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What is the Risk of Anal Carcinoma in Patients with Anal Intraepithelial Neoplasia III?

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Abstract

BACKGROUND: The risk of anal carcinoma following prior diagnosis of anal intraepithelial neoplasia III is unclear.

OBJECTIVE: Estimate the risk of anal carcinoma in patients with anal intraepithelial neoplasia III, and identify predictors for subsequent malignancy.

DESIGN: Retrospective review using the Surveillance, Epidemiology, and End Results registry (1973–2014).

SETTING: Population-based cancer registries from the United States.

PATIENTS: Patients who were diagnosed with anal intraepithelial neoplasia III.

MAIN OUTCOME MEASURES: The primary outcome was rate of subsequent anal squamous cell carcinoma. Predictors for anal cancer were identified using logistic regression and Cox proportional hazard models.

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A video abstract has been attached to our manuscript, as Supplemental Digital Content.

Conflicts of Interest: The authors have no conflicts of interest.

RESULTS: 2,074 patients with anal intraepithelial neoplasia III were identified and followed for a median (interquartile range) time of 4.0 (1.8–6.7) years. Of the cohort, 171 patients (8.2%) subsequently developed anal cancer. Median (interquartile range) time from anal intraepithelial neoplasia III diagnosis to anal cancer diagnosis was 2.7 (1.1–4.5) years. Fifty-two patients (30.4%) who developed anal carcinoma were staged T2 or higher. Ablative therapies for initial anal intraepithelial neoplasia III were associated with a reduction in risk of anal cancer (odds ratio 0.3, 95% confidence interval 0.1–0.7, p=0.004). Time-to-event analysis revealed the 5-year incidence of anal carcinoma after anal intraepithelial neoplasia III was 9.5%, or approximately 1.9% per year.

LIMITATIONS: The registry did not record HIV status, surveillance schedule, use of high resolution anoscopy, or provider specialty.

CONCLUSIONS: In the largest published cohort of patients with anal intraepithelial neoplasia III, nearly 10% of patients were projected to develop anal cancer within 5 years. Nearly one-third of anal cancers were diagnosed at stage T2 or higher despite a prior diagnosis of anal intraepithelial neoplasia III. Ablative procedures were associated with decreased risk of cancer. This study highlights the considerable rate of malignancy in patients with anal intraepithelial neoplasia III and the need for effective therapies and surveillance. See **Video Abstract** at http://links.lww.com/DCR/Axxx.

Keywords

Ablation; AIN; Anal cancer; HSIL; Surveillance; Treatment

INTRODUCTION

Anal intraepithelial neoplasia (AIN) III, a dysplastic condition of squamous tissue that develops from contact with oncogenic human papillomavirus (HPV) strains, is considered a premalignant stage of anal squamous cell carcinoma (SCC).[1] Though progression of AIN III to anal SCC parallels the pathway of cervical dysplasia to cervical cancer, AIN III is thought to be more persistent, rarely regressing spontaneously.[2,3] HPV infections tend to be asymptomatic, making surveillance for AIN and anal cancer critical.[1]

Adding urgency to the discussions on anal cancer surveillance is the concerning statistic that rates of anal SCC are increasing by about 2% per year,[4] and incidence of AIN is increasing at an even higher rate, estimated at 11% per year in a population-based cohort from San Francisco.[5] Despite the increasing prevalence of disease, the risk of anal SCC following a prior diagnosis of AIN III is unclear. Most of the literature is single-institution studies that cite a 0.4–2.1% per year risk of anal cancer after a diagnosis of AIN III,[6–12] though one small study estimated a 6.1% annual risk of anal cancer in HIV-positive men who have sex with men with high-grade AIN.[13] These studies are difficult to interpret, as sample sizes were small and patients varied in terms of HIV status, sexual practices, degree of dysplasia of initial AIN, and AIN treatment.

