INTRODUCTION

Due to the advancement of antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection has become a chronic disease. HIV-infected patients have a 28-fold higher risk to be diagnosed with anal cancer. SCCA is more prevalent in men who have sex with men and it is strongly associated with human papilloma virus (HPV) infection types 16 and 18. The SCCA precursor, high-grade anal intraepithelial neoplasia or high-grade squamous intraepithelial lesion, has been found in about 30% of HIV-infected men who have sex with men (MSM). At diagnosis, the involvement of regional lymph nodes is present in 30-40% of SCCA cases, whereas 5-8% of patients have distant metastasis. Whenever possible, a loco-regional treatment is suggested, in order to preserve anal function and to maintain the best quality of life. In terms of prevention, HPV vaccine and early antiretroviral therapy are recommended to reduce the risk of developing anal cancer.

KEY WORDS: Anal cancer, Human immunodeficiency virus (HIV), Human papilloma virus (HPV), Men who have sex with men (MSM).
and they are detected in one third of MSM. However, the low incidence of anal cancer suggests that few HSILs progress to cancer each year, as they spontaneously regress or persist without progression. Cellular immune responses are one of the major mechanisms underlying HSIL regression. HIV-related CD4+ T-cell immunodeficiency is an important risk factor for anal HPV and its related lesions. HIV is also an independent risk factor for anal cancer, as it increases the risk of being infected with multiple HPV strains and increases the prevalence and persistence of HPV infection. Rates of anal squamous intraepithelial lesions (SILs) in HIV-infected MSM are detected in one third of MSM. Nevertheless, anal infection increases HPV persistence and the risk of anal cancer.

In the present review, we summarize the main aspects of anal cancer in HIV-infected patients, with a focus on treatment and screening.

**Epidemiology and Risk Factors**

Anal cancer is a rare disease (only 1.5% of GI cancers), whose prevalence is estimated to be approximately 1-2 per 100,000 individuals. However, recent studies report an increasing incidence: in 2014, it is estimated that 7,210 new cases of anal cancer and 950 deaths will be caused by this disease in the United States. The median age at diagnosis is 60 years. Main risk factors include: HPV infection; history of receptive anal intercourse and MSM. Finally, the morbidity associated with anal cancer and its treatment is significant: although local excision is a feasible option for small well-differentiated lesions, in most cases chemotherapy radiation is needed, with its potential long-term side effects, such as impotence.

The virus type that is more closely related to SCCA is HPV type 16. The progression to high-grade anal intraepithelial neoplasia (HGAIN) is strictly related to HPV 16 infection. Some authors have identified the following factors as predictors of progression: HPV 16 or HPV 18 infection, multiple HPV infections, HIV infection, older age and higher AIN grade. Few data suggest the possibility of spontaneous regression from HGAIN to lower AIN or normal cytology. Unfortunately, there is currently no good diagnostic test to distinguish HGAIN lesions that will progress to cancer from those that will not.

**Anatomy**

The anal canal extends from the anorectal junction to the anal margin. Palpable landmarks are the puborectal sling and the intersphincteric groove. The cylindric epithelium of the rectum extends to 1 cm above the dentate line, where the anal transitional zone begins; below this line, the epithelium is squamous. The anal margin is the pigmented region surrounding the anal orifice, extending to a lateral radius of about 5 cm. At diagnosis the distinction between anal canal and anal margin tumour is often difficult, so some authors have classified into 3 different regions, intra-anal, perianal and skin tumours. Proximal lymphatic drainage is to perirectal nodes along the inferior mesenteric artery; above the dentate line drainage is to internal pudendal nodes (internal iliac system); infra-dentate and perianal skin drainage to the inguinal, femoral and external iliac nodes.

**Histology**

It is possible to distinguish tumours of the anal margin, which are generally well-differentiated and more common in men, from those of the anal canal, which are poorly differentiated and more
common in women. Some authors have reported that the basaloid subtype has a higher risk of developing metastatic disease; on the other hand, the biology and prognosis of keratinising and non-keratinising tumours of the anal canal appear to be similar. Verrucous carcinomas, often described as giant condylomas of Buschke-Lowenstein, have a better prognosis than SCCA, and are usually amenable to surgical treatment.

**DIAGNOSIS**

Diagnosis of SCCA is often delayed because it often presents with bleeding, that is commonly attributed to haemorrhoids. It can also present with any combination of mass, non-healing ulcer, pain, bleeding, itching, discharge, faecal incontinence and fistulae. The diagnosis is made on biopsy-proven histology, that is mandatory, as other histologies are possible, including melanoma, adenocarcinomas, gastrointestinal cancers, neuroendocrine tumours and lymphomas. Lymph node involvement at diagnosis is observed in 30-40% of cases while systemic spread is very uncommon, with distant extrapelvic metastases recorded in only 5-8% of cases. Examination should include digital rectal examination (DRE), to examine the anal lesion and perirectal nodal involvement, and in women a vaginal examination, to determine the site and size of the primary tumour, vaginal/vaginal-septal involvement, mucosal involvement and the presence of fistulae. If there is a vaginal involvement, a defunctioning stoma is required because of the risk of an anorectal-vaginal fistula. Proctoscopy by a specialist surgeon or radiation oncologist may be appropriated to facilitate biopsy, to determine anatomical relations and to allow accurate clinical staging. Colonoscopy is not required as synchronous lesions in the proximal bowel have not been reported.

