Original Article

Multidisciplinary management of anal intraepithelial neoplasia and rate of progression to cancer: a retrospective cohort study.

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Abstract

Purpose: To describe the regional burden of AIN and rate of progression to cancer in patients managed in specialist and non-specialist clinic settings.

Methods: Patients with a histopathological diagnosis of AIN between 1994-2018 were retrospectively identified. Clinicopathological characteristics including high-risk status (chronic immunosuppressant use or HIV positive), number and type of biopsy (punch/excision) and histopathological findings were recorded. The relationship between clinicopathological characteristics and progression to cancer was assessed using logistic regression.

Results: Of 250 patients identified, 207 were eligible for inclusion: 144 from the specialist and 63 from the non-specialist clinic. Patients in the specialist clinic were younger (<40 years 31% vs 19%, p=0.007), more likely to be male (34% vs 16%, p=0.008) and HIV positive (15% vs 2%, p=0.012). Patients in the non-specialist clinic were less likely to have AIN3 on initial pathology (68% vs 79%, p=0.074) and were more often followed up for less than 36 months (46% vs 28%, p=0.134). The rate of progression to cancer was 17% in the whole cohort (20% vs 10%, p=0.061). On multivariate analysis, increasing age (OR 3.02, 95%CI 1.58-5.78, p<0.001), high risk status (OR 3.53, 95% CI 1.43 – 8.74, p=0.006) and increasing number of excisions (OR 4.88, 95%CI 2.15 – 11.07, p<0.001) were related to progression to cancer.

Conclusion: The specialist clinic provides a structured approach to the follow up of high-risk status patients with AIN. Frequent monitoring with specialist assessments including high

resolution anoscopy in a higher volume clinic are required due to the increased risk of progression to anal cancer.

Abbrevations:

AIN Anal intra-epithelial neoplasia

APR Abdominoperineal resection

ASCC Anal squamous cell cancer

CRT Chemoradiotherapy

HIV Human immunodeficiency virus

HPV Human papillomavirus

MuFIN Multifocal intraepithelial neoplasia

MDT Multidisciplinary team

1.1 Introduction

Anal squamous cell cancer (ASCC) is an uncommon entity, with 29,000 new cases recorded worldwide in 2018[1]. However, incidence rates continue to rise[2,3], particularly in high-risk groups. Patients on long-term immunosuppressant therapy, those with a history of anogenital human papillomavirus (HPV) infection, patients living with HIV and men who have sex with men are at higher risk of developing ASCC[4]. Anal intra-epithelial neoplasia (AIN), the precursor lesion to anal cancer, is detectable by high-resolution anoscopy, prompting some to advocate for dedicated screening and surveillance programmes in high risk groups[5]. However, evidence of effective interventions to prevent progression of AIN to ASCC from randomised trials is lacking[6,7,8]. Furthermore, the natural history of AIN remains unclear, with reports of the risk of progression to cancer ranging from 2 to 26%[9,10,19–26,11–18].

In our institution, patients with biopsy-proven multifocal (anal, cervical, vulval or vaginal) intra-epithelial neoplasia are followed in a dedicated multifocal intraepithelial neoplasia (MuFIN) clinic. Patients are assessed by a multidisciplinary team (MDT) of colorectal surgeons and gynaecological oncologists in a one-stop setting with high resolution colposcopy and anoscopy facilities. Concentrating the management of anogenital intraepithelial neoplasia in the hands of a dedicated MDT has several potential benefits: experience in the detection of subtle abnormalities, the opportunity to observe patients closely, regular liaison with a pathologist with specialist interest in anogenital disease and early detection and management of potentially malignant transformation. Here we describe the regional outcomes from a cohort of patients with AIN, the majority of whom were reviewed in a specialist clinic.

Specifically, we sought to report rates and determinants of progression to ASCC to provide a comparison with other series.

