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An overview of Human Papillomavirus (HPV) as an etiological factor of the anal cancer

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ABSTRACT

Human papillomavirus (HPV) is a DNA tumour virus that is the primary cause of sexually transmitted infections (STIs). The direct connection between HPV and cervical cancer was discovered in 1980, however, many physicians and the general public are still oblivious to the association of HPV and anal cancer; most individuals find out about this relationship after a confirmed diagnosis, and therefore, it is important to raise awareness about HPV as an etiological agent in anal cancer. There is a quadrivalent vaccine available, which prevents an individual from being infected with HPV, thus anal cancer is mainly a preventable cancer when caused by HPV, and ultimately, preventing cancer is better than curing cancer, especially when there is no definite cure.This article aims to review the microbiology, pathophysiology, epidemiology, clinical presentation, diagnostic evaluation, prophylaxis and treatment options for HPV as an etiology agent in anal cancers in light of recent literature.

Contents

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Introduction

Human papillomavirus (HPV) is a DNA tumour virus that leads to epithelial proliferation on both mucosal and cutaneous surfaces; HPV is responsible in being the primary cause of sexually transmitted infections (STIs). Currently, there is a research focused drive on HPV, owing to the severity of HPV associated diseases, including anal cancers. Although anal cancers are uncommon, there has been an increasing incidence for both males and females [1].

Over the preceding decades, the fundamental understanding of the pathophysiology and treatment of anal cancer has drastically evolved. Presently, more than 90% of anal cancer cases are linked to HPV infections, especially with the high risk (HR) HPV subtype (HPV-16); these brands anal cancer as a largely preventable malignancy [2].

This article aims to review the microbiology, pathophysiology, epidemiology, clinical presentation, diagnostic evaluation, prophylaxis and treatment options of the HPV infection and the anal cancer in light of recent literature.

Human papillomavirus (HPV)

The nomenclature of HPV is based on recommendations derived from the Study Group of Papillomavirus and established by the International Committee on Taxonomy of Viruses (ICTV).

HPV has a long evolutionary history spanning more than 300 million years, and comprises of a diverse group of more than 150 related viruses that have slowly evolved with their host. Papillomavirus genomes have been isolated and characterised from reptiles, birds and multiple other mammalian species, however, humans are the only known reservoir for HPV [3].

HPV is a small double-stranded, non-enveloped DNA virus; around 60 of these HPV types are detected in the mucosa epithelium, and are restricted to the basal cells located in the stratified epithelium [3]. HPV comprises of 8000 base-pairs (bp) that are bound to cellular histones and enveloped by a protein shell that is composed of two late open reading frame (ORF) molecules called: L1 and L2; L1 makes up 80% of the viral protein. There is also the coding capacity for six early ORFs proteins called: E1–E7 which are a requirement for replication and assembly within an infected cell. E6 and E7 proteins inactivate two tumour suppressor proteins, p53 and retinoblastoma protein (pRb) respectively. Both sets of ORF genes are separated by a 1000 bp upstream regulatory region which contains cis-elements for the regulation of genes, replication of the genome and packaging into virus particles. HPV has the ability to exploit their host's enzymatic mechanism, thus guaranteeing a low mutation rate and a high degree of proof reading [4].

HPV can be divided into the following classes: alpha, beta, gamma, mu, and nu; viruses from the beta group can infect cutaneous epithelia, whereas the remaining types are responsible for the formation of papillomas that are typically not subject to neoplastic transformation [3]. Subtype HPV-6 and -11 of the alpha 10 species are mainly responsible for genital warts and respiratory papillomas, which are both low risk (LR) types as they tend to cause warts but not cancer; the HPV subtypes 39, 56, 59, 66, and 68 are considered LR. Despite individuals with condyloma acuminatums being infected with LR sub types of HPV, they have an amplified risk of acquiring anal cancer since they are more likely to acquire a HR HPV subtype, such as: 16, 18, 31, 33 and 45. These sub types are liable for over 80% of the cervical cancers; HPV-16 is the most likely to cause anal cancer [5].

