

## Original Research

# Acute Nutritional and Intestinal Changes after Pelvic Radiation

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**Key words:** radiotherapy, actinic enteritis, pelvic radiation, intestinal permeability

**Objective:** Pelvic radiotherapy induces acute small bowel injury but its effects on nutritional status are unknown. The objective of this study was to prospectively evaluate nutritional, functional and morphologic intestinal changes, after radiotherapy.

**Methods:** Fifteen patients were studied before and after pelvic irradiation. A clinical, nutritional and routine clinical laboratory assessment was performed. Nutritional parameters included dietary recall, subjective global assessment, anthropometric measurements (body mass index, skinfold thickness at four sites and circumferences of arm, waist and hip), hand grip strength, indirect calorimetry and Dual Energy X-ray absorptiometry (DEXA). Intestinal parameters included permeability to sugars (assessed by lactulose and mannitol urinary excretion), intestinal transit time (measured by hydrogen breath test after ingestion of lactulose) and jejunal biopsies.

**Results:** Thirteen patients presented diarrhea during radiation therapy. After five weeks, intestinal permeability increased, while intestinal transit time decreased. The second biopsy showed hypertrophy of villae and crypts. Simultaneously, patients lost weight at the expense of fat free mass. Resting energy expenditure was elevated prior to treatment and declined after five weeks. Changes in caloric ingestion were not significant.

**Conclusions:** Our results indicate that pelvic radiation induces a loss of fat free mass along with intestinal morphologic and functional changes.

## INTRODUCTION

Radiation therapy plays a fundamental role in malignancy treatment; however, it has clinical limitations due to its adverse effects, mainly damage to critical normal tissues. One of the most serious complications of abdominal or pelvic radiotherapy is actinic damage to the bowel, leading to nausea, vomiting, diarrhea and abdominal cramps during or shortly after therapy [1]. These usually last for a few weeks after treatment and then disappear [2,3,4], but up to 61% of patients develop persistent diarrhea or increased frequency of bowel movements, typical of chronic radiation enteritis [4]. Prognosis of this chronic condition is adverse because morbidity and mortality of surgical interventions for complications of chronic radiation enteritis are high [5]. Descriptions of acute radiation damage are mostly retrospective, include both abdominal and pelvic radiation and

do not evaluate nutritional variables, which may concur to chronic complications.

The terminal ileum, sigmoid colon and rectum are the sites most frequently damaged by pelvic radiation, while jejunum and proximal ileum are seldom involved; nevertheless, mortality of radiation enteritis is fourfold higher than colonic lesions [6]. Whether significant tissue injury occurs in organs distant to the radiation field is still controversial [1,18].

In humans, acute histologic changes shortly after radiation consist of reduction of crypt mitoses, villous shortening, plasma cell infiltration of the lamina propria, megalocytosis of epithelial cells and, less frequently, formation of microabscesses of the crypts, all which are potentially reversible [1]. Both acceleration of intestinal transit time and decreased bile salts resorption at the terminal ileum play a role in the appearance of diarrhea [7,8,9,10]. Simultaneously, intestinal permeability to

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water soluble macromolecules increases after intestinal radiation [4]. Most studies demonstrate that acute changes of permeability recover after several weeks of completion of radiation therapy. However, the impact of the above mentioned alterations on the clinical course or nutritional status of the patient have not been systematically assessed.

Morphologic and functional small bowel alterations and changes in gastrointestinal motility, together with anorexia, are considered relevant determinants of the long term detrimental effect on nutritional status observed in these patients [11]. To improve therapeutic strategies for patients that develop chronic bowel actinic damage, it is crucial to understand the factors that influence the acute phase of the damage and that may represent risk factors for chronic damage. Following this line of thought in this study we investigated clinical symptoms and nutritional changes after external pelvic radiation, relating them to functional and morphologic modifications of the small bowel, after five weeks of treatment. Thus, results will provide a systematic description of acute changes, to what extent small intestinal changes may participate in the alterations observed, and will serve as a basis for future characterization of chronic damage in these patients.

