

## Prevalence of adverse effects of external beam teletherapy in patients with cervical cancer in the Serra Catarinense region, in Southern Brazil

### Prevalência dos efeitos adversos da teleterapia em pacientes com câncer de colo uterino na Serra Catarinense

### Prevalencia de efectos adversos de la teleterapia en pacientes con cáncer de cuello uterino en la región de Serra Catarinense, Brasil

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**Objective:** to analyze the frequency of adverse effects in patients with cervical cancer undergoing external beam radiation therapy (teletherapy) in a cancer treatment center. **Methods:** cross-sectional, exploratory and descriptive study, carried out between May and June 2022, through interviews and documentary research, in the Serra Catarinense region, in Southern Brazil. **Results:** seven patients aged between 38 and 64 years, in different stages of the disease, were considered. The most common adverse effects presented were diarrhea, intestinal pain, abdominal cramps, rectal urgency and dysuria; therefore, the gastrointestinal and urinary systems are the most affected by the treatment. **Conclusion:** the use of methods that reduce the occurrence of the effects of external beam radiation therapy is an investigative demand, since these effects directly imply the quality of life and well-being of patients.

**Descriptors:** Radiotherapy; Teletherapy; Drug-Related side effects and adverse reactions; Toxicity; Uterine cervical neoplasms.

**Objetivo:** analisar a frequência dos efeitos adversos em pacientes com câncer do colo do útero submetidas a teleterapia em um centro de tratamento oncológico. **Método:** estudo seccional, de caráter exploratório e descritivo, realizado entre maio e junho de 2022, por meio de entrevista e pesquisa documental, na região da Serra Catarinense. **Resultados:** considerou-se sete pacientes com idades entre 38 e 64 anos, em diferentes estágios da doença. Os efeitos adversos mais comuns apresentados foram diarreia, dor intestinal, cólica abdominal, urgência retal e disúria; portanto, os sistemas gastrointestinal e urinário são os mais acometidos pelo tratamento. **Conclusão:** o uso de métodos que diminuem a ocorrência dos efeitos da teleterapia é uma demanda investigativa, visto que estes efeitos implicam diretamente na qualidade de vida e bem-estar das pacientes.

**Descritores:** Radioterapia; Teleterapia; Efeitos colaterais e reações adversas relacionados a medicamentos; Toxicidade; Neoplasias do colo do útero.

**Objetivo:** analizar la frecuencia de efectos adversos en pacientes con cáncer de cuello uterino sometidas a teleterapia en un centro de tratamiento oncológico. **Método:** estudio seccional, exploratorio y descriptivo, realizado entre mayo y junio de 2022, a través de entrevistas e investigación documental, en la región de la Serra Catarinense, Brasil. **Resultados:** fueron consideradas siete pacientes con edad entre 38 y 64 años, en diferentes estadios de la enfermedad. Los efectos adversos más comunes presentados fueron diarrea, dolor intestinal, cólico abdominal, urgencia rectal y disuria, por lo que los sistemas gastrointestinal y urinario son los más afectados por el tratamiento. **Conclusión:** la utilización de métodos que reduzcan la ocurrencia de los efectos de la teleterapia es una demanda de investigación, ya que estos efectos implican directamente en la calidad de vida y bienestar de las pacientes.

**Descriptorios:** Radioterapia; Teleterapia; Efectos colaterales y reacciones adversas relacionados con medicamentos; Toxicidad; Neoplasias del cuello uterino.

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## INTRODUCTION

**T**he global incidence of cervical cancer (CC) for the year 2020 was 604,127 new cases. This rate is considered high, being more significant in low and middle-income countries<sup>1</sup>. In Brazil, with the exception of cases of non-melanoma skin cancers, CC is the second most frequent type of cancer in the Northern, Northeastern and Central-Western regions; and it is the fourth most frequent in the Southern and fifth most frequent in the Southeastern region<sup>2</sup>.

