Anal Squamous Intraepithelial Lesions and Anal Cancer Management in Low Resource Settings

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Abstract

A low resource setting (LRS) is defined as a health care system which does not meet the criteria defined by the World Health Organization (WHO) or other national/international organizations in the following areas: infrastructure, materials, and human resources.[1] Patients encounter barriers which limit their access to care and services that are considered standard of care. While LRS is most commonly associated with developing countries, it is easy to overlook communities in developed countries which lack the financial resources to afford basic health care. This article describes the societal implications and barriers to care for both squamous intraepithelial lesions (SILs) and anal cancer in LRS, the existing screening/surveillance approaches, available treatment approaches to anal cancer, and it also discusses potential evidence-based approaches to bridge the gap for these disparities in anal cancer care.

Keywords

- squamous intraepithelial lesions
- anal cancer
- high-resolution anoscopy

Societal Implications and Barriers to Care

Barriers to care of both squamous intraepithelial lesions (SILs) and anal cancer are multidimensional and consist of a lack of tangible resources, as well as intangible biases that occur with an already vulnerable patient population.[1] As stated previously, low resource settings (LRS) lack the tangible health care resources of infrastructure, materials, and human resources.[2,3] In LRS, health care access may be impeded by financial resources of medical institutions, as well as the patient's ability to access health care. Patients may have insufficient income, lack health care insurance, may have reliance on subsidized health care, and face difficulty in finding transportation to their health care visits.[1,4] Oftentimes, these patients are cared for by a limited number of medical providers, who are difficult to access due to travel distance, a high patient demand to low provider supply, and unequal health care systems created by socially disparate communities.

Even in a developed country, such as the United States, there is a dearth of medical providers that are trained in high-resolution anoscopy (HRA), an anal cancer screening procedure. Specialized equipment, such as a colposcope, is required and patients are followed by a multidisciplinary team, which may consist of the primary care provider, infectious diseases specialist, gastroenterologist, and general or colorectal surgeon.[5] The interpretation of anal pathology also requires a skilled pathologist, familiar with human papillomavirus (HPV) disease. HRA remains unfamiliar to many providers in health care and patients are unaware that anal cancer screening exists. Early results of clinical trial data evaluating the impact of anal cancer screening are emerging; and thus, the lack of evidence to support anal cancer screening adds uncertainty to the value of screening and adoption of this practice. Thus, practices for anal cancer screening vary widely across providers.

Health care professionals may omit addressing the anus due to time constraints and due to the avoidance of causing personal embarrassment of the patient or physical discomfort by visual inspection or digital anorectal examinations. Oftentimes, patients are unaware of anal complaints. Providers also exhibit limited comfort levels in their discussion of anal symptoms, such as fear of "opening a floodgate."[6] In a

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study by Walker et al, 36% of people living with HIV were reported discussing anal health with their HIV primary care providers in the previous year.[3] In a study by Rosa-Cunha, et al, 22% of women, 32% of heterosexual men, and 54% of men who have sex with men (MSM) reported discussing anal health with their HIV providers in the prior 12 months.[6]

More specific to anal cancer screening and management is the LGBTQ (lesbian, gay, bi-sexual, transgender, queer/questioning) community that makes up the highest-risk cohort for anal cancer. As per a report published by the International Lesbian, Gay, Bisexual, Trans and Intersex Association in March 2019, 70 (35%) countries which belong to the United Nations criminalized consensual same sexual acts with 11 countries designating same sexual acts as punishable by death.[7] Social stigma exists for the LGBTQ population and as a result, they encounter blackmail, violence, and discrimination.[4,8,9] Due to fear of retribution, patients may not disclose their contact information, sexual orientation, and express distress when discussing sensitive topics with their health care providers, making the diagnosis of anal cancer difficult. Medical providers may feel uncomfortable asking about a patient's sexual orientation or make assumptions regarding their sexual practices.

Existing Screening/Surveillance Approaches

Strategies for anal cancer screening and surveillance vary immensely due to the lack of data and specific consensus guidelines that exist. The following sections describe methods of detection of anal cancer:

Visualization/inspection, digital anorectal examination (DARE): This examination includes parting the buttocks to evaluate the anus for abnormalities. A DARE identifies and evaluates lesions within the anal canal and rectum. The European AIDS Clinical Society recommends DARE every 1 to 3 years for HIV-positive MSM. As per NIH guidelines, annual DAREs are recommended for individuals who are HIV positive.[10] However, even in developed countries, performance of a DARE is lacking. Farooq et al demonstrated that 46.2% of the patients referred for the confirmed diagnosis of rectal cancer, did not recall having a DARE by their primary care provider, despite having anorectal symptoms or a positive fecal immunochemical test. Female patients were less likely to have a DARE (28.6%), compared with males (47.3%).[11] Reasons for not performing a DARE include patient discomfort, reluctance to perform a DARE by the primary care provider, time constraints during the physical examination, and limited experience and education of the primary care provider in delineating what they feel on DARE.