## **METHODS**

Fifteen female patients, aged 27 to 60, were studied before and after completing 45 to 50 Gy of pelvic external radiation, as treatment for gynecological neoplasms. Radiation was delivered by a Cobalt-60 unit (Phoenix 80, SSD 80 cm) using the four-field box technique. The doses were fractioned in 180–200 cGy per day (dose calculation to the mid plane), during five weeks. The study was performed in a national cancer center, (Fundación Arturo López Pérez), in Santiago, Chile. Participants signed a written informed consent, according to our local Ethics Committee and the Helsinki Declaration.

Exclusion criteria were diabetes mellitus, chronic renal failure (serum creatinine >2 mg/dL), liver or cardiac failure, other cancers, chronic diarrhea, intestinal or gastric resections, and previous radiation treatments.

Nutritional status of each patient was classified by means of the Subjective Global Assessment (SGA) [12] immediately after incorporation to the protocol. Clinical symptoms and medications prescribed were registered throughout the study period. Before beginning and immediately after completing the five-week pelvic radiation, the following nutritional and gastrointestinal parameters were studied: nutrient intake by means of a 24-hour dietary recall; percent of body fat, calculated on the basis of anthropometric measurements (weight, height, skinfold thickness using a Lange caliper at four standard locations) according to Durnin and Womersley [13] and circumferences of arm, waist and hips; grip muscle strength, using a hand grip dynamometer (Therapeutic Instruments, Model 0032); body fat mass and fat-free mass, measured by Dual Energy

X-ray absorptiometry (DEXA) in a LUNAR densitometer (LUNAR Corp. Madison, WI); resting energy expenditure (REE), by indirect calorimetry in a canopy system (Sensor Medics 2900). After an overnight fast, blood samples were drawn to perform routine clinical laboratory tests (blood cell count, blood glucose, creatinine, blood urea nitrogen, total protein, albumin, total bilirubin, hepatic aminotransferases, total cholesterol, triglycerides, uric acid and electrolytes), using automated methods. Urinary lactulose/mannitol and sucrose excretion tests were used to assess intestinal and gastric permeability respectively [14,15]. Orocecal transit time was evaluated by the hydrogen breath test after ingestion of lactulose, following routine procedures described elsewhere [16]. Jejunal biopsies were obtained before and within 48 hours after finishing radiotherapy in eight patients. The tissue was obtained with a fluoroscopically guided double port Crosby-Kugler capsule at the Ligament of Treitz, fixed in Bouin, serially sectioned at 5 $\mu$  and stained with hematoxylin-eosin. Histological assessment followed the classic 1–4 scale in which 1 represents normal mucosa and 4 severely damaged (flat) mucosa [17]. Due to ethical considerations only two samples were obtained from each participant. In well-oriented sections villus and crypt heights were measured by two observers in a blind fashion. On the basis of these measurements total mucosal thickness was calculated. Each figure represents the average of at least three measurements, done in at least two different areas of the biopsies.

Gastrointestinal and general symptoms were recorded during the five-week study period. Participants marked on a list of symptoms those they had experienced during the week. Each symptom was graded from 0 (absent) to 3 (severe enough to alter activities of daily living). Diarrhea was defined as stools with an increase in water content or an increase in the number of bowel movements.

## **RESULTS**

Diagnoses in the participants were: 10 cervical carcinoma (stage I B in five, II B in three, and III B in two cases), three endometrial adenocarcinoma (two stage I C and one stage II), one uterine rhabdomyosarcoma and one vaginal cupula invasive carcinoma. Staging was done according to FIGO classification (International Federation of Gynecological Oncology). Surgical resection of the tumor prior to radiotherapy was performed in six patients; however, in nine of the 15 patients surgical procedures were performed years before; the most frequent being open cholecystectomy.

During the study period, most patients developed gastrointestinal symptoms, mainly diarrhea (13 patients), abdominal pain (12 patients) and nausea (1 patient). In addition, 12 patients had urologic complaints, with positive urine cultures in four. Episodes of diarrhea were mild and intermittent, lasting between 2–13 days,

and were managed as outpatients, with 6 mg Loperamide/day, restriction of dietary fiber and oral hydration.