HPV infection and anal carcinogenesis

The transformation of infected HPV cells into cancer cells is a multistep process. The virus targets actively proliferating basal cell situated in the transformation zone; this is within the rectal columnar mucosa distal to the dentate line, and spreads proximally from the squamocolumnar junction. Cellular proliferation, and subsequent immortalisation and malignant transformation are a result of oncoproteins: E6 and E7 [6].

Two replication modes of HPV in infected cells are known, these include: stable replication in the basal cells or vegetative replication in more differentiated cells to generate a progeny virus. Initially, the viral genome is copied 100 times, and preserved for varying periods, whilst simultaneously replicating essential components that include: E1 and E2. The activation of the E2F transcription factor occurs when E7 binds to pRB, triggering the expression of proteins vital for DNA replication. The mature virions are only produced in the utmost superficial layer, and in the terminal stage the cells migrate to the suprabasal compartment, where they instigate the terminal differentiation phase and these cells lose their ability to divide.

Malignancies do not arise from LR HPV subtypes due to disparities between regulation and promoter positioning, the pattern of mRNA splicing, as well as the weaker binding of the target protein to E6 and E7. It is hypothesised that anal cancers of squamous cell origin are directly linked to a complex inflammatory process generally caused by HPV-16 and -18 [7].

The tumour node metastasis (TNM) staging system developed by the American Joint Committee on Cancer grades the extent of anal cancer; the grading of anal cancer echoes the grading of cervical dysplasia. Anal intraepithelial neoplasia (AIN) archives the dysplastic changes in the anal canal that are presumed to be the precursors to invasive anal carcinoma and squamous cell carcinoma. AIN-I is a low grade dysplasia, whereas both AIN-II and AIN-III are high grade dysplasia, and can be involved in invasive cancer. A study among high risk patients, recorded the progression of 12.6% male patients, from AIN I to AIN III and the highest hazard ratio of 2.8 was documented in patients with human immunodeficiency virus (HIV). In the study, the CD4 count did not play a noteworthy factor in progression rates. There were also regression rates of 47% of a group of 55 patients from AIN III [8]. A similar study followed 556 HIV positive males, which had a progression rate of 10.5/100 person-years for 649 person years and concluded that if the patient was on anti-retroviral therapy or in a stable relationship they were subsequently protected, with a progression rate of only 2.8/100 person-years [9]. Further, study reported a progression of 19.6% in individuals who have had a history of HSIL [9]. These studies show that despite the risk of progression from AIN to cancer, the progression rates are much higher in high risk population.

During the spread of anal cancer, the involvement of anal musculature arises early on since the mucosa is local to the underlying sphincter, and the cancer propagates circumferentially causing a stenosis of the anal sphincter. In anal cancers, liver metastasis is more common than other metastasis, although there has been records of metastases to the brain and the iris. It is important to note that once there is an active infection, the virus has the ability to spread to others, thus meaning that the exact source of infection is difficult to establish due to the time it takes from active infection to clinical presentation of the disease [10].

HPV and anal cancer epidemiology

Annually, there is an estimated 27,000 new cases of anal cancer worldwide, with a ratio of female to male being as high as 5:1. Historically, females have had a higher rate of anal cancers compared to males, and recent publications have shown that the rates for females of the anus, anal canal and anorectal cancers in all races and ages has more than doubled [11]. Despite the rates being significantly higher in white woman compared to black woman, the

opposite is true for males as black men have a significantly higher incident rate of anal squamous cell carcinomas [12].

In 2013, there was a total of 152,555 deaths in Europe with Germany experiencing the majority of deaths (25,745) due to malignant neoplasms of: colon, rectosigmoid junction, rectum, anus and anal canal, whilst Poland had 11,300 deaths owing to these malignant neoplasms [13]. Rates of recorded anal cancer in Poland are highest in the Lower Silesia region for both sexes. There were 55 reported cases of anal cancer in males and 101 cases in females during the period from 2003 to 2007, in Lower Silesia [14]. A study in both Sweden and Demark, that involved 386 anal cancer patients, Frisch et al. observed that HPV was positive in 83% and 95% of patients respectively [15].

