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RESEARCH ARTICLE

Evaluation of Relationship Between Testicular Dose and Hormonal Changes After Radiotherapy in Patients With Rectal Cancer

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Abstract

Background: Colorectal cancer globally affects more than 1 million people every year. It is more common in men and it is the second most common cause of cancer mortality. Optimal treatment of colorectal cancer is a multidisciplinary approach which can be included of surgery, medical oncology, and radiation therapy.

Objectives: The aim of this study was evaluation of relationship between testicular dose and hormonal changes after radiotherapy in male patients with rectal cancer.

Patients and Methods: In this study 25 patients with rectal cancer were enrolled. The serum levels of luteinize hormone (LH), follicle stimulating hormone (FSH), and testosterone (T) before and 3 - 6 weeks after chemoradiotherapy were compared and testicular dose was determined using a 3-dimension treatment planning system and relationship between hormonal changes and testicular dose was assessed.

Results: 25 patients with rectal cancer with mean (± SD) age of 56.08 (±14.30) years were evaluated. The mean (± SD) testes dose was 2.35 (± 2.32) Gy that was 6.09% of total dose. The levels of FSH and LH significantly increased (P = 0.001), however, the level of testosterone non -significantly decreased after 3 - 6 weeks of radiation therapy (P = 0.79). No significant correlation was found between testes dose and sex hormones change (LH, P = 0.33; FSH, P = 0.16; testosterone, P = 0.95). Furthermore the testes dose did not correlate with the lower border of treatment field (P = 0.26), total given dose to the patients (P = 0.81) and tumor location (P = 0.09).

Conclusions: The testes dose in this study was 6.09% of total dose. Radiotherapy of rectal cancer causes damage to the testis, as shown by increased levels of gonadotropins after radiotherapy. The radiation therapy significantly increased LH, FSH and non-significantly decreased testosterone level in patients with rectal cancer. No correlation could be found between changes of hormones and doses to the testis, probably due to the low number of evaluated patients. Larger studies are needed to establish the correlation between testicular radiation dose and hormonal changes in this group of patients.

Keywords: *Radiotherapy; Rectal Cancer; Colorectal Cancer*

1. Background

Colorectal cancer globally affect more than 1 million people every year (1). It is more common in men (2, 3) and it is the second most common cause of cancer mortality (4, 5). Optimal treatment of colorectal cancer is a multidisciplinary approach which can be included of surgery, medical oncology, and radiation therapy (5). Radiation therapy is an acceptable method of treatment for rectal cancer that can reduce the risk of locoregional recurrence. Testes are the radiosensitive organs that lie close to the rectum and are usually affected by the scattered radiation during the pelvic radiotherapy procedure (6, 7). It is established that scattered radiation delivered to the testes can result in sexual dysfunction in male gender (6). Previous studies indicated that a single dose of 3.5-6 Gy to the testicles results in long-term or permanent oligo- or azospermia (8), and in doses more than 15 Gy, leydig cell function compromised (9). It is indicated that radiation therapy in prostate and rectal cancer can increase the levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) and decrease testosterone level (8, 10, 11). Additionally one of the most common chemotherapeutic agent in rectal cancer is 5-Fluorouracil (5-FU) and some studies confirmed that 5-FU decreases testosterone levels (12, 13). There is limited published data on the evaluation

relationship between testicular doses from pelvic radiotherapy for rectal cancer and male sex hormone changes.

2. Objectives

In this study, we evaluated the role of pelvic irradiation in patients with rectal cancer on serum levels of male sex hormones (FSH, LH, and testosterone), and measured the testis dose to determine the relationship between testicular dose and these hormone levels.

3. Patients and Methods

This study was approved by the local study review and ethics board of the Shohada hospital in compliance with the 1975 Helsinki Declaration and its revision in 2000 and for this reason the written consent was given to the patients before the study. This was a quasi-experimental study and considering a confidence. Level of 68% and using formula N = Z2S2/d2, 22 samples was computed to be incorporated (x = 0.5, d = 10, SD = 24.7, X = 55). 25 males with stage II-III rectal cancer were treated with chemoradiation before and after surgical resection between march 2012 to march 2014. The Inclusion criteria were patients with no distant metastasis and normal sexual hormone levels before treatment.

