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RESEARCH ARTICLE

Analysis of the Clinical-Epidemiological Profile and Cytopathological Follow-Up of Women with Cervical Cancer Undergoing Radiotherapy

Cátia Martins Leite Padilha
ORCID: https://orcid.org/0000-0002-0468-4900
Corresponding author: catialeitepadilha@gmail.com

Lucas Gomes Padilha Filho
ORCID: https://orcid.org/0000-0001-5527-3506

Rosana da Paz Ferreira
ORCID: https://orcid.org/0000-0001-6832-4165

Sérgio Augusto Lopes de Souza
ORCID: https://orcid.org/0000-0002-7901-4805

ABSTRACT
The objectives of this study were to identify the clinical-epidemiological profile of patients undergoing radiotherapy for malignant neoplasia of the cervix; describe the main cytological changes induced by radiation during post-radiotherapy follow-up; verify the incidence of locoregional recurrence, according to the cytopathological diagnosis and identify the disease-free survival and overall survival of patients followed in the study. The methodological design had a descriptive approach with a quantitative nature and longitudinal character, whose population was composed of 407 patients with cervical cancer who underwent radiotherapy and were followed up for a minimum of 5 years and a maximum of 7 years. The project was approved by the Research Ethics Committee of the National Cancer Institute, Rio de Janeiro, Brazil. Sociodemographic variables and associated risk factors were evaluated; categorical variables (cytopathological) and dependent variables for the outcome of locoregional recurrence, death and disease-free survival. The epidemiological profile of the study population revealed a mean age of 51 years, with an age range primarily from 41 to 50 years, with risk factors associated with smoking being present in 32% of patients. The percentage of alcoholics was just 5.5%. Regarding the number of sexual partners, the average was 4 partners throughout life. Squamous cell carcinoma was the most common histological type (84%). Regarding clinical staging, 2B (42.9%) and 3B (33.7%) were predominant. Of the exams with satisfactory quality for analysis, more than half (64.9%) showed actinic effects. The incidence of locoregional recurrence, according to the cytopathological diagnosis, was 11.8%, of which almost half (47.9%) died. The analysis of locoregional recurrence that impacts disease-free survival was 69.5%. The overall survival found in the analyzed population was 75.7%. The difficulties related to actinic (radiotherapy) effects show the importance of the experience of professionals involved in the analysis of irradiated cells and reflection on the subjectivity of the method. Observing these changes is useful for evaluating the impact of actions taken during the period and planning future actions.

Keywords: Actinic Effects. Radiotherapy. Uterine Cervical Cancer. Cytopathology.

Introduction

In the context of public health, cancer represents a challenge of global relevance1. In the last ten years, a 20% increase in the incidence rate of the disease has been observed, projecting an estimate of around 25 million new cases by the year 2030[1,2].

According to the World Health Organization – WHO (2023), cervical cancer represents the fourth most prevalent type of cancer among women worldwide, with an estimated 604,000 new cases registered in 2020. Among the 342,000 deaths estimated by cervical cancer in the same period, approximately 90% of these fatalities occurred in developing countries[3].

In relation to cervical cancer, Brazil has a substantial infrastructure for screening pre-malignant and malignant lesions. However, its approach is predominantly based on technology considered obsolete, with conventional cytology (Pap smear) as the main screening method), accompanied by colposcopy and treatment in cases of positivity for neoplastic lesion[4].

Furthermore, there are significant disparities in access to preventive cytopathological examination, impacting the effectiveness of screening and treatment strategies between different regions of the country, which compromises the early identification of the disease and its effective treatment, leading to a more invasive approach and therefore sometimes palliative, including radiotherapy[5,6].

Delays in diagnosis lead to more aggressive and less effective treatments, in addition to increasing hospitalization costs and mortality rates[7]. This occurs, among other reasons, because a large proportion of Brazilian women do not regularly undergo preventive examinations for cervical cancer, whether due to shame, fear, difficult access, or lack of information, thus leaving them on the margins of prevention and detection actions[5]

The vast majority of patients with malignant neoplasm of the uterine cervix, who are referred for radiotherapy, present with advanced stage disease, this fact determines high rates of loco-regional recurrence[8]. For control in cases of cervical cancer, cytopathological examination must be carried out to control possible residual neoplasia or recurrence of neoplasia after radiotherapy treatment[8–10]

In the treatment of cervical cancer, radiotherapy is an integral part of the management of locally advanced disease, either as an adjuvant treatment after surgery in the presence of risk factors or as a primary therapeutic treatment, used in combination with chemotherapy and brachytherapy booster[11].

The use of radiotherapy in the therapeutic protocol for cervical cancer causes morphological changes in both normal and neoplastic cells. These changes make it difficult to assess the presence of residual lesions, which results in challenges in the routine monitoring carried out by cytopathology[10,12].

Given this context, the objectives of this study were to identify the clinical-epidemiological profile of patients undergoing radiotherapy (tele and brachytherapy) for malignant neoplasia of the cervix; describe the main cytological changes induced by radiation during post-radiotherapy follow-up; verify the incidence of locoregional recurrence, according to the cytopathological diagnosis and identify the disease-free survival and overall survival of patients followed in the study.

Material and Methods

This study had a descriptive approach with a quantitative nature and longitudinal character, whose population was composed of patients with cervical cancer who underwent treatment, including radiotherapy, at the Cancer Hospital II (HC II) of the National Cancer Institute (INCA), located in Rio de Janeiro Brazil. The project was approved by the Research Ethics Committee of the National Cancer Institute and received the Certificate of Presentation of Ethical Appreciation (CAAE) number 57701616.6.0000.5274.

All patients included in the study completed the radiotherapy protocol. Through analysis of medical records, it was observed that radiation treatment involved a combination of external radiotherapy: megavoltage at a dose of 45 to 50 Gy, in 25 fractions, followed by intracavitary brachytherapy: high dose rate (HDR), with micro source of Iridium 192, generally with 3 insertions of 8Gy, at weekly intervals, totaling 80Gy.

