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# Anal cytology in women: Experience from a single tertiary center

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ABSTRACT

*Introduction:* Anal cytology (AC) can be used as a screening tool for detection of anal HPV associated lesions, mainly in men who have sex with men and in immunosuppressed patients. Our aim is to review our experience with AC in women.

Material & methods: We have retrospectively reviewed all AC diagnosed between 2010–2017 in a single tertiary hospital (n = 644) and selected those performed in women (n = 158).

*Results:* 24.53% of AC were performed in women. 14.7% of all women were HIV positive and 56.7% referred anal intercourse. Squamous lesions were found in 27.2% of women, most of them ASCUS and LSIL (14% and 11.5%). HPV DNA was detected in 38.6% of patients, and 63.9% of them showed positivity for multiple high-risk types. Anal biopsy showed high grade lesions in 20% of biopsied patients. We observed a significant relationship between HPV status and receptive anal sex, and the association between HPV status and anal histological diagnosis tended to significance. Sensitivity, specificity, negative predictive value and positive predictive value for anal cytology were 57%; 83%; 28% and 94%, respectively. 70.9% of women had synchronous cervical cytology, and squamous cervical lesions were detected in 46.4% of the cases, most of them LSIL or ASCUS (21.4% and 15.2%). We did not confirm a significant association between cytological diagnosis of cervical and anal samples.

*Conclusions:* AC is less widely used in women than in homosexual men. However, women show important rates of anal lesions, regardless of their HIV status. More studies should be performed to assess the potential impact of screening protocols in this population.

## 1. Introduction

Anal cancer is an uncommon disease [1,2], with incidence rates under 2 per 100,000 per year [1]. However, its incidence has been increasing in the last decades [3]. In fact, incidence rates of anal carcinoma in countries such as United States or Australia have been reported to increase by 2.6% and 3.4% per year, respectively [1]. Anal cancer comprises two different histological subtypes: squamous cell carcinoma (SCC) and adenocarcinoma. SCC is the most frequent subtype and it has been shown to be related to human papillomavirus (HPV) infection [2]. Due to its similarities with cervical cancer, anal SCC is potentially preventable and premalignant lesions can be detected and treated [4]. The most recognized risk factors for anal cancer are HIV infection or immunosuppression, receptive anal intercourse and high risk sexual behavior. Cigarette smoking has been identified as an independent risk factor in some studies [5,6]. In women, a history of cervical and/or vulvar HPV-related cancer has been also associated with anal cancer [7]. No national guidelines for anal cancer screening have been developed, but screening protocols analogous to those employed for cervical cancer have been implemented in certain high-risk groups, mainly men-who-have sex with men and HIV patients [8–10]. Several screening tools can be used, such as digital anorectal exams, anal Pap tests, HPV testing, high-resolution anuscopy and anal biopsy [9]. Reported sensitivity and specificity rates for anal cytology vary between studies, but it is generally considered a cost-effective screening tool [9]. In respect of female patients, few reports have addressed the features of anal cancer in women [11]. Screening protocols have been used to identify anal cancer precursors in some high-risk groups, such as HIV-infected patients or women with abnormal cervical cytology and/or cervical HPV infection [10,12]. Many controversies exist in the literature regarding the real incidence of anal cancer, the pathogenic impact of sexual behaviour, the natural history of anal lesions, the

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accuracy of screening tools for the identification of high-grade lesions, the selection of high-risk patients for screening, the significance of a diagnosis of atypical squamous cells of undetermined significance (ASCUS) or low-grade dysplasia and the rate of malignant transformation of high-grade dysplasia. In women, anal cancer features are not clearly defined due to the limited number of studies available.

In this study, we have retrospectively reviewed our experience with anal cytology in women. Our aims are to estimate the prevalence of anal squamous dysplasia and to evaluate the general performance of cytology, histology and HPV hybridization for detecting anal squamous lesions in female patients.

## 2. Material and methods

We have retrospectively reviewed all anal cytologies diagnosed in women between 2010 and 2017 in a large tertiary center in Madrid (Spain).

In our institution, the sample is collected using a moistened swab and placed in CytoLyt solution for thin-layer preparation (ThinPrep). Smears are stained with Papanicolaou stain. Polymerase chain reaction (PCR) for HPV DNA detection is performed with Clart® HPV system (Genomica SAU, Spain). This system detects 49 different serotypes of the HPV, including the most prevalent high and low risk ones.

In patients with abnormal cytology or high clinical suspicion, high-resolution anuscopy is performed after application of acetic acid and Lugol's solution, and suspicious lesions are biopsied. Biopsy is formalin fixed and paraffin embedded, sectioned into 4 μm slides and stained with hematoxylin-eosin for routine histological study.

