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Evaluation of testis as organ at risk in carcinoma rectum with various radiotherapy delivery techniques

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Abstract

Background: Due to the close approximation of testis to radiotherapy treatment field in male carcinoma rectum patients, it receives either scattered or direct radiation. The present study aimed to investigate the impact of considering testis as organ at risk with different radiotherapy techniques.

Material and methods: This mono-centric, multi-arm, prospective, observational study was conducted with 160 male rectal cancer patients between 2019 to 2024, aged >18years treated with neo-adjuvant radiotherapy followed by total mesorectal resection. We designed two-dimensional, three-dimensional, intensity modulated and volumetric modulated arc

radiotherapy, with 40 patients in each technique. Tumor stage, length and thickness, testicular dose and volume, planned target volume and its distance from anal verge in each technique was considered, along with the assessment of testis as organ at risk. SPSS-22.0, R environment-3.2.2 and Microsoft excel were used for data analysis. The two-tailed t-test and Analysis of variance (ANOVA) were performed to assess the level of significance with $P<0.05$.

Results: The mean dose to right and left testis (in centi-gray) with two-dimensional radiotherapy was 925.79 and 776.70, while the dose contribution to testis when considered as organ at risk resulted in 336.23 and 206.65 with three-dimensional radiotherapy, 165.15 and 140.25 in intensity modulated radiotherapy and 209.2 and 229.2 in volumetric modulated arc therapy. Planned target volume, testis as organ at risk and treatment technique showed statistical significance with testicular dose received.

Conclusions: Considering testis as organ at risk contributed to significant dose reduction in conformal technique, with better sparing observed in intensity modulated radiotherapy whereas testicular shielding is needed in two-dimensional radiotherapy.

Keywords: Testis, Organs at Risk, Neoadjuvant Therapy, Radiotherapy, Rectal Neoplasms

Introduction

The treatment of rectal cancer involves interdisciplinary, multimodal approach with pre-operative external beam radiation therapy shown to decrease local recurrence. In the past, the focus was mainly on improving oncologic outcomes, while now there is increasing attention towards patients' quality of life as well as the functional aspects of various modes of treatment.[1-4] One such parameters of quality of life is sexual life[5], the incidence of sexual dysfunction among patients with rectal cancer varies in the literature from 5% to 88%.[6] Total mesorectal resection being the recommended surgical standard of care, sexual dysfunction due to autonomic nerve damage (erection and ejaculation) has been the focus[7,8]; however, the effects of

radiotherapy for rectal cancer on testicular function are less explored.

Testis is one of the most radiosensitive tissues, with very low doses of radiation causing significant impairment of its function. Damage may be caused during direct irradiation of the testis or from scattered radiation during treatment to surrounding tissues.[9] Doses as low as 0.11 gray (Gy) recorded significant suppression of sperm count, the time required for recovery increases with greater doses, complete recovery can be expected 9–18 months following radiation of <1 Gy, but exposure greater than 2–6 Gy can lead to permanent azoospermia and also fractionated doses can lead to greater delays in spermatogenic recovery.[9,10]

Testicular shield is a spherical lead shield placed locally to decrease the absorbed dose received by the testis[11], with proper testicular shielding, doses as low as 0.28% of the prescribed dose can be achieved. This low dose is believed to maintain the fertility of the patient.[12]

In the present study, the variation in dose received by testis with different radiotherapy treatment modalities is assessed in rectal malignancy to ascertain the need for testicular shield and to evaluate testis as organ at risk (OAR), which is often ignored in carcinoma rectum.