These limited data have led to uncertainty about the true risk of progression to anal cancer, and appropriateness of surveillance for anal dysplasia. A recent survey of colorectal

surgeons found that only 48% screen for anal dysplasia, despite knowingly managing high-risk patients in their practices.[14] Though high resolution anoscopy is effective and recommended for AIN screening,[6,15] most colorectal surgeons are not formally trained and there is substantial variability in technique.[14] Therefore, the primary aim of this study was to quantify the risk of subsequent anal SCC diagnosis in patients with prior AIN III using a national dataset. The secondary aim was to identify predictors for malignant transformation from AIN III to anal SCC.

METHODS

Study Design

We conducted a retrospective study of a cohort of patients with AIN III diagnosed between 1973–2014 in the Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence – SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases (Nov 2016 submission). The SEER registry, organized by the National Cancer Institute, collects cancer incidence, prevalence, and survival data from population-based cancer registries covering approximately 28% of the United States population. SEER*Stat version 8.3.4 was used to link separate tumors based on patient identification number.

For patients with multiple diagnoses of AIN III, the first recorded diagnosis was identified as the index diagnosis for analysis. Likewise, for patients with multiple diagnoses of anal cancer, the first diagnosis was chosen as the index case. Any tumors diagnosed within ≤2 months were considered synchronous. Patients who had a diagnosis of anal cancer prior to AIN III diagnosis were excluded from the analysis. The Institutional Review Board approved this study (Protocol #2017P001718).

Variable Definitions

Basic demographic characteristics were obtained, including age, sex, race, marital status, and United States region (based on United States Census bureau designations). Surgery type for initial AIN III was categorized as follows: no procedure, ablative surgery (thermal ablation, electrocautery, fulguration, local tumor destruction, photodynamic therapy, or laser), excisional surgery (local tumor excision, polypectomy, excisional biopsy, or laser excision), and surgery not otherwise specified. Rationale for why a patient did not receive surgery was also recorded. Tumor size was defined as the largest dimension of the primary tumor (centimeters). Squamous cell anal cancers were assigned T stage by tumor size (tumors ≤2 cm were T1, tumors >2 cm and ≤5 cm were T2, tumors >5 cm were T3), based on the American Joint Commission on Cancer 8th edition.

Diagnoses of AIN III and anal squamous cell carcinoma were confirmed based on a primary site of “Anus, Anal Canal and Anorectum” and specific ICD-O-3 codes based on histopathologic specimens (Appendix 1). Histology codes of squamous cell carcinoma in situ were included as diagnoses of AIN III. HPV-related tumors were defined as any anal, cervical, oropharyngeal (tongue, tonsil, oropharynx), penile, vaginal, or vulvar neoplasm. Acquired immune deficiency syndrome (AIDS)-defining malignancies were defined as

Kaposi sarcoma, non-Hodgkin's lymphoma, and cervical cancer. Tumors could be recorded as both HPV-related and AIDS-defining malignancies. The primary outcomes were subsequent anal cancer diagnosis and time (years) between initial AIN III diagnosis and subsequent anal cancer diagnosis.

Statistical Analysis

Variables were summarized as median (interquartile range (IQR)) or count (percentage, 95% confidence interval (CI)) as appropriate. Categorical variables were compared with the Fisher Exact test, continuous variables were compared with the 2-sample t test, and multivariable logistic regression was used to adjust for potential confounders. Time-to-event analysis was performed with Kaplan-Meier curves and multivariable Cox proportional hazards models. All statistical analyses were performed using Stata software, version SE 14.0 (StataCorp, College Station, TX, USA). All tests were 2-sided and statistical significance was accepted at the $p<0.05$ level.

RESULTS

Overall cohort

We identified 2,129 patients with a diagnosis of AIN III between 1973–2014. Of those, 55 patients had a diagnosis of anal cancer prior to AIN III diagnosis, and were therefore excluded from the analysis. Thus, our final cohort included 2,074 patients.

Of the cohort, 60.3% were male and 84.3% were white, with a median (IQR) age of 52 (44–61) years (Table 1). In terms of marital status, 47.2% were single, 22.8% were married or with a domestic partner, and 13.0% were divorced, separated, or widowed. For their initial AIN III, 14.3% of patients underwent ablative surgery, 55.5% underwent excisional surgery, and 28.5% had no procedures. The median (IQR) follow-up time was 4.0 (1.8–6.7) years.

