Treatment Related Acute Toxicities Between Treatment with 3D-CRT and IMRT in Localised Prostate Cancer

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ABSTRACT

Objective: To compare the acute toxicities of two radiation treatment techniques, intensity modulated radiation therapy (IMRT), and 3-dimensional conformal radiation therapy (3D-CRT) in localised prostate adenocarcinoma.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Oncology, Dr. Ziauddin Hospital, Karachi, Pakistan, from July 2016 to June 2022.

Methodology: Patients with localised prostate adenocarcinoma who underwent treatment using two different advanced radiotherapy techniques i.e., IMRT and 3D-CRT were recruited during the study period. They were followed up for six months for acute gastrointestinal (GI) and genitourinary (GU) adverse events (acute toxicities) related to both treatment modalities according to Modified radiation therapy oncology group (RTOG) criteria. The acute toxicities were assessed at the 2nd, 4th, and 6th week during treatment and at the 3rd and 6th month after treatment.

Results: There were 78 patients, with 39 patients in each group. The mean age was 68 ± 10 years in the 3D-CRT and 68 ± 07 years in the IMRT group. Patients in the IMRT group exhibited markedly lower treatment-related acute GI and GU effects at the end of 4th and 6th weeks for anorectal pain ($p = 0.04$) and ($p = 0.01$) and burning micturition ($p = 0.003$) and ($p = 0.01$), respectively. Furthermore, at 3 months anorectal pain ($p = 0.02$), loose stools ($p = 0.005$), and burning micturition ($p = 0.01$) were present and at 6 months anorectal pain was ($p = 0.01$) still present.

Conclusion: Radiation therapy modalities 3D-CRT and IMRT both showed acceptable toxicity profile in the management of localised prostate cancer, while IMRT group exhibited significantly lower treatment-related acute GI and GU effects.

Key Words: *3D-CRT (3-Dimensional Conformal Radiation Therapy), IMRT (Intensity-Modulated Radiation Therapy), Radiation toxicity.*

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INTRODUCTION

Prostate cancer is the second most common malignancy in men all over the world, with 1,276,106 new cases and 358,989 deaths that were recorded in 2018 alone.[1] During 1998 to 2002, it was found to be the fourth most common malignancy recorded in men in Karachi, Pakistan. The incidence rate according to age standardisation was 10.1 per 100,000 men while the mean age of the prostate cancer patients calculated was 67.4 years.[2] The risk factors found to be associated with prostate cancer were family history, old age, obesity, sedentary lifestyle, and smoking.[3,4]

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The treatment modalities for prostate cancer include active surveillance, surgery, brachytherapy, external beam radiation therapy (3D-CRT, IMRT, proton therapy), hormonal therapy, and chemotherapy. The choice of treatment varies according to the patient's preference, the expected survival of the patient, and the risk group assigned at the time of diagnosis.[5]

With the advancements in technology, there have been improvements in the accurate delineation of the prostate normal tissue and areas of intra-prostatic disease, along with developments in the treatment of regional disease. Synchronously, radiation therapy (RT), a widely used treatment modality, started to be incorporated into computer online monitoring and optimisation. This allowed to improve the therapeutic ratio i.e. to increase the dose to the target and decrease the dose to organ-at-risks.[6]

Dose escalated RT is a commonly adopted treatment method which improves tumour control and outcomes in prostate cancer. Escalated RT dose has been supported with level I evidence for localised prostate cancer patients in all risk groups.[7] The preference of RT technique with minimal radiotherapy-associated toxicity is substantial in improving quality of life in prostate cancer patients.[8] Majority of diagnosed localised prostate

cancer cases may survive more than a decade. However, higher radiation therapy doses are linked to adverse effects i.e. late GI and GU toxicity.[9]