1.2 Material and methods

Patients with a histopathological diagnosis of AIN between 1994 and 2018 were identified by keyword searching of the prospectively-maintained pathology database of the local health board. Patients were grouped according to whether their management was undertaken by the specialist clinic or in a general surgery or colorectal service. The MuFIN clinic is a tertiary referral service. Therefore, if patients were referred from a general or colorectal service to the clinic, their management was considered to have been undertaken by the MuFIN clinic. Patients referred from other health boards were identified from a database of MuFIN attendees to ensure those who did not undergo further biopsies were identified and included.

Inclusion criteria were a histopathological diagnosis of AIN of any grade and a minimum follow up duration of 6 months. Exclusion criteria included patients presenting with de novo ASCC, patients under surveillance for vulval and/or cervical disease only and patients for whom no clinical record was available. Patients who were HIV-positive or were taking immunosuppression, including long-term oral steroids, were deemed high risk. This term was used to describe patient status rather than pathological characteristics.

The case record of patients presenting prior to 2008 and the medical electronic record of patients from 2008 onwards were reviewed retrospectively. Data on age at first histopathological diagnosis of AIN, biopsy type (punch or excision), histopathological grade of AIN, use of immunosuppressant medications, HIV status and smoking history were

abstracted. Findings at subsequent follow-up and biopsy were recorded, including biopsy type (punch or excision) and pathology. The terminology used to describe an increasing degree of dysplasia changed during the study period from AIN 1, 2 and 3 to low-grade squamous intra-epithelial lesion (LSIL, previously AIN 1) and high-grade squamous intra-epithelial lesion (HSIL, previously AIN 2 or 3)[27]. However, the LSIL and HSIL classification was restricted to the latter years of this study and was not uniformly applied in this cohort. For consistency, the terms AIN 1 to 3 are therefore used. In patients who progressed to ASCC, treatment characteristics and outcome were recorded. In patients who died during the study period, cause of death was determined from the clinical record. Survival data were censored in February 2020.

The protocol for management of AIN practised by the MuFIN clinic recommends that lesions with changes suggestive of AIN are either biopsied if diffuse or excised if localised. In some situations, topical agents including imiquimod were used in preference to excision, guided by the clinical scenario and patient preference. In patients with widespread AIN 3, wide local excision is undertaken with plastic surgical reconstruction preferred. In some cases, typically in patients with circumferential high grade AIN, stoma formation may be required to assist healing. Patients undergo surveillance for 5 years from the date of last histopathological confirmation of AIN 3. Patients are discharged if no recurrence is demonstrated during the surveillance period. In patients who develop recurrence, surveillance is continued for a further 5 years following appropriate treatment.

1.2.1 Statistical analysis

Descriptive statistics were used to summarise demographic and clinicopathological characteristics. Associations between clinicopathological characteristics and AIN progression were assessed using the chi-square or Mantel Haenszel test. Binary logistic regression analysis was used to assess the relationship between clinico-pathological characteristics and progression to ASCC. To avoid collinearity, the number of excisions rather than number of biopsies was included in multivariate model. Variables with a p-value <0.1 on univariate analysis were entered in to a multivariate model and assessed using a backward conditional model. Statistical analyses were performed using IBM SPSS version 25.0 for Mac (Chicago, IL, USA).

1.3 Results

During the study period, 250 patients who had a histopathological diagnosis of AIN were identified (Figure 1). Among the exclusions were 8 patients whose cases notes were not available or destroyed, 4 patients who had cervical, vulval and/or vaginal disease only and 3 patients who presented with de novo ASCC associated with AIN. A further 28 patients were excluded as they had a single-biopsy with no follow up (n=15) or less than 6 months follow up data available (n=13). The study cohort comprised 207 patients, of whom 144 had been managed by the MuFIN clinic and 63 patients managed in general clinics.

