Original Article
Middle East Journal of Cancer 2010; 1(3): 115-122

Impact of Scattered Radiation on Testosterone Deficiency and Male Hypogonadism in Rectal Cancer Treated with External Beam Pelvic Irradiation

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Abstract

Background: We performed a prospective study to evaluate the effects of pelvic irradiation on FSH, LH and testosterone levels in male patients with rectal adenocarcinoma. Our aim was to compare the level of male sex hormones in peripheral blood serum before and after pelvic irradiation.

Methods: The eligible participants were 40 men with rectal adenocarcinoma who underwent pelvic radiotherapy as part of their treatment for primary tumor, either before or after surgery. All patients received a 50-Gy radiation dose to the pelvis, 2 Gy per fraction, five days per week. Blood was sampled three times during the study: once before radiation, at the end of the radiation course and 4 to 6 weeks after radiotherapy.

Results: Median age of the patients was 58 years (range 18-82). The mean testis dose of radiation per fraction in all 40 patients was 16.3 cGy with a standard deviation of 15.22 (range 5.5-64.8). Serum levels of FSH revealed a significant increase from 7.5 ± 1.7 IU/L (before treatment) to 20.9 ± 17.8 IU/L [end of radiotherapy (P<0.001)] and 24.1 ± 20.5 IU/L [4 to 6 weeks after radiotherapy (P<0.001)]. Serum LH levels were significantly elevated from 8.04 ± 1.2 IU/L before radiation to 11.6 ± 11.5 IU/L at the end of radiotherapy (P<0.001) and 12.5 ± 9.9 IU/L 4 to 6 weeks after the final course of radiotherapy (P<0.001). There was a decrease in serum testosterone from 5.3±2.1 ng/mL before radiation to 4.2 ± 1.9 ng/mL at the end of radiotherapy (P=0.004) and 4.5 ± 2 ng/mL 4 to 6 weeks after radiotherapy (P=0.035). No significant correlation was seen between age and differences in sex hormones (LH, P=0.605; FSH, P=0.380; testosterone, P=0.161).

Conclusion: There was a significant change in serum levels of male sex hormones after pelvic irradiation for rectal cancer (total dose, 50 Gy) that indicates considerable testicular damage under these circumstances. Thus, it seems logical to use techniques that reduce the radiation dose to the testicles and to consider the benefits of hormone replacement therapy as well as semen cryopreservation for high-risk patients who desire children in the future.

Keywords: Rectal carcinoma, Male sex hormones, Pelvic irradiation, LH, FSH, Testosterone

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Received: May 1, 2010; Accepted: June 12, 2010

Introduction

Colorectal cancer remains a major health problem[1] and worldwide, approximately one million new cases per year are diagnosed, with 529,000 deaths.[2] Sporadic colorectal cancer increases dramatically above the age of 45 to 50 years.[3] The management of rectal cancer has undergone a dramatic change in the past decade. Until recently, surgery was the primary treatment modality,[4] but recent results of national cooperative group studies and several European randomized trials indicate that multimodal treatment including concurrent chemoradiation therapy, as an adjuvant (postoperative) or neoadjuvant (preoperative), results in a significantly better outcome than surgery alone.[5-8] The goal of this treatment approach is curative and it is important to determine the side effects related to multimodal therapies to develop ways to minimize them, and to restore organ function with replacement therapy if indicated.[9-12]

Some studies have evaluated the effect of pelvic irradiation on testicular function and male sex hormones.[9,10,13-27] Functionally, testicular tissues have two compartments related to radiation damage. First, the seminiferous tubules responsible for spermatogenesis are considered to be radiosensitive. Second, the testosterone-producing cells (Leydig cells) are relatively resistant to radiation.[9,28-32] Available data suggest that hormonal function and spermatogenesis may be compromised at dose levels as low as 0.5 Gy, and that cumulative doses above 2 Gy probably result in a significant decrease in serum testosterone levels.[10] Also a single dose of 3.5-6 Gy to the testicles will result in long-term or permanent oligo- or azoospermia.[10] At higher radiation doses (>15 Gy), Leydig cell function will be compromised.[32] Damage to the seminiferous tubules can be evaluated by monitoring follicle stimulating hormone (FSH) in serum, and Leydig cell damage can be evaluated by measureing serum luteinizing hormone (LH) and testosterone levels.