In a US study, anal cancer incidence rates were markedly higher amongst the cohort of 447,953 people coinfected with HIV infections, especially in men who have sex with men (MSM), those of increased age and AIDS sufferers, compared to the general population. The rate of anal cancer incidence with HIV increased annually by 32.8% between 1996 to 2000; thereafter and up until 2008, there was a plateau which was reached. Incidence rates have declined from 2008 to 2012 at an annual rate of 7.2% [16].

Normally, HPV is a transient disease especially in young woman, with statistics showing that 70% of woman that become infected become HPV negative within 1 year, and 91% were HPV negative in two years with a median duration of disease being only 8 months. On the other hand, HPV-16 is considered as one of the most dangerous sub-types and is more persistent, with a 24-month clearance rate of 72% [17].

There are numerous risk factors involved and current epidemiological studies that have highlighted the increase risk in certain subpopulation, specifically MSM and individuals infected with HIV; there is a clear association between HIV and anal cancer, however anal cancer is not an AIDS-defining malignancy. In the past, the number of individuals who had contracted anal cancer was estimated to be 60 times greater in HIV infected MSM than the general population; since the use of highly active antiretroviral therapy (HAART) there has been an increase in HPV associated anal cancers [18]. Furthermore, HIV positive men who have a CD4 cell count of $<200/mm^3$ are associated with a three times higher transformation rate of normal or atypical epithelium to anal squamous intraepithelial lesions, or to a higher AIN grade [19].

There is an increased prevalence of anal cancer in individuals undergoing a solid organ transplant due to chronic immunosuppression. Also, a history of venereal diseases, including: genital warts, anal warts, gonorrhoea, syphilis, chlamydia, trichomoniasis, labial herpes and hepatitis increases an individual's risk of HPV infection. Similarly, smokers have an augmented risk due to the genotoxic damage of the anal epithelium [20]. Crohn's sufferers, especially those with active perianal disease, are predisposed to anal cancer with an incident rate of about 14% [7].

HPV transmission

There are numerous identifiable risk factors, with an increased risk seen in individuals who have multiple sexual partners, and practice promiscuous sexual behaviours.

The transmission of HPV is through direct skin to skin contact, and the mode of transmission is through the medium of intercourse, mainly penetrative vaginal, anal, or oral sex, although this is not necessarily true for all cases. A study with 603 college students found that most HPV infections are acquired in the first few years of sexual activity. In this study, 40% of the students acquired HPV infections within the first two years and that the risk was proportional to the number of sexual partners [21].

HPV infection can spread from one area to another, for example: it can originate in the genitals and extend to another part, such as the anus. The virus can even be spread via hand to genital contact and both asymptomatic and symptomatic individuals can pass the infection on. Additionally, much like other sexually transmitted diseases like: HIV, Hepatitis B virus (HBV), Herpes simplex virus 2 (HSV-2), Neisseria Gonorrhoea, genital HPV can be spread from mother to child during pregnancy or during the delivery period via vertical and perinatal transmission; this is evident as genital HPV can be present is sexually naive populations including infants and virgins. In anal carcinoma, the most predominant subtype is HPV-16 (73.4%), followed by HPV-18 (5.2%) and HPV-33 (4.8%) [22].

Clinical presentation of HPV infection and anal cancer

HPV infection can either have latent, subclinical, or clinical presentation. The presentation of the disease varies according to the anatomical area involved; many individuals infected with HPV do not have genital warts or other signs of infection. There are various pathologies that can be present during an active HPV infection; these may include: common warts, plantar warts, flat warts, anal dysplasia, laryngeal papillomatosis, mouth papilloma's and focal epithelial hyperplasia. If genital warts are present, then there are many different possible appearances, for example: raised, flat, pink or flesh coloured or even cauliflower shaped and they may be present in multiple numbers or alone [23].

Early on in cancers associated with HPV, there may be benign lesions or other indications of anal cancers including: fissures, haemorrhoids, dermatitis, pain in the anal region, loss of bowel control and anorectal fistulas, with discharge present in more than 50% of cases, nevertheless, 20% of cases may present asymptomatically [24]. A mass or growth in the anal canal may appear in later stages. Additionally, literature shows that anal cancer patients can have unusual presentations, for instance: isolated inguinal lymphadenopathy due to metastasis, multiple abscesses, cerebral metastasis, iris metastasis or disseminated carcinomatosis of bone marrow [25]. Inguinal lymphadenopathy metastasis may be misdiagnosed as an inflammatory node or even hernia leading to serious delay in treatment.

