

## Anus neoplasm: study of a case series

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**ABSTRACT:** Anus neoplasm accounts for 2 to 4% of colorectal tumors, being more prevalent around the seventh and the eighth decades. Females are mostly affected, and the ratio is 3:1. Its increased prevalence amongst the population in the past years is probably related to the higher number of people that are affected by sexually transmitted diseases, mainly human papillomavirus (types 16 and 18, mostly) and/or the human immunodeficiency virus. Diagnosis is based on clinical findings and anatomopathological tests. The treatment of choice is radiochemotherapy, and the rescue surgery with abdominoperineal resection is used for recurrence and persistence cases. A retrospective and prospective longitudinal observational study was performed with 11 patients diagnosed with anal neoplasm from 2004 to 2010. Six (54.5%) were females and five (45.5%) were males. The incidence was higher in the sixth decade, at the mean age of 54.45 years. The most frequent histological type observed was the epidermoid carcinoma, and the most frequent cell differentiation type was the moderately differentiated. Chemotherapy associated with radiotherapy was used in 81.9% of the patients, and abdominoperineal resection was necessary as a rescue surgery in 18.2% of the patients.

**Keywords:** anus neoplasms; diagnosis; chemotherapy; radiotherapy; surgery.

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### INTRODUCTION

The anus neoplasm is not prevalent in the population, and corresponds to 2 to 4% of the neoplasms that affect the large intestine<sup>1</sup>.

It is more prevalent after the sixth decade of life, and some of the risk factors associated with the neoplasm are: infection by the human papillomavirus (HPV), subtypes 16 and 18, smoking and immunosuppression; it is also more prevalent among patients who have the human immunodeficiency virus (HIV) around the third and fourth decades of life, due to the immunologic depression<sup>2-8</sup>.

In a study conducted in Sergipe, which involved almost all databases of pathology laboratories in the State, the incidence rate ranged from 0.18 to 0.83 per 100,000 people, with mean age of 63.8 years; also, there is the proportion of 3.3 women for each man who have the anal carcinoma<sup>3</sup>.

Even if some patients are asymptomatic, more than half of the anus neoplasm cases present with bleeding. Besides, other findings may be present, such as pruritus, mucus discharge, changes in bowel habit, anal pain and changes in stool diameter<sup>9,10</sup>.

Since 1974, with the work conducted by Nigro, the treatment of choice for cases of anus neoplasms has

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been radiotherapy associated with chemotherapy as the initial treatment, with the use of mitomycin and 5-fluorouracil; cisplatin was the alternative when mitomycin was being tested<sup>2,3,7,9,11-13</sup>. The surgical treatment with abdominoperineal resection can be used as rescue therapy<sup>2,9,11</sup>.

This paper aims to study a case series of anus neoplasm with the objective to define the profile of patients who have this condition, focusing on the diagnosis and follow-up, and also showing determined tests and treatments.

## SAMPLE AND METHOD

### Sample

It is a retrospective and prospective longitudinal observational study of the case series based on two groups. Group A was comprised of all the patients who had been diagnosed with and treated for anus neoplasm from 2004 to 2008 at the Coloproctology Service of the University Hospital of *Universidade Federal de Sergipe* (HU/UFS); Group B was prospective and comprised of all the patients who had been diagnosed and followed-up from 2009 to 2010 in the same service.

### Exclusion criteria

Patients who abandon the treatment/follow-up or those who could not be contacted were excluded from the study.

### Method

Patients in group A were analyzed by the medical records of patients who died. The living patients were contacted for a periodical review and evaluation of the studied variables.

Patients in group B were prospectively analyzed with the same variables.

- a. **Studied variables:** demographic data: (age, gender, provenance); family history, data related to the tumor (histological type, topographic location, tumor differentiation, lymphatic, neural and vascular invasion, staging); data related to the treatment (type, efficacy, recurrence, complications, treating the complications); and mortality rates.
- b. **Ethical considerations:** the project was submitted to the Research Ethics Committee of UFS.

All patients were enlightened as to the objectives of the research and signed the informed consent form. This research offered no risks or extra expenses to the subject of study. The participants remained anonymous, and his right not to answer the questionnaire was assured.

- c. **Statistical analysis:** the collected data were inserted in a database system, thus being submitted to statistical analysis with the software *Statistics Package of the Social Science (SPSS/PC+)*, version 9.0 (1998). In order to characterize the sample, simple frequency tables were used, as well the definition of median, mean and standard deviation.

## RESULTS

Eleven patients diagnosed with anus neoplasm were analyzed. Six (54.5%) belonged to Group A, and were diagnosed before 2009; five (45.5%) belonged to Group B, and were diagnosed after 2009. Out of these, five (45.5%) were males, and six (54.5%) were females.