The main cause of cervical cancer is a viral infection in the reproductive system by the human papillomavirus (HPV), and the development of the disease is directly related to the chronic infection of the virus<sup>3</sup>. In the last ten years, the HPV vaccine has shown effective results in terms of safety and prevention of persistent infections<sup>4</sup>.

Screening for CC, according to the National Cancer Institute (INCA), should be carried out in association with gynecological examination, cytopathological examination (Papanicolaou technique), colposcopy and biopsy<sup>5</sup>. CC is treated at an early stage, in most cases surgically, while radiotherapy is used in locally advanced or metastatic cancers. In addition, chemotherapy is also used, which can be associated with radiation therapy<sup>6</sup>.

In radiotherapy, the treatment can be combined in two modalities, brachytherapy and external radiation beam therapy (also known as teletherapy). Considering the toxicity of radiation exposure, the organs at risk in external radiation beam therapy (rectum, bladder, femoral head, sigmoid and peritoneal cavity) are outlined for evaluation and dose restrictions<sup>7</sup>. Although there are currently radiotherapy techniques that minimize radiotoxicity, the tissues surrounding the target of treatment still receive a dose of radiation and, therefore, may suffer effects of the treatment<sup>8</sup>.

Toxicities related to radiotherapy for CC occur in the genitourinary and gastrointestinal tracts<sup>9</sup>. The effects of radiotherapy may appear in the long term, such as changes in bladder function (urinary urgency or incontinence, urinary frequency, pain when urinating due to chronic interstitial cystitis and bladder pain, detrusor instability, urinary retention and vesicovaginal fistula), the intestine (diarrhea, rectal urgency, incontinence or stool leakage), loss of ovarian function in premenopausal women, in addition to sexual difficulties, such as: low sexual desire, vaginal dryness, dyspareunia and vaginal shortening<sup>10</sup>. Considering the toxicities that involve oncological therapy, this research aims to analyze the frequency of adverse effects in patients with cervical cancer undergoing external radiation beam therapy in an oncological treatment center.

## METHODS

Study of multiple cases of exploratory and descriptive character. A field survey was carried out whose data collection was carried out through interviews and documentary research between the months of May and June 2022 in an oncological treatment center located in the Serra Catarinense region, in Southern Brazil. The study was approved by the Research Ethics Committee of the institution under opinion No 5,244,746.

Considering the collection time range, the population is characterized as a census study, so that all individuals who met the inclusion criteria (female patients who are in the last five days of treatment with radiotherapy in the form of external radiation beam therapy for the CCU) were included in the survey. According to TABNET public domain data from DataSUS<sup>11</sup>, during the years 2020 and 2021, 27 and 22 patients were treated in the Serra Catarinense meroregion, respectively.

The first phase of collection (interview) was performed by an oncology nurse using a questionnaire adapted from two international instruments<sup>12,13</sup>. The “Expanded Prostate Cancer Index Composite” (EPIC)<sup>12</sup> tool aims to analyze urinary and gastrointestinal functions, while the “Female Sexual Function Index” (FSFI)<sup>13</sup> seeks to assess sexual function in women. Both instruments were adapted to better meet the sociodemographic needs of the population. For documentary collection, information was extracted from the clinical history and oncological treatment. The information collected was analyzed and based on descriptive statistics (measures of central tendency).

## RESULTS

The population consisted of 7 patients, with a minimum age of 38 and a maximum of 64 years, with an average of 51.42 years, who underwent external radiation beam therapy for CC. The diagnosis of malignant neoplasm of the cervix with invasive lesion in 57.14% of the patients, followed by malignant neoplasm of the exocervix in 42.85%. The anatomopathological result indicated the presence of invasive squamous cell carcinoma (SCC) in 100% of the patients (No=7). Table 1 shows the characteristics of the investigated patients.

