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Correlation between Irradiated Small Bowel Volume and Toxicity in Rectal Cancer Patients Receiving Concomitant Pelvic Irradiation and 5-Fluorouracil Chemotherapy

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Abstract. The aim is to study the relationship between radiation induced small bowel toxicity and radiation dose received by the small bowel during pelvic irradiation for patients with rectal cancer treated with pelvic radiotherapy and concomitant 5-Fluorouracil. Thirty-two patients with rectal cancer were referred for either a postoperative or preoperative pelvic irradiation concomitant with 5-Fluorouracil chemotherapy at the Radiotherapy Unit of King Abdulaziz University Hospital. All patients had computerized 3D treatment planning. Radiation therapy was given in two phases, to a total dose of 5040 cGy / 28 fractions / 5.5 weeks. Small bowel loops were contoured on CT cuts and a dose volume histogram was constructed and the mean radiation dose received by the small bowel, the volume of the small bowel irradiated and the mean radiation dose / volume of small bowel involved ratio. Univariate analysis showed a significant association between small bowel toxicity and mean radiation therapy dose received by small bowel ($p = 0.001$), the volume of small bowel involved ($P = 0.043$) and the type of surgical intervention with higher incidence for those patients who had abdominoperineal resection ($P = 0.003$). In conclusion, this study confirms the relation between small bowel toxicity and the volume of small bowel receiving radiotherapy.

Keywords: Rectal carcinoma, small bowel, dose volume histogram.

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Introduction

The standard adjuvant treatment for rectal cancer is the combination of pelvic irradiation and adjuvant 5-Fluorouracil (5-FU) chemotherapy. Despite the significant advantage in local control and survival achieved with this approach; it is still associated with significant grade III intestinal toxicity[1]. Severe diarrhea may lead to prolonged treatment interruptions, premature termination of radiation therapy dose, or reduction in total radiation dose; all factors may reduce the effectiveness of therapy. The best example of this is the report done by intergroup trial 0114, which showed that severe diarrhea was the main factor in failure to complete radiation therapy in 20% of patients for rectal cancer treated with pelvic irradiation and 5-FU adjuvant chemotherapy[2]. The dose-volume histogram for small bowel involved in the radiation field for pelvic irradiation is not a routine part of target planning for these patients. The aim of this study is to find whether the dose and/or volume of radiation received by the small bowel have any association with small bowel toxicity. Thus, it can be recommended as part of critical organ evaluation during treatment planning of pelvic radiation therapy in rectal cancer patients.

Materials and Methods

Study Design

This is a correlation study to measure any association between small intestinal toxicity as per Radiation Therapy Oncology Group (RTOG) criteria[3] and the radiation dose received by the small bowel and volume of small bowel involved in the pelvic radiation field for the treatment of rectal cancer patients.

Eligibility Criteria

All patients were required to have pathological proof of diagnosis of rectal cancer either from biopsy material (in case of neoadjuvant preoperative treatment) or postoperative material (in case of adjuvant postoperative treatment). Patients had stage T3, T4 or N+ rectal carcinoma. Patients with other co-morbid diseases that might increase the intestinal toxicity like ulcerative colitis were excluded. Patients were required to sign an informed written consent.

Details of the Study

Patients were treated at the Radiotherapy Unit, King Abdulaziz University Hospital (KAUH), Jeddah from July 2001 till December 2003. Radiation therapy was given with concurrent chemotherapy 5-FU 500 mgm/m^2 IV daily for 3 consecutive days during the first- and fifth-weeks of radiation therapy.

All patients had a 3D treatment planning computerized tomography (CT) scan in the treatment position, prone with full urinary bladder. A series of CT scan cuts were taken at 1 cm intervals using CT scanner (GE, light speed), then images were digitally transferred to the treatment planning system (Cad Plan, Varian Medical Systems).

A three field's isocentric technique using direct posterior pelvic field with 6 MV photon energy and 2 laterals wedged fields using 18 MV photons energy was used. Customized blocks were used to shield normal tissues outside target volume.

Phase I received 4,500 cGy in 25 fraction over 5 weeks and the fields boarders were set as follow: the superior border at L5-S1 junction; the lateral border at 1.5 cm from bony pelvis; the inferior border at 3 cm below tumor or at the bottom of obturator foramen (whichever was lower) for those who had low anterior resection (LAR) and to include the perineal scar for those who had abdominoperineal resection (APR), posterior boarder behind the sacrum, and anterior boarder behind symphesis pubis. For Phase II (boost) field receives 540 cGy in 3 fractions to cover tumor (or tumor bed) with 2 cm margin.

