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ORIGINAL ARTICLE

Expectant management surveillance for patients at risk for invasive squamous cell carcinoma of the anus: a large US healthcare system experience

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Abstract

Purpose To determine the impact of expectant management surveillance for patients at risk for squamous cell carcinoma of the anus (SCCA).

Methods Adult patients at risk for anal cancer, specifically those with human immunodeficiency virus (HIV) or known human papilloma virus (HPV) infections (anal dysplasia, anogenital warts, cervical dysplasia, or cervical cancer), underwent expectant management surveillance with targeted therapy of only grossly abnormal or symptomatic anoderm lesions. A retrospective analysis investigated the SCCA incidence in these surveilled populations and in the general population patients without known HIV or HPV infection.

Results There were 452 incident SCCA in a population of 5,978,510 patients (mean follow-up per patient of 5.4 years). Four hundred ten cancers (90.7%) developed in 5,750,501 HIV-negative patients without documented history of HPV infection (cumulative incidence 0.007%). In at-risk patient populations, the cumulative incidence was 0.69% in patients with anal dysplasia (6 out of 872 patients), 0.14% in HIV+ patients (8 out of 5626 patients), and less than 0.1% in the remaining at-risk groups: cervical cancer (1 out of 1168 patients), cervical dysplasia (14 out of 125,604 patients), and genital warts (14 out of 94,739 patients).

Conclusions Expectant management surveillance, with targeted treatment for symptomatic or abnormal lesions, is an effective strategy for the diagnosis of anal cancer in at-risk patient populations. In this study, most patients who developed anal cancer had no known risk factors. A screening strategy for the general population needs to be further delineated.

Keywords Anal cancer · HIV · HPV · Anal intraepithelial neoplasia · Expectant management

Introduction

Invasive squamous cell carcinoma of the anus (SCCA) is associated with human papilloma virus (HPV) infection, and 90% of SCCA cases are associated with HPV serotypes 16 and 18 [1, 2]. Although these and other high-risk HPV serotypes are included in the recently introduced HPV vaccine [3], the SCCA incidence is rising with 8580 new cases projected for 2018 in the USA [4, 5]. This increase has been attributed to the longer patient survival during the antiretroviral therapy (HAART) era of the human immunodeficiency virus (HIV) epidemic, and the lack of a professional consensus for SCCA screening of high-risk patients or the general population [6, 7].

Papanicolaou (Pap) smear-based screening programs for cervical cancer have been very successful at reducing the incidence of this disease [8]. During Pap screening, microscopic foci of cervical dysplasia are eradicated using local ablative techniques [9]. As such, there has been interest in the early detection and treatment of pre-malignant anal HPV infections to prevent SCCA [2]. Most of the available scientific data on the management of anal HPV infection comes from studies involving small numbers of patients considered at risk for the development of anal dysplasia and subsequent progression to SCCA [10]. Traditionally, at-risk populations have included patients with HIV infections, men who have sex with men

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(MSM), patients with known anogenital HPV infections (manifesting as anogenital warts, cervical or anal dysplasia, or cervical cancer), and medically immunosuppressed patients such as organ transplant recipients [11–14]. Current thinking suggests that chronic, indolent HPV infection generates abnormal precancerous lesions which can then transform into invasive cancer [15]. In many patients, however, HPV infections are self-limited and never progress to invasive disease.

While there are specific Pap-based guidelines for the prevention of cervical cancer, there is no consensus for SCCA screening. Some advocates surveil only the highest risk populations, but others follow any patient with a documented anogenital HPV infection or systemic immunosuppression. Moreover, there are disparate recommendations for the method of surveillance for at-risk populations. Some authors recommend routine anal Pap smears, high resolution anoscopy (HRA), or anal mapping of asymptomatic patients, with targeted destruction of microscopic foci of anal dysplasia [16–18]. Others propose an expectant management (EM) approach, in which ablative interventions are reserved only for grossly abnormal or symptomatic lesions [19, 20]. The 2018 American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for SCCA acknowledges this clinical confusion, "What remains unclear is whether screening to identify and ablate premalignant lesions will decrease the incidence of SCCA" [7]. Finally, for the general population patients without known HIV or HPV infections, there is no clear strategy of SCCA prevention except for prophylactic vaccination to prevent the initial HPV transmission [21, 22].