**Table 1.** Health conditions of patients undergoing radiotherapy, Serra Catarinense region, Brazil, 2022.

Variables	% (No)
<b>Age</b>	Mean(SD)51.42
<b>Diagnosis</b>	
Malignant neoplasm of cervix with invasive lesion	57.14 (4)
Malignant neoplasm of the exocervix	42.85 (3)
<b>Anatomopathological results</b>	
Invasive squamous cell carcinoma	85.71 (6)
Microinvasive squamous cell carcinoma	14.28 (1)
<b>Staging</b>	
I	14.28 (1)
IAI	14.28 (1)
II	14.28 (1)
IIB	42.85 (3)
IIIB	14.28 (1)
<b>Hysterectomy surgery</b>	
Yes	57.14 (3)
No	42.85 (4)

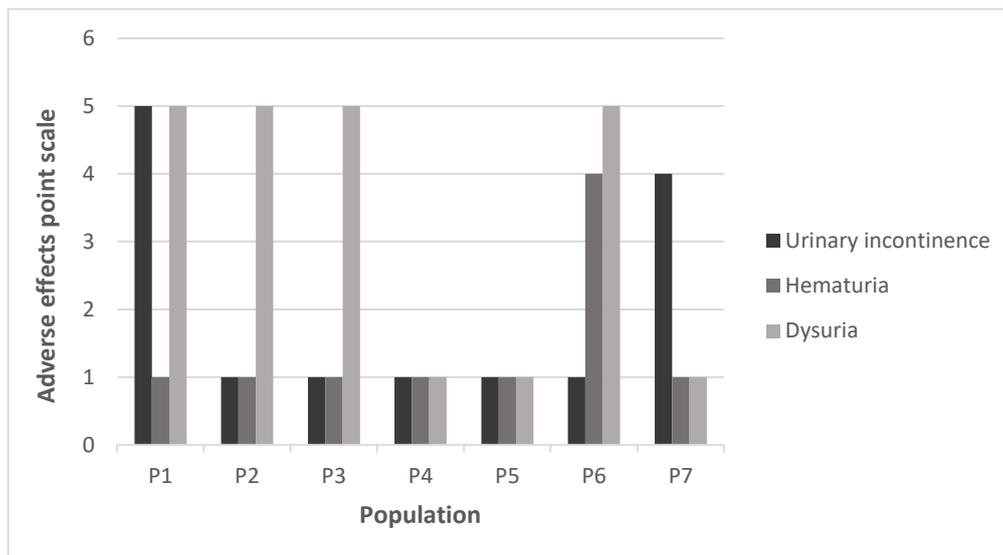
Locally advanced cervical cancer was observed in 5 patients (71.41%), with stage IIB being the most frequent, with presentation in 3 cases (42.85%) of the cases. Also, 3 patients underwent hysterectomy surgery, but only 1 (P2) underwent surgery as the primary treatment, and chemoradiation was the therapeutic approach defined for the treatment of local recurrence of cervical cancer. The other patients (P3 and P7) underwent a previous hysterectomy for the treatment of uterine fibroid.

Concomitant chemoradiation was administered to 6 patients. The information on whether or not to undergo chemotherapy for the treatment of CC was not included in the clinical history of one participant (P3).

The modality of conventional three-dimensional radiotherapy (3D-CRT) was adopted for all patients, and 6 of them (85.71%) received radiation with curative intent (radical), and in 1 (14.28%) the therapy had analgesic proposal. The administered doses ranged between 45 Gy and 50.4 Gy, segmented into 25 or 28 fractions (Table 2) following the standard fractioning scheme, and the highest Planning Target Volume (PTV) has given to patient P1, followed by patients P6, P7, P4, P2, P3 and P5.

Adverse effects were analyzed according to urinary, gastrointestinal and genital tracts. In all domains, reactions were present in at least one patient. As shown in Graph 1, among the effects related to the urinary system, dysuria was the most prevalent reaction, with 4 occurrences (57.1%), which indicated that the dysfunction occurred more than once a day.