Identification, Tracking and Information Collection

Through the Hospital Cancer Registry (HCII), patients with cervical cancer who underwent radiotherapy and were followed up for at least five years were selected. Initially, the inclusion criterion was the performance of at least two cytopathological examinations after radiotherapy treatment throughout the observation period. Those without reference for radiotherapy treatment, without information on the clinical staging of the lesions, those who did not undergo at least two post-

radiotherapy cytological examinations and those who did not have at least two cytopathological smears with satisfactory cellularity for analysis were excluded.

Clinical-epidemiological data were cataloged through medical records available in the HCII / INCA archives. A systematic reevaluation of cytopathological smears and categorization of the description of actinic effects, which are compatible with radiotherapy action, was carried out. This information was complemented by the cytopathological reports available in the files of the Pathology Division (DIPAT) - INCA. Data were collected using instruments developed for this purpose. Sociodemographic variables and associated risk factors were evaluated, such as:

- Age at Diagnosis: the full date of birth and age in years at the date of cancer diagnosis were noted. In statistical analysis, it was studied as a continuous and dichotomous variable.
- Race/Color/Ethnicity: refers to identification data according to attributes adopted by the Brazilian Institute of Geography and Statistics that classifies race/color into the following categories: white, black, yellow, brown and indigenous and not informed.
- Marital Status: refers to the patient's marital status at the time of opening hospital registration. The available categories are: married; single; divorced/separated/divorced; widow and not informed.
- Education: the moment when registration was opened was considered: illiterate; Incomplete 1st degree; Complete 1st degree; Incomplete 2nd degree; Complete 2nd degree; incomplete higher education; complete higher education; postgraduate and not informed.
- Alcoholism: refers to the history of alcohol consumption, not just the current situation, but the preponderant occurrence. The available categories are yes; no; former alcoholic and not informed.
- Smoking: refers to the use of tobacco. The assessment of smoking considers the patients' entire lives, and not just the current situation. The available categories: yes; no; former smoker and not informed.
- Number of Partners: refers to the number of sexual partners you have had throughout your life.
- Date of Diagnosis: the date of the histopathological examination to confirm the diagnosis was considered.
- Clinical Staging: this variable refers to the assessment of the extent of the malignant neoplasm before treatment, for planning therapy and preparing a prognosis for the evolution of the disease, according to the International Federation of Gynecology and Obstetrics Classification.
- Histological Type: this variable refers to the characterization of the cellular structure of the tumor (tumor morphology) through microscopic examination.

Cytopathological Analysis (categorical variables)

For qualitative analysis of the cytopathological samples, a binocular optical microscope (Nikon Eclipse E-200) was used, with the following magnifications and objective apertures: 4x / 0.10; 10x / 0.25; 40x / 0.65. In some cases, it was necessary to use a 100x / 1.25 immersion objective to analyze details not completely identifiable by the 40x objective.

The slides were observed based on the Greek bar reading technique, alternating the vertical direction with the horizontal direction. Photographic documentation of the smears included in the study was carried out. The slides were photographed with cameras attached to the trinocular optical microscope (Nikon E200 trinocular with digital imaging system 1280 x 1024), to compose the records and documentation of the work.

Actinic cytopathic effects were evaluated based on criteria described in the literature[13–16]. The accompanying non-epithelial elements of relevance to the topic were catalogued, such as: leukocyte exudate / purulent material, histiocytic exudate; numerous red blood cells/hemorrhagic material and abundant mucus.

Dependent Variables (outcomes)

For the outcome, the following variables were considered:

- Locoregional recurrence: it was considered when there was a reappearance of neoplasm (lesion) at the site of origin, confirmed by cytological examinations. The results of the last two exams were considered throughout the follow-up.
- Death: Death was considered related to the evolution of cancer, considering the date described on the death certificate.
- Disease-free survival: in the absence of recurrence or metastasis.
- Overall survival: cases were censored at the end of follow-up, in case of absence of death. When this occurred, the time (in months) between the cancer diagnosis and the date of death was considered a failure. For those lost to follow-up, the date of the last information contained in the hospital record was censored.

Sample Size

Initially, the search was carried out from January 2007 to December 2012. According to the

Integrator system in the HCII Hospital Cancer Registry, 4,588 cases of cervical cancer were registered during this period. This population was the total number of eligible patients, with an estimated 600 patients undergoing radiotherapy.

To verify the statistical feasibility of the study, the sample size was calculated, considering the proportion of recurrence in the group with neoplastic cytological changes (malignant), which, according to the literature[10,13,13,14,16] is 60% and in the group without changes, 50%, with a significance level of 5% and test power of 95%. Therefore, for the relevance of the study, the inclusion of at least 303 patients was considered.

To meet the inclusion criteria, the period established for monitoring the evolution of the disease was 5 to 7 years from diagnosis. Based on the sample size calculation, 24 months was sufficient to select at least 303 patients. Thus, the period of inclusion of patients from the diagnosis of the disease was from January 2009 to December 2010. The completion of the follow-up of patients undergoing radiotherapy included in the study was on December 31, 2015. The total number of patients included in the sample was 407 and follow-up was carried out through cytopathological exams.

Statistical Analysis

All collected data were tabulated in the Microsoft® Excel program and statistical tests were analyzed using the SPSS v20.3 program. For statistical analyses, other tools were also used, such as: jamovi.org software and Minitab statistical software.

A descriptive analysis of the study population was carried out using measures of central tendency and dispersion for continuous variables and frequency distribution for the categories.

The association between outcomes and independent variables was analyzed by bivariate analysis, using crude and adjusted odds ratios (OR), assuming 95% confidence intervals.

The exploratory evaluation was carried out through survival analysis using the Kaplan-Meier (KM) method. To identify possible significant differences in the survival curve for each exposure group and significance level, the following tests were used: Log-Rank (LR), Gehan and Tarone-Ware.

