



A PROSPECTIVE STUDY TO ASSESS THE IMPACT OF NEOADJUVANT ANDROGEN DEPRIVATION THERAPY ON TUMOR VOLUME, RECTAL AND BLADDER DOSES WITH IMAGE GUIDED RADIATION THERAPY IN LOCALLY ADVANCED PROSTATE CANCER

Oncology

Dr. Taruni Bhattacharya	DNB Radiation Oncology Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur.
Dr. Arpit Jain*	MS, DNB Surgical Oncology, Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur. *Corresponding Author
Dr. Seema Mutha	MD Resident, Radiation Oncology, Bhagwan Mahaveer Cancer Hospital & Research Center, Jaipur.

ABSTRACT

Background & Objective: Prostate cancer has ranked among top ten leading sites of cancer. aim to compare the prostate size, rectal and bladder doses at specified volumes before initiating NAHT and after NAHT, just before starting radiotherapy. We want to assess, if NAHT decreases the dose to bladder and rectum by shrinking prostate, thus reducing treatment related toxicity, & thereby increasing the patient compliance.

Methods: This is Observational and Prospective study

Results: In the present study, 23.4% ($P < 0.001$) reduction was seen in target volume after 3-4 months of NAHT. Our study, had 19 patients (51.4%) from intermediate risk group while 8 patients were from high risk group (48.6%). The mean prostate volume before NHT was 62.5 ± 22.1 cm³. mean Sr. PSA levels reduction was 38.6% with the use of NAHT. The mean Dmax of rectum in current study, before and after NAHT was 47.93 ± 22.82 Gy and 47.81 ± 22.83 Gy, the average Dmean before and after NAHT was 65.57 ± 21.38 Gy and 65 ± 21.42 Gy. Both had significant reduction in values of 0.11 & 0.21. Average Dmean of bladder, in our study before and after NAHT is 51.32 ± 17.24 Gy & 50.99 ± 17.18 Gy; average Dmax before and after were 65.57 ± 21.38 Gy & 65 ± 21.42 Gy which showed non-significant decrease of 0.33 & 0.44 respectively.

Conclusion: the present study demonstrated that neoadjuvant hormonal therapy of minimum 3 months duration decreased the prostate volume and Sr. PSA

KEYWORDS

Prostate Cancer, PSA, Hormonal therapy

INTRODUCTION

Prostate cancer is the second most common cause of cancer and the fifth leading cause of cancer death among men worldwide. Based on GLOBOCAN 2018 estimates, 1,276,106 new cases of prostate cancer were reported worldwide in 2018, with higher prevalence in the developed countries. The worldwide prostate cancer burden is expected to grow to 1.7 million new cases by 2030 simply due to the growth and ageing of the global population. Incidence rate (per 100,000) vary by nearly 25 fold worldwide, largely because of prostate specific antigen (PSA) testing and subsequent biopsy¹.

Prostate cancer has ranked among top ten leading sites of cancer in many cities of India including Bangalore, Barshi, Bhopal, Chennai, Delhi etc². It has become a major health problem in industrialized world during the last few decades, contributing to three fourth of the registered cases across the globe.

95% of these tumors are adenocarcinoma originating from the glands and proximal ducts epithelium in the prostate, five percent of prostate cancer cases are made up of other types originating from transitional epithelial cells in the urethra or pars prostatic urethra (urothelial carcinoma), support tissue (sarcoma) or lymphoid tissue (lymphoma). Adenocarcinomas are often multifocal, heterogenous and follow a papillary, cribriform, comedo or acinar pattern.^{3,4}

Of those patients diagnosed in the early stages of prostate cancer, despite adequate local therapy, 15%–40% still go on to develop progressive, usually systemic disease and, one third of prostate cancer patients might suffer biochemical relapse with a rise in serum PSA after radical prostatectomy without salvage treatment. These recurrences are likely due to micro-metastatic foci present at the time of local therapy rather than due to inadequate local techniques. Therefore, identifying patients at high risk of developing recurrent disease and on optimizing therapy to increase the number of those men who are cured is needed. Prostate cancer patients when treated with IMRT (intensity modulated radiotherapy) get a highly conformal dose distributions for the planning target volume (PTV) while minimizing the dose given to the organs at risk and with short delivery time⁵.

