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Original Article

Surgical excision of anal intraepithelial neoplasia

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ABSTRACT

INTRODUCTION. Anal intraepithelial neoplasia (AIN) is a premalignant lesion caused by human papillomavirus. Surgical excision is the preferred treatment, but recurrence rates are high, and the risk of progression to squamous cell carcinoma of the anus (SCCA) remains.

METHODS. This retrospective study included all patients with histologically confirmed AIN treated and/or followed at Herlev Hospital, Denmark, from 1 October 2021 to 30 September 2022. Standard treatment was surgical excision or electrocautery. Data on demographics, clinical characteristics, histology, recurrence, progression to SCCA and complications were collected. Median follow-up was 30 months.

RESULTS. A total of 77 patients were included (median age 51 years; 80.5% female); 21% were infected with HIV and 9% were immunosuppressed. High-grade squamous intraepithelial lesions were present in 90.9% of primary resections. Recurrence occurred in 59.7%, with a median time to recurrence of nine months; female sex was significantly associated with recurrence ($p = 0.037$). Eight patients (10.4%) developed SCCA, mostly stage T1, with no nodal or distant metastases. No significant predictors of cancer development were identified. One patient (1.3%) experienced a severe surgical complication.

CONCLUSIONS. AIN has a high recurrence rate after excision and a notable risk of progression to SCCA. Early-stage detection supports the importance of structured long-term surveillance.

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TRIAL REGISTRATION. The study was a quality development study (WorkZone no.: 25007943).

Anal intraepithelial neoplasia (AIN) is dysplasia of the squamous cell epithelia of the anal canal. The condition is induced by human papillomavirus (HPV) infection and is recognised as a premalignant lesion with the potential to develop into squamous cell carcinoma of the anus (SCCA) [1]. Histologically, AIN is classified as low-grade or high-grade squamous intraepithelial lesions (LSIL or HSIL, respectively) [2]. LSIL include condyloma acunatum, and approximately 90% of cases are caused by low-risk HPV types, e.g., HPV 6 and 11 [3]. In contrast, HSIL is often caused by high-risk HPV types, e.g., HPV 16 and 18, and has the potential to develop into SCCA [3]. The incidence of AIN is approximately 0.5 pr 100,000 pr year, with higher rates reported in females, immunosuppressed persons and people living with HIV [4, 5]. AIN is often an accidental finding following benign anal surgery. Symptoms are non-specific and include pruritus and anal fissure [6].

The progression rate from AIN to SCCA remains poorly defined. In a database study including 11,231 patients, the five-year risk of developing SCCA after resection of LSIL was 0.05%, compared with 3.7% after resection of HSIL [7]. Among high-risk groups – such as men who have sex with men (MSM), HIV-positive individuals or

immunosuppressed patients – the five-year risk is 14% [7]. Additionally, progression from LSIL to HSIL or regression from HSIL to LSIL occurs in 20-27% of cases [8, 9].

The primary aim in AIN treatment is to prevent progression to SCCA and to relieve symptoms. Several treatment options for AIN exist, including topical treatment with trichloroacetic acid, 5-fluorouracil (5-FU) or imiquimod, and surgical approaches such as infrared coagulation or surgical excision. There is no consensus on the optimal treatment, but surgical excision is the first choice [10]. Recurrence rates following excision are high, ranging from 9% to 63% [11, 12]. Patients will often need more than one treatment, and a thorough follow-up programme is essential to prevent progression to SCCA.

The aim of this study was to examine the everyday handling and outcome in a mixed cohort of patients with newly diagnosed AIN and patients followed for AIN over a period in the outpatient clinic at a large Danish University Hospital. The primary outcomes were progression rates from AIN to SCCA and recurrence rates after AIN excision. The secondary outcomes were to identify risk factors for progression from AIN to SCCA, recurrence of AIN following treatment and complications of AIN treatment.

Methods

The study was designed to give a real-world overview of the treatment and follow-up of all patients treated or followed for AIN in a one-year period. Therefore, in a snapshot-like design, all patients treated or followed for histologically confirmed AIN between 1 October 2021 and 30 September 2022 in the surgical outpatient clinic at Herlev Hospital, Copenhagen, were identified and included. This produced a mixed cohort of both patients with newly diagnosed AIN and patients with a longer history of AIN.