HPV infection and anal cancer diagnosis

Anal cancers have numerous similarities to cervical cancers which include, but are not limited to both being squamous cell cancers and caused by similar HR HPV types. Due to the comparable cervical cancer rates before the introduction of the screening protocol paralleled to current anal cancer rates in MSM, there is an increased awareness that it would be beneficial to screen HR groups for anal cancer precursors [22].

Anal Papanicolaou smears (pap) provides a cytological examination by inserting and rubbing a Dacron swab past the squamocolumnar junction in the anal canal and using the same sample, HPV can be detected. However, this is not a beneficial screening tool in the HR groups, since about 67% of HIV positive MSM have abnormal anal cytology, with around 10% having high grade squamous intraepithelial lesions. The gold standard for diagnosis of high grade disease high resolution anoscopy (HRA), is done by examining the squamocolumnar junction, anal canal, and the perianal skin under magnification using an anoscope, vinegar and Lugol iodine to stain the area in an attempt to localise the source of atypical cells, and permitting the visualisation of any flat, dysplastic and neoplastic lesions which can then be biopsied [26]. Also, a physical examination can demonstrate a characteristic grey or pink fleshy cauliflower-like growths of variable sizes or dysplastic lesions in the perianal area.

Since viral multiplication in HPV is confined to the nucleus, the most characteristic features under the microscope are koilo-

Table 1
DNA testing methods of HPV infection [27].

Method	Sample types	Methods profile
FISH (fluorescence in situ hybridization with filters)	Homogenate tissue	• Fast examination (approximate turnaround time of 48–72 h) • Low sensitivity, low specificity • Specimen architecture remains intact • Archived samples of up to 7 years old can be used
NISH (non-isotopic in situ hybridization)	Tissue histological and cytological slides	• Direct HPV examination in tissue cells • Low sensitivity, substantial labour consumption
Southern blot	Purificated DNA	• Moderate sensitivity and high specificity • More expensive than many tests • Labour intensive
Dot blot	Purificated DNA	• High sensitivity and high specificity • Simultaneous screening of many samples can be done • Substantial labour-consumption, since initial isolation of plasmid DNA is needed
PCR	Purificated DNA, tissue, smears	• High sensitivity and specificity genotyping possibility • Low cost • Little sample tissue needed • Fast examination • High contamination risk

cytes which might be enlarged and hyper-chromatic with double nuclei, and a clear perinuclear zone around mature squamous cells. Diagnosis can be confirmed histologically via a biopsy under direct visualisation. The traditional methods of viral diagnosis, including: cell culture, electron microscopy, and immunological methods are not suitable for detecting HPV. Other tests to consider are imaging and DNA testing: fluorescence in situ hybridisation with filters, non-isotopic in situ hybridisation, southern blot, dot blot, and PCR. DNA testing can be undertaken and this is summarised in Table 1 [27]. Southern blotting is the gold standard for HPV genomic analysis [26].

Imaging is also important in diagnosis, with the use of endoanal ultrasound that can determine the depth of the penetration of the cancer. Otto et al found endoanal ultrasound was able to provide 100% sensitive in detection of anal cancer, and was 67% accurate in assessing the depth of tumour as compared to histopathological analysis of selected specimen. Also, CT scanning can be used to directly visualise anal cancer as a hypoattenuated necrotic mass on a contrast enhanced CT scan. The tumour may however be isoattenuated when compared to the musculature, and suspicion might only arise from indirect signs like symmetrical bulging of the anal sphincters or asymmetry in the thickness of the sphincter. MRI scanning is another effective imaging modality for anal cancer and the imaging of choice for loco-regional images, primary and recurrent tumours have high signal intensity on T2 weighted images compared to skeletal muscle, and low to intermediate signal intensity on T1 weighted images. Initial staging and post treatment restaging uses PET or CT scanning with 18F-fluorodeoxyglucose scanning which helps to differentiate viable anal cancer and post treatment necrosis and fibrosis able to recognise tumours less than 2 cm in diameter [28].