Other primary malignancies

Of the overall AIN III cohort, 935 (45.1%, 95% CI 43.0–47.2%) patients had a primary malignancy before their first AIN III diagnosis, while 912 (44.0%, 95% CI 41.9–46.1%) patients had a primary malignancy afterwards (Table 2). Approximately 323 (15.6%, 95% CI 14.1–17.2%) patients went on to develop an additional HPV-related neoplasm, including 171 (8.2%, 95% CI 7.1–9.5%) who went on to develop anal SCC, and 56 (2.7%, 95% CI 2.1–3.5%) went on to develop an AIDS-defining malignancy. Additionally, 317 (15.3%, 95% CI 13.8–16.9%) patients developed recurrent AIN III.

Of the 171 patients who were diagnosed with anal SCC after an initial diagnosis of AIN III, 73.1% were male, 80.7% were white, 53.2% were single, and median (IQR) age was 50 (44–60) years. For their initial AIN III treatment, 3.5% underwent ablative surgery, 71.4% underwent excisional surgery, and 22.8% had no procedure. Median (IQR) time from AIN III diagnosis to anal SCC diagnosis was 2.7 (1.1–4.5) years. At diagnosis, 32.9% of anal SCC were stage T1, 22.4% were stage T2, 8.2% were stage T3, and the stage was unknown or not recorded for 36.5% (Table 3). By the end of the follow-up period, 14.3% of patients

with T1 anal cancers, 21.1% of those with T2 tumors, and 42.9% of those with T3 tumors had died (p=0.06).

Predictors of subsequent diagnosis of anal SCC

Comparing the demographics of patients who were or were not subsequently diagnosed with anal SCC revealed significant differences on univariate analysis (Table 4). Patients who were subsequently diagnosed with anal SCC tended to be 41–50 years old (40.9% vs 29.3%, p=0.02) and male (73.1% vs 59.1%, p<0.001). In terms of marital status, more single (53.2% vs 46.6%) people tended to be diagnosed with anal cancer, as opposed to divorced people (5.9% vs 13.7%) (p=0.02). There were no differences in race or region of the United States. Patients who were subsequently diagnosed with anal cancer tended to undergo excisional surgery for their initial AIN III (71.4% vs 54.0%, p<0.001), not ablative surgery (3.5% vs 15.2%, p<0.001), as compared to patients who did not develop anal cancer.

These trends remained significant on multivariable analysis (Table 4). Independent predictors of subsequent diagnosis of anal carcinoma in patients with previous AIN III included being 41–50 years old (OR 1.69, 95% CI 1.01–2.83, p=0.047) and male (OR 2.18, 95% CI 1.47–3.24, p<0.001). Patients who were divorced, separated, or widowed were less likely to be diagnosed with anal SCC (OR 0.45, 95% CI 0.22–0.93, p=0.03) than single patients. In terms of treatment for AIN III, patients who underwent excisional surgery were more likely to be diagnosed with anal SCC (OR 1.82, 95% CI 1.23–2.70, p=0.003), while ablative surgery was associated with decreased likelihood of subsequent diagnosis of anal cancer (OR 0.27, 95% CI 0.11–0.66, p=0.004).

Factors associated with shorter time between AIN III and anal SCC diagnoses

In time-to-event analysis of the overall cohort, we examined “anal SCC-free survival”, with subsequent anal cancer diagnosis as the primary endpoint. We found that 9.5% of patients developed anal SCC within 5 years of AIN III diagnosis (Figure 1a). Separating patients by treatment of initial AIN III, 2.0% of patients who underwent ablation, 8.0% of patients who received no procedure, and 12.2% of patients who underwent excision were diagnosed with anal cancer within 5 years (p<0.001) (Figure 1b). There was no significant correlation between time from AIN III diagnosis to anal cancer diagnosis and T stage of the subsequent anal cancer. The median (IQR) times from AIN III to anal cancer diagnosis were 2.8 (1.0–4.8), 3.1 (1.1–4.4), and 3.4 (1.2–4.6) years for T1, T2, and T3 cancers, respectively (p>0.05).

