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High-Grade Anal Intraepithelial Neoplasia: Progression to Invasive Cancer Is Not a Certainty

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Word count: 3473

Background: The incidences of high-grade anal intraepithelial neoplasia (HSIL) and superficially invasive squamous cell carcinomas (SISCCA) related to human papillomavirus (HPV) have increased. These lesions can progress to invasive anal cancer. The aim of the study was to assess the clinical outcome with a special focus on the healing rate.

Methods: Forty-six consecutive patients (M/F:35/11; HIV+:30) with histologically proven HSIL lesions (N = 41) or SISCCA (N = 5) were enrolled in a follow-up survey.

Results: Of the 46 patients, 40 were treated by excision (n=9), electrocoagulation (n=13), topical treatment (n=2) or combined strategies (n=16). After a mean follow-up of 35 (27-43) months, only one patient progressed to an invasive cancer. Regression and healing were observed in 14(30%) and 15(33%) patients. The cumulative probabilities of healing were 14%, 49% and 74% after 1, 3 and 5 years. None of the current smokers healed. Heterosexual patients, sexual abstinence, patients older than 44 years old, non-smokers, patients without any past history of condyloma and those with less than 2 high-risk HPVs at baseline were more likely to heal.

Conclusion: Progression to invasive cancer is a rare event. Large, prospective cohort studies are needed to plan coherent strategies for both follow-up and treatment.

Introduction

The incidences of anal cancer and its putative precursor (high-grade squamous intraepithelial lesions: HSIL) have greatly increased in recent decades (1,2,3) particularly in special population subgroups: men who have sex with men (MSM), those infected with human immunodeficiency virus (HIV), and women with previous cervical human papillomavirus (HPV)-related disease (4).

Anal carcinoma increased from 0.2 to 0.5/100 000 person-years among men and from 0.7 to 1.3/100 000 person-years among women from 1982 to 2012. (3).

Regarding cervical cancer, it is widely recognized that HSIL and superficially invasive squamous cell carcinoma (SISCCA) can preclude invasive cancer. The latter is defined as a nearly stage tumours ≤ 10 mm, corresponding to HSIL which has an invasive depth of ≤ 3 mm from the basement membrane of the point of origin, with horizontal spread of ≤ 7 mm at its maximal extent (5). Both types of lesions are induced by persistent infections of carcinogenic HPV (6, 7). Conventionally, they are likely to progress to an invasive cancer (5). Little is known about the natural history of anal HPV infections and HSIL. One study estimated a HSIL regression rate of 23.5% per year (8).

The lack of data about the natural progression of HSIL and SISCCA to invasive cancers has led to unclear and controversial therapeutic strategies. Management of HSIL varies according to the doctor's expertise, ranging from expectant management with close surveillance (9,10) to surgical treatment (11), topical application of chemotherapeutic agents (12) or photodynamic therapy (13). To date, the recommended treatment for SISCCA is radiotherapy, but it has been

associated with anatomical and functional side effects unless effective (14,15,16). After we collected the data of consecutive patients with histologically proven HSIL, the aim of this study was to assess the clinical outcome with a special focus on the healing rate.

Patients and Methods

Patients

This cross-sectional study was conducted in a single tertiary gastroenterology unit (Rennes University Hospital, France) using the records of a central database. All patients with histories of HSIL (only AIN3 in the former classification) or SISCCA proven on anal biopsy, from March 2002 to May 2014, were invited to participate in a new evaluation. Medical records, using both retrospective (2002-2006) and prospective (2007-2014) databases, were extracted with special emphases on MSM and women with HPV-related genital lesions and HPV-related lesions, as well as smoking habits and immunosuppressant use. Data about life style and HIV disease were collected using a standardized questionnaire sent to the patient: gender, age, sexual activity, past history of sexually transmitted infections, and HIV status, including CDC stage, highly active antiretroviral therapy (HAART), CD4 cell count, and HIV viral load. Patients who did not respond to the questionnaire were solicited by phone and by sending new mail. To identify clinically relevant events that might interfere with clinical outcome, each treatment procedure was noted: surgery (specifying with or not healthy margins); destruction of the lesion (including electrocoagulation and infrared); or application of imiquimod. We also reported the periods of duration of therapies and the number of surgical events.