For recurrence and progression to anal cancer, the last follow-up was done on 10 March 2025. For progression to anal cancer, the inclusion date was defined as the last day of the inclusion period (31 September 2022), yielding a total follow-up time of 30 months. For recurrence, the inclusion date was defined as the day of the primary diagnosis of AIN. Again, this method was chosen from a real-world perspective to answer the question: “From a mixed cohort of patients treated in the outpatient clinic, what is the risk of recurrence and progression to cancer?”

In our department, AIN lesions are treated with surgical excision or electrocautery under general anaesthesia as the standard approach. Follow-up after excision was done in accordance with guidelines from the Danish Anal Cancer Group, recommending clinical exam with anoscopy and rectal exploration every six months for two years and a final control for LSIL at three years and clinical exam with anoscopy and rectal exploration every six months for two years, and annual control until final control for HSIL at five years [13]. Follow-up is not performed exclusively by a specialised team but typically by a colorectal surgeon or a younger colleague with access to colorectal supervision.

Medical journals were reviewed and a database was established, including data on age at inclusion, gender, WHO performance score at inclusion (0: Asymptomatic, 1: Symptomatic but completely ambulatory, 2: Symptomatic, ≤ 50% in bed during the day, 3: Symptomatic, > 50% in bed, but not bedbound, 4: Bedbound), American Society of Anesthesiologists (ASA) score at inclusion (ASA I: A person in good health, ASA II: A mild but well-managed or treated condition, ASA III: A serious condition that has an impact on a person’s overall health, ASA IV: A severe condition that’s life-threatening, ASA V: A life-threatening condition that needs immediate surgery to increase survival odds), HIV status, immunosuppressive treatment, use of tobacco, alcohol consumption above 7/14 units per week (female/male), for women; history of or current cervical intraepithelial neoplasia (CIN), medical history of AIN prior to inclusion, number of treatments for AIN prior to inclusion, largest diameter of AIN lesion (at primary resection), histological grading of primary AIN resection (LSIL/HSIL),

time from primary excision of AIN to inclusion, time from primary excision to recurrence, surgical complications related to AIN resection graded with the Clavien-Dindo score [14], development of anal cancer, time from primary excision to development of anal cancer, TNM stage of anal cancer at diagnosis and treatment of anal cancer.

Due to the lack of a clear, normal distribution across all variables, non-parametric statistical methods were applied. Dichotomous variables were compared using Fisher's exact test or logistic regression. All statistical analyses were conducted using SPSS software, version 19.

All procedures were performed in compliance with relevant laws and institutional guidelines. The study was characterised as a quality development study and approved by the Hospital management. According to local guidelines and Danish law, informed consent is not required in such projects.

Trial registration: The study was characterised as a quality development study (WorkZone no.: 25007943).

Results

A total of 77 patients were included. Median age was 51 years (range: 22-82); 80.5% were female. Most had a performance score of 0 (88.3%) and an ASA score of 1 (57%). Sixteen (21%) were living with HIV, and 9% were immunosuppressed. A history of or current CIN was present in 48.1% (**Table 1**).

TABLE 1 Baseline characteristics of the study population (N = 77).

Age at inclusion, median (range), yrs	51 (22-82)
Sex, n (% of total)	
Female	62 (80.5)
Male	15 (19.5)
Performance score, n (% of total)	
0	68 (88.3)
1	8 (10.4)
2	1 (1.3)
ASA score, n (% of total)	
1	44 (57.1)
2	26 (33.8)
3	7 (9.1)
Tobacco use, n (% of total)	26 (33.8)
Alcohol use, n (% of total)	1 (1.3)
Living with HIV, n (%)	16 (20.8)
Immunosuppression, n (% of total)	
Prednisolone	4 (5.2)
Biologic medicine	3 (3.9)
Any	7 (9.1)
History of/current CIN, n (% of total)	37 (48.1)

ASA = American Society of Anesthesiologists; CIN = cervical intraepithelial neoplasia.