Multivariable time-to-event analysis revealed that age 41–50 years old (HR 1.74, 95% CI 1.05–2.87, p=0.03) and male sex (HR 1.84, 95% CI 1.26–2.71, p=0.002) were associated with earlier time to development of anal cancer (Table 5). Patients who were divorced, separated, or widowed tended to develop anal cancer later than single patients (HR 0.49, 95% CI 0.24–0.98, p=0.04). Race and region of the United States were not associated with time to development of anal cancer. Compared to no procedure for initial AIN III, ablations were associated with significantly later development of anal cancer (HR 0.31, 95% CI 0.13–0.74, p=0.01), while excisions were associated with significantly earlier development of anal carcinoma (HR 1.51, 95% CI 1.04–2.19, p=0.03).

DISCUSSION

This study represents the largest published cohort of patients with AIN III. In this group of 2,074 patients, the 5-year incidence of anal SCC after prior AIN III diagnosis was 9.5%, or approximately 1.9% per year. This cohort, comprised of patients drawn from population-based national registries, is likely more representative of the true risk of malignancy than prior single-institution studies, most of which involved small groups of patients who received variable treatments.[6–12]

Undergoing ablative surgery for AIN III was significantly associated with decreased risk of subsequent anal cancer, while excisional procedures for AIN III were significantly associated with increased risk of subsequent anal SCC. This difference may have been seen because surgeons excised larger, visible AIN lesions that may have had more malignant potential. Though high resolution anoscopy is not recorded in SEER, it is also possible that surgeons who performed ablations also used high resolution anoscopy more often and thus obtained better visualization of the areas of anal dysplasia, therefore enabling more complete eradication of disease.[16] It is also possible that patients who underwent ablations were followed more closely with surveillance exams than those whose lesions were excised, and that the correlation between treatment type and rate of subsequent anal cancer was due in part to surveillance regimen, however it is impossible to ascertain with this dataset.

AIN is becoming widely recognized as a multifocal disease of the anal squamocolumnar junction. In patients at high risk for anal dysplasia, random biopsies of the anal canal in areas thought to be free of disease have later been found to have high-grade dysplasia.[17] Furthermore, in a small prospective trial, patients with high-grade dysplasia who underwent circumferential ablation of the anal squamocolumnar junction had no evidence of recurrent or persistent disease after two treatments, suggesting that AIN often occurs at multiple locations throughout the anal canal, not just in visible abnormalities on screening exams.[18] Our findings support this idea that AIN is multifocal, therefore simply excising visible or palpable lesions is inadequate for removing all disease and preventing progression to anal cancer. Patients who underwent excision for AIN III may have had remaining disease that went unidentified and therefore untreated, which may have then progressed to cancer.

This study also found that patients who had no procedure for AIN III were less likely to develop subsequent anal SCC than patients whose AIN III was excised. This difference appears more pronounced as more time lapses after AIN III diagnosis (Figure 1b). This interesting finding is likely due to a combination of factors including AIN III lesion size (patients with larger lesions were probably more likely to be excised) and surveillance schedule (patients with no procedure for AIN III may have been more closely followed, whereas patients who were excised may have only returned to care after developing symptoms). Other potential contributing factors include patients moving to states not captured by the SEER registry, physicians using topical treatments not recorded in the database, differences in immunosuppressed status, and spontaneous regression of anal dysplasia. Nevertheless, compared to patients with no recorded procedure for AIN III, patients who underwent ablations were significantly less likely to develop anal cancer. These differences again emphasize that AIN is a multifocal disease, requiring close surveillance for

recurrence or progression, and that simply excising a visible lesion is unlikely to completely eradicate the disease.