The demographic, clinical and pathological characteristics of patients are shown in Table 1. The majority of patients were female (n=148, 72%), between 40 to 60 years old (n=118, 57%) and were current smokers (n=119, 57%). Initial pathology was AIN 3 in 158 patients (76%). Compared to the MuFIN clinic, patients managed in a general clinic were older (25% vs 11% >60 years, p=0.007), less likely to be male (16% vs 34%, p=0.008) and to be HIV positive (2% vs 15%, p=0.012). Although not statistically significant, trends were also noted in initial pathology and duration of follow up. Patients from the general clinic were less likely to have AIN 3 on initial pathology (68% vs 79%, p=0.074) and were more often followed up for less than 36 months (46% vs 28%, p=0.134) than patients in the MuFIN clinic.

Median follow up for patients attending the MuFIN clinic was 54 (minimum 8) months and 37 (minimum 9) months in patients attending a general clinic. Of 16 patients presenting with AIN 1, 2 (13%) progressed to higher grade (n=1 (2%) general, n=1 (1%) MuFIN); there were no cases of progression to ASCC. Of 33 patients presenting with AIN 2, 12 patients (36%)

progressed to higher grade (n=5 (8%) general, n=11 (8%) MuFIN); 6 patients progressed to ASCC (n=1 (2%) general, n=5 (4%) MuFIN clinic). Of 158 patients presenting with AIN 3, 29 patients progressed to ASCC (n = 5 (8%) general, n=24 (17%) MuFIN). Rates of progression to higher grade AIN were similar between patients managed in the general and MuFIN clinic (8% versus 8%, p=0.941). A higher proportion of patients in the MuFIN clinic progressed to ASCC when compared with those managed in a general clinic (20% versus 10%, p=0.061).

Median follow up for survivors was 47 (minimum 8) months. During follow-up, 35 patients developed ASCC, 7 of whom (20%) were immunosuppressed and 5 (14%) were living with HIV. The overall rate of progression from AIN to ASCC was 17%. Complete data on treatment of ASCC and subsequent follow up was available for 33 patients. Table 2 outlines the pathological and treatment characteristics of patients who developed ASCC across the two clinic types. Earlier tumours (TNM I-II vs III) were more common in the MuFIN clinic (93% vs 50%, p=0.031).

There were no statistically significant differences in ASCC treatment between the two clinic types (Table 2). In total, 21 patients underwent surgery as the first mode of treatment for ASCC. Local excision was the surgical approach in 18 patients (14 patients from MuFIN clinic, 4 patients from general clinics). Abdominoperineal resection with curative intent was performed in 3 patients from the MuFIN clinic. Primary chemoradiation (CRT) was undertaken in 11 patients. Induction chemotherapy was administered to one patient with diffuse T4 disease with the intention of proceeding to curative intent CRT. However, marked disease progression occurred during the induction phase and subsequent treatment was palliative.

No cases of salvage surgery for persistent disease following chemoradiation were observed in this cohort.

Rates of micro-invasive ASCC were higher in patients from the MuFIN clinic (41% vs 33%, p=0.558). Micro-invasive ASCC was found in 13 patients, of whom 7 were managed by primary excision alone. In those with incompletely excised microinvasive disease, 4 patients proceeded to chemoradiotherapy and 2 patients were observed as CRT was precluded by comorbidity. In 5 patients, local excision of early-stage tumours was performed. Of these, 2 patients had T1 tumours and proceeded to adjuvant chemotherapy while 3 patients had T2 tumours, of whom one proceeded to CRT and two were observed due to previous pelvic radiotherapy and frailty respectively. Abdominoperineal resection with curative intent was the first mode of treatment in a further 3 patients, all of whom had been managed in the MuFIN clinic. Adjuvant chemoradiation was given to one patient following APR in whom the presence of perineal sinuses raised the possibility of margin involvement. In total, 7 patients who developed ASCC died during follow up, of whom 1 was managed in a general clinic. Death attributable to ASCC occurred in 3 cases.

The associations between clinico-pathological characteristics and AIN progression are shown in Table 3. For progression to higher grade AIN, associations with immunosuppression (p=0.039) and an increasing number of biopsies (p<0.001) or excisions (p=0.027) were noted. Trends were noted with higher rates of progression among smokers (p=0.078) and those with a longer duration of follow up (p=0.072). For progression to ASCC, associations were evident with increasing age (p=0.018), immunosuppression (p=0.051) and an increasing number of

biopsies or excisions (both p<0.001). A trend was also noted with longer duration of follow up and progression to ASCC (p=0.085).