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. There is limited published data on the measurement and evaluation of testicular doses from pelvic radiotherapy for rectal cancer directly in patients (in vivo, as opposed to using phantoms).[9,10,15,22] The dosimetric measurements were made with a recommended semiconductor diode in vivo

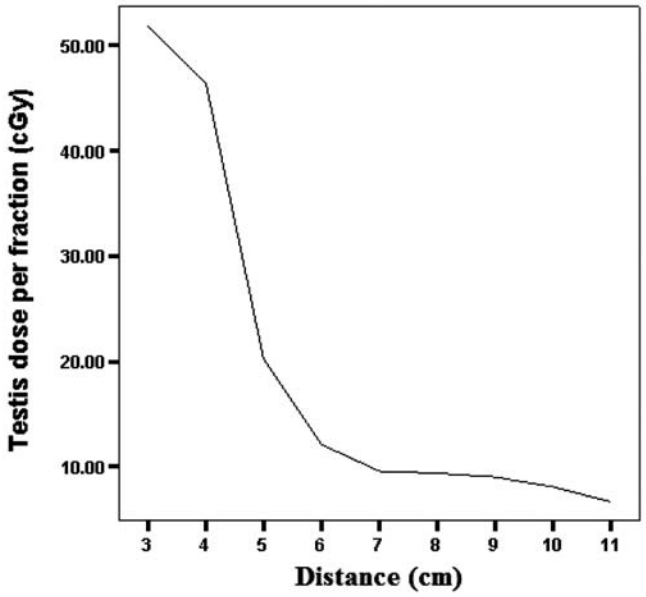

Figure 1. Relationship between testis dose and the distance between the diode (placed between the two testicles) and the caudal edges of the fields.

dosimeter specially designed for out-of-field measurements.

Patients and Methods

We considered for inclusion a total of 50 men with histologically proven rectal adenocarcinoma who were referred to our department for chemoradiation therapy in an adjuvant or neoadjuvant setting. Ten patients were excluded at the beginning of or during treatment because of early termination of radiation or abnormal sex hormone levels before starting radiotherapy. Radiotherapy was administered with cobalt-60 gamma rays. All patients received a 50-Gy radiation dose to the pelvis in a prone position, 2 Gy per fraction, five days per week with a fixed source-to-skin distance, four-field antero-posterior/lateral technique (pelvic box). The caudal edge of the radiation fields included the perineum in patients with abdomino-perineal resection and was placed at the bottom of the obturator foramina in patients with low abdominal surgery. Also, all patients received 5-FU-based chemotherapy concurrently with radiation. Testis dosimetry was done for all patients with a calibrated in vivo semiconductor diode (Scanditronix/IBA EDD5 p-type) twice at random during the radiation course. The diode was fixed to the scrotum between the testicles at the midpoint of the longitudinal extension, normal to the caudal edge of the posterior radiation field. The distance between the diode and the caudal edge of the posterior field in the horizontal plane was measured in every dosimetry session, separately in each patient. Serum sex hormones (LH, FSH and testosterone) were measured three times: once before the beginning of radiation, at the end of the radiation course, and 4 to 6 weeks after completion of radiation, all at the same laboratory. Reference values were LH: 0.5-10 IU/L, FSH: 1.3-11.5 IU/L, testosterone: 3-12 ng/mL (IRMA KIT, Beckman Coulter Co, London, UK).

Statistics

All data analyses were done with SPSS v.15 software using NPAR tests and the Wilcoxon test for pre- and post-treatment paired samples. *P* values less than 0.05 were considered statistically significant.