In this study, other independent predictors of subsequent diagnosis of anal cancer were male sex and single status. This likely represents the subset of patients who were men who have sex with men, who are significantly more likely to have anal-receptive intercourse, HIV infection,[19] and high number of sexual partners.[20] Also, men have been shown to be less compliant with follow-up appointments, making it possible that they missed more screening opportunities.[21]

Of note, despite a prior diagnosis of AIN III, one-third of anal cancers were diagnosed at stage T2 or higher. This demonstrates the importance of emphasizing close surveillance with both providers and patients. An interesting survey of members of the American Society of Colon and Rectal Surgeons found that, though nearly all responders recognized risk factors for AIN and 92% treated patients with anal dysplasia, less than half conducted anal dysplasia screening.[14] Only 31% of those surgeons used acetic acid with some form of magnification to evaluate for anal dysplasia, and only 35% performed high resolution anoscopy, of whom 46% were formally trained. Of the providers who did not screen, 52% stated that they were never formally trained, while 23% did not think it was a priority. In light of this data demonstrating a nearly 10% incidence of anal cancer within 5 years of AIN III diagnosis, and a protective association with ablation of AIN III lesions, colorectal surgeons must not only make ablation a key part of their training and practice, but also maintain close surveillance of their patients with AIN III, regardless of treatment performed.

Stronger screening guidelines for patients at high-risk of anal cancer are needed to ensure standardization of the most appropriate practices.[22,23] In our cohort, nearly one-third of anal cancers were diagnosed at stage T2 or higher, suggesting that anal cancers were missed at early stages. The Practice Parameters for Anal Squamous Neoplasms published by Steele et al. in 2012 lay an excellent foundation,[24] and several prospective trials examining screening strategies are underway, including the Study of the Prevention of Anal Cancer and the Anal Cancer HSIL Outcomes Research study.[25] Strong guidelines from colorectal surgery societies would increase awareness among patients and providers about the high incidence of malignancy and need for standardized surveillance in patients with AIN III.

This study has a number of limitations. The SEER registry does not record HIV status, sexual preferences, number of sexual partners, or immunosuppressed status. It also does not document the use of high resolution anoscopy, non-procedural treatments for AIN, frequency of surveillance, number of treatments, how the anal lesion was detected, or specialty of the provider performing the procedure for AIN. We were also unable to classify lesions as high-or low-grade squamous intraepithelial lesions, which have become the new consensus terminology for classifying anal dysplasia, instead using the former terminology of AIN III. Additionally, though it is possible to link neoplasms in the same patient, it is impossible to determine if an AIN III lesion progressed to a subsequent anal cancer. Furthermore, only patients with a neoplasm diagnosed between 2004–2014 are entered into this registry, and their prior neoplasms are then recorded, leading to potential for selection bias in this study. It is also possible that the SEER registry is not fully representative of the

United States population, as it captures data from specific states and intentionally over-represents ethnic minorities and underserved populations. However, the population-based estimates provided by SEER are more likely to be generalizable to the practicing clinician across the country than single-institution studies.

CONCLUSION

This study highlights the high rate of malignancy in patients with AIN III, and the need for effective therapies and close surveillance. Nearly 10% of patients with AIN III are diagnosed with anal cancer within 5 years, and nearly one-third of those anal cancers are diagnosed at stage T2 or higher. There is an urgent need for prospective trials to identify the most effective treatments for AIN III, and provide the basis for stronger guidelines for AIN III and anal cancer surveillance and management.

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Appendix 1.

Histology codes used to define AIN III and anal squamous cell carcinoma, with a primary site of “Anus, Anal Canal and Anorectum”.