Before radiotherapy, clinical laboratory parameters in all patients were within normal ranges, except for five cases that had low hematocrit. Hematologic parameters and cholesterol decreased significantly, while triglycerides increased after radiotherapy (Table 1).

According to the SGA, ten patients were classified as A (well nourished) and five were classified as B, that is, moderate malnutrition or risk of undernutrition. By using BMI criterion, four patients were overweight, four were obese and the rest were classified as normal weight for height. Weight decreased in most patients during the treatment ( $\Delta - 0.9 \pm 1.4$  Kg,  $p = 0.03$ ), as did arm circumference ( $\Delta - 0.4 \pm 0.7$  cms,  $p = 0.04$ ). Body fat calculated from anthropometric measurements, decreased slightly ( $\Delta - 1 \pm 1.4\%$ ,  $p = 0.05$ ). Likewise, after the 5 weeks period of pelvic radiation, DEXA detected a significant decrease in total body mass ( $\Delta - 0.7 \pm 1.3$  Kg,  $p = 0.03$ ), and fat free mass ( $\Delta - 1.1 \pm 1.5$  Kg,  $p = 0.001$ ), without modification of fat mass (Table 2).

Caloric intake was similar throughout the study period. Whole body REE values averaged 125% of calculation by Harris-Benedict equation before radiation. After five weeks of radiation treatment, measured energy expenditure fell significantly, without changes in REE/LBM (Table 3).

Lactulose/mannitol ratio increased significantly ( $p = 0.027$ ), due to a twofold increase in lactulose urinary excretion, without significant variation of mannitol excretion (Table 4 and Fig. 1). This ratio did not correlate with the nutritional variables studied. When comparing patients operated prior to radiotherapy, *versus* those who were not, only mannitol excretion decreased significantly in the former ( $p = 0.03$ ).

Mean intestinal orocecal transit time decreased from  $1.7 \pm$

**Table 2.** Nutritional Parameters during the Treatment

| Anthropometry                           | Before<br>(Mean $\pm$ SD) | After<br>(Mean $\pm$ SD) | Paired <i>t</i><br>test ( <i>p</i> ) |
|-----------------------------------------|---------------------------|--------------------------|--------------------------------------|
| Body Mass Index<br>(kg/m <sup>2</sup> ) | 26.8 $\pm$ 5.0            | 26.5 $\pm$ 5.0           | 0.02                                 |
| Arm Circumference<br>(cm)               | 29.8 $\pm$ 3.7            | 29.4 $\pm$ 4.1           | 0.04                                 |
| Body Fat (%)*                           | 36.1 $\pm$ 5.8            | 35.0 $\pm$ 6.0           | 0.05                                 |
| Handgrip Muscle<br>strength (kg)        | 26.4 $\pm$ 4.9            | 26.3 $\pm$ 4.4           | 0.4                                  |
| DEXA                                    |                           |                          |                                      |
| Total Mass (kg)                         | 62.3 $\pm$ 13.3           | 61.6 $\pm$ 13.6          | 0.03                                 |
| Fat Free Mass (kg)                      | 37.8 $\pm$ 5.6            | 36.7 $\pm$ 5.6           | 0.005                                |
| Fat Free Mass (%)                       | 65.3 $\pm$ 6.5            | 64.3 $\pm$ 6.7           | 0.06                                 |
| Fat Mass (kg)                           | 22.2 $\pm$ 8.5            | 22.6 $\pm$ 8.5           | 0.14                                 |
| Fat Mass (%)                            | 34.7 $\pm$ 6.5            | 35.7 $\pm$ 6.7           | 0.06                                 |
| Bone Mineral<br>Content (g)             | 2209.2 $\pm$ 330.3        | 2200.3 $\pm$ 338.0       | 0.32                                 |

\* % Body fat was calculated using anthropometric data.

0.9 to  $1.36 \pm 0.9$  hours after five weeks of radiation ( $p = 0.05$ ), and did not correlate with the rise of lactulose/mannitol ratio. However orocecal transit time after radiation decreased more in those patients operated before treatment ( $p = 0.05$ ).