Cytological diagnoses were retrieved from the database of the Surgical Pathology Department (PatWin). Electronic medical records were also reviewed and subsequent follow-up data and histological diagnoses were collected. All the information was stored in an Excel file and analyzed with the SPSS 20.0 for Windows statistical package. For the analysis of association between variables, we have employed either $\chi 2$ (chi)-squared test (qualitative variables) or Student's *t*-test (to compare means between dichotomic quantitative variables). The statistical significance was settled at a p-value $< 0.05$. All qualitative data were represented with percentage and absolute numbers.

We have also reviewed the literature and compared our results with those previously reported.

## 3. Results

644 anal cytologies were diagnosed in our institution between 2010 and 2017. Female patients constituted 24.53% of all patients (n = 158) and mean age was 40 years. 14.7% of all women were HIV positive and 56.7% of patients referred previous receptive anal sex. Only 3.2% of anal cytological samples were considered inadequate. Squamous lesions were found in 27.2% of women (n = 43). Women with squamous abnormalities showed atypical squamous cells of unknown significance (ASCUS), low grade squamous intraepithelial lesion (LSIL), high grade squamous intraepithelial lesion (HSIL) and squamous cell carcinoma (SCC) in 51.1%, 41.8%, 4.6% and 2.3% of cases, respectively. PCR for HPV was performed in 54.4% of cases (n = 86). PCR results are summarized in Table 1. HPV DNA was detected in 38.6% of patients (n = 61), and 45.3% of all samples were positive for multiple high-risk HPV types (n = 39). Anal biopsy was performed in 31.6% of patients (n = 50). Histological diagnoses are shown in Table 2. High-grade lesions (including high-grade dysplasia and SCC) were detected by histology in 20% of biopsied patients.

The association between anal HPV status in cytology and histological diagnosis tended to significance (p = 0.064). Non-infected patients showed mainly negative results (60%), most patients infected with high-risk types showed anal dysplasia (anal intraepithelial neoplasia –AIN- I or anal condylomas in 56.5%, AIN II-III and SCC in 43.5%), and 83.3% of patients infected with low-risk types were diagnosed with anal condylomas or AIN I. We found a significant relationship between HPV status and receptive anal sex. 76.1% of non-infected patients had no anal sex, and 60% of patients infected with high-risk HPV types had previous anal intercourse. We did not identify an association between anal HPV status and anal cytological diagnosis. 50% of negative anal cytologies showed high-risk HPV positivity. HIV status was not associated with anal cytological or histological diagnosis. In fact, most anal high-grade lesions and SCC were detected in HIV-negative patients.

**Table 1**
PCR HPV results (anal cytology).

| HPV[a] type | % of all patients with PCR[b] HPV (n = 86) |
|---|---|
| No HPV | 29% (n = 25) |
| HPV 16 | 8.1% (n = 7) |
| HPV 16 and 18 | 4.6% (n = 4) |
| > 2 high-risk types | 45.3% (n = 39) |
| > 2 low-risk types | 12.8% (n = 11) |

[a] HPV: human papillomavirus.
[b] PCR: polymerase chain reaction.

**Table 2**
Histological diagnosis (anal biopsy).

| Histological diagnosis | % of patients with anal biopsy (n = 50) |
|---|---|
| Negative | 22% (n = 11) |
| Condyloma | 42% (n = 21) |
| LSIL[a] | 16% (n = 8) |
| HSIL[b] | 6% (n = 3) |
| SCC[c] | 14% (n = 7) |

[a] LSIL: low grade squamous intraepithelial lesion.
[b] HSIL: high grade squamous intraepithelial lesion.
[c] SCC: squamous cell carcinoma.

Correlation between anal cytological and histological diagnoses is summarized in Table 3. Negative Thin-Prep smears were AIN I, AIN II-III or SCC in 4%, 4% and 20% of cases. Most ASCUS cases showed AIN I or condylomas in histology (40% and 30%, respectively) and all HSIL cases were diagnosed as SCC or AIN II-III. LSIL was a heterogeneous category, including mainly condylomas (41.6%), but also AIN I and SCC (25%, 8.3%).

Most SCC were classified as negative or LSIL by cytology (85.7%), and AIN II-III lesions were heterogeneously diagnosed as ASCUS, LSIL or HSIL.

Sensitivity, specificity, negative predictive value and positive predictive value for anal cytology were 57%; 83%; 28% and 94%, respectively. Thus, the overall accuracy of cytology for diagnosing anal lesions in women was at best moderate.

In 70.9% of all women, a synchronous cervical cytology was performed (n = 112), and squamous lesions were detected in 46.4% of these cases, most of them ASCUS or LSIL (15.2% and 21.4%, respectively). HPV PCR was performed in 37.3% of cervical samples, and 52.5% of patients showed infection by multiple high-risk HPV types. Cervical cytology results are summarized in Table 4. In 23.7% of patients a cervical biopsy was performed (n = 27), and histological diagnoses were negative, LSIL and HSIL in 25.92%, 33.3% and 37% of cases.

