Impact of Treatment Technique on Testicular Dose and Sexual Activity in Rectal Cancer Patients

Poornachandra Tejaswi-Siddappa[1] Shamsundar Sunkappa[2] Jagannath Kunigal-Puttaswamy[2] Aradhana Katke[2] Nanda Ramanand[2] Thejaswini Boraiah[2]

[1] Department of Radiation Oncology, Karnataka Cancer Therapy and Research Institute, Hubballi, Karnataka, India.
[2] Department of Radiation Oncology, Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India.

Address for correspondence Poornachandra Tejaswi-Siddappa, BA, MD, Department of Radiation Oncology, Karnataka Cancer Therapy and Research Institute, Hubballi, 580025, Karnataka, India (e-mail: pct.teju@gmail.com; shubha30891@gmail.com).

Braz J Oncol 2024;20:s00441791981.

Abstract

Objective To estimate the incidental radiation dose delivered to the testicles in three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and volumetric-modulated arc therapy (VMAT) in rectal cancer patients and its impact on sexual activity using a quality-of-life questionnaire.

Materials and Methods The present study included 40 male patients, aged between 25 and 50 years. with locally-advanced rectal cancer, who would undergo neoadjuvant radiotherapy at a dose of 45 Gray (Gy) in 25 fractions (fr) in the supine position. Planning was performed for three techniques: 3DCRT, IMRT, and VMAT. The testicular dose, testicular volume, planning target volume (PTV), the distance of the tumor from the anal verge, and tumor thickness and length in each plan were recorded. A quality-of-life questionnaire pertaining only to sexual activity by the European Organization for Research and Treatment of Cancer–Quality of Life in Colorectal (EORTC QLQ-CR29) and the Functional Assessment of Cancer Therapy–Colorectal (FACT-C) were used to assess the posttreatment effect on sexual life.

Results The mean values for tumor length, thickness, and PTV were of 8.9 cm, 1.77 cm and 1,352 cm^3 respectively. The mean dose to the right and left testicles (in centigray, cGy) were as follows: 3DCRT – 336.23 and 206.65; IMRT – 165.15 and 140.25; and VMAT – 209.2 and 229.2 respectively. A significant correlation was observed involving the PTV and testicular volume and the incidental testicular dose received. The questionnaire-based analysis of sexual activity included 31 patients who were alive, of whom 27 had resumed their normal sexual life 3 months after the treatment without difficulty (score 4).

Conclusion The IMRT showed a significant reduction in the testicular dose when compared to 3DCRT and VMAT. The PTV and testicular volume presented a statistically significant impact on the testicular dose, and the main reason for abstinence was nervousness about disease recurrence.

Keywords
- quality of life
- toxicity
- testis
- rectal Neoplasms
- radiotherapy
- conformal

received
February 16, 2024
accepted
August 16, 2024

DOI https://doi.org/10.1055/s-0044-1791981.
ISSN 2526-8732.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Introduction

Irradiation of the pelvis is an essential component of the contemporary multidisciplinary approach to treat locally-advanced rectal cancer. Neoadjuvant therapy consisting of concurrent radiation and 5-fluorouracil (5-FU) chemotherapy prior to surgery has been shown to improve both recurrence-free and overall survival rates in patients with locally-advanced rectal cancer. Patients who are of reproductive age run a significant risk due to the presence of seminiferous tubules adjacent to the radiation treatment field. Even a single dose as low as 0.78 Gy is sufficient to cause azoospermia in almost all cases.[1–6]

More focus has been placed on the adverse effects of the multimodal treatment in recent years as a result of an increase in the percentage of patients with advanced rectal cancer who are still alive.[7]

In terms of the effects of radiation on the testicles, there are two distinct compartments. First, the highly radiosensitive seminiferous tubules, which is the site of spermatogenesis in the male reproductive system. Second, the Leydig cells, which are those that produce testosterone, are thought to be less radiosensitive than spermatogonia.[8] Recovery depends on the dose that was administered; a treatment of more than 2 Gy will, in most patients, result in azoospermia that is irreversible.[8] It has been shown[9] that exposure to fractionated radiation, which is the most prevalent kind of therapeutic radiation exposure, is more harmful to the germline cells than exposure to a single dose of radiation.

