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Assessment of Variations in Serum Testosterone, Follicle Stimulating Hormone, and Luteinizing Hormone Levels in Patients Receiving Radiotherapy for Rectal Cancer

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Abstract

Background: Testes being in close proximity to radiation fields in patients of rectal cancer treated with radiotherapy, inadvertently receive a part of the radiation dose. This study was conducted to evaluate the variation of male sex hormones during the course of radiotherapy in patients with rectal cancer.

Method: In this single-institution prospective study, 20 patients with carcinoma rectum were included. The patients were treated with 3-dimensional conformal radiation therapy or intensity modulated radiation therapy technique to a dose of 50.4 Gy for five weeks. Serum testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) levels were obtained prior to and in the meantime of radiotherapy. The post treatment hormone levels were compared to the baseline values.

The mean, percentage, standard deviation, and paired t-test were used for statistical analysis.

Results: The mean dose received by the testes was 2.65 Gy (1.96 Gy to 4.96 Gy), which accounted for 5.25% of the total dose. The baseline values of serum testosterone, FSH, and LH were 4.65 ± 0.7 ng/ml, 7.57 ± 1.2 mIU/ml, and 7.93 ± 1.1 mIU/ml, respectively. There was a 32.1% drop in the post treatment testosterone levels compared with the baseline. There was a 77% rise in the post treatment FSH and 40.2% rise in the post treatment LH levels compared with the baseline. There was a significant difference in the rise of LH levels in the patients who received a testicular dose more than 2Gy compared with those who received a dose less than 2 Gy.

Conclusion: Radiation therapy was found to have a significant acute impact on male sex hormones in patients receiving radiotherapy for rectal cancer.

Keywords: Hormones, Rectum, Radiotherapy

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Introduction

Radiotherapy plays an important role in the multimodality treatment of rectal cancer. Although neoadjuvant chemoradiotherapy is the current standard of care in the management of rectal cancers, radiotherapy is also used in adjuvant settings when indicated.[1] Testes being in close proximity to the radiation fields, inadvertently receive some dose of radiation during the course of treatment.[2] Studies in the literature have reported that testes receive 3 to 17% of the radiation dose applied for the treatment of rectal cancer.[1-4]

Testicular tissues have two components with respect to radiation damage: firstly, the seminiferous tubules corresponding to the sites of spermatogenesis; secondly, the Leydig cells that correspond to the testosterone producing cells.[4] The seminiferous tubules are extremely radiosensitive. A single dose as low as 0.78 Gy leads to transient azoospermia in nearly all patients[5] and a total dose exceeding 1.5–2.0 Gy to the testes may lead to permanent sterility.[1,6] The Leydig cells account for 70%-75% of the total testosterone production in a normal adult male. The Leydig cells are more resistant against damage from radiation compared with seminiferous tubules.[6] Damage to the Leydig cells, leading to an increase in the luteinizing hormone (LH) levels, rises as a compensatory mechanism. Low levels of testosterone may result in decreased libido, sexual function, changes in personality, reduced stamina, as well as depression.[7-8] In addition, recent studies have shown a strong association between low levels of testosterone and features of metabolic syndromes.[9]

Damage to the seminiferous tubules could be evaluated by monitoring follicle stimulating hormone (FSH) in the serum of patients. The Leydig cell damage could be evaluated through biochemical measurement of LH and testosterone levels in serum.[4,7,10] To compensate for cell damage, LH and FSH rises above the normal levels in about 20%-40% of patients receiving radiation to their testes.[11-13] A few studies in the literature have assessed the variation of male sex hormones during the course of radiotherapy.[14-22]

The current study aimed to measure the dose of radiation received by the testes during the course of radiotherapy in patients of rectal cancer and to measure the variation of serum testosterone, FSH, and LH before and after the course of radiotherapy.