The 3-dimensional conformal radiation therapy (3D-CRT), a more advanced option, delivers a dose conforming to the tumour target-volumes,[10] thereby reducing the vulnerability of surrounding normal organs.[11] A further evolved variant of 3D-CRT is intensity modulated radiation therapy (IMRT), which effectively creates non-homogenous radiotherapy fields to escalate the radiation dose to the target volume while minimising the dose to the adjacent normal organs.[12] The results of conformal radiotherapy are comparable to the outcomes of surgical treatment with the same clinical T3 Stage of prostate cancer.[13] However, the marginal-miss probability is a limitation of IMRT. Additionally, the dose homogeneity, rise of radiation therapy doses to larger healthy tissue volumes and slightly longer time warranted for treatment planning need to be considered in the IMRT application. The escalation of total body exposure and monitor units increases the second malignancy risk with IMRT in comparison with conventional radiotherapy.[14]The objective of this study was to compare two radiation techniques (IMRT and 3D-CRT) in localised prostate cancer, for the assessment of toxicities.

METHODOLOGY

This is a descriptive study conducted between July 2016 and June 2022 at the Oncology Department, Dr. Ziauddin Hospital Karachi, Pakistan. It was approved by the Institutional Research Advisory Council and Ethics Committee. All patients and/or their guardians provided informed consent for all treatments and procedures, as per institutional requirements. The inclusion criteria comprised patients aged 50 years and above, patients with histologically confirmed localised adenocarcinoma of prostate on either transrectal ultrasound scan (TRUS) guided or transurethral resection of the prostate (TURP), patients with performance status Eastern cooperative oncology group (ECOG) 0 or 1, and patients who had given informed consent after explaining both radiation modalities, benefits and risks. The exclusion criteria comprised patients who were previously treated for prostate cancer with surgery, chemotherapy or radiotherapy, and who had metastatic diseases and were non-compliant.

More than 90% of patients had received some form of hormonal treatment along with radiotherapy. The patients were treated with a total dose >74 Gy using two different advanced radiotherapy techniques i.e., IMRT and 3D-CRT. Sample size was calculated *via* Open-Epi, version 3.01 for toxicity profile/radiation induced GI and GU side-effects. In this study, RTOG criteria were used to assess the acute GI and GU toxicities related to radiotherapy. The fundamental principles and primary issues of treatment included local and regional control of disease, preservation of urinary function, preservation of bowel function, duration and morbidity of treatment, and quality of life (QOL). The proforma was developed for the data collection tool section that included the patient's demographics, radiation therapy technique and the toxicities (abdominal pain, loose stools, burning/painful micturition, and haematuria) observed on the defined follow-up periods of the patient undergoing radiation treatment for prostate cancer.

Patients themselves chose the treatment modality (3D-CRT or IMRT) on their own discretion after discussing all the pros and cons of each modality with their primary physician. Before the initiation of radiation therapy, all the patients were inquired with subsequent documentation of pretreatment symptoms (especially GI and GU) in a questionnaire. All the patients were followed up during and just after the course of radiation therapy (i.e., 2nd, 4th, 6th week during XRT, and 3rd, 6th months post XRT) for related symptoms of GI and GU toxicity.

Data were analysed using SPSS version 20. For categorical variables, frequency and percentages were calculated and for numerical variables, mean and standard deviation were calculated. The Chi-Square test was applied to find association of toxicities with interventions with a p-value <0.05 considered statistically significant.

RESULTS

Total recruited participants of the study according to sample size were 78 that were divided into two groups. All the patients were treated in two equal groups with almost similar demographic characteristics. Baseline characteristics of the patients are presented in Table I.

Table I: Baseline characteristics of patients in both groups.

