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Skin Cancer Back to Basics

Anogenital Squamous Cell Carcinoma

Soneet Dhillon and Eden Lake

ABSTRACT: Anogenital squamous cell carcinoma is rare but an often-invasive malignancy that is becoming an increasingly prevalent public health problem. Infection with high-risk human papillomavirus variants plays a critical role in disease progression and occurrence. Immunosuppressive treatment, positive HIV status, number of sexual partners, and history of smoking increase neoplastic progression. Early diagnosis and treatment are pivotal in managing anogenital malignancies to improve quality of life and minimize extensive surgical excision. This article reviews lesion categorization, epidemiology, human-papillomavirus-driven dysplastic epithelial changes, risk factors, diagnostic criteria, treatment options, and prophylactic measures to improve patient outcomes.

Key words: Anogenital Squamous Cell Carcinoma, Condyloma Acuminata, Genital Warts, HPV Vaccine, Human Papilloma Virus (HPV), Squamous Intraepithelial Neoplasia

DEFINITION AND CATEGORIZATION

Anogenital squamous cell carcinoma (SCC) describes intraepithelial SCC and invasive anogenital SCC presenting on the anus, vagina, vulva, scrotum, and penis. Invasive SCC is a commonly occurring anogenital malignancy, making it a significant health problem (Henquet, 2011). Genital human papillomavirus (HPV) infection often plays a critical role in anogenital malignancies and premalignancies, typically transmitted via sexual contact with an affected partner (Kutlubay et al., 2013). For the scope of this article, cervical cancer has not been included.

Superficial anogenital neoplasms associated with the HPV infection are known as squamous intraepithelial lesions (SILs) and are further classified as high-grade SIL (HSIL) or low-grade SIL. Anogenital epidermal neoplasia and epidermal carcinoma in situ can also be classified as intraepithelial neoplasia (IN), which can be further categorized as vulvar, penile, or anal IN (Kutlubay et al., 2013). Squamous IN includes Bowenoid papulosis (which manifests as papular lesions), Bowen's disease (which presents as solitary plaques that progressively grow larger), and erythroplasia of Queyrat (which is a form of noninfiltrating erythematous plaques also known as Bowen's disease of the penile glans, prepuce, and labia majora; Henquet, 2011).

Most anal cancers are SCC, often caused by a persistent high-risk HPV (HR-HPV) infection. Anal IN (AIN) 1–3 are precancerous lesions that may progress to SCC, and high-grade AINs (AIN3) are more likely to become invasive SCC (van der Zee et al., 2019). Anal SCC can be subdivided by the anatomic location (as perianal or anal canal). Perianal SCC is easier to treat with local treatment, whereas anal canal cancer often needs adjuvant therapy to achieve similar long-term outcomes (Maccabe et al., 2021).

Vulvar SCC (VSCC) represents over 90% of vulvar malignancies and can develop in the presence of an HR-HPV infection or independently of HPV infection (Del Pino et al., 2013). HPV-associated VSCCs predominantly occur in younger women and represent 40% of all VSCCs, whereas non-HPV-related vulvar neoplasia often develops from chronic inflammatory skin conditions (such as lichen planus) in older women (Rasmussen et al., 2018). HPV-positive VSCC has a better prognosis than HPV-negative tumors (Wakeham et al., 2017). Unlike other anogenital lesions, flat atypical superficial VIN 1 lesions are uncommon in the vulva; rather, they present as exophytic condyloma acuminata with low-grade dysplasia (Del Pino et al., 2013).

Precursor penile cancer neoplasms associated with HPV infection are penile IN and are commonly found in the prepuce and glans (Medeiros-Fonseca et al., 2020). Basaloid and warty penile INs are strongly associated with HPV and represent over 90% of all invasive penile cancers in the United States, 42% of penile carcinomas, and 90% of dysplastic lesions (Kidd et al., 2017). Similar to vulvar cancer, HPV-negative penile cancers are more aggressive and often associated with lichen sclerosis and lichen planus (Spiess et al., 2016).