Results

Regarding treatment, most patients underwent radiotherapy concomitantly with chemotherapy, corresponding to more than half of the study population corresponding to 82.1%, exclusive radiotherapy was performed in 8.6% of patients and the combination with surgery in 9.4% of therapeutic choices **(Table 1).**

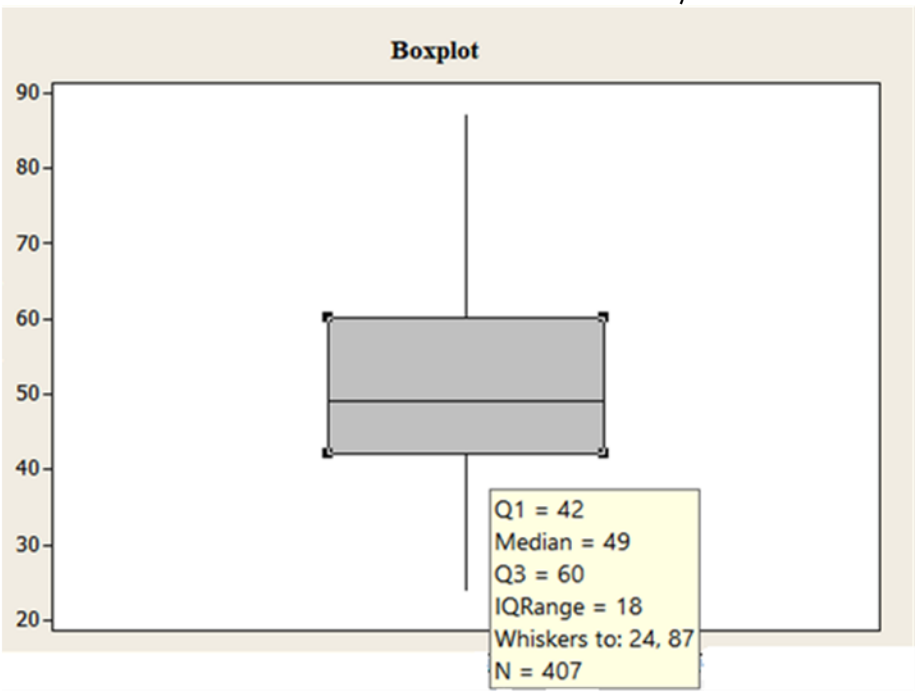
Table 1 – Distribution of patients according to treatment.

TYPE OF TREATMENT PERFORMED	Patients	
	n	%
1- Exclusive Radiotherapy	**35**	**8,6**
2- Radiotherapy + Chemotherapy	**334**	**82,1**
3- Radiotherapy + Surgery	**6**	**1,5**
4- Radiotherapy + Chemotherapy + Surgery	**32**	**7,9**
TOTAL	**407**	**100**

To facilitate the study of the raw data of the 407 patients included, data were analyzed grouped by class intervals relative to age, with 5 class intervals, where the absolute frequency was the number of patients (n) and the relative frequency was the percentage (%) of patients. The two frequencies are called simple frequencies. At these frequencies, the values of each class interval are accumulated. Thus, it can be observed that up to 50.4% of patients are aged up to 50 years.

Figure 1 shows the BoxPlot, through this graph it was possible to observe whether there are discrepant values for age, however it appears that there are no outliers for this variable. The analysis of the discrete quantitative variable shows, through the database, that there were two patients aged 24 years. This age was the lowest verified. In the case of the oldest patient, it was found that she was 87 years old. It was found that 50% of patients were under 49 years old, 25% were under 42 years old and 25% were over 60 years old. These measurements are known as quartiles, respectively, 2nd quartile or median (Q2), 1st quartile (Q1) and 3rd quartile (Q3).

Figure 1 – Boxplot graph of the ages of patients with cervical cancer undergoing radiotherapy (the Statistical Software Minitab®19 was used)



Analysis of other sociodemographic variables revealed that the majority of patients were married (38.3%). Regarding the ethnicity reported by the patients, the highest frequency was white (56%), followed by mixed race (33.2%). As for education, more than half did not complete primary education (61%), of these 6.9% had no education, only 2.4% completed higher education. It was observed that many patients were not alcoholics (91.6%), and 5.5% declared themselves alcoholics and 2.2% former alcoholics. When analyzing the characteristics of the study population according to some risk factors associated with cervical cancer, it was observed that 32% of patients are smokers and 10.6% are ex-smokers. Regarding the number of sexual partners, the majority of patients in the study reported having had relationships with four or more partners throughout their lives (32.9%) and the minority (14.5%) reported having only one sexual partner **(Table 2).**

Table 2 - Distribution of patients with cervical cancer undergoing radiotherapy treatment, according to socio-demographic data and risk factors.

Characteristics	Patients (n)	Percentage (%)
Year of Diagnosis		
2009	197	48,4%
2010	210	51,6%
Marital Status		
Single	92	22,6%
Married	156	38,3%
Widow	65	15,9%
Judicially separated	50	12,3%
consensual union	1	0,2%
No information	43	10,7%
Ethnicity/Race		
White	228	56,0%
black	44	10,8%
brown	135	33,2%
Education		
None	28	6,9%
Elementary Incomplete	220	54,1%

Characteristics	Patients (n)	Percentage (%)
Elementary Complete	74	18,2%
Middle level	70	17,2%
Incomplete Higher	5	1,2%
Complete Superior Level	10	2,4%
No information	-	-
Alcoholism		
Never	373	91,6%
Former consumer	9	2,2%
Yes	22	5,5%
No information	3	0,7%
Smoking		
Never	233	57,2%
Ex smoker	43	10,6%
Yes	130	32,0%
No information	1	0,20%
Number of Partners		
01	59	14,5%
02	127	31,2%
03	83	20,4%
≥04	134	32,9%
No information	04	1,0%

The results regarding the distribution of the characteristics of the study population according to factors related to diagnosis and clinical staging are shown in **Table 3**. Regarding staging, the range of IIB (41.9%) and IIIB (33. 7%) was predominant, representing 75.6% of all cases, while in IB they accounted for 19.9% of patients. In patients with more advanced stages IVA and IVB, 0.4% were found. Regarding histological type, squamous cell carcinoma was the most common (84%), followed by adenocarcinoma (12.8%).