The purpose of this study was to determine the incidence of SCCA in at-risk populations undergoing EM surveillance. Furthermore, we aimed to understand the incidence of SCCA in general population patients without known risk factors for SCCA.

Methods

The study was conducted using the databases of Kaiser Permanente Southern California (KPSC), one of the largest healthcare systems in the USA. The care within KPSC is delivered by the Southern California Permanente Medical Group (SCPMG), a multispecialty physician group practice which provides the entire spectrum of care within its 14 hospitals and outpatient clinics. All KPSC facilities are linked through a single electronic healthcare record which is continuously updated with patients' clinical information.

SCPMG physicians involved in the care and surveillance of patients at risk for SCCA include general and colorectal surgeons, infectious disease specialists, family medicine and internal medicine physicians, and gynecologists. An EM approach for patients at risk for SCCA was the standard practice at KPSC for the duration of the study period and included routine visual inspection of the perineum, digital rectal examination, and anoscopy at interval times ranging from 3 to 12 months (shorter interval if symptomatic or dysplastic lesion, and longer if asymptomatic). Only patients with grossly abnormal or symptomatic lesions, including perianal warts, were treated with one of the following interventions: clinic-based punch biopsy, excisional biopsy, or fulguration in the operating room. Notably, SCPMG physicians did not perform routine anal Pap smears, high resolution anoscopy, or other surveillance techniques to identify or destroy microscopic foci of dysplasia in the grossly normal anoderm of asymptomatic patients.

The KPSC Institutional Review Board (IRB) approved this study. A retrospective review was conducted of all KPSC patients treated between January 1, 2005 and December 31, 2015 who had a least 1 year of active membership with KPSC. ICD-9 coding data from the electronic healthcare record was abstracted and analyzed by the KPSC regional research division. The abstracted patient data was then correlated with the disease-specific KPSC registries for HIV infection, SCCA, and cervical cancer, as well as the underlying cause of death (UCOD) registry maintained by the Center for Disease Control and Prevention. Patients with prevalent SCCA diagnoses before January 1, 2005 were excluded from the analysis.

Patients at risk for the development of SCCA were identified using ICD-9 coding. Table 1 defines the groups of patients that were the focus of this study: HIV-positive patients, those with known HPV infections (high- and low-grade anal dysplasia, genital warts, cervical dysplasia, and cervical cancer), and the general population not perceived at risk for SCCA (HIV-negative patients without known HPV infections). These patients were followed until they reached one of the defined study end points: development of invasive SCCA, cancelation of KPSC membership, or patient death. Index at-risk diagnoses within 30 days of the SCCA diagnosis were considered as part of the same patient presentation, instead of as distinct, pre-existent diagnoses.

SCCA incidences were calculated in each subgroup of patients as cumulative incidences during the study period and as annualized incidence rates (new SCCA events per 100,000 person-years of follow-up). For the highest risk group, patients with documented anal dysplasia, the SCCA incidence during the study period was compared with published data from other high-volume HIV referral centers [16–20, 23–25] and with the published California Cancer Registry data between the years 2005 and 2015 [26]. Ninety-fifth percentile confidence interval and statistical significance between incidence rates were calculated using Student's *t* test.

To validate the level of care within the KPSC system, the oncologic outcomes of the incident SCCA population during the study period were evaluated. Initial staging for SCCA patients was obtained through the KPSC anal cancer registry, and underlying causes of death were identified through