Histological assessment of duodenal biopsies obtained before radiotherapy revealed normal mucosal morphology (stage 1 or 2 in the scale 1/4) in all cases. After pelvic radiation, in most biopsies there were significant changes, which consisted of patchy areas with longer villi, and figures of several crypts opening to one single villus (Fig. 2). Because this technique requires a well-oriented section, the areas suitable to perform morphometry were those in which these two main findings were less prominent. Due to this histologic appearance it was not adequate to carry out morphometric measurements on second biopsies.

**Table 1.** Clinical Laboratory Parameters during Radiation

|                                              | Normal<br>Range | Before<br>(Mean $\pm$ SD) | After<br>(Mean $\pm$ SD) | Paired <i>t</i><br>test ( <i>p</i> ) |
|----------------------------------------------|-----------------|---------------------------|--------------------------|--------------------------------------|
| Hematologic                                  |                 |                           |                          |                                      |
| Hematocrit (%)                               | 37–46           | 37.6 $\pm$ 5.1            | 36.1 $\pm$ 4.1           | 0.02                                 |
| ESR (mm/h)                                   | 1–15            | 38.5 $\pm$ 34.5           | 25.9 $\pm$ 15.5          | 0.30                                 |
| Platelets ( $\times$ cm <sup>3</sup> )       | 150–350         | 289 $\pm$ 102             | 196 $\pm$ 62             | 0.001                                |
| Leucocyte Count ( $\times$ cm <sup>3</sup> ) | 4100–9000       | 7388 $\pm$ 2390           | 3867 $\pm$ 939           | 0.0003                               |
| Lymphocyte Count (indir)                     | > 1900          | 1900 $\pm$ 646            | 451 $\pm$ 165            | 0.0002                               |
| Blood Chemistry                              |                 |                           |                          |                                      |
| Glycaemia (mg/dL)                            | 60–108          | 92 $\pm$ 7                | 92 $\pm$ 9               | 0.5                                  |
| Creatinine (mg/dL)                           | 0.5–0.9         | 0.7 $\pm$ 0.3             | 0.7 $\pm$ 0.1            | 0.2                                  |
| BUN (mg/dL)                                  | 5–25            | 12.5 $\pm$ 3.3            | 13.2 $\pm$ 3.9           | 0.9                                  |
| Total Protein (g/dL)                         | 6.5–8.4         | 7.3 $\pm$ 0.5             | 7.4 $\pm$ 0.6            | 0.6                                  |
| Albumin (g/dL)                               | 3.5–5.0         | 4.2 $\pm$ 0.5             | 4.3 $\pm$ 0.3            | 0.09                                 |
| Total Bilirubin (mg/dL)                      | 0.2–1.0         | 0.6 $\pm$ 0.3             | 0.8 $\pm$ 0.6            | 0.13                                 |
| SGOT (U/L)                                   | 10–35           | 27.2 $\pm$ 18.1           | 27.3 $\pm$ 11.8          | 0.13                                 |
| ALAT (U/L)                                   | 9–43            | 32.4 $\pm$ 25.2           | 34.3 $\pm$ 28.8          | 0.22                                 |
| Total Cholesterol (mg/dL)                    | < 200           | 207 $\pm$ 43              | 190 $\pm$ 28             | 0.015                                |
| Triglycerides (mg/dL)                        | < 200           | 124 $\pm$ 49              | 162 $\pm$ 86             | 0.019                                |
| Uric Acid (mg/dL)                            | 2.5–6.2         | 3.9 $\pm$ 1.2             | 3.3 $\pm$ 0.9            | 0.14                                 |

