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ORIGINAL CONTRIBUTION

High-Resolution Anoscopy Surveillance After Anal Squamous Cell Carcinoma: High-Grade Squamous Intraepithelial Lesion Detection and Treatment May Influence Local Recurrence

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See "Editorial" on page 1343.

BACKGROUND: Local recurrence is a significant risk after anal squamous cell carcinoma.

OBJECTIVES: This study aimed to examine the occurrence of high-grade squamous intraepithelial lesions and local recurrence after anal cancer at surveillance with high-resolution anoscopy.

DESIGN: This is a retrospective observational study.

SETTING: This study was conducted at an anogenital neoplasia referral center.

PATIENTS: There were 76 anal/perianal cancers from 1998 to 2018. Sixty-three patients were eligible and 3 were excluded, for a total of 60 patients; 35 of 60 (58%) patients were male.

INTERVENTION: High-resolution anoscopy after chemoradiation or excision only for anal squamous cell carcinoma was performed.

MAIN OUTCOME MEASURES: The primary outcomes measured were local recurrence and high-grade squamous intraepithelial lesion detection rates.

RESULTS: Sixty patients, 27% HIV positive, underwent surveillance over a median 42 (range 7–240) months of follow-up. Seven had had a prior local recurrence at study entry so were analyzed separately. Thirty of 53 underwent chemoradiation (57%) and 23 of 53 underwent excision alone (43%); 33 had perianal cancer and 20 had anal cancer. Ten of 30 of the chemoradiation group had had stage 1 (33%) disease in comparison with 22 of 23 of the excision only group (96%, $p < 0.001$).

OUTCOMES: High-grade squamous intraepithelial lesions were detected in 4 of 30 (13%) patients after chemoradiation and in 17 of 23 (74%) patients after excision only ($p < 0.001$). Twenty of 21 (95%) high-grade lesions were treated with ablation. Six of 7 (86%) patients with prior local recurrence had high-grade squamous intraepithelial lesions over a median of 21 months follow-up. One local recurrence (T1N0M0) occurred during surveillance after primary chemoradiation (0.56/1000 person-months), none occurred after excision only, and 2 of 7 with prior local recurrence developed further local recurrence (6.86/1000 person-months). All 3 local recurrences occurred after treatment of high-grade squamous intraepithelial lesions. There were no

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metastases, abdominoperineal excisions, or deaths from anal squamous cell carcinoma.

LIMITATIONS: Retrospective data were used for this study.

CONCLUSIONS: High-grade squamous intraepithelial lesions after anal squamous cell carcinoma are more common after excision only than after chemoradiation. Local recurrence is low in this high-resolution anoscopy surveillance group in which high-grade squamous intraepithelial disease was ablated. Excision of small perianal cancers appears safe; however, a subset of patients is at excess risk. See **Video Abstract** at http://links.lww.com/DCR/B285.

VIGILANCIA POR ANOSCOPÍA DE ALTA RESOLUCIÓN EN CASOS DE CARCINOMA ANAL A CÉLULAS ESCAMOSAS: LA DETECCIÓN Y TRATAMIENTO DE UNA LESIÓN INTRAEPITELIAL ESCAMOSA DE ALTO GRADO (HSIL) PUEDE INFLUIR EN LA RECURRENCIA LOCAL

ANTECEDENTES: La recurrencia local tiene un riesgo significativo después del carcinoma anal a células escamosas.

OBJETIVO: Evaluar la aparición de lesiones intraepiteliales escamosas de alto grado (HSIL) y su recurrencia local durante la vigilancia con anoscopía de alta resolución en casos de cancer anal.

DISEÑO: Estudio observacional retrospectivo.

AJUSTE: Centro de referencia de neoplasia anogenital.

PACIENTES: Se diagnosticaron 76 cánceres anales / perianales entre 1998 y 2018. Un total de 63 pacientes fueron elegidos, 3 excluidos (n = 60), 35/60 (58%) fueron varones.

INTERVENCIÓN: Anoscopía de alta resolución después de la quimio-radioterapia, o solo excisión en casos de carcinoma anal a células escamosas.