The age of the patients ranged from 36 to 89 years, with mean age of 54.45 years median of 55 years and standard deviation  $\pm 14.45$ . Two (18.2%) patients were in the fourth decade of life, two (18.2%) were in the fifth decade, five (45.5%) were in the sixth decade, one (9.1%) were in the seventh decade, and one (9.1%) in the ninth decade.

Mean age among females was 61 years, ranging from 48 to 89 years and standard deviation  $\pm 14.63$ . As to males, mean age was 50.6 years, ranging from 36 to 59 years, and standard deviation  $\pm 10.83$ .

As to provenance, six (54.5%) patients lived in the capital, and five (45.5%) lived in the countryside.

Eight patients (72.7%) had epidermoid carcinoma, 2 (18.2%) patients had cloacogenic tumor, and one (9.1%) of squamous verrucous carcinoma.

Seven (63.6%) patients had anal canal neoplasm, and four (36.4%) had anal margin cancer. There were four (36.4%) cases of well differentiated carcinoma, six cases (54.5%) of moderately differentiated carcinoma and we could not obtain such information from one patient (9.1%).

Bleeding was observed in seven (63.3%) patients, mucus in stool was seen in six patients (54.5%),

proctalgia was present in six patients (54.5%); dizziness was observed in four patients (36.4%), pruritus, in three (27.3%), diarrhea, in three (27.3%), weight loss, in two (18.2%), and fever, in two (18.2%). Syncope, anal incontinence, purulent discharge, anemia, abdominal distention, anal mass sensation and constipation corresponded to one case each (9.1%). All patients (100%) presented with at least two symptoms each (Graphic 1).

Anuscopy was used as the diagnostic method for all patients. Ulcerative lesion was present in four medical records (36.4%), and tumor was found in seven records (63.7%).

Three patients (27.3%) had T1 tumors, four (36.3%) had T2 tumors (27.3%), one (9.1%) had T3 tumor, one (9.1%) had T4 tumor, and two (18.2%) patients had no data concerning the size of the tumor. Six patients had no lymph node compromise, one (9.1%) were in N2, one (9.1%) was in N1 and three (27.3%) had no data. One patient (9.1%) had lung metastasis. Thus, one (9.1%) was in stage I, three (27.3%) were in stage II, one (9.1%) was in stage IIIA, and one patient (9.1%) was in stage IV. Two patients (18.2%) still had not been submitted to imaging examinations, and one had T4NXMX. Two patients (18.2%) had no information concerning staging.

Nine patients (81.9%) underwent radiochemotherapy. The other two patients (18.2%) are under oncologic analysis until the present time, thus not being treated.

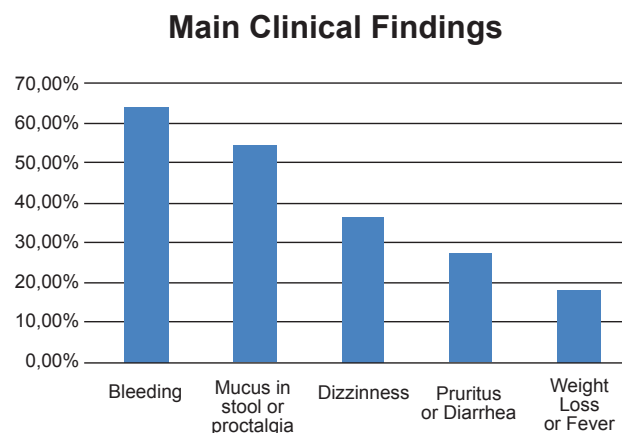
Four patients (36.4%) presented with tumor recurrence at follow-up biopsy; one of them (9.1%) had not initially adhered to the previously established treatment. Two (18.2%) underwent abdominoperineal resection for the rescue surgery, and one (9.1%) had another series of chemoradiotherapy sessions.

Three patients (27.3%) with epidermoid carcinoma presented recurrence, and one (9.1%) died. There was one case of recurrence in a patient with squamous verrucous carcinoma, and recurrence was not observed in any patient with basaloid tumor (Table 1).

One of the patients (9.1%) died and two patients (18.2%) were no longer followed-up.

