World Cancer Research Journal WCRJ 2014; 1 (4): e405

ANAL CANCER IN HIV-POSITIVE PATIENTS

R. FONTANA DEL VECCHIO, M.R. PINZONE, B. CACOPARDO, G. NUNNARI

Department of Clinical and Molecular Biomedicine, Division of Infectious Diseases, University of Catania, Catania, Italy

Abstract: *Squamous cell carcinoma of the anal canal (SCCA) is a relatively uncommon cancer, whose incidence, however, has been increasing in recent years, particularly in human immunodeficiency virus (HIV)-positive individuals. HIV-infected patients have a 28-fold higher risk to be diagnosed with anal cancer. SCCA is more prevalent in men who have sex with men and it is strongly associated with human papilloma virus (HPV) infection types 16 and 18. The SCCA precursor, high-grade anal intraepithelial neoplasia or high-grade squamous intraepithelial lesion, has been found in about 30% of HIV-infected men who have sex with men (MSM). At diagnosis, the involvement of regional lymph nodes is present in 30-40% of SCCA cases, whereas 5-8% of patients have distant metastasis. Whenever possible, a loco-regional treatment is suggested, in order to preserve anal function and to maintain the best quality of life. In terms of prevention, HPV vaccine and early antiretroviral therapy are recommended to reduce the risk of developing anal cancer.*
In this review, we summarize the main aspects of anal cancer in HIV-infected patients, with a focus on treatment and screening.

KEY WORDS: *Anal cancer, Human immunodeficiency virus (HIV), Human papilloma virus (HPV), Men who have sex with men (MSM).*

INTRODUCTION

Due to the advancement of antiretroviral therapy (ART), human immunodeficiency virus (HIV) infection has become a chronic disease[1]. Anal cancer is a rare gastrointestinal (GI) cancer (1.5% of all GI cancers)[2], whose prevalence in the general population is around 1-2 per 100,000 individuals[3]. Anal cancer includes malignancies arising from the squamous and glandular epithelia of the anus, including tumours from both the anal canal and anal margin[2,3]. The anal canal is lined by mucosa, whereas the anal margin is covered by epidermis. Approximately 80% of the anal canal tumours are squamous cell carcinomas (SCCA)[2]. It is estimated that 80% of cases are caused by human papilloma virus (HPV) infection, especially the high-risk types 16 and 18[1,4]. Despite its rarity, in recent years the incidence of SCCA has been rising in the overall population, especially in certain risk groups[4]. Known risk factors for anal cancer include: HPV infection[5,6], HIV infection[7], anoreceptive intercourse and cigarette smoking[8,9], sexually transmitted diseases (STD), cervical, vulvar or vaginal cancer, immunosuppression following solid organ transplantation, hematologic malignancies, certain autoimmune disorders[2]. The highest SCCA incidence has been reported among HIV-infected men who have sex with men (MSM)[4], but it is higher among women than among men in the general population[10]. Anal high-grade squamous intraepithelial lesions (HSILs) are precursors of SCCA[11]

Corresponding Author: Giuseppe Nunnari, MD; e-mail: gnunnari@hotmail.com

and they are detected in one third of MSM[12]. However, the low incidence of anal cancer suggests that few HSILs progress to cancer each year, as they spontaneously regress or persist without progression[13]. Cellular immune responses are one of the major mechanisms underlying HSIL regression. HIV-related CD4+ T-cell immunodeficiency is an important risk factor for anal HPV and its related lesions[13]. HIV is also an independent risk factor for anal cancer, as it increases the risk of being infected with multiple HPV strains and increases the prevalence and persistence of HPV infection[14]. Current guidelines for the management of HIV-infected subjects from the Infectious Disease Society of America recommend performing anal cytology screening in all HIV-infected persons with genital warts, women with a history of cervical dysplasia and/or receptive intercourse and MSM[15]. Finally, the morbidity associated with anal cancer and its treatment is significant: although local excision is a feasible option for small well-differentiated lesions, in most cases chemo-radiotherapy is needed, with its potential long-term side effects, such as impotence[3].