Anoscopy: An anoscope or a plastic tube is placed as a retractor into the anus with an associated light source to evaluate for anorectal pathology. Biopsies may be obtained for evaluation by pathology.

Anal cytology: A moistened Dacron swab is inserted approximately 3 to 5 cm into the anorectum. The swab is firmly pressed against the mucosa while translating in a circular motion throughout the anal canal and then submitted as liquid-based cytology. A semi-automated process encompasses creation of an evenly dispersed thin monolayer of cells, which is then examined by the cytopathologist. Anal cytology is then reported as follows: atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, high-grade intraepithelial lesion (HSIL), cannot exclude HSIL (ASC-H), or squamous cell carcinoma. The sensitivity ranges from 42 to 98%; the specificity ranges from 16 to 96%.[12–21] This large variation in sensitivity and specificity of anal cytology can be attributed to sampling error and pathological interpretation. Currently, the bulk of anal cytology is performed by health care providers specialized in HIV care and surgeons who specialize in anal cancer screening and treatment. Anal cytology results should not solely be used in the diagnosis and management of anal intraepithelial lesions.[10] Most providers consider cytology as a useful test for triaging patients to determine who should be referred for HRA.

HRA: HRA involves anoscopy with identification of the squamocolumnar junction and targeted biopsies. Topical acetic acid or Lugol's iodine solution is applied to the anal canal with evaluation via a colposcope to identify abnormal vascular patterns, such as punctations, mosaicism, warty vessels, and corkscrewing of the blood vessels. While there is a long learning curve for this procedure, the sensitivity is 90.9 to 100% and specificity is 65.63 to 74.7%, positive predictive value of detecting HSIL is 47.62 to 79.8%, and negative predictive value 82.3 to 100%.[22–24] This technique may be performed in a clinic setting or in the operating room.

Endoscopic approaches: While the aforementioned techniques in the screening of anal cancer are considered standard of care, gastroenterologists have started to use endoscopy in the detection of anal intraepithelial neoplasia. Introduced by Inkster et al, an endoscope is introduced through a lighted anoscope under intravenous sedation. Acetic acid is applied to the squamocolumnar junction, and inspected using white light and narrow band imaging.[25] However, colonoscopic evaluation does not detect distal anal canal and perianal intraepithelial lesions.[10]

Anoscopy, HRA, and endoscopy present the opportunity for therapeutic intervention of dysplastic pathology.

While national and international organizations have published consensus guidelines, these guidelines remain vague regarding screening and surveillance of anal cancer. As the Anal Cancer HSIL Outcomes Research (ANCHOR) and Study of the Prevention of Anal Cancer (SPANC) clinical trials are completed, then this will allow us to understand the natural history of anal HPV disease and progression with the development of more concrete guidelines for implementing anal cancer screening programs. Recently, the ANCHOR Study published a press release, stating that ablation of anal HSIL reduces the chance of progression to anal cancer.[26] Specific valued results of this study are currently pending.[27]

Available Treatment Approaches and Outcomes

Squamous Intraepithelial Lesion

Traditional treatment options for SIL are often separated into surveillance or more aggressive interventional strategies. The current literature suffers from a dearth of major