Table 1 ICD-9 coding and definitions for at-risk KPSC patient populations

At-risk group	Abbreviation	ICD-9 codes	Other diagnostic names
Genital warts	GW	78.1, 78.11, 78.19	Anal wart Genital wart Condyloma acuminatum
Low-grade anal dysplasia	LGD	569.44, 796.70 796.71, 796.72 796.73	Anal dysplasia (mild, moderate) Anal intraepithelial neoplasia 1 and 2 (AIN1, AIN2) Low-grade squamous intraepithelial lesion (LGSIL)
High-grade anal dysplasia	HGD	230.5, 230.6, 796.74, 796.76	Anal dysplasia (severe or high) Anal intraepithelial neoplasia 3 (AIN3) High-grade squamous intraepithelial lesion (HGSIL) Squamous cell carcinoma in situ (SCCIS) Bowen disease
Low-grade cervical dysplasia	LCD	622.1, 622.12 795, 795.01–03 795.05–07, 795.09–13	Low-grade squamous intraepithelial lesions (LGSIL) Cervical intraepithelial neoplasia, level 1 or 2 Low-grade, mild, or moderate cervical dysplasia Atypical squamous cells of uncertain significance (ASCUS)
High-grade cervical dysplasia	HCD	233.1 622.1, 622.12 795.04, 795.14	Cervical dysplasia (severe or high grade) Cervical intraepithelial neoplasia (CIN-3) High-grade squamous intraepithelial lesion (HGSIL) Cervical carcinoma in situ (CCIS)
History of cervical cancer	HCC	Defined by patient inclusion in KPSC Internal Cancer Registry	
Human immunodeficiency virus	HIV+	Defined by patient inclusion in KPSC Internal HIV Registry	

KPSC, Kaiser Permanente Southern California

UCOD codes C20 and C210 in the CDC registry. These data were confirmed by direct review of the incident SCCA patients' electronic medical records. Five-year overall survival and disease-specific Kaplan-Meier survival rates were calculated. KPSC mortality rates due to SCCA during the study interval were then compared to state SCCA mortality from the published California Cancer Registry database [26]. SCCA mortality rates are presented as the number of events per 100,000 person-years of follow-up. Chi-square testing was used to evaluate if there was a significant difference in the stage distribution of the incident SCCA cases between the at-risk patient and general populations.

Results

Within a KPSC population of 5,978,510 patients between January 1, 2005 and December 31, 2015, there were 228,009 at-risk patients identified compared to 5,750,501 patients without perceived risk (Fig. 1). Five thousand six hundred twenty-six patients were HIV-positive, of which 25 also had high-grade anal dysplasia (HGD) and 108 had low-grade anal dysplasia (LGD). In the HIV-negative population, there were 353 HGD patients; 386 LGD patients; 1168 patients with a history of cervical cancer; 15,711 patients with high-grade cervical dysplasia; 109,893 patients with low-grade cervical dysplasia; and 94,739 patients with anogenital warts.

Table 2 shows the SCCA incidences within KPSC during the 11-year study period. There were 452 incident SCCA in the entire population during a mean follow-up of 5.4 years (standard deviation, 3.7 years). The mean age of SCCA diagnosis was 63.8 years (range, 33 to 98), and 318 of the SCCA cases developed in women (70%). For the 42 SCCA cancers in the at-risk populations, the mean age of diagnosis was 59.0 years, and 28 of the patients were female (66.7%). The annualized SCCA incidence was slightly lower than the SCCA incidence seen in the California Cancer Registry (1.30 versus 1.79 events per 100,000 person-years, p = NS). Four hundred ten of the 452 SCCA cases (90.7%) occurred in general population patients with no perceived risk for SCCA. The stage distribution was as follows: 110 stage 1 patients, 151 stage 2 patients, 158 stage 3 patients, and 31 stage 4 patients. In the high-risk patient populations, the stage distribution was as follows: 16 stage 1 patients, 17 stage 2 patients, 13 stage 3 patients, and 1 stage 4 patient. There was no significant SCCA downstaging noted in the high-risk versus general populations ($p = 0.20$).

Patients with anal dysplasia had the highest rate of malignant progression to SCCA, with an overall incidence of 191.5 events per 100,000 person-years of follow-up. Anal HGD and LGD patients had similar SCCA incidence rates, with 193.3 and 188.1 events per 100,000 person-years of follow-up, respectively. Eight cases of SCCA developed in the HIV population, including one in a patient with co-existent anal HGD. This corresponds to a SCCA incidence of 28.8 events per 100,000 person-years of follow-up for all HIV-positive patients. Although 34 additional SCCA cases developed in patients with history of cervical cancer, cervical dysplasia, or