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Unlike other anogenital cancers, scrotal cancer is rare, and there is no site-specific staging classification. The Lowe Staging System (established in 1983) and the tumor, nodes, and metastases classification system are both in use to stage scrotal cancer (Pagliaro, 2016). Scrotal SCC is classified as A1, A2, B, C, or D (Vyas et al., 2014). Stage A1 diseases are limited to the affected scrotal tissue, and A2 includes continuous spread to adjacent structures, including the penis, perineum, and so forth, without lymph node involvement and evident metastasis (Pagliaro, 2016). Stage B and C diseases describe lymph node metastasis that is resectable and unresectable, respectively. Stage D disease describes aggressive metastasis that is beyond regional lymph nodes (Pagliaro, 2016).

Verrucous carcinoma is a squamous cell malignancy variant that is highly recurrent with low neoplastic potential (Trøstrup & Matzen, 2019). A Buschke-Löwenstein tumor, also known as giant condyloma acuminatum (GCA), is a highly differentiated anogenital verrucous carcinoma with deep infiltrative growth associated with mucosal HPV infection that is distinct from condylomata acuminata (genital warts) and SCC (Nordsiek et al., 2015). For this article, Buschke-Löwenstein tumors and GCAs will be referred to as GCAs. Given low incidence, it is unclear whether verrucous carcinoma and GCA represent the same tumors but are often grouped (Trøstrup & Matzen, 2019). GCA may progress onto malignant SCC in up to 50% of GCA cases in approximately 5 years (Bolhassani, 2018). GCA presents as an invasive, cauliflower-like, large (may exceed 10 cm), exophytic, disfiguring, papillomatous, and irregular tumor (Kutlubay et al., 2013).

HUMAN PAPILLOMAVIRUS

HPV infection is the most common sexually transmitted infection in the United States, and HPV 16 is the most commonly detected HPV type associated with anogenital cancer (Kutlubay et al., 2013; Moscicki et al., 2015). HPV is a double-stranded DNA virus that infects the squamous epithelium. There is a broad spectrum of HPV types associated with the risk for developing anal cancer (Table 1). HR-HPV types (most commonly HPV 16, 18, 31, 33, and 45) are found in anogenital cancers, whereas low-risk types typically cause condylomata acuminata (Kutlubay et al., 2013).

TABLE 1. Classification of HPV Types Based on Anogenital Cancer Risk

Risk	HPV Type
High	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 56, 58, 59, 68, 69, 73
Low	2, 6, 11, 40, 42, 43, 44, 53, 54, 55, 57, 62, 64, 67, 69, 70, 71, 72, 81, 83, 84, 89

Note. HPV = human papillomavirus.
Sources: Bacopoulou et al., 2016; Moscicki et al., 2014.

HPV infection is common in the early reproductive years, and it often transiently appears without cytological abnormality, but persistent infections by the same HPV type are associated with neoplastic changes (Crum et al., 2018). However, most HPV infections are immunologically cleared within a year and do not progress (Bolhassani, 2018). HPV interacts with squamous epithelia by supporting virion production via transiently appearing precancerous lesions with viral oncogene overexpression and dysregulated epithelial differentiation (Darragh et al., 2012). Dysplastic changes occur when the viral genome integrates into the host genome, marking the end of clonal selection of cells by altering functional genes, which allows for uncontrolled growth that can progress into invasive cancer (Kidd et al., 2017).