Table 3 – Distribution of patients with cervical cancer in post-radiotherapy follow-up, according to clinical staging and histopathological classification.

Characteristics	Patients (n)	Percentage (%)
Clinical Staging		
IA	1	0,2%
IB	81	19,9%
IIA	13	3,2%
IIB	170	41,9%
IIIA	3	0,7%
IIIB	137	33,7%
IVA	1	0,2%
IVB	1	0,2%
Total	**407**	**100%**
Histological Type		
Squamous Cell Carcinoma	342	84,0%
Adenocarcinoma	52	12,8%
Unknown	13	3,2%
Total	**407**	**100%**

Considering the follow-up of patients for a minimum period of 5 years and a maximum of 7 years, with entry registration starting from January/2009 to December/2010 and completion of follow-up in December/2015, of the 407 patients included in the study during this period, it was It was observed that 99 (24.3%) patients died. **Table 4** presents the list of associations between types of treatments and death, where in this table, censored cases represent patients who did not die (alive). Most patients underwent radiotherapy concomitantly with chemotherapy and the combination of radiotherapy with other forms of treatment increased the patients' survival rate.

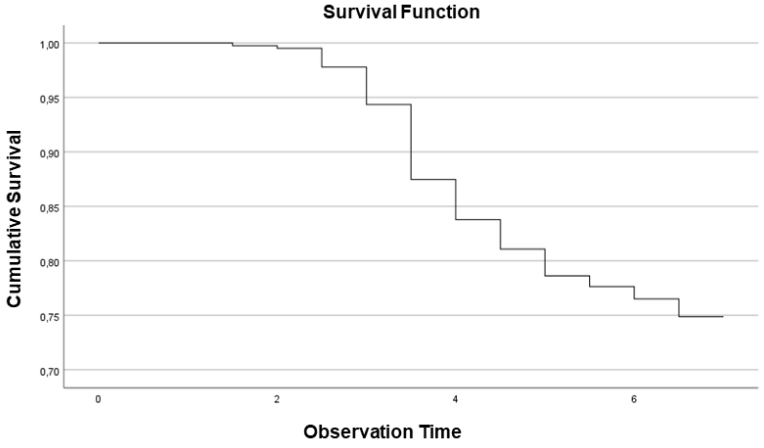
Table 4 – Distribution of patients with cervical cancer in relation to associations between types of treatment and death.

Treatment	Total (n) Patients	Events (n) Deaths	Censorship	
			Patients (n)	Percentagem (%)
1	35	15	20	57,1%
2	334	79	255	76,3%
3	6	1	5	83,3%
4	32	4	28	87,5%
Total	407	99	308	75,7%

Treatments: *1- Exclusive radiotherapy. 2- Radiotherapy + Chemotherapy. 3- Radiotherapy + Surgery. 4- Radiotherapy + Chemotherapy + Surgery*

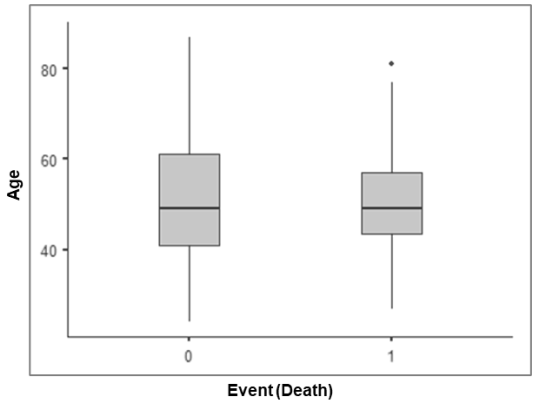
Considering that over the observation period (5 to 7 years) 99 deaths were identified, the overall survival rate was 75.7% and the free survival rate was 69.5%. The frequency of recurrence in the cases analyzed was 11.8%. **Figure 2** shows the graph with the KM survival curve of patients undergoing radiotherapy during the observation times (in years).

Figure 2 – Graph showing the survival analysis of patients undergoing radiotherapy for cervical cancer (Kaplan-Meier Curve)



The event of interest (death) is coded in **Figure 3**, which presents a graph (outlier), with the values: 0 = non-death (patients alive / censored) and 1 = (event / death) in relation to age, where they are demonstrated, the average ages for the events are approximately equal (0 = 51.4 and 1 = 51.1). We can observe that 6% of patients who received exclusive radiotherapy survived and 15% died. In the association between radiotherapy and chemotherapy, the frequency of deaths (80%) was close to survival (83%).

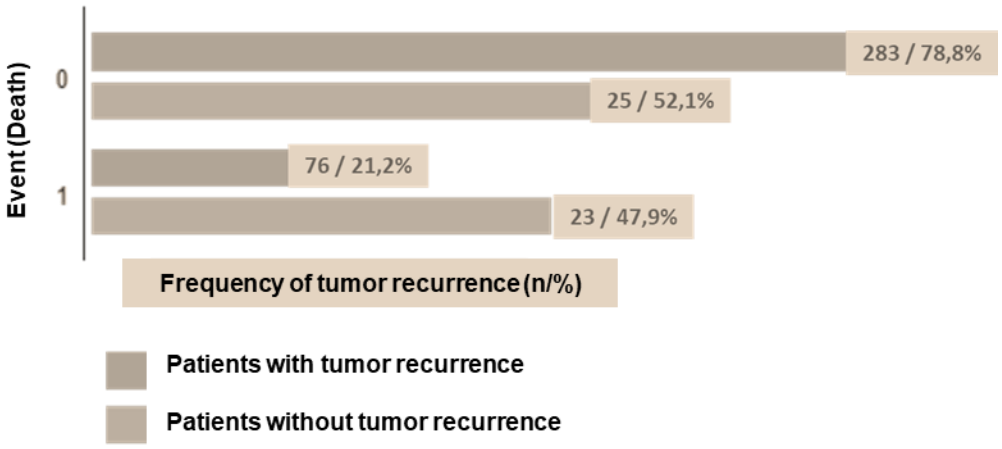
Figure 3 – Distribution of age in relation to the event (death) of patients undergoing radiotherapy for cervical cancer.