The IMRT and both VMAT techniques both result in lower doses to normal critical structures than 3D-CRT plans. The VMAT plans required fewer monitor units than the IMRT plans but more than for the 3D-CRT plans. The IMRT and VMAT techniques although, achieve

highly conformal treatment plans. The VMAT technique, has more favorable dose distributions than the IMRT, and reduced the monitor units required compared with IMRT.⁵

The goal of RT is the delivery of tumoricidal dose of radiation while minimizing radiation to surrounding normal tissues, since prostate is a midline structure that lies in close proximity to the rectum and bladder, major toxicities of normal tissue irradiation (gastrointestinal and genitourinary) can be manifested by persistent diarrhea, tenesmus, rectal urgency. RT planning takes into account the volume and anatomic distribution of both the tumor and normal structures.⁶

In this study we aim to compare the prostate size, rectal and bladder doses at specified volumes before initiating NAHT and after NAHT, just before starting radiotherapy. We want to assess, if NAHT decreases the dose to bladder and rectum by shrinking prostate, thus reducing treatment related toxicity, & thereby increasing the patient compliance

AIM AND OBJECTIVES

To compare the prostate size, rectal and bladder doses at specified volumes before start of androgen deprivation therapy and before start of radiotherapy by IGRT

OBJECTIVES

Primary Objective:

- To assess if NAHT decreases the dose to bladder and rectum by shrinking of prostatic size by using dose volume histograms

Secondary Objectives:

- Whether the decrease in dose to normal structures (bladder & rectum) reduces the toxicity thereby increasing the patient compliance

MATERIAL AND METHODS

- The study was conducted in the department of Radiation Oncology at Bhagwan Mahaveer Cancer Hospital And Research Centre (BMCHRC), Jaipur, Rajasthan, after taking ethics committee approval.
- Study type:** Observational
- Study design:** Prospective study
- Study Site:** Department of Radiation Oncology, Bhagwan Mahaveer Cancer Hospital and Research Centre, Jaipur.

- **Study Population:** Cancer prostate patients.
- **Study Duration:** December 2018 to May 2019 or till desired sample size is attained
- **Sample size:** Sample size is calculated at 80% study power & alpha error 0.05 assuming standard deviation of absolute reduction in prostate volume after NAHT of 13 cm³ as found in reference study by Krishna R. Jethwa et al, 2016.

PATIENT SELECTION CRITERIA

INCLUSION CRITERIA:-

- Patients who provide informed consent
- Newly diagnosed, histologically confirmed adenocarcinoma of prostate (T1c-T3b, N0, M0 with intermediate-risk & high-risk factors according to National Comprehensive Cancer Network. Prostate Cancer) (Version 2.2017))
- Karnofsky Performance Status (KPS) > 70
- Age > 18 years and less than 80 years
- Non metastatic disease
- Life expectancy of more than 5 yrs.

EXCLUSION CRITERIA:-

- T4 tumors, distant metastatic disease
- Patients who have undergone B/L orchiectomy
- Second malignancy
- Renal disease
- Previous history of pelvic surgery, radiotherapy or neoadjuvant hormonal therapy for more than 3 months.

METHODOLOGY

PATIENT SELECTION AND EVALUATION

After recording the detailed history, performing a thorough clinical examination and the relevant investigations, the patients were staged accordingly. An informed consent form was taken before enrolling them in the study. A detailed counselling was done about androgen deprivation therapy, radiotherapy planning and treatment methods.

Locally advanced cancer prostate has no universally accepted definition. The term, however, is loosely used to encompass a spectrum of disease profiles that may include any of the following.¹⁶

A) Clinical stage American Joint Committee on Cancer (AJCC 7th edition) T3 (tumors extending to the periprostatic area or into seminal vesicles), T4 (larger tumours invading the external sphincter, bladder neck, rectum, levator ani muscles or fixed to the pelvic side wall) or N1 (regional pelvic lymph node involvement associated with any local T stage), without evidence of distant metastases M0.

(B) Clinical stages T1 and T2 at diagnosis,

(C) Pathological stage pT2 or pT3 disease, with high-risk features owing to upstaging from additional pathological information after radical prostatectomy.

The risk stratification: (National Comprehensive Cancer Network. Prostate Cancer (Version 2.2017))

- Low-risk patients: stage T1c, T2a and PSA level < or = 10 ng/mL and Gleason score < or = 6
- Intermediate-risk patients: stage T2b or Gleason score of 7 or PSA level > 10 and < or = 20 ng/mL
- High-risk patients: stage T2c or PSA level > 20 ng/mL or Gleason score > or = 8

Preparing the patient:-

Patients were simulated with a comfortably full bladder. According to protocol all patients were instructed to empty the bladder 60 minutes before simulation and then were asked to drink 3 cups (750ml) of liquid during the subsequent 15 minutes, finishing 45 minutes before simulation. They were also advised to take laxatives, the previous night for bowel preparation. This process was done twice, once before the start of androgen deprivation therapy and second time before planning for radiation treatment. The patients were immobilized comfortably in supine position using 4 clamp customized thermoplastic mask of pelvis. External fiducial markers were placed over the mask in pelvic region.