3.1. Study Design and Treatment

The chemotherapy was performed with Capecitabine (Xeloda) orally 825 mg/m^2 in radiotherapy days. Computed tomography scan was obtained in supine position from L1 to 2 cm below the inferior border of the testes using a multislice CT scanner (sensation; Siemeeos, Germany) providing transverse images with a slice thickness of 5mm. Patients were asked to empty their rectum before simulation. Three markers were positioned in the intersection of the lasers on the patient body for better positioning. Planning of the radiation fields were done with ISOGRAY (version 4.1, Dosisoft co. France) 3D computer based treatment planning system (TPS) based on CT scans in DICOM format (Digital Imaging and Communication in Medicine format, http://dicom.nema.org). To ensure the accuracy of the doses delivered, clinical commissioning tests of the TPS were performed according to the IAEA-TEC Doc 1583 report. GTV, CTV, PTV, bladder, and femoral heads as well as testes were contoured on each slice. The filed borders were defined regarding tumor location and type of surgery. Lower border in patients with abdomenoperineal resection was defined at under perinea, in patients with anterior resection at 5 cm under tumor bed and in patients that were treated before surgery; the border was defined at 5 cm under lower edge of the tumor. Dose calculation was done using collapse cone algorithm used in TPS system with dose voxel size of 5 × 5 × 5. Radiation therapy was performed with box (3 Patients, 12%) or two AP/PA (22 Patients, 88%) technique using 6 MV photon beams emitted from compact linear accelerator (ELEKTA Co.) in an isocenteric technique to deliver 1.8 -2 Gy/day, in 5 consecutive days per weeks up to total dose of 45-50.4 Gy.

3.2. Hormonal Tests

Before start of radiation therapy and at 3 - 6 weeks after completion of the radiotherapy a blood sample was taken and serum levels of male sex hormones were measured. Follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone (T) were determined all at the same laboratory by Elisa kits.

3.3. Statistical Analysis

Statistical analysis was done using SPSS (software version: 21). Data were presented as mean ± SD or frequency. Non parametric related test were used for statistical analyses before and after treatment. Spearman correlation test were used to evaluate the correlation between variables. P values, 0.05 were considered statistically significant.

4. Results

In this quasi-experimental study 25 patients with mean (± SD) age of 56.08 (± 14.30) years (range: 28 - 80 years) were evaluated. Patients were followed for 3 - 6 weeks after completion of radiation therapy. Patients demographic, tumor characteristics, and dosimetric data were shown in Table 1. The mean (± SD) distance of tumor from anal verdge was 8.44 (± 4.50) cm and the mean (± SD) distance between lower border of field and testes was 3.52 (± 1.51) cm. The mean (± SD) testes dose was 2.35 (± 2.13) Gy (range: 0.3-13.2 Gy) that was 6.09 percent of prescribed dose. The testes dose greater than 2 Gy was seen in 8 patients (32%). The hormonal changes with their normal ranges were shown in Table 2. The level of FSH and LH significantly increased after chemoradiation therapy (P = 0.001), however, the level of testosterone non -significantly decreased after radiation (P = 0.79) (Table 2). The mean of testosterone change before and after treatment was 0.12 that did not correlate with testes dose (P = 0.06), moreover, the levels of FSH and LH changes before and after treatment was 8.66 and 3.32 respectively, and did not correlate with testes dose (P = 0.46 and P = 0.146, respectively). Furthermore, the testes dose did not correlate with the lower border of treatment field (P = 0.26), total given dose to the patients (P = 0.81) and tumor location (P = 0.09), however, total dose has significantly associated with the number of treatment field (P = 0.001).

Table 1. Demographics Characteristics, Tumor Characteristics, and Dosimetric Data of 25 Patients With Rectal Cancer [a]

Features	Frequency
Number	25
Age range, y	58.08 ± 14.30
Stage	
II	9 (36)
III	16 (64)
Mean tumor distance from anal verge, cm	8.44 ± 4.50
Mean distance between lower border of treatment field and testes, cm	3.52 ± 1.51
Number of Radiation Fields	
2	3 (12)
4	22 (88)
Position	
Prone	21 (84)
Supine	4 (16)
Boost	
Yes	14 (56)
No	11 (44)
Treatment	
Adjuvant	7 (28)
Neoadjuvant	11 (72)
Testes Dose	
Mean dose	2.35 ± 2.13
Range	0.3 - 13.20
Percent	6.09
< 2, Gy	8 (32)
> 2, Gy	17 (68)

[a] Data are presented as No. (%) or mean ± SD.