Event 0 = non-death (censored / patients alive). Event 1 = death

When analyzing the frequency of recurrence, it was observed that 24.3% of the study patients (n=48) presented neoplastic atypia in post-radiotherapy follow-up, of which 47.9% (n=23) died. Of the 359 patients who did not present a recurrence during follow-up, 21.2% (n=76) died. In the graph shown in **Figure 4**, it is possible to observe the frequency of recurrence cases in relation to the event (death).

Figure 4 - Distribution of recurrence cases in relation to the event (death)



Regarding cytopathological analysis, the total number of conventional cytologies performed by the 407 post-radiotherapy patients was 2168, with an average of 5 cytologies per patient. Regarding the quality of the cytopathological smears, 68% (n=1475) were satisfactory for the oncotic evaluation, 26.8% (n=581) were limited (when there is some interference, however, it does not make the diagnosis unfeasible), where the main reasons were, respectively: thick, hemorrhagic, purulent, fibrosis/necrosis, atrophy/degeneration. **Table 5** shows that 5.2% of the results were unsatisfactory for the oncotic evaluation, where the main reasons were, respectively: purulent, hemorrhagic, thick, scanty and dry, more than half (61.2%) presented actinic effects (compatible with post-radiotherapy changes).

Table 5 – Distribution of the results of cytopathological tests performed by the patients included in the study, regarding the presence of actinic effects.

Examinations Conducted	EA		NE		UNSATISFACTORY		TOTAL	
	n	%	n	%	n	%	n	%
1ª Cytology	269	12,4	100	4,6	38	1,8	407	18,8
2ª Cytology	270	12,5	114	5,2	23	1,1	407	18,8
3ª Cytology	238	11,0	103	4,7	15	0,7	356	16,4
4ª Cytology	185	8,5	99	4,6	13	0,6	297	13,7
5ª Cytology	161	7,4	89	4,1	11	0,5	261	12,0
6ª Cytology	117	5,4	86	3,9	02	0,1	205	9,4
7ª Cytology	56	2,6	65	3,0	06	0,3	127	5,9
8ª Cytology	25	1,2	41	1,9	03	0,1	69	3,2
9ª Cytology	02	0,1	26	1,2	01	0,0	29	1,3
10ª Cytology	04	0,2	04	0,2	00	0,0	08	0,4
11ª Cytology	00	0,0	02	0,1	00	0,0	02	0,1
TOTAL	**1327**	**61,2**	**729**	**33,6**	**112**	**5.2**	**2168**	**100**

EA = With actinic (radiotherapeutic) effects. NE =No actinic (radiotherapeutic) effects

Figure 5 shows microscopic images of conventional cytology's with actinic changes (post radiotherapy) in cytopathological smears negative for malignancy. The changes highlighted by red arrows are: binucleation (Figure 5A), dyskeratosis (Figure 5B), prominent nucleolus (Figure 5C) and intracytoplasmic vacuolation (Figure 5D).

Figure 5 – Micrographs performed under optical microscopy (400x magnification) demonstrating actinic effects in benign cells (conventional post-radiotherapy cytology). A - binucleation B - dyskeratosis. C - prominent nucleolus. D - intracytoplasmic vacuolation.

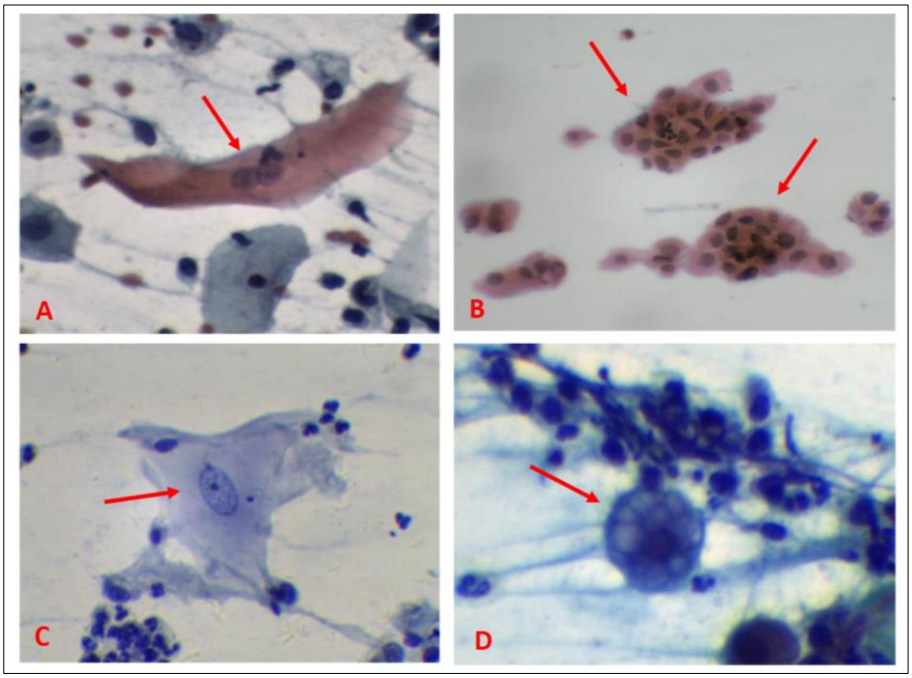
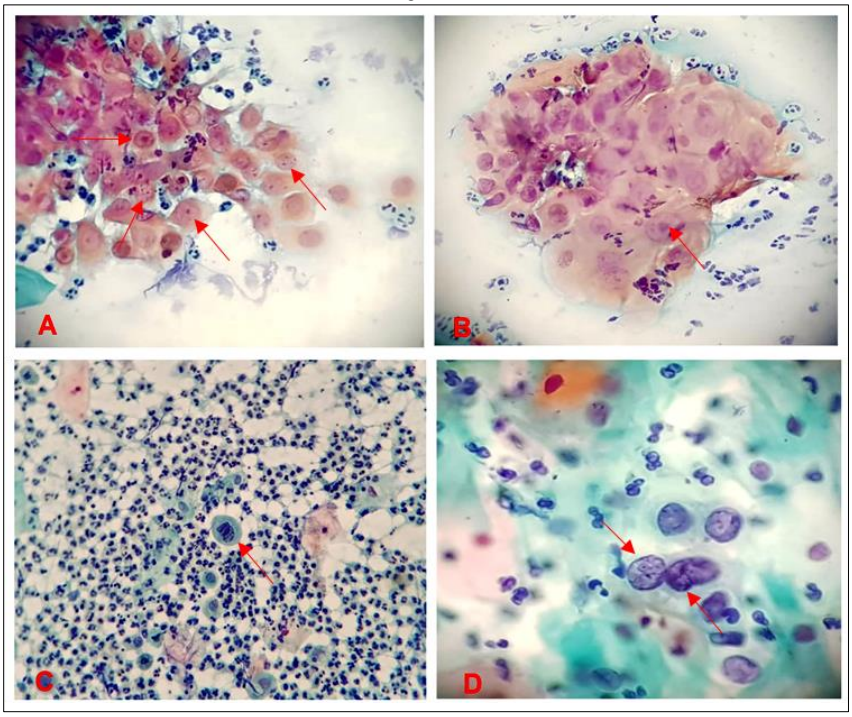


