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Rev Inves Clin. 2018;70:112-6 BRIEF REVIEW

Epidemiological Profile, Gastrointestinal Toxicity, and Treatment of Pelvic Cancers in Patients Managed with Radiotherapy to the Abdominal Pelvic Area

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ABSTRACT

Mexico has seen an increase in cancer prevalence in its entire population as well as particular age ranges, predominantly the older segment. The most frequently reported pelvic cancers in Mexico are cervical, endometrial, bladder, prostate, rectum, and anal canal. Approximately 80% of the population diagnosed with pelvic cancers present with locally advanced tumors and require concomitant chemoradiotherapy, sequential chemoradiotherapy, or radiotherapy alone. The toxicity of any of these treatment modalities may be manifested as intestinal injury, a significant problem that can compromise the response to treatment, the patient's nutritional state, quality of life, and survival. In this article, we will approach key aspects in nutrition as well as the epidemiological characteristics and toxicities in patients affected by these pelvic tumors. (REV INVES CLIN. 2018;70:112-6)

Key words: Epidemiology. Pelvic cancer. Radiotherapy. Chemotherapy. Gastrointestinal toxicity.

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INTRODUCTION

Cancer is an important public health problem throughout the world and particularly in Mexico. Some authors have reported a 15% global increase per year[1]. Mexico has also seen an increase in the incidence of cancer in its entire population in different age ranges but predominantly in individuals over 65 years of age[2]. Pelvic tumors refer to those located within the anatomical area of the pelvis, which extends from the fourth lumbar vertebra to the anal triangle[3]. In our population, the most frequent pelvic cancers that have been treated with radiotherapy of the pelvic region are cervical, endometrial, bladder, prostate, rectum, and anal canal (Table 1).

Radiotherapy is one of the most important treatment modalities in cases of inoperable pelvic tumors. Treatment is administered with a curative intent in some cases – as in locally advanced stages – and as a palliative in more advanced cancers[4].

In recent years, improved technology and the concerted efforts of physicists and physicians have transformed radiotherapy into a timely, efficient, and less toxic treatment modality. Furthermore, the introduction of advanced techniques such as intensity modulated radiation therapy, image-guided radiation therapy, and the CyberKnife has increased the precision of radiation treatments[5-8]. However, the toxicity resulting from radiotherapy alone, concomitant chemoradiotherapy, sequential chemoradiotherapy, and radiotherapy in its neoadjuvant, adjuvant, or palliative modalities, continues to be a problem compromising treatment response, the patient's nutritional state, quality of life, and survival in cases that develop pelvic radiation disease[9-11].

Pelvic radiation disease may be defined as "transient or longer-term problems, ranging from mild to very severe, arising in non-cancerous tissues and resulting from radiotherapy treatment for a tumor of pelvic origin"[12]. There are two types of toxicity: "acute toxicity," defined as the toxicity manifested in "early-reacting tissues" or rapid renewal tissues, such as the epithelial surfaces and bone marrow; injury is clinically manifested within days after initial radiation exposure and up to 90 days later. "Late toxicity" refers to that manifested in "late-reacting tissues" in which cellular turnover is much slower, such as connective tissue; injury may, therefore, become manifest months or even years after exposure and definitely after 90 days of finalizing treatment. Other toxic consequences include "indirect" effects, reactive phenomena that occur in response to radiation-induced injury in other cells or tissues, such as parenchymal cell depletion secondary to vascular damage; these effects also include "bystander" fallout and tissue reactions to cell lethality, including the effects of vasoactive, pro-coagulant, and inflammatory mediators, such as cytokines, growth factors, and chemokines[12,13].

During the treatment period, which may range from 5 to 7 weeks or more, 80-90% of patients develop variable toxicity manifestations in the gastrointestinal tract and other pelvic organs[14]. Chronic radiation

Table 1. Incidence and mortality of pelvic cancers in Mexico

Cancer site	Incidence		Mortality
	Number of cases*[1] (%)	Standardized rate by age*	Number of cases* (%)
Gynecological			
Uterine cervix	13,960 (16.9)	23.3	4,769 (11 9)
Endometrial	2,733 (3.3)	4.8	550 (1.4)
Urological			
Bladder	3,245 (2.2)	2.9	1,166 (1.5)
Prostate	14,016 (21.4)	27.3	6,367 (8.1)
Gastrointestinal			
Rectal[31]	1268 (ND)	33.4	424 (0.4)
Anal canal[32]	ND (0.18)	ND	ND (ND)
Total	42,605 (37.7)	66.1	17,546 (28.9)

ND: not described; *Number of cases per 100,000 population.