29.7% of women had previous cervical lesions and 11.4% had previous infection with high-risk HPV types.

Correlation between anal and synchronous cervical cytology is summarized in Table 5. 57.5% of patients with anal squamous atypia and synchronous cervical cytology showed cervical squamous atypia. We have not observed a significant association between cytological diagnosis of cervical and anal samples. Cervical cytology and anal biopsy were not correlated either. In fact, most patients with SCC and AIN II-III confirmed by histology and synchronous cervical tests showed

**Table 3**
Correlation between cytological and histological diagnosis (anal samples).

| Cytological diagnosis | Negative (n = 109) | ASCUS[a] (n = 22) | LSIL[b] (n = 18) | HSIL[c] (n = 2) |
|---|---|---|---|---|
| Biopsy | 23% (n = 25) | 45.5% (n = 10) | 66.6% (n = 12) | 100% (n = 2) |
| Histological diagnosis | Negative 24% (n = 6) | Negative 20% (n = 2) | Negative 25% (n = 3) | AIN II-III 50% (n = 1) |
| | Condyloma 48% (n = 12) | Condyloma 30% (n = 3) | Condyloma 41.6% (n = 5) | SCC 50% (n = 1) |
| | AIN[d] I 4% (n = 1) | AIN I 40% (n = 4) | AIN I 25% | |
| | AINN II-III 4% (n = 1) | AIN II-III 10% (n = 1) | (n = 3) AIN II-III 0% | |
| | SCC[e] 20% (n = 5) | SCC 0% | SCC 8.3% (n = 1) | |

[a] ASCUS: atypical squamous cells of undetermined significance.
[b] LSIL: low grade squamous intraepithelial lesion.
[c] HSIL: high grade squamous intraepithelial lesion.
[d] AIN: anal intraepithelial neoplasia.
[e] SCC: squamous cell carcinoma.

**Table 4**
Cytological diagnosis and PCR HPV results of cervical samples.

| | |
|---|---|
| Cervical cytological diagnosis (n = 112) | Negative 53.6% (n = 60) |
| | ASCUS[a] 15.2% (n = 17) |
| | LSIL[b] 21.4% (n = 24) |
| | HSIL[c] 9.8% (n = 11) |
| Cervical HPV[d] type (n = 59) | Negative 25.4% (n = 15) |
| | HPV 16 10.2% (n = 6) |
| | HPV 16 and 18 5.1% (n = 3) |
| | > 2 high risk types 52.5% (n = 31) |
| | > 2 low risk types 6.8% (n = 4) |

[a] ASCUS: atypical squamous cells of undetermined significance.
[b] LSIL: low grade squamous intraepithelial lesion.
[c] HSIL: high grade squamous intraepithelial lesion.
[d] HPV: human papillomavirus.

negative cervical smears (75%).

## 4. Discussion

Anal cancer constitutes less than 2.5% of gastrointestinal cancers, but its incidence is increasing in both sexes [13–15]. Several studies have observed a 2-fold increase in the incidence of anal cancer in the last 30 years, and a 5-fold increase in several high-risk groups [14,16,17]. The prevalence of anal cancer varies between countries depending on patients' gender [1]. In the US, anal cancer is more frequent in women and white population with a mean age of 60 years [11]. Most authors have also observed a female-predominance of anal cancer [2,18]. Similar incidences in both genders have been described in other reports [19]. Sauter et al. observed that anal cancer of the outer margin was significantly more frequent in men, and women tended to show lesions in the anal channel [20]. Gender predominance can also vary between HPV-associated or non-HPV associated anal cancers and between histological subtypes (SCC and adenocarcinoma) [21]. In our experience, women constituted only 24.53% of all patients screened by anal cytology and mean age for histologically confirmed SCC was slightly lower (55.8 years). This male predominance could be due to geographical reasons and prevalence of risk factors in our population (smoking, sexual behavior, higher percentage of homosexual men), but it is most probably due to patient selection bias. Clinicians and general population seems to be more aware of the risk of anal cancer in homosexual and HIV-positive men than in women. In female patients, the identification of risk factors other than immunosuppression for anal cancer is difficult, controversial, and it requires a personal interview on sexual practices, which is not generally performed in the clinical practice. In addition, women who are routinely screened for cervical cancer may not be routinely informed about risks for anal cancer and benefits of anal cancer screening.

