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Chronic enteritis in patients undergoing pelvic radiotherapy: prevalence, risk factors and associated complications

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Abstract

Introduction: **the radiation of tumours located in pelvic organs can cause mucositis in the bowel. The aim of this study was to determine the prevalence, risk factors, and complications of chronic radiation enteritis in patients who had received pelvic radiotherapy.**

Patients and methods: **cross-sectional study recruiting 150 patients that had been treated with radiation therapy during the year 2008 because of a prostate, cervical, endometrial or rectal cancer. The patients were asked about symptoms related to enteritis, and about changes in body weight and in dietary patterns. Sex, age, treatment modalities, acute enteritis, and type of cancer were considered possible risk factors, and were analysed with univariate and multivariate methods.**

Results: **the study included 100 patients, 84% males, median age 72.3 years. Chronic radiation enteritis was found in 20% of the patients, most of them grade 1 (45%). Furthermore, 10% had lost ≥ 5 kg of weight, 3% had been hospitalized due to diarrhoea or bowel obstruction, and 11% had changed their diet, mainly by removing vegetables, legumes and pastry. Male gender, age, previous acute radiation enteritis, and chemotherapy were associated with chronic enteritis, but only chemotherapy remained independently related to bowel toxicity after multivariate analysis (OR = 3.59 [95% CI 1.20–10.73]).**

Conclusion: **chronic enteritis is common among patients treated with pelvic radiotherapy, especially if chemotherapy is associated. The complication rate is low, but a significant number of patients change their usual diet in order to prevent symptoms.**

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Key words: *Enteritis. Radiotherapy. Cancer. Diet. Malnutrition.*

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ENTERITIS CRÓNICA EN PACIENTES SOMETIDOS A RADIOTERAPIA PÉLVICA: PREVALENCIA, FACTORES DE RIESGO Y COMPLICACIONES ASOCIADAS

Resumen

Introducción: **la radiación de los tumores de la cavidad pélvica puede provocar mucositis a nivel intestinal. El objetivo de nuestro estudio fue determinar la prevalencia, los factores de riesgo y las complicaciones de la enteritis rádica crónica en los pacientes tratados con radioterapia pélvica.**

Pacientes y métodos: **estudio transversal sobre 150 pacientes tratados con radioterapia pélvica durante el año 2008 debido a un cáncer de próstata, cérvix, endometrio o recto. Se interrogó a los pacientes sobre la presencia de síntomas sugestivos de enteritis y sobre cambios en el peso habitual y modificaciones en su dieta. Los parámetros considerados como posibles factores de riesgo de enteritis crónica (sexo, edad, tratamiento antitumoral, enteritis aguda previa y tipo de tumor) se analizaron con métodos univariantes y multivariantes.**

Resultados: **el estudio incluyó finalmente a 100 pacientes, el 84% varones, con una mediana de edad de 72,3 años. Se encontró una prevalencia de enteritis rádica crónica del 20%, en la mayoría de grado 1 (45%). Por otra parte, el 10% referían una pérdida de peso ≥ 5 kg, el 3% habían requerido hospitalización debido a diarrea incoercible o a obstrucción intestinal, y el 11% habían modificado su patrón de alimentación habitual, reduciendo principalmente el consumo de verduras, legumbres y dulces. Se encontró asociación entre la enteritis rádica crónica y el sexo masculino, la edad, la enteritis rádica aguda previa y la quimioterapia, pero solo esta resultó asociarse de forma independiente con el desarrollo de enteritis rádica crónica después del análisis multivariante (OR = 3,59 [95% CI 1,20–10,73]).**

Conclusión: **la enteritis crónica es una entidad frecuente en los pacientes tratados con radioterapia pélvica, sobre todo cuando se asocia con quimioterapia. La tasa de complicaciones por esta patología es baja, pero un número importante de pacientes realiza modificaciones en su dieta habitual para aliviar o evitar la sintomatología derivada de aquella.**

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Palabras clave: *Enteritis. Radioterapia. Cáncer. Dieta. Malnutrición.*

Introduction

Nowadays, radiotherapy (RT) is commonly indicated to treat different kinds of cancer. It can be used alone or in association with other treatments such as chemotherapy (CHT) or surgery. The use of RT is based on the effects of the ionizing radiation on the cells, which causes cellular damage by several mechanisms including DNA damage, changes in cellular membrane, mitochondrial injury, apoptosis, inflammation, generation of reactive oxygen species and vascular damage[1]. Both tumour and healthy tissue are affected by ionizing radiation, thus RT administration should try to minimize the damage to healthy cells while destroying malignant cells.