**Graph 1.** Urinary adverse effects of patients who underwent radiotherapy, Serra Catarinense, Brazil, 2022.

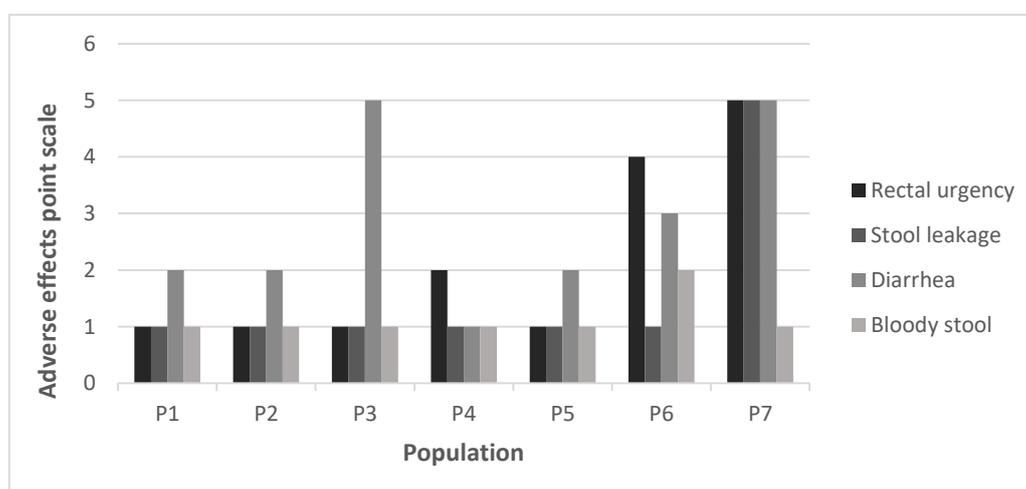


**Key:** (1) rarely or never (2) about once a week (3) more than once a week (4) about once a day (5) more than once a day.

Furthermore, it can be observed that urinary incontinence was reported in 2 patients (28.56%) and, due to this, one of them (P1) needed to use at least one diaper or cloth per day to control the leakage. In addition, 1 patient (P6) had hematuria about once a day during treatment.

Among the gastrointestinal reactions, diarrhea occurred in 3 participants (P3, P6 and P7) more frequently. Rectal urgency occurred at least once a week in 3 participants (42.85%). Only 1 patient reported the occurrence of stool leakage (P7), but this dysfunction occurred with considerable frequency in the last four weeks.

**Graph 2.** Gastrointestinal adverse effects of patients who underwent radiotherapy, Serra Catarinense, 2022.



**Key:** (1) rarely or never (2) about once a week (3) more than once a week (4) about once a day (5) more than once a day.

Abdominal colic including pelvis or rectum was also analyzed in 5 patients (71.41%) on a constant basis. Intestinal pain occurred in 6 patients (85.71%).

Regarding gynecological alterations, abnormal vaginal discharge and bleeding (4 and 3 patients, respectively) were identified, which were present on a larger scale compared to dryness (1 patient). Of the patients who had abnormal vaginal bleeding, 2 (28.56%) reported little bleeding and 1 (14.28%) moderate bleeding. In 2 patients (P4 and P6), the occurrence was sporadic, and 1 of them did not answer the question.

## DISCUSSION

The investigated patient population had at least one toxicity in the urinary, gastrointestinal and genital tracts. Alterations in the gastrointestinal and genitourinary tracts can occur significantly in patients undergoing 3D-CRT who have previously undergone total hysterectomy. This occurs due to the presence of these tissues in the irradiated area<sup>14</sup>. However, in the present study, there were no differences between the adverse reactions manifested in the hysterectomized patients (P2, P3 and P7) and in the other patients.

The most prevalent histological type was squamous cell carcinoma in the histological analysis of cervical cancer, corroborating previous studies that reveal that SCC is the most common anatomopathological result for this neoplasm, occurring in about 70 to 85% of cases<sup>15</sup>.

The combination of chemoradiation in the treatment of CC makes this the most indicated therapeutic protocol for this neoplasm<sup>16</sup>, and it was the most adopted approach (85, 71%). Even patients initially diagnosed in early stages (I or Ia1) were treated with chemoradiation, as it was a case of local recurrence.

