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Anal Cancer in the Modern Era: Evolving Risks, Emerging Therapies, and the Impact of Public Health Initiatives in Brazil

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ABSTRACT

The increase in the incidence of anal cancer has been mitigated with the implementation of HPV vaccination, particularly evidenced by a decline in prevalence among younger populations. However, suboptimal vaccination rates, high-risk sexual behaviors, and the ongoing high incidence of AIDS hinder a more significant reduction in the prevalence of squamous cell carcinoma of the anal canal (SCCA). Addressing this issue requires early identification and mitigation of key risk factors, alongside a more comprehensive understanding of the tumor's molecular biology, which could ultimately contribute to more effective management of advanced disease. Current treatment for localized and locally advanced SCCA largely consists of chemoradiation therapy, while recent developments have incorporated immunotherapy with chemotherapy as a standard first-line option for palliative care. This review examines the epidemiology and pathology of anal cancer, diagnostic and staging protocols, and the evolution of public health policies targeting risk factors especially within Brazil along with recent advancements in SCCA management strategies.

Keywords

Anal cancer, Squamous cell carcinoma of the anus, HPV, Immunotherapy.

Background

Anal cancer represents only 2% of all gastrointestinal tract malignancies; however, its incidence has shown a marked increase over the past decade [1-3]. This upward trend is closely associated with high-risk sexual behaviors, a resurgence in human immunodeficiency virus (HIV) infections, and insufficient coverage of the human papillomavirus (HPV) vaccine [4].

In Brazil, multiple policies have been implemented to mitigate the rise in HIV and HPV infections, both of which directly impact on the incidence of anal canal cancer. Key measures include tobacco control, HIV management programs, and expanded HPV vaccination initiatives [4]. Those critical and concerning factors driving the increase in anal cancer incidence in Brazil may similarly affect other emerging countries.

The approach to anal cancer management has undergone significant evolution, moving from HPV vaccination as a preventive strategy to definitive chemoradiation therapy (CRT) for organ preservation. Additionally, recent advancements in systemic treatments, including immunotherapy for advanced anal cancer and treatment adjustment based on risk stratification, are reshaping therapeutic options for patients with both advanced and localized disease.

This review examines the epidemiology and pathology of anal cancer, diagnostic and staging procedures, the progression of public health policies addressing risk factors, management strategies for localized disease, and the recent integration of immunotherapy as

a first-line treatment for advanced cases.

Epidemiology Overview

Anal cancer is a relatively rare malignancy with an estimated global incidence of approximately 55,000 new cases and 22,000 deaths per year [1]. Its incidence rate (IR) and mortality have progressively increased over the last few decades. Based on US Cancer Statistics data, the IR rose from 1.20 per 100,000 in 2001-2005 to 1.56 per 100,000 in 2011-2015, representing a steady increase of 2.7% per year [5].

However, more recent data indicate that this increase is restricted to individuals aged 50 years and older, with an actual decline observed in the 40-44 age range during the same period [6]. This decrease in the younger population may reflect the success of vaccination efforts for HPV infection, which is the main risk factor for squamous cell carcinoma of the anus (SCCA), with more than 90% of the cases attributable to a persistent infection [7].

Risk Factors

The most well-known risk factors are HPV anal infection and, ultimately, anoreceptive intercourse. However, non-sexual routes of infection have also been documented, including intrapartum transmission, hands to genitals, surfaces in medical settings, public environments, and even hotel towels [8,9].

Relevant risk factors for anal HPV infection include a higher number of sexual partners, men who have sex with men (MSM), female sex (accounting for about two-thirds of new cases), a history of prior sexually transmitted diseases including anogenital warts other HPV-associated malignancies, and HIV infection [10].

Other important risk factors include tobacco use and chronic immunosuppression, which can result from organ transplants, treatment for autoimmune disorders, and HIV infection [10]. However, the impact of the latter may be confounded by its association with anal sex, given that, unlike other HIV-associated malignancies, the incidence of anal cancer has not proportionally decreased in the era of highly active antiretroviral therapy [11].

