शोध □ध्ययन में भाग लेने के आपके निर्णय से आपकी चिकित्सा देखभाल या जांचकर्ता या संस्थान के साथ आपके संबंध प्रभावित नहीं होंगे। आपका डॉक्टर □भी भी आपकी देखभाल करेगा और आप किसी भी लाभ को खो देंगे नहीं जिसके लिए आपहकदार हैं।

क्या आप शुरू करने के बाद अध्ययन में भाग लेने से रोकने का फैसला कर सकते हैं?

इस शोध में भागीदारी पूरी तरह से स्वैच्छिक है और आपको बिना किसी कारण बताए □ध्ययन के दौरान किसी भी समय इस□ध्ययन से वापस लेने का □धिकार है।

क्या जांचकर्ता आपको अध्ययन से बाहर ले जा सकता है?

यदि आप जांचकर्ताओं या शोध दल के निर्देशों का पालन नहीं करते हैं या यदि जांचकर्ता सोचता है कि आगे की भागीदारी सेआपको नुकसान हो सकता है तो आपको □पनी सहमति के बिना □ध्ययन से बाहर ले जाया जा सकता है

नई जानकारी का अधिकार

यदि इस शोध □ ध्ययन के दौरान शोध दल को कोई नई जानकारी मिलती है जो □ ध्ययन में भाग लेने के आपके फैसले को प्रभावित कर सकती है, या कुछ संदेह उठा सकती है, तो आपको उस जानकारी के बारे में बताया जाएगा।

संपर्क करें

□ धिक जानकारी / प्रश्नों के लिए, आप निम्नलिखित पते पर हमसे संपर्क कर सकते हैं:

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ANNEXURE – IV

PROFORMA

Patient ID:

BASIC INFORMATION OF PATIENT

Name	
Age (in years)	
Sex	
Hospital No.	
Address	
Phone number	
Index Diagnosis	

CHIEF COMPLAINTS

COMPLAINTS	**YES**	**NO**	**DURATION**
Urinary retention			
LUTS (Lower Urinay Tract Symptoms)			
Back pain			
Hematuria			
Weight loss			
Decreased weight			
Others			

ADDICTION

NATURE	**YES**	**NO**	**DURATION**	**ABSTINENCE**
Alcohol				
Smoking				
Tobacco chewing				

Patient ID:

CO MORBIDITIES

ILLNESS	**YES**	**NO**	**DURATION**
Systemic Hypertension			
Diabetes Mellitus			
CAD			
COAD/ Bronchial Asthma			
Others			

Ht..... Wt.....BMI……. ECOG…….

DRE:

PSA

	PSA level
Initial	
After 3 cycles	
After 6 cycles	

TRUS guided prostate biopsy:

Imaging

	Initial	**After 6 cycles of Docetaxel**
CT		
MRI		
PSMA PET Scan		
Bone scan		

Patient ID:

TNM Stage of disease at presentation:

ADT (Surgical/Medical):

Surgical ADT (Any Adverse event):

Medical ADT

ADT	Adverse event

Chemotherapy

No of cycle	Prechemo CBC	Postchemo CBC	Nausea	Vomiting	Neutropenia	Diarrhoea	Inj Filgrastim (If needed)	Any other adverse events
1								
2								
3								
4								
5								
6								

Clinical Response

	Clinical Response
After 3 cycles of Chemotherapy	
After 6 cycles of Chemotherapy	

ANNEXURE – V

MASTER CHART