Original article

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What should we do about anal condyloma and anal intraepithelial neoplasia? Results of a survey

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Abstract

Aim There is a lack of standardization regarding diagnosis, treatment and surveillance of patients with anal HPV infection.

Method An Internet-based survey was sent to members of international, surgical and dermatological societies. Answers were obtained from 1017 dermatologists and 393 colorectal surgeons (n = 1410).

Results More dermatologists than surgeons provided noninvasive treatment of anal condyloma with 5% imiquimod (80.4 *vs* 28.2%; $P < 0.001$), whereas the situation was reversed for surgical excision (56.8 *vs* 91.3%; $P < 0.001$). To detect dysplastic lesions, 42.0% of surgeons used acetic acid only, 23.2% used this in combination with high-resolution anoscopy and 19.5% applied intra-anal cytological smears. Likewise, 64.6% of dermatologists applied acetic acid only, 16.5% combined acetic acid with high-resolution anoscopy and 30.2% performed intra-anal cytological smears (all $P < 0.001$ compared with surgeons). The therapy for anal intraepithelial lesions was not influenced by the grade of dysplasia, but it was by immune status.

Conclusion There were significant differences in practice between colorectal surgeons and dermatologists. These findings highlight the need for international and cross-disciplinary clinical guidelines.

Keywords Anal condyloma, anal intraepithelial neoplasia, surveillance, screening, treatment

Introduction

Concern regarding human papilloma virus (HPV)-related diseases of the anal canal has increased in recent years because several studies have shown a strong correlation between HPV infection and anal squamous cell cancer (SCC). In human immunodeficiency virus (HIV)-positive patients and in men who have sex with men (MSM), the prevalence of anal HPV infection is especially high (45–95%) [1,2], and these patients have an increased risk of anal intraepithelial neoplasia (AIN), the putative precursor of anal SCC [3]. The prevalence of anal SCC is increasing steadily, reaching 35 per 100 000 in HIV-negative and 70 per 100 000 in HIV-positive MSM, respectively [4,5]. Today, anal SCC in HIV-positive MSM is over nine times more common than cervical cancer in women and has become one of the most common non-AIDS-defining malignancies in HIV-positive patients [6]. The current incidence of anal SCC is comparable to the incidence of cervical cancer before contemporary surveillance programmes were widely introduced into clinical practice [7]. The management of HPV-related lesions is debated because different management options are available and a 'gold standard' is lacking [8]. Various strategies ranging from 'watchful waiting' and intensive surveillance [9] to wide excision with skin grafting to prevent anal SCC [10] have been proposed for patients with high-grade AIN (AIN II and III). As the natural history of HPV-related anal diseases is largely unknown, there is also no consensus regarding the appropriate methods of surveillance in patients with anal HPV infection. Consensus is further hampered because both colorectal surgeons and dermatologists are involved in the management of HPV-related anal diseases.

As a first step towards the establishment of consensus clinical guidelines, this study assessed current practices regarding diagnosis, therapy and surveillance of patients

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with HPV-related anal diseases using an internet-based survey targeted on members of international surgical and dermatological societies.

Method

An Internet-based survey was sent to members of surgical and dermatological societies to evaluate current practice regarding diagnosis, treatment and surveillance of patients with HPV-related anal diseases. It consisted of 16 multiple-choice questions and could be filled out completely online in less than 5 min. Members of the following societies were contacted by email: The Association of Coloproctology of Great Britain and Ireland, the German Society of Coloproctology, the Colorectal Surgical Society of Australia and New Zealand, the Austrian Study Group for Coloproctology, the European Academy of Dermatology and Venerology, the German Dermatological Society, the Society of Dermatology and Venerology of Austria, the Swiss Society of Dermatology and of Coloproctology and the International League of Dermatological Societies. In total, 6065 dermatologists and 1667 colorectal surgeons were contacted. Responses were obtained from 1017 (16.7%) and 393 (23.6%), respectively.

Statistical analysis

The χ^2 test and Mann–Whitney *U*-test were used where appropriate. The level of significance was set at $P < 0.05$.