Material and Methods

This mono-centric, multi-arm, prospective, observational study included 160 male patients from 2019 to 2024 with locally-advanced rectal cancer, aged >18 years and planned for neoadjuvant therapy followed by total mesorectal resection. This study was approved by the scientific review board and institutional medical Ethics Committee and assigned as KCTRI/IEC/10/19. Staging done as per American joint committee on cancer (AJCC) and the international union against cancer (UICC) 8th edition. A neoadjuvant RT dose of 45 Gy in 25fractionfr with 1.8 Gy per fraction with thermoplastic immobilization in supine position was planned. Concurrent chemotherapy

consisted of oral capecitabine 825 mg/m2 on the days of the radiation treatment. American society for radiation oncology clinical practice guidelines[13,14] was used to choose the treatment delivery technique upon informed written consent. Planning was performed with Monaco5.11.03 treatment planning system for four techniques: Two-dimensional radiotherapy (2DRT) via 6-Megavoltage (MV), Three-dimensional conformal radiotherapy (3DCRT), Intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT), with each technique having 40 patients in total for treatment. Testicular dose, tumour stage, length of tumour, planned target volume (PTV) and distance from inferior edge of PTV to anal verge in each plan was recorded. 2DRT with 6MV treatment done only during COVID-19 pandemic. In case of conformal technique- 3DCRT, IMRT, VMAT, once again the same parameters were evaluated by considering testis as OAR to evaluate its impact in testicular dose contribution. The need for testicular shielding assessed based on adequate dose coverage and normal tissue toxicity, with respect to dose to testis. Thermo-luminescent dosimeters (TLD) was not used to estimate testicular doses instead of treatment planning system, and Dose-volume histogram was used for this purpose.

Statistical Methods

We conducted descriptive and inferential statistical analyses; the continuous variables were expressed as mean standard deviation (SD) values, and the categorical variables were expressed as numbers and percentages. The significance level was set to 5%. One-way ANOVA was employed to determine if there were any statistically significant differences regarding the mean values of three or more independent (unrelated) groups. The Student t-test (two-tailed, independent) was used to find the significance of study parameters on continuous scale between two groups (intergroup analysis) on metric parameters.

The homogeneity of variance was assessed through the Levene test. The Pearson correlation was applied to the study variables to find their degree of relationship. *P*-value was determined by referring to a t-distribution with n-2 degrees of freedom.

We used the IBM SPSS Statistics for Windows (IBM Corp., Armonk, NY, United States), version 22.0, and R environment (R Foundation for Statistical Computing, Vienna, Austria), version 3.2.2, for the analysis of the data, and the Microsoft Word and Excel (Microsoft Corp., Redmond, WA, United States) were used to generate graphs, tables, etc.[15]

Results

In our study, the median age of the study participants was 42 years, and most patients reported with moderately-differentiated adenocarcinoma, and most common presentation seen is 1b nodal status, T2 tumor stage, and Tumor, Node, Metastasis (TNM) stage IIIC. The observed values of study parameters are described in Table 1.

The lower length of tumour correlated to lower TNM stage and vice versa whereas lesser distance from anal verge to PTV correlated to higher stage and vice versa (Figures 1 and2) with P=0.009, but when evaluated for testicular dose it was found to be statistically insignificant. The correlation of stage of rectal cancer to treatment technique resulted in statistically significant difference to the dose delivered to testis in VMAT with P=0.008 (Figure 3). The tumour thickness and testicular volume did not have a significant effect on testicular dose.

The mean PTV observed was 1306.80±345.15 (in cubic centimeter-cc). The PTV Coverage with various treatment technique and effect of PTV on testicular dose shows that IMRT had a statistically significant effect with P<0.005 (Figure 4).

2DRT and 3DCRT neither correlated statistically to TNM stage nor to the PTV volume in terms of testicular dose.

Since in the 2D technique, we could only comment on the dose received, data about testis as OAR in 2DRT was not recorded. The comparison of dose contribution with radiotherapy techniques analysed in the study, with and without considering testis as OAR (Table 2) showed a statistical significance with *P*-value<0.002. Among these techniques, IMRT shows significant dose reduction to testis compared with other radiotherapy modalities whereas 2DRT fared poorly in terms of dose to testis.

Discussion

Our study result shows IMRT achieved dose reduction in comparison with other techniques, with PTV correlating to IMRT and TNM stage correlating to VMAT implying their role in dose contribution to testis. Tumour length, thickness, distance from anal verge and testicular volume did not show appreciable impact. 2DRT resulted in higher doses to testis, requiring testicular shielding.