Sexual Behavior Changes

The rising incidence of SCCA in Western countries can be attributed to increasing trends in higher-risk sexual behavior, including a larger number of partners over a lifetime and, specifically, more anoreceptive sex among both women and men. The British National Survey of Sexual Attitudes and Lifestyles, which is one of the largest and most detailed scientific studies of sexual behavior in the world, showed that the percentage of women reporting [heterosexual insertive] anal sex in the past year in the UK was as follows: 6.5% (1990–1991), 11.3% (1999–2001), and 15.1% (2010–2012) [12]. The rate was particularly high among females aged 16-24, with percentages of 10.5%, 17.6%, and 29.2% for the same time periods [13].

An increase in sexual behavior associated with anal HPV infection can also be inferred in the male population. First, the proportion of men who openly identified themselves as homosexual or bisexual in the UK almost doubled between 2012 and 2022, rising from 1.9% to 3.7%, with an even more pronounced increase among 16-24 year-olds (from 3.8% to 7.9%) [14]. Second, the rate of MSM engaging in condomless sex rose from 1990 onwards, possibly due to the introduction of antiretroviral therapy, and saw a sharper increase after (Pre-Exposure Prophilaxis) PrEP became available in 2012 [15].

Anal HPV and HSIL prevalence

The prevalence of anal HPV and high-grade squamous intraepithelial lesions (HSIL) has been reported in numerous studies with heterogeneous methodologies and populations. The largest pooled analysis of females to date (n = 13,427 from 36 studies) examined the relationship between cervical and anal HPV and HSIL, reporting a strong correlation [16]. Among HIV-negative women with a positive cervical HPV16, the prevalence of anal HPV16 was 41%, compared to 2% in cervical HPV16-negative women. For HIV-positive women, the prevalence was 46% versus 11%. Similar associations were observed with cervical cytohistopathology: in HIV-negative women, anal HSIL rates increased from 1% in those with normal cytology to 22% in those with cervical HSIL, and from 7% to 25% among HIV-positive women [16].

In men, a large pooled analysis of 64 studies (n = 29,900) evaluated the age-specific prevalence of anal HPV and HSIL, stratified by HIV status and sexuality [17]. The analysis found that HIV-positive MSM had the highest prevalence of anal HPV16 (28.5%) and any high-risk HPV (74.3%), compared to HIV-negative MSM (13.7% and 41.2%, respectively), HIV-positive men who have sex with women (MSW) (8.7% and 26.9%), and HIV-negative MSW (1.8% and 6.9%). Age-specific trends revealed increasing HPV16 prevalence among HIV-positive MSM, peaking at 31.7% in those aged 25–34 years, and higher rates of HSIL+ in this group compared to other populations, suggesting that HIV is a significant predictor for HSIL+ (adjusted prevalence ratio 1.54) [17].

Pathology

The anal canal extends from the rectal ampulla to the anal margin and is primarily lined with squamous epithelium. Proximally, it transitions into the glandular epithelium of the rectum, starting at the dentate line (which includes the anal valves) and extending 0.5 to 1 cm distally. This transition zone is particularly vulnerable to HPV infection. Distally, the canal forms a squamous-mucocutaneous junction with the perianal skin at the anal margin [2].

HPV infection is the primary pathogenic factor in the development of anal cancer, present in approximately 90% of cases (Figure 1), with 86% attributed to the HPV 16 genotype. This association is also observed in other anatomical sites, including cervical (91%), vaginal and vulvar (75%), oropharyngeal (70%), and penile cancers (60%), highlighting a significant global public health issue [18].

Persistent HPV infection leads to the integration of the virus into

host DNA, disrupting the regulation of specific oncogenes and promoting the expression of oncoproteins E6 and E7 [18,19]. These oncoproteins impair critical tumor suppressor proteins, such as p53 and retinoblastoma (Rb), resulting in genomic instability and uncontrolled cell proliferation. Additionally, HPV infection is linked to the dysregulation of cellular autophagy a vital process for the degradation and recycling of cellular components. Impaired autophagy hinders viral clearance, contributing to chronic cellular damage and facilitating the progression of preneoplastic lesions to invasive carcinoma [18,19].

Due to its strong association with HPV infection, most anal canal tumors are squamous cell carcinomas, accounting for 80% of cases. Other rare histological types include adenocarcinoma, lymphoma, gastrointestinal stromal tumors (GIST), melanoma, and neuroendocrine carcinoma [20].