randomized studies. Most data are derived from single institutions, case–control series, or case reports.[28] Treatment options for low- or high-grade lesions include excision, fulguration, laser therapy, or topical treatments such as trichloroacetic acid (TCA), imiquimod or 5-fluorouracil (5-FU). A small subset of patients with anal HSIL may benefit from having their HRA and ablation in the operating room. TCA has a good safety profile with few major side effects. It can be applied during examination and is usually well-tolerated. TCA results in clearance of HSIL in approximately 75%% of patients, but is unlikely to be effective with larger lesions, and for more extensive HSIL.[29] 5-FU is a chemotherapy agent that inhibits DNA synthesis and, with topical application, can clear SIL. Clearance rates vary, but prospective data observes a complete clearance of 90%, with a recurrence rate of 50% at 6 months.[30] Side effects include skin irritation or hypopigmentation. Imiquimod (trade name Aldara) is a synthetic immune modulator that upregulates a patient's innate immune system to include antiviral activity. In HIV-positive individuals, imiquimod has been shown to downgrade high-risk lesions to low-risk lesions in randomized trials,[31] and 61% of patients in a randomized study had absence of high-grade lesions with imiquimod treatment.[32] A small randomized trial comparing topical imiquimod versus 5-FU or electrocautery concluded that electrocautery had a higher rate of complete resolution than either topical therapy, and rates of grade 3 to 4 treatment-related side effects were highest with imiquimod.[33] Though not yet peer-reviewed, the multicenter ANCHOR trial was halted early given the observation that removing HSIL drastically reduces the chance of progression to anal cancer.[27]

Challenges to the treatment of SIL in LRS are numerous. Providers may lack specialized training in management of SIL. Pathologic support for accurate diagnosis and grading of SIL is often lacking. Access to therapeutic agents varies widely by setting. Most LRS will not have access to HRA. Active surveillance is made difficult due to overall access to health care and lack of education for both providers and patients as to the importance of follow-up.

Anal Cancer

Anal cancer has traditionally been considered a rare disease with an incidence rate of 2.0 per 100,000 persons overall with 1.6 per 100,000 in men and 2.3 per 100,000 in women. Anal cancer encompasses 0.5% of all new cancer cases.[34] In the past three decades, an increasing incidence of anal cancer by 2% per year has been observed and, in 2020, worldwide diagnoses of approximately 50,865 cases have been observed.[35,36] The majority are squamous cell carcinomas. Approximately 90% of anal squamous cancers are linked to HPV, and related to HPV-16 in >75% of these cancers.[37] Many studies have reported a high rate of anal HPV in HIV-infected women with most reporting prevalence rates >70%.[38] Globally, >4% of all types of cancer cases are associated with HPV and of these approximately 2% in high-income countries and approximately 8% in low-income countries, especially in Sub-Saharan Africa.[38] HPV-related anogenital cancers are increasing worldwide.[39]

The present standard of care for the treatment of squamous cell carcinoma of the anus (SCCA) is the modified NIGRO protocol with primary chemoradiotherapy with fluorouracil (FU) and mitomycin C. This results in a high level of disease control for small, early-stage SCCA.[40–42] More advanced cancers fare poorly with this treatment, and the disease relapses locoregionally in the majority of cases (30–50% of patients), which requires a salvage abdominoperineal resection (APR). Metastatic disease is rare at presentation, with less than 20% of all patients with SCCA presenting with surgically unresectable or metastatic disease. This portends poor survival with an estimated 5-year relative survival of 68.7%.[34] Chemotherapeutic options for this group of patients with surgically unresectable or metastatic disease are currently limited. Immunotherapy drugs, such as pembrolizumab and nivolumab are now being used for advanced anal cancers.

Care of patients with SCCA in LRS is hampered by several factors. Screening programs, especially for high-risk individuals (HPV infection, immunosuppression, a prior history of sexually transmitted disease [especially HIV], and tobacco abuse), are rare. Access to chemotherapeutic agents as well as radiotherapy is variable and mostly confined to urban areas. Provider education in the diagnosis and treatment of SCCA can be lacking. Long-term surveillance is challenging due to access of care, which results in a delay of detection of recurrence that may be amenable to salvage APR. Finally, a large number of patients present with later stage cancers, which severely limit treatment options.[43]

Despite these challenges, treatment of SCCA in LRS is possible. A study from South Africa described the management of 268 patients with SCCA.[44] Half the patients were eligible for definitive therapy at the time of diagnosis. Notable within this study was the observation that the proportion of patients who did not receive any treatment at all was higher among HIV-positive patients than among those who were HIV-negative (24 vs 12%). Reasons for patients receiving no treatment included failure to return, prior resection, and poor performance status.

Future Directions

As detailed above, screening, surveillance, and treatment of both anal SILs and anal cancer are made difficult by a myriad of challenges. Opportunities to improve care can be found in education, resource building, access, and novel treatment strategies. While the literature remains sparse in details, two central themes emerge. The first is general capacity building with the realization that investment in health care and cancer treatment can have a significant return in terms of both health and economic benefits. Second, HPV vaccination has the potential to prevent anal SILs and ultimately anal cancer. Implementation strategies have been described and have met with varying degrees of success.