If the therapy causes hypogonadism, this may have a profound impact on quality of life (QoL). This is frequently demonstrated by subtle changes, such as a reduction in lean body and muscle mass, as well as the development of psychological problems, such as a loss of libido, energy, and drive, or even depression and anxiety.[1,10,11]

Hence in the present study, we determined the radiation doses that were administered to the testicles of male patients undergoing radiotherapy (RT) for the treatment of rectal cancer. We paid particular attention to the dose contribution of different radiation-delivery techniques to the testicles. In addition, we analyzed the effect of the treatment on sexual life using a QoL questionnaire. This research was submitted to and approved by the Ethics Committee under submission number KMIO/MEC/011/03.2018.

Materials and Methods

Study Criteria

The study included 40 male patients with locally-advanced rectal cancer, who were sexually active, aged between 25 and 50 years, who would undergo neoadjuvant therapy followed by total mesorectal resection. Patients with comorbidities (diabetes, hypertension, cardiac diseases, and psychiatric illness), using drugs that affected sexual performance, and those with preexisting sexual/genital abnormalities were excluded. A neo adjuvant RT dose of 1.8 Gy per fr 5 days per week totaling a dose of 45 Gy in 25frs delivered in the supine position with thermoplastic immobilization was administered. Oral capecitabine 825 mg/m^2 was adminstered concurrently on the days of the radiation treatment. Planning was performed for three techniques: three-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and volumetric-modulated arc therapy (VMAT); the testicular dose, testicular volume, tumor length and thickness, planning target volume (PTV), and the distance of the tumor from the anal verge in each plan were recorded. Finally, the effect of the treatment on sexual life was assessed through the QoL questionnaire pertaining only to sexual activity by European Organization for Research and Treatment of Cancer Quality of Life in Colorectal EORTC (QLQ-CR29) and the Functional Assessment of Cancer Therapy–Colorectal (FACT-C) after a minimum follow-up of 3 years.

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 ad numbers and percentages. The significance level was set to 5%.

One-way analysis of variance (ANOVA) was employed to determine if there were any statistically significant differences regarding the means of three or more independent (unrelated) groups. Specifically, it tests the null hypothesis.

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. The *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 the 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.[12,13]

Results

In the present study, the median age of the sample was of 38 years, and most patients presented moderately-differentiated adenocarcinomas, most commonly of 1b nodal status, T2 tumor stage, and Tumor, Node, Metastasis (TNM) stage IIIC; moreover 26/40 participants had a PTV ranging from of 1,000 to 1,500 cc.

The overview of the factors assessed in the study (►**Table 1**) shows that 31 (77.5%) patients completed the minimum follow-up period. The comparison of three techniques regarding the length and thickness of the tumor, as well as the distance from anal verge, showed no statistically significant difference (►**Table 2**).

The dose of radiation delivered by IMRT to both right and left testis and the external genitalia was higher in patients in stage IIA than in those in stage IIIC (►**Fig. 1**). However, this difference was not statistically significant. Whereas PTV

Table 1 Patient characteristics

Age: median (range)	38 (range: 20–50) years
Histology (adenocarcinoma): n(%)	Well-differentiated: 14(35%)
	Moderately-differentiated: 22(55%)
	Poorly-differentiated: 4(10%)
Tumor, Node, Metatstasis stage: n(%)	IIA- 6(15%)
	IIIA- 11(27.5%)
	IIIB- 10(25%)
	IIIC- 13(32.5%)
Volume of the right testicle (cm^3): mean ± SD	21.29 ± 9.72
Volume of the left testicle (cm^3): mean ± SD	17.47 ± 6.95
External genitalia (cm^3)	264.63 ± 70.9
Planning target volume (cm^3): mean ± SD	1350.9 ± 340.88
Tumor length (cm): mean ± SD	7.17 ± 2.71
Tumor thickness (cm): mean ± SD	1.71 ± 1.12
Distance of the tumor from the anal verge (cm): mean ± SD	3.6 ± 2.48
Follow-up	Minimum of 3 years; all patients completed the follow-up
Patients alive at the end of the follow-up: n(%)	31(77.5%)
Participants assessed through the EORTC QLQ-CR29 and FACT-C: n(%)	27(67.5%) out of 31(77.5%) alive included

Abbreviations: EORTC QLQ-CR29, European Organization for Research and Treatment of Cancer Quality of Life in Colorectal; FACT-C, Functional Assessment of Cancer Therapy–Colorectal; SD, standard deviation.

coverage with IMRT and its dose contribution to external genitalia, was found to be statistically significant ($p = 0.007$).

The dose delivered to the right testis by 3DCRT was higher in patients in stage IIIC, but was higher in the left testis and external genitalia in subjects in stage IIA (►**Fig. 2**). However, this difference was not statistically significant. The dose delivered to the right and left testis and the external genitalia correlated with PTV > 1,500 cc. But when the testicular volume was compared to the PTV, no statistically significant difference was observed.