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

EPIDEMIOLOGY AND RISK FACTORS

Anal cancer is a rare disease (only 1.5% of GI cancers)[2], whose prevalence is estimated to be approximately 1-2 per 100,000 individuals[3]. However, recent studies report an increasing incidence: in 2014, it is estimated that 7,210 new cases of anal cancer and 950 deaths will be caused by this disease in the United States[7]. The median age at diagnosis is 60 years[2]. Main risk factors include: HPV infection; history of receptive anal intercourse; immunosuppressive conditions, including HIV infection, solid organ transplantation, hematologic malignancies, autoimmune disorders; sexually transmitted diseases (STD); any genital cancer; tobacco use[2]. Due to advances in ART, HIV can be considered a chronic disease. As a consequence, a significant increase in the incidence of non-AIDS-defining diseases, including anal cancer, has been observed. HIV-infected people (especially MSM) have a 28-fold higher risk of developing anal cancer in comparison to the general population[14]. In fact, HIV infection increases HPV persistence and the risk of acquiring/reactivating HPV infection[15]. Rates of invasive anal cancer continue to increase in the post-highly active antiretroviral therapy (HAART) era, with an incidence of 131 cases per 100,000 person-years in HIV-infected MSM[15]. Nevertheless, anal HPV infections are not restricted to MSM and are not rare in heterosexual men[4]. Some authors hypothesize that anal infections in people who do not engage in receptive anal intercourse may occur through autoinoculation[16,17]. It is still debated whether CD4+ T-cell count can affect the incidence rate of anal HPV infection[4]: some studies found that a low nadir CD4+ count was significantly correlated with anal intraepithelial neoplasia (AIN), but others did not[4]. Gonzalez et al demonstrated that the number of anal HPV types was the only factor significantly associated with anal squamous intraepithelial lesions (SILs): this may be due to the degree of immune deficiency or to a very high sexual exposure or both[4]. The virus type that is more closely related to SCCA is HPV type 16[18,19,20]. The progression to high-grade anal intraepithelial neoplasia (HGAIN) is strictly related to HPV 16 infection[4]. Some authors have identified the following factors as predictors of progression: HPV 16 or HPV 18 infection, multiple HPV infections, HIV infection, older age and higher AIN grade[21-27]. Few data suggest the possibility of spontaneous regression from HGAIN to lower AIN or normal cytology. Unfortunately, there is currently no good diagnostic test to distinguish HGAIN lesions that will progress to cancer from those that will not[4].

ANATOMY

The anal canal extends from the anorectal junction to the anal margin. Palpable landmarks are the puborectal sling and the intersphincteric groove. The cylindric epithelium of the rectum extends to 1 cm above the dentate line, where the anal transitional zone begins; below this line, the epithelium is squamous. The anal margin is the pigmented region surrounding the anal orifice, extending to a lateral radius of about 5 cm. At diagnosis the distinction between anal canal and anal margin tumour is often difficult, so some authors have classified into 3 different regions, intra-anal, perianal and skin tumours. Proximal lymphatic drainage is to perirectal nodes along the inferior mesenteric artery; above the dentate line drainage is to internal pudendal nodes (internal iliac system); infra-dentate and perianal skin drain to the inguinal, femoral and external iliac nodes[26].

HISTOLOGY

It is possible to distinguish tumours of the anal margin, which are generally well-differentiated and more common in men, from those of the anal canal, which are poorly differentiated and more

common in women. Some authors have reported that the basaloid subtype has a higher risk of developing metastatic disease; on the other hand, the biology and prognosis of keratinising and non-keratinising tumours of the anal canal appear to be similar. Verrucous carcinomas, often described as giant condylomas of Buschke-Lowenstein, have a better prognosis than SCCA, and are usually amenable to surgical treatment[26].