PRINCIPALES MEDIDAS DE RESULTADO: Recurrencia local primaria y tasas de detección de lesión intraepitelial escamosa de alto grado.

RESULTADOS: Sesenta pacientes, 27% VIH positivos, fueron sometidos a vigilancia durante una mediana de 42 (rango 7–240) meses de seguimiento. Siete habían tenido una recurrencia local antes de ser incluidos en el estudio, por lo que se analizaron por separado. Treinta de 53 se sometieron a quimio-radioterapia (57%) y 23/53 solo a excisión (43%). 33 eran lesiones perianales, 20 de canal anal. 10/30 del grupo de quimio-radioterpia se encontraban en Fase 1 (33%) comparados con 22/23 del grupo de excisión (96%, p <0.001).

RESULTADOS: Se detectaron lesiones intraepiteliales escamosas de alto grado en 4/30 (13%) después de la quimio-radioterapia, y en 17/23 (74%) solo después de la excisión ($p < 0.001$). 20/21 (95%) lesiones de alto grado fueron tratadas con ablación. Seis de siete (86%) con recurrencia local previa tenían lesiones intraepiteliales escamosas de alto grado durante una mediana de seguimiento de 21 meses. Se produjo una recurrencia local (T1N0M0) durante la vigilancia después de la quimio-radioterapia primaria (0.56/1000 persona-meses), ninguna después de la excisión sola y 2/7 con recurrencia local previa desarrollaron una recurrencia local adicional (6.86/1000 persona-meses). Las 3 recidivas locales ocurrieron después del tratamiento de las lesiones intraepiteliales escamosas de alto grado. No hubieron metástasis, excisiones abdominoperineales o muertes por carcinoma anal a células escamosas.

LIMITACIONES: Datos retrospectivos.

CONCLUSIONES: Las lesiones intraepiteliales escamosas de alto grado en casos de carcinoma escamocelular anal son más comunes después de la excisión sola que después de la quimio-radioterapia. La recurrencia local es baja en este grupo de vigilancia de anoscopía de alta resolución en el que se retiró la enfermedad intraepitelial escamosa de alto grado. La excisión de pequeños cánceres perianales parece segura; sin embargo, un subconjunto de pacientes tiene un riesgo excesivo. Consulte **Video Resumen** en http://links.lww.com/DCR/B285. (*Traducción—Dr. Xavier Delgadillo*)

KEY WORDS: Anal intraepithelial neoplasia; Anal cancer; High-resolution anoscopy; high-resolution anoscopy; High-grade squamous intraepithelial lesion; Local recurrence; Surveillance.

Treatment for anal squamous cell carcinoma (ASCC) can offer long-term survival. Primary chemoradiation (CRT) is the mainstay, although T1 (<2 cm) fully excised perianal cancers may be treated with excision only (EO).[1] Anal squamous cell carcinoma is known to arise due to human papillomavirus and within a background of anal intraepithelial neoplasia, now termed high-grade squamous intraepithelial lesion (HSIL)[2,3]; it is considered potentially precancerous. For fully excised perianal T1[4] ASCCs with ≥1-mm margins, EO is acceptable if there is no regional spread.[1] Serendipitous excision of anal canal (AC) T1 ASCC can occur with some evidence of noninferior outcomes to CRT.[5] Nonetheless, EO remains controversial[6] and a prospective UK study is underway.[7] Patients with inadequate excision margins and those with greater than stage T1N0 disease are treated with adjuvant CRT. Local recurrence (LR) can occur after successful ASCC treatment,[4] with the LR rate after CRT being 9.89/1000 person-months.[8,9] However, this figure dates from 2005, and radiotherapy has improved since then.[10] Local recurrence after ASCC treatment results in morbid-

ity and potential mortality; long-term survival can require salvage abdominoperineal excision of the anorectum with permanent stoma.

United Kingdom guidance[1] on follow-up after ASCC treatment does not recommend high-resolution anoscopy (HRA) as part of follow-up. However, London regional guidelines recommend HRA in addition to clinical surveillance to detect LR (Table 1).[1,11] A recent UK article[9] suggested that HRA to detect and treat HSIL might reduce the LR rate after ASCC.