Figure 6 shows cells with dikaryotic atypia in cytopathological smears positive for malignancy from stage 1 patients. The highlighted atypia are: multiple nucleoli, anisonucleolosis (Figure 6A), macronucleoli (Figure 6B), inversion of the nucleus-cytoplasmic relationship in favor of the nucleus, hyperchromatism, irregularity in the nuclear contour (6C), thickening of the nuclear membrane and clumped chromatin (6D).

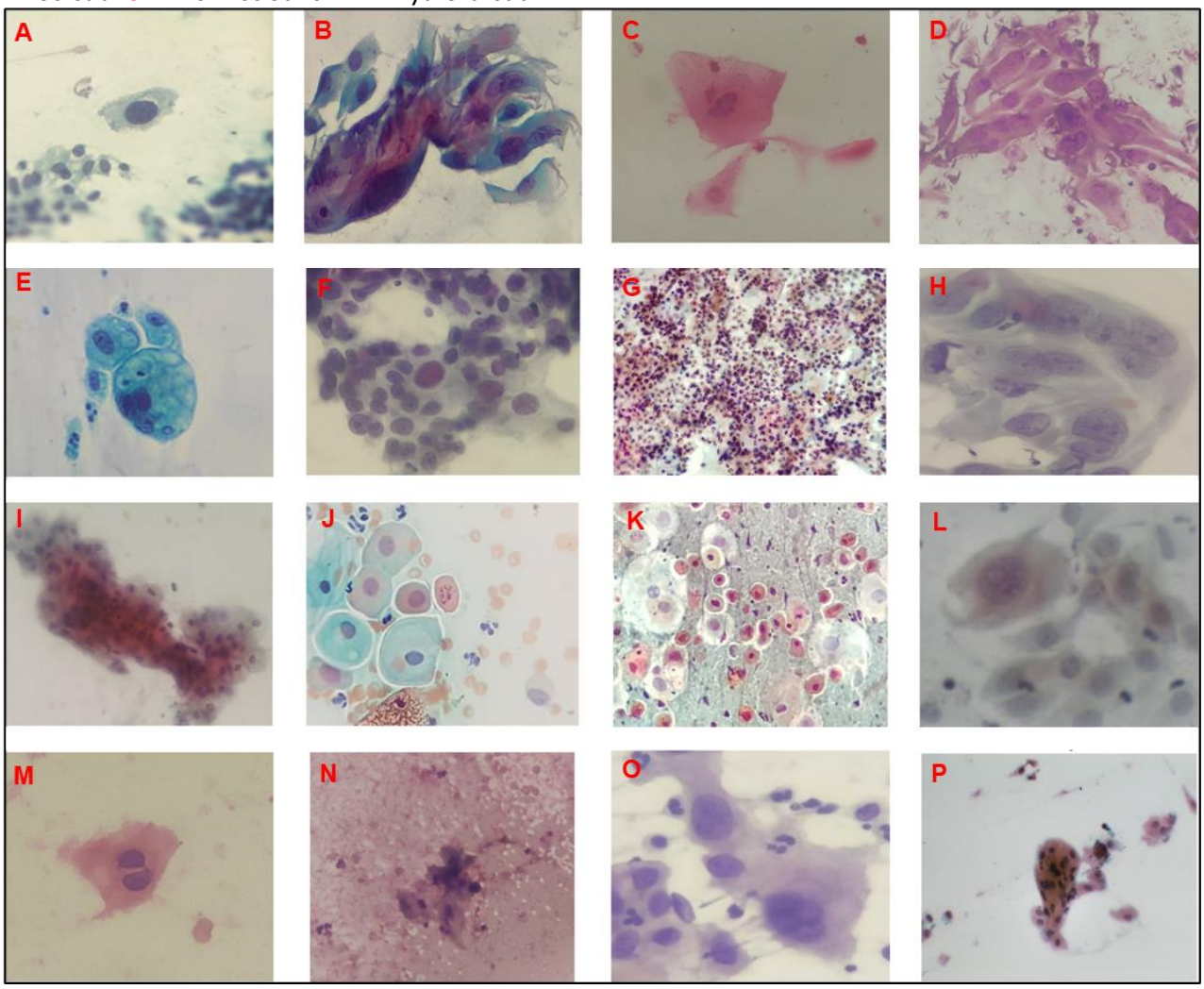
Figure 6 – Micrographs performed under optical microscopy (400x magnification) showing atypical cells in smears positive for malignancy from post-radiotherapy patients. A - Multiple nucleoli and anisonucleolysis. B – Macronucleolus. C - Inversion of the nucleus-cytoplasmic ratio in favor of the nucleus, hyperchromatism and irregularity in the nuclear contour. D - Thickening of the nuclear membrane and chromatin in lumps.