Gul et al. evaluated incidental testicular dose with TLD during prostate IMRT and found significant difference in testicular dose between whole pelvis radiotherapy and prostate only radiotherapy and concluded that testicles should be contoured as an OAR for the estimation of absorbed doses in carcinoma prostate.[16] A systemic review conducted by Farhood et al. found that different RT techniques used for prostate cancer treatment resulted in scattered testicular dose ranging from 0.06 to 6.48 Gy which, in turn, caused testicular atrophy, variation of the male sex hormones, and quality of sexual life as per there study data.[17] By taking notes from these studies and considering the proximity of testis to the rectal cancer treatment volumes, we assessed testicular dose contribution by various treatment techniques in carcinoma rectum and its impact as an OAR. Our study results, clearly depicts dose reduction with

consideration of testis as OAR and importance of contouring it.

Testicular shield is a protective shield placed over the scrotum (the external sac that contains the testicles) during radiation to the pelvic area to minimise dose and to preserve fertility. Singhal et al.[12, 17] analysed its use and concluded that unwanted incidental testicular doses can be restricted with shielding. Since the purpose of our trial was to estimate dose impact on testis with or without considering it as OAR, we limited the use of shield, only upon final dose calculation after various treatment delivery planning. Our study results showed that conventional techniques need shielding, while the conformal technique can achieve cumulative doses of ≤2Gy.

Since the majority of previous studies concentrated on conventional treatment modalities, one of the major differences between previous studies and our study is that we compared whether conformal technique can give a much-needed edge in achieving acceptable toxicity profile, and we found that it indeed resulted in dose reduction with IMRT out-performing other techniques.

Few studies suggest that testicular dose has an effect on hormonal changes[18, 19] so that biochemical assessment could have added further weightage to our study. But since we were focusing on methods to reduce testicular dose by variation in the RT technique and consideration of testis as OAR, hormonal assessment was not considered.

In the recent years, many trials have been performed to assess position variability, prone versus supine in carcinoma rectum treatment.[20-22] Since none of the trials found superiority with prone position except for small bowel toxicity, which again was well within acceptable norms, we did not assess testicular doses in prone position. However, none of the prone position trial with conformal treatment modalities ever considered testis as OAR which needs to be assessed in further trials.

One of the major limitations of our study is that we have not compared short course radiotherapy and long course radiotherapy in carcinoma rectum with testis as organ at risk.

Conclusion

IMRT can result in significant reduction in testicular dose when compared with other techniques while testicular shielding is required in 2DRT. Consideration of testis as OAR also contributed to significant dose reduction in the conformal technique.

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Authors' Contributions:

Poornachandra Tejaswi Siddappa: Study design, data gathering, drafting and reviewing the manuscript.

Shamsundar Sunkappa: Data gathering and reviewing the manuscript.

Vinay Desai: Data gathering and reviewing the manuscript.

Jagannath Kunigal Puttaswamy: Data gathering and reviewing the manuscript.

Nanda Ramanand: Drafting and reviewing the manuscript.

Aradhana Katke: Drafting and reviewing the manuscript.

Thejaswini Boraiah: Drafting and reviewing the manuscript.

All authors have read and approved the final manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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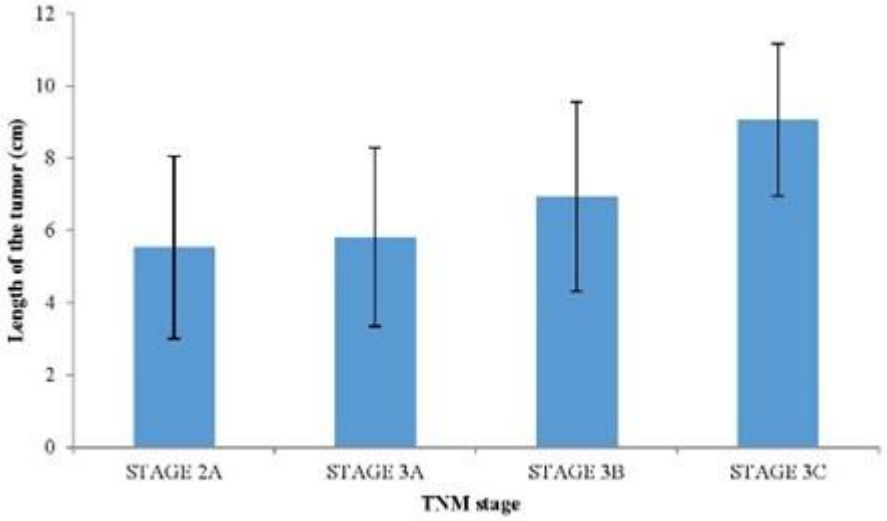