Table 2. Prevalence of toxicity symptoms in different cancer tumors

Toxicity	Uterine cervix	Bladder	Anal/rectal	Prostate	Endometrial
Hematologic (%)					
Leukopenia	4-47	2.9-8.6	3-24	ND	25.5
Neutropenia	ND	2.9	<1-3	ND	ND
Fatigue	0-24	5.7-31.4	1.3-6.8	ND	7.8
Gastrointestinal (%)					
Nausea/vomiting	0-14	2.9-31.4	<1-5	ND	ND
Rectal bleeding	ND	ND	ND	<1-12	ND
Diarrhea	0-21	2.9-31.4	6.9-10	<1-13	11.8
Fecal incontinence	ND	ND	ND	ND	ND
Abdominal pain	1	2.9-20	0.3-3.4	ND	ND
Tenesmus	ND	ND	1.4-5.5	ND	ND
Genitourinary (%)					
Hematuria	ND	ND	ND	<1-7.1	ND
Dysuria	0-17	5.7-20	ND	<1-26.8	ND
Urinary incontinence	ND	ND	ND	<1-10.7	ND
Urinary frequency	ND	5.7-20	ND	<1-27.9	ND

% of patients presenting each symptom according to the type of tumor. ND: not described. Data were obtained from different sources: uterine cervix[19,33] bladder[34], anal/rectal[35,36], prostate[37,38], and endometrial[39].

enteritis occurs in 0.5-16.9% of patients receiving abdominopelvic irradiation. Although symptoms may vary, these are remarkably similar to inflammatory bowel disease[15,16] and are characterized by changes in bowel habits (94%), occult fecal blood (80%), increased frequency of bowel movements (74%), fecal urgency (39%), fecal incontinence (37%), and after treatment conclusion, and symptoms may persist in up to 50% of patients[17]. The prevalence of these symptoms may vary according to the area irradiated and the type of treatment applied (Table 2).

There are different clinical scales to measure oncologic toxicities. Among the most important are toxicity criteria CTCAE v. 4-5, RTOG, EORTC, and Lentsoma; these have been validated and are used as international criteria[18-20].

Other ways to evaluate toxicity include molecular techniques that measure the expression of inflammatory mediators in peripheral blood, such as citrulline, C-reactive protein, eosinophil cationic protein, inflammatory cytokines, and the determination of gene expression[21-25]. Other authors have reported that the neutrophil-derived proteins, calprotectin, and lactoferrin are important molecules directly related to gastrointestinal toxicity and inflammation[25]. Further, due to the inflammatory response generated during the acute phase, Th1 and Th2 immune responses may also play a significant role in radiotherapy-induced inflammation[26].

Several factors have been correlated with the risk of developing late post-irradiation complications in gynecologic malignancies[27,28]. These factors could perhaps help predict and prevent late normal tissue injury. In their paper, Heemsbergen et al. studied whether there is a direct relationship between acute and late gastrointestinal toxicity, concluding that acute gastrointestinal toxicity is an independent significant predictor of late gastrointestinal toxicity[28]. There was no correlation between acute and late urinary toxicity[27,28].

Other factors that may influence late bowel toxicity are the patient's age and gender, tumor location, tumor size, tumor volume, and the number of daily bowel movements. In addition, some comorbidities such as inflammatory bowel disease, immune dysregulation, abnormal microbial flora, environmental factors, and genetic susceptibility could also influence the development of gastrointestinal toxicity[16,29].

Radiotherapy causes damage to the gastrointestinal mucosa and affects secretory and absorptive functions that, in turn, may interfere with normal

gastrointestinal physiology as well as nutrient absorption and digestion. It is manifested 2 weeks after radiotherapy is initiated and is dependent on the fraction dosage and radiation volume. It leads to changes in the intestinal flora and increases in mucosal cell permeability and intestinal motility as well as to the generation of free oxygen radicals and subsequent vascular insufficiency, ischemia, fibrosis, intestinal obstruction, chronic proctitis, and the development of fistulae. Clinically, these signs are translated as a malabsorption syndrome. Histopathologic changes are also observed, including thickening of the serosa, mucosal ulcerations, epithelial atypia, vascular sclerosis, intestinal wall fibrosis, lymph congestion, and ileitis cystica profunda[30].

Some pharmacological interventions have attempted to prevent or at least diminish the damage described; they have achieved a slight reduction in the severity of the symptoms of gastrointestinal toxicities, but to date, conclusive findings are limited.

Nutritional intervention has been deemed necessary to maintain the nutritional status of the patient during treatment, to avoid malnutrition, to decrease the severity of treatment, and finally, to improve response to treatment. In this consensus, we pretend to lay the groundwork for dietary intervention and describe the available nutritional tools used to assess the patient's nutritional status and possible nutritional interventions that may modify the patient's course.

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