DIAGNOSIS

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

STAGING

Considering its indolent natural history and a low probability of metastases, SCCA is usually amenable to locoregional treatments. Magnetic resonance imaging (MRI) of the pelvis or, if not available, endoanal ultrasound (EUS), provide excellent information about tumour size, local extension and involvement of adjacent organs and lymph nodes[28]. The TNM clinical staging system is based on the assessment of size (T), regional node involvement (N) and distant metastasis (M). Node involvement indicates the distance from the primary site rather than the number of nodes involved. Biopsy is usually performed only for palpable inguinal nodes or enlarged lymph nodes (>10 mm on Computed Tomography or MRI).

TREATMENT

There are many relevant factors to consider in treatment decision-making for SCCA. They can be divided into two groups: disease-related and patient-related factors. Disease-related factors include: TNM stage; site of tumour (margin, canal, rectal); extent of tumour (i.e. involvement of vagina); response to treatment (early and at 26 weeks); need for symptom control. Patient-related factors include: patient preference; age; renal function; Charlson geriatric assessment; comorbidities; current medications and performance status; socio-economic and psychological factors; severity of initial symptoms[26]. The European Organisation for Research and Treatment of Cancer (EORTC) has shown that skin ulceration, nodal involvement and male gender are independent variables associated with locoregional failure and reduced overall survival[29]. The Radiation Therapy Oncology Group (RTOG) has also demonstrated that cancer diameter over 5 cm is an independent factor predicting reduced disease-free survival and overall survival. Furthermore, HIV testing is recommended to all patients[30]. Before the introduction of HAART, HIV-positive patients showed higher toxicity resulting from chemoradiotherapy, mainly those with CD4 count <200/μl[31]. However, more recent studies have reported similar response and survival rates in both HIV-negative and HIV-positive patients receiving HAART[32,33].

The primary aim of SCCA treatment is to cure the disease trying to preserve patient's quality of life, especially maintaining as much as possible the anal function. Therefore, it is necessary to set up a multi-disciplinary approach, involving radiotherapists, oncologists, surgeons, radiologists and pathologists[26].

Surgical treatment

Until the 1980s, surgery was the main type of treatment for anal cancer. Then, with the advancement of a multidisciplinary approach, surgery is not considered as first-line therapy and local excision is preferred to treat small lesions (<2 cm in diameter), involving the anal margin and not poorly differentiated[26]. Until the introduction of chemoradiation (CRT), abdominoperineal resection (APR) was considered as the primary therapy for all tumours (except those amenable to local excision). However, it

is currently used only for those patients who have been previously irradiated in the pelvic region or have persistent disease or have developed locoregional failure following CRT[2,26]. Salvage APR is a radical surgery which expose patients to wound complications: reconstructive surgery with a vertical rectus abdominis myocutaneous flap is an effective measure to reduce this risk[2].

Chemoradiation therapy (CRT)

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

Treatment in HIV-positive patients

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

SCREENING

Given the increased incidence of SCCA in HIV-positive individuals, a systematic screening program has been proposed[4]. The development of this program is based on the association of anal cancer with a viral infection (HPV) and the possibility to detect precancerous lesions[26]. In fact, overall survival from anal cancer is significantly higher if it is treated at an early stage (5-year survival of 80% for tumours <2 cm, 45-65% for tumours >2 cm, 20% for metastatic disease[3]). SCCA screening aims at detecting early cancers using regular digital ano-rectal examination (DARE) and detecting precursor lesions using anal citology-based programs with diagnostic high resolution anoscopy (HRA), to identify high-grade squamous intraepithelial lesion[3]. The last approach is similar to cervical cancer: in fact, similarly to the cervix, the anus has a transformation zone from squamous to columnar epithelium and this zone is the most vulnerable to dysplasia from HPV infection. Anal pap