Results

Treatment of anal condyloma

Different therapeutic approaches were used for the treatment of anal condyloma (Fig. 1); the majority (91.3%) of colorectal surgeons preferred excision compared with 56.8% for dermatologists ($P < 0.001$). Most dermatologists preferred imiquimod cream (5%; Aldara®; 3M Pharmaceutical, Rüschlikon, Switzerland), a topical immune response modifier, or podophyllin, whereas colorectal surgeons used these treatments less frequently (80 and 57% *vs* 28 and 28%, respectively; $P < 0.001$). Ablative techniques, including cryotherapy and laser treatment, were used by dermatologists in 55 and 40% of patients, respectively, compared with 7.6 and 14% of patients for colorectal surgeons ($P < 0.001$).

Histological examination of anal condyloma

Thirty-two per cent of colorectal surgeons and 38% of dermatologists never requested histological examination, while 29 and 37%, respectively, did so only in high-risk patients or in those with recurrent disease. Thirty-nine per cent of the colorectal surgeons routinely performed a biopsy before or after resection, whereas this was performed by only a quarter of dermatologists (25%; $P < 0.001$).

Determination of HPV subtypes

In HPV-related anal disease, 59% of colorectal surgeons and 56% of dermatologists did not determine HPV

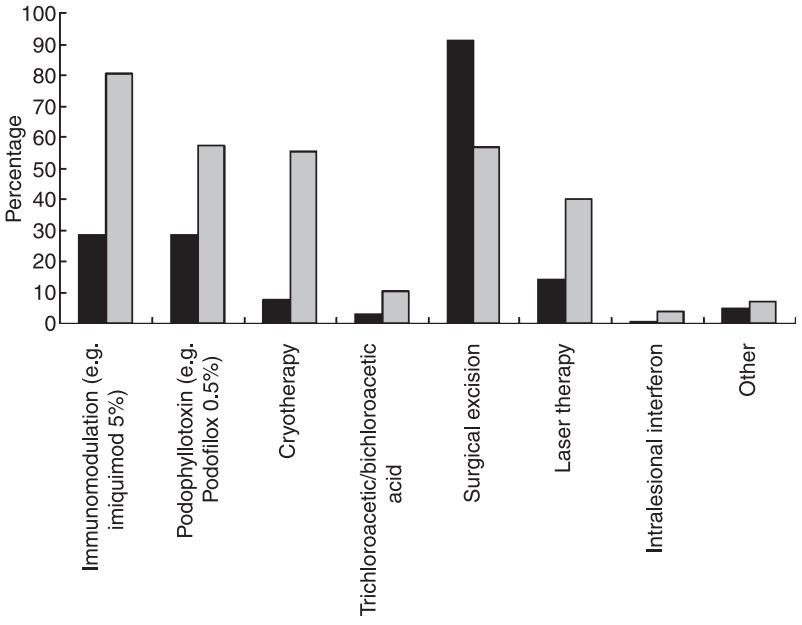

Figure 1 Treatment of anal condyloma (black bars, colorectal surgeons; grey bars, dermatologists).