The latest edition of the WHO classification system for anal canal carcinoma has consolidated all previous histological subtypes basaloid, transitional, cloacogenic, and keratinizing under the single category of "squamous cell carcinoma (SCC)," recognizing that these subtypes exhibit similar progression and prognosis [21].

In the histopathological diagnostic approach, immunohistochemical staining for cytokeratins 5 and 6 (CK5 and CK6) supports the diagnosis of SCC, helping to distinguish it from well-differentiated neuroendocrine carcinoma and poorly differentiated adenocarcinoma. This diagnosis is further confirmed by p63 staining, a specific marker for SCC [22]. Additionally, p16 immunohistochemistry demonstrates 100% sensitivity in HPV-positive cases, while abnormal p53 expression shows both 100% sensitivity and specificity for detecting TP53 mutations [21].

The molecular characterization of SCC is linked not only to HPV infection status but also to prognosis. HPV-positive SCC samples exhibit a higher correlation with PIK3CA mutations or amplifications (30%) and FBXW7 mutations (10%). In contrast, HPV-negative tumors are more frequently associated with TP53 (53%) and CDKN2A (21%) mutations. HPV-positive, TP53 wild-type tumors are associated with better overall survival (OS) and lower rates of local recurrence, while HPV-negative tumors with TP53 mutations are linked to resistance to chemoradiotherapy (CRT) and poorer prognosis [21].

Consistent with these findings, translational analyses using whole-exome sequencing have identified recurrent mutations, deletions, amplifications, and copy number alterations in the PI3K/AKT/mTOR pathway in up to 60% of evaluated tumors. However, despite these promising insights suggesting potentially druggable pathways, no targeted therapies have been established for SCCA to date [23].

Translational analyses and exploratory data from randomized studies have indicated the prognostic and predictive value of tumor mutational burden (TMB)-High, PD-L1 (programmed death ligand 1) expression, and high CD3 and CD8 tumor-infiltrating lymphocyte density as biomarkers. These markers suggest improved survival outcomes and enhanced treatment responses to both CRT and immunotherapy [24].

Simultaneously, efforts to identify additional biomarkers for SCCA management have focused on the role of HPV circulating tumor DNA (ctDNA). Promising results have shown sensitivities exceeding 90%, along with correlations between ctDNA levels, treatment response, and survival outcomes. Nevertheless, randomized studies are needed to validate these findings and confirm their clinical utility [25].

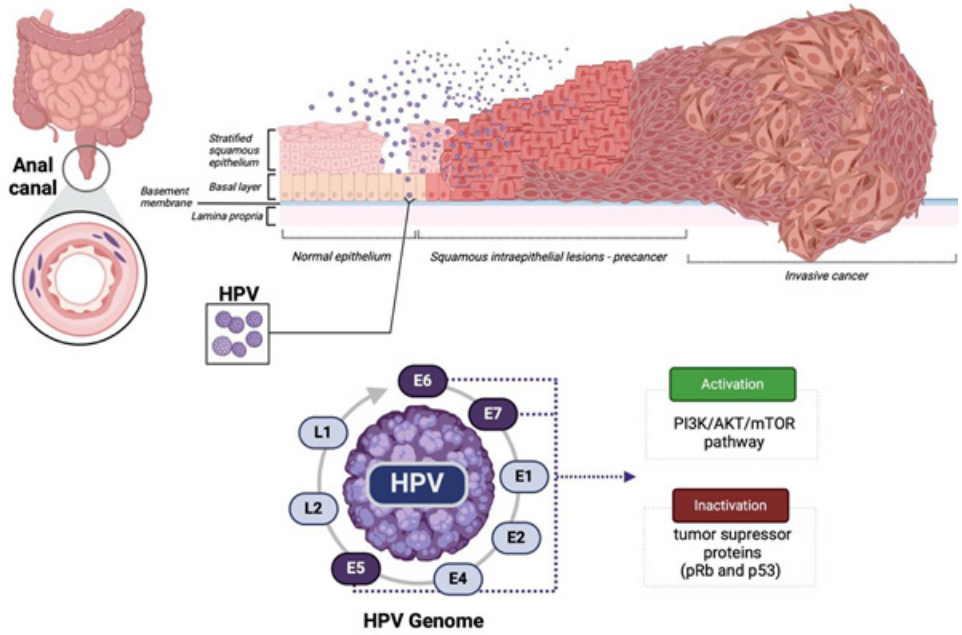

Figure 1: Correlation of HPV infection and anal squamous cell carcinoma. Created in BioRender. Mathias, M. (2024) https://BioRender.com/k48q056