test involves swabbing the anal canal with a moistened Dacron swab, that is placed in a liquid-based medium or fixed on a slide for cytological examination. Precancerous lesions are then classified using the same Bethesda grading system for cervical dysplastic lesions[14]. Similarly to cervical colposcopy, HRA is requested after an abnormal Pap test to identify any dysplastic lesions and obtain a biopsy for histological confirmation[14]. However, HRA has also significant barriers to be implemented as a systematic screening service, including low sensitivity to detect HSILs due to a large percentage of HIV-infected MSM with abnormal citology, lack of high-resolution anoscopists and no evidence from randomized controlled trials that treatment of HSILs prevents development of anal cancer[3]. The primary care guidelines for the management of HIV-infected people from the HIV Medicine Association of the Infectious Disease Society of America recommend performing anal cytology screening in all patients with genital warts, women with a history of cervical dysplasia and/or anal receptive intercourse and MSM[15]. In 1968, Wilson and Jungner elaborated a set of 10 criteria for appraising the viability, effectiveness and appropriateness of a screening programme: 1) the condition should be an important health problem; 2) there should be an accepted treatment for patients with recognized disease; 3) facilities for diagnosis and treatment should be available; 4) there should be a recognizable early symptomatic stage; 5) there should be a suitable test or examination for diagnosis; 6) the test should be acceptable to the population; 7) the natural history of the condition should be adequately understood; 8) there should be an agreed policy on patients that should undergo treatment; 9) the cost of case-finding should be economically balanced in relation to possible expenditures on medical care as a whole; 10) case-finding should be a continuing process and not a "once and for all" project[4]. Unfortunately these criteria are not completely fulfilled when considering the group with the highest risk for SCCA, HIV-infected MSM. In fact, it is unclear if the treatment of HGAIN really prevents the development of invasive cancer, facilities for diagnosis and treatment are not widely available outside University clinics and research settings and, most importantly, the natural history of the disease is not well understood, because the basis of progression from HGAIN to cancer are unclear. So, most authors recommend continuous observation for AIN-1 and treatment for AIN-3, while there is no consensus for AIN-2[4]. Therefore, it appears too early to recommend SCCA screening among HIV-infected MSM as a general policy. Furthermore, screening strategies for SCCA lack evidence of effectiveness and safety: there is no proven treatment for anal high-grade squamous intraepithelial lesions and complete excision is not possible without unacceptable morbidity[13].

CONCLUSIONS

In conclusion, even if the natural history of HIV infection has been profoundly modified in recent years, HIV-infected patients are at risk of developing non-AIDS-defining diseases, including malignancies[47,48]. Current evidence suggests that the incidence of anal cancer is higher in the HAART era[49,50]. There is a need for more research evaluating the most effective therapeutic and preventive strategies in this specific setting.

Conflict of Interests:
The Authors declare that they have no conflict of interests.