Figure 1. Comparison of length of tumor in centimetre (cm) with Tumor, Node, Metastasis (TNM) stage of disease, showing the incremental effect with the increase in stage

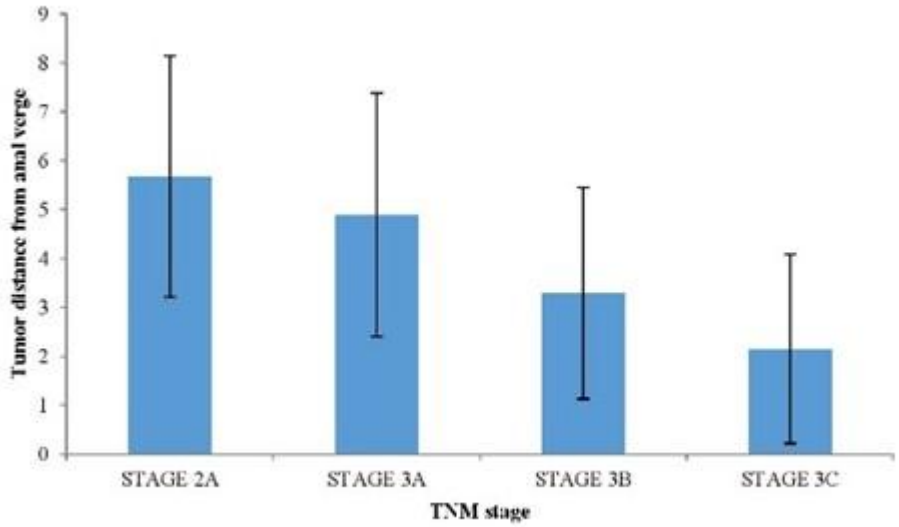

Figure 2. Comparison of distance from anal verge with Tumor, Node, Metastasis (TNM) stage of the disease, showing that the higher the stage is, the lowest the distance from anal verge will be.