The damage of normal tissue produces symptoms that can compromise the completion of treatment. Radiation-induced toxicity can be classified as acute – when symptoms appear during or immediately after RT – or chronic – when symptoms appear months to years after finishing RT – each of them with different clinical manifestations and different treatment. The damage of nearby healthy tissues remains one of the main limiting factors when using RT for tumour treatment, because of the symptoms it can cause and the risk of turning the initially healthy cells into cancerous ones. As with other kinds of cancers, in those which affect the abdominal or pelvic cavity, toxicity on healthy tissues is the main dose-limiting factor when RT treatment is used. Moreover, in these tumours, local radiation toxicity causes intestinal damage, which is one of the factors that influence cure rates being lower than expected[2].

Radiation-induced side effects are more common in organs with a high cell replication rate, such as bone marrow or gut. RT to the head and neck area typically produces oropharingeal mucositis, to the chest, radiation oesophagitis, and to the abdominal or pelvic cavity radiation enteritis[3,4,5]. Mucositis is the toxicity that affects the mucous layer of different organs due to cancer treatments, mainly when RT and CHT are used together.

Radiation enteritis is one of the clinical manifestations of gastrointestinal mucositis, and its typical symptoms comprise diarrhoea, cramping, incontinence, bowel obstruction and bleeding. Acute radiation enteritis (ARE) appears between the first three weeks of treatment and six weeks after finishing it. On the other hand, chronic radiation enteritis (CRE) occurs months or years after the completion of RT, and it is characterized by local stenosis, bacterial overgrowth, ulcers in the mucosa, fistula formation and malabsorption of several nutrients. Although the prevalence of CRE is difficult to determine, as it depends on the characteristics of the studied population and the scales used for diagnosis, some studies suggest it could be higher than 50%. Several factors such as age, gender, treatment modalities, BMI, or comorbidities like diabetes or hypertension, could influence the development of radiation enteritis[6]. Moreover, it has been described that nearly 50% of patients with CRE make changes in their daily intake, mainly by reducing the consumption of fat and fibre[7].

The main aim of this study was to determine the prevalence and severity of CRE in patients treated with pelvic RT. Secondary objectives of the study were to identify the risk factors of CRE, to determine the complications associated to gut toxicity, and the changes in nutritional status and dietary patterns due to gastrointestinal symptoms.

Patients and methods

A cross-sectional study was performed including patients that had been treated with RT during the year 2008 because of a pelvic cavity tumour (prostate, endometrial, cervix or rectal) in the Complejo Asistencial Universitario de León (Spain). The study was evaluated by the local Research Ethics Committee, which confirmed that it complied with the ethical and legal standards included in the Declaration of Helsinki. The study consisted of a telephonic survey carried out five years after the completion of RT, in which patients were informed about the study and informed consents were requested by researchers. If the patient accepted taking part in the study, the interviewer proceeded to follow a structured questionnaire.

The items included in the questionnaire were patient's personal data (gender, name and surname, date of birth, and date of the survey), treatment modalities (radiotherapy dose, brachytherapy, chemotherapy, surgery), gastrointestinal symptoms (number of daily stools, changes in the consistency of the stools and presence of blood or mucus in them) and its duration, treatments required to control the symptoms (drugs and surgical treatments), weight loss (<5 kg, 5–10 kg, >10 kg), and changes in patient's usual dietary intake because of gastrointestinal symptoms. After collecting the data, all patients were classified according to their answers to the grade of CRE following the criteria of the Radiation Therapy Oncology Group (RTOG)[8], shown in table I.