Diagnostic and Staging Work-up

The symptoms of anal cancer that lead to medical consultation are non-specific: persistent bleeding often attributed to hemorrhoids, anal discomfort or persistent itching, palpation of a mass in the anal region, and changes in bowel habits. These changes can range from persistent diarrhea to constipation, with alterations in stool caliber [26]. The diagnosis of anal cancer can often be delayed due to the non-specific and subtle presentation of its symptoms. Additionally, the stigma surrounding its association with sexual behavior and orientation may further contribute to postponements in patients seeking timely medical evaluation. Furthermore, given the anatomical characteristics of the anal region and its role in defecatory function, early diagnosis can prevent the need for aggressive interventions and reduce perineal complications associated with locally advanced disease [27].

Medical history, including sexual habits, and a physical examination are the initial steps in diagnosing anal cancer. During a digital anorectal examination, the size and location of the lesion can be assessed, as well as the tone of the anal sphincter. For women, a gynecological examination is also recommended to evaluate for vaginal involvement or the presence of a fistula. Complementary methods include anoscopy, which allows for direct visualization of the anal canal and the biopsy of any suspected lesions to confirm malignancy. If enlarged inguinal lymph nodes are present, a fine-needle biopsy may be required to assess the extent of the disease [28].

As SCC is the most common histology, immunohistochemistry for p16 a surrogate marker for HPV status should be performed due to its role as a prognostic biomarker for treatment response [29]. HIV testing is also recommended if the patient's status is unknown, as retrospective data suggest that HIV status may serve as a prognostic biomarker for treatment toxicity and OS in localized anal cancer [30].

An adequate staging work-up is crucial for selecting the best treatment modality. The preferred imaging method for local evaluation of the tumor is high-resolution magnetic resonance imaging (MRI) of the pelvis. This type of exam allows for better discrimination between the high-signal intensity of the tumor area and the low-signal intensity of the muscle layers, anal sphincters, and muscularis propria of the rectal wall. The distant extension of the disease is assessed using contrast-enhanced chest and abdominal CT scans [31].

There is no consensus on the use of FDG-PET scans; while they can be useful in evaluating suspected metastatic disease in locally advanced anal cancer, they are also beneficial for radiotherapy planning, particularly in determining whether to include regional lymph nodes in the target treatment area [32].

The TNM system is the most widely used staging system, with the most recent version being the 9th edition, revised by the American Joint Committee on Cancer (AJCC) (Table 1). Changes from the 8th edition primarily affect stages IIB, IIIA, and IIIC. Large database analyses have indicated that stage IIIA has better survival rates than stage IIB, while stage IIIC has heterogeneous outcomes. Consequently, changes included the elimination of stage 0, modifications to stage IIB (from T3N0 to T1-T2N1), stage IIIA (from T1-T2N1 to T3N0-N1), and stage IIIC (from T3-T4N1 to T4N1) [33].

Table 1: Differences between the 8th and the 9th edition of TNM staging from the AJCC for anal cancer.

Stage	8th Edition	9th Edition
0	Tis N0 M0	NON EXISTENT
I	T1 N0 M0	Same
IIA	T2 N0 M0	Same
IIB	T3 N0 M0	T1-T2 N1 M0
IIIA	T1-T2 N1 M0	T3 N0-N1 M0
IIIB	T4 N0 M0	Same
IIIC	T3-T4 N1 M0	T4 N1 M0
IV	Any-T Any-N M1	Same

Public Policies

Tobacco use

Identifying the factors that determine the initiation and cessation of tobacco use, as well as strategies for the surveillance and monitoring of tobacco product consumption, is fundamental for planning specific actions for tobacco control.