Most of the patients were evaluated every 6 months to ensure the lack of progression. Any abnormalities were evaluated by high-resolution anoscopy (HRA) (performed using 5% acetic acid and Lugol's solution to magnify the visualization of abnormal anal tissue), and multiple targeted biopsies were performed (to limit heterogeneity and to ensure that the highest grade of dysplasia was identified). Random biopsies were also collected from regions that appeared normal at the level of the dental line. Finally, control biopsies of previous HSIL sites were realized at the end of the follow-up to determine whether the lesion persisted (HSIL), was down-staged (LSIL) or had healed (normal histology).

HPV DNA detection and genotyping

Before anoscopy, one Dacron swab was collected from the anal canal and was immediately suspended in Thin Prep PreservCyt medium (Hologic, Inc. Bedford, MA, USA). This sample was sent for virological analysis. Specimens were maintained at +4°C before processing for analyses and then were aliquoted and stored at -80°C. DNA testing was performed using the PreservCyt medium: 200 µL were used for DNA extraction on MagNA Pure LC (Roche, Bâle, Switzerland). Anal specimens were tested for 35 HPV genotypes with CLART Human Papillomavirus 2 (Genomica, Madrid, Spain), a commercial kit for the detection of 15 low risk HPV (6, 11, 40, 42, 43, 44, 54, 61, 62, 71, 72, 81, 83, 84, 89), and 20 high risk HPV strains (16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82, 85). The tests included a cellular control and an internal control. Microarray studies were analysed using a Clinical Arrays Reader (Genomica). A sample of 2 mL of each liquid-based medium was then frozen at -80°C. The Ahr-HPV DNA test was considered positive if at least one hr-HPV genotype was detected.

Follow-up

The initial histology reporting HSIL or SISCCA was the first point of follow-up, and the last point was the most recent histology. Follow-up continued until June 30, 2014. Loss to follow-up was defined by the lack of response to any questionnaire or the inability to find the patient.

Most of the patients were evaluated every 6 months to ensure the lack of progression. Any abnormalities were biopsied. Regression was defined by Regression was defined by the stable regression of HSIL to a less invasive state (LSIL or normal) from the first change to the last biopsy of the follow-up. Regression had to be stable throughout the follow-up. In the regression group, we distinguished down-staged (LSIL) and healed (normal histology) states.

Progression was defined by the occurrence of SISCCA for patients with HSIL or invasive carcinoma for patient with SISCCA or HSIL.

The patients were separated into three groups according to their follow-up status: regression and/or healing; persistence of HSIL/SISCCA; or progression to invasive cancer.

Ethics

The database was authorized by the national regulatory institution, Commission Nationale Informatique et Liberté, and the study was approved by our institutional ethical committee (October 17, 2013: n°13.59). All of the responding participants provided written informed consent.

Statistics

Quantitative variables are described as the mean \pm standard deviation (SD). Categorical variables are presented as totals and percentages of the cohort. Wilcoxon's non-parametric

signed-rank test for continuous variable and Pearson's non-parametric Pearson test for categorical variable were used to compare disease characteristics. Univariate analyses identified parameters associated with sustained healing. Effect of population studies do not allow for confident multivariate analysis. A p value <0.05 was considered significant. Finally, the cumulative probabilities of healing were estimated using the Kaplan-Meier method from the diagnosis of HSIL or SISCCA to the occurrence of healing. Statistical analyses were performed using JMP® Pro software, version 10.2,2013 (SAS Institute Inc., Cary, NC, USA).

Results

Population

From March 2002 to June 2014, 59 patients with HSIL or SISCCA on biopsy were referred to the Rennes University Hospital, France. We excluded 8 patients due to misdiagnoses: they had a true invasive anal squamous carcinoma at the time of initial diagnosis with a discrepancy between histological consideration and macroscopically ulcerative and infiltrative aspects. As a result, 51 patients with histologically confirmed HSIL or SISCCA were available for follow-up. Five patients (9.8%) (4 patients with HSIL and one patient with SISCCA) did not have a control biopsy for several reasons (two lost to follow-up, two with follow-ups that were too short, one due to unrelated death from ovarian cancer), leaving forty-six patients adequately followed (Figure 1). Self-perception of the follow-up strategy was assessed: 7 of 46 (15%) did not respond to these items; 23 of 46 patients (50%) judged it as compelling, 32 of 46 (70%) were aware of the need for regular monitoring, and 33 of 46 (72%) reported some anxiety with it.