Both the uterine cervix and the anal canal show a squamous-columnar junction, and most anal cancers are SCC arising from this transitional area [12]. The pathogenesis of anal cancer is therefore supposed to be analogous to that of cervical cancer [22], and cytology and biopsy are generally used for diagnosing precursor lesions. One of the main problems in assessing anal cytology is the lack of standardized criteria for sample interpretation. In cytological specimens, most physicians and cytotechnologists apply the criteria set forth in the Bethesda System for cervico-vaginal cytology [7,23]. Both cytoplasmic and nuclear changes should be assessed, and preneoplastic lesions are classified as ASCUS, LSIL, HSIL or SCC. Nuclear features include nuclear enlargement, hyperchromasia, nuclear membrane irregularities and bi or multinucleation. Keratinization and koilocytosis can also be seen [23]. However, this lack of terminologic specificity can explain why most cytological diagnosis of low-grade squamous intraepithelial neoplasia (LSIL) in our study turned out to be condylomas by histology. We can attribute these errors to the use of concepts widely employed in Pap smears, such as considering HPV-related lesions directly as LSIL. This might be misleading in anal samples, for condyloma without dysplasia is much more frequent in the anal region than in other body locations. Histologically, the thickness of the epithelium affected is evaluated for diagnosing AIN I, II or III, and invasive lesions are diagnosed as SCC. Immunohistochemical techniques can be helpful in doubtful cases [24].

As seen in cervical cancer, anal SCC has been shown to be related to long-term HPV infection, and HPV 16 and 18 cause 80–90% of anal cancers [2]. However, the risks of lesion upgrading and development of SCC are unknown [9]. Some studies have reported a progression rate from premalignant to invasive lesions ranging from 2 to 9% [25], but

**Table 5**
Correlation between anal and cervical cytology.

| Anal cytology | Negative (n = 109) | ASCUS[a] (n = 22) | LSIL[b] (n = 18) | HSIL[c] (n = 2) |
|---|---|---|---|---|
| Patients with cervical smears | 66.9% (n = 73) | 72.7% (n = 16) | 83.3% (n = 15) | 50% (n = 1) |
| Cervical cytology | Negative 58.9% (n = 43) | Negative 37.5% (n = 6) | Negative 46.6% (n = 7) | LSIL 100% (n = 1) |
| | ASCUS 10.9% (n = 8) | ASCUS 18.75% (n = 3) | ASCUS 26.6% (n = 4) | |
| | LSIL 19.2% (n = 14) | LSIL 37.5% (n = 6) | LSIL 20% (n = 3) | |
| | HSIL 10.9% (n = 8) | HSIL 6.2% (n = 1) | HSIL 6.6% (n = 1) | |

[a] ASCUS: atypical squamous cells of undetermined significance.
[b] LSIL: low grade squamous intraepithelial lesion.
[c] HSIL: high grade squamous intraepithelial lesion.

other studies have found higher rates in immunocompromised patients (13–50%) [9,26]. No direct estimates or prospective studies have been performed with the aim of analyzing the natural history of HPV infection and anal intraepithelial lesions [23]. In our study, the association between anal histological diagnosis and anal HPV infection tended to be significant. High-risk HPV subtypes were positive both in low grade and high grade lesions, and low-risk HPV subtypes were detected mainly in AIN I and condylomatous lesions.

The main risk factors for anal cancer are HPV infection, anal sexual exposure to HPV (mainly receptive anal intercourse), immune deficiency and cigarette smoking [1,11]. Women's risk factors show some peculiarities: the association of receptive anal sex and anal cancer in women seems to be weaker than in men [1], and women with previous HPV-related diseases show higher risk of developing anal cancer [11,12,15,27–35]. In our study, we have found a statistically significant association between anal HPV status and receptive anal sex. Most non-infected patients had no anal sex and 60% of patients infected with high-risk HPV types had previous receptive anal intercourse. Therefore, anal sex seems to be related to HPV infection and cancer pathogenesis in our population. Some studies have reported similar results [18,36].

As previously stated, anal lesions and HPV infection appear to be more frequent in HIV-positive women. In fact, many studies on anal cancer in women have included immunosuppressed patients [37,38]. Stier et al. performed a systematic review and observed a prevalence of high-risk HPV and high-grade dysplasia of 16–85% and 3–26% in HIV-positive women [15]. Other authors have published similar results [37,38]. Patients with low CD4 T-cell counts and high viral low seem to be at higher risk for anal dysplasia [39,40]. However, we have not observed an association between HIV status and anal cytological or histological diagnosis. In fact, in our study population, most high-grade lesions were detected in immunocompetent patients. This could be caused by the relatively low prevalence of HIV infection in our patients (14.7%). Our HIV-infected women could therefore be scarcely representative of the general HIV-positive population. In addition, these HIV-positive women may represent patients with appropriate medical follow-up and well-controlled infection, who seek for routinely medical attention and agree to be participant in cervical and anal screening programs.