RESULTS AND DISCUSSION

The role of hormone therapy in the treatment of prostate cancer has evolved over the years. For decades it has been used as a systemic treatment for metastatic prostate cancer. Neoadjuvant hormone therapy

has two potential benefits in limited prostate cancer: downsizing and downstaging. It has been studied as a means of optimizing therapy to increase the number of men who are cured, theoretically, through downstaging the disease and eradicating subclinical deposits at the earliest possible time. (Farley et al). Image -guided-IMRT has been accepted as the standard treatment technique in prostate malignancy as it has ability to target the CTV while sparing surrounding normal tissues. Lesser doses delivered to rectum and prostate could mean lesser side effects and morbidity to the patients leading to better utilization of available resources and cost-effective treatment and lesser admission or hospitalization. The present study suggests that neoadjuvant hormonal therapy ie hormonal therapy given to locally advanced cancer prostate patients before IGRT significantly decreases the prostate size, serum prostate specific antigen levels. This decrease in size in turn led to decrease in the doses delivered to the normal structures at risk ie rectum and bladder.

Target volume reduction

In the present study, 23.4% (P<0.001%) reduction was seen in target volume after 3-4 months of NAHT. Krishna R. Jethwa et al⁷, deduced that in prostate, volume decreased by approximately one third after 4.9 months of NHT with a maximum reduction of 63% observed. Initial prostate volume was the greatest predictor of prostate volume reduction following NHT. The mean prostate volume before NHT was 62.5 ± 22.1 cm³ (Interquartile range: 46-76 cm³), and after NHT, it was 37.0 ± 14.5 cm³ (Interquartile range: 29-47 cm³). The mean prostate volume reduction was 23.4 cm³ (35.9%). Pilar M. Samper et al⁸, prospectively showed in 28 patients, that NHT reduced the prostate volume, significantly, by 24%. Comparative analysis of the dose-volume histograms of the first versus the second CT shows a reduction in the planned volume GTV1 (prostate) (81.33 cc vs 63.96 cc, p < 0.05). And, PTV1 (prostate and margin), 197.51 cc vs 168.38 cc, (p < 0.001) and PTV2 (prostate, vesicles and margin) 340.5 cc vs 307.26 cc, (p < 0.05). Zelefsky et al⁹ showed that NHT effectively reduced target volume to high radiation doses in the majority of treated patients. In their study, a 27% reduction in the size of the target volume was seen.

Sr. PSA Reduction

In our study, The mean Sr. PSA levels reduction was 38.6% (p<0.001) with the use of NAHT. Pu XY et al¹⁰, comparatively evaluated 55 patients of clinically localized prostate cancer. The mean serum PSA decreased by 97.8% (25 patients), in patients who underwent 3 months NHT.⁴⁷ In the study by Krishna Jethwa et al⁷, mean serum prostate specific antigen levels decreased significantly from 38.6 to 0.44 ng/ml before and after NHT.⁴⁵

Dosimetry of bladder & rectum

The mean Dmax of rectum in current study, before and after NAHT was 47.93±22.82 Gy and 47.81±22.83 Gy, the average Dmean before and after NAHT was 65.57±21.38 Gy and 65±21.42 Gy. Both had significant reduction in values of 0.11 & 0.21. Average Dmean of bladder, in our study before and after NAHT is 51.32±17.24 Gy & 50.99±17.18 Gy; average Dmax before and after were 65.57±21.38 Gy & 65±21.42 Gy which showed non-significant decrease of 0.33 & 0.44 respectively. In Samper et al⁸, the average Dmax of bladder before and after NAHT were 70.58±2.36 Gy v/s 69.55±3.56 Gy resp. and average Dmean of bladder before and after NAHT was 55.27±6.25 Gy and 53.19±7.84 Gy. The average Dmax of rectum before and after were 71.02±2.03 Gy and 70.87±2.26 Gy respectively. The average Dmean of rectum before and after NAHT were 50.63±7.41 Gy & 49.83±6.76 Gy.⁴⁴