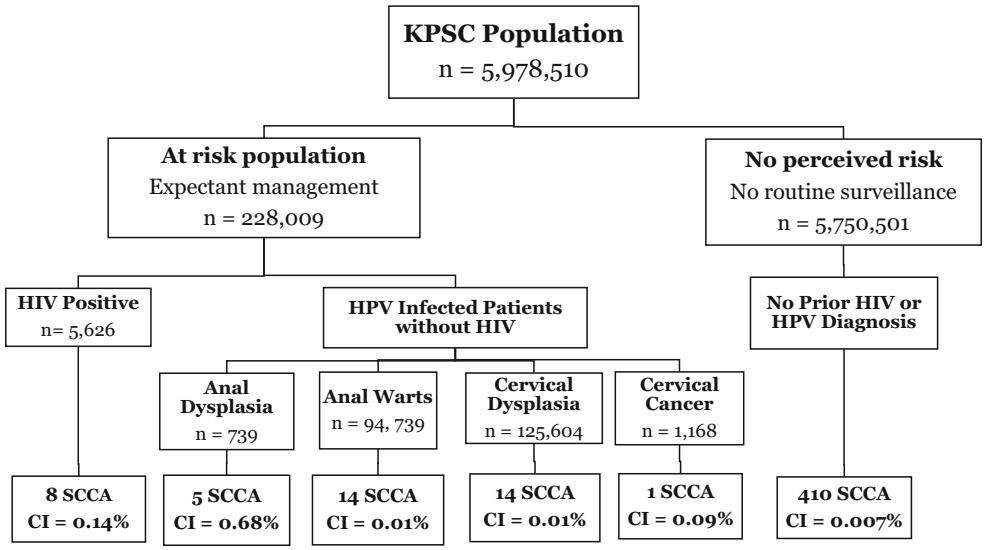

Fig. 1 Identification of at-risk patient populations and surveillance regimens. CI = cumulative incidence (number of incident SCCA cases in at-risk population over duration of study period)

genital warts, each of these groups had SCCA incidences less than 10 events per 100,000 person-years of follow-up.

During a mean interval of 3.3 years from SCCA diagnosis (range, 0.0 to 11.0 years), 159 of the 452 SCCA patients died (overall mortality rate, 35.2%). For 91 of these patients, SCCA was identified as the cause of death (disease specific mortality, 20.1%). The stage-specific 5-year disease-specific survival was as follows: stage 1, 91.3%; stage 2, 77.4%; stage 3, 81.2%; and stage 4, 25.5% (Fig. 2). The stage-specific five-year overall survival for SCCA patients by stage was as follows: stage 1, 74.0%; stage 2, 67.8%; stage 3, 70.7%; and stage 4, 15.6%. The SCCA disease-specific mortality rate at KPSC was not significantly different from the reported SCCA mortality rate in the California Cancer Registry (0.21 versus 0.25 events per 100,000 person-years of follow-up, p = NS).

Table 2 Incidence of anal squamous cell cancer in at-risk KPSC populations

High-risk group	HIV status	No. of patients	Anal SCCA events	Mean years of follow-up (SD)	Patient-years at risk	Incidence[a]	Cumulative incidence[b]	p value[c]
High-grade anal dysplasia	+	*25*	*1*	*2.8 (2.5)*	*71.2*	*193.3* (72.6–515.1)	*1.06%*	*< .0001*
	–	*353*	*3*	*5.9 (5.4)*	*2069.1*			
Low-grade anal dysplasia	+	*108*	*0*	*2.3 (1.6)*	*250.3*	*188.1* (47.0–751.9)	*0.40%*	*< .0001*
	–	*386*	*2*	*2.8 (1.8)*	*1063.5*			
Anal dysplasia	+	*133*	*1*	*2.4 (1.8)*	*324.4*	*191.5* (86.0–426.3)	*0.69%*	*< .0001*
	–	*739*	*5*	*4.2 (4.2)*	*3132.6*			
HIV-positive	+	*5626*	*8*	*4.9 (3.4)*	*27,730.3*	*28.8* (12.0–53.0)	*0.14%*	*< .0001*
Cervical cancer	NA	*1168*	*1*	*8.9 (7.5)*	*10,358.6*	*9.7* (1.4–68.5)	*0.09%*	*0.04*
High-grade cervical dysplasia	NA	*15,711*	*5*	*7.3 (6.9)*	*114,031.4*	*4.4* (1.8–10.5)	*0.03%*	*0.006*
Genital warts	NA	*94,739*	*14*	*5.7 (4.5)*	*537,036.4*	*2.6* (1.7–4.6)	*0.01%*	*0.003*
Low-grade cervical dysplasia	NA	*109,893*	*14*	*6.4(6.4)*	*708,689.5*	*2.0* (1.2–3.3)	*0.01%*	*0.11*
General population	–	*5,750,501*	*410*	*5.4 (3.6)*	*30,984,711*	*1.3* (1.2–1.4)	*0.007%*	ref
Overall		*5,978,510*	*452*	*5.4(3.7)*	*32,386,011.1*	*1.30* (1.2–1.5)	*0.008%*	