To explore the relationship between factors related to AIN progression and the development of ASCC, binary logistic regression was performed (Table 4). On multivariate analysis, increasing age (OR 3.02, 95%CI 1.58-5.78, p<0.001), high risk status (OR 3.53, 95% CI 1.43 – 8.74, p=0.006) and a greater number of excisions (OR 4.88, 95%CI 2.15 – 11.07, p<0.001) were independently related to progression to ASCC.

1.4 Discussion

To our knowledge, this is the first study to assess the impact of a multidisciplinary clinic on the progression rate of AIN to ASCC. Patients managed in the MuFIN clinic had more than double the risk of developing ASCC when compared with those managed in a general clinic. This finding is likely a reflection of the higher risk status of patients managed by the MuFIN clinic, as evidenced by higher rates of AIN 3 and HIV positivity. It can be seen that this patient group experience progression to ASCC more frequently and therefore management in a specialist service represents an appropriate strategy to address the increased risk of adverse outcome.

Given the relative rarity of anal cancer, a colorectal surgeon is estimated to see one case every 3 to 5 years[28]. The volume-outcome relationship that is well documented in other solid tumours is also evidenced in anal cancer, where cytotoxic treatment in a high-volume centre is independently associated with improved survival[29]. Incorporating a specialist approach to the pre-malignant phase may be expected to yield similar benefits by virtue of early detection. Indeed, this is evidenced in the preponderance of micro-invasive and early stage disease in this cohort, enabling the use of surgical monotherapy in carefully selected patients. Moreover, local excision was possible in several patients who may have required more extensive surgery or APR had disease been detected at a more advanced stage.

Recognition of early malignant change is critical in the context of a rare disease with a detectable pre-malignant phase and an available treatment. Screening methods based on anoscopy and anal cytology or biopsy are limited by their acceptability[30] meaning that even

in high-risk groups, a coordinated screening programme remains unlikely. As such, regular surveillance in a clinic staffed by a multidisciplinary group of surgical oncologists facilitates early detection through basic provisions including continuity of care and availability of specialist equipment. Of arguably greater importance is the availability of expertise in the detection of subtle vascular abnormalities including punctate changes and mosaicism. Gynaecologic oncologists are attuned to the phenotypic features of intraepithlelial neoplasia given the frequency with which it is encountered in cervical disease[31]. Moreover, women with genital HPV-related disease with or without HIV are at substantially higher risk of AIN[32–34]. The ability to provide an integrated review within a one-stop setting benefits patients by reducing delays to treatment that may arise from the need for separate review. Further benefits include the facilitation of inter-speciality training and education and the provision of a sustainable pathway for trainees to acquire subspecialty skills and experience. Finally, the development of HPV vaccines for therapeutic use in patients with anogenital IN is evolving[35,36] and a structured clinic setting as is described here lends itself to the close monitoring and multi-speciality input required for clinical trials.

The median duration of follow up was longer in patients attending the MuFIN clinic compared to those attending a general clinic. While numerical differences were evident when time in follow up (<36 months, 36-72 and >72 months) was compared between the clinic types, there was no statistically significant difference. This likely reflects the differing risk profiles of patients seen and managed in general clinics, where AIN 1 was more common and patients were more often older. Such factors may have shifted the risk-benefit of continued follow up towards a pragmatic approach, facilitating earlier discharge. The proportion of patients who developed ASCC despite prolonged follow up in the MuFIN clinic reinforces the need for

continuous review of our current surveillance protocol and consideration of a tailored approach to review frequency and duration in patients with either high risk pathology or the presence of high risk host features including immunosuppression.