Table 2. Male Sex Hormone Levels Before and After Radiation in 25 Patients With Rectal Cancer [a, b]

	Pre Chemoradiation	Post Chemoradiation	Mean Changes	P Value
FSH, IU/L	7.34 ± 3.31	16.00 ± 9.78	8.66	0.001
LH, IU/L	3.95 ± 2.64	6.91 ± 3.50	3.32	0.001
T, IU/L	4.52 ± 2.11	4.40 ± 2.04	0.12	0.79

[a] Abbreviations: FSH, follicular stimulating hormone; LH, luteinizing hormone; T, testosterone.
[b] Data are presents as Mean ± SD.

5. Discussion

Previous studies have established the impact of radiation on the level of male sex hormones (8, 10-13). In this cohort we indicated a significant increase in serum levels of LH and FSH and non-significant decrease in testosterone level after pelvic chemoradiation therapy for rectal cancer to a total dose of 45 or 50.40 Gy that indicated considerable damage to the testicles. In line with our findings Dueland et al. (8) reported that a cumulative testicular dose of 3.3 Gy induced significant increase in FSH, and LH as well as decreased testosterone levels. Consistently, Zagars and Pollack demonstrated a significant drop in testosterone levels in 85 patients receiving a testicular dose of 2 Gy (10). In present survey, the mean testes dose was 6.09% (2.35 ± 2.13 Gy) of total prescribed dose given to the patients that was similar to testicular irradiation dose during radiotherapy for rectal cancer which previously was measured by Hermann et al. (14). They demonstrated that the mean testes dose was 7.1% (3.56 Gy) of total dose (50 Gy) measured with an ionisation chamber. In a study by Mazonakis et al. testicular dose was measured in an anthropomorphic phantom made of tissue equivalent-material that showed the testis dose was 0.8 - 4.8% (0.32 to 2.16 Gy) of the prescribed target dose (45 Gy) (15) that was lesser than this study. It can be related to different methods used for dose calculation. In this study, total volume of testes was contoured and testes dose was determined by 3-dimension treatment planning system whereas in Mazonakis et al. study testes dose was measured using phantom and in the point with certain distance from isocenter. In this study the mean tumor distance from anal verge was 8.44 ± 4.50 cm and the mean distance between lower border of treatment field and testes was 3.52 ± 1.51 cm (Table 1). However, the testes dose did not correlate with the lower border of treatment field (P = 0.26), and tumor location (P = 0.09). Budgell et al. measured scattered tes-

ticular doses during radiotherapy for rectal cancer with distances between 3 and 11 cm from the testes to the lower field edge, and the testes dose was recorded as 1.9 - 4.1% of the prescribed dose and oppose to our findings the testicular dose correlated with the distance between the caudal edge of the radiation field and the center of the testicles (16). It was possibly due to the low number of samples in this study. In current study, with short term patients follow up, we could not establish whether the changes in plasma levels of FSH and LH, and the reduction in testosterone levels were a temporary or permanent finding in patients who received chemoradiotherapy to a maximum total tumor dose of 50.40 Gy. Yoon et al. indicated that chemoradiation in men with rectal cancer caused persistent increases in FSH and LH levels and decreases in testosterone levels (17). Moreover, another study by Joos et al. (18) indicated a temporary hormone elevation in patients with testicular scatter doses as low as 0.55 Gy. Furthermore, they confirmed, FSH elevations peaked 6 months post therapy in patients but returned to within normal ranges after 36 months. Similar hormonal dynamics were detected in LH serum values. Mean LH levels remained within normal ranges post therapy (18). In a study by Hennies et al. (19) 83 male patients were treated for locally advanced rectal cancer [total dose 50.4 Gy, concomitant chemotherapy with two cycles of 5-fluorouracil (FU) or 5-FU and Oxaliplatin]. Testicular radiation doses were analyzed and correlated with hormone levels [luteinizing hormone (LH), follicle stimulating hormone (FSH), total testosterone, and free androgen index (FAI) serum levels], QOL, and sexual functioning, which were determined before and up to 1 year after RCT. Similar current study, there was no statistical correlation between testicular radiation dose and changes in hormone level, as well as QOL, or sexual functioning (19). Several limitations are inherent to the present study, as small sample size and short duration of study that limit the ability to generalize the result of our survey. Further investigations are recommended with longer follow-up and larger series to validate the findings reported here and will answer the question regarding whether chemoradiation therapy is true male sex hormone modifiers. Testes dose significantly increased serum level of LH and FSH and non-significantly decreased testosterone level. Testes dose was 6.09% of total dose given to the patients. Patients who will receive radiotherapy for rectal cancer must be instructed about a risk of hypogonadism and a probable risk of infertility. Further studies should evaluate the impact of increased LH levels after pelvic irradiation on quality of life.

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