REFERENCES

1. Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Sattern GA, Aschman DJ, Holmberg SD. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. New Engl J Med 1998; 338: 853-860.
2. Ahmed S, Eng C. Optimal treatment strategies for anal cancer. Curr Treat Options Oncol 2014; 15: 443-455.
3. Ong JJ, Chen M, Grulich AE, Fairley CK. Regional and antional guideline recommendations for digital ano-rectal examination as a means for anal cancer screening in HIV positive men who have sex with men: a systematic review. BMC Cancer 2014, 14: 557.
4. Schim van der Loeff MF, Mooij SH, Richel O, de Vries JC, Prins JM. HPV and anal cancer in HIV-infected individuals: a review. Curr HIV/AIDS Rep 2014; 11: 250-262.
5. Ghosh I, Ghosh P, Bharti AC, Mandal R, Biswas J, Basu P. Prevalence of human papillomavirus and co-existent sexually transmitted infections among female sex workers, men having sex with men and injectable drug abusers from eastern India. Asian Pac J Cancer Prev 2012; 13: 799-802.
6. Asfhar RM, Mollaie HR, Fazlalipur M, Arabzadeh SA. Prevalence and type distribution of human papillomavirus infection using the INNo-Lipa assay, Kerman, Southeast Iran. Asian Pac J Cancer Prev 2013; 14: 5287-5291.
7. Pittyanont S, Yuthavisuthi P, Sananpanichkul P, Thawonwong N, Techapornroong M, Suwannarurk K, Bhamarapravatana K. Prevalence of abnormal anal cytology in HIV-infected women: a hospital-based study. Asian Pac J Cancer Prev 2014; 15: 6405-6409.
8. Baranoski AS, Tandon R, Weinberg J, Huang FF, Stier EA. Risk factors for abnormal anal cytology over time in HIV-infected women. Am J Obstet Gynecol 2012; 207: 107.e1-8.
9. Zhang HY, Tiggelaar SM, Sahasrabuddhe VV, Smith JS, Jiang CQ, Mei RB, Wang XG, Li ZA, Qiao YL. HPV prevalence and cervical intraepithelial neoplasia among HIV-infected women in Yunnan Province, China: a pilot study. Asian Pac J Cancer Prev 2012; 13: 91-96.