When VMAT protocol was delivered, the radiation dose to the right and left testis and the external genitalia was

Table 2 Correlations of tumor length and thickness and distance of the tumor from the anal verge with IMRT, 3DCRT, and VMAT parameters

Correlation with	Tumor length (cm)		Tumor thickness(cm)		Distance of the tumor from the anal verge (cm)	
	r-value	*p*-value	*r*-value	*p*-value	*r*-value	*p*-value
IMRT (mean)						
Dose to the right testis (cGy)	0.003	0.987	0.149	0.358	-0.004	0.982
Dose to the left testis (cGY)	-0.039	0.812	0.170	0.294	0.031	0.851
Dose to the external genitalia (cGy)	0.193	0.234	0.251	0.119	-0.234	0.146
3DCRT (mean)						
Dose to the right testis (cGy)	0.070	0.667	0.164	0.312	-0.101	0.534
Dose to the left testis (cGY)	-0.104	0.523	0.169	0.296	-0.104	0.525
Dose to the external genitalia (cGy)	0.061	0.706	0.260	0.105	-0.248	0.123
VMAT (mean)						
Dose to the right testis (cGy)	0.202	0.212	0.286	0.174	-0.091	0.577
Dose to the left testis (cGY)	0.128	0.431	0.283	0.177	-0.063	0.697
Dose to the external genitalia (cGy)	0.309	0.523	0.268	0.195	-0.273	0.188

Abbreviations: 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; VMAT, volumetric-modulated arc therapy.

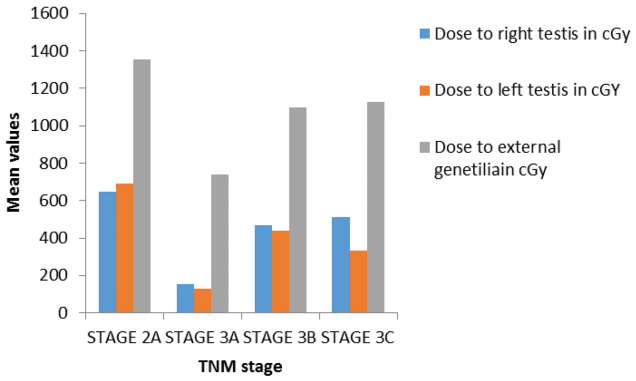

Fig. 1 Dose of intensity- modulated radiotherapy (IMRT) based on the Tumor, Node, Metastasis (TNM) stage.

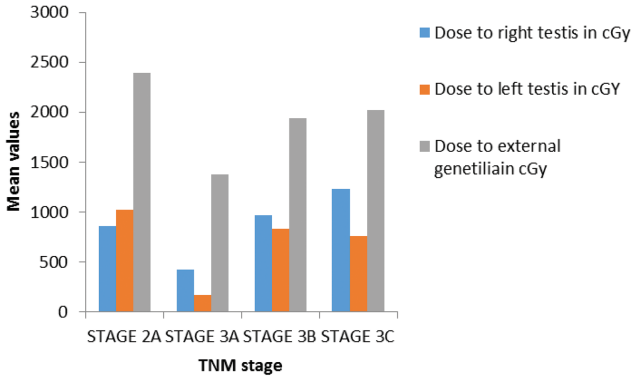

Fig. 2 Correlation of the dose delivered to the TNM stage.

compared with the staging. There was a statistically significant difference regarding the stages of rectal cancer and the dose delivered to the left testis. However, when we compared the dose delivered to the PTV, there was no statistically significant difference regarding the right and left testis and the external genitalia (►**Table 3**).

The 31 patients who were alive were submitted to a QoL analysis in terms of sexual activity: 4 patients did not respond, but the 27 patients who responded said they had resumed sexual activity without difficulty (score of 4). Most subjects had resumed their normal sexual life three months after the treatment. All patients reported that the main reason for delay in resuming sexual activity was nervousness about disease recurrence.

Discussion

The present study results shows that treatment technique and PTV bear an influence on the incidental testicular dose, and it also highlights whether or not the tumor length and thickness, as well as the distance from the anal verge contribute enough to have an impact. One of the most interesting aspects of the study is the assessment of sexual life, which is also an integral QoL domain.