**STAGING**

Considering its indolent natural history and a low probability of metastases, SCCA is usually amenable to locoregional treatments. Magnetic resonance imaging (MRI) of the pelvis or, if not available, endoanal ultrasound (EUS), provide excellent information about tumour size, local extension and involvement of adjacent organs and lymph nodes. The TNM clinical staging system is based on the assessment of size (T), regional node involvement (N) and distant metastasis (M). Node involvement indicates the distance from the primary site rather than the number of nodes involved. Biopsy is usually performed only for palpable inguinal nodes or enlarged lymph nodes (>10 mm on Computed Tomography or MRI).

**TREATMENT**

There are many relevant factors to consider in treatment decision-making for SCCA. They can be divided into two groups: disease-related and patient-related factors. Disease-related factors include: TNM stage; site of tumour (margin, canal, rectal); extent of tumour (i.e., involvement of vagina); response to treatment (early and at 26 weeks); need for symptom control. Patient-related factors include: patient preference; age; renal function; Charlson geriatric assessment; comorbidities; current medications and performance status; socioeconomic and psychological factors; severity of initial symptoms. The European Organisation for Research and Treatment of Cancer (EORTC) has shown that skin ulceration, nodal involvement and male gender are independent variables associated with locoregional failure and reduced overall survival. The Radiation Therapy Oncology Group (RTOG) has also demonstrated that cancer diameter over 5 cm is an independent factor predicting reduced disease-free survival and overall survival. Furthermore, HIV testing is recommended to all patients. Before the introduction of HAART, HIV-positive patients showed higher toxicity resulting from chemoradiotherapy, mainly those with CD4 count <200/µl. However, more recent studies have reported similar response and survival rates in both HIV-negative and HIV-positive patients receiving HAART.

The primary aim of SCCA treatment is to cure the disease trying to preserve patient’s quality of life, especially maintaining as much as possible the anal function. Therefore, it is necessary to set up a multi-disciplinary approach, involving radiotherapists, oncologists, surgeons, radiologists and pathologists.

**Surgical treatment**

Until the 1980s, surgery was the main type of treatment for anal cancer. Then, with the advancement of a multidisciplinary approach, surgery is not considered as first-line therapy and local excision is preferred to treat small lesions (<2 cm in diameter), involving the anal margin and not poorly differentiated. Until the introduction of chemoradiation (CRT), abdominoperineal resection (APR) was considered as the primary therapy for all tumours except those amenable to local excision. However, it
is currently used only for those patients who have been previously irradiated in the pelvic region or have persistent disease or have developed locoregional failure following CRT\(^2,26\). Salvage APR is a radical surgery which expose patients to wound complications: reconstructive surgery with a vertical rectus abdominis myocutaneous flap is an effective measure to reduce this risk\(^2\).

**Chemoradiation therapy (CRT)**

The introduction of CRT almost 40 years ago was a milestone in the management of SCCA. Nigro et al first demonstrated the benefits of combined-modality therapy (CMT) in 1974\(^34\). Analogously, Flam et al showed 100% complete remission for patients treated with 5-fluorouracil (5-FU)/ mitomycin (MMC) and concurrent 30-50 Gy of radiation therapy (RT)\(^26,35\). To date 5-FU/MMC plus RT are considered the first-line therapy for SCCA\(^26\). The UK Coordinating Committee on Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups (EORTC) independently demonstrated the superiority of CRT over RT alone for locally advanced SCCA\(^36,37\). Some authors investigated the role of cisplatin to replace MMC\(^37\), but there was no evidence of increased complete response rates, improved local control and reduced overall toxicity\(^29,38,39,40\). About the RT, the patient is usually treated in the supine position with doses of at least 45-50 Gy for T1-2, N0 without a treatment gap, although a prone position is preferred in cases of exophytic tumours and higher doses are required if a treatment gap is planned\(^29\). Boost doses (ranging from 15 to 25 Gy) are used in case of a poor response\(^26\). Of course, RT may be associated with acute or chronic complications. Acute toxicities include fatigue, myelosuppression and radiation dermatitis; chronic toxicities are due to the proximity to dose-sensitive structures (such as small bowel, rectum, bladder, femoral heads, perineum and external genitalia\(^29\)) and may include radiation proctitis, small bowel enteritis, urinary and sexual dysfunctions and rare cases of pelvic insufficiency fracture\(^2\). In 1990, Intensity-Modulated Radiation Therapy (IMRT) was introduced to reduce RT chronic toxicities. IMRT is an advanced form of tridimensional planning which delivers high-dose radiation to target tissues, sparing noncancerous tissues\(^2\). Curative brachytherapy as a single modality of RT is not recommended, but may be applied as a boost following response to CRT\(^26\). Supportive care, including antiemetics, analgesia, skin care, nutrition advices and psychological support, may help to achieve the maximum tolerance to treatment. Hormone replacement therapy may be appropriate in women with iatrogenic menopause\(^26\). About 20-30% of patients present with distant metastases: the most common sites are the paraortic nodes, liver, lungs and skin. Only 10% of these patients survive 2 years or more. They can be considered for surgical salvage therapy or chemotherapy, usually a combination of cisplatin and 5-FU. Pain due to recurrent pelvic metastatic disease often requires the combined use of opiate and non-opiate drugs, sedatives and anxiolytics\(^26\).