Results

Patients

The mean and median ages of the 40 eligible patients were 58.5 and 58 years, respectively (range 18-82). Twenty-one patients (52.5%) received radiation in a neoadjuvant setting whereas

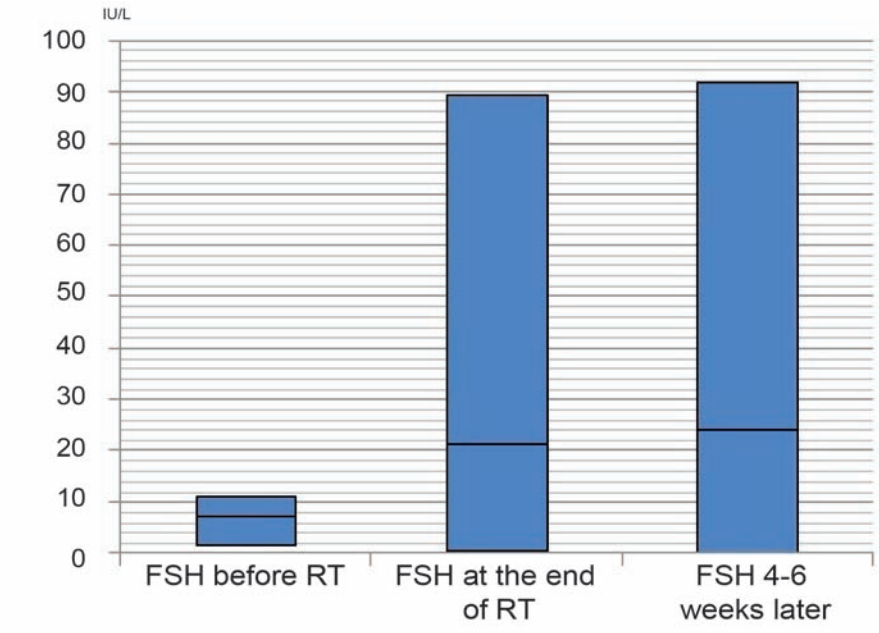

Figure 2. Changes in serum levels of FSH (IU/L) before and after radiotherapy (RT).

the remaining 19 (47.5%) patients were treated adjuvantly. Regarding tumor stage (AJCC 6thed, 2002), all patients who received preoperative radiation had local or locoregional disease (Stage I-III). Among the patients who underwent postoperative radiation, there were 2 (11%) stage I, 11 (58%) stage IIA, 1 (5%) stage IIB, 0 (0%) stage IIIA and 5 (26%) stage IIIB.

Testis radiation doses

The mean testis dose of radiation per fraction in all 40 patients was 16.3 cGy with a standard deviation of 15.2 (range 5.5-64.8). The contributions to this dose from the four fields were on average 30.5% from the postero-anterior field, 24.5% from the antero-posterior field and 22.5% from each lateral field.

The horizontal distance between the caudal edge of the posterior field on skin and the diode plane varied between 3.0 to 11.0 cm (standard deviations 2.1 and 1.8 in the first and second measurements) with a mean distance of 7.3 cm. Decreases in the distances to the radiation field increased the testicular dose sharply ($P<0.001$), especially for the 4-5 cm distance (Figure 1). The distance varied with deviations between 1 and 2 cm from the first to the second dosimetric measurement for each patient in 63.5% of patients. This was due to variability in testis position in different treatment fractions.

Effect of testis dose on male sex hormones

Serum levels of FSH increased significantly from 7.5±1.7 IU/L before treatment to 20.9±17.8 IU/L at the end of radiotherapy ($P<0.001$) and 24.1±20.5 IU/L, 4-6 weeks after radiotherapy ($P<0.001$) (Figure 2). There was a marked positive correlation between the testicular dose and differences in hormone levels ($P<0.001$).

Serum LH levels increased significantly from 8.04±1.2 IU/L before radiation to 11.6±11.5 IU/L at the end of radiotherapy ($P<0.001$) and 12.5±9.9 IU/L, 4-6 weeks after radiotherapy ($P<0.001$) (Figure 3). There was a positive correlation between the testicular dose and hormone levels ($P=0.013$).

There was a decrease in serum levels of testosterone from 5.3±2.1 ng/mL before radiation to 4.2±1.9 ng/mL at the end of radiotherapy ($P=0.004$) and to 4.5±2 ng/mL, 4-6 weeks after radiation ($P=0.035$). In 25% of patients, serum testosterone levels were below the lower limit of reference at the end of radiotherapy (Figure 4). A negative correlation existed between the testis dose and testosterone levels ($P=0.026$).

No significant correlation was found between age and the differences in sex hormones (LH, $P=0.605$; FSH, $P=0.380$; testosterone, $P=0.161$).