The main characteristics of the study population are summarized in Table 1. The mean age was 48 ± 2.1 years old. In the cohort, all of the men with HIV infection were homosexual, except two and 4 HIV-negative who were homosexual. All except one were Caucasian.

Table 2 summarizes the symptoms, the physical evaluation and the first virology at referral. Twenty-five patients (49%) were symptomatic on presentation. Macroscopic signs of HPV were observed in 34 patients (66.5%), including external condyloma ($n=13$) and/or endocanal lesions ($n=21$), whereas 17 patients (33%) had no abnormalities at clinical examination. DNA genotyping was not routinely performed before 2011; thus, 19 patients (37%) had their first virology after their diagnosis of HSIL, whereas 25 (49%) had their diagnoses the same time. For seven patients (14%), virology was never performed.

Among 41 patients with HSIL, 6 were treated by excision, 13 by destruction, 2 by application of imiquimod, and 14 by combined treatment, and 6 received a conservative approach because no macroscopic lesion was observed. Among the 5 patients with SISCCA, 3 were treated by excision and two by combined treatment. None received radiotherapy to treat either HSIL or SISCCA.

Follow-up

The mean follow-up was 34.6 ± 3.9 months. Among the patients with HSIL at inclusion, 14 (34%) had persistent lesions of HSIL at the end of the study, 14 (34%) regressed to LSIL after 18 ± 4.1 months, and 13 (32%) healed after 22 ± 3.8 months. Among the patients with initial SISCCA, 2 (40%) had persistent lesions of HSIL, 2 (40%) healed after a mean follow-up of 51.5 ± 0.5 months, and one (20%) progressed to an invasive cancer. The latter was surgically removed as a prior strategy. After an initial follow-up of 6 years showing no significant regression of persistent HSIL, he developed an invasive cancer of stage pT1N0M0, which was

treated only by excision because he refused radiotherapy: he progressed 6 years later to a more severe cancer.

Another patient with initial HSIL progressed to SISCCA four years after the diagnosis and then regressed to HSIL after an excision.

Down-staging was finally observed in 29 patients (63%), including 15 who healed (33%). Thus, persistence of HSIL was found in 16 patients (35%) at the end of follow-up.

Figure 2 illustrates the healing rate according to the length of follow-up. The cumulative probabilities of healing were 14%, 49% and 74% after follow-ups of 1, 3 and 5 years, respectively.

Virology

The mean number of viruses and HR viruses were, respectively, 2.23 ± 0.29 and 1.74 ± 0.23 (HSIL: 2.3 ± 0.3 , 1.8 ± 0.25 and SISCCA: 1.8 ± 1.1 , 1.2 ± 0.6) at the end of the follow-up. Between the baseline and final virology, the number of high-grade viruses decreased for twenty-one patients (46%) (mean: -1.8 ± 0.25), increased for four patients (9%) (mean: 1.8 ± 0.49) and remained the same for eleven patients (24%). Seven patients (14%) had no virology at referral. For three patients (6.5%), we did not find viruses either at baseline or at the end of follow-up, but virology was entirely realized after histology, so viral clearance could have occurred. Only two patients had complete viral clearance; one other patient eliminated high-grade viruses, but a low-grade virus persisted. Among the patients who healed (15 patients), the final virology found complete viral clearance only in 1 of 11 (9%) when virology realized. The healed subjects had a significantly lower rate of viruses at baseline than the others (mean viruses: 1.58 vs 2.8, $p=0.048$), and those who had at least two high-grade viruses at referral were less likely to regress (16.5% vs 44.5%, $p=0.049$).

Factors associated with a better rate of healing

The main factors associated with sustained healing are reported in Table 3. At referral, patients with a better chance to heal were older, heterosexual, with no past history of condyloma and less than 2 identified high-risk HPV. At the end of the follow-up, none of the 14 current smokers healed. HIV status, immunosuppression total number of sexual partners over one's life, HPV16 status, and a past history of anal sex were not significantly associated with a higher healing rate. Among patients with HIV, those infected for more than 10 years a greater likelihood to heal than the others (36% vs 0%, $p=0.045$).