Characteristics	IMRT	3D-CRT
No. of patients	39 (100%)	39 (100%)
Age: Mean age +/- SD, years	68 ± 10.36	68 ± 7
Baseline Gleason score		
2 to 6	1 (2.5%)	0
7	17 (43.5%)	17 (43.5%)
8 to 10	21 (54%)	22 (56.5%)
Tumour characteristics		
T1a- T2a	3 (7.6%)	3 (7.6%)
T2b	6 (15.4%)	8 (20.5%)
T2c-T3b	30 (77%)	28 (71.8%)
Risk classification		
Low	0	2 (5.1%)
Intermediate	3 (7.6%)	2 (5.1%)
High	36 (92.4%)	35 (89.8%)

After 2nd week of the treatment, none of the participants reported acute GI or GU toxicities. However, there was a significant difference in reporting of anorectal pain (p = 0.042) and burning micturition (p = 0.003) in participants of 3D-CRT after 4th week. Though, the loose stools were reported in 3D-CRT group, but the results were not as significant as in the IMRT group (in which no patient reported loose stools).

Data after the sixth week revealed that there was a significant difference in occurring frequency of anorectal pain (p = 0.018), loose stools (p = 0.060) and burning micturition (p = 0.010) in between 3D-CRT arm and IMRT arm. Only one participant of 3D-CRT group reported haematuria at the end of the treatment. On the contrary, the participants of group 2 (IMRT) reported less toxicities. The percentage of reporting toxicities was similar in data collected after 3rd month of the treatment.

Table II: Maximal grade ≥2 acute gastrointestinal (GI) and genitourinary (GU) toxicities during and after radiotherapy in both groups and their significance (Chi-square test).

Treatment Group	3D-CRT		IMRT		p-value
Week 02					
Radiation induced effects	Yes	No	Yes	No	
Anorectal pain	0	39 (100%)	0	39 (100%)	-
Loose stools	0	39 (100%)	0	39 (100%)	-
Burning micturition	0	39 (100%)	0	39 (100%)	-
Heamaturia	0	39 (100%)	0	39 (100%)	-
Week 04					
Anorectal pain	13 (33.3%)	26 (66.6.7%)	02 (5.1%)	37 (94.8%)	0.042*
Loose stools	03 (7.6%)	36 (92.3%)	0	39 (100%)	0.077
Burning micturition	07 (17.9%)	32 (82.1%)	02 (5.1%)	37 (94.8%)	0.003*
Heamaturia	0	39 (100%)	0	39 (100%)	-
Week 06					
Anorectal pain	14 (35.8%)	25 (94.8%)	04 (10.2%)	35 (89.7%)	0.018*
Loose stools	09 (10.25%)	30 (76.9%)	04 (10.2%)	35 (89.7%)	0.060*
Burning micturition	16 (41%)	23 (58.9%)	05(12.8%).	34 (87.1%)	0.010*
Haematuria	01 (2.5%)	38 (97.5%)	0	39 (100%)	0.382
After 03 months					
Anorectal pain	16 (41%)	23 (58.9%)	06 (15.3%)	33 (84.6%)	0.022*
Loose stools	12 (30.8%)	27 (69.2%)	02 (5.1%)	37 (94.8%)	0.005*
Burning micturition	10 (25.6%)	29 (74.4%)	07 (17.9%)	32 (82.1%)	0.018*
Haematuria	0	39 (100%)	0	39 (100%)	-
After 06 months					
Anorectal pain	11 (17.9%)	28 (82.1%)	02 (2.5%)	37 (97.5%)	0.010*
Loose stools	04 (5.1%)	35 (94.8%)	0 (2.5%)	39 (97.5%)	0.165
Burning micturition	06 (15.3%)	33 (84.6%)	01 (2.5%)	38 (97.5%)	0.455
Haematuria	0	39 (100%)	0	39 (100%)	-

In the sixth month, the authors observed decline in reporting of toxicities in 3D-CRT group and data regarding loose stools and burning urination became insignificant, however, there was a significant difference in reporting of anorectal pain in both groups i.e. ($p = 0.010$). The participants who were treated with IMRT showed less GI and GU toxicities than participants of 3D-CRT group throughout the follow-up of six months. Table II shows the maximal grade ≥2 acute GI and GU toxicities during and after radiotherapy in both groups and their significance.