Women with previously diagnosed HPV-related diseases (cervical, vulvar and vaginal lesions) also show higher rates of high-grade anal lesions (ranging from 2.6% to 28%) [25,30–33]. Tatti. et al. observed that women with cervical intraepithelial neoplasia (CIN) 2–3 ha d 2 times the odds of developing AIN compared with women with CIN 1 [41]. In our statistical analysis, we have not been able to found an association between previous cervical HPV status or cervical diagnosis and anal dysplasia. This discordance could be due to the fact that high-risk groups such as women with cervical HPV-positive are routinely screened in some institutions and anal dysplasia could be therefore detected more frequently in these women than in patients with no cervical abnormalities. It could also be due to differences in patient population. In our study, most women had previous anal sex regardless of their HIV status or previous cervical diagnosis.

The main role of screening for anal or cervical cancer is the identification of persistent high-grade dysplasia or early invasive disease [9]. Several scientific groups and specialized centers have proposed to screen men who have sex with men and HIV individuals [2,42–44]. However, the low incidence of anal cancer does not support the implementation of screening protocols in the general population [30]. In addition, no national guidelines have been developed and no screening protocol has been standardized [8–10]. Our hospital is a reference center for anal pathology in Madrid, covering a large population and some high risk areas (prostitution, homosexual people). Screening is opportunistic and it is performed to high risk groups (immunosuppressed and HIV infected patients), and also to women with prior cervical pathology.

Several tools can be used for anal cancer screening, including digital anorectal exams, anal cytology, HPV studies, high-resolution anuscopy and anal biopsy [8,9]. Despite the differences in reported sensitivity and specificity for anal cytology, experts recommend the use of anal smears as a selection method for referral for high-resolution anuscopy [45,46]. It needs to be emphasized that high-grade lesions are usually underestimated by cytology [10]. In our experience, the overall accuracy of cytology for the diagnosis of anal lesions in women was at best moderate, with sensitivity and specificity rates of 57% and 83%, respectively. Indeed, SCC and high-grade lesions were heterogeneously diagnosed as ASCUS, LSIL or HSIL by cytology. Several authors have reported similar results, and have suggested high-resolution anoscopy to be performed in patients with any cytological abnormality [10,47–49].

As for the feasibility of implementing anal screening protocols, Slama et al. performed a cost-effectiveness analysis and suggested that anal cancer screening in women with previous CIN II-III is cost-effective, but it may affect the quality of life [50]. In our opinion, a clear identification of high-risk groups is needed for optimal selection of patients for anal screening. Blankenship et al. highlighted the importance of counseling about anal cytology and inform patients in order to increase the acceptability of screening [51]. Ferris et al. observed that women were receptive to screening despite limited knowledge about anal cancer [52]. However, Koskan et al. performed interviews with HIV-positive men and reported that lack of information was the main factor influencing patient participation in anal screening programs [53]. Thus, education of clinicians and patients is extremely important, because educational interventions could improve screening adherence and decrease psychological adverse events and lost to follow-up cases.

Management guidelines have been published, and anal invasive cancer is mainly treated by chemoradiotherapy. Only small lesions and persistent or recurrent tumors are surgically excised [54,55]. New therapies, mainly related to molecular pathology and new biological agents, are also being developed [13]. However, treatment of preneoplastic lesions is more heterogeneous, and some authors recommend patient referral to expert centers [56]. Topical therapy and local ablative therapy are the main tools for AIN treatment, and surgical therapy is generally not used [7]. Several authors have highlighted the consequences of rectal and anal cancer treatment in women [57–59]: surgery and adjuvant therapy can lead to nerve damage, bowel dysfunction or sexual problems. In our center, local ablative techniques are used for non invasive premalignant lesions and chemoradiation therapy for invasive ones, in an intent to preserve the anus.

Finally, we must keep in mind that prophylactic HPV vaccination may decrease the incidence of anal lesions, the risk of recurrence or the natural history of HPV infection and anal cancer [60].

## 5. Conclusions

In our institution, anal cancer screening is routinely performed in high risk, HIV or immunosupressed patients and also in women with prior cervical pathology. Women constituted only 24.53% of patients screened, but they showed an important rate of anal dysplasia: in 6.1% of all women high-grade lesions or SCC were detected by anal biopsy. Previous anal receptive intercourse was a significant risk factor for high-risk HPV infection. In respect of screening tools, the overall accuracy of anal cytology was low, but the association between anal HPV status and anal biopsy tended to be significant. So, PCR for HPV could be a useful adjunct for anal cancer screening. Cervical and anal lesions did not seem to be related in our population.

More studies are needed to clarify the epidemiology and natural history of preneoplastic and invasive anal lesions in women, and screening protocols should be revised accordingly. In our experience, anal screening should be at least considered in women who have anal sex. It is also necessary to homogenize the diagnostic terminology and not only adapt the one used for cervico-vaginal screening, but rather

develop specific criteria that allow improved diagnostic yield of this technique in this population.