Subjects and Methods

This was a single-institution prospective study. Ethical clearance was obtained from the Institutional Ethics Committee prior to the start of the study (Code- 437/2019).

We conducted this work in our department from February 2019 to December 2019. 20 patients with histologically proven stage II or III carcinoma rectum receiving neoadjuvant or adjuvant radiotherapy according to the indications were included in the study. The inclusion criteria were histological evidence of malignancy, adequate renal and hematological parameters, and good performance status. The patients with distant metastasis, other active malignancy, and prior history of radiotherapy to the pelvis were excluded. A written informed consent was obtained from all the participants prior to the initiation of the study. All the patients underwent 1.5 T magnetic resonance imaging (MRI) of pelvis for staging evaluation. Serum testosterone, serum FSH, and serum LH were measured before the initiation of radiotherapy and on the day of completion of radiotherapy.

Planning computed tomography (CT) scan was obtained in supine position from T10 to midthigh using a multi-slice CT scanner providing transverse images with a slice thickness of 5mm. Gross tumour volume (GTV), clinical target volume (CTV), planning target volume (PTV), bladder, and femoral heads, as well as testes were contoured on each slice. The testes were delineated on planning CT as one volume according to the RTOG contouring atlas 23 excluding other scrotal structures, such as skin, soft tissue, or epididymis. The subjects were treated with bowel and bladder protocols. Pelvic radiation was delivered with 3-dimensional conformal radiation therapy (3DCRT) or intensity modulated radiation therapy (IMRT) technique with a 6 MV linear photon accelerator

and a dose of 50.4 Gy for five weeks. We carried out the treatment planning with Eclipse Aria version 13 treatment planning software. PTV D98%, PTV D95%, PTV volume, testes volume, the mean dose to testes, the mean dose to femoral head, and bladder were assessed during plan evaluation. The data pertaining to the volume and dose received by the testes were obtained via the planning system using dose volume histogram. All the patients received concurrent capecitabine 825 mg/m^2 twice a day, five days a week along with radiation therapy.

Statistical analysis

The data were compared to the frequency, mean, percentage, and standard deviation. The comparison of post-RT hormone levels with baseline hormone levels was performed using paired t-test. Statistical significance was defined as *P* value <0.05. All the statistical analyses were done utilizing SPSS version 19.

Results

A total of 20 patients participated in our study. Their median age was 59.5 years; 33 % had stage II disease and 67% had stage III disease. 3DCRT was used for 30% of the patients and IMRT was employed for 70% of them. Seven to nine beams were used in IMRT planning. 33% of the patients received treatment as neoadjuvant therapy and 67% received treatment as adjuvant therapy post-surgery. They all received radiation to dose of 50.4 Gy delivered in 28 fractions, 1.8 Gy per fraction, 1 fraction a day for five weeks. They also received Capecitabine 825 mg/m^2 on the days of RT. Table 1 represents the patients' characteristics.

Table 1. Patient characteristics

Patient characteristics	n=20
Median Age	55.9 years
Histology	
Adenocarcinoma	20 (100%)
Stage	
Stage II	5 (33%)
Stage III	15 (67%)
Therapy	
Neoadjuvant	5 (33%)
Adjuvant	15 (67%)
Technique	
3DCRT	6 (30%)
IMRT	14 (70%)
Dose	50.4 Gy

3DCRT: 3 dimensional conformal radiation therapy; IMRT: Intensity modulated radiation therapy

The mean testicular volume was 37.42 cm^3 (Range: 22 cm^3 to 50.23 cm^3). The mean dose received by the testes was 2.65 Gy (1.96 Gy to 4.96 Gy), which was 5.25% of the total dose. The mean dose received by the testes in neoadjuvant group and adjuvant group were 3.75 Gy and 2.29 Gy, respectively. The baseline values of serum testosterone, FSH, and LH were 4.65 ± 0.7 ng/ml, 7.57 ± 1.2 mIU/ml, and 7.93 ± 1.1 mIU/ml, respectively.