[a] Incidence is reported as events per 100,000 person-years of follow-up. Parentheses indicate 95th percentile confidence intervals

[b] Cumulative incidence is percentage of patients who developed SCCA during study follow-up interval

[c] p values calculated against general population

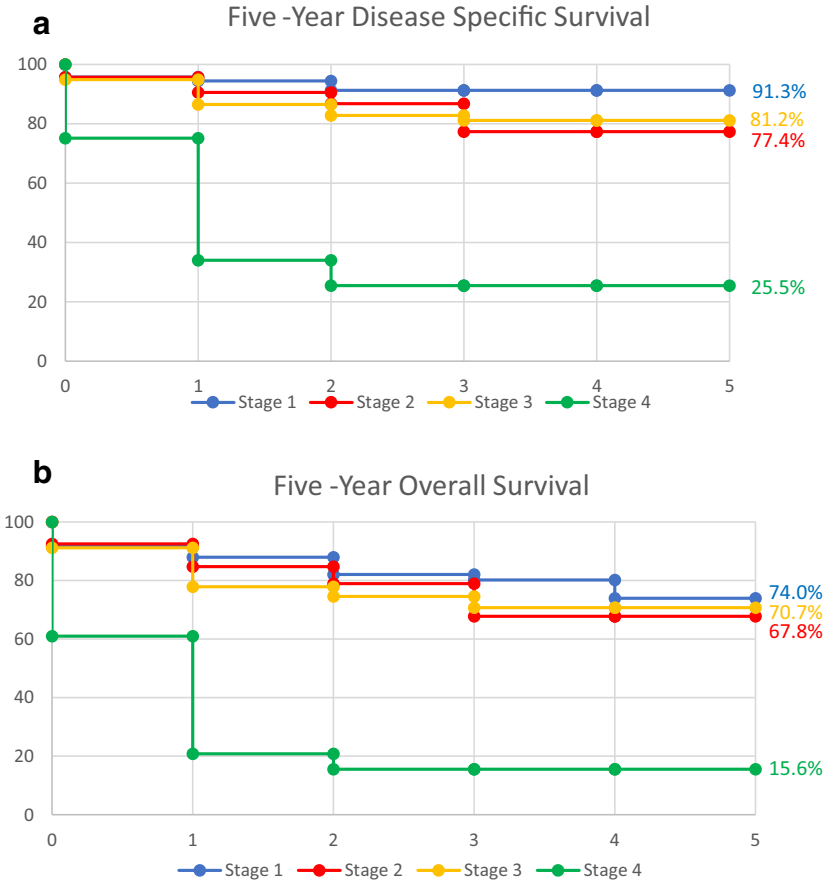

Fig. 2 Five-year survival curves

Discussion

Increasing SCCA incidence has prompted a call for surveillance of at-risk populations, but there is little consensus in the literature regarding which populations to surveil or even which screening modality is optimal [7, 27, 28]. This study, the largest population-based analysis of the SCCA incidence in the available literature, shows that the malignant progression to SCCA in at-risk populations managed expectantly with treatment of symptomatic or abnormal lesions is lower than previously described [19, 20, 23–25]. Since patients undergoing EM are simply observed for progressive disease during surveillance, the SCCA incidence during this approach provides the closest possible approximation of the natural progression of the disease. These findings have significant implications for the management of patients at risk for SCCA.