Other diagnostic markers used to detect HPV in head and neck squamous cell carcinomas (HNSCC) include biomarkers; the gold standard for HNSCC classification is HPV E6/E7 mRNA identification. This is due to these types of HPV-associated tumours requiring the expression of viral oncogenic proteins E6/E7 which are fundamental for neoplastic transformation. Other markers include p16, which has a well documented prognostic role, and the sensitivity (60–99%) of this marker is very high in comparison with the gold standard HPV E6/E7 mRNA diagnosis method, however the specificity (33–76%) is much lower [29].

HPV infection prophylaxis

Prevention plays a significant role in reducing the incidences of cancer. The pap test is currently considered the main method of prevention, but the quadrivalent vaccination is fast becoming an increasingly important factor for successfully preventing anal cancer and other HPV related diseases such as cervical cancers.

In 2015, the vaccine became available, and it is given in three doses. The vaccine is able to offer protection against infection and disease related to HPV subtypes: 31, 33, 45, 52, and 58 in a susceptible population, and has generated an antibody response to HPV subtypes: 6, 11, 16, and 18. In Poland, the HPV vaccination was incorporated in the second part of the Programme of Preventive Vaccination and is only free to females if the local government finance the vaccine since it is not financed by the Ministry of Health. In 2010, 150 entities funded the scheme which resulted in 30,000 girls being vaccinated. At present, there is no system for collecting data about vaccination against HPV, so there is no comprehensive method to assess the health outcomes of this vaccination, however under objective 12, the cancer control strategy for Poland 2015–2024 outlined the necessity to prevent infection-induced cancers with the vaccination against HPV [30].

The most effective method for complete prevention of HPV infection is absolute avoidance of contact by infected person with the anogenital areas. Condoms have been found to offer some protection against HPV, however, condoms cannot offer full protection because they do not cover every possible HPV-infected area of the body. Moreover, adolescents are using anal intercourse for birth control, so advocating a health educational program that encourages sexual safety is also a major key in minimising HPV and HIV transmission [31]. A lower incidence rate of HPV infection is seen in circumcised men, the reason for this remains unclear, but it is hypothesised that it might be due to the changes in the glans penis skin changing after circumcision or that the foreskin that is removed is more susceptible to HPV infection, but this does not provide guaranteed protection from infection of HPV [32].

Education plays important role in prophylaxis of HPV infection and cancer. A recent study presented that the general knowledge

and awareness of HPV was variable depending upon the sociodemographic factors; these factors included, but were not limited to age, gender, income and employment. The results demonstrated that more woman (60%) had previously heard about HPV, compared to only 44% of men. Furthermore, the knowledge of a link between HPV and cervical cancers were high in contrast to the knowledge of an association between HPV and non-cervical cancers which were low. Additionally, many of the participants believed that the vaccine was not adequate [33]. Moreover, a study which examined the public education on the potential impact of HPV on the male health demonstrated a lack of knowledge from parents on the association of HPV and male cancers, and once given brief knowledge on HPV, the majority would choose to vaccinate their sons if the vaccination program was extended to men, therefore, concluding that education is paramount to making an informed decision [34]. Another way to educate the public is via one-to-one consultations with medical professionals, social media, as well as mass advertising.

Treatment methods of HPV infection and anal cancer

At this time, there is no specific treatment for HPV infections, because more often than not, the viral infection clears on its own; conversely, some experts argue that the infection might not be completely eliminated, and could just be reduced to undetectable levels. For anal cancer of any stage, patients who are diagnosed with squamous cell carcinoma have a more favourable outcome than those patients with a diagnosis of non-squamous cell carcinoma of the anal canal [35]. Additionally, a male patient with a tumour of $\geq$5 cm and with nodal involvement have unfavourable outcomes [36]. The treatment of anal cancers requires management by a multidisciplinary team, with concurrent chemotherapy and radiation therapy as well as surgery for early stages, or even late stages when the cancer does not respond to other treatment.