Health Capacity Building

Investment in cancer care in LRS is expensive, mainly due to improvements in infrastructure for imaging and treatment.

However, when the benefits of such expansions are considered, substantial gain can be observed. Ward et al, used a previously developed model of global cancer survival and estimated stage-specific cancer survival and life-years gained in 200 countries and territories for patients diagnosed with one of 11 cancers (including anal cancer).[45] They estimated that without scale-up (i.e., with current availability of treatment, imaging, and quality of care) there will be 76 million cancer deaths (95% UI 73·9–78·6) globally for patients diagnosed between 2020 and 2030, with more than 70% of these deaths occurring in low- to middle-income countries. Comprehensive scale-up of treatment, imaging, and quality of care could avert 12.5% (95% UI 9.0–16.3) of these deaths globally, ranging from 2.8% (1.8–4.3) in high-income countries to 38.2% (32.6–44.5) in low-income countries. Globally, they estimate that comprehensive scale-up would cost an additional $232.9 billion (95% UI 85.9–422.0) between 2020 and 2030 (representing a 6.9% increase in cancer treatment costs), but produce $2.9 trillion (1.8–4.0) in lifetime economic benefits, yielding a return of $12.43 (6.47–33.23) per dollar invested. Scaling up treatment and quality of care without imaging would yield a return of $6.15 (2.66–16.71) per dollar invested and avert 7.0% (3.9–10.3) of cancer deaths worldwide. These findings demonstrate that scaling up both treatment and imaging capacity could yield significant survival gains for patients with cancer. Expanding traditional modalities in lower-income settings might be a feasible pathway to improve survival before scaling up more modern technologies.

HPV Vaccination

While current prophylactic HPV vaccines have demonstrated outstanding results in preventing HPV infection, barriers to vaccine distribution have limited their widespread use in LRS, where the burden of HPV-associated AIN and anal cancer is highest. HPV vaccination prevents new anogenital HPV infections and does not cure existing HPV infection. The Centers for Disease Control (CDC) recommended HPV vaccination for everyone of age 26 years and above.[46,47] In June 2019, the Advisory Committee on Immunization Practice recommended shared clinical decision-making for HPV vaccination of adults aged 27 to 45 years.[47] Therapeutic HPV vaccines that generate T cell-mediated immunity against HPV infection and associated diseases are needed to reduce the incidence of disease in those with existing HPV infection.[48]

The World Health Organization (WHO) recommends that routine HPV vaccination of young adolescent girls could be integrated in national immunization programs if five key criteria are fulfilled.[49] These include: (1) Prevention of anal cancer, cervical cancer, and other HPV related-diseases, constitutes a public health priority; (2) Vaccine introduction is programmatically feasible; (3) Sustainable financing can be secured; (4) The cost-effectiveness of vaccination strategies in the country or region is considered, (5) HPV vaccination is targeted to adolescent girls prior to sexual debut.

There are emerging studies that demonstrate that HPV vaccination is both beneficial and cost-effective in decreasing anal HSIL recurrence after ablation and decreasing lifetime development of anal cancer in HIV-positive MSM.[50–52]

Several barriers to successful implementation of HPV vaccination exist, including financing, access of vaccine, distribution, acceptability (providers, parents and adolescents, cultural barriers, and operational challenges).[53] A successful nationwide HPV vaccination program requires a well-established vaccine delivery system with adequate cold chain transportation, human resources, and monitoring capacity. Collaboration between public and private institutions within the framework of strong national ownership is critical for long-term sustainability.[54] An analysis of HPV vaccine acceptability in Botswana found 74% of study participants would have their daughters vaccinated against HPV at school if the vaccine was available.[55] An important element to the success of vaccination campaign was sensitization and training of school teachers to assist in recruitment and follow-up of girls for the study. Such training was found to be an essential component of the success of a school-based HPV vaccine program in Peru.[56] Additionally, effective use of schools as venues for HPV vaccine programs is an important factor in successful adoption of HPV vaccine in LRS.[57] In sub Saharan Africa, Rwanda serves as an example of an effective vaccination program. In 2010, Rwanda partnered with Merck to begin an HPV vaccination rollout. In so doing, Rwanda became the world's first low-income country to provide universal access to the HPV vaccine.[58]

Conclusion

Anal cancer screening and treatment options are limited in LRS. There remains a need for better infrastructure within society and the health care system to deliver adequate anal cancer care. Anal cancer continues to affect patient cohorts that may not be accepted by current societal beliefs and thus presents an even greater health care challenge.

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