The most important finding of this study is that the clear majority (90.7%) of incident SCCA cases developed in HIV-negative patients with no previously documented HPV infection. This result strongly suggests that protocols aimed at screening at-risk populations are insufficient to prevent most cases of SCCA. Prior HPV infection is the etiologic factor in the development of SCCA [1, 2], so it stands to reason that the low-risk KPSC patients who developed SCCA must have harbored occult HPV infections. Identification of all the occult HPV infections within the larger general population would be challenging, if not impossible. Given the extremely low rates of progression to SCCA, knowing a patient's HPV status may not even be clinically relevant. For example, the prophylactic identification of the 14 SCCA cases in known cervical dysplasia patients would have required around 800,000 surveillance exams over 7 years. These data suggest that proactive SCCA surveillance of these large HPV-infected populations would be relatively low yield as well.

Patients with HIV infections, especially men who have sex with men, historically have been considered one of the highest risk groups for SCCA. As such, aggressive surveillance of the HIV-positive MSM population has been advocated, including the widespread adoption of anal Pap smear and high resolution anoscopy [2, 7, 11]. In this study, only eight incident SCCA developed in the HIV population, corresponding to a cumulative incidence of 0.14% over 4.9 years of follow-up. The SCCA incidence in the HIV-positive cohort of this study is comparable to a recent meta-analysis of HIV-positive MSMs (28.8 versus 46 per 100,000 person-years) [14]. These very low rates of malignant progression to SCCA in these two very large at-risk patient populations suggest that aggressive SCCA surveillance in asymptomatic HIV-positive individuals may not be justified, especially in the absence of anal dysplasia.

This study's SCCA cumulative incidence was highest in the high-grade anal dysplasia population, 1.06% over 5.9 years of follow-up. Table 3 shows that the SCCA incidence in the entire KPSC anal dysplasia population (0.69% over 4.2 years) is lower than previously published reports on EM surveillance protocols (2.4–11%) and comparable to the incidences of centers advocating more aggressive surveillance regimens (0.3–4.5%) [16–20, 23–25]. The consistently low rates of malignant progression of anal dysplasia point to the limited efficacy of prophylactic surveillance for SCCA in this population as well, since the chances of developing SCCA are extremely low even without any intervention. Based on these data, however, we still recommend SCCA surveillance for patients with known anal dysplasia, since the SCCA incidence in this cohort is significantly higher than that of the general population (192 versus 1.3 events per 100,000 person-years of follow-up, $p < 0.0001$) and SCCA can develop in asymptomatic high-risk patients [29]. Moreover, many authors describe SCCA developing in at-risk patients who did not undergo surveillance as recommended [17, 18, 20]. Regular surveillance provides an opportunity to examine these patients and to remind them of the importance of seeking care between examinations should they develop worrisome symptoms.

It is important to note that anal intraepithelial neoplasia 2 (AIN 2 or intermediate grade AIN) was counted as an anal LGD diagnosis in our study, although other authors have counted this entity as anal HGD. This choice was made because the ICD-9 coding system includes AIN 2 in low-grade dysplasia diagnosis (ICD-9 code, 569.44). One of the 26 AIN 2 patients in this study developed SCCA during follow-up. Had these 26 patients been included in the anal HGD cohort, the cumulative SCCA incidence of the anal HGD population would have increased to 1.24% while decreasing the cumulative SCCA incidence in the anal LGD to 0.21%.

The current study shows that EM is an effective and feasible option for the surveillance of patients at risk for SCCA. While some authors point to the low 1–2% cumulative incidence of SCCA in aggressively surveilled at-risk populations at high volume HIV referral centers, Table 3 shows that a less invasive EM approach can be just as effective at identifying invasive SCCA (192 versus 162–357 events per 100,000 patient years of follow-up). A recent review of an HRA-based surveillance protocol found that digital rectal examination *alone* was sufficient to diagnose 23 of the 27 (85%) incident SCCA that developed during surveillance [29]. Based on these findings, we conclude that the identification and prophylactic destruction of microscopic anal dysplasia does not prevent progression to SCCA or decrease SCCA mortality any more effectively than a less invasive EM surveillance approach.