10. Kojic EM, Cu-Uvin S, Conley L, Bush T, Onyekwuluje J, Swan DC, Unger ER, Henry K, Hammer JH, Overton ET, Darragh TM, Palefsky JM, Vellozzi C, Patel P, Brooks JT. Human papillomavirus infection and cytologic abnormalities of the anus and cervix among HIV-infected women in the study to understand the natural history of HIV/AIDS in the era of effective therapy (the SUN study). Sex Transm Dis 2011; 38: 253-259.
11. Darragh TM1, Colgan TJ, Cox JT, Heller DS, Henry MR, Luff RD, McCalmont T, Nayar R, Palefsky JM, Stoler MH, Wilkinson EJ, Zaino RJ, Wilbur DC; Members of LAST Project Work Groups. The Lower Anogenital Squamous terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. J Low Genit Tract Dis 2012; 16: 205-242.
12. Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, Hillman RJ, Petoumenos K, Roberts J, Tabrizi SN, Templeton DJ, Grulich AE. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol 2012; 13: 487-500.
13. Tong WW, Shepherd K, Garland S, Meagher A, Templeton DJ, Fairley CK, Jin F, Poynten IM, Zaunders J, Hillman RJ, Grulich AE, Kelleher AD, Carr A; on behalf of the Study of the Prevention of Anal Cancer (SPANC) team. Human Papillomavirus 16-Specific T-Cell Responses and Spontaneous Regression of Anal High-Grade Squamous Intraepithelial Lesions. J Infect Dis 2014 Aug 19. pii: jiu461. [Epub ahead of print].
14. Wells JS, Holstad MM, Thomas T, Bruner DW. An integrative review of guidelines for anal cancer screening in HIV-infected persons. AIDS Patient Care STDS 2014; 28: 350-357.
15. Cachay ER, Mathews WC. Use of human papillomavirus vaccine in HIV-infected men for the prevention of anal dysplasia and cancer. AIDS Rev 2014; 16: 90-100.
16. Goldstone SE. Some straight talk about anal human papillomavirus infection. J Infect Dis 2010; 201: 1450-1452.
17. Goodman MT, Shvetsov YB, McDuffie K, Wilkens LR, Zhu X, Thompson PJ, Ning L, Killeen J, Kamemoto L, Hernandez BY. Sequential acquisition of human papillomavirus (HPV) infection of the anus and cervix: the Hawaii HPV Cohort Study. J Infect Dis 2010; 201: 1331-1339.
18. Glick SN, Feng Q, Popov V, Koutsky LA, Golden MR. High rates of incident and prevalent anal human papillomavirus infection among young men who have sex with men. J Infect Dis 2014; 209: 369-376.
19. de Pokomandy A, Rouleau D, Ghattas G, Vezina S, Cote P, Macleod J, Allaire G, Franco EL, Voutlee F; HIPVIRG Stoudy Group. Prevalence, clearance and incidence of anal human papillomavirus infection in HIV-infected men: the HIPVIRG cohort study. J Infect Dis 2009; 199: 965-973.
20. Darwich L, Canadas MP, Videla S, Coll J, Molina-Lopez RA, Sirera G, Clotet B; Can Ruti HIV-HPV Team. Prevalence, clearance and incidence of human papillomavirus type-specific infection at the anal and penile site of HIV-infected men. Sex Transm Dis 2013; 40: 611-618.
21. Coutlee F, de Pokomandy A, Franco EL. Epidemiology, natural history and risk factors for anal intraepithelial neoplasia. Sex Health 2012; 9: 547-555.
22. Phanuphak N, Teeratakulpisarn N, Keelawat S, Pankam T, Barisri J, Triratanachat S, Deesua A, Rodbamrung P, Wongsabut J, Tantbirojn P, Numto S, Ruangvejvorachai P, Phanuphak P, Palefsky JM, Ananworanich J, Kerr SJ. Use of human papilloomavirus DNA, E6/E7 mRNA, and p16 immunocytochemistry to detect and predict anal high-grade squamous intraepitheliallesions in HIV-positive and HIV-negative men who have sex with men. PLoS One 2013; 27: 401-406.
23. Mlakar B, Kocjan BJ, Hošnjak L, Fujs Komloš K, Miloševi M, Poljak M. Betapapillomaviruses in the anal canal of HIV positive and HIV negative men who have sex with men. J Clin Vir 2014; 61: 237-241.
24. Bernard HU, Burk RD, Chen Z, van Doorslaer K, ZurHausen H, de Villiers EM. Classification of papillomaviruses (PVs) based on 189 PV types and proposal of taxonomic amendments. Virology 2010; 401: 70-79.
25. de Villiers EM. Cross-roads in the classification of papillomaviruses. Virology 2013; 445: 2-10.
26. Glynne-Jones R, Nilsson PJ, Goh V, Peiffert D, Cervantes A, Arnold D. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Radiother Oncol 2014; 111: 330-339.
27. ZurHausen H. Papillomaviruses causing cancer: evasion from host-cell control in early events in carcinogenesis. J Natl Cancer Inst 2000; 92: 690-8.
28. Goh V, Gollub FK, Liaw J, Wellsted D, Przybytniak I, Padhani AR, Glynne-Jones R. Magnetic resonance imaging assessment of squamous cell carcinoma of the anal canal before and after chemoradiation: can MRI predict for eventual clinical outcome? Int J Radiat Oncol Biol Phys 2010; 78: 715-721.
29. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, Peiffert D, van Glabbeke M, Pierart M. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 1997; 15: 2040-2049.
30. British HIV Association, British Association of Sexual Health and HIV, British Infection Society. UK national guidelinesfor HIV testing 2008. www.bhiva.org/hivtesting2008.aspx [14.04.14, date last accessed].
31. Oehler-Jänne C, Huguet F, Provencher S, Seifert B, Negretti L, Riener MO, Bonet M, Allal AS, Ciernik IF. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol 2008; 26: 2550-2557.
32. Wexler A, Berson AM, Goldstone SE, Waltzman R, Penzer J, Maisonet OG, McDermott B, Rescigno J. Invasive anal squamous-cell carcinoma in the HIV-positive patient; outcome in the era of highly active antiretroviral therapy. Dis Colon Rectum 2008; 51: 73-81.
33. Fraunholz I, Rabeneck D, Gerstein J, Jäck K, Haberl A, Weiss C, Rödel C. Concurrent chemoradiotherapy with 5-fluorouracil and mitomycin C for anal carcinoma: are there differences between HIV-positive and HIV-negative patients in the era of highly active antiretroviral therapy? Radiother Oncol 2011; 98: 99-104.
34. Nigro ND, Vaitkevicius VK, Considine Jr B. Combined therapy for cancer of the anal canal: a preliminary report, 1974. Dis Colon Rectum 1993; 36: 709-711.
35. Flam MS, John M, Lovalvo LJ, Mills RJ, Ramalho LD, Prather C, Mowry PA, Morgan DR, Lau BP. Definitive nonsurgical therapy of epithelial malignancies of the anal canal. A report of 12 cases. Cancer 1983; 51: 1378-1387.
36. [No authors listed]. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet 1996; 348(9034): 1049-1054.
37. James RD1, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, Maughan T, McDonald A, Essapen S, Leslie M, Falk S, Wilson C, Gollins S, Begum R, Ledermann J, Kadalayil L, Sebag-Montefiore D. Mytomicin