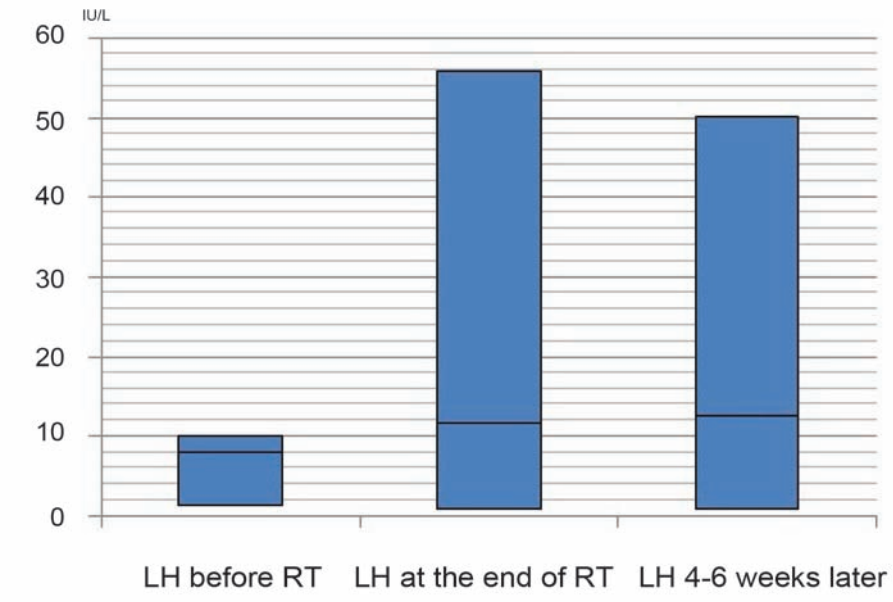

Figure 3. Changes in serum levels of LH (IU/L) before and after radiotherapy (RT).

Discussion

We found a significant change in serum levels of male sex hormones after pelvic irradiation (pelvic box) for rectal cancer to a total dose of 50 Gy that indicated considerable damage to the testicles, in particular to the seminiferous tubules responsible for spermatogenesis. However, 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 radiotherapy to a total tumor dose of 50 Gy. Yoon et al. determined that chemoradiation in men with rectal cancer caused persistent increases in FSH and LH levels and decreases in testosterone levels.[15]

All patients received 5-FU-based chemotherapy; therefore, chemotherapy can be ruled out as a cause of testicular damage. Hermann et al. could not discriminate between the gonadal effects of radiotherapy and chemotherapy,[9] but in this study, we determined that the differences in hormone levels were related exclusively to the amount of testicular radiation dose, although this does not preclude a role for chemotherapy in testicular damage. An older study, however, showed no significant alteration in serum levels of LH and FSH up to 3 hours after the administration of 5-FU-based chemotherapy.[33] In a study by Takizawa et al. in male rats, no histological changes in Leydig cells were observed and no differences in serum LH or FSH were detected after 2 to 4 weeks of 5-FU.[34]

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 as 0.8-4.8% of the prescribed target dose.[27] However, in our study all measurements were made directly in patients during radiotherapy and the testis dose was recorded as 2.7-32.4% (mean 8.13%) of the target dose. This dose was 1.6-18.7% (mean 7.1%) according to Hermann et al.[9] Budgell et al. measured scattered testicular doses during radiotherapy for rectal cancer with 4 MV photons.[18] Their measurements were made in a phantom with distances between 3 and 11 cm from the testes to the lower field edge, and the testis dose was recorded as 1.9-4.1% of the prescribed dose. In both studies the testicular dose correlated with the distance between the caudal edge of the radiation field and the center of the testicles, which was similar to our findings.[9,18]

Budgell et al. found that the ratio of contributions to the testicular dose from the anterior, posterior and lateral fields was 2:2:118, and Hermann et al. determined that the posterior field delivered approximately 60% of the testicular dose.[9] In our study, we observed the scattered