## References


[1] A.E. Grulich, I.M. Poynten, D.A. Machalek, F. Jin, D.J. Templeton, R.J. Hillman, The epidemiology of anal cancer, Sex. Health 9 (2012) 504.
[2] R.J. Medford, I.E. Salit, Anal cancer and intraepithelial neoplasia: epidemiology, screening and prevention of a sexually transmitted disease, Can. Med. Assoc. J. 187 (2015) 111–115.
[3] J.R. Wilkinson, E.J.A. Morris, A. Downing, P.J. Finan, A. Aravani, J.D. Thomas, et al., The rising incidence of anal cancer in England 1990-2010: a population-based study, Colorectal Dis. 16 (2014) O234–O239.
[4] W.G. Willeford, L.H. Bachmann, Uncertainty abounds in the world of anal dysplasia screening, Sex. Transm. Dis. 43 (2016) 436–437.
[5] J.R. Daling, M.M. Madeleine, L.G. Johnson, S.M. Schwartz, K.A. Shera, M.A. Wurscher, et al., Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer, Cancer 101 (2004) 270–280.
[6] M. Frisch, B. Glimelius, J. Wohlfahrt, H.O. Adami, M. Melbye, Tobacco smoking as a risk factor in anal carcinoma: an antiestrogenic mechanism? J. Natl. Cancer Inst. 91 (1999) 708–715.
[7] J.R. Roberts, L.L. Siekas, A.M. Kaz, Anal intraepithelial neoplasia: a review of diagnosis and management, World J. Gastrointest. Oncol. 9 (2017) 50.
[8] J. Patel, I.E. Salit, M.J. Berry, A. de Pokomandy, M. Nathan, F. Fishman, et al., Environmental scan of anal cancer screening practices: worldwide survey results, Cancer Med. 3 (2014) 1052–1061.
[9] I.L. Leeds, S.H. Fang, Anal cancer and intraepithelial neoplasia screening: a review, World J. Gastrointest. Surg. 8 (2016) 41.
[10] E.A. Holly, M.L. Ralston, T.M. Darragh, R.M. Greenblatt, N. Jay, J.M. Palefsky, Prevalence and risk factors for anal squamous intraepithelial lesions in women, J. Natl. Cancer Inst. 93 (2001) 843–849.
[11] A.-B. Moscicki, T.M. Darragh, J.M. Berry-Lawhorn, J.M. Roberts, M.J. Khan, L.A. Boardman, et al., Screening for anal Cancer in women, J. Low. Genit. Tract Dis. 19 (2015) S26–S41.
[12] D.C. Koppe, C.B. Bandeira, M.R.D. Rosa, E. Cambruzzi, L. Meurer, R.B. Fagundes, Prevalence of anal intraepithelial neoplasia in women with genital neoplasia, Dis. Colon Rectum 54 (2011) 442–445.
[13] M. Ghosn, H.R. Kourie, P. Abdayem, J. Antoun, D. Nasr, Anal cancer treatment: current status and future perspectives, World J. Gastroenterol. 21 (2015) 2294.
[14] J. Wise, Anal cancer rates quadruple among UK women in past 40 years, BMJ 348 (2014) g3747.
[15] E.A. Stier, M.C. Sebring, A.E. Mendez, F.S. Ba, D.D. Trimble, E.Y. Chiao, Prevalence of anal human papillomavirus infection and anal HPV-related disorders in women: a systematic review, Am. J. Obstet. Gynecol. 213 (2015) 278–309.
[16] B.K. Edwards, E. Ward, B.A. Kohler, C. Eheman, A.G. Zauber, R.N. Anderson, et al., Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates, Cancer 116 (2010) 544–573.
[17] E.P. Simard, E.M. Ward, R. Siegel, A. Jemal, Cancers with increasing incidence trends in the United States: 1999 through 2008, CA Cancer J. Clin. 62 (2012) 118–128.
[18] S.A. Salati, A. Al Kadi, Anal cancer — a review, Int. J. Health Sci. (Qassim) 6 (2012) 206–230.
[19] J.M. Palefsky, M. Rubin, The epidemiology of anal human papillomavirus and related neoplasia, Obstet. Gynecol. Clin. North Am. 36 (2009) 187–200.
[20] M. Sauter, G. Keilholz, H. Kranzbühler, N. Lombriser, M. Prakash, S.R. Vavricka, et al., Presenting symptoms predict local staging of anal cancer: a retrospective analysis of 86 patients, BMC Gastroenterol. 16 (2016) 46.
[21] A. Nielsen, C. Munk, S.K. Kjaer, Trends in incidence of anal cancer and high-grade anal intraepithelial neoplasia in Denmark, 1978-2008, Int. J. Cancer 130 (2012) 1168–1173.
[22] G.F.C. Castor M das, H.J. da Silva, D.B. Gondim Martins, R.J.V. de Mello, HPV and precancerous lesions of anal canal in women: systematic review, Int. J. Colorectal Dis. 27 (2012) 271–276.