High-resolution anoscopy involves using a colposcope to magnify (up to ×30) and inspect the perianal and intraanal epithelium, with the application of 5% acetic acid, and Lugol iodine if required, to identify HSIL and confirm with biopsy under local anesthetic.[12] It is the standard for the detection of AC/perianal HSIL.[13] Units worldwide treat HSIL with topical or ablative surgical interventions to prevent the progression to ASCC.[3,14–16] A randomized controlled trial of anal HSIL treatment is in progress.[17] The pathophysiology of HSIL in LR after ASCC is not currently well understood, and the role of HRA in reducing LR after ASCC treatment is not yet established.[3,13]

The objectives of this study are to examine the HSIL detection and LR rates in a post-ASCC surveillance program at a national HRA referral center for the detection and treatment of HSIL.

MATERIALS AND METHODS

The prospectively collected database of a tertiary referral anal neoplasia unit receiving patients mainly from the region, but also from across the country, was interrogated for consecutive patients undergoing HRA surveillance after ASCC from 1998 to 2018. Six months follow-up from treatment completion, being either the end of CRT[18] or definitive EO surgery, was the minimum for inclusion in the study. There was a variation in how long after ASCC patients were referred to our center for HRA surveillance: the surveillance data are from patients followed from 2004 onward, but with cancers diagnosed from 1998 onward.

Anal squamous cell carcinoma treatment before HRA-led surveillance followed 1 of 2 pathways: CRT or EO with adequate margins. Cases with excision followed by adjuvant CRT are included in the CRT group (n = 6, data not shown). Outcomes were compared between the CRT and EO groups. Excision only lesions were excised with treatment of HSIL (if within our unit); other cases were referred from external units/hospitals for HRA follow-up at variable times after EO/CRT. Cases that crossed the anal verge were considered perianal if the operation could be completed without an anal speculum. The perianus was defined as the circumferential skin up to 5 cm from the anal verge,[4] but we have modified this definition to include the anal margin but not the vulvovaginal fourchette. Cases from external units were categorized as anal/perianal by the referring surgeon. The term "anal margin" was considered within the perianus. A small number of patients was referred for HRA surveillance only after they had undergone treatment for local recurrence(s) for an already treated (EO, CRT) primary ASCC. These were treated in the same manner within the program, but their outcome is considered separately.

If HSIL was suspected during surveillance, HRA-guided biopsies were taken. Targeted HSIL treatment was offered with ablation (laser under local or general anesthetic). High-resolution anoscopy surveillance was resumed thereafter.

Data collected included demographics, any immunosuppression, and previous anogenital cancers; index ASCC stage, treatment, date of diagnosis; subsequent diagnoses and treatments of anal HSIL and LR; regional/distant recurrence; death, cause of death, and survival; and length of follow-up.

The follow-up period is from the end of ASCC treatment until the most recent HRA. Data were censored when a patient withdrew from HRA surveillance, stopped attending, developed LR, or died (whichever happened first). For patients who left the program, data up to the most recent HRA are included.

Primary outcomes were rate of LR and time to first HSIL detection; secondary outcomes were number of HSIL treatments, death from any cause, ASCC-specific death, and lymph node metastases. Local recurrence was defined as any invasive cancer within the AC or perianus irrespective of the exact location of the primary tumor. This was due to the absence of accurate documentation regarding the exact site of the original ASCC in patients referred from other units.

Patients were excluded who did not attend at least 1 surveillance HRA 6 months after ASCC treatment; who had nonsquamous histology; and who experienced failure of primary CRT, defined as persistent invasive ASCC at or within 6 months of CRT.[18]

TABLE 1. London regional guidelines for HRA-led surveillance after anal squamous cell cancer[11]

Follow-up modality	*First 2 years*	*Thereafter*
Clinical examination and HRA	3–4 mo	6 mo until 5 y, then annual
PET scan	6 mo ± 3 mo	Only if concern for recurrence
MRI scan	6 mo	2 further scans until 3 y, then only if concern for recurrence
CT scan chest, abdomen, pelvis	12 mo	1 further scan at 3 y, then only if concern for recurrence

HRA = high-resolution anoscopy.

Ethics

Permission was granted from the local ethics board reference: