



## Review Article

# Anal canal squamous carcinoma<sup>☆</sup>



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### ABSTRACT

**Background:** Anal canal carcinoma is a rare neoplasm, representing 2% of the digestive tumors, and the most common is squamous cell carcinoma, with an increasing incidence.

**Objective:** The study aims to elucidate the pathogenesis of an increasingly prevalent disease, as well as to update treatment and prognosis.

**Methods:** A literature search in *Pubmed* database, including articles from 2005 to 2015 and cross-research articles with the initial research.

**Results:** Several studies prove the role of HPV as a major risk factor in the development of squamous cell carcinoma of anal canal, as well as a greater prevalence of this neoplasia in HIV-positive people and in those who practice receptive anal intercourse. In the last two decades chemoradiotherapy remains the treatment of choice, and abdominoperineal resection is reserved for those cases of treatment failure or recurrence. Evidence advances in order to adapt the treatment to each patient, taking into account individual prognostic factors and biological tumor characteristics.

**Conclusions:** Squamous cell carcinoma of the anal canal is a neoplasm associated with HPV; therefore, screening and vaccination programs of male individuals, by way of prevention, should be started. Many studies are needed in order to achieve development in the treatment as well as in the evaluation of the biological characteristics of the tumor.

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## Carcinoma epidermóide do canal anal

### R E S U M O

**Introdução:** O carcinoma do canal anal é uma neoplasia rara, representando 2% dos tumores digestivos, sendo o epidermóide o mais comum com uma incidência crescente.

**Objetivo:** Este estudo pretende elucidar sobre a etiopatogenia desta patologia cada vez mais prevalente, assim como atualizar sobre o tratamento e prognóstico.

**Métodos:** Pesquisa bibliográfica na base de dados *Pubmed*, incluindo artigos de 2005 a 2015, assim como artigos de pesquisa cruzada com os artigos iniciais.

#### Palavras-chave:

Carcinoma escamoso

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**Resultados:** Diversos estudos provam o papel do HPV como um fator de risco major no desenvolvimento de carcinoma epidermóide do canal, assim como uma maior prevalência desta neoplasia na população HIV positiva e nos que praticam sexo anal receptivo. O tratamento continua a ser desde há duas décadas a quimiorradioterapia, reservando a ressecção abdominoperineal para casos de falência do tratamento ou recorrência. A evidência avança no sentido de adequar o tratamento a cada doente, tendo em conta fatores prognósticos individuais e as características biológicas do tumor.

**Conclusões:** O carcinoma epidermóide do canal anal é uma neoplasia associada ao HPV, logo deveria iniciar-se programas de rastreio e vacinar o sexo masculino como prevenção. Muitos estudos são necessários para evoluir no tratamento, assim como na avaliação das características biológicas do tumor.

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## Introduction

### Anatomy and histology of the anal canal

The anal canal measures approximately 4 cm in length, being shorter in women. This channel is the lower portion of the gastrointestinal tract.<sup>1</sup> Its surgical margins are the anal verge distally and the anorectal junction proximally.<sup>1,2</sup>

Histologically, in the anal canal, one can find several types of epithelia.<sup>1,2</sup> Proximally, the channel is formed by columnar epithelium similar to the intestinal epithelium, which, in the anal canal, has folds in the mucous membrane forming the anal columns. These columns are connected transversely by folds called anal valves, which, together constitute the pectineal line.<sup>1,2</sup> The non-keratinized squamous epithelium that is located distally to the pectineal line lacks hair follicles and sebaceous and sweat glands, unlike the keratinized epithelium which is continuous in the anal verge.<sup>1-4</sup> In addition, between the pectineal line and the non-keratinized squamous epithelium there is a transition zone in which the epithelium may be of the columnar, cubic, transitional (as in bladder), or squamous type. This transition zone is very specific to the anal area, and may also be called of cloacogenic zone, for embryological reasons.<sup>1-4</sup>

### Classification of neoplasms of the anal canal

Classically, the generic term “anus” comprises the anal canal and the anal verge.<sup>5</sup> Thus, neoplasms of this zone are divided between these two locations.<sup>5</sup> The tumors of the anal verge, known as perianal cancers, are identical to squamous or epidermoid cutaneous tumors, and therefore do not enter into the World Health Organization (WHO) classification of digestive tumors.<sup>5</sup> In view of the lack of clarity between tumors of the anal canal and anal verge, WHO has proposed a pragmatic definition, stating that “a tumor of the anal canal is a tumor that cannot be seen entirely with the help of a subtle pull of the buttocks”.<sup>5</sup> There are several types of tumors, depending on the type of epithelium involved, including squamous or epidermoid tumor, which is the predominant histologic type, while other rarer types include adenocarcinoma,

neuroendocrine tumors, stromal tumors, lymphomas and secondary tumors.<sup>5</sup>

Given the similarities between the epidermoid carcinoma of the anal canal and that of the uterine cervix, there is a cytological and histological classification for anal lesions similar to the classification for the cervix.<sup>6</sup> The modified Bethesda cytological classification system divides squamous anal lesions into high- and low-grade intraepithelial lesions, and these lesions still have intermediate classifications, called “probable low- and high-grade lesions”.<sup>6</sup> There is also a classification of invasive squamous cell carcinoma.<sup>6</sup>

Despite the high malignant potential of the high-grade intraepithelial lesions,<sup>7</sup> less than 1% per year will progress to cancer.<sup>3</sup>

### Epidemiology of anal canal neoplasms

Malignant tumors of the anal canal represent 0.43% of all malignancies and 2% of the digestive malignant tumors.<sup>5,8</sup> Overall, the most prevalent cancer of the anal canal is squamous cell carcinoma (85%), followed by adenocarcinoma (10%). The other types are rare, representing less than 5% of all diagnosed tumors of the anal canal.<sup>8</sup>

Anal cancer increased by 50% over the past 25 years, but this is still a rare neoplasm.<sup>6</sup> Its annual incidence has been of 1 in 100,000 people, and is higher in women. In the last two decades, a significant modification in survival after 5 years was not observed, ranging from 66% to 44% in Central and Eastern Europe, respectively.<sup>9</sup>

Most existing epidemiological information refers to squamous cell carcinoma. Thus, according to statistics, the squamous cell type is more prevalent in women, its risk increases with age (the average age at diagnosis is 60 years) and when it occurs in young, often these patients are immunocompromised.<sup>5</sup> However, the occurrence of diagnoses in increasingly younger people has been found.<sup>6</sup>

## Methods

The literature survey was conducted in Pubmed database. The phrases “epidermoid carcinoma of the anal canal” and “squamous cell carcinoma of the anal canal” were used. Only

articles published from 2005 to 2015 and performed in humans were considered. A language filter for search only in English, Portuguese and Spanish was included. Opinion articles and letters to the authors were excluded. After reading the title and abstract, and subject to an availability of the article, 36 articles were obtained in Pubmed. Articles obtained by cross-searching with the articles of the initial research and books with relevant information were also added.

## Results

### *Etiology and pathogenesis of squamous cell carcinoma*

Some risk factors have been suggested for the development of this neoplasm, particularly female gender, Human papillomavirus (HPV) infection, history of sexually transmitted disease, a number greater than 10 sexual partners, receptive anal sex history, previous history of warts or genital malignancy injuries, Human immunodeficiency virus (HIV) infection, immunosuppression, smoking, and prolonged use of corticosteroids.<sup>3,4</sup>

Over the years, it has been found that HPV infection is an important cause.<sup>10</sup> Ouhoumane et al., in a study conducted in Quebec, obtained results favoring this hypothesis.<sup>11</sup> Ninety-two percent of cases of epidermoid carcinoma were colonized with HPV, and the most prevalent type was HPV 16.<sup>11</sup>

HPV infection is the most prevalent sexually transmitted disease.<sup>12</sup> This agent is a double-stranded DNA virus with 160 different types described and with specific tissue tropism. Thirty types exhibit tropism for anogenital epithelium, and types 16 and 18 are those with greater malignant potential, although they are also involved in benign lesions.<sup>12</sup>

The pathogenesis of the lesions caused by this agent in the anal canal has been related to the pathogenesis in the uterine cervix.<sup>10</sup> Similar to what happens in the cervix, the carcinogenesis in the anal canal by HPV courses the following time sequence: Infection, persistence of infection, dysplasia development, and progression to an invasive cancer.<sup>10</sup> These steps can be reversed by the regression of the infection.<sup>10</sup>