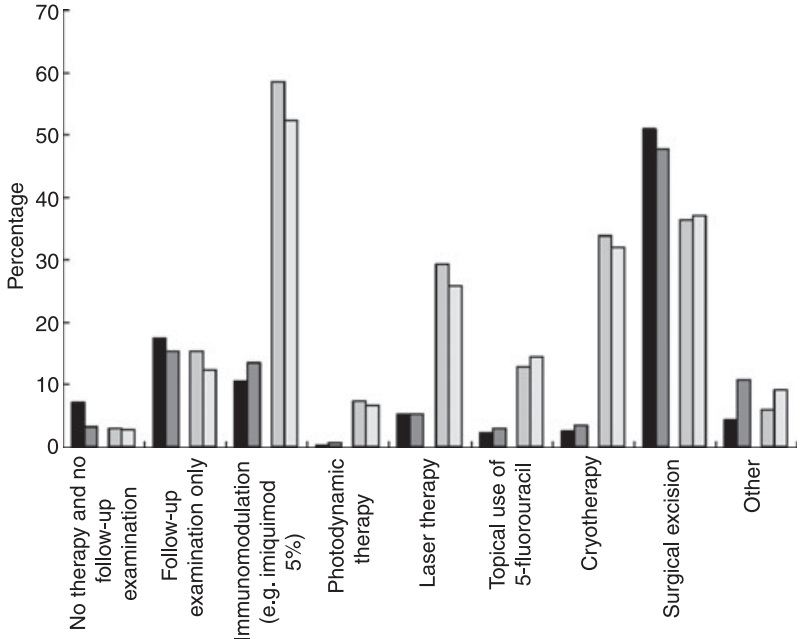

Figure 2 Therapy of low- and high-grade anal intraepithelial neoplasia (AIN) in HIV-negative patients (black bars, colorectal surgeons/low-grade AIN; black-striped bars, colorectal surgeons/high-grade AIN; grey bars, dermatologists/low-grade AIN; grey-striped bars, dermatologists/high-grade AIN).

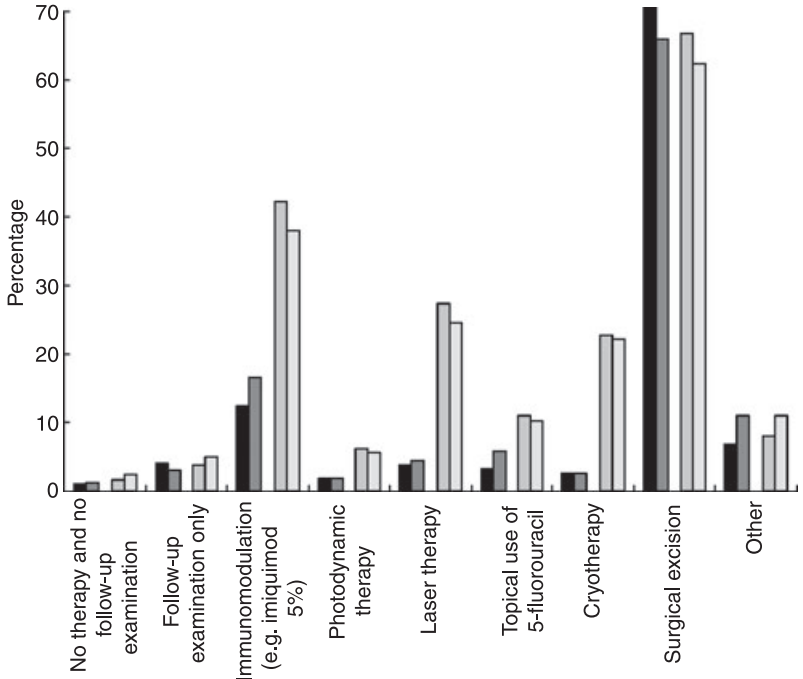

Figure 3 Therapy of low- and high-grade anal intraepithelial neoplasia (AIN) in HIV-positive patients (black bars, colorectal surgeons/low-grade AIN; black-striped bars, colorectal surgeons/high-grade AIN; grey bars, dermatologists/low-grade AIN; grey-striped bars, dermatologists/high-grade AIN).

subtypes. Polymerase chain reaction (PCR) or *in situ* hybridization for the identification of HPV subtypes was requested by 14 and 13%, respectively, and 27 and 31% requested this only in high-risk patients ($P = 0.25$).

Treatment of AIN

The preferred therapies of HIV-negative and HIV-positive patients with low- and high-grade AIN (AIN I and AIN II/III, respectively) are shown in Figs 2 and 3.

Anal cancer surveillance

Forty-two per cent of colorectal surgeons used acetic acid to detect AIN (without the use of a colposcope), 19.5% applied intra-anal cytological smears and 23.2% used high-resolution anoscopy (HRA). These proportions for

dermatologists were 65, 30 and 16%, respectively (all $P < 0.001$).