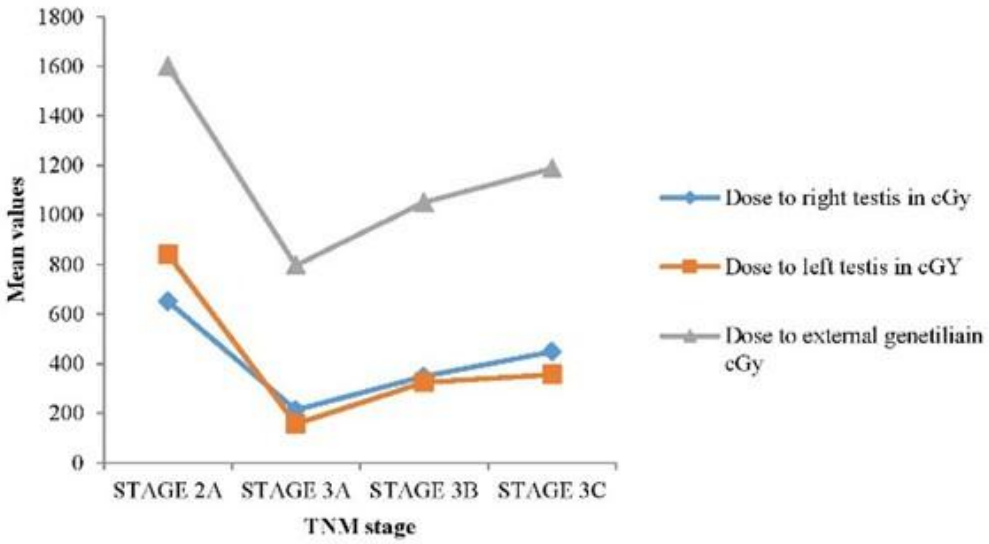

Figure 3. Line diagram comparing volumetric modulated radiotherapy (VMAT) with tumor, node, metastasis (TNM) staging shows the impact of stage of disease on doses (cGy-centigray) received by testis.

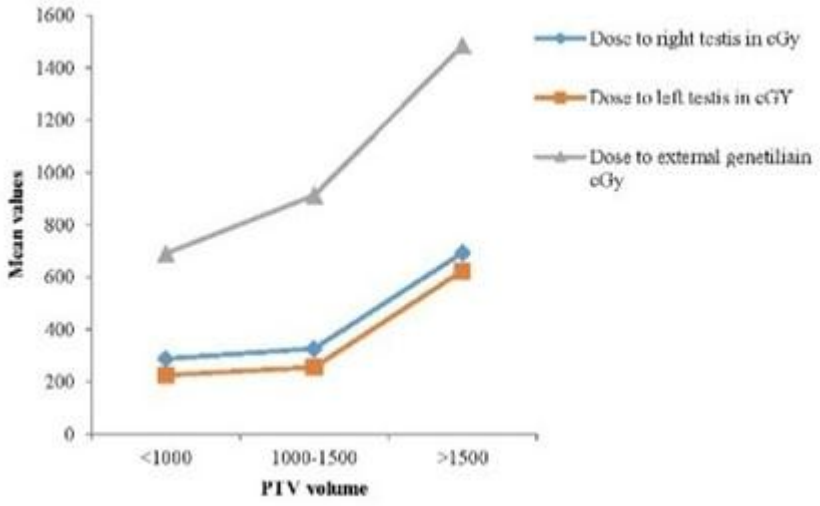

Figure 4: Line diagram comparing intensity modulated radiotherapy with planned target volume (PTV) showing dose (cGy-centigray) to testis is well within the acceptable norm.

1.7.3 Tables

Table 1. General patient characteristics and parameters observed in the study

	Observed values
Age	Median 42 years (range: 22–80) years
Histology (adenocarcinoma): n(%)	Well-differentiated: 40(25.00%) Moderately-differentiated: 93(58.12%) Poorly-differentiated: 27(16.87%)
Tumor, Node, Metastasis staging: n(%)	IIA- 17(10.62%), IIIA- 47(29.37%), IIIB- 38(23.75%), IIIC- 58(36.25%).
Right testis (cc)	23.29±8.92
Left testis(cc)	18.37±7.75
External genitalia(cc)	289.54±80.91
PTV volume (cc)	1306.80±345.15
Length of the tumor (cm)	7.56±2.61
Tumor thickness (cm)	1.81±1.21
Tumor distance from anal verge (cm)	3.41±2.28

cc-Cubic centimetre, cm-Centimeter, n-number of patients, PTV-Planning target volume

Table 2: Testicular dose received with and without considering testis as OAR with commonly practiced radiotherapy treatment delivery techniques

2DRT-two-dimensional radiotherapy, 3DCRT-three-dimensional conformal radiotherapy, cGy-centigray, OAR-organ at risk, IMRT intensity

Technique	Right testis (Not as an OAR) in cGy.	Right testis (as an OAR) in cGy.	Left testis (Not as an OAR) in cGy.	Left testis (as an OAR) in cGy.
2DRT	925.79		776.70	
3DCRT	891.83	347.33	646.74	316.61
IMRT	414.48	171.25	344.63	166.15
VMAT	473.77	201.20	401.68	209.10

modulated radiotherapy, VMAT- volumetric modulated arc therapy