The type of therapeutic procedure (including imiquimod, destruction, excision, combined treatment or simple monitoring) was not significantly associated with a higher healing rate. Moreover, among the 6 patients who were untreated, all regressed, and 3 healed.

Discussion

This study, analysing the clinical outcome of anal dysplasia, was the first to define the factors and to quantify the healing of HSIL in a cohort of HIV-infected and uninfected-patients.

The data of the present study emphasize some aspects of the clinical outcome of HSIL.

HSIL is not only an HIV+ related disease. Our data emphasized that a large proportion of HSIL and SISCCA lesions were found in HIV-uninfected, heterosexual, immunocompetent patients (11 patients, 21.5%) (including 4 active smokers, 2 with past histories of high-grade cervical

dysplasia, and 1 who had undergone haemorrhoidectomy). Indeed, although immunosuppression has been clearly recognized as a risk factor for HSIL and anal carcinoma, only 8% of anal cancers occur in HIV patients (17,18).

There have been no studies determining the population of patients with HSIL. All of the previous published series have been performed in selected high-risk groups: HIV-positive subjects, homosexual men or women with past histories of cervical HPV infection. In cervical dysplasia, only 5 to 8% of patients are HIV positive (19). An American cases series described penile intraepithelial neoplasia in 7 men, and only one was HIV positive, while the others were all immunocompetent (20).

These results suggested that anal dysplasia is not a condition that is only related to a patient's HIV patient's status, and it could also be found in immunocompetent, heterosexual patients.

Progression to invasive cancer is a rare event. We confirmed previous findings that progression of HSIL to anal cancer is uncommon (9,10,11,21,22), and the expected rate of anal cancer for HSIL is lower than that for cancer of the cervix, where 31.3% and 50.3% of women with cervical intraepithelial neoplasia will progress to cervical cancer over time in the absence of treatment (23).

In our study, only one HIV patient progressed to an invasive cancer. We can, however, speculate that the length of the follow-up was probably too short to observe malignant transformation. This fact might limit the validity of our conclusions. Indeed, most of the published studies have reported median times of 3 to 6 years before progression to cancer (10,11,22), which might be a rationale for shortening the interval of screening in selected groups. From a semantic point of view, SISCCA is defined as a nearly stage invasive cancer limited in depth of ≤ 3 mm from the basement membrane. By contrast, HSIL has no invasion

across the basement membrane. For these reasons, one may speculate to exclude these cases from the present cohort study. But, this very rare condition is discussed in multidisciplinary staff and the therapeutic strategy is currently similar to HSIL. In other words, simple surgical R0 excision is preferred over radiotherapy or radiochemotherapy. By contrast to HSIL, SISCCA has a limited area of involvement among larger HSIL surface. After excision, HSIL may persist after removal of the SISCCA target.

Spontaneous regression and healing can occur. Two-thirds of HSIL lesions in the present study regressed, and half of them healed within a 3-year period of time. These results were in agreement with a previous study that reported a rate of 37.1% per year of spontaneous regression in HIV-uninfected patients, but the regression rate was lower in subjects with HIV (19.2% per year) (8). Mechanisms leading to healing remain however unclear. Viral clearance does not explain healing by itself (only one patient who was cured had complete viral clearance), and cofactors could be implicated, such the level of co-infections, because most of the patients who were cured had fewer viruses than at baseline.

We can speculate that healing might precede clearance of oncogenic HPV infection. These results were previously described by Schiffman *et al*, who found that cytologic abnormalities regressed 77 days before HPV DNA (23). The authors compared cytologic abnormalities to “tip of the iceberg” HPV infections, and they occurred in the middle of the natural history of some, whereas HPV DNA detection lasted longer. Moreover, in epidemiologic studies, HPV DNA detection precedes and predicts subsequent cytologic and histologic abnormalities (24).

Other mechanisms could explain HSIL healing. The impact of genetic factors on the regression of high-grade cervical dysplasia was already suggested by Trimble *et al* (25). Women expressing HLA*A201 and infected with a high-risk virus were three time more likely to

regress than others. To date, no authors have studied the susceptibility of genetic factors in high-grade dysplasia healing or regression.