EPIDEMIOLOGY AND RISK FACTORS

Sexual activity is related to the presence of HPV infection and particularly HR-HPV genotypes. Anogenital cancer is linked to practices that increase the likelihood of HPV infection, including receptive anal intercourse, a higher number of male sexual partners, lower age at first sexual experience, and cigarette smoking (Bolhassani, 2018). For women, the risk of HPV infection decreases with age, whereas men remain susceptible to HPV infection throughout their lives, but they are also more likely to clear oncogenic HPV infections as they age (Giuliano et al., 2011). Patients with human immunodeficiency virus (HIV) infection or on chronic immunosuppressive treatment are at an increased risk for developing HPV-related diseases. Anal HPV types have been shown to be more common among men who are coinfected with HIV, and multiple HR-HPV types are associated with CD4 T-cell counts below 200/mm^3 (Henquet, 2011). Women who are HIV-positive have a higher prevalence of known HPV-related pathology of the vulva, vagina, and anus as well as higher incidence of HR-HPV in the anus compared with HIV-negative women (Stier et al., 2015). In addition, countries with high economic inequality and fewer resources, including some African and Latin American nations and India, present the highest incidence of anogenital SCC (Medeiros-Fonseca et al., 2020).

Anal SCC represents 85% of all anal cancers (Nasioutziki et al., 2020). Although the prevalence in the general population is low, in the United States, the incidence of anal cancer has been steadily rising approximately at 1.8% per year (Howlader et al., 2018). Diagnosed patients are typically in their 60s and 70s, with the highest incidence in the white population and then Black, Hispanic, and Asian populations (Shiels et al., 2015). Women have a higher incidence of anal cancer than men in the United States, as well as higher rates of invasive anal SCC in recent years, making up nearly two thirds of all cases (Moscicki et al., 2014). Women who have previous HPV-related gynecological neoplasia have an increased risk of developing anal cancer. Data indicate that posttoilet wiping front to back significantly increased the prevalence of HR-HPV types

in women who had HPV-related gynecological neoplasia, whereas posttoilet dabbing behaviors were associated with decreased prevalence (Simpson et al., 2016).

Although women have a higher rate of anal SCC, anal HSIL (AIN2/3) incidence is 10 times more likely in men, possibly because HIV-positive men typically undergo relatively higher screening compared with women regardless of their HIV status (Simard et al., 2013). Using international population-based cancer registries between 1983 and 2007, the incidence of anal SCC increased in both men and women in the United States, Canada, most of Europe, and Australia but remained unchanged in Asian countries, which could be attributed to the difference in the prevalence of environmental risk factors that increase the persistence of anal HPV (Islami et al., 2017).

Vulvar cancer is rare, but the incidence and death rate has been increasing over recent years to a rate of 2.5 new cases and 0.6 deaths per 100,000 people (Howlader et al., 2018). It is most commonly diagnosed in women over 60 years old, although it is now becoming more prevalent in younger women (Rasmussen et al., 2018). Progression of VIN to VSCC occurs in 6%–10% of all cases and is less likely to progress if it presents in younger women (Wakeham et al., 2017). A study of 112 patients also found that HR-HPV-positive cases of VIN had a lower rate of disease progression to cancer than HR-HPV-negative cases.

Penile cancer is an uncommon disease in developed nations, representing less than 0.4%–0.6% of all cancers and 0.1% of all cancer deaths in the United States and Europe, but it is significantly more prevalent in developing countries (Douglawi & Masterson, 2017). However, despite the low incidence of penile cancer, several studies have shown the presence of external genital HPV in men can be up to 71%–73% (Spiess et al., 2016). In addition, the risk of developing penile cancer in the United States is 43% greater in men who live in regions where ≥20% of the population is at or below the poverty level compared with more affluent areas (Hernandez et al., 2008). Penile SCC incidence is 72% higher in Hispanic men than non-Hispanics, twofold lower in Asians/Pacific Islanders, and similar in whites and Blacks (Hernandez et al., 2008). Black and Hispanic men were diagnosed at significantly younger ages and have higher mortality compared with other racial-ethnic groups in the United States (Hernandez et al., 2008).