Regarding the monitoring of cytopathological diagnoses after radiotherapy, of the 2168 smears analyzed, 5.2% / (n=112) presented inadequate quality (unsatisfactory for oncotic assessment), the main reasons for inadequacy were: purulent, hemorrhagic, thick, paucicellular smear , scarce or acellular, excluding these cases and considering that the number of cytology tests per patient varied from 2 to 11, the majority of cases (84% / n=1725) were negative for neoplastic cells, 0.7% (n=15) presented atypical squamous cells of undetermined significance throughout follow-up, 7.1% (n=150) presented atypical glandular cells of undetermined significance at some point during follow-up, 2.7% (n=56) evolved into an intraepithelial lesion and 1, 2% (n=24) were positive for malignancy. It is important to highlight that 4.2% (n=86) of the cases presented atypia that did not meet the criteria for malignancy, however the changes described as post-radiotherapy effects generated significant doubts, requiring repeat collection for cyto-oncotic reevaluation, and were described as dubious.

Figure 7 shows the main actinic changes in conventional cytology smears stained by the Papanicolaou technique, the most frequent were, respectively: nuclear activation (Figure 7A), cytoplasmic increase (Figure 7B), cellular gigantism (Figure 7C), cellular pleomorphism (Figure 7D), cytoplasmic vacuolation (Figure 7E), anisokaryosis (Figure 7F), leukocyte infiltrate (Figure 7G), macro and multiple nucleoli (Figure 7H), amphophilia (Figure 7I), karyorrhexis (Figure 7J), nuclear pyknosis (Figure 7K), nuclear vacuolation (Figure 7L), binucleation (Figure 7M), necrosis (Figure 7N), multinucleation (Figure 7O) and dyskeratosis (Figure 7P).

Figure 7 – Actinic alterations present in the cytopathological smears of the study group (optical microscopy, 400x magnification). A - Nuclear activation. B - Cytoplasmic increase. C - Cellular gigantism. D - Cellular pleomorphism. E - Cytoplasmic vacuolation. F – Anisokaryosis. G - Leukocyte infiltrate. H - Macro and multiple nucleoli. I – Amphophily. J – Karyorrhexis. K - Nuclear pyknosis. L - Nuclear vacuolation. M – Binucleation. N – Necrosis. O – Multinucleation. P – Dyskeratosis.



Discussion

Guidelines for the early detection of cervical cancer were implemented in Brazil in the 1980s by the Ministry of Health. These initiatives included the recommendation of the Pap smear during routine gynecological consultations, as part of the Comprehensive Health Care Program of Women in 1984. In 1986, the Oncology Program conceived a project to expand the prevention and control of cervical cancer, aiming to integrate existing programs and create a network of services at different levels of care[1,17].

In the mid-1990s, with the implementation of the Unified Health System (SUS), the Viva Mulher program was developed to control cervical cancer. In 1999, more prevention and control actions were added, but it was only in 2003 that this process was significantly strengthened. Finally, in 2005, the National Cancer Care Policy established goals to be met by federal agencies in cancer control[2,18].

However, issues such as low education and low income have been described in several studies as characteristics of the population affected by this neoplasm and are reinforced in this study[12,19]. White race/ethnicity was the most common in our study population. In studies related to other regions of Brazil, this data is different, as in the state of Pernambuco, 75.2% were of African descent (black + brown) and 23.8% were white, in the State of Acre, studies show the predominance of brown people (73.3%) white women account for around 16.7%[5,12].

According to Rama (2008)[20] in the city of Campinas / SP, the majority of those with cervical cancer are white women, followed by black and mixed-race women. Certainly, issues related to climate, colonization, geography, racial mixing in each region also influence self-declaration due to the characteristics of different races in the individual. Based on Barreto (2012)[21], radiotherapy is the most recommended treatment for patients with advanced cervical cancer. All patients included in the study underwent the complete radiotherapy protocol, which involved the combination of external radiotherapy: megavoltage at a dose of 45 to 50 Gy, in 25 fractions, followed by intracavitary brachytherapy: high dose rate (HDR), with micro source of Iridium 192, generally with 3 insertions of 8Gy, at weekly intervals, totaling 80Gy.

De acordo com a literatura, ainda não há consenso sobre a melhor metodologia, no que se refere ao fracionamento e início da braquiterapia, embora algumas diretrizes já tenham sido recomendadas pela Sociedade Americana de Braquiterapia[22]. Alguns autores citam a dose de 30 Gy em 5 inserções semanais de braquiterapia de alta taxa de dose, no ponto A, podendo a dose alcançada, neste ponto, ser superior a 85 Gy, nos casos avançados[23,24].

There is substantial evidence supporting the use of radiotherapy, with or without chemotherapy, in definitive and postoperative settings. Brachytherapy plays a crucial role in definitive treatment, and volumetric planning is widely recommended. Intensity modulated radiotherapy (IMRT) can be employed to minimize acute and late toxicity. Therefore, the use of radiation continues to be an essential component for women with cervical cancer to achieve a cure[11].

For several years, exclusive radiotherapy was proposed as standard treatment, however, the duration of radiotherapy treatment was considered the main determining factor in the response and evolution of the disease[25]. From 1999 onwards, several randomized articles published demonstrated survival gains with the addition of chemotherapy to radiotherapy; concomitant chemotherapy and radiotherapy treatment began to be considered standard treatment in advanced stages[22,25–27,27].