Type of histology	ICD-O-3 code
AIN III	
Squamous cell carcinoma in situ, NOS	8070/2
SCC, keratinizing, NOS, in situ	8071/2
SCC, large cell, non-keratinizing, in situ	8072/2
SCC in situ with question of stromal invasion	8076/2
Squamous intraepithelial neoplasia, grade III	8077/2
Bowen disease	8081/2
Anal squamous cell carcinoma	
Neoplasm, malignant	8000/3
Carcinoma, NOS	8010/3
Squamous cell carcinoma, NOS	8070/3
SCC, keratinizing, NOS	8071/3
SCC, large cell, non-keratinizing	8072/3
SCC, micro-invasive	8076/3
Basaloid squamous cell carcinoma	8083/3

Type of histology	ICD-O-3 code
Basaloid transitional cell carcinoma	8123/3

AIN: anal intraepithelial neoplasia; ICD-O-3: International Classification of Diseases for Oncology; NOS: not otherwise specified; SCC: squamous cell carcinoma

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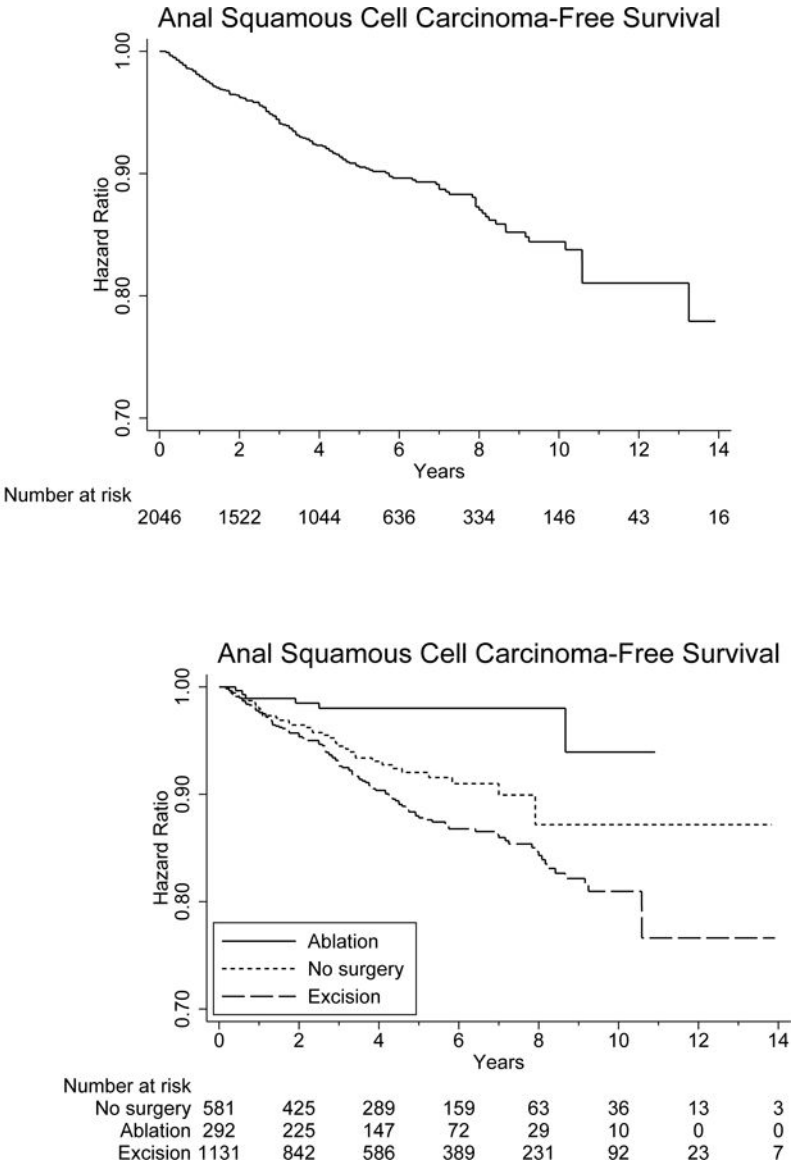

Figure 1.

Kaplan-Meier curves depicting anal squamous cell carcinoma-free survival in patients with previous AIN III in (a) the overall cohort, and (b) separated by type of surgical intervention for prior AIN III.

Table 1.

Demographics of 2,074 patients with diagnosis of AIN III.