Both opaque and non-opaque small bowel loops were contoured for each CT slice (Fig. 1).

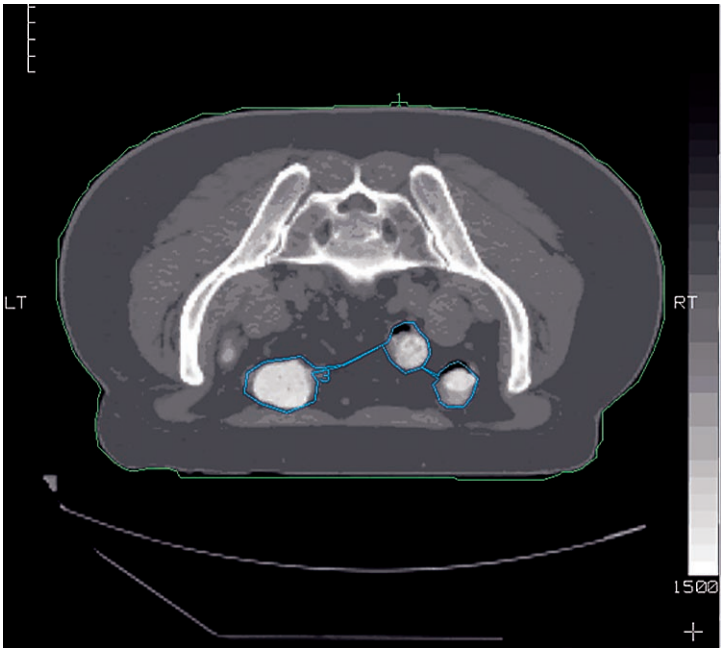

Fig. 1. CT cut view showing small intestinal loops with contrast contoured on the treatment planning system.

A dose volume histogram (DVH) was done for the small bowel for each patient. From DVH, the mean radiation dose received by the small bowel (D), the small intestinal volume (V) for each patient in cubic centimeters, and the ratio of mean dose to the volume (D/V) was determined.

RTOG's toxicity criteria were used to grade small bowel toxicity[3].

Statistical Analysis

A Statistical Package for the Social Sciences (SPSS), version 11.5 for Windows, was used for descriptive analysis of all categorical and numerical variables and a univariate analysis for each variable versus small intestinal toxicity was done.

Results

Thirty-two patients were included in the study, age of patients ranged from 2-74 years (mean 52 years, median 50.5, standard deviation [SD] 10.9). Patients' criteria are shown in Table 1.

Table 1. Criteria for the 32 rectal cancer patients in the study.

Criteria	Number	Percentage
Male	17	53.1
Female	15	46.9
T3	17	87.5
T4	15	12.5
N0	12	37.5
N1	20	62.5
Postoperative	16	50.0
Preoperative	16	50.0

The mean radiation dose received by small intestine for these patients was 21.5 Gray (median: 22.5, SEM = 1.8), the mean volume of small intestine was 169.5 cc (median: 154, SEM = 22.3), the mean ratio of radiation dose to the volume of small bowel involved was 0.9 (median: 0.1, SEM = 0.6).

Twenty (62.5%) patients developed grade I/II RTOG (mild) small bowel toxicity and 12 (37.5%) patients developed grade III/IV (marked) toxicity. Figure 2 shows the toxicity of the patients in the study.