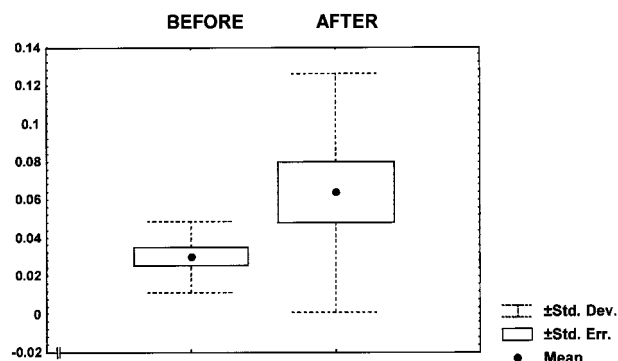
**Table 3.** Energy Expenditure and Caloric Intake during the Study

|                              | Before<br>Mean ± SD | After<br>Mean ± SD | Paired <i>t</i> test<br>( <i>p</i> ) |
|------------------------------|---------------------|--------------------|--------------------------------------|
| Caloric Intake<br>(kcal/day) | 2143.5 ± 799.2      | 1829.7 ± 1192.6    | 0.18                                 |
| REE (kcal/day)               | 1672.6 ± 487.9      | 1585.0 ± 274.9     | 0.05                                 |
| REE/FFM (kcal/kg)            | 44.4 ± 12.0         | 43.3 ± 4.1         | 0.22                                 |
| RQ                           | 0.7 ± 0.2           | 0.7 ± 0.05         | 0.33                                 |

REE = resting energy expenditure; FFM = fat free mass; RQ = respiratory quotient.

**Table 4.** Intestinal Permeability before and after Pelvic Radiation

| Parameter          | Before<br>(Mean ± SD) | After<br>(Mean ± SD) | Paired <i>t</i> test<br>( <i>p</i> ) |
|--------------------|-----------------------|----------------------|--------------------------------------|
| Mannitol (%)       | 14.5 ± 4.8            | 11.8 ± 4.4           | 0.061                                |
| Lactulose (%)      | 0.4 ± 0.3             | 0.7 ± 0.6            | 0.042                                |
| Sacarose (%)       | 82.6 ± 72.6           | 91.0 ± 96.1          | 0.353                                |
| Lactulose/Mannitol | 0.030 ± 0.019         | 0.064 ± 0.062        | 0.027                                |

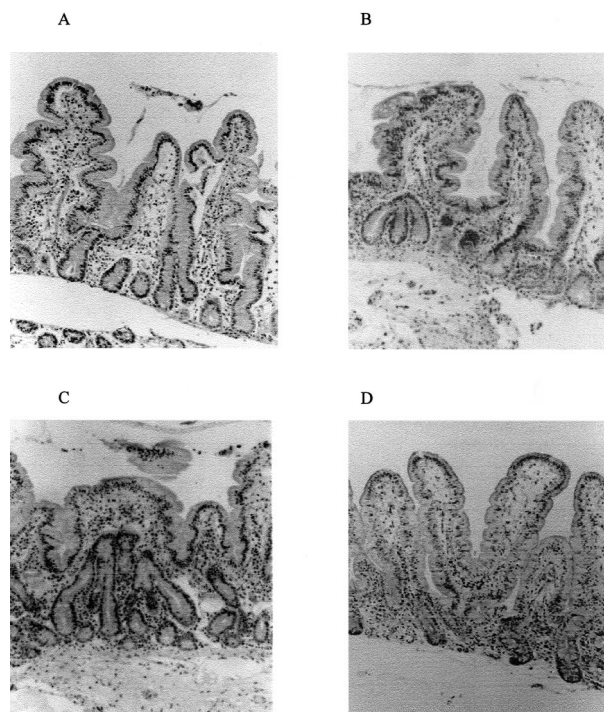


**Fig. 1.** Lactulose/mannitol ratio before and after pelvic radiation. Intestinal permeability assessed by lactulose/mannitol urinary excretion, increased significantly after five weeks of pelvic radiation (*p* = 0.027).

## DISCUSSION

The present results show that after five weeks of mega voltage pelvic radiotherapy to treat gynecologic neoplasms, there are acute changes in the small bowel, detectable by morphologic as well as functional parameters, which are associated with nutritional deterioration, especially over the lean compartment.