Dosimetric changes due to NAHT

A significant decline in V30–V75 bladder values in NAHT given <= 3 months were seen in CT planning before and after NAHT. The V30, V40, V50, V60, V70, V75 decreased for bladder significantly in the before and after NAHT radiation treatment plans by 5.3%, 6.1%, 6.3%, 6.1%, 5.4%, 1.5% respectively. The V20 increased by 4.9%. Samper et al⁸, a significant reduction of the rectal V60 (52.45 ± 15.8% vs 28.22 ± 15.77%, p = 0.046) and bladder V60 (41.78 ± 17.98% vs 51.67 ± 20.29%, p = 0.004) were shown after NAHT. Zelefsky et al⁹, in the planning of radiotherapy after hormonal therapy observed: an average reduction of 25% in the target volume; 78% (10 out of 15 patients) who had rectal volume of D95 > 50% before HT responded to HT with an average reduction of 25%; an average reduction of 50% of the bladder volume receiving D95 in 9 out of 10 patients (90%)⁴⁸

Risk Grouping

Our study, had 19 patients(51.4%) from intermediate risk group while 8 patients were from high risk group(48.6%).In Samper et al⁸,the risk grouping of patients was:low risk -one patient (5.6%);intermediate risk, eight patients (28.6%) and high risk,19 patients (67.9%). Our results,show that when neoadjuvant hormonal therapy is given in patients of locally advanced cancer prostate patients for a minimum duration of 3 months there is decrease in the size of prostate,serum PSA levels,the percentages of volume receiving specific doses & the mean and maximum doses received by rectum and bladder.This relates to a dosimetric and volumetric benefit in treatment of locally advanced cancer prostate patients by IGRT

CONCLUSION

In conclusion, the present study demonstrated that neoadjuvant hormonal therapy of minimum 3 months duration decreased the prostate volume and Sr. PSA. The study also concluded that there is a dosimetric reduction in doses to bladder and rectum after NHT. Since, this dosimetric benefit could result in a better side effect profile for the patients their compliance to treatment is expected to increase.

Limitations of the study

We, at our study centre found the following limitations for our current study:

- Sample size is small
- Single centre study
- Shorter duration of study,so the duration between hormonal therapy and radiation therapy could not be increased by more months,also chronic side effect profile and other long term outcomes could not be observed

REFERENCES

1. Harold Evelyn Taitt. Global Trends and Prostate Cancer: A Review of Incidence, Detection, and Mortality as Influenced by Race, Ethnicity, and Geographic Location. *Am J Mens Health*. 2018 Nov; 12(6): 1807–1823.
2. Hariharan K, Padmanabha V. Demography and disease characteristics of prostate cancer in India. *Indian J Urol* 2016;32:103-8
3. Vinay K, Abul KA, Jon CA, Nelson F. Robbins and Cotran Pathologic Basis of Disease. Eight ed. Elsevier; Lyon, France: 2010.
4. Ehemann CR, Shaw KM, Ryerson AB, Miller JW, Ajani UA, White MC. The changing incidence of in situ and invasive ductal and lobular breast carcinomas. *Cancer Epidemiol Biomarkers Prev*. 2009;18(6):1763–9.
5. Ben W. Fischer-Valuck, Yuan James Rao, and Jeff M. Michalsk. Intensity-modulated radiotherapy for prostate cancer. *Transl Androl Urol*. 2018 Jun; 7(3): 297–307.
6. Akila N. Viswanathan, Ellen D. Yorke, Lawrence B. Marks, Patricia J. Eifel, and William U. Shipley. Radiation Dose–Volume Effects Of The Urinary Bladder. *Int J Radiat Oncol Biol Phys*. 2010 March 1; 76(3 Suppl): S116–S122.
7. Krishan R. Jethwa, Keith M. Furutani, Lance A. Mynderse, Torrence M. Wilson, Richard Choo, Bernard F. King, Eric Bergstrahl, and Brian J. Davis. Predictors of prostate volume reduction following neoadjuvant cytoreductive androgen suppression. *J Contemp Brachytherapy*. 2016 Oct; 8(5): 371–378.
8. Samper PM, López Carrizosa MC, Pérez Casas A, et al. Impact of neoadjuvant hormonal therapy on dose-volume histograms in patients with localized prostate cancer under radical radiation therapy. *Clin Transl Oncol*. 2006;8:599–605.
9. Zelefsky MJ, Leibel SA, Burman CM, et al. Neoadjuvant hormonal therapy improves the therapeutic ratio in patients with bulky prostatic cancer treated with three-dimensional conformal radiation therapy. *Int J Radiat Oncol Biol Phys*. 1994;29:755–761.
10. Pu XY, Wang XH, Wu YL, et al. Comparative study of the impact of 3- versus 8-month neoadjuvant hormonal therapy on outcome of laparoscopic radical prostatectomy. *J Cancer Res Clin Oncol*. 2007;133:555–562