Despite being the most indicated protocol, it is believed that the use of chemotherapy along with radiotherapy is an aggravating factor in the adverse effects on organs at risk. Reactions to normal tissues were observed, but it is not possible to judge that the severity was potentiated due to concomitant chemotherapy and radiotherapy.

The effects of radiation can be observed mainly after the first two weeks of radiotherapy treatment, and in the last week, the symptoms tend to worsen<sup>18</sup>. In the treatment of cervical neoplasia, acute adverse reactions are mainly related to the gastrointestinal and genitourinary systems<sup>9</sup>. In the research in focus here, all patients manifested side effects in at least one of these systems.

There is the appearance of acute changes when part of the intestine is irradiated, and the most common signs/symptoms resulting from damage to the gastrointestinal mucosa are diarrhea and abdominal pain<sup>19</sup>. Diarrhea can occur in about 68.0% to 96.2% of cases of patients

with cervical cancer undergoing pelvic irradiation<sup>16</sup>, while abdominal pain can affect up to 30% of patients who receive such treatment<sup>20</sup>. Despite manifesting itself at a relatively low frequency in the majority of the population, diarrhea was an effect observed in the entire population, while intestinal pain was present at some point during the treatment in 85.71%.

The fact that the bladder is within the pelvic irradiation field causes it to receive high doses in its total volume, contributing to the appearance of adverse reactions, especially when the total doses received by the bladder approach 50-60 Gy<sup>21</sup>. In the present study, dysuria was reported by 57.1%. In addition, 28.56% had urinary incontinence, another common dysfunction caused by radiotherapy and which may lead to a decline in the quality of life of patients undergoing CC treatment<sup>22</sup>.

Symptoms related to the genital system such as discharge and vaginal bleeding were observed in 57.1% and 42.85%, respectively. These alterations are not necessarily related to radiotherapy, as they are characteristic symptoms of the disease<sup>5</sup>.

The total size of the irradiated volume is considered an important variable for the appearance and worsening of adverse reactions to radiotherapy<sup>7</sup>, and, in the present study, this factor was significantly important in the manifestation of side effects in the gastrointestinal and urinary systems. Patients with an irradiation area between 1000 cm<sup>3</sup> and 1300 cm<sup>3</sup> had three to four reactions with different degrees of toxicity. Patients with PTV >1500 cm<sup>3</sup> presented between five and seven signs/symptoms in these domains. The patient who had the least adverse effects (P3) also had the smallest irradiated area (PTV= 142.7 cm<sup>3</sup>). This participant reported a rare occurrence of diarrhea during treatment.

## CONCLUSION

From this research, it is possible to observe the characteristics of the patients submitted to external radiation beam therapy for the treatment of cervical and uterine cancer, with a mean age of 52.47 years, diagnosed with squamous cell carcinoma, submitted to the 3D-CRT modality, with doses between 45 Gy and 50.4 Gy, and with chemoradiation in 85.71% of the investigated patients.

Gastrointestinal and urinary disorders were perceived by all participants, with more than one effect being observed in approximately 85%. The most recurrent adverse effects were: diarrhea, abdominal, pelvic or rectal pain, rectal urgency and dysuria.

As a limitation, there is the number of patients surveyed as a function of the time range of data collection, which may present memory bias among the investigated. However, it was

possible to demonstrate the scenario of adverse effects arising from gynecological radiotherapy in an oncological service in the Serra Catarinense region.

Thus, it is suggested to carry out expanded follow-up studies, with other epidemiological designs. Also, investigations on methods to reduce the adverse effects triggered by radiotherapy become fundamental, since this is still a frequent problem that interferes with the quality of life and physical well-being of patients.

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Cássila Laís Florêncio Contini and Mauricio Mitsuo Monção contributed to the writing and revision. Charlene da Silva, Karen Emanuelle de Brito Malaquias and Yasmim dos Santos Maria participated in the conception of the study and its design, data collection and analysis, writing and revision. Juliana dos Santos Müller collaborated in data collection and analysis, writing and revision.

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