or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 x 2 factorial trial. Lancet Oncol 2013; 14: 516-524.
38. UKCCCR (1996). Epidermoid anal cancer: results from UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mytomicin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet 1996; 348: 1049-1054.
39. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, Quivey J, Rotman M, Kerman H, Coia L, Murray K. Role of mytomicin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 1996; 14: 2527-2539.
40. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB 3rd, Thomas CR Jr, Mayer RJ, Haddock MG, Rich TA, Willett C. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 2008; 299: 1914-1921.
41. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB 3rd, Thomas CR Jr, Mayer RJ, Haddock MG, Rich TA, Willett CG. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival, relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol 2012; 30: 4344-4351.
42. Oehler-Jänne C, Huguet F, Provencher S, Seifert B, Negretti L, Riener MO, Bonet M, Allal AS, Ciernik IF. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol 2008; 26: 2550-2557.
43. Peddada AV, Smith DE, Rao AR, Frost DB, Kagan AR. Chemotherapy and low-dose radiotherapy in the treatment of HIV-infected patients with carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 2997; 44: 127-131.
44. Kim JH, Sarani B, Orkin BA, Young HA, White J, Tannebaum I, Stein S, Bennett B. HIV-positive patients with anal carcinoma have poorer treatment tolerance and outcome than HIV-negative patients. Dis Colon Rectum 2001; 44: 1496-1502.
45. Hoffman R1, Welton ML, Klencke B, Weinberg V, Krieg R. The signifcance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. Int J Radiat Oncol Biol Phys 1999; 44: 127-131.
46. Stadler RF, Gregorcyk SG, Euhus DM, Place RJ, Huber PJ, Simmang CL. Outcome of HIV-infected patients with invasive squamous-cell carcinoma of the anal canal in the era of highly active antiretroviral therapy. Dis Colon Rectum 2004; 47: 1305-1309.
47. Pinzone MR, Fiorica F, Di Rosa M, Malaguarnera G, Malaguarnera L, Cacopardo B, Zanghì G, Nunnari G. Non-AIDS-defining cancers among HIV-infected people. Eur Rev Med Pharmacol Sci 2012; 16: 1377-1388.
48. Berretta M, Cinelli R, Martellotta F, Spina M, Vaccher E, Tirelli U. Therapeutic approaches to AIDS-related malignancies. Oncogene 2003; 22: 6646-6659.
49. Zanet E, Berretta M, Martellotta F, Cacopardo B, Fisichella R, Tavio M, Berretta S, Tirelli U. Anal cancer: Focus on HIV-positive patients in the HAART-era. Curr HIV Res 2011; 9: 70-81.
50. Martellotta F, Berretta M, Cacopardo B, Fisichella R, Schioppa O, Zanghì A, Spartà D, Cappellani A, Talamini R, Izzi I, Ridolfo A, Torresin A, Fiorica F, Tirelli U. Clinical presentation and outcome of squamous cell carcinoma of the anus in HIV-infected patients in the HAART-era: a GICAT experience. Eur Rev Med Pharmacol Sci 2012; 16: 1283-1291.