The percentage of adult smokers in Brazil has significantly declined over the past decades due to numerous actions developed by the National Tobacco Control Policy. In 1989, 34.8% of the population aged 18 and older were smokers. A significant drop was observed in 2003, when the percentage fell to 22.4%. By 2008, this percentage had decreased to 18.5%. The most recent data from 2019 indicate a total percentage of adult smokers at 12.6%. According to the National Health Survey, there was a reduction in the prevalence of current adult smokers aged 18 and older from 14.7% in 2013 to 12.6% in 2019. This reduction occurred among both men (18.9% in 2013; 15.9% in 2019) and women (11.0% in 2013; 9.6% in 2019) [34].

Since 2006, the Vigitel survey has annually monitored health-related behaviors through telephone interviews with adults aged 18 and older across all Brazilian state capitals. The 2023 edition reported that 9.3% of adults in Brazil identified as smokers, with prevalence rates of 10.2% among men and 7.2% among women [34].

Tobacco use ranks second on the list of the most commonly experimented drugs in Brazil. The average age of tobacco experimentation among Brazilian youth is 16 years for both boys and girls. Nationally, the frequency of young male smokers tends to be higher than that of females. Studies show that tobacco experimentation is higher among students from public schools, and the frequency of tobacco use in the past 30 days is also greater in public educational institutions. Compared to previous surveys, the results indicate improvements in experimentation indicators, a decrease in the percentage of tobacco users in the past 30 days, and

an increase in the average age of experimentation [34].

Regarding e-cigarette experimentation, the highest percentages were observed among students aged 13 to 17 in private schools across all major regions of Brazil in 2019. The highest percentages of e-cigarette experimentation were noted in the Central-West Region (23.6% in public schools and 24.3% in private schools). The lowest percentages occurred among students in public schools in the Northeast Region (10.3%) and the North Region (11.9%) [34].

HIV/AIDS

According to the 2023 Brazilian HIV/AIDS epidemiological report, the number of people infected with HIV has been increasing. Comparing the years 2020 and 2022, the number of cases in Brazil increased by 17.2% [35]. The sex ratio has changed over time: in 2007, it was 14 men for every 10 women, but from 2020 onward, it has been 28 men for every 10 women. Regarding age groups, it was observed during the analyzed period that 23.4% of cases are among young people aged 15 to 24 years, representing 25% and 19.6% of cases in males and females, respectively [35]. This data highlights the importance of targeted public policies for this population on a continuous basis.

In 2022, new HIV infections in women of reproductive age (15 to 49 years) accounted for 78.3% of the total female cases, emphasizing the need for reproductive planning, the provision of anti-HIV testing for early detection of infection, and the initiation of therapy to prevent vertical transmission of the virus. The percentage of cases among women aged 50 and older increased from 11.4% in 2012 to 20.3% in 2022, while among men it increased from 8.7% to 11.4%, respectively. Notably, new cases in the 20 to 29 age group accounted for 40.7% of male cases in 2022 [35]. From 2007 to June 2023, among individuals aged 13 or older, the primary exposure category for males was MSM (52.6%), while for females it was heterosexual practices (86.4%). In the vertical transmission category, there was a 32.8% increase between 2019 and 2022 [35].

From 2012 to 2022, however, there was a 25.5% decrease in the age-standardized HIV/AIDS mortality rate in Brazil, from 5.5 to 4.1 deaths per 100,000 inhabitants [35]. This means, fortunately, that people with HIV/AIDS are living longer. However, they are also at increased risk for developing tumors associated with the condition over time, such as SCCA.

Table 2: Smoking and HIV infection between 2008 and 2022 in Brazil.

	2008	2018	2022
Smoking*	18.5%	12.6%	9.3%
HIV from high risk sex**	49,1%	62%	54.3%
HIV infection***	7.805	46.426	42.975

* percentage of Brazilian population over 18 years

** reported cases of 13 years or older of HIV acquisition due to homosexual or bisexual relationship

*** Total number of reported cases aged 13 and over

source: INCA - National Cancer Institute. National Tobacco Control Policy Observatory. 2024

Ministry of Health. HIV / AIDS Epidemiological Report 2023.

HPV Immunization

Vaccination is a highly cost-effective intervention and a safe, effective method for preventing infections. Since 2014, Brazil's Unified Health System (SUS) has provided the quadrivalent HPV vaccine through the National Immunization Program (PNI). The current target group includes children and adolescents aged 9 to 14, who receive a single-dose schedule. Individuals aged 9 to 45 living with HIV/AIDS, cancer patients, those with recurrent respiratory papillomatosis, and transplant recipients are recommended to receive three doses of the vaccine. Additionally, individuals aged 15 to 45 who are immunocompetent victims of sexual violence are also included in the PNI [36]. With these recommendations, Brazil is among the leading countries in the Americas in HPV vaccination.