The mean testosterone level post radiation therapy was 3.15 ng/ml (1.99 -4.11 ng/ml). There was a 32.1% (mean 1.49 ng/ml) drop in the serum

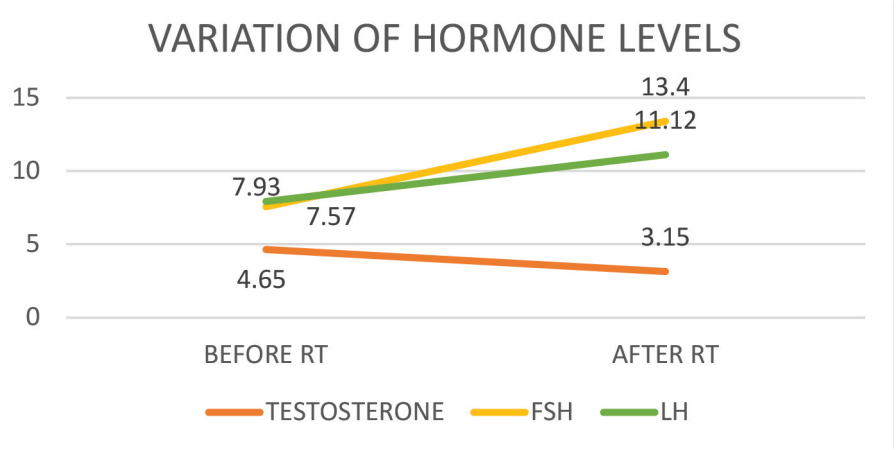

Figure 1. This figure shows the variation in hormone levels in radiotherapy-receiving patients for rectal cancer.
FSHL: Follicle stimulating hormone; LH: Leuteinizing hormone; RT: Radiotherapy

Table 2. Variation in hormones

Hormone	Before RT Mean±SD	After RT Mean±SD	Mean change	Percentage change
Testosterone	4.65 ± 0.7 ng/ml	3.15 ± 0.5 ng/ml	-1.49ng/ml	32.1%
FSH	7.57 ± 1.2 mIU/ml	13.4 ± 2.2 mIU/ml	+5.83 mIU/ml	77%
LH	7.93 ± 1.1 mIU/ml	11.12 ± 1.8 mIU/ml	+3.19 mIU/ml	40.2%

FSHL: Follicle stimulating hormone; LH: Leuteinizing hormone

levels of testosterone from the pre-treatment values (Table 2 and Figure1). Prior to starting the radiotherapy, 15 patients had their testosterone levels in the normal range. Following the radiotherapy, five patients (33%) had testosterone levels below the normal lower limit.

The mean FSH level after the radiotherapy was 13.4 mIU/ml. There was a rise by 77% in the FSH levels (mean 5.83 mIU/ml) from the baseline values. Prior to starting the radiotherapy, 15 patients had their FSH levels in the normal range. Following the radiotherapy, 14 patients (70%) had FSH levels above the normal upper limit. The mean LH level in the post-radiotherapy was 11.12 mIU/ml. There was a rise by 40.2% in the LH levels (mean 3.19 mIU/ml) from the baseline values. Prior to starting the radiotherapy, 15 patients had their LH levels in the normal range (Table 2 and Figure 1). After the radiotherapy, 17 patients (85%) had LH levels above the normal upper limit.

We further compared the variations of hormone levels of the patients who received a testicular dose of 2 Gy or more to those of the patients who received a testicular dose less than 2 Gy. Eight patients received a dose less than 2 Gy and 12 patients more than 2 Gy. There were no statistical differences concerning the decrease in testosterone levels between those who received a testicular dose of equal or more than 2 Gy compared to those who received a testicular dose less than 2 Gy (P = 0.13). There were no statistical differences in the rise in FSH levels between the patients who received a testicular dose equal or more than 2 Gy and the subjects who received a testicular dose less than 2 Gy (P = 0.85). We observed a significant difference concerning the increase in LH levels between those who received a testicular dose equal or more than 2 Gy and those who received a testicular dose less than 2 Gy (P = 0.04).