Regarding the time interval for cancer surveillance, colorectal surgeons and dermatologists concurred. The median surveillance interval for physical examination for dermatologists and colorectal surgeons was 6 months in HIV-negative patients with low-grade AIN and 3 months for HIV-positive patients with low- and high-grade AIN.

Partner examination

Most of the participating physicians advised an examination of the patient's partner in cases with HPV-related anal disease (dermatologists 97%; colorectal surgeons 80%; $P < 0.001$).

Discussion

In the past 30 years, the incidence of anal SCC has risen from 3.7 to 20.6 per 100 000 patients in all men between 40 and 64 years, irrespective of their sexual orientation [11]. In HIV-infected MSM, an even higher incidence of 224 per 100 000 has been reported [12]. Human papilloma virus-induced AIN have been attributed to the development of SCC. The prevalence of anal HPV infection is high in HIV-positive patients and MSM, being 85–93% of HIV-positive and 61% of HIV-negative MSM and 46% of heterosexual HIV-positive patients [1,2]. The prevalence of high-grade AIN (AIN grade II and III), the putative precursor of SCC, is also significant, being 18–49% in HIV-positive [2,13] and 5% in HIV-negative MSM [14]. Early detection and management of high-grade AIN is considered to be crucial, especially in HIV-positive patients because morbidity and mortality of anal SCC in such patients is substantial.

Screening by cytology and stringent surveillance have substantially decreased the incidence of cervical cancer. In contrast to cervical intraepithelial lesions, there is no generally accepted surveillance policy for patients with AIN despite the biological similarities between these conditions. However, the New York State Department of Health AIDS institute recently proposed annual anal cytology screening for MSM and any patients with a history of anogenital condyloma with referral for HRA and/or biopsy in patients with an abnormal finding [15]. High-resolution anoscopy can identify subclinical AIN and map out the extent of the disease, thus allowing targeted biopsies and treatment. A recent study revealed that about 50% of all AIN are missed if HRA is not performed [16]. In a mathematical model, this approach was shown to increase life expectancy and to be cost effective in HIV-positive and HIV-negative MSM [17,18] Despite these findings, this survey demonstrates that cytological smears and HRA are still not a routine part of the practice of colorectal surgeons or dermatologists.

Histological assessment of anal condyloma has been recently recommended to prevent missing epithelial dysplasia [8]. Although anal condylomas are believed to have a low risk of progression to invasive cancer, the incidence of anal dysplasia and anal SCC was found to be significant; this warrants consideration of biopsy in all patients [19]. However, according to our survey, only 40% of the colorectal surgeons and 25% of the dermatologists routinely send specimens for pathological evaluation. Likewise, HPV typing is also rarely performed in anal disease, although the addition of HPV typing to cytology is increasingly recommended in cervical cancer surveillance programmes [20]. There is also strong evidence that infection with HPV 16 and 18 as well as infection with multiple HPV subtypes predispose to high-grade AIN, suggesting HPV typing to be valuable also in anal infection [6], although definitive evidence to support HPV typing on a routine basis is lacking.

Studies on surgical excision of AIN reported high rates of recurrences in both HIV-positive and HIV-negative MSM and showed a high proportion of postoperative discomfort [21,22]. Nevertheless, most colorectal surgeons still preferred this approach to treatment. Better results have been reported for infrared coagulation. Our survey reveals, however, that infrared coagulation is infrequently used in clinical practice, with cryotherapy or laser therapy being offered more frequently, especially by dermatologists, but outcome data are scarce, hampering the validation of such treatments.

The topical application of the immunomodulator imiquimod (Aldara®) has been presented as an effective therapy for AIN. In a small study, 18 HIV-positive MSM patients with perianal and intra-anal dysplasia were treated for 16 weeks with imiquimod cream (5%) or imiquimod suppositories. Fourteen (77%) patients were completely free of AIN at the completion of therapy [23]. In another study of imiquimod in HIV-positive MSM, 46% had complete resolution of all lesions, with a recurrence rate of 29% [24]. Imiquimod seems to be the most commonly used therapy by dermatologists for anal condylomas and AIN in HIV-negative patients; however, colorectal surgeons use it only rarely.