Several factors might be associated with a higher healing rate. Our findings emphasized the importance of smoking, as well as sexually active lifestyles, homosexual sex, HPV high-risk genotyping, and a past history of condyloma as predictive factors for lack of healing. Interestingly, older patients appeared to have a better healing rate, thus contrasting previous reports (8). Confounding variables could explain these discrepancies, such as the number of sexual partners, an active sexual life and current exposure to tobacco.

In our study, HIV status was not associated with a lower healing rate. Most studies report that Highly active antiretroviral therapy (HAART) does not increase the probability of regression, (26). One hypothesis is that our cohort was not powered to assess an association between HIV and healing: both the population size and follow-up were insufficient to draw conclusions.

Treatment strategies have been somewhat disappointing. Our results emphasized that treatments (excision, destruction, imiquimod) did not impact the healing rate. Moreover, among the 6 HIV patients who were only assessed (no visible lesions so no treatment), all of them regressed, and three healed. These data led us to believe that, in most cases, HSIL lesions regress regardless of the care realized. Although no prospective randomized trials have been performed on the expectant management of HSIL, some retrospective studies have supported our hypothesis: Tong *et al* found a spontaneous HSIL regression rate of 23.8% per year (8), but in other reports, treatment has been needed to avoid progression (27,28). In the present study, varied treatments have been applied to different conditions (visible and non visible lesions). Thus, this small cohort does not allow concluding a preferred strategy. In

another hand, treatment did not better cure as compared to simple observation. Moreover, the present cohort has probably a too short follow-up to point the rare events of progression to invasive cancer. Finally, the main message is a long standing state of HSIL and the negative statistical link of tobacco on healing. Larger and prospective randomized studies are expected to standardize the strategy to adopt, including close surveillance for patients who are likely to regress. Local treatment might be reserved for patients at risk to progress and or cases of SISCCA with macroscopic targets to treat. This hypothesis could be tested in prospective, multicentre and interventional studies.

The strengths of our study include our robust histology-based definition of HSIL, whereas most of studies have defined progression and regression using cytology. In fact, compared to cervical cytology, anal cytology is significantly less sensitive and specific for detecting high-grade disease (29). Moreover, we avoided selection bias by not including AIN2 lesions: indeed, we know that AIN2 lesions can be prone to confusion between high and low grade lesions. Our choice of subjects, including men, women, HIV-infected and uninfected patients, men who have sex with men and heterosexual people, made our study population very close to real life, rather than a very selected group of subjects who are MSM.

Our study, however, had a number of potential limitations. Some of the data were retrospective, the follow-up was quite short, and our cohort had a relatively small number of patients, which prevented us from realizing multivariate analysis. Moreover, although HRA remains the standard for the detection of anal dysplasia, it is by no means perfect, and lesions might not have been detected, leading to an underestimation of recurrence rates. Finally, the heterogeneity of the received treatment (with small numbers in each group) is also a limit.

In summary, our study made some important and innovative points. First, it was the first study to quantify the healing rate and associated healing factors of HSIL lesions. Second, we demonstrated that HSIL lesions were also found in immunocompetent patients and were not only an HIV-related disease. Third, healing occurred in most cases, likely regardless of the received treatment. Finally, the absence of viral clearance to explain healing was also a very important message, compelling us to search for other mechanisms involved in HSIL healing.

Conclusion

Progression to cancer was a rare event after a three-year follow-up. Clinical regression and healing occurred far more commonly in the clinical outcome of HSIL. This finding suggested that patients might not require treatment in the initial phase of the diagnosis. Tobacco, sexually active lifestyles, homosexual sex, a number of high risk viruses at baseline and a past history of condyloma seemed to be predictive factors for more difficult healing. Future larger-scale studies are necessary to plan coherent surveillance and treatment strategies and to stratify patients according to their progression risks.

Titles of tables and figures.