Various studies in literature have evaluated changes in the testicular dose among patients receiving external-beam RT for pelvic malignancy. Piroth et al.[14] evaluated the dose to the testicles from scattered irradiation following RT for rectal cancer. A total cumulative dose of 50.4 Gy was administered to 18 patient susing a 3-field method during their treatment. The cumulative dose to the testicles was of 1.6 (0.98–3.19) Gy, which is almost half of the dose that was measured in a study conducted by Hermann et al.,[1] whose findings o were comparable to those of the present study. This could be the result of discrepancies between the studies in the distribution of the site of the tumor, and in the treatment and immobilization procedures used (four-field versus three-field method), as well as the treatment volumes. External beam radiation administered to the pelvis using a four-field approach for the treatment

Table 3 Comparison of treatment techniques to the PTV

	PTV cc			*p*-value
	< 1,000	1,000-1,500	> 1,500	
IMRT: mean ± SD				
Dose to the right testis (cGy)	287.93 ± 394.19	326.72 ± 475.09	693.27 ± 803.73	0.212
Dose to the left testis (cGY)	225.78 ± 277.7	255.25 ± 413.89	624.56 ± 675.09	0.120
Dose to the external genitalia (cGy)	690.43 ± 343.9	912.82 ± 472.63	1485.17 ± 615.78	0.007**
3DCRT: mean ± SD				
Dose to the right testis (cGy)	909.23 ± 1455.77	708.26 ± 904.89	1362.18 ± 1232.33	0.257
Dose to the left testis (cGY)	789.4 ± 1242.17	434.81 ± 552.76	1140.69 ± 1353.26	0.107
Dose to the external genitalia (cGy)	1932.53 ± 1082.5	1658.17 ± 892.22	2341.09 ± 1276.84	0.206
VMAT: mean ± SD				
Dose to the right testis (cGy)	254.68 ± 342.73	381.98 ± 478.74	400.09 ± 277	0.837
Dose to the left testis (cGY)	229.13 ± 302.55	356.35 ± 469.94	342.04 ± 221.29	0.847
Dose to the external genitalia (cGy)	736.75 ± 370.34	1034.82 ± 574.39	1333.49 ± 576.02	0.171

Abbreviations: 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; PTV, Planning target volume; SD, standard deviation; VMAT, volumetric-modulated arc therapy.

of prostate and rectal cancers has been demonstrated to result in a radiation dose to the testicles that falls somewhere in the range of 200 to 400 cGy.[1,3]

Martin et al.[2] assessed a cohort of 16 patients with prostate cancer and found that the mean dose to the testicles was minimal regardless of the modality used: the value ranged from 21.1 to 93.4cGy, with a maximum value lower than 400 cGy. Accidental irradiation of the testicles due to the use of IMRT to treat prostate cancer was reported by King et al.[5] Within the scope of their research, they considered the additional contribution of the dose brought about by factors such as field size, beam energy, and the use of daily imaging guiding.[5] A prostate-alone field treated with 6-megavolt (MV) photons resulted in a mean testicular dose of 68cGy, while a pelvic nodal field treated with 15-MV photons resulted in a mean testicular dose of 220cGy.[5]

We would like to point out that most of the trials in the literature evaluate incidental testicular RT dose in prostate malignancy, whereas there is very limited data on dose contribution in carcinoma of the rectum. And even in those studies, a major limiting factor is the assessment restricted to the 3 and 4-field RT delivery techniques. Hence, the analysis of the contribution of the radiation dose performed in the present study, with currently-employed conformal techniques (3DCRT, IMRT, and VMAT) in the treatment of rectal cancer around the world, is helpful in providing the much needed data.

In our institutional Scientific Review Board, it was pointed out to us the non-inclusion/non-utilization of testicular shielding, prone position, dose beyond 25 fr as a boost, and short-course RT. In the routine clinical practice, testicular shielding is not included in the treatment of carcinoma of the rectum, and since we perform long-course RT, with 45Gy/25fr as per the institutional protocol based on ACCORD 12/0405 PRODIGE 2 randomized trial,[15] an additional RT dose was not delivered beyond planned 25 fr. However, we do agree that a comparison of the variations in position could have added further weight to the present study.

One of the major limitations to the present study was the lack of assessment of testosterone levels prior to, during, and after the treatment. Since the planned treatment for rectal cancer was neoadjuvant therapy followed by mesorectal excision, the goal of the study was to assess whether there is any toxicity in the routine treatment practice; hence, we did not assess the testosterone levels in the present study.

In a review, Cherven et al.[16] stated that one of the most prevalent and upsetting side effects of cancer treatment is sexual dysfunction. It has been demonstrated[16] that severe sexual dysfunction has a detrimental impact on QoL. Many survivors do not feel prepared for potential sexual changes and frequently do not receive adequate support to manage this issue, even though there are many intervention strategies that can help patients cope with treatment-related sexual problems.