Childhood circumcision provides the greatest protection against developing penile cancer, whereas phimosis and poor penile hygiene are substantial risk factors for malignancy (Misra et al., 2004). Circumcised men were 6 times more likely to clear a persistent infection with oncogenic HPV than noncircumcised men (Bolhassani, 2018). Heavy alcohol consumption is also associated with an increased risk for HPV infection in men (Schabath et al., 2015).

Scrotal cancer is rare and associated with occupational hazards. Paraffin, tar, creosote, cotton mule, shale oil, pitch workers, machine tool workers, and more recently in car mechanics, car and airplane manufacturers, gas workers, engineers, and steel and aluminum workers have chronic carcinogen exposure to polycyclic aromatic hydrocarbons that increase the susceptibility of developing scrotal cancer (Vyas et al., 2014). However, with the increasing protection in industrial working conditions, scrotal cancer incidence has decreased (Verhoeven et al., 2010). Chronic mechanical irritation, rubber urinal use, topical nitrogen mustard, and coal tar are also associated with scrotal SCC (Vyas et al., 2014). Scrotal cancer is rare, with an estimated incidence rate of 0.95–1.5 per 1,000,000 persons (Verhoeven et al., 2010; Wright et al., 2008). SCC is the predominant form of scrotal cancer and the most common form of scrotal malignancy (Vyas et al., 2014). In Black men, 69% of all scrotal tumors are SCC, compared with 31% of all scrotal tumors in white men (Wright et al., 2008). Scrotal SCC has the second-worst survival rates compared with other types of scrotal cancer, including melanoma, basal cell carcinoma, and sarcoma (Vyas et al., 2014). Survival for adnexal skin tumors was the lowest (Vyas et al., 2014). Scrotal cancer typically occurs in men older than 50 years (Verhoeven et al., 2010).

Condyloma acuminatum is the most common anogenital sexually transmitted infection, with an incidence rate of 0.1% in the general population (Paraskevas et al., 2007). Condyloma acuminatum typically forms 1–6 months after HPV infection and may rarely overgrow and develop into GCA (Tas et al., 2012). In men, GCAs are more common (having a 2.7:1 male-to-female ratio), and this ratio is increased in patients less than 50 years old (Trombetta & Place, 2001). As with other anogenital SCCs, risk factors for malignant transformation include immune suppression and alcoholism (Tas et al., 2012).

DIAGNOSTIC CRITERIA AND TREATMENT

Spontaneous regression of clinically visible anogenital warts may occur without treatment, but this cannot be predicted and may lead to disease progression (Bolhassani, 2018). Anogenital warts typically present as exophytic warty or basaloid lesions, and they may also be erythematous, keratinizing, and ulcerating. Anal SCC tumors often present with rectal bleeding, pain, and perianal swelling with an ulcerative or wart-like mass (Pessia et al., 2020). Likewise, VIN can present as undifferentiated basaloid lesions or warty condylomas, and these subtypes are morphological variants because both presentations can often be found on the same lesion (Wakeham et al., 2017). Penile SCC presents as an erythematous, indurated papule/plaque or ulcerations (Marchionne et al., 2017). Invasive subtypes often appear as keratinizing or mixed warty–basaloid lesions (Brady et al., 2013). Scrotal SCC commonly presents as an erythematous nodule or plaque with ulceration and pruritus (Vyas et al., 2014), whereas locally aggressive, large, exophytic cauliflower-like anogenital lesions that can harbor regions of invasive SCC are characteristic of GCAs (Nieves-Condoy et al., 2021).

Early diagnosis is an essential factor in improving anogenital prognosis (Kutlubay et al., 2013). However, diagnosis

may be difficult given the site of involvement, patient hesitation in pursuing treatment, and methods to take samples (including brushing and tissue biopsy; Cai et al., 2018). Anogenital warts can be treated topically or with ablative therapy. Topical treatments are further divided into those that can be applied at home (including imiquimod and podophyllotoxin) versus those applied in the clinic (including trichloroacetic acid and podophyllin; Barton et al., 2019). Of the patient-applied topicals, podophyllotoxin is the most effective in achieving complete clearance. There are no FDA-approved topical treatments for anal HSIL, but imiquimod, 5-fluorouracil, cidofovir, and trichloroacetic acid are viable topical options given the pathophysiological similarities with other genital SCC lesions (Megill & Wilkin, 2017).