Discussion

In our study, serum testosterone, FSH, and LH were measured twice, once prior to the initiation of RT and once after the completion of RT. The obtained data indicated that in the patients with rectal cancers, treated with radiotherapy to a dose of 50.4 Gy, there was a significant reduction in testosterone levels and increase in the FSH and LH levels, which in turn shows the significant effect of radiation on testes.

In our study, we observed a 32.1% drop in the post-treatment testosterone levels compared with those of the baseline. Moreover, 33% of the patients had testosterone levels below the normal lower limit at the end of radiation therapy. Similar outcomes were seen in a few other studies. Dueland et al. reported a 25% decrease in testosterone levels in 25 patients treated for rectal carcinoma with radiotherapy.[3] Hermann et al. reported a 22% decrease in serum testosterone levels in patients of rectal cancer after radiotherapy.[4] Zagars et al. demonstrated a 10% fall in testosterone levels following three months of radiotherapy.[11]

FSH and LH are pituitary hormones that regulate the testicular function. FSH secretion functions under the negative feedback control of gonadal steroids and inhibin.[14] LH secretion is under the negative feedback of gonadal steroids.[14]

In our study, we demonstrated a 77% increase in FSH and 40.2% increase in LH levels after the radiotherapy. Additionally, 70% of the patients had FSH levels above the normal upper limit and 85% of them had LH levels above the normal upper limit after completion of RT. Our results are consistent with those of other studies published in the literature. Dueland et al. reported a100% increase in FSH and 40% increase in LH levels after RT in rectal cancer patients.[3] Bruheim et al. demonstrated an increase in FSH level by three

times and LH levels by 1.7 times.[14]

Our data did not show any significant relations between the dose received and variation in testosterone levels or FSH levels, yet indicated a significant relation with variation in LH levels. LH levels were found to increase by 49% in the patients who received a dose of 2 Gy or more to the testes compared to those who received less than 2 Gy, who exhibited an increase in LH levels by only 26%.

Mazonakis et al.[15] compared the effect of shielding the testes during radiotherapy and reported a 66% reduction in the dose to the testes using a commercially available round shield compared with a conventional 8 cm lead block.

Negative effects of hypogonadism on body composition, bone loss, atherosclerosis, cognitive function, and depression have been reported, but require further documentation. The effect on libido and sexual function is well-known, yet probably not generalizable to all the patients. All these patients have had major surgery to the pelvis and it is difficult to determine whether impaired sexual function is due to the surgery or radiotherapy. It is known that radiotherapy can affect sexual functions; however, it is uncertain whether this is mainly because of fibrosis, neuropathy, or a result of hormonal changes.[12-15]

In sum, the findings of this review suggested the impact of radiotherapy for rectal cancer on male sex hormone levels, which could be variable, but of clinical importance for those individuals that develop testosterone deficiency. Knowledge on the effects on testosterone levels and the prevalence of symptoms precipitating testosterone deficiency would be conducive to promote the quality of life in these patients.

The limitations of our study included the small sample size and a short duration of the follow-up. The observed changes might have been accelerated through the use of concurrent chemotherapy. Most of the patients received adjuvant chemoradiotherapy neoadjuvant, which limits the extrapolation to the current practice. It could be suggested that patients be followed up for a longer duration in order to determine the variation in hormonal levels in the long run.

Conclusion

In conclusion, our results revealed that radiation therapy for rectal carcinoma has a significant acute impact on male sex hormones. We demonstrated a fall in serum testosterone levels and an increase in serum FSH and LH levels in our study. Further studies are needed to examine the long-term effect of radiation on male sex hormones.

Conflict of Interest

None declared.

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