## DISCUSSION

Anal canal neoplasm is not frequent in the gastrointestinal tract, corresponding to 1 to 2% of large



**Graphic 1.** Graphic showing the prevalence of clinical findings in patients with anus neoplasms.

**Table 1.** Distribution as to number of recurrences per histological subtype.

Staging	Follow-up Biopsy	
	Recurrence	No recurrence
Squamous cell carcinoma	3	5
Basaloid carcinoma	0	2
Squamous verrucous carcinoma	1	0
Total	4	7

intestine cancers, and 3 to 3.5% of anorectal tumors. In Sergipe, its incidence is 0.18 to 0.83 per 100,000 people/year<sup>3,10</sup>. In this study, this corresponded to 11 diagnosed patients who were followed-up at the coloproctology service of HU/UFS, which reinforces the idea that this is the least frequent tumor in the digestive tract. The low sample was a result of the low incidence and prevalence of the neoplasm, which made it difficult to effectively make the statistical analysis.

The anal carcinoma is more prevalent among women, at a proportion of 1.6:1 to 5:1. In our study, data analysis confirmed the prevalence of anal carcinoma among females (54.5%), at a proportion of 1.2:1<sup>2,3,14</sup>.

The anal cancer is more frequent at the seventh and eighth decades of life, and the mean age reported is 63.8 years<sup>3</sup>. The most affected age group is comprised of people in the sixth decade of life. Mean age of female patients was 61 years, from 48 to 89, and stan-

standard deviation of  $\pm 14.63$ . As to males, mean age was 50.6 years, from 36 to 59 years, and standard deviation of  $\pm 10.83$ . The three patients (27.3%) aged less than 50 years were males. There are reports regarding the increased prevalence of anus neoplasm in homosexual male patients, maybe due to the association with HPV. This fact could be the cause for a higher prevalence of anus neoplasm among men than young women<sup>3,5</sup>.

The increased incidence of anus neoplasm has been reported in urban centers, which was also found in our study, in which 54.5% of the patients lived in the capital<sup>10</sup>.

The epidermoid carcinoma was the most common histopathological finding (72.7%), followed by two patients (18.2%) with cloacogenic tumor, and one (9.1%) with the rare variable of squamous verrucous carcinoma. This is in accordance with literature, in which the epidermoid type is more prevalent, followed by the cloacogenic tumor<sup>3,14</sup>. It is important to emphasize that we observed the squamous verrucous carcinoma in our series, which is a rare variable of the epidermoid carcinoma that can manifest as a mass that resembles a cauliflower, pale rose, at the anal margin or anal canal. Histopathological examination shows a well differentiated lesion that can invade subjacent tissues, despite being apparently benign<sup>9</sup>. The squamous verrucous carcinoma in the series was well differentiated, as demonstrated in literature. The anal canal is the most affected site, which is also in accordance with our study<sup>10</sup>.

About 20% of the patients affected by the anal canal tumor are asymptomatic, and the most common clinical finding is bleeding<sup>2,10</sup>. The mass sensation and/or rectal pain correspond to 30% of the patients with neoplasm. Other findings include pruritus, anal incontinence, changes in bowel habit and mucus discharge<sup>4</sup>. No patient was asymptomatic at diagnosis. Thus, bleeding was present in 63.7% of the patients, proving to be the most common finding. Mass and/or anal pain were observed in 36.4% of the patients, as described in the review. Such symptoms and signs are also present in other conditions, such as fissure and hemorrhoid, which are important for the differential diagnosis of anal neoplasm<sup>9,10</sup>.

The anus neoplasm diagnosis is based on anamnesis and physical examination. Anuscopy is essential for the diagnosis, to be confirmed by the lesion biopsy

that will define histological type and level of differentiation<sup>10</sup>. This routine was adopted to diagnose the lesions of all patients in the present series. Anuscopy not only defines if the lesion is anal canal or anal margin, but also describes the aspect of the lesion, which was ulcerous in four cases, and its size, which is important for staging.

The size of the tumor is an important prognostic factor<sup>10</sup>. Despite the few patients in this series, the only one who had a T4 tumor was the same person who had the worst prognosis, developing recurrence after radiochemotherapy, thus being submitted to abdominoperineal resection to rescue, confirming this observation.

About 50 to 60% of the patients have T1 and T2 tumors, with survival rates of 80 to 90%. In our study, 63.3% of the cases corresponded to these sizes<sup>4</sup>.

The patient in stage IV (9.1%) with distant metastasis showed recurrence to radiochemotherapy, with posterior abdominoperineal resection, which shows the prognostic importance of staging<sup>10</sup>. Five of them (45.5%) presented incomplete data as to TNM grading, which is partly due to lack of information in medical records (27.3%), and also because (18.2%) these patients were still being clinically investigated.

As to staging, the thoracic x-ray and the computed tomography of abdomen and pelvis were used. Recently, the importance of the endorectal ultrasound has been increasing, since it enables to define the level of invasion in the anal wall and to assess perirectal ganglion to define ganglion metastasis. At the moment, we still do not dispose of this examination for semiologic complement<sup>10</sup>.