Providers can also choose to treat patients with a combination of topical and ablation therapy. Ablation debulks the lesion, and treatment options include cryotherapy (cryoprobe or liquid nitrogen spray), scissor excision, electrotherapy, electrosurgery (cautery, hyfrecation), and laser therapy (Barton et al., 2019). Although ablative treatment is more effective in completely clearing anogenital warts, studies have shown that patients prefer a topical treatment that they can apply at home, and it may minimize the scarring, deformation, and subsequent impaired function noted with surgery (Kutlubay et al., 2013). Carbon dioxide laser therapy is the most effective treatment in achieving complete clearance, but subsequent treatment with surgical ablation most effectively decreases the recurrence risk of anogenital warts (Barton et al., 2019). However, ablation is not recommended in patients with extensive disease and bleeding disorders or on anticoagulant therapy (Megill & Wilkin, 2017).

Surgery and adjuvant/neoadjuvant therapy (as needed) is standard treatment for more advanced lesions for most patients. After biopsy confirmation of a suspicious lesion, the early-stage anogenital disease is treated with local excision of the tumor with negative margins, except in anal cancer. Radiation therapy combined with chemotherapy (5-fluorouracil, mitomycin, capecitabine, and/or cisplatin) has shown to be successful in treating anal cancer and increasing colostomy-free survival without surgery, as well as advanced-stage anogenital SCCs (Gunderson et al., 2012).

PREVENTION AND THE HPV VACCINE

Prophylactic HPV vaccination is becoming increasingly prevalent to prevent HPV-associated diseases. Currently, bivalent (HPV 16 and 18), tetravalent (HPV 6, 11, 16, and 18), and nonavalent vaccines (HPV 6, 11, 16, 18, 31, 33, 45, 52, and 58) are available and have shown to be effective in reducing most HPV-mediated cancers (Nasioutziki et al., 2020). The incidence of high-grade cervical, vulvar, or vaginal dysplasia with HPV 31, 33, 45, 52, and 58 among individuals receiving the nonavalent HPV vaccine was 0.5 cases per 10,000 person-years compared with 19.0 cases per 10,000 person-years for the tetravalent vaccines (Huh et al., 2017). Both the nonavalent and tetravalent vaccines have similar immunogenicity for HPV 6, 11, 16, and 18 (Huh et al., 2017). There is a reduced prevalence of HPV 6, 11, 16, and 18 in quadrivalent vaccinated individuals compared with unvaccinated individuals, both men and women (Brouwer et al., 2019).

Routine vaccination coverage levels are increasing and recommended for females aged 11–26 years and males aged 11–21 years (Simard et al., 2013). Furthermore, men who have sex with men and those who are immunocompromised (including those coinfected with HIV) are recommended for routine vaccination until 26 years old, and it is available for them until the age of 45 years (Meites et al., 2019). However, insurance coverage is often not provided until the age of 45 years (Daniels et al., 2021). Educating young adults about HPV and HPV vaccination by school staff and nurses has increased positive attitudes regarding HPV vaccination and improved understanding of HPV-related cancer prevention (Davies et al., 2017). In addition to schools, primary care and outpatient clinics provide clinical opportunities to improve vaccination rates (Hoover & Mayer, 2020). Common reasons for refusing HPV vaccination include an inadequate understanding of the need for HPV vaccination, concern about side effects, and thoughts that the vaccine will lead to increased sexual activity (Hoover & Mayer, 2020). Appropriate educational resources and clinical counseling can help address these concerns. Furthermore, doctor and parental support for HPV vaccination have shown to be more influential than friends' support for vaccination (Stout et al., 2020).

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