Although the HPV life cycle in the epithelium of the cervix and in the anal canal is the same, the natural history of the intraepithelial lesions is not identical, since the anatomy, physiology, and immune response are different in the cervix and in the anal canal.<sup>6</sup>

Initially, the method that the virus uses to colonize the host is to evade the innate immunity mechanisms, particularly the physical barrier, antimicrobial peptides, Toll-like receptors, and various immune cells.<sup>6</sup> Circumventing these mechanisms delays activation of adaptive immunity,<sup>6</sup> which facilitates virus entry into cells. By integrating into the host genome, the virus will cause cellular changes that are predominantly the responsibility of two viral proteins, E6 and E7.<sup>13</sup> One of the mechanisms used to modify the cell cycle is the alteration of tumor suppressor genes.<sup>13</sup> p16 (inhibitor of kinase 4), a cell-cycle regulatory protein, interacts with CDK4 and CDK6 inhibiting the binding of these substances to cyclin D and consequently reducing its kinase activity. This inhibition prevents the phosphorylation of Rb protein, thus inhibiting the transcriptional activation by the E2F complex,

which, in turn, prevents the passage of G1 to the S phase of the cell cycle.<sup>14</sup> The E7 protein, by integrating into the genome, changes the normal p16 protein functioning.<sup>6</sup> On the other hand, E6 is responsible for suppressing the normal functioning of p53, another regulatory protein of the cell cycle and responsible for activating the transcription of genes that encode p16-like proteins.<sup>6</sup> E6 protein also promotes the activation of telomerase, perpetuating the transformation and immortalization of the cell.<sup>6</sup>

The change of p16 and p53 expression has been linked to HPV, to the point of differentiating HPV-positive and HPV-negative cancer of the anal canal based on the deregulation of the expression of these genes.<sup>13</sup> The expression of p16 is the most affected in cases of HPV infection, while p53 mutation is associated with HPV-negative carcinoma.<sup>15</sup> This distinction between HPV-positive and HPV-negative carcinoma proves to be important because there is a direct implication of the biological differences between the two types in the response to treatment and in prognosis.<sup>13</sup>

As already mentioned in this paper, HIV infection is a risk factor for squamous cell carcinoma.<sup>10</sup> Even not being a primary etiologic agent, HIV is a co-infection marker for other sexually transmitted diseases, including HPV,<sup>10</sup> and one may observe a high prevalence of co-infection by HPV in HIV-positive populations.<sup>16</sup> However, not all patients infected with HPV develop intraepithelial lesions resulting from infection.<sup>6</sup> Over the years and especially in the era of antiretroviral therapy, the carcinoma epidermoid of anal canal has become the more prevalent acquired immunodeficiency syndrome (AIDS) non-defining neoplasm in HIV-positive adult subjects, being 30 times more prevalent in this population than in the general population.<sup>6</sup> In addition to the higher incidence in relation to the general population, patients with HIV also show higher likelihood of progression to a high-grade, intraepithelial lesion-invasive, anal carcinoma.<sup>17</sup>

Another already cited risk factor is the practice of receptive anal intercourse.<sup>6</sup> Some studies have compared the frequency of high-grade intraepithelial anal lesions in HIV-positive and HIV-negative men who have anal sex with other men, and the results revealed no significant difference between these groups.<sup>6</sup> This finding may suggest that the immunological deficits in HIV infection may not play such a decisive role as had been previously thought in the development of high-grade lesions through high-risk HPV.<sup>6</sup> Some studies conducted specifically with HPV 16 found that in certain variants of the virus there is a progression to carcinoma whether or not in the presence of HIV infection and irrespective of CD4+ T-lymphocyte count.<sup>6</sup>

Those studies which were conducted in order to evaluate the impact of the immune system, particularly of regulatory CD4+ T cells, in HPV infection, focused on intra-epithelial lesions and on carcinomas of the uterine cervix.<sup>6</sup> These studies showed that these cells play an important role in the regression of infection, and consequently in the lesions caused by HPV, especially HPV type 16.<sup>6</sup> Therefore, given that the HIV infection induces immunodeficiency in CD4+ lymphocytes, the HIV infection is considered as a risk factor for infection by HPV, for intraepithelial lesions and for invasive anal carcinoma, taking into account the role of CD4+ T cells in the control and progression of HPV infection.<sup>6</sup> However, some

authors stick to the hypothesis that there are other determinants in the carcinogenesis process,<sup>6</sup> taking into account that the antiretroviral therapy did not reduce the incidence of anal cancer in people with HIV.<sup>18</sup>

### Prevention and screening

The identification of a major etiological agent, such as HPV, has allowed the development of a vaccine preventing infection by certain strains, particularly the most common and pathological, and concomitantly preventing squamous cell carcinoma.<sup>9</sup> This vaccine has been developed in order to prevent carcinoma of the cervix, however, it is anticipated it also prevents 80% of anal carcinoma.<sup>9</sup>

Based on the results of cervical cytology in the prevention of cervix carcinoma, screening programs with anal cytology and high-resolution anoscopy have been proposed for risk groups for anal cancer, including individuals practicing receptive anal sex, HIV patients, and patients with a history of anogenital malignancies caused by HPV.<sup>9</sup> In conjunction with the high-resolution anoscopy, one can add acetic acid, which differentiates low- and high-grade intraepithelial lesions, staining in white color those precursor lesions of high-grade dysplasia.<sup>19</sup>

The screening can enable the identification of malignancies in their early stage and a timely treatment, as well as the diagnosis of those precursor intraepithelial lesions, often asymptomatic.<sup>20</sup>

Anal cytology has low sensitivity but great specificity.<sup>21</sup> Inadequate specimen collection continues to be a major limitation of this test, and this procedure should be improved for making the anal cytology a recommended screening test for all patients at risk of anal carcinoma.<sup>21</sup>

### Diagnosis

Clinical history is always critical, regardless of the area of medicine, and anal cancer is no exception. One must determine all the symptoms and predisponent risk factors that could suggest this diagnosis.<sup>9</sup>

Anal carcinoma is characterized by an indolent natural history,<sup>9</sup> with a presentation of anal bleeding, the most common symptom,<sup>3</sup> often confused with a bleeding of hemorrhoidal origin, which delays diagnosis.<sup>9</sup> The second most common symptom is proctalgia,<sup>3</sup> which may be accompanied by a mass, an ulcer which does not heal, itching, mucus emission, fecal incontinence, and fistulae.<sup>9</sup> However, 20% of patients are asymptomatic at diagnosis.<sup>22</sup>

Currently, the recommended diagnostic tests are the digital rectal examination and proctoscopy, that should be carried out by an expert doctor and, if necessary, under sedation to allow for an adequate histological biopsy, a critical step to diagnosis.<sup>9,23</sup> Additionally, a diagnostic test for HIV and a CD4+ T-lymphocyte count should be carried out.<sup>23</sup>

The gynecological exam is an important procedure for female patients, in order to evaluate vaginal involvement, especially in lower and earlier tumors, as well as to rule out the presence of fistulae.<sup>9</sup> The gynecologic evaluation is also important because often synchronous and metachronous genital neoplasms related to HPV develop in the context of an anal

squamous cell carcinoma in women.<sup>9</sup> A cytology test for cervix cancer screening should also be held.<sup>23</sup>

### Staging

For the staging of neoplasia, the TNM system is used. This system is based on tumor size (T), on regional nodular involvement (N), and on the presence of metastasis (M).<sup>9</sup> Nodular involvement is assessed taking into account the distance to the primary site and not the number of nodes involved.<sup>9</sup>

Imaging evaluation is essential to assess local involvement, with the help of nuclear magnetic resonance (NMR) images or of an endoanal pelvic echography, a procedure quite effective to determine the transmural depth of the tumor, especially in the case of small T1 lesions, where this procedure shows better accuracy.<sup>9</sup> With magnetic resonance, one can obtain information on the size of the tumor, invasion of adjacent organs, and nodular involvement.<sup>9</sup>

Obtaining a thoracic and abdominal computed tomography (CT) is also desirable, in order to detect distant metastases,<sup>9,23</sup> which are present at diagnosis in 5-8% of cases.<sup>9</sup> On the other hand, one can also consider a PET (positron emission tomography) study, although this does not replace a CT scan.<sup>23</sup> However, when this procedure is performed with fluorodeoxyglucose, shows high sensitivity to detect nodular involvement, such that several studies have demonstrated a shift in the tumor stage in 20% of cases.<sup>9,22</sup> When this occurs, the trend is in favor of increasing the stage, which changes the treatment plan and influencing particularly the radiotherapy in approximately 3-5% of cases.<sup>9</sup> This technique is of importance because at diagnosis nodal involvement is found in 30-40% of cases.<sup>9</sup> Additionally, an assessment by palpation of the presence of inguinal adenopathy, particularly surface and medial ones,<sup>9,23</sup> is critical; if detected, these injuries should be biopsied by fine-needle aspiration,<sup>23</sup> as well as those increased nodes with more than 10 mm, detected on imaging studies.<sup>9</sup>

Inguinal lymph involvement is an independent prognostic factor in patients with anal carcinoma.<sup>24</sup> Therefore, to improve the diagnostic accuracy with respect to node involvement and radiotherapy regime, John Spratt in 2000 proposed a sentinel lymphatic node biopsy as a diagnostic test of ganglion micro-metastases.<sup>25</sup> At the same time, Spratt suggested that the prophylactic surgical dissection of the inguinal lymph nodes is not required, but may be curative in many cases with nodular involvement or which present a positive sentinel node biopsy.<sup>25</sup> However, due to the high false-negative rate found in some studies, this procedure is not yet part of the routine tests advised.<sup>24</sup> However, Mistrangelo et al., in 2013, in the study in which a review of clinical trials that assess the precision of this technique was performed, obtained a false negative rate of 3.7%, which was considered acceptable. These authors concluded that the procedure can be performed in patients with anal carcinoma and that this is an easy and perfectly feasible technique, with a high detection rate of 98.4% reported in the literature.<sup>24</sup>

### Treatment and complications

The main goal of treatment is to obtain a cure with locoregional control, concomitant with the preservation of anal



sphincter function and maintaining the best possible quality of life.<sup>9</sup>

Treatment of squamous cell carcinoma of the anal canal requires a multidisciplinary approach, essentially when in the presence of a state of immunosuppression.<sup>26</sup> The involvement of radiotherapists, oncologists, surgeons, radiologists and pathologists is mandatory.<sup>9</sup>

Initially, up to the 1980s surgery was the treatment for all anal carcinomas, mainly with abdominoperineal resection.<sup>9,23</sup> Several studies carried out in the 1970s<sup>26</sup> prompted the publication by Nigro et al. in 1983 of a study which concluded that combination therapy with chemotherapy and radiation therapy was effective enough to dismiss surgery if the injury would have completely regressed, and that this was proven through appropriate diagnostic ancillary laboratory tests.<sup>27</sup> This conservative therapeutic strategy allowed an excellent local control, disease-free survival, and quality of life.<sup>27</sup>

The exclusive use of surgery has a high recurrence and a survival at 5 years of 30–70%.<sup>23</sup> This strategy also presents the disadvantages of a permanent colostomy and high rates of genitourinary complications.<sup>23</sup> Chemoradiotherapy has given better results versus surgery, with fewer complications and a survival at 5 years of 61–85%.<sup>18</sup>

Thus, the standard treatment for non-metastatic squamous cell carcinoma of the anal canal has been a combination therapy, with chemotherapy using 5-fluorouracil (5FU) 750 mg/m<sup>2</sup>/day by continuous infusion and mitomycin C (MMC) 12 mg/m<sup>2</sup> on day 1 of each cycle,<sup>23</sup> and radiotherapy with a radiation typically between 50 and 54 Gy,<sup>26</sup> providing a complete regression in 80–90% of patients.<sup>9</sup> These recommendations are based on six multicenter clinical trials evaluating the results of the combined treatment.<sup>28</sup>

Abdominoperineal resection and permanent colostomy are procedures reserved for patients with residual or recurrent disease after a complete treatment of chemoradiotherapy.<sup>29</sup> Surgery after recurrence allows a local control in 60% of cases and a survival at 5 years of 30–60%.<sup>9</sup> The fact that we are in face of a radical surgical intervention, in an irradiated site, increases the risk of complications of the surgical wound.<sup>26</sup> In order to minimize these complications, a myocutaneous reconstruction using the *rectus abdominis* muscle can be held, and that was shown to be an effective technique.<sup>26</sup>

The risk of needing a permanent colostomy has been evaluated in several studies, with the conclusion that there are pretreatment independent risk factors, particularly male gender, tumor size, and hemoglobin levels, that may prove useful for prediction of combination therapy failure, with the possibility of offering to these patients the surgical treatment as an initial therapy.<sup>30</sup>

One consideration that must be borne in mind during treatment is HIV infection.<sup>26</sup> Other than immunosuppression, these patients show little tolerance to the treatment and a poorer toxicity profile.<sup>26</sup> Some studies have found that HIV-positive patients have a worse prognosis with chemoradiotherapy than HIV-negative patients.<sup>31</sup> One of the problems with the treatment are the high doses of radiation, poorly tolerated by patients with HIV. Some studies have proposed to reduce the dose commonly used in favor of less toxic levels that could simultaneously achieve the regression of the neoplasm.<sup>26</sup> Most of these patients who showed a profile of

little tolerance with routine radiation levels had a low CD4+ cell count.<sup>26</sup> Thus, some studies suggest initiating an antiretroviral therapy in order to increase the patient's CD4+ cell count to more than 200 cells/L, before starting the treatment for anal carcinoma.<sup>23,28</sup> This strategy is supported by Wexler et al., that, in their study, obtained therapeutic outcomes similar both in HIV-negative and HIV-positive patients treated with antiretroviral therapy.<sup>32</sup> However, these authors found significant toxicity in HIV-positive patients with the standardized treatment for anal carcinoma, despite the controlled viral load levels and CD4+ cell counts.<sup>32</sup> On the other hand, evidence suggests that after the implementation of the appropriate treatment of the HIV infection, the treatment for anal carcinoma is standardized, that is, a combination therapy using 5-FU and, and radiotherapy with normal radiation doses.<sup>28,33</sup>

Although we refer to the usual doses of radiation, the truth is that the optimal dose of radiation has not yet been established, nor the ideal scheme.<sup>28,34</sup> There are different approaches to radiation therapy, but in general conventional radiotherapy encompasses primary tumor and affected local lymph nodes.<sup>9</sup> A number of studies suggest that the optimal dose of radiation varies with the tumor; there are tumors that need a higher dose, as well as others that may regress at a lower dose.<sup>35</sup> Thus, a biomarker would be useful for the prediction of tumor response. Accordingly, multi-parameter magnetic resonance is used as such in other squamous carcinomas during chemoradiotherapy, and there is evidence which suggests its effectiveness in the anal squamous carcinoma as a predictor of the individual patient response, allowing an adjustment of the dose and of the radiation therapy regimen.<sup>35</sup>

Another group that should be taken into account when using radiotherapy are the elderly, as this age group may not tolerate the full dose of radiation commonly used.<sup>3</sup> This puts them at risk of being undertreated; thus, the current recommendations are that one do not evaluate the suitability of radiotherapy only taking into account the patient's age, but also assessing his/her physiological status, which has been increasingly better with the increase in mean life expectancy.<sup>9</sup>

The high toxicity of radiation therapy has stimulated the use of more conformational techniques, with a three-dimensional planning that allows a more directed approach, such as modulated-intensity radiotherapy,<sup>26</sup> which has proven to reduce morbidity in some studies, particularly in the Radiation Therapy Oncology Group (RTOG) 0529 study.<sup>36</sup> This technique achieves in a lesser degree the adjacent organs free of neoplasia, as the bladder, rectum, small intestine, genitals, femoral head, and perianal skin.<sup>9,26</sup> With the use of this technique, one can achieve a full dose in a shorter period of time.<sup>9</sup>

Brachytherapy is a variant of conventional radiotherapy but at an interstitial level, in which a high dose of radiation, directly in contact with the primary tumor, is emitted, not reaching the normal surrounding tissue, the contralateral mucosa, and the sphincter.<sup>9</sup> In isolation, brachytherapy is not recommended, but the technique can be used after a response to standard chemoradiotherapy.<sup>9</sup> However, Falk et al. in 2014 published the results of a clinical trial, in which these authors concluded that high-dose brachytherapy is an excellent

technique for specifically targeting tumors and reducing the total time total of treatment.<sup>37</sup>

The acute toxicity of radiation therapy involves primarily the skin, yielding a radiation dermatitis, hematologic complications, including myelosuppression; on the other hand, the patient may also present with fatigue and gastrointestinal complications.<sup>9,26</sup> The long-term complications can be fibrosis of the rectum and anal canal, anal sphincter dysfunction, skin irritation, vaginal atrophy, and erectile dysfunction<sup>3,35</sup>; radiation enterocolitis can also occur and is a severe, however rare, adverse side effect.<sup>38</sup>

Side effects and long-term complications of radiotherapy and chemotherapy have raised the hypothesis of using alternative treatments, such as submucosal endoscopic dissection, restricted to carcinomas *in situ*, and that has proved successful in similar squamous carcinomas in the esophagus and pharynx.<sup>38</sup>

Metastatic disease occurs in 10–20% of patients, and the most affected sites are distant lymph nodes, liver, and lung.<sup>29</sup> The less affected sites are the peritoneum, bones, brain and skin.<sup>29</sup> The 5-year survival for these patients, reported in the literature, is 18–21%.<sup>29</sup> The mean time to onset of metastatic disease was 2 years after treatment for *in situ* anal carcinoma.<sup>18</sup>

Due to the low prevalence of metastasized anal carcinoma, no clinical phase III clinical study was completed on the treatment of squamous cell carcinoma of the metastasized anal canal.<sup>26</sup> Currently, the only recommended treatment for patients with distant metastases or with local recurrence unfit for surgery is chemotherapy with cisplatin and 5-FU, due to the hematological toxicity associated with the prolonged use of 5-FU and MMC,<sup>9</sup> with a one-year survival rate of 62.2% and with a 5-year survival of 32.2%, and mean survival of 34.5 months.<sup>39</sup> Cisplatin was also studied in patients with *in situ* anal carcinoma in place of MMC, and showed similar results, and that drug can be considered for combination therapy with 5-FU, not only in cases of metastatic carcinoma as in carcinoma locally advanced.<sup>40</sup>

The treatment regimen consists of a continuous infusion of 5-FU 750 mg/m<sup>2</sup>/day for 5 days, and an intravenous dose 75 mg/m<sup>2</sup> of cisplatin on day one every 28 days.<sup>18,39</sup> Phase II studies comparing 5-FU and cisplatin with carboplatin and paclitaxel for the treatment of metastatic squamous cell carcinoma of the anal canal are underway, but with limitations, since 5-FU/cisplatin combination is most widely used, which makes difficult a direct comparison between the two combinations.<sup>18,26</sup> Trials with other chemotherapeutics that have proven effective in other squamous carcinomas are also under way.<sup>39</sup> The results reported by Kim et al. suggest that the combination of docetaxel, cisplatin, and 5-FU can be beneficial for the remission of long-term metastatic anal carcinoma, however the number of patients is again a restriction.<sup>41</sup>

Palliative surgery and radiation should be considered in the treatment of such patients.<sup>26</sup> Eng et al. showed that patients undergoing resection of metastases, notably liver, obtain better results in disease-free time and mean survival, when compared with patients not undergoing resection of metastases.<sup>23</sup> However, this procedure is not recommended, and more studies are needed to explore surgical criteria.<sup>23</sup>

Squamous cell carcinoma of the anal canal, as well as other squamous carcinomas in other sites, exhibits an increased expression of epidermal growth factor receptors (EGFR), also known as HER-1 and c-erbB-1.<sup>26</sup> Biological therapy targeting these receptors have been widely developed in the treatment of other squamous carcinomas, and recently clinical trials have been conducted in order to evaluate their effectiveness in locally advanced and metastatic anal carcinomata.<sup>23</sup>

### Follow-up

There is controversy regarding the period of time that must elapse to consider that chemoradiotherapy had failed; typically, 6 months should elapse for the occurrence of tumor regression, but in some patients, the period may be longer.<sup>23</sup>

Patients in complete remission are referred for magnetic resonance imaging every 6 months for 3 years, as evidence suggests that only <1% of tumors will recur after 3 years.<sup>9</sup> Anoscopy is highly painful in these patients undergoing radiation therapy, so this procedure is not recommended.<sup>9</sup> Any suspicious lesion should be biopsied.<sup>9</sup>

Patients undergoing abdominoperineal resection for lack of therapeutic response or recurrence should be reassessed every 3–6 months for 5 years, with a clinical evaluation. Additionally, these patients should perform a chest and abdominal CT and a pelvic NMR annually for 3 years.<sup>23</sup>

Immunodepressed patients should be evaluated every 4 weeks from the onset of treatment, in order to monitor regressions.<sup>23</sup>

### Prognosis

Poor prognostic factors for anal cancer include male gender, positive lymph nodes (especially inguinal nodes), and primary tumor >5 cm.<sup>9</sup> Skin ulceration was also identified in clinical trials as a poor prognostic factor for local control and mean survival.<sup>9</sup> Baseline hemoglobin levels were also pointed out as a prognostic factor for poor local-regional control, death, and low mean survival.<sup>9</sup> Smokers with anal carcinoma appear to have a worse mean survival, when compared to nonsmoker patients.<sup>9</sup>

In squamous carcinomas of the pharynx and larynx, a better prognosis was seen, when HPV infection and mutation of p16 were detected, with consequent abnormal expression.<sup>42</sup> Meulendijks et al. proved in their study that the presence of HPV infection and of an alteration of p16 expression in patients with squamous cell carcinoma of the anal canal also provide a better prognosis, taking into account that these patients showed better local-regional control and mean survival.<sup>15</sup>

Studies related to serum antigen from squamous carcinoma established a correlation between pretreatment serum levels and clinical classification of the tumor, nodular involvement, response to therapy, risk of recurrence, and death. Their authors concluded that elevated serum levels of antigen were related with a worse prognosis.<sup>43</sup>

## Discussion

After this systematic review, it appears that there is still much to be clarified, especially in the treatment area. Despite a rising incidence of anal carcinoma, the low number of patients and the exclusion of HIV-positive patients in clinical trials, in whom the prevalence of this disease is higher, have not allowed the completion of studies evaluating new therapies.

Recently, some studies have included patients with HIV in clinical trials,<sup>23</sup> which is crucial since there is much controversy on the possible increased toxicity with the use of the standard treatment in these patients, in addition to allowing, as already mentioned, a larger sample with more significant and generalizable results, since one of the limitations of those studies excluding patients with HIV is that they do not allow a generalization of their results to this population. Similarly, women should be included in studies that test receptive anal intercourse as a risk factor, since most studies have only reported this influence in men, excluding women with the same sexual behavior.

As stated above, a reduction of 80% of anal cancers with the administration of the HPV vaccine occurs; it appears, therefore, that the national vaccination plan should also be extended to men.

The treatment of both local and metastatic carcinoma has shown little progress in the last two decades, again thanks to the shortage of the number of patients; however, positive results begin to emerge in studies testing therapies that have proved effective in other squamous carcinomas from other sites, notably biological therapy.

The suitability of the individual use of radiotherapy, taking into account the individual prognostic factors (already mentioned) and the biological characteristics of the tumor, is a promising strategy. In line with this, more directed radiation techniques have evolved and are of extreme importance in order to reduce the toxicity, morbidity, and the impact on quality of life.

## Conclusion

Squamous cell carcinoma of the anal canal is one of the most prevalent malignancies in patients with HIV, which is a risk factor for HPV infection, which in turn is a major cause of anal carcinoma. Receptive anal sex is also an important risk factor.

Some studies have been published and continue to emerge in an attempt to find more effective and alternative cytostatic agents; however, we do not count on a sufficient body of evidence in order to replace the recommended combination of 5-FU and MMC in localized carcinomata, and of 5-FU and cisplatin in metastatic tumors.<sup>23</sup>

Many studies are needed to promote progress in the treatment of squamous cell carcinoma of the anal canal, as well as in the evaluation of the biological characteristics of the tumor that enable a prognosis of the answer to treatment, besides an individual and more effective therapeutic suitability. On the other hand, considering that this neoplasia is a preventable disease in most cases, in the future, one can count on advances

in primary and secondary prevention through vaccination and screening, respectively.

## Conflicts of interest

The author declares no conflicts of interest.

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