Anal intraepithelial neoplasia characteristics and recurrence

Fifteen (19.5%) patients were diagnosed with AIN during the inclusion period between 1 October 2021 and 30 September 2022; the remaining had a prior diagnosis. The median interval from primary excision to end of inclusion was 1,204 days (range: 41-10,146). Histology after primary excision showed LSIL in four participants (5.2%) and HSIL in 70 participants (90.9%). The grade of neoplasia was not registered in three participants (3.9%). Lesion size was reported for 60 participants (77.9%); the median lesion size was 12.5 mm (range: 1-45 mm). p16 positivity was found in 65 lesions (84.4%); data were missing in 12 (15.6%) lesions.

Recurrence occurred in 46 cases (59.7%) (**Table 2**). The median time to recurrence after complete clinical

resection was 273 days (range: 14-1,439). The median number of subsequent resections was three (range: 1-20). One participant developed post-operative bleeding requiring surgery (Clavien–Dindo grade 4).

TABLE 2 Univariate analysis of risk factors for anal intraepithelial neoplasia recurrence (N = 77).

	Recurrence, n (% of group)	No recurrence, n (% of group)	p value
Sex			0.037
Female	41 (66.1)	21 (33.9)	
Male	5 (33.3)	10 (66.7)	
Age at inclusion			0.250
22-51 yrs	26 (66.7)	13 (33.3)	
52-82 yrs	20 (52.6)	18 (47.4)	
HIV			1.000
Positive	9 (56.3)	7 (43.7)	
Negative	21 (40.4)	31 (59.6)	
Immunosuppression?			0.463
Yes	6 (75.0)	2 (25.0)	
No	40 (58.0)	29 (42.0)	
Tobacco use?			0.326
Yes	18 (69.2)	8 (30.8)	
No	28 (54.9)	23 (45.1)	
Lesion size			0.300
≤ 12.5 mm	19 (61.3)	12 (38.7)	
> 12.5 mm	13 (44.8)	16 (55.2)	

Development of anal cancer

During the 30-month follow-up, eight participants (10.4%) developed anal cancer. The median time from primary AIN excision to anal cancer diagnosis was 30.5 months (range: 9.3-332.5 months). TNM stage at diagnosis was T1 in six participants (75%), T2 in one participant (12.5%) and T3 in one participant (12.5%). No lymph node involvement or distant metastases were observed. Three participants (37.5%) were treated with local excision; five (62.5%) received chemoradiotherapy.

Discussion

In this cohort of 77 individuals with AIN, we observed a high recurrence rate following primary excision, and a notable proportion developed anal cancer during follow-up. These findings underscore the chronic and relapsing nature of AIN and the potential for malignant transformation despite surgical intervention.

Eight participants (10.4%) developed anal cancer during a median follow-up of 30.5 months. This is a rather high rate of anal cancer development compared with 0.9% at a median 25.8-month follow-up in an active monitoring group in a recent RCT comparing active monitoring with high-resolution-guided treatment in a cohort of people living with HIV (PLHIV) [15], and 3.2% five-year risk of progression from AIN to anal cancer in HIV-negative

participants in a Danish registry study [7].

The high rate of anal cancer development may be explained by the limited number of participants in our study, which increases the risk of selection bias. Urbute et al. [16] demonstrated this in a Danish registry study from 1998 to 2018, where anal cancer was diagnosed three times more frequently than AIN. Given that AIN is an anal cancer precursor, its incidence would be expected to exceed that of anal cancer, suggesting that many cases of AIN may remain undiagnosed. An opposite, more natural, pattern is observed in CIN, which shares characteristics with AIN. In the US, owing to systematic screening, approximately 100,000 women are treated for CIN annually, whereas only about 14,000 are diagnosed with cervical cancer [17]. In Denmark, as in many other countries, no systematic AIN screening programme is currently in place. Such a programme may increase AIN detection rates.

Importantly, most cancers were diagnosed at an early stage (T1 in 75%), and none had lymph node or distant metastases, suggesting that surveillance facilitated early detection. Half of the cancers were treated with local excision alone, highlighting the potential benefits of timely diagnosis and intervention.