[23] R. Nayar, D.C. Wilbur (Eds.), The Bethesda System for Reporting Cervical Cytology : Definitions, Criteria, and Explanatory Notes, 3rd ed., Springer, New York, 2015.
[24] S.M. Bean, I. Eltoum, D.K. Horton, L. Whitlow, D.C. Chhieng, Immunohistochemical expression of p16 and Ki-67 correlates with degree of anal intraepithelial neoplasia, Am. J. Surg. Pathol. 31 (2007) 555–561.
[25] P.V. Chin-Hong, J.M. Palefsky, Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus, Clin. Infect. Dis. 35 (2002) 1127–1134.
[26] A.J.M. Watson, B.B. Smith, M.R. Whitehead, P.H. Sykes, F.A. Frizelle, Malignant progression of anal intraepithelial neoplasia, ANZ J. Surg. 76 (2006) 715–717.
[27] M. Gaudet, J. Hamm, C. Aquino-Parsons, Incidence of ano-genital and head and neck malignancies in women with a previous diagnosis of cervical intraepithelial neoplasia, Gynecol. Oncol. 134 (2014) 523–526.
[28] E.A. Stier, E.Y. Chiao, Anal cancer and anal cancer precursors in women with a history of HPV-related dysplasia and cancer, Semin. Colon Rectal Surg. 28 (2017) 97–101.
[29] P. Sananpanichkul, S. Pittyanont, P. Yuthavisuthi, N. Thawonwong, M. Techapornroong, K. Bhamarapravatana, et al., Anal papanicolaou smear in women with abnormal cytology: a thai hospital experience, Asian Pac. J. Cancer Prev. 16 (2015) 1289–1293.
[30] L.H. Cardinal, P. Carballo, M.C.C. Lorenzo, A. García, V. Suzuki, S. Tatti, et al., A six-year experience with anal cytology in women with HPV in the lower genital tract: utility, limitations, and clinical correlation, Diagn. Cytopathol. 42 (2014) 396–400.
[31] J.T. Santoso, M. Long, M. Crigger, J.Y. Wan, H.K. Haefner, Anal Intraepithelial Neoplasia in Women With Genital Intraepithelial Neoplasia, Obstet. Gynecol. 116 (2010) 578–582.
[32] A.C. ElNaggar, J.T. Santoso, Risk Factors for Anal Intraepithelial Neoplasia in Women With Genital Dysplasia, Obstet. Gynecol. 122 (2013) 218–223.
[33] B. Cronin, A. Bregar, C. Luis, S. Schechter, P. Disilvestro, L. Pisharodi, et al., Evaluation of anal cytology and dysplasia in women with a history of lower genital tract dysplasia and malignancy, Gynecol. Oncol. 141 (2016) 492–496.
[34] W. Jiménez, L. Paszat, R. Kupets, A. Wilton, J. Tinmouth, Presumed previous human papillomavirus (HPV) related gynecological cancer in women diagnosed with anal cancer in the province of Ontario, Gynecol. Oncol. 114 (2009) 395–398.
[35] F.L. Sand, C. Munk, S.M. Jensen, M.F. Svahn, K. Frederiksen, S.K. Kjaer, Long-term risk for noncervical anogenital cancer in women with previously diagnosed high-grade cervical intraepithelial neoplasia: a Danish Nationwide Cohort Study, Cancer Epidemiol. Biomarkers Prev. 25 (2016) 1090–1097.
[36] M.S. Hosseini, D. Khosravi, F. Farzaneh, A. Ebrahimi, M. Arab, T. Ashraf Ganjoie, et al., Evaluation of anal cytology in women with history of abnormal pap smear, cervical intraepithelial neoplasia, cervical cancer and high risk HPV for anogenital dysplasia, Asian Pac. J. Cancer Prev. 19 (2018) 3071–3075.
[37] L.P.B. Volpini, N.A.T. Boldrini, L.B. de Freitas, A.E. Miranda, L.C. Spano, The high prevalence of HPV and HPV16 European variants in cervical and anal samples of HIV-seropositive women with normal Pap test results, PLoS One 12 (2017) e0176422.
[38] I. Heard, I. Etienney, V. Potard, I. Poizot-Martin, C. Moore, A.C. Lesage, et al., High prevalence of anal human papillomavirus-associated cancer precursors in a contemporary cohort of asymptomatic HIV-infected women, Clin. Infect. Dis. 60 (2015) 1559–1568.
[39] J.Y. Hou, D. Smotkin, R. Grossberg, M. Suhrland, R. Levine, H.O. Smith, et al., High prevalence of high grade anal intraepithelial neoplasia in HIV-Infected women screened for anal Cancer, JAIDS J. Acquir. Immune Defic. Syndr. 60 (2012) 169–172.
[40] A. Gingelmaier, T. Weissenbacher, B. Kost, R. Kaestner, M. Sovric, I. Mylonas, et al., Anal cytology as a screening tool for early detection of anal dysplasia in HIV-infected women, Anticancer Res. 30 (2010) 1719–1723.