In 2024, the single-dose schedule for immunocompetent children and adolescents was adopted in line with the latest guidance from the World Health Organization (WHO) and the Pan American Health Organization (PAHO) [37]. This change effectively doubles the capacity of available vaccine stocks in the country. In July 2024, individuals aged 15 to 45 on HIV Pre-Exposure Prophylaxis (PrEP) were also included in the HPV vaccination program [36].

According to the National Health Data Network (RNDS), since the HPV vaccination began in SUS in 2014, 75.8% of the female target group received the first dose, and 58.2% received the second dose across Brazil. Vaccination coverage for males, which started in 2017, stands at 53.1% for the first dose and 33.2% for the second dose [36]. At the time these data were collected, HPV vaccination was administered in two doses.

In 2023, over 6.1 million doses of the HPV vaccine were given, marking the highest number since 2018 (5.1 million) and a 42% increase compared to 2022, when just over 4 million doses were administered. School-based vaccination played a key role in achieving this positive outcome [38]. However, despite this progress, challenges remain in HPV vaccination efforts.

A systematic review by the Brazilian Cancer Foundation identified 16 cross-sectional studies involving 7,712 children and adolescents aged 10 to 19, 3,335 parents/guardians aged 18 to 82, and 2,727 healthcare professionals (doctors, nurses, nursing assistants, community health agents) [39]. Among the children and adolescents, 26% to 37% were unaware that the vaccine prevents certain types of cancer, while 36% to 57% believed the vaccine could be harmful. Among parents and guardians, 17% did not know the vaccine prevents some types of cancer; 20% thought it could be harmful; 22% believed it might encourage early sexual initiation; and between 34% and 61% were unaware of the eligible target population for vaccination. Among healthcare professionals, 33% felt unconfident providing information about the vaccine; 49% did not see themselves as responsible for educational efforts; and only 36% consistently inquired about vaccination status during consultations for other reasons [39].

To address these informational barriers, it is crucial to enhance knowledge about the vaccine's safety, effectiveness, and target population. Educational initiatives aimed at both the public and healthcare professionals are necessary to improve understanding and uptake of the HPV vaccination.

Management of SCCA

Localized and Locally advanced disease

The treatment of anal canal tumors has significantly advanced over the past few decades, leading to improved oncological outcomes and a marked reduction in the morbidity traditionally associated with these therapies [40].

In the 1970s, Nigro and colleagues established definitive CRT as the cornerstone of treatment, reserving surgical options for cases that did not respond to initial therapy. They transformed treatment paradigms by integrating 5-fluorouracil (5-FU) and Mitomycin C (MMC) into radiotherapy (RT) prior to performing an abdominoperineal resection (APR), typically six weeks after completing CRT. In their initial report, two of three patients who underwent surgery showed a complete pathological response, while the third patient declined surgery and maintained a sustained clinical complete response [41]. These findings were further supported by a subsequent series involving 45 patients with localized disease treated with RT and 5-FU plus MMC, demonstrating an impressive complete response rate (RR) of 84% [42]. Based on these results and other studies, CRT with 5-FU and MMC has become the standard treatment for SCCA, despite the lack of randomized trials directly comparing surgery and CRT in this context.

Randomized studies have consistently shown that CRT is more effective than RT alone in improving response rates and disease-free survival. In the UKCCCR ACT I trial, 585 patients with SCCA or anal margin (stages T1–T4) were randomly assigned to receive either RT alone or RT combined with 5-FU and MMC. The CRT group had a significantly lower rate of locoregional recurrence (36% vs. 59%; relative risk 0.54, 95% CI 0.42–0.69; $p < 0.0001$) [43]. Similarly, an EORTC study found better outcomes with CRT in patients with advanced SCCA. Those who received CRT had higher 5-year locoregional control (68% vs. 50%; $p = 0.02$), colostomy-free survival (72% vs. 40%; $p = 0.02$), and complete response rates (80% vs. 54%) [44].