Table 1: Characteristics of the study group (N=51)

Table 2: Complaints and examinations at referral (N=51)

Table 3: Factors associated with sustained healing (N=46)

Figure 1: Flow chart of the cohort

Figure 2: Healing rate

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Table 1. Characteristics of the study group (N=51)

		N	%
Sex	Male	37	73
	Female	14	27
Age (years, mean)		48 ± 2.1	
BMI (mean)		24 ± 1.2	
Past history of STI not related to HPV	Yes	18	35
	No	33	65
Past history of condyloma/HPV infection	Yes	24	47
	No	27	53
Past history of cervical cancer or conization	Yes	05	36
	No	09	64
Past history of LSIL	Yes	07	14
	No	44	86
HIV	Yes	33	65
	No	18	35
MSM	Yes	32	86
	No	5	14
Immune-suppression treatment *	Yes	03	6
	No	48	94
Smoking	Current and/or past	25	49
	Never	26	51
Past history of anal sex	Yes	37	72.5
	No	12	23.5
	Unknown	2	4
Total number of sexual partners	<5	4	7.5
	[5-10[9	17.5
	[10-50[14	27.5
	> 50	18	35.5
	Unknown	6	12
Sexually active life	Yes	30	59
	No	19	37
	Unknown	2	4
* One Horton disease and two renal transplantations			
Abbreviations: BMI: Body Mass Index, HAART: Highly Active Antiretroviral Therapy, HIV: Human Immunodeficiency Virus, HPV: Human Papillomavirus, LSIL: Low grade Superficial Intra-epithelial Lesion, MSM: Men who have Sex with Men, STI: Sexually Transmissible Infection.			

Table 2. Complaints and examinations at referral (N=51)

		HSIL	SISCCA	Total	
		N=45	N=6	N=51	
Clinical	Symptoms	Pain	4 (9%)	0	4 (8%)
		Rectal bleeding	8 (18%)	2 (33.5%)	10 (20%)
		Soiling	5 (11%)	1 (17%)	6 (12%)
		Palpable lesion	4 (9%)	0	4 (8%)
		Pruritus	0	1 (17%)	1 (2%)
		No abnormalities	24 (53.5%)	2 (33.5%)	26 (50.5%)
	Examination	Flat suspicious lesion	13 (29%)	3 (50%)	16 (31.5%)
		Induration	0	1 (17%)	1 (2%)
		Anal fissure	1 (2%)	1 (17%)	2 (4%)
		Condyloma	13 (29%)	0	13 (25.5%)
		Ulceration	1 (2%)	0	1 (2%)
		Polypoid lesion	1 (2%)	0	1 (2%)
		No abnormalities	16 (35.5%)	1 (17%)	17 (33%)
First virology*	Number of viruses (mean)	3.45 ± 0.37	1.5 ± 1.19	3.26 ± 0.36	
	Number of HR HPV (mean)	2.61 ± 0.3	0.7 ± 0.5	2.45 ± 0.29	
	HPV 16	20 (44.4%)	2 (33.5%)	22 (43%)	
	HPV 18	1 (2%)	0	1 (2%)	
	No virus	1 (2%)	2 (33.5%)	3 (6%)	
	Not realized	6 (13.5%)	1 (17%)	7 (14%)	
Abbreviations: HSIL: High-grade squamous intraepithelial lesions, SISCCA: Superficially invasive squamous cell carcinoma, LSIL: Low grade superficial intra-epithelial lesion, ASCUS: Atypical squamous cells of undetermined significance, HPV: Human papillomavirus, HR: High risk *realized at the same time as the first histology or after					

Table 3. Factors associated with a sustained healing (N=46)

	Sustained healing (N, %)	p
Past history of condyloma (N = 46)		0.009
Yes	4 (16%)	
No	11 (52%)	
Age (N = 46)		0.007
< 44 years	2 (10.5%)	
≥ 44 years	13 (48%)	
Active sexual life (N = 46)		0.045
Yes	6 (21.5%)	
No	9 (50%)	
MSM* (N = 35)		0.011
Yes	7 (23%)	
No	4 (80%)	
Active smoking (N = 46)		0.002
Yes	0 (0%)	
No	15 (47%)	
≥ 2 high-grade virus at baseline** (N = 39)		0.049
Yes	4 (16.5%)	
No	8 (44.5%)	
Past history of anal sex (N = 46)		0.135
Yes	9 (26,5%)	
No	6 (50%)	
HIV (N = 46)		0.240
Yes	8 (27%)	
No	7 (44%)	
HPV 16 or 18 at baseline** (N = 39)		0.845
Yes	6 (28%)	
No	6 (30%)	
Abbreviations: MSM: Men who have sex with men		
*analysis including only men		
**analysis including patients with a realized virology at baseline		