Table I
RTOG criteria for chronic radiation enteritis

Grade	*Symptoms and signs*
0	No symptoms
1	Mild diarrhoea: mild cramping, 6 stools/d, slight rectal bleeding
2	Moderate diarrhoea: >5 stools/d, intermittent rectal bleeding, excessive rectal mucus
3	Intestinal obstruction or bleeding requiring surgery
4	Necrosis, perforation or fistula
5	Enteritis-related death

Statistical analysis

The statistical analysis was performed using the SPSS 19.0 program. First of all, the Kolmogorov–Smirnov test was performed in order to check the normal distribution of the variables. The Mann–Whitney U test was used for quantitative variables and the chi-squared analysis was used for qualitative variables. Finally, a multivariate analysis with logistic regression was performed. Quantitative variables were expressed as mean and standard deviation (SD), or median and interquartile range (IQR), and qualitative variables as proportions. A p value < 0.05 was considered statistically significant.

Results

One hundred patients were finally included in the statistical analysis from the initial sample of 150 (fig. 1). Patients' characteristics are summarized in table II.

Gastrointestinal symptoms and chronic radiation enteritis

Among the studied patients, 28.3% referred to changes on the number of daily stools and 35% to the consistency of their stools (46.7% soft stools, 20% liquid stools), in comparison with before having received RT. Moreover, 12.1% said that they had blood or mucus in the stools. CRE was found in 20% of patients, most of them presenting mild grades of enteritis (grade 1 – 45% of patients; grade 2 – 30% of patients; grade 3 – 10% of patients; grade 4 – 15% of patients).

Gastrointestinal complications and outcomes

Due to gastrointestinal complications, 3% of patients needed to be hospitalized: 2% because of bowel obstruction and 1% because of severe diarrhoea. Bowel obstruction was treated with NPO and fluid therapy, and diarrhoea with antidiarrhoeical drugs. Three per cent needed surgery to correct enterocutaneous fistulas.

Weight loss and dietary changes

No differences were found in unintentional weight loss between patients with and without CRE (9.5% vs. 9.9%, p = 0.961). The amount of weight loss and its frequency is shown in table III.

Changes in dietary intake were found in 11% of patients, and represented the decrease or removal of several foods from their regular diet due to gastroin-

Table II
Characteristics of patients

		N (% of patients)
Gender	Male	84 (84%)
	Female	16 (16%)
Age (years)		72.3 (IQR=13.4)
Tumour	Prostate	68%
	Rectum	27%
	Endometrial	5%
Tumoural stage	I	30.1%
	II	40.6%
	III	26.3%
	IV	3%
Treatment	CHT	22%
	BT	8%
	Previous surgery	11%
Radiation dose (Gy)		72 (IQR=27)

(CHT: chemotherapy; BT: brachytherapy; IQR: interquartile range)

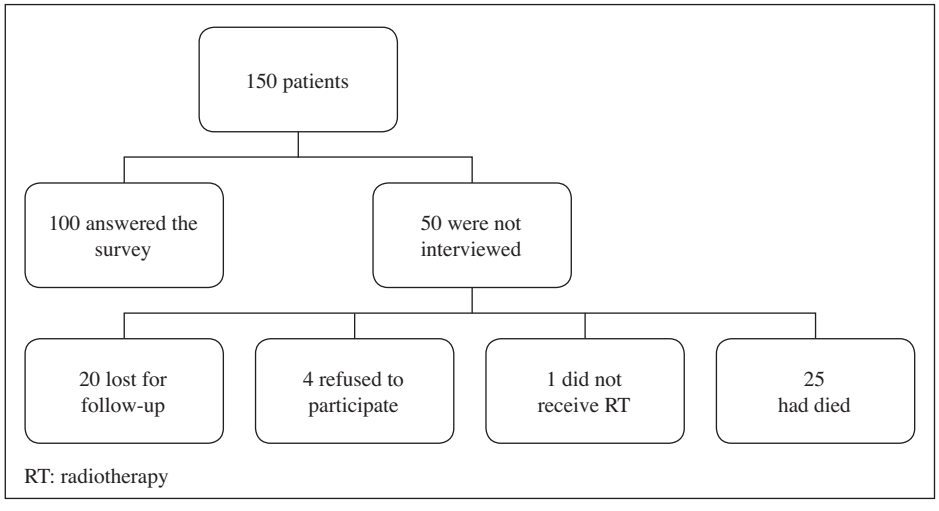

Fig. 1.—Flow chart of the study.