Characteristic	N (%)
Age at diagnosis of AIN III (median, IQR)	52 years (44–61)
Sex	
Male	1,250 (60.3%)
Female	824 (39.7%)
Race	
White	1,749 (84.3%)
Black	244 (11.8%)
Other (Asian, American Indian)	60 (2.9%)
Unknown	21 (1.0%)
Marital status at diagnosis of AIN III	
Single (never married)	978 (47.2%)
Married or domestic partner	472 (22.8%)
Divorced, separated, or widowed	270 (13.0%)
Unknown	354 (17.1%)
Region of the United States	
Northeast	163 (7.9%)
Midwest	97 (4.7%)
South	279 (13.5%)
West	1,535 (74.0%)
Year of initial AIN III diagnosis	
Before 2006	329 (15.9%)
2006 – 2008	536 (25.8%)
2009 – 2011	648 (31.2%)
2012 – 2014	561 (27.1%)
Surgery type for initial AIN III	
None	589 (28.5%)
Ablative surgery	295 (14.3%)
Excisional surgery	1,147 (55.5%)
Surgery not otherwise specified or unknown	37 (1.8%)
Reason for no surgery for initial AIN III	
Surgery performed	1,514 (71.11%)
Not recommended	538 (25.27%)
Contraindicated due to other conditions	5 (0.23%)
Recommended, unknown why not performed	29 (1.36%)
Patient refused	10 (0.47%)

Characteristic	N (%)
Recommended, unknown if performed	21 (0.99%)
Unknown if surgery performed	12 (0.56%)

AIN: anal intraepithelial neoplasia; IQR: interquartile range

Table 2.

Patients with AIN III who were diagnosed with other primary neoplasms.

Type of other primary neoplasm	Before first AIN III diagnosis N (%)	After first AIN III diagnosis N (%)
Any other primary neoplasm	935 (45.1%)	912 (44.0%)
Any other HPV-related tumor	343 (16.5%)	323 (15.6%)
Anal carcinoma	n/a	171 (8.2%)
Cervical neoplasm	55 (2.7%)	2 (0.1%)
Oropharyngeal malignancy	15 (0.7%)	22 (1.1%)
Penile malignancy	5 (0.2%)	6 (0.3%)
Vaginal malignancy	27 (1.3%)	10 (0.5%)
Vulvar malignancy	278 (13.4%)	117 (5.6%)
Any AIDS-defining malignancy	262 (12.6%)	56 (2.7%)
Kaposi sarcoma	172 (8.3%)	24 (1.2%)
Non-Hodgkin lymphoma	89 (4.3%)	30 (1.4%)
Cervical cancer	8 (0.4%)	2 (0.1%)

AIN: anal intraepithelial neoplasia; HPV: human papillomavirus; AIDS: acquired immune deficiency syndrome

Table 3.

Demographics of 171 patients who developed anal squamous cell carcinoma after prior diagnosis of AIN III.

Characteristic	N (%)
Time from AIN III diagnosis to anal SCC diagnosis (median, IQR)	2.7 years (1.1–4.5)
T stage of anal SCC	
T1 (tumor ≤ 2 cm)	56 (32.9%)
Microscopic focus	14 (8.2%)
Tumor < 1 cm	21 (12.4%)
Tumor 1–2 cm	21 (12.4%)
T2 (tumor > 2 cm but ≤ 5 cm)	38 (22.4%)
T3 (tumor > 5 cm)	14 (8.2%)
Unknown	62 (36.5%)
Vital status at end of follow-up period	
Alive	138 (80.7%)
Dead	33 (19.3%)

AIN: anal intraepithelial neoplasia; SCC: squamous cell carcinoma; IQR: interquartile range

Table 4.

Univariate and multivariable analyses of predictors of developing subsequent anal squamous cell carcinoma in patients with prior AIN III.