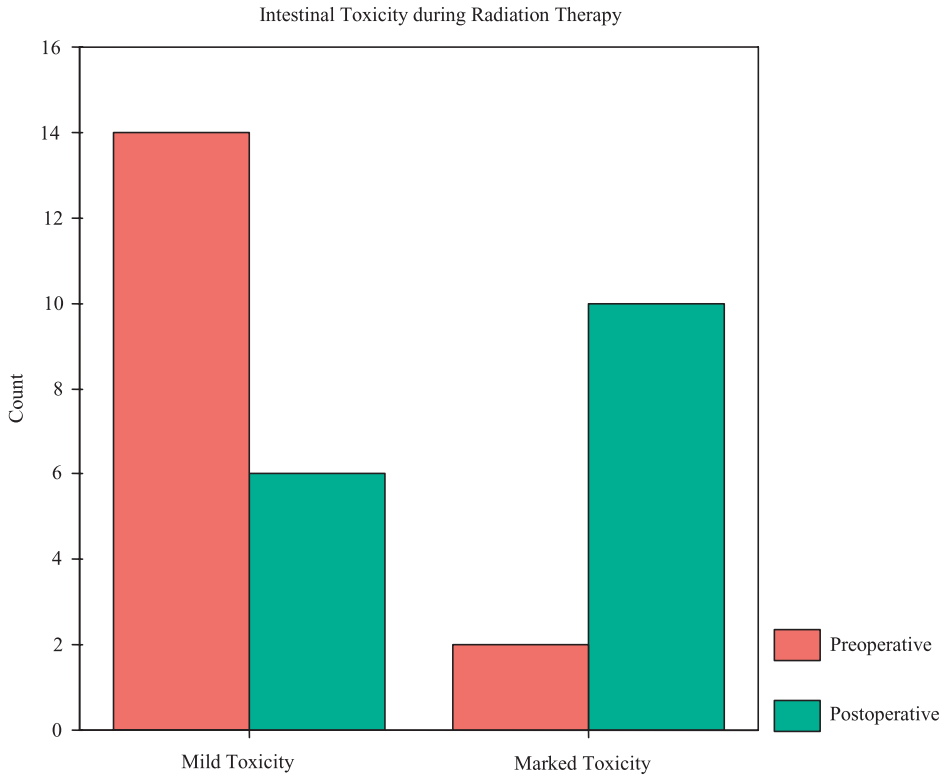

Fig. 2. Correlation of intestinal toxicity with timing of radiation therapy.

Univariate analysis comparing different clinical and treatment related parameters showed significant relations between small bowel toxicity and the mean radiation dose in cGy received by the small intestine ($p = 0.0001$), the volume of the small bowel involved ($p = 0.044$), the type of surgery performed ($p = 0.005$) with higher incidence among those who had APR and wither radiotherapy was give postoperative or preoperatively, marked toxicity were in 62.5% and 21.5% of patients, respectively ($p = 0.005$). Other variables like age, sex, T or N stage, distance of tumor from the anal verge, and ratio of the mean dose to the volume of bowel involved were of statistical significance.

Discussion

Acute toxicity due to small bowel irradiation is a common cause of morbidity during chemoradiation for rectal cancer, and the overall incidence of acute grade 3-4 diarrhea was found to be 20%-35% in prospective randomized trials for patients who received postoperative radiation therapy[4].

Complications of pelvic radiation therapy are a function of radiation field volume, overall treatment time, radiation fraction size, radiation energy, total radiation dose and technique of radiation therapy, and there are many ways to reduce small bowel toxicity during pelvic irradiation such as the use of multiple field techniques for both Phase I and rectal boost, positioning the patient in a prone position, designing the treatment using 3D computerized radiation dosimetry, and the use of higher energy radiation in lateral pelvic fields[5].

Surgical methods to reduce the incidence of small bowel toxicity during pelvic irradiation include the placement of removable intra pelvic tissue expanders, placement of permanent Silastic prosthesis[6], insertion of an absorbable synthetic mesh or omental sling[7], and retroversion of uterus or reperitonealization of the pelvic floor[8].

One method used to reduce the small bowel loop volume in the radiation fields was to administer a small bowel contrast at the time of simulation to design a customized small bowel shielding[9]. The use of small bowel contrast for detection of small bowel involvement or for changing the technique of radiation therapy to reduce the amount of small bowel in radiation field had been established by many oncologists[10-13].

Although the above mentioned methods to reduce small bowel toxicity during pelvic irradiation are generally accepted and have a role in minimizing small bowel toxicity during pelvic irradiation, the clinical application of dose volume histogram of small bowel involved in the radiation field is still not a routine part of treatment planning for these patients and is applied only on a research basis.

The aim of this study is to confirm the relationship of small bowel toxicity and the volume of irradiated small bowel during pelvic irradiation for rectal cancer patients. Thus, it can be recommended as part of critical organ assessment during treatment planning for these patients.

The current study involved 32 patients with rectal cancer referred for pelvic irradiation; there was a statistical significance in association between marked intestinal toxicity (RTOG grade III/IV) and the mean radiation dose received by the small bowel ($p = 0.001$), and the volume of small bowel involved in radiation field ($p = 0.043$).

In a recent study Baglan *et al*.[14], evaluated forty-patients with rectal cancer of whom: 72.5% were treated on postoperative basis; 22.5% were treated on neoadjuvant basis; and 5% were treated for local recurrence. A small bowel dose volume histogram was generated for all patients. Twenty-five percent of

patients developed GIII RTOG small intestinal toxicity, and a statistically significant association was found between toxicity and the volume of small bowel involved in the radiation field ($p < 0.001$).