testinal symptoms. The foods whose consumption was most frequently decreased or removed are shown in table IV. Nevertheless, there were some of them which did not suffer any changes of daily intake, such as eggs, potatoes, rice and pasta.

Risk factors of CRE

CRE was more frequent in females than in males (43.8% vs. 15.5%, p = 0.013), among patients who had developed acute enteritis (34.5% vs. 14.1%, p = 0.01), among patients treated with chemotherapy (40.9% vs. 14.1%, p = 0.006), in patients undergoing surgery (45.5% vs. 16.9%, p = 0.025), and those treated with brachytherapy (50.0% vs. 17.4%, p = 0.027). There were no differences between patients with CRE and those without enteritis regarding age [73.7 yr (IQR =15.1) vs. 72.3 yr (IQR =9.5)], but patients who developed chronic enteritis had received a lower dose of radiation [58 (27.3) Gy vs. 71.0 (28.5) Gy, p =0.008). Chronic enteritis was found in 14.7% of patients with prostate cancer, 29.6% with rectal cancer and 40% with endometrial tumours (p = 0.082).

After performing the multivariate analysis, only chemotherapy was independently associated with CRE with an [OR = 3.59 (95% CI 1.20–10.73).

Table III
Patients' weight loss

		CRE		*Total*
		Yes	*No*	
Weight loss	<5 kg. (%)	50%	62.5%	60%
	5-10 kg. (%)	50%	25%	30%
	>10 kg. (%)	0%	12.5%	10%
Total		100%	100%	100%

(p=0.732)

Analysis of mortality

There were 25 patients from the initial sample of 150 whose death was confirmed. Some factors that were found to be related to these deaths were the type of tumour (cervix 100%, rectal 29.3%, endometrial 16.7%, prostate 12.5%, p = 0.004) and the tumour stage at diagnosis (stage I 8%, stage II 28%, stage III 40%, stage IV 4%, p = 0.017). Nevertheless there was no association with the development of acute radiation enteritis [enteritis 32% vs. no enteritis 68%, p = 0.756, OR = 1.16 (CI 95%: 0.45–2.98)].

Discussion

There are only a few studies that have analysed the prevalence of CRE, and they are particularly limited over the last decade which has seen RT techniques evolve, in order to improve the outcomes of using RT on cancer treatment. Moreover, most of the pre-existing studies have investigated wheter the development or CRE stands in relation to different kinds of pelvic tumours, or have described the occurrence of certain gastrointestinal symptoms after RT without classifying them as CRE. This trial has found that chronic radiation enteritis is common, as it affects up to 20% of patients with pelvic tumours, but it usually presents as mild grades.

Previous studies have found that the prevalence of CRE ranges between 0.5% and 25% or even around 50%[9,10,11]. But the studies that showed a higher prevalence are mainly those including patients treated by older RT techniques or those that only took into account the symptoms related by patients, without classifying them according to their grade of CRE. Therefore, the prevalence found in our study is in agreement with those previously described. However, the range of the prevalence of CRE reported to date is quite large, maybe due to the use of different scales used to classify patients' symptoms and to define the grade of CRE.

Table IV
Modified frequency of food consumption by patients

		CRE		*p value*
		Yes	*No*	
Global consumption modification		19%	6.2%	0.064
Modified foods consumption	Milk	0%	25%	0.236
	Dairy products	0%	25%	0.236
	Green leafy vegetables	80%	25%	0.099
	Fruit	60%	0%	0.058
	Legumes	40%	25%	0.635
	Bread	20%	0%	0.343
	Pastry	20%	25%	0.858

Furthermore, previous prevalence given by other studies could be underestimated because the symptoms are unspecific (so they can be easily confused with other illnesses) or because most patients with CRE suffer from mild grades of it (so they do not demand medical attention), or because many of these patients die because of the tumour they are being treated for[10].