Cosmetically, warts that appear can be removed using over-the-counter treatment or cryotherapy but this is only feasible in premalignant lesions. Topical therapy of direct application including trichloroacetic acid (TCA), 5-flurouracil or imiquimod to the specific lesion or the entire anal canal can be used. In a retrospective study, it was found that 71–79% of cases regressed from HSIL to LSIL or complete resolution when using TCA [37].

Additionally, local ablative therapy can be applied to anal lesions, with a more favourable response from electrocautery therapy with multiple sessions. While, radiofrequency ablation has shown to be safe, but efficacy is presently unknown [38].

Several surgical treatments exist, especially after failed topical treatment; the benefit of this would encompass: fewer doctors' visits, safe in pregnant patients, and the tissue can be tested further. The preferred method for small lesions is fulguration and electrocautery and with larger or suspicious lesions cold excision with fulguration of the base of the lesion being preferred. Some authors have recommended a two-staged operation after punch biopsy and permanent histology due to the significant morbidity after wide local excision for larger lesions [39].

Post treatment surveillance is essential; therefore, rigorous follow up care is recommended, as frequent as every 3–6 months as long as dysplasia is present as well as in immunosuppressed or immunocompromised individuals. Patients receiving chemoradiotherapy for oropharyngeal cancers and were HPV positive had a more favourable outcome. The 3-year disease free survival rate was 85.7% in HPV positive patients and 22.2% in HPV negative patients; this result was similar to the 5-year disease-specific survival after treatment, with 85.7% versus 11.1% respectively. The recent data showed that the overall and disease-free survival were much higher in T4 HPV positive patients compared to negative patients [40].

Conclusion

Now, with a better understanding of HPV and anal cancers, there comes new challenges and questions. It is evident that HPV is a preventative etiological agent for anal cancer and other cancers. With cancer, currently a major global health burden, which leads to significant morbidity and mortality, diagnostic programs should be implemented, especially focusing on populations at risk, in addition to awareness being raised amongst physicians and individuals in regards to the link between HPV and cancers, especially anal cancers. Furthermore, the HPV vaccination should be used prophylactically, and it is worth considering implementing a vaccination programme on a worldwide basis which could aid in preventing many cancers, because ultimately prevention is better than cure, especially when something has no cure. Development of educational programs related to HPV should have high worldwide priority. Understanding of HPV biology and HPV-related cancers, including anal cancer is a fundamental tool and might be critical in improving vaccine intake and reducing HPV infection.

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References

[1] Mirabello L, Clarke MA, Nelson CW, Dean M, Wentzensen N, Yeager M, et al. The intersection of HPV epidemiology, genomics and mechanistic studies of HPV-mediated carcinogenesis. Viruses 2018;10:E80, http://dx.doi.org/10.3390/v10020080.

[2] Maniar KP, Nayar R. HPV-related squamous neoplasia of the lower anogenital tract: an update and review of recent guidelines. Adv Anat Pathol 2014;21:341–8, http://dx.doi.org/10.1097/PAP.0000000000000035.

[3] Bernard HU, Burk RD, Chen Z, van Doorslaer K, zur Hausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010;401:70–9, http://dx.doi.org/10.1016/j.virol.2010.02.002.

[4] Schiffman M, Doorbar J, Wentzensen N, de Sanjosé S, Fakhry C, Monk BJ, et al. Carcinogenic human papillomavirus infection. Nat Rev Dis Primers 2016;2:16086, http://dx.doi.org/10.1038/nrdp.2016.86.

[5] Li Y, Xu C. Human papillomavirus-related cancers. Adv Exp Med Biol 2017;1018:23–4, http://dx.doi.org/10.1007/978-981-10-5765-6_3.

[6] Jin J. HPV infection and cancer. JAMA 2018;319:1058, http://dx.doi.org/10.1001/jama.2018.0687.

[7] Boda D, Docea AO, Calina D, Ilie MA, Caruntu C, Zurac S, et al. Human papilloma virus: apprehending the link with carcinogenesis and unveiling new research avenues (Review). Int J Oncol 2018;52:637–45, http://dx.doi.org/10.3892/ijo.2018.4256.

[8] Chin JY, Hong TS, Wo JY. Anal cancer: current and future treatment strategies. Gastointestinal Cancer Targets Ther 2013;3:19–27, http://dx.doi.org/10.2147/GICTT.S25844.