Energy released by ionic radiation induces several events, especially in fast replicating cells, such as hematopoietic tissues and intestinal epithelium, leading to its damage and death. During acute continuous exposure to radiation, the main defense mechanism is cellular renovation, stimulated by depletion of actively proliferating cells. Therefore, actinic damage is



**Fig. 2.** Jejunal biopsies before and after pelvic radiation. A shows normal histologic appearance before radiotherapy. Biopsies after five weeks of pelvic radiation (B, C and D) show branched villae and several crypt openings to one single villus.

lessened when cellular depletion is balanced with cellular proliferation [18]. Radiation-induced injury is explained by cytotoxic effects of free radicals, damaging the endothelial cells of intestinal capillaries. The ensuing mucosal damage is reflected in morphologic and functional impairment, such as increased permeability to macromolecules [19]. Evidence indicates that microvascular injury is one of the main determinants of intestinal dysfunction after radiation, which becomes more evident in chronic radiation enteritis [20].

The small bowel is specially susceptible to radiation injury, but the mechanisms involved are not completely understood. Several clinical and functional manifestations of this damage were apparent in this study, namely mild diarrhea, decreased intestinal transit time and increased permeability. Interestingly, these changes were associated with morphologic changes suggestive of mucosal recovery (enlargement and duplication of villae) in the proximal intestinal segments, which received a considerably smaller fraction of the radiation dose (calculated as 2 Gy). This suggests that either such a dose is capable of inducing damage or that there are indirect mechanisms involved. Both alternatives deserve further study.

With the information obtained in this study it was not possible to assess whether previous surgery or low weight induces more actinic damage to the small bowel, as previously described; among Chilean women, obesity and overweight are currently highly prevalent, and this was also the case among the

study patients [21]. At the same time, most of the study patients had previous abdominal surgery (such as cholecystectomies, cesarean sections, appendectomies, adnexectomies and hysterectomies) making it difficult to identify subgroups.

Nutritional status deterioration was mainly at the expense of fat free mass, as assessed by DEXA. Our intra-assay variability is less than 1% [22]. Variations of total body water also influence LBM assessment by DEXA [23], although we have employed it successfully in cirrhotic patients [24]. It is unlikely that the changes reported here would be due to dehydration because, although most patients had diarrhea, the episodes were mild, and ceased well before the second evaluation. Moreover, the decrease in LBM is in agreement with a reduction of whole body REE (which were elevated before treatment in these patients), without changes in REE corrected by unit of FFM, which was not dependent on a reduction in caloric intake, as assumed previously by other authors [25].

The selective loss of FFM observed in this study, associated with an increase of serum triglycerides, resembles a systemic inflammatory reaction in response to intestinal radiation [26]; it is also possible that it is related to a decrease in macronutrient availability due to low dietary intake, but this seems not to be the case since this latter did not change significantly; finally nutrient malabsorption may also play a role but was not investigated in this study. An increased permeability to bacteria or endotoxins has been proposed as the event that could initiate and perpetuate the systemic inflammatory response (SIRS) in several conditions leading to nutritional wasting [27,28,29] and multiple organ failure [30,31]. However, several recent studies suggest that intestinal damage predisposes to distant organ injury, even in the absence of detectable bacteria or endotoxins. It has been proposed that certain gut-derived factors, such as cytokines, could produce these systemic effects via the lymphatic route [26]. The effects of ionizing radiation on vascular endothelial cells are also consistent with the initiation of an inflammatory response, including adhesion of leukocytes and increased vascular permeability. Local liberation of pro-inflammatory mediators and production of free radicals and proteases by leukocytes seem to be directly involved in tissue damage [32]. This reaction to radiation resembles intestinal damage due to ischemia-reperfusion [19] and has been prevented by free radical scavengers in animal models [33,34,35]. Further studies in humans must be performed in order to demonstrate if this mechanism explains SIRS and wasting in human beings under radiation treatment.

In conclusion, standard external pelvic radiation for treatment of gynecological malignancies induced acute intestinal alterations, which are associated with a wasting-like pattern of body composition changes. The mechanisms involved, and whether the severity of acute alterations is associated with a higher probability of progression to chronic actinic enteritis, deserve further investigation.

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