No studies comparing the prevalence of CRE among men and women were found, so we cannot know how our results compare or not regarding this aspect, but we can try to explain the fact that in our study there are more women suffering from CRE than men. We think that these differences could be due mainly to the size of pelvic area irradiated to treat the different kinds of tumour included in this study, because the volume of the bowel on which the radiation falls upon is correlated with the occurrence of CRE. Thus, although the doses of radiation currently used for prostate cancer treatment are higher than those used to treat gynaecological cancers, the radiation in the first is more focused on the organ to be treated, while in cervical and endometrial cancers the irradiated pelvic area is wider. Likewise, the differences between men and women might be related to the combination of RT and CHT used to treat gynaecological cancers, so that the risk of intestinal damage increases as a result of each of those treatments. To explain the differences it could be added that most patients of our sample were males with prostate cancer, so they received higher doses of radiation, but this was more focused on the gland and caused less damage to the organs around it.

The rate or hospitalization in our sample was lower than those mentioned in other studies[12], maybe due to the fact that more than 50% of our patients suffering from CRE had a mild grade of it (1 or 2), which does not usually require the patient to be in hospital to cure it. Nevertheless, previous studies that have analysed the rate of hospital placement of these patients, the necessity for surgical interventions and the mortality due to CRE, included patients with a moderate or severe grade (3 or 4) of this condition, which usually requires hospital treatment for it to be resolved. Regarding the frequency of occurrence of one or the other grades of CRE among patients treated with RT, there are no previous studies that have collected these percentages.

With regard to patients' nutritional status, the percentage of them that were undernourished or at risk of suffering from undernourishment was not negligible. We think that there are certain reasons, therefore, that they may become malnourished, starting with the cancer they are suffering from and the treatments used against it. Among patients with CRE, it seems that the intestinal symptoms (diarrhoea, malabsorption, and bowel obstruction) and the treatment needed to manage them, might contribute to the impairment of their nutritional state. Regarding the risk of malnutrition of these patients, the changes made by many of them to their daily intake should be noted. The most likely reason for this seems to be that they stop eating certain kinds of food because they realize that these foodstuffs make their symptoms worse (in fact, the foods that most patients removed in our study were those with a higher amount of fibre, as is also referred to in previous studies)[7].

With regard to the role of CHT in the occurrence of CRE, it should be remembered that these drugs can cause intestinal damage themselves, mainly in the form of diarrhoea. So it is not surprising that the combined use of RT and CHT increases the risk of the emergence of any side effects that both treatments could cause separately, as is described in previous literature[5,6].

The kind of tumour and the tumoural stage were the only factors that were found to be associated with patient deaths. Those tumours responsible for most patients' deaths were cervical and rectal tumours, which are usually more severe than prostate and endometrial cancer. Referring to the tumoural stage, it makes sense that a higher number of patients diagnosed at more severe stages (such as III and IV) died than those patients diagnosed at earlier tumoural stages (such as I and II). However, no association was found between mortality and previous ACE.

The main strength of this study includes the initial sample size (150 patients) and the small rate of patient losses (14%). However, some limitations should be mentioned. First, the survey was made by telephone, making the information obtained from patients less objective. Second, information bias may have occurred due to the fact that patients with more severe symptoms could better remember everything related to their illness and their symptoms.

In conclusion, the prevalence of CRE among patients treated with pelvic RT in our hospital is 20% and most of these patients suffer from a mild grade of this illness (grade 1). The onset of this illness leads to patients changing their daily food intake due to their symptoms. Moreover, few patients with CRE suffered a significant weight loss, which in some cases could be considered suggestive of some degree of malnutrition, but in most is a mild grade of it. Finally, CHT used before or at the same time as radiotherapy is the only one factor associated with the development of CRE.

The authors declare no conflict of interest.

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