Characteristic	No subsequent anal SCC (n = 1,903)	Subsequent anal SCC (n = 171)	P-value[a]	OR (95% CI)	P-value[b]
Age at diagnosis of AIN III			0.02		
≤ 40 years old	286 (15.0%)	21 (12.3%)		Reference	
41–50 years old	558 (29.3%)	70 (40.9%)		1.69 (1.01–2.83)	0.047
51–60 years old	562 (29.5%)	42 (24.6%)		1.10 (0.63–1.92)	0.74
> 60 years old	497 (26.1%)	38 (22.2%)		1.26 (0.70–2.26)	0.44
Sex			<0.001		
Female	778 (40.9%)	46 (26.9%)		Reference	
Male	1,125 (59.1%)	125 (73.1%)		2.18 (1.47–3.24)	<0.001
Race			0.60		
White	1,611 (84.7%)	138 (80.7%)		Reference	
Black	219 (11.5%)	25 (14.6%)		1.19 (0.73–1.91)	0.49
Other (Asian, American Indian)	54 (2.8%)	6 (3.5%)		1.35 (0.56–3.28)	0.51
Unknown	19 (1.0%)	2 (1.2%)		1.62 (0.35–7.43)	0.53
Marital status at diagnosis of AIN III			0.02		
Single (never married)	887 (46.6%)	91 (53.2%)		Reference	
Married or domestic partner	428 (22.5%)	44 (25.7%)		1.06 (0.69–1.63)	0.79
Divorced, separated, widowed	260 (13.7%)	10 (5.9%)		0.45 (0.22–0.93)	0.03
Unknown	328 (17.2%)	26 (15.2%)		0.80 (0.50–1.28)	0.35
Region of the United States			0.38		
Northeast	147 (7.7%)	16 (9.4%)		Reference	
Midwest	87 (4.6%)	10 (5.9%)		1.11 (0.48–2.60)	0.81
South	251 (13.2%)	28 (16.4%)		0.96 (0.49–1.86)	0.90
West	1,418 (74.5%)	117 (68.4%)		0.77 (0.43–1.37)	0.37
Surgery type for AIN III			<0.001		
None	550 (29.0%)	39 (22.8%)		Reference	
Ablative surgery	289 (15.2%)	6 (3.5%)		0.27 (0.11–0.66)	0.004
Excisional surgery	1,025 (54.0%)	122 (71.4%)		1.82 (1.23–2.70)	0.003
Surgery NOS or unknown	33 (1.7%)	4 (2.3%)		2.17 (0.70–6.69)	0.18

AIN: anal intraepithelial neoplasia; SCC: squamous cell carcinoma; OR: odds ratio; CI: confidence interval; NOS: not otherwise specified

[a] P-value based on univariate analysis.

[b] P-value based on multivariable analysis.

Table 5.

Multivariable time-to-event analysis of predictors of *early* development of subsequent anal squamous cell carcinoma in patients with prior AIN III.

Characteristic	Hazard Ratio (95% CI)	P-value
Age at diagnosis of AIN III		
≤ 40 years old	Reference	
41–50 years old	1.74 (1.05–2.87)	0.03
51–60 years old	1.43 (0.83–2.46)	0.19
> 60 years old	1.74 (0.98–3.08)	0.06
Sex		
Female	Reference	
Male	1.84 (1.26–2.71)	0.002
Race		
White	Reference	
Black	1.34 (0.86–2.09)	0.20
Other (Asian, American Indian)	1.32 (0.58–3.01)	0.51
Unknown	0.92 (0.13–6.60)	0.93
Marital status at diagnosis of AIN III		
Single (never married)	Reference	
Married or domestic partner	1.13 (0.74–1.71)	0.57
Divorced, separated, or widowed	0.49 (0.24–0.98)	0.04
Unknown	0.88 (0.56–1.39)	0.58
Region of the United States		
Northeast	Reference	
Midwest	1.06 (0.47–2.37)	0.89
South	0.91 (0.48–1.72)	0.77
West	0.59 (0.34–1.04)	0.07
Surgery type for AIN III		
None	Reference	
Ablative surgery	0.31 (0.13–0.74)	0.01
Excisional surgery	1.51 (1.04–2.19)	0.03

AIN: anal intraepithelial neoplasia; CI: confidence interval