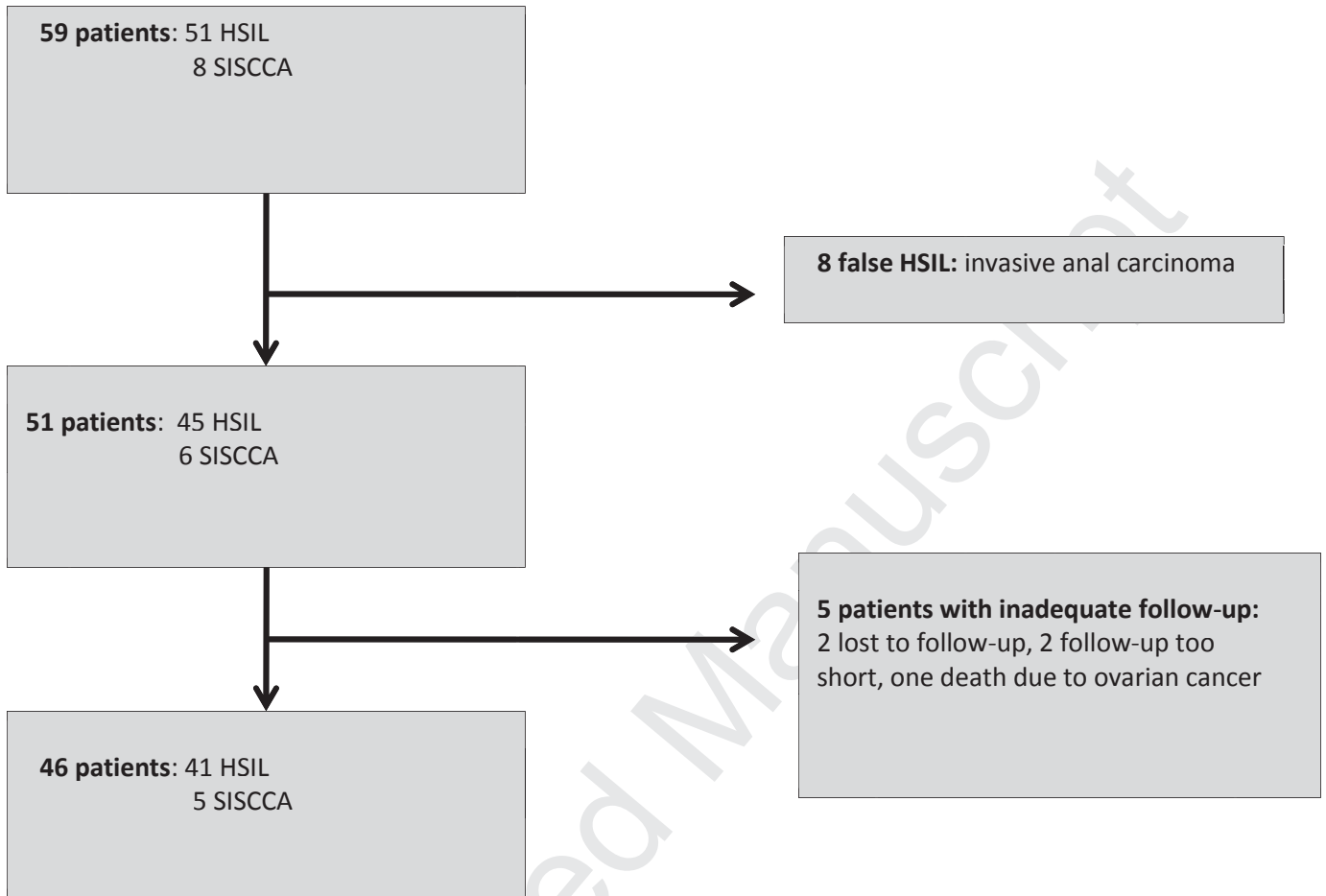
Figure 1. Flow chart

Figure 2. Healing rate