**Treatment in HIV-positive patients**

Some authors demonstrated that HIV-positive patients with SCCA had worse outcomes than HIV-negative ones while on CRT\(^42\). Peddada et al recommended to use a lower dose of radiation (30 Gy instead of 50 Gy), with concurrent administration of 5-FU/MMC to avoid major toxicities\(^43\). Kim et al showed worse outcomes in HIV-positive patients with low CD4 count who were treated with a standard radiation dose of 50 Gy plus chemotherapy\(^44\). Hoffman et al established that patients with CD4 count >200/µl were more likely to receive the standard dose, while patients with CD4 counts <200/µl developed intractable diarrhea and moist desquamation. About 50% of them needed a colostomy; none of patients in this subgroup could complete the treatment\(^45\). With the introduction of HAART, HIV-positive patients may receive the optimal treatment for SCCA, without dose reductions\(^46\).

**SCREENING**

Given the increased incidence of SCCA in HIV-positive individuals, a systematic screening program has been proposed\(^7\). The development of this program is based on the association of anal cancer with a viral infection (HPV) and the possibility to detect precancerous lesions\(^26\). In fact, overall survival from anal cancer is significantly higher if it is treated at an early stage (5-year survival of 80% for tumours <2 cm, 45-65% for tumours >2 cm, 20% for metastatic disease\(^3\)). SCCA screening aims at detecting early cancers using regular digital ano-rectal examination (DARE) and detecting precursor lesions using anal citology-based programs with diagnostic high resolution anoscopy (HRA), to identify high-grade squamous intraepithelial lesion\(^3\). The last approach is similar to cervical cancer: in fact, similarly to the cervix, the anus has a transformation zone from squamous to columnar epithelium and this zone is the most vulnerable to dysplasia from HPV infection. Anal pap
test involves swabbing the anal canal with a moistened Dacron swab, that is placed in a liquid-based medium or fixed on a slide for cytological examination. Precancerous lesions are then classified using the same Bethesda grading system for cervical dysplastic lesions. Similarly to cervical colposcopy, HRA is requested after an abnormal Pap test to identify any dysplastic lesions and obtain a biopsy for histological confirmation. However, HRA has also significant barriers to be implemented as a systematic screening service, including low sensitivity to detect HSILs due to a large percentage of HIV-infected MSM with abnormal citology, lack of high-resolution anoscopists and no evidence from randomized controlled trials that treatment of HSILs prevents development of anal cancer. The primary care guidelines for the management of HIV-infected people from the HIV Medicine Association of the Infectious Disease Society of America recommend performing anal cytology screening in all patients with genital warts, women with a history of cervical dysplasia and/or anal receptive intercourse and MSM. In 1968, Wilson and Jungner elaborated a set of 10 criteria for appraising the viability, effectiveness and appropriateness of a screening programme: 1) the condition should be an important health problem; 2) there should be an accepted treatment for patients with recognized disease; 3) facilities for diagnosis and treatment should be available; 4) there should be a recognizable early symptomatic stage; 5) there should be a suitable test or examination for diagnosis; 6) the test should be acceptable to the population; 7) the natural history of the condition should be adequately understood; 8) there should be an agreed policy on patients that should undergo treatment; 9) the cost of case-finding should be economically balanced in relation to possible expenditures on medical care as a whole; 10) case-finding should be a continuing process and not a “once and for all” project. Unfortunately these criteria are not completely fulfilled when considering the group with the highest risk for SCCA, HIV-infected MSM. In fact, it is unclear if the treatment of HGAIN really prevents the development of invasive cancer, facilities for diagnosis and treatment are not widely available outside University clinics and research settings and, most importantly, the natural history of the disease is not well understood, because the basis of progression from HGAIN to cancer are unclear. So, most authors recommend continuous observation for AIN-1 and treatment for AIN-3, while there is no consensus for AIN-2. Therefore, it appears too early to recommend SCCA screening among HIV-infected MSM as a general policy. Furthermore, screening strategies for SCCA lack evidence of effectiveness and safety: there is no proven treatment for anal high-grade squamous intraepithelial lesions and complete excision is not possible without unacceptable morbidity.

CONCLUSIONS

In conclusion, even if the natural history of HIV infection has been profoundly modified in recent years, HIV-infected patients are at risk of developing non-AIDS-defining diseases, including malignancies. Current evidence suggests that the incidence of anal cancer is higher in the HAART era. There is a need for more research evaluating the most effective therapeutic and preventive strategies in this specific setting.

CONFLICT OF INTERESTS:
The Authors declare that they have no conflict of interests.

REFERENCES