When cumulative percentages of toxicities were compared between both the groups (3D-CRT and IMRT), less occurrence of GI toxicity was noted in the IMRT group than 3D-CRT and the same observation was seen for GU toxicities.

DISCUSSION

IMRT has proved to be efficient in minimising damage to the surrounding tissues i.e., bladder and rectum. Patient's mean age was consistent with both international cohort study and a national study.[15,16]

There was no significant association of decline in PSA level between 3D-CRT or IMRT. On the contrary, Fukuokaya *et al*. documented that treatment with 3D-CRT resulted in a significant decline in PSA levels at different time intervals.[17] The post-treatment findings with both the treatment modalities were parallel with the findings of Inaba *et al.*, at completion of treatment.[18] Contrary to the findings of this study, it has been documented that after IMRT treatment, there can be a rise in PSA levels which is not associated with tumour recurrence. They further mentioned that this rise is due to regeneration of new prostate cells.[19]

During the course of follow-up, participants were inquired about anorectal pain, loose stools, burning micturition and haematuria at different time intervals as shown in Table II.

After two weeks, participants of both groups did not complain about anorectal pain, loose stools, and burning urination. So, there was no significant difference noted between both the treatment modalities. Similarly, IMRT is the safest treatment modality in the treatment of prostate cancer when compared to 3D-CRT, and there are very less chances of development of side-effects after IMRT.[20-22]

After four weeks of treatment, significant difference was observed between the groups, 33.3%, 7.6%, and 17.9% participants who were treated with 3D-CRT reported anorectal pain, loose stools, and burning micturition, respectively. Similarly, observations were noted after 6 weeks. Contrary to this, only 5.1% participants of the IMRT group reported anorectal pain and burning micturition 3D-CRT. Many schools of thought have documented the same observation and have tagged the IMRT superior to 3D-CRT.[20,23]

On the contrary, Badr *et al.* mentioned that at 3rd and 6th months both the treatment modalities are comparable however, in this study development of side-effects i.e. anorectal pain, loose stools, and burning micturition were more prominent in 3D-CRT group when compared to IMRT at 3rd month whereas data at 6th month came to be comparable as observed in 3rd month of IMRT.[23]

It has been identified that localised approach in IMRT treatment prevents damage to other surrounding tissues that

decreases the chances of post-irradiation complications when compared to 3D-CRT. IMRT has shown beneficial effects not only in prostate cancer treatment but in anal and rectal cancers as well as in chronic inflammatory bowel disease when compared to other treatment modalities.[24,25]

The results of this study showed that after completion of radiation therapy minimal or acceptable GI and GU toxicities were observed with the IMRT in comparison to the 3D-CRT group.

Although being a single-centric study with a relatively smaller sample size, the results of this study are encouraging to treat those patients on 3D-CRT, who cannot afford more expensive radiotherapy treatment technique like IMRT. The authors recommend multicentred study with a larger sample size to draw evidence-based inferences on a larger scale to evaluate and observe the impact and effectiveness of different hormonal regimens along with radiotherapy treatments on the disease control process and PSA count.

CONCLUSION

Both 3D-CRT and IMRT equally exhibited significant treatment responses in localised prostate cancer, but patients treated with IMRT showed markedly lower treatment-related acute GI and GU effects (better tolerance profile) compared to 3D-CRT.

ETHICAL APPROVAL:

The Ethical Research Committee of the Dr. Ziauddin University had reviewed and then issued the approval prior to this research work.

PATIENTS' CONSENT:

All patients and/or their guardians provided informed consent for all treatments, procedures, as per institutional requirements.

COMPETING INTEREST:

There were no personal, financial or professional interests associated with the interpretation of my findings in this research.

AUTHORS' CONTRIBUTION:

SH: Conception of the study, data collection and analysis, and manuscript writing.
AHO: Manuscript drafting and reviewing.
JM: Conception of the study and overall supervision.
All authors approved the final version of the manuscript to be published.

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