Koelbl *et al.*[15] emphasized the importance of doing small bowel dose volume histogram when determining the radiation dose to the small intestine in patients with rectal cancer who were treated on postoperative basis, and the effect of different positions of belly board on dose volume histogram of small bowel, and he recommended placing the lower border of the belly board at lumbosacral junction to achieve the least amount of small bowel involved in radiation field.

Another study done by Koelbl *et al.*[16] pointed to another clinical application of the use of dose volume histogram (DVH) of small bowel for rectal cancer patients who received postoperative radiation therapy; in which they compared 3 techniques of pelvic irradiation: Four field (box) technique, 3 fields technique, and 2 fields (AP/PA) fields techniques on DVH of small intestine. They found that the median dose to small bowel was less for the 3 field technique than that for the 4 field technique (30.8% versus 54.5%) ($p = ‹ 0.005$).

A third study by Koelbl *et al.*[17] addressed the influence of patient positioning on dose-volume histogram and normal tissue complication probability for small bowel and bladder in patients with rectal cancer receiving postoperative pelvic irradiation using a 3D planning system and a radiobiological model. They found that the median dose to small bowel was 30.85% (15.4 Gy) in the prone position and 47.35% (23.9 Gy) in the supine position ($p < 0.001$). According to the radiobiological model method of Lyman, the normal tissue complication probability of small bowel was significantly lower for patients treated while prone rather than in a supine position, and they recommended the prone position with a standard belly board should be the standard positioning technique. Thus, both irradiated volume and total dose to the organs at risk can be reduced significantly.

Capirci *et al.*[18] used a polystyrene bowel displacement standard mold created and added to a customized Vac-Lok vacuum cushion formed around the abdomen and legs of each patient in the prone position. Two hundred seventy-seven consecutive patients with pelvic malignancies treated with the UDT devices were compared with one historic series (68 cases) treated on standard 4 fields' box technique. Small bowel contrast dyes at the time of simulation were used in all patients. They found that, the average volume of small bowel within the planning target volume was 100 cc in the series treated with standard box technique and 23 cc in the series treated with the UDT ($p < 0.001$). The average volume of small bowel included in any isodose (any-dose volume) was 505 cc

and 158 cc for patients treated on standard box and those with UDT respectively ($p < 0.001$). The incidence of GI, GII, and GIII acute enteric toxicity (RTOG's criteria) in the UDT series was 16%, 15%, and 1.5%; in the standard box technique, it was 28%, 25%, and 3%, respectively ($p < 0.05$). The incidence of acute enteric toxicity directly correlated with the irradiated small bowel volume. In the UDT series, the 5-year actuarial incidence of G3 chronic enteric toxicity was 1.8%.

Conclusion

In conclusion, this study confirms the connection between small bowel toxicity and the volume of small bowel receiving radiotherapy. Dose volume histogram of small bowel should be done routinely during pelvic radiotherapy and every effort should be made to minimize the amount of small bowel volume in the radiation field.

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العلاقة بين حجم الأمعاء الدقيقة المتعرضة للأشعة والآثار الجانبية فى مرضى سرطان المستقيم المعالجين بالأشعة للحوض مع (٥) الفلورو – يوراسيل الكيماوي

ياسر عبد العزيز بهادر

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جـــدة – المملكة العربية السعودية

المستخلص. الهدف هو دراسة العلاقة بين الآثار الجانبية للأمعاء الدقيقة نتيجة الأشعة وحجم الأمعاء المتعرضة للأشعة وجرعة الأشعة لمنطقة الحوض في مرضى سرطان المستقيم المعالجين بالأشعة مع الفلورو- يوراسيل الكيماوى .

اثنان وثلاثون مريضًا بسرطان المستقيم تم علاجهم قبل أو بعد العملية بالأشعة لمنطقة الحوض في مستشفى جامعة الملك عبدالعزيز. جميع المرضى عمل لهم تخطيط ثلاثي الأبعاد بالكمبيوتر.

الأشعة أعطيت بجرعة ٥٠٤٠ جراى على ٢٨ جلسة لمدة ٥,٥ أسبوع. تم تحديد الأمعاء الدقيقة على الأشعة المقطعية وتحديد جرعة الأشعة وحجم الأمعاء ونسبة الجرعة إلى الحجم.

وجدنا علاقة بين الآثار الجانبة للأمعاء الدقيقة ومتوسط جرعة الأشعة ($P = 0.001$) وحجم الأمعاء ($P = 0.043$) ونوع العملية ($P = 0.003$)، وهذه الدراسة تؤكد وجود هذه العلاقة.