In spite of the liver being the most common location of distant metastasis, according to literature, the lung was the only location (9.1%) affected by dissemination in our study<sup>4</sup>.

There are other important factors in prognosis, such as histological type, anemia, irradiation dose and gender. Epidermoid carcinomas have more chances of therapy failure and causes more obits than the cloacogenic subtype, which is confirmed in our study, in which three patients with squamous cell carcinoma had recurrence, and no cloacogenic presented therapy failure<sup>10</sup>.

Since Nigro's study from 1974, in which radiochemotherapy would at first be used as a neoadjuvant

therapy for the abdominoperineal resection, until there was no residual lesion in the response, the treatment with 5-fluorouracil and mitomycin with radiotherapy became essential to resolve anal neoplasm, thus going through changes with time as to doses and number of radiochemotherapy sessions<sup>9,10,12,13</sup>. Such therapy was used for 9 (81.9%) patients, thus becoming the treatment of choice. The other two cases (18.2%) are still in oncologic evaluation.

The role of the rescue surgery for a recurrent or persistent disease is still relevant, besides the palliative care for the anus neoplasm. Two (18.2%) out of the three patients who presented with recurrence underwent abdominoperineal resection<sup>2,11</sup>.

Predisposing factors for anal tumor are usually infection by HPV subtypes 16 and 18<sup>4,5,8</sup>. Thus, detecting and eliminating HPV clinical and subclinical lesions may provide better prognosis and prevent the tumor from becoming malignant<sup>15</sup>.

Genetic studies may be used in the future to track patients who are more prone to anal canal and anal margin neoplasm. Studies have tried to establish the relation between genetic changes and anus neoplasm. Such studies showed the increased expression of 14-3-3 $\sigma$ , inhibitor regulator of p53 in its association with anus neoplasm. However, there is no relation between this protein and p53, or the association of the neoplasm with p16<sup>16,17</sup>.

A significant part of the medical records had incomplete data as to staging, although the patients had been properly staged at diagnosis, undergoing radiochemotherapy. The need to computerize the information of medical records is urgent, so that important

data concerning the patients' follow-up cannot be lost. Since we are dealing with a university hospital, such fact makes it difficult to access the information and conduct scientific work. The American Joint Committee on Cancer (AJCC) observes that "the classification and the staging of cancer enable doctors and cancer registers to stratify the patients, which will lead to better decisions as to treatment and the development of a common language"; this organizes the assistance to patients and the therapy of choice, analyzing prognosis, enabling the professionals to change experiences and assess therapy results<sup>18</sup>.

## CONCLUSION

- Seven patients were diagnosed with anal canal cancer, and four were diagnosed with anal margin cancer;
- It was more prevalent among females in relation to males;
- The incidence peak was during the sixth decade of life;
- The most frequent histological type was epidermoid carcinoma, followed by the cloacogenic carcinoma. The rare squamous verrucous carcinoma was found;
- The moderately differentiated level was present in 54.5% of the cases, and the well differentiated level was found in 36.4% of the cases;
- Radiochemotherapy was the most used technique, and the abdominoperineal resection was necessary as a rescue therapy in 18.2% of the patients.

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**RESUMO:** Neoplasias do ânus correspondem de 2 a 4% dos tumores de intestino grosso, sendo predominante nas sétima e oitava décadas. A maior prevalência é em gênero feminino, com proporção de 3:1. O aumento da prevalência na população nos últimos anos provavelmente está relacionado ao número maior de pessoas com doenças sexualmente transmissíveis, principalmente o papilomavírus humano (tipos 16 e 18, mais comumente) e/ou o vírus da imunodeficiência humana. O diagnóstico é feito a partir de achados clínicos somados ao exame anatomopatológico. O tratamento de escolha baseia-se na radioquimioterapia, sendo a cirurgia de resgate com amputação abdominoperineal utilizada para casos de recidiva ou persistência. Foi feito um estudo observacional longitudinal retrospectivo e prospectivo, com 11 pacientes diagnosticados com neoplasia anal no período de 2004 a 2010. Seis (54,5%) eram do gênero feminino e 5 (45,5%) do masculino. O pico de incidência foi em sexta década, com média de idade de 54,45 anos. O tipo histológico mais encontrado foi o carcinoma epidermoide (72,7%), sendo o moderadamente diferenciado o mais frequente grau de diferenciação. A quimioterapia associada à radioterapia foi instituída em 81,9% dos pacientes, sendo necessária a cirurgia de amputação abdominoperineal como terapia de resgate em 18,2% dos pacientes.

**Palavras-chave:** neoplasias do ânus; diagnóstico; quimioterapia; radioterapia; cirurgia.

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