The finding that therapy is not influenced by the grade of dysplasia but depends almost exclusively on the HIV status is striking. In HIV-negative patients, most dermatologists prefer nonablative treatments irrespective of the grade of AIN. However, the colorectal surgeons preferred excision, with grade of dyplasia having little impact on decision making. On the contrary, in HIV-positive

patients, both dermatologists and colorectal surgeons chose excision, again irrespective of the histological grade.

The reported follow-up intervals for patients with HPV-related anal disease range from 3 to 12 months depending on the perceived risk of SCC. In HIV-negative patients with low-grade AIN, clinical review was proposed every 12 months and in HIV-positive or patients with high-grade AIN every 4–6 months [8]. Palefsky suggested clinical and cytological screening every 12 months in HIV-infected patients, every 6 months for those with low-grade AIN and every 3 months in patients with high-grade dysplasia [25]. Based on our survey, most colorectal surgeons and dermatologists advocated a 6-month interval in low-risk patients (low-grade AIN and HIV negative) and 3 months for high-risk patients (high-grade AIN and/or HIV positive). The discrepancy between the recommendations in the literature and the surveillance intervals commonly used in clinical practice reflects the lack of evidence-based data.

Three points have to be considered critically while interpreting our results. First, despite the large number of medical practitioners who responded, the survey may not be representative because the overall response rate was low. Email-based surveys often show lower response rates than those based on posted paper questionnaires [26], but the response rate of about 20% is in line with other email-based surveys [27]. Second, differences in patient selection between colorectal surgeons and dermatologists cannot be excluded. This could in part explain the differences observed between colorectal surgeons and dermatologists because both groups might see a distinctly different group of patients. Third, the survey only obtained replies from colorectal surgeons and dermatologists and not from other physicians, including venereologists or gastroenterologists. In the USA, anal cytologie smears and HRA are often performed by interns. However, exact figures on how many anal SCC screenings are performed by each speciality are lacking for both the USA and Europe.

The study has shown that there is no consensus on diagnosis, treatment and surveillance of anal HPV-related diseases. The facts that anal SCC has become one of the most common non-AIDS malignancies and that these cancers share biological properties with cervical cancer highlight the need for universal guidelines regarding the clinical management of HPV-related anal disease, especially in high-risk patients.

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References

1 Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV-negative homosexual men. *J Infect Dis* 1998; **177:** 361–7.
2 Piketty C, Darragh TM, Da Costa M *et al.* High prevalence of anal human papillomavirus infection and anal cancer precursors among HIV-infected persons in the absence of anal intercourse. *Ann Intern Med* 2003; **138:** 453–9.
3 Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 2000; **92:** 1500–10.
4 Melbye M, Cote TR, Kessler L, Gail M, Biggar RJ. High incidence of anal cancer among AIDS patients. The AIDS/Cancer Working Group. *Lancet* 1994; **343:** 636–9.
5 Goedert JJ, Cote TR, Virgo P *et al.* Spectrum of AIDS-associated malignant disorders. *Lancet* 1998; **351:** 1833–9.
6 Chin-Hong PV, Palefsky JM. Natural history and clinical management of anal human papillomavirus disease in men and women infected with human immunodeficiency virus. *Clin Infect Dis* 2002; **35:** 1127–34.
7 Melbye M, Rabkin C, Frisch M, Biggar RJ. Changing patterns of anal cancer incidence in the United States, 1940–1989. *Am J Epidemiol* 1994; **139:** 772–80.
8 Abbasakoor F, Boulos PB. Anal intraepithelial neoplasia. *Br J Surg* 2005; **92:** 277–90.
9 Devaraj B, Cosman BC. Expectant management of anal squamous dysplasia in patients with HIV. *Dis Colon Rectum* 2006; **49:** 36–40.
10 Marchesa P, Fazio VW, Oliart S, Goldblum JR, Lavery IC. Perianal Bowen's disease: a clinicopathologic study of 47 patients. *Dis Colon Rectum* 1997; **40:** 1286–93.
11 Cress RD, Holly EA. Incidence of anal cancer in California: increased incidence among men in San Francisco, 1973–1999. *Prev Med* 2003; **36:** 555–60.
12 Diamond C, Taylor TH, Aboumrad T, Bringman D, Anton-Culver H. Increased incidence of squamous cell anal cancer among men with AIDS in the era of highly active antiretroviral therapy. *Sex Transm Dis* 2005; **32:** 314–20.
13 Palefsky JM, Holly EA, Ralston ML, Jay N, Berry JM, Darragh TM. High incidence of anal high-grade squamous intra-epithelial lesions among HIV-positive and HIV-negative homosexual and bisexual men. *AIDS* 1998; **12:** 495–503.
14 Chin-Hong PV, Vittinghoff E, Cranston RD *et al.* Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study. *J Natl Cancer Inst* 2005; **97:** 896–905.
15 Mathews C, Caperna J, Cachay ER, Cosman B. Early impact and performance characteristics of an established anal dysplasia screening program: program evaluation considerations. *Open AIDS J* 2007; **1:** 11–20.
16 Watson AJ, Smith BB, Whitehead MR, Sykes PH, Frizelle FA. Malignant progression of anal intra-epithelial neoplasia. *AN ZJ Surg* 2006; **76:** 715–7.