In the current study, we found that many patients were reluctant to resume their sexual life out of concern about recurrence, fear of transferring an illness to the spouse/partner, and a feeling of embarrassment to discuss their sexual life with the clinicians or even with their spouse/partner. Most patients started showing improvements in QoL at the third month of follow-up, once they had gained enough confidence. According to a review by Bober and Varela,[17] various factors, including emotional trauma and treatment outcomes, have an impact on QoL and sexual activity.

The main idea behind the present study was to assess if the conformal techniques used to treat carcinoma of the rectum can lead to sexual dysfunction due to incidental testicular dose or not. The study findings shed light on the need to address the physical aspect of treating the disease, as well as the psychosocial, sexual and emotional aspects associated with the treatment; the findings also highlight the need for comprehensive patient counseling to clear any doubts which may hinder cancer survivals to resume their normal lives,. thereby mitigating any apprehensions faced by the patients and their spouse/partner while making treatment decisions based on the suggestions made by the clinicians.

Conclusion

In the current study, IMRT showed a significant reduction in the testicular dose when compared to 3DCRT and VMAT, the PTV had a statistically significant impact on the testicular dose, and, after the third month of follow-up, most patients resumed their sexual life.

Author's Contributions

PTS: collection and assembly of data, conception and design, data analysis and interpretation, final approval of the manuscript, manuscript writing, and provision of study materials or patients; SS, JKP, AK, NR, and TB: final approval of the manuscript, manuscript writing, and provision of study materials or patients.

Ethics Committee Number

KMIO/MEC/011/03.2018.

Clinical Trials

None.

Funding

The authors declare that they did not receive financial support from agencies in the public, private or non-profit sectors to conduct the present study.

Conflict of Interests

The authors have no conflict of interests to declare.

References

1 Hermann RM, Henkel K, Christiansen H, et al. Testicular dose and hormonal changes after radiotherapy of rectal cancer. Radiother Oncol 2005;75(01):83–88
2 Martin JM, Handorf EA, Price RA, et al. Comparison of testicular dose delivered by intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) in patients with prostate cancer. Med Dosim 2015;40(03):186–189
3 Buchli C, Martling A, Arver S, Holm T. Testicular function after radiotherapy for rectal cancer–a review. J Sex Med 2011;8(11):3220–3226

4 Nichols RC, Hu C, Bahary JP, et al. Serum testosterone changes in patients treated with radiation therapy alone for prostate cancer on NRG oncology RTOG 9408. Adv Radiat Oncol 2017;2(04): 608–614
5 King CR, Brooks JD, Gill H, Presti JC Jr. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. Int J Radiat Oncol Biol Phys 2012;82(02): 877–882
6 Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002;53 (05):1111–1116
7 Ghadimi M, Rödel C, Hofheinz R, Flebbe H, Grade M. Multimodal treatment of rectal cancer. Dtsch Arztebl Int 2022;119(33-34):570–580
8 Meistrich ML. Effects of chemotherapy and radiotherapy on spermatogenesis in humans. Fertil Steril 2013;100(05):1180–1186
9 Izard MA. Leydig cell function and radiation: a review of the literature. Radiother Oncol 1995;34(01):1–8
10 Kinsella TJ, Trivette G, Rowland J, et al. Long-term follow-up of testicular function following radiation therapy for early-stage Hodgkin's disease. J Clin Oncol 1989;7(06):718–724
11 Dueland S, Guren MG, Olsen DR, Poulsen JP, Magne Tveit K. Radiation therapy induced changes in male sex hormone levels in rectal cancer patients. Radiother Oncol 2003;68(03):249–253
12 Suresh K, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci 2012;5 (01):7–13
13 Corp IBM. Released 2013IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.
14 Piroth MD, Hensley F, Wannenmacher M, Zierhut D. [Male gonadal dose in adjuvant 3-d-pelvic irradiation after anterior resection of rectal cancer. Influence to fertility]. Strahlenther Onkol 2003; 179(11):754–759
15 Gérard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012;30(36):4558–4565
16 Cherven B, Sampson A, Bober SL, et al. Sexual health among adolescent and young adult cancer survivors: A scoping review from the Children's Oncology Group Adolescent and Young Adult Oncology Discipline Committee. CA Cancer J Clin 2021;71(03): 250–263
17 Bober SL, Varela VS. Sexuality in adult cancer survivors: challenges and intervention. J Clin Oncol 2012;30(30):3712–3719