[9] Edge SB, Compton CC. The American Joint Committee on cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4, http://dx.doi.org/10.1245/s10434-010-0985-4.

[10] Salati SA, Al Kadi A. Anal cancer—a review. Int J Health Sci (Qassim) 2012;6:206–30.

[11] CANCER CONTROL STRATEGY FOR POLAND 2015—2024 10 June 2014 2015.

[12] Joseph DA, Miller JW, Wu X, Chen VW, Morris CR, Goodman MT, et al. Understanding the burden of human papillomavirus-associated anal cancers in the US. Cancer 2008;113:2892–900, http://dx.doi.org/10.1002/cncr.23744.

[13] Gilbert LK, Alexander L, Grosshans JF, Jolley L. American Social Health Association. Answering frequently asked questions about HPV. Sex Transm Dis 2003;30:193–4, http://dx.doi.org/10.1097/00007435-200303000-00002.

[14] Eurostat Causes of death—malignant neoplasms of colon, rectosigmoid junction, rectum, anus and anal canal, residents,

2013, 2013. http://ec.europa.eu/eurostat/statistics-explained/index.php/File:Causes_of_death_—_malignant_neoplasms_of_colon,_rectosigmoid_junction,_rectum,_anus_and_anal_canal,_residents,_2013. png.
[15] Levi F. Cancer incidence in five continents, vol. VI. vol. 29. 1993. 10.1016/0959-8049(93)90227-7.
[16] Colón-López V, Shiels MS, Machin M, Ortiz AP, Strickler H, Castle PE, et al. Anal cancer risk among people with HIV infection in the united states. J Clin Oncol 2018;36:68–75, http://dx.doi.org/10.1200/JCO.2017.74.9291.
[17] Crooms JW, Kovalcik PJ. Anal lesions: when to suspect carcinoma. Postgrad Med 1985;77:85–90, http://dx.doi.org/10.1080/00325481.1985.11698948.
[18] Rughani AI, Lin C, Tranmer BI, Wilson JT. Anal cancer with cerebral metastasis: a case report. J Neurooncol 2011;101:141–3, http://dx.doi.org/10.1007/s11060-010-0218-5.
[19] Tougeron D, Tougeron-Brousseau B, Nasser Z, Benzerroug M, Lefebure B, Hamidou H, et al. Unusual iris metastasis from anal cancer: a case report. Dig Liver Dis 2009;41:2007–9, http://dx.doi.org/10.1016/j.dld.2007.11.023.
[20] Nielson CM, Harris RB, Nyitray AG, Dunne EF, Stone KM, Giuliano AR. Consistent condom use is associated with lower prevalence of human papillomavirus infection in men. J Infect Dis 2010;202:445–51, http://dx.doi.org/10.1086/653708.
[21] Durragh TM, Colganterence J, Cox T, Heller D. The lower anogenital squamous terminology standardization project for Hpv-associated lesions. Arch Pathol Lab Med 2012;136:1266–7, http://dx.doi.org/10.5858/arpa.
[22] De Vuyst H, Clifford GM, Nascimento MC, Madeleine MM, Franceschi S. Prevalence and type distribution of human papillomavirus in carcinoma and intraepithelial neoplasia of the vulva, vagina and anus: a meta-analysis. Int J Cancer 2009;124:1626–36, http://dx.doi.org/10.1002/ijc.24116.
[23] Salit IE, Lytwyn A, Raboud J, Sano M, Chong S, Diong C, et al. The role of cytology (Pap tests) and human papillomavirus testing in anal cancer screening. Aids 2010;24:1307–13, http://dx.doi.org/10.1097/QAD.0b013e328339e592.
[24] Gómez DT, Santos JL. Human papillomavirus infection and cervical cancer: pathogenesis and epidemiology. Appl Microbiol 2007:680–8.
[25] Muñoz N, Castellsagué X, de González AB, Gissmann L. HPV in the etiology of human cancer. Vaccine 2006;24:1–10, http://dx.doi.org/10.1016/j.vaccine.2006.05.115. Chapter 1.