In this study, the majority of patients were treated with a combination of radiotherapy and chemotherapy. Surgery was associated with radiotherapy in only 1.5% of patients and concomitantly with radiotherapy and chemotherapy (7.9%). Exclusive radiotherapy was the treatment performed in 8.6% of patients.
When monitoring patients with cervical cancer undergoing radiotherapy, cytopathology is an important tool for controlling the effectiveness of treatment by detecting residual, recurrent neoplasms or benign reactional changes[10,25,27].

Radiation can cause both morphological and molecular changes in cancerous and non-cancerous cells due to its interference in the structures and functionalities of nucleic acids, mitotic activity and cytochemical changes, leading to the denaturation of proteins and the release of enzymes, resulting in cellular degeneration[10,11,26,28].
In the population of the present study, more than half of the cytologies showed actinic effects (61.2%) post-radiotherapy. The most frequent findings are similar to those described in the literature: nuclear enlargement/activation, cytoplasmic enlargement, cellular gigantism, pleomorphism, cytoplasmic vacuolization,

anisokaryosis, leukocyte infiltrate, macro and multiple nucleoli, anisonucleolosis, amphophilia, karyorrhexis, nuclear pyknosis, nuclear vacuolization, necrosis , binucleation, necrosis and multinucleation[10,13,14,16,29].

Several authors describe cases of cellular changes induced by radiation that persist for many years. These chronic changes may include increases in cytoplasmic quantity (cytomegaly), nuclear increase (karyomegaly) without changes in the nuclear to cytoplasmic ratio, mild hyperchromasia, neutrophilic invasion and polychromatic cytoplasmic staining[10,26,30].

Zannoni et al. (2008)[12] demonstrated in their work, which included 50 women with a histological diagnosis of advanced cervical carcinoma, submitted to radiotherapy, that the residual neoplastic cells presented a wide pattern of cytoplasmic and nuclear changes, the most common cytoplasmic changes were: eosinophilia, vacuolization and pleomorphism. In addition, the nuclei were enlarged and irregular, with clumped chromatin and prominent nucleoli.

There is a consensus that some benign cells with actinic changes could be confused with atypical cells from recurrent lesions, which could lead to a false-positive diagnosis[9,10,13,27]. On the other hand, smears from irradiated patients may also show radiation-effect tumor cells, and these changes must be carefully differentiated from radiation changes in benign cells[10,13,16,29,30].

The cytologies included in this study with intense radiotherapy changes were reviewed by more than one experienced professional. Based on the analysis of the frequency of recurrence, it was observed that of the patients in the study, 24.3% (n=48) presented neoplastic atypia in post-radiotherapy follow-up, of which 47.9% (n=23) died.

In work carried out by Shield (1995)[26], which evaluated the action of cytopathology for the detection of recurrent cervical carcinoma after radiotherapy, revealed that the cytopathological diagnosis of carcinoma was present in 32.8% (23/70) of cases with histological confirmation.

Post-radiotherapy recurrence rates increase according to tumor staging, stages III and IV are more likely and can have an incidence of 60% - 80%[12,31], in our study, the majority of patients were in stage IIB (41.9%) and IIIB 33.7%).

Upon completion of the work carried out by Barreto (2021)[21], where he analyzed survival and prognostic factors in patients with invasive cervical cancer, only clinical staging was a prognostic factor in the evolution of the disease, with statistical significance. The other variables analyzed, such as age, histological type and grade, duration and modality of oncological treatment, did not demonstrate an association with the response obtained at the end of the initial treatment, nor with the patients' overall survival.

Survival analysis is important when the time between exposure and event is of clinical interest[5,21]. When monitoring irradiated patients in the study, over a period of 5 to 7 years, we observed an overall survival of 75.7% and the disease-free survival rate was 69.5%.

In work published by Mayer et al. (2004)[32], involving 210 patients in stages: IIA=10, IIB=113 and IIIB=87, treated with external radiotherapy and high dose rate brachytherapy, in two modalities: sequential (4 insertions 8 Gy) and continuous (5 insertions 6 Gy), observed a 5-year disease-free survival of 71% for the continuous group and 56% for the sequential group.

Windschall et al. (2005)[33], described that the treatment of recurrent lesions has limited results, with chemotherapy and radiotherapy being indicated, with surgery being an eventual option. In this study, an overall survival rate of 39% was reported for patients who presented central recurrence, but also presented a good result. with radiochemotherapy for small volume pelvic recurrences.

Although cervicovaginal cytology is considered a low sensitivity method, it is an important test for the diagnosis of local recurrence after radiotherapy and can provide an early diagnosis of tumor recurrence or persistence, in some cases before the onset of clinical signs[26,31].

Conclusion

Analysis of the epidemiological profile of the study population revealed the average age of 51 years, with an age range primarily from 41 to 50 years, with risk factors associated with the habit of smoking present in 32% of patients. Considering that all samples were performed using conventional cytology, stained using the Papanicolaou technique, the number of unsatisfactory cytological exams for cyto-oncotic evaluation was 5.2%. Of the exams with satisfactory quality for analysis, more than half (64.9%) showed actinic effects (post-radiotherapy.

The main actinic effects (post-radiotherapy changes) observed in the smears were: nuclear activation, cytoplasmic increase, cellular gigantism, cellular pleomorphism, cytoplasmic vacuolization, anisokaryosis, leukocyte infiltrate, macro and multiple nucleoli, amphophilia, karyorrhexis, nuclear pyknosis, nuclear vacuolization, binucleation, necrosis, multinucleation and dyskeratosis. Regarding the incidence of locoregional recurrence, a frequency of 11.8% of cases was observed, of which almost half of the patients died. The analysis of locoregional recurrence impacts disease-free survival, which in our study was 69.5%. The overall survival found in the analyzed population was 75.7%, although several studies presented an approximate percentage, there is no consensus in the literature. However, it is important to highlight the influence of variables such as clinical staging, age and type of treatment on overall and disease-free survival.

The difficulties related to actinic (radiotherapy) effects show the importance of the experience of professionals involved in the analysis of irradiated cells and reflection on the subjectivity of the method. Observing these changes is useful for evaluating the impact of actions taken during the period and planning future actions.

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