There are several advantages to expectant management when compared to HRA-based surveillance protocols. Digital rectal examination with anoscopy is a simple, inexpensive, office-based procedure that can be readily performed by general practitioners, while HRA is more expensive and complicated to perform [30, 31]. The published rates of recurrent microscopic dysplasia after ablative attempts during HRA range from 50 to 90%, often despite multiple interventions, since these procedures cannot eradicate all microscopic dysplastic disease [32–37]. In addition, anal procedures can be painful for patients and often require time off work for recovery, so it is not surprising that many patients do not comply with recommended follow-up during aggressive surveillance regimens [16, 20]. Finally, repeated anal interventions can

Table 3 Published anal cancer incidences in large anal dysplasia populations

Author, year	No. of patients	HIV+ status (%)	Method of SCCA surveillance	SCCA events	Years of follow-up	Person years at risk	Incidence[a]	Cumulative SCCA incidence (%)
Tomassi 2017	872	15	EM	6	4.2	3457	192	0.7
Scholefield et al. 2005 [24]	35	0	EUA + biopsy	3	5.3[b]	184	1630	8.6
Devaraj and Cosman 2006 [19]	40	100	EM	3	2.7	108	2777	7.5
Watson et al. 2006 [25]	72	7	EUA + biopsy	8	5.0[b]	360	2222	11
Crawshaw et al. 2015 [20]	204	72	EM	2	3.0[b]	540	370	6.0
Fazendin et al. 2017 [23]	83	100	EM	2	3.0	249	803	2.4
Pineda et al. 2008 [16]	246	79	HRA	3	3.4	841	357	1.2
Goldstone et al. 2014 [17]	727	62	HRA	5	2.2[b]	1613	309	2.0
Dalla Pria et al. 2014 [18]	268	100	HRA	5	4.2	1835	272	0.3 (5 year)
Crawshaw et al. 2015 [20]	220	75	Annual Pap	1	3.1[b]	617	162	4.5

Incidence is presented as number of events per 100,000 person-years of follow-up.

Original paper reported median time of patient follow-up, rather than mean.

SCCA, squamous cell carcinoma of anus; *EM*, expectant management; *HRA*, high resolution anoscopy

lead to anal canal scarring and resultant defecatory dysfunction. Watson et al. reported that 9 of their 72 surveilled patients developed fecal incontinence, with four requiring permanent fecal diversion [25].

While we feel confident about the conclusions of this research, we would like to acknowledge some of this study's limitations. This was a retrospective review without a protocol that prospectively defined at-risk patients, quality of anoscopic examination, or the interval and frequency of follow-up. The SCPMG expectant management protocol was based on general recommendations of how to surveil patients, but specific compliance with such recommendations was not recorded. Patient examinations were performed by a heterogeneous group of practitioners with disparate levels of expertise. In addition, reliance on ICD-9 coding carries the potential limitations of any large patient database study, as patient chart information may have been coded incompletely or even incorrectly. Finally, despite abstracting over a decade of data from a large healthcare system, it is conceivable that a longer follow-up may be necessary to discover all progressions to invasive SCCA. Some authors report cervical cancer progression rates as lifetime incidences, since it may take decades for the malignant progression of cervical dysplasia to occur [38].

Conclusion

These data define the risk of malignant progression to SCCA in a very large patient population surveilled with expectant management and show that an EM approach which addresses only gross or symptomatic abnormalities, without actively searching for microscopic foci of anal dysplasia, is safe and effective even in high-risk patients. The disease-specific survival rates in this study and the fact that the KPSC SCCA mortality rates are no different from the rest of the state (0.21 events versus 0.25 events per 100,000 person-years of follow-up) confirm the efficacy of the EM approach at KPSC. Importantly, most anal cancers in this study were diagnosed in patients without any known risk factor. A surveillance protocol that follows only at-risk patients will have limited efficacy at decreasing the incidence of SCCA, and future attempts at surveillance should be implemented within a larger effort to identify other risk factors that predispose some HPV-infected patients to develop SCCA.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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