17 Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Welton ML, Palefsky JM. The clinical effectiveness and cost-effectiveness of screening for anal squamous intraepithelial lesions in homosexual and bisexual HIV-positive men. *JAMA* 1999; **281:** 1822–9.
18 Goldie SJ, Kuntz KM, Weinstein MC, Freedberg KA, Palefsky JM. Cost-effectiveness of screening for anal squamous intraepithelial lesions and anal cancer in human immunodeficiency virus-negative homosexual and bisexual men. *Am J Med* 2000; **108:** 634–41.
19 Metcalf AM, Dean T. Risk of dysplasia in anal condyloma. *Surgery* 1995; **118:** 724–6.
20 Mayrand MH, Duarte-Franco E, Rodrigues I *et al.* Human papillomavirus DNA versus Papanicolaou screening tests for cervical cancer. *N Engl J Med* 2007; **357:** 1579–88.
21 Chang GJ, Berry JM, Jay N, Palefsky JM, Welton ML. Surgical treatment of high-grade anal squamous intraepithelial lesions: a prospective study. *Dis Colon Rectum* 2002; **45:** 453–8.
22 Pineda CE, Berry JM, Jay N, Palefsky JM, Welton ML. High resolution anoscopy in the planned staged treatment of anal squamous intraepithelial lesions in HIV-negative patients. *J Gastrointest Surg* 2007; **11:** 1410–5.
23 Kaspari M, Gutzmer R, Kaspari T, Kapp A, Brodersen JP. Application of imiquimod by suppositories (anal tampons) efficiently prevents recurrences after ablation of anal canal condyloma. *Br J Dermatol* 2002; **147:** 757–9.
24 Sanclemente G, Herrera S, Tyring SK *et al.* Human papillomavirus (HPV) viral load and HPV type in the clinical outcome of HIV-positive patients treated with imiquimod for anogenital warts and anal intraepithelial neoplasia. *J Eur Acad Dermatol Venereol* 2007; **21:** 1054–60.
25 Palefsky JM. Anal squamous intraepithelial lesions in human immunodeficiency virus-positive men and women. *Semin Oncol* 2000; **27:** 471–9.
26 Kongsved SM, Basnov M, Holm-Christensen K, Hjollund NH. Response rate and completeness of questionnaires: a randomized study of Internet versus paper-and-pencil versions. *J Med Internet Res* 2007; **9:** e25.
27 Kim HL, Benson DA, Stern SD, Gerber GS. Practice trends in the management of prostate disease by family practice physicians and general internists: an internet-based survey. *Urology* 2002; **59:** 266–71.