The phase III RTOG 98-11 trial examined whether cisplatin (CDDP) could replace mitomycin C (MMC) and tested the benefit of induction chemotherapy. Patients with stage T2–T4, N0–N3 anal cancer were randomly assigned to either standard CRT with 5-FU and MMC, or to induction chemotherapy with 5-FU and CDDP followed by CRT. At three years, those who received MMC had lower colostomy rates (10% vs. 16%; $p = 0.02$), though there were no significant differences in disease-free survival (DFS) or overall survival (OS) at that time. However, long-term results showed better 5-year DFS (67.8% vs. 57.8%; $p = 0.006$), OS (78.3% vs. 70.7%; $p = 0.026$), and a small improvement in colostomy-free survival (71.9% vs. 65%; $p = 0.05$) in the MMC group [45].

In the ACT II trial, 940 patients with non-advanced squamous cell anal cancer were randomized in a 2x2 factorial design to compare CRT with 5-FU plus CDDP versus 5-FU plus MMC. After CRT, they were further randomized to either two cycles of maintenance chemotherapy with 5-FU/CDDP or observation. The study found no advantage of using CDDP over MMC, with similar complete response rates at 26 weeks (90.5% vs. 89.6%; $p = 0.64$) and no significant differences in DFS at three years ($p = 0.63$), regardless of maintenance chemotherapy ($p = 0.70$). Both groups experienced similar rates of severe side effects (71% with MMC vs. 72% with CDDP), though hematological toxicity was higher in the MMC group (26% vs. 16%; $p < 0.001$) [46].

For more than a decade, MMC has not been available in Brazil. It has been especulated that low-profit margins have discouraged its production. In addition, the demand for mitomycin may not be high enough to justify the efforts associated with its production and distribution. Patients in Brazil may still have the option to import mitomycin at their own expense, but the associated out-of-pocket costs, along with the availability of cisplatin as a potential alternative, have led many oncologists to move away from using mitomycin. The financial burden of importation, combined with cisplatin's relative accessibility and established efficacy in chemoradiation protocols, often makes cisplatin the preferred choice to be combined with a fluoropyrimidine and radiation therapy.

Capecitabine demonstrated efficacy and safety comparable to 5-FU in a prospective study, despite a higher incidence of grade 3-4 toxicity [47]. However, a treatment intensification strategy combining triple therapy (5-FU, MMC, and CDDP) with RT was deemed excessively toxic (89% grade 3-5 toxicities) in a multicenter phase II study and is not recommended [48]. Additionally, the inclusion of epidermal growth factor receptor (EGFR) inhibitors in standard CRT for non-advanced SCCA should be avoided due to a lack of clear benefit in locoregional control and significant side effects, as indicated by phase II studies [49-52].

Advanced Disease

The first-line treatment for recurrent or metastatic anal cancer has been significantly altered by the presentation of the POD1UM-303/InterAACT 2 study at ESMO Congress 2024. This phase III trial randomized 308 patients to receive either carboplatin-paclitaxel for six cycles plus retifanlimab or placebo for 12 months. Notably, 90% of participants tested positive for PD-L1 expression (≥1), and fewer than 4% were HIV positive [53]. The study achieved its primary endpoint of progression-free survival (PFS), reporting 9.3 months for the immunotherapy arm compared to 7.4 months for the control arm (HR 0.63; 95% CI 0.47–0.84; $p = 0.0006$). In an interim OS analysis, the combination arm showed 29.2 months versus 23 months for the control (HR 0.70; 95% CI 0.49–1.01; $p = 0.0273$), although 44.8% of control patients crossed over to receive the experimental treatment. When adjusting for this crossover, the immunotherapy arm demonstrated an OS gain of 10.1 months (29.2 vs 19.1 months; HR 0.63; 95% CI 0.44–0.9; $p = 0.0055$). Additionally, the experimental arm exhibited a higher

overall response rate (ORR) of 55.8% compared to 44.2% (p = 0.0129), although it also experienced greater toxicity, with grade ≥3 treatment-emergent adverse events (TEAEs) reported at 83.1% versus 75% [53]. This study marks the first randomized phase III trial to demonstrate the benefits of immunotherapy as a first-line systemic treatment, potentially changing clinical practice.

While the immunotherapy combination awaits approval for first-line use in metastatic SCCA, the current preferred treatment option remains carboplatin plus paclitaxel, as outlined in the NCCN Clinical Practice Guidelines (NCCN Guidelines®) [54], based on findings from the InterAACT trial [55]. This randomized multicenter phase II trial included 91 patients with locally advanced or metastatic SCCA, comparing a treatment arm (carboplatin + paclitaxel, n = 45) with a control arm (5-FU and CDDP, n = 46). The treatment arm showed a significantly improved median OS of 20 months compared to 12.3 months in the control arm (HR: 2.0; p = 0.014), along with lower rates of grade ≥3 toxicity (71% vs 76%; p = 0.016) [55].

Docetaxel plus CDDP and 5-FU (DCF) has been considered a potential standard treatment; however, this regimen has been associated with high toxicity rates. A modified DCF (mDCF) regimen with lower chemotherapy doses may offer better tolerability [56]. A pooled analysis of 115 patients from two studies evaluating standard DCF versus mDCF demonstrated an objective RR (ORR) of 87.7%, with 40.3% achieving complete responses. The median PFS was 12.2 months (95% CI, 10.6–16.1), and the median OS was 39.2 months (95% CI, 26.0–109.1), with no significant differences in OS (p = 0.57) or PFS (p = 0.99) between DCF and mDCF [57]. Patients tolerated the mDCF regimen significantly better, leading to its inclusion as a frontline treatment option for newly diagnosed metastatic SCCA.

Alternatively, a regimen of 5-FU and lower doses of CDDP demonstrated an ORR of 48% (95% CI, 32.6%–63%), a median PFS of 7.1 months (95% CI, 4.4–8.6), and a median OS of 21.1 months (95% CI, 16.9–28.1) in the retrospective FOLFCIS study [58].

Single-agent immunotherapies have a role in managing refractory metastatic or advanced SCCA in the second-line setting, according to phase II studies [59-62]. The current NCCN Guidelines® recommend immune checkpoint inhibitors, including nivolumab and pembrolizumab, as second-line treatment options for metastatic SCCA, although they have not yet received FDA approval [54].

While some retrospective analyses suggest benefits from anti-EGFR antibodies in recurrent SCCA [63,64], the prospective phase II CARACAS study indicated that combining anti-EGFR therapy with avelumab did not improve median OS (13.9 months vs 7.8 months) but showed potential improvements in median PFS (2 months vs 3.9 months) and the primary endpoint of ORR (10% vs 17%). However, this combination was associated with a higher incidence of grade ≥3 adverse events (33.3% vs 13.3%) compared to avelumab alone [62]. While results from the avelumab monotherapy arm align with other single-agent immunotherapy options in current guidelines, the impact of anti-EGFR therapy either alone or in combination on improving outcomes for patients with SCCA remains uncertain.

Unfortunately, there are no randomized trials assessing the efficacy of chemotherapy specifically in the second-line or later-line settings for metastatic SCCA. In clinical practice, due to the limited data and treatment options, many oncologists may consider ablative therapies for patients with oligometastatic progression after first-line treatment with carboplatin and paclitaxel. For patients who experience disease progression after a treatment break, a reintroduction of carboplatin and paclitaxel or mDCF may be an option [65]. Other second-line options include single-agent irinotecan, FOLFIRI (a combination of 5-FU and irinotecan), or a fluoropyrimidine alone. These regimens are selected based on patient tolerance and prior treatment history, though the lack of high-quality data necessitates a more individualized approach to therapy in these settings.

Conclusion

The rising incidence of anal cancer underscores the need for continued advancements in both prevention and treatment. Despite being a rare malignancy, anal cancer has become a growing public health concern, particularly given its association with high-risk sexual behaviors, HIV, and suboptimal HPV vaccination coverage. Public health initiatives in Brazil and other countries have aimed to reduce these risk factors through expanded HPV vaccination, HIV management programs, and tobacco control measures, yet the impact on anal cancer incidence remains limited. The management of anal cancer has evolved significantly, with chemoradiation therapy firmly established as the cornerstone for localized and locally advanced disease, while recent advancements in systemic therapies, especially immunotherapy, are shifting the landscape for advanced cases. However, treatment for metastatic anal cancer remains challenging due to limited randomized evidence guiding second-line and later-line therapies.

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