[26] Lytwyn A, Salit IE, Raboud J, Chapman W, Darragh T, Winkler B, et al. Interobserver agreement in the interpretation of anal intraepithelial neoplasia. Cancer 2005;103:1447–56, http://dx.doi.org/10.1002/cncr.20927.
[27] Abreu A, Souza R, Gimenes F, Consolaro M. A review of methods for detect human papillomavirus infection. Virol J 2012;9:1–9, http://dx.doi.org/10.1186/1743-422X-9-262.
[28] Ciombor KK, Ernst RD, Brown G. Diagnosis and diagnostic imaging of anal canal cancer. Surg Oncol Clin N Am 2017;26:45–55, http://dx.doi.org/10.1016/j.soc.2016.07.002.
[29] Smeets SJ, Hesselink AT, Speel EJ, Haesevoets A, Snijders PJ, Pawlita M, et al. A novel algorithm for reliable detection of human papillomavirus in paraffin embedded head and neck cancer specimen. Int J Cancer 2007;121:2465–72.
[30] Krengli M, Milia ME, Turri L, Mones E, Bassi MC, Cannillo B, et al. FDG-PET/CT imaging for staging and target volume delineation in conformal radiotherapy of anal carcinoma. Radiat Oncol 2010;5:10, http://dx.doi.org/10.1186/1748-717X-5-10.
[31] Baldwin JI, Baldwin JD. Heterosexual anal intercourse: an understudied, high-risk sexual behavior. Arch Sex Behav 2000;29:357–73.
[32] Zhu YP, Jia ZW, Dai B, Ye DW, Kong YY, Chang K, et al. Relationship between circumcision and human papillomavirus infection: a systematic review and meta-analysis. Asian J Androlo 2017;19:125–31, http://dx.doi.org/10.4103/1008-682X.175092.
[33] McBride KR, Singh S. Predictors of adults' knowledge and awareness of HPV, HPV-associated cancers, and the HPV vaccine: implications for health education. Health Educ Behav 2018;45:68–76, http://dx.doi.org/10.1177/1090198117709318.
[34] Sherman SM, Nailer E. Attitudes towards and knowledge about Human Papillomavirus (HPV) and the HPV vaccination in parents of teenage boys in the UK. PLoS One 2018;13:e0195801, http://dx.doi.org/10.1371/journal.pone.0195801.
[35] Wierzbicka M, Józefiak A, Szydłowski J, Marszałek A, Stankiewicz C, Hassman-Poznańska E, et al. Recommendations for the diagnosis of human papilloma virus (HPV) high and low risk in the prevention and treatment of diseases of the oral cavity, pharynx and larynx Guide of experts PTORL and KIDL. Otolaryngol Pol 2013;67:113–34, http://dx.doi.org/10.1016/j.otpol.2013.01.003.
[36] Burgos J, Curran A, Tallada N, Guelar A, Navarro J, Landolfi S, et al. Risk of progression to high-grade anal intraepithelial neoplasia in HIV-infected MSM. AIDS 2015;29:695–702, http://dx.doi.org/10.1097/QAD.0000000000000603.
[37] Berry JM, Jay N, Cranston RD, Darragh TM, Holly EA, Welton ML, et al. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. Int J Cancer 2014;134:1147–55, http://dx.doi.org/10.1002/ijc.28431.
[38] Cranston RD, Baker JR, Liu Y, Wang L, Elishaev E, Ho KS. Topical application of trichloroacetic acid is efficacious for the treatment of internal anal high-grade squamous intraepithelial lesions in HIV-positive men. Sex Transm Dis 2014;41:420–6, http://dx.doi.org/10.1097/OLQ.0000000000000145.
[39] Porpiglia AS, Sigurdson ER. Surgical options in the treatment of lower gastrointestinal tract cancers. Curr Treat Options Oncol 2015;16:46, http://dx.doi.org/10.1007/s11864-015-0363-3.
[40] Lill C, Bachtiary B, Selzer E, Mittlboeck M, Thurnher D. A 5-year update of patients with HPV positive versus negative oropharyngeal cancer after radiochemotherapy in Austria. Wien Klin Wochenschr 2017;129:398–403, http://dx.doi.org/10.1007/s00508-017-1171-5.