An increased number of excision biopsies was performed in patients from the MuFIN clinic, suggesting persistent or recurrent high-grade AIN. A greater number of excisions was also the strongest predictor of progression to ASCC on multivariate analysis, independent of age and high-risk status. It can be inferred that this reflects a drawback of current AIN management: the underlying viral aetiology, in conjunction with host immune function, is not effectively engaged by removal of areas of dysplastic change. However, alternative approaches including ablative therapies have been afflicted by high AIN recurrence rates while topical treatments lack tolerability and high-quality evidence to support their use[6]. Reduced rates of anogenital dysplasia are expected as a consequence of HPV vaccination of adolescents. However, both basic science and clinical research targeting upregulation of the immune response to anogenital HPV infection combined with therapeutic approaches to enhance its clearance are urgently required.

Direct comparison to other series requires caution due to the bias introduced by the differing demographics of the included population and temporal changes in management. Several series have reported rates of progression solely in HIV positive men who have sex with men[18,21,23,24,26,37]. Of those examining progression rates in mixed populations similar to that reported here, a recent study using data from a population-based Danish registry found an overall 5-year rate of progression of 3.4% in patients with AIN of any grade[38]. When assessed according to HIV status, the absolute risk of anal cancer was 14% among HIV positive

individuals compared with 3% in HIV negative individuals. It is a limitation of registry-based data that treatment and surveillance characteristics are not routinely reported. However, it can be seen that the high-risk cohort of patients require close monitoring over a prolonged period that can be facilitated by specialist clinics such as that described here.

The limitations of this study include missing data on the use of topical treatments such as imiquimod. While desirable, the reliability of such data is restricted by poor compliance with treatment due to side-effects[6,39]. Data on patient-related outcomes including quality of life and faecal continence after multiple or extended excisions would enable a better appreciation of the consequences of surgical and cytotoxic management of AIN and ASCC. Furthermore, the discrepancy between the number of patients identified (n=250) and number of patients included (n=207) raises the possibility of selection bias. This included historical patients who had died or moved, reflecting the attrition seen in routine clinical practice. The exclusion of those with insufficient follow up highlights the need for continued data collection and monitoring. It is also possible that the presence of a specialist clinic within the health board region limits generalisability as patients perceived as high risk may have been referred early to the MuFIN clinic and those deemed low risk or significantly comorbid not referred. Finally, data on the health economics relating to the cost-benefit ratio of specialist services such as the MuFIN clinic is currently not available.

1.4.1 Conclusion

In conclusion, the multi-focal intra-epithelial neoplasia clinic provides a structured approach to the follow up of high-risk status patients with AIN. Frequent monitoring with specialist

assessments including high resolution anoscopy in a higher volume clinic are required due to the increased risk of progression to ASCC.

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Table 1: Demographic and clinico-pathological data of patients.

		All n=207 (%)	Combined clinic n=144 (%)	General clinic n=63 (%)	p-value*
Age (years)	<40	57 (28)	45 (31)	12 (19)	0.007
	40-60	118 (57)	83 (58)	35 (56)	
	>60	32 (15)	16 (11)	16 (25)	
Gender	Male	59 (28)	49 (34)	10 (16)	0.008
	Female	148 (72)	95 (66)	53 (84)	
HIV status[a]	Negative	182 (88)	121 (84)	61 (97)	0.012
	Positive	24 (11)	22 (15)	3 (2)	
Immunosuppression[a]	No	184 (89)	129 (89)	55 (87)	0.533
	Yes	22 (10)	14 (10)	8 (13)	
Smoking status	No	88 (43)	66 (46)	22 (35)	0.144
	Yes	119 (57)	78 (54)	41 (65)	
Initial pathology	AIN I	16 (8)	9 (6)	7 (11)	0.074
	AIN II	33 (16)	20 (14)	13 (21)	
	AIN III	158 (76)	115 (80)	43 (68)	
Number of excisions	None	17 (8)	11 (8)	6 (10)	0.080
	1-2	154 (75)	103 (72)	51 (80)	
	>2	36 (17)	30 (20)	6 (10)	
AIN progression (to higher grade)	No	191 (92)	133 (92)	58 (92)	0.941
	Yes	16 (8)	8 (8)	8 (8)	
AIN to ASCC	No	172 (83)	115 (80)	57 (90)	0.061
	Yes	35 (17)	29 (20)	6 (10)	
Time in follow up (months)	<36	69 (33)	40 (28)	29 (46)	0.134
	36 - 72	87 (42)	69 (48)	18 (29)	
	>72	51 (25)	35 (24)	16 (25)	

[a] n= 206 * chi-squared/Mantel-Haenszel test for association.