[41] S. Tatti, V. Suzuki, L. Fleider, V. Maldonado, R. Caruso, Mde L. Tinnirello, Anal intraepithelial lesions in women with human papillomavirus — related disease, J. Low. Genit. Tract Dis. 16 (2012) 454–459.
[42] HIV Clinical Resource: Anal Dysplasia and Cancer. New York: Office of the Medical Director New York State Department of HEalth AIDS Institute, (2007).
[43] EACS Guidelines: Version 7.02, European AIDS Clinical Society, Brussels (Belgium), 2014.
[44] J.M. Lam, J.S. Hoch, J. Tinmouth, M. Sano, J. Raboud, I.E. Salit, Cost-effectiveness of screening for anal precancers in HIV-positive men, AIDS 25 (2011) 635–642.
[45] S. Pernot, P. Boucheron, H. Péré, M.-L. Lucas, D. Veyer, N. Fathallah, et al., Comparison of anal cancer screening strategies including standard anoscopy, anal cytology, and HPV genotyping in HIV-positive men who have sex with men, Br. J. Cancer 119 (2018) 381–386.
[46] S.M. Bean, D.C. Chhieng, Anal-rectal cytology: a review, Diagn. Cytopathol. 38 (2009) 538–546.
[47] A.C.C. Pereira, Lacerda H.R. de, R. Barros RC do, Diagnostic methods for prevention of anal cancer and characteristics of anal lesions caused by HPV in men with HIV/AIDS, Braz. J. Infect. Dis. 12 (2008) 293–299.
[48] D.J. Zaccarini, K.K. Khurana, Histopathologic and cytologic follow-up in high risk male patients with unsatisfactory anal cytology, Patholog. Res. Int. 2017 (2017) 9780213.
[49] L.A. Panther, K. Wagner, J. Proper, D.K. Fugelso, P.A. Chatis, W. Weeden, et al., High resolution anoscopy findings for men who have sex with men: inaccuracy of anal cytology as a predictor of histologic high-grade anal intraepithelial neoplasia and the impact of HIV serostatus, Clin. Infect. Dis. 38 (2004) 1490–1492.
[50] I. Cromwell, M. Gaudet, S.J. Peacock, C. Aquino-Parsons, Cost-effectiveness analysis of anal cancer screening in women with cervical neoplasia in British Columbia, Canada, BMC Health Serv. Res. 16 (2016) 206.
[51] S.A. Blankenship, P. Debnath, A.W. Szlachta-McGinn, K. Maguire, J.J. Garcia, A. Aserlind, et al., Knowledge and acceptability of anal cytology screening among women, J. Low. Genit. Tract Dis. 20 (2016) 90–96.
[52] D. Ferris, R. Lambert, J. Waller, P. Dickens, R. Kabaria, C.-S. Han, et al., Women's knowledge and attitudes toward anal pap testing, J. Low. Genit. Tract Dis. 17 (2013) 463–468.
[53] A.M. Koskan, N. LeBlanc, I. Rosa-Cunha, Exploring the perceptions of anal Cancer screening and behaviors among gay and bisexual men infected with HIV, Cancer Control 23 (2016) 52–58.
[54] M.C. Osborne, J. Maykel, E.K. Johnson, S.R. Steele, Anal squamous cell carcinoma: an evolution in disease and management, World J. Gastroenterol. 20 (2014) 13052–13059.
[55] R. Glynne-Jones, P.J. Nilsson, C. Aschele, V. Goh, D. Peiffert, A. Cervantes, et al., Anal cancer: ESMO–ESSO–ESTRO clinical practice guidelines for diagnosis, treatment and follow-up, Radiother. Oncol. 111 (2014) 330–339.
[56] J.R. Roberts, L.L. Siekas, A.M. Kaz, Anal intraepithelial neoplasia: a review of diagnosis and management, World J. Gastrointest. Oncol. 9 (2017) 50–61.
[57] C. Benedict, E.J. Philip, R.E. Baser, J. Carter, T.A. Schuler, L. Jandorf, et al., Body image and sexual function in women after treatment for anal and rectal cancer, Psychooncology 25 (2016) 316–323.
[58] K. DuHamel, T. Schuler, C. Nelson, E. Philip, L. Temple, L. Schover, et al., The sexual health of female rectal and anal cancer survivors: results of a pilot randomized psycho-educational intervention trial, J. Cancer Surviv. 10 (2016) 553–563.
[59] G. Knowles, R. Haigh, C. McLean, H. Phillips, Late effects and quality of life after chemo-radiation for the treatment of anal cancer, Eur. J. Oncol. Nurs. 19 (2015) 479–485.
[60] E.A. Stier, N.L. Chigurupati, L. Fung, Prophylactic HPV vaccination and anal cancer, Hum. Vaccin. Immunother. 12 (2016) 1348–1351.