The recurrence rate of LSIL/HSIL in our study is consistent with previously reported rates in high-risk populations, including people living with HIV and immunosuppressed individuals, in whom recurrence after treatment is known to be common [18, 19]. Interestingly, female sex was significantly associated with a higher recurrence rate. However, in our cohort, neither HIV status, immunosuppression, nor tobacco use was significantly associated with recurrence or progression to cancer, although trends suggested higher recurrence rates among immunosuppressed individuals and smokers. The limited sample size likely restricts the power to detect such associations, and these results should therefore be interpreted with caution.

Previous studies have identified several risk factors for progression to anal cancer, including immunosuppression, history of anal intercourse, HIV infection, increased number of sexual partners and lesion size [7, 20]. No statistically significant predictors of anal cancer development were identified in the present study. Notably, lesion size and the number of re-resections – a proxy for persistent or multifocal disease – were not associated with cancer progression (**Table 3**). Similarly, time from primary excision to study inclusion did not differ significantly between those who developed cancer and those who did not.

TABLE 3 Univariate analysis of risk factors for development of anal cancer (N = 77).

	Anal cancer, n (% of group)	No anal cancer, n (% of group)	p value
Sex			0.182
Female	5 (8.1)	57 (91.9)	
Male	3 (20.0)	12 (80.0)	
Age at inclusion			
22-30 yrs	0	8 (100)	0.999
31-40 yrs	1 (11.1)	8 (88.9)	0.6
41-50 yrs	2 (11.8)	15 (88.2)	0.565
51-60 yrs	1 (5.2)	18 (94.8)	0.246
61-70 yrs	2 (14.3)	12 (85.7	0.712
71-82 yrs	2 (20.0)	8 (80.0)	0.08
HIV			1.000
Positive	1 (6.3)	15 (93.8)	
Negative	7 (11.5)	54 (88.5)	
Immunosuppression?			0.192
Yes	2 (25.0)	6 (75.0)	
No	6 (8.7)	63 (91.3)	
Tobacco use?			0.710
Yes	2 (7.7)	24 (92.3)	
No	6 (11.8)	45 (88.2)	
Lesion size			
≤ 12.5 mm	3 (50.0)	3 (50.0)	
> 12.5 mm	28 (51.9)	26 (48.1)	
Number of re-resections			0.632
0-3	6 (9.5)	57 (90.5)	
> 3	2 (14.3)	12 (85.7)	
Time from primary excision to end of inclusion			0.711
0-1,204 days	5 (12.8)	34 (87.2)	
1,205-10,146 days	3 (7.9)	35 (92.1)	

Our findings have several clinical implications. First, the high rate of recurrence and progression emphasises the need for long-term surveillance. Second, the lack of strong predictive markers for recurrence or cancer progression highlights the challenges in risk stratification. Third, the predominance of early-stage cancer at diagnosis suggests that structured follow-up can enable timely detection and intervention. Furthermore, the study adds data on outcomes in a non-PLHIV and non-MSM cohort.

This study has limitations. The retrospective design and moderate sample size limit its generalisability and statistical power. The mixed cohort of participants with both newly diagnosed AIN and patients with a longer history of AIN may obscure the interpretation of the results. However, we believe that the results reflect everyday clinical challenges when treating AIN.

High-resolution anoscopy is increasingly applied as a standard diagnostic and treatment tool in recent studies on AIN [15, 18, 19]. Although it has limitations in accurately identifying AIN [9] and is not yet implemented as a standard treatment at our institution or in Denmark, it may hold potential for reducing the progression rate from AIN to anal cancer.

Conclusions

Our data confirm the high recurrence rate of AIN following surgical excision and demonstrate a non-negligible risk of progression to anal cancer. These findings support the need for individualised, long-term follow-up strategies for patients treated for AIN, even after apparently successful initial treatment.

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Declaration of AI use During the preparation of this work, the authors used ChatGPT to improve readability and language. After using this tool, the authors reviewed and edited the contents as needed and take full responsibility for the contents of the publication

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