Table 2: Pathological and treatment characteristics of patients who developed ASCC (n=33, Fisher's exact test).

		Combined clinic n=27 (%)	**General clinic n=6 (%)**	**p-value**
TNM stage	I - II	25 (93)	3 (50)	0.031
	III	2 (7)	3 (50)	
Micro-invasive disease	No	16 (59)	4 (67)	0.558
	Yes	11 (41)	2 (33)	
1st treatment CRT	No	17 (63)	4 (67)	0.626
	Yes	10 (37)	2 (33)	
1st treatment surgery	No	10 (37)	2 (33)	0.626
	Yes	17 (63)	4 (67)	
Local excision*	No	3 (18)	0 (0)	0.511
	Yes	14 (82)	4 (100)	

*n=21

Table 3: Clinico-pathological factors related to AIN progression.

		Low grade to high grade AIN (n=172)		p-value	AIN to ASCC (n=207)		p-value
		No	Yes		No	Yes	
Age (years)	<40	49 (31)	2 (17)	0.627	51 (30)	6 (17)	0.018
	40-60	90 (56)	9 (75)		99 (57)	19 (54)	
	>60	21 (13)	1 (8)		22 (13)	10 (29)	
Gender	Female	116 (73)	9 (75)	0.851	125 (73)	23 (66)	0.407
	Male	44 (27)	3 (25)		47 (27)	12 (34)	
Immunosuppression*	No	147 (93)	9 (75)	0.039	156 (91)	28 (80)	0.051
	Yes	12 (7)	3 (25)		15 (9)	7 (20)	
HIV*	No	141 (89)	11 (92)	0.751	152 (89)	30 (86)	0.595
	Yes	18 (11)	1 (8)		19 (11)	5 (14)	
Smoking history	No	65 (41)	8 (67)	0.078	73 (42)	15 (43)	0.964
	Yes	95 (59)	4 (33)		99 (58)	20 (57)	
Number of biopsies	<2	46 (29)	0 (0)	0.001	46 (27)	0 (0)	0.001
	2-4	98 (61)	5 (42)		103 (60)	21 (60)	
	>4	16 (10)	7 (58)		23 (18)	14 (40)	
Number of excisions	None	16 (10)	0 (8)	0.027	16 (9)	1 (3)	0.001
	1-2	125 (78)	8 (67)		133 (77)	21 (60)	
	>2	19 (12)	4 (33)		23 (14)	13 (37)	
Time in follow up (months)	<36	58 (36)	3 (25)	0.072	61 (35)	8 (23)	0.085
	36 - 72	69 (43)	3 (25)		72 (42)	15 (43)	
	>72	33 (21)	6 (50)		39 (23)	12 (34)	

* n=206

Table 4: Analysis of factors associated with progression to ASCC.

	Univariate			Multivariate		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age (years) (<40/40-60/>60)	2.00	1.12 – 3.57	0.020	3.02	1.58 – 5.78	0.001
Sex (Female/Male)	1.39	0.23 – 3.01	0.407	-	-	-
Smoking status (No/Yes)	0.98	0.47 – 2.05	0.964	-	-	-
High risk (No/Yes)	2.12	0.96 – 4.68	0.063	3.53	1.43 – 8.74	0.006
Number of excisions (0/1-2/>2)	3.40	1.61 – 7.15	0.001	4.88	2.15 – 11.07	0.001
Time in follow up (months) (<36/36-72/>72)	1.53	0.94 – 2.49	0.087	1.41	0.82 – 2.44	0.215

Abbreviations: OR – odds ratio; CI – confidence interval.

Figure 1: Flow chart showing study cohort.