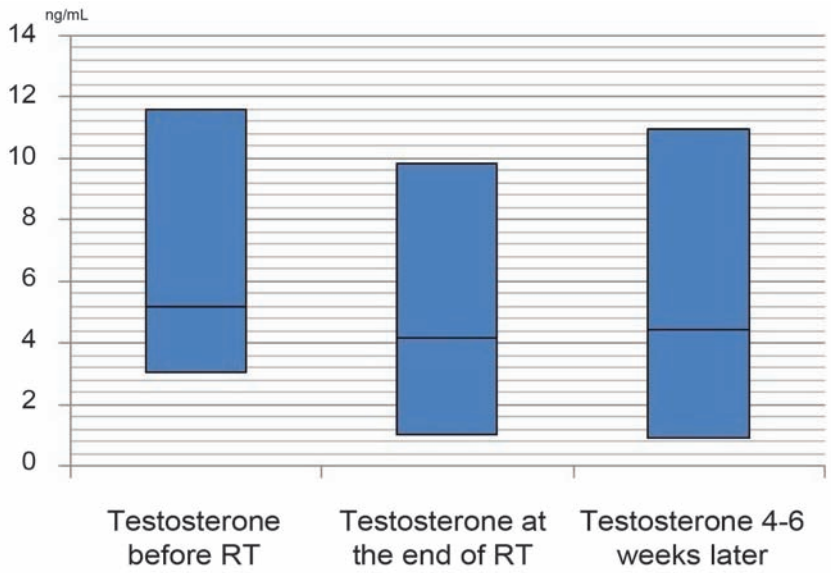

Figure 4. Changes in serum levels of testosterone (ng/mL) before and after radiotherapy (RT).

testicular dose from the posterior field to be about 30.5%, with the anterior and lateral fields contributing 24.5% and 22.5%, respectively. The differences were related to the differences in the distance between the testicles to the caudal edge of the fields: at shorter distances the testicles receive higher radiation doses due to divergence of the posterior field.

Dueland et al. and Piroth et al. measured the testis dose with thermoluminescent dosimeters (TLDs) in patients,[10,35] however Budgell et al. and Mazonakis et al. used an ionization chamber and a phantom,[18,27] whereas Hermann et al. used an ionization chamber for in vivo dosimetry on patients.[9] In the present study, dosimetry was performed directly in patients and the dosimeter (a calibrated in vivo semiconductor diode) was different from previous studies.[36] Together with TLDs, diodes are a standard, and recommended device for in vivo dosimetry, with the advantages of high sensitivity and instant readout over TLDs, and no need to use an ionization chamber with approximately 300 V in contact with patient, which might have possible safety risks.[37] Further, the diodes used were specially designed for out-of-field measurements.

Mazonakis et al.[27] compared a conventional lead block (8 cm thick) on the shadow tray abutted to the inferior border of the treatment fields and a commercially available 1.27-cm thick round shield to protect the testes. The conventional shield reduced the testicular dose by less than 41% but the round shield reduced the gonadal dose by more than 66%. The measurements were performed on an artificial testicle made of Perspex, so investigation of the effect of shielding on clinical and biological end points was not possible.

In the present study, the mean cumulative radiation dose to the testicles was 4.0 Gy (range, 1.4-16.2 Gy) which was similar to the dose in a study by Yoon et al., in which the median cumulative dose was 4 Gy (range, 1.5-8.9 Gy) and persistent decreases in testosterone levels were noted 4 years after chemoradiation. These authors concluded that there was a continued decrease in Leydig cell function over time. In our study, although the last follow-up period for measurement was brief, a persistent decrease in testosterone level was expected.[15]

A reduction in serum testosterone levels in men reduces their quality of life and may lead to morbidity such as obesity, osteoporosis and reduced sexual function. Therefore it seems logical to consider the benefits of hormone replacement therapy in these patients where indicated.[12]

Conclusion

Patients who receive radiotherapy for rectal cancer are at greater risk for testicular damage, hypogonadism and infertility. In our study, we found that 25% of the patients had serum testosterone levels below the lower reference limit at the end of radiation treatment. The conventional radiotherapy methods for rectal cancer (4-field box or 3-field) should be modified in the future, using highly conformal radiotherapy techniques with possible fixation of the testicles during radiotherapy to distance them from the radiation ports, or by using secondary shielding to reduce the dose to the testicles. Semen cryop-reservation should be considered for high-risk patients who wish to have children in the future. A lead scrotal block, with a thickness approximately equivalent to five half-value layers, positioned above the scrotum immediately outside the portal can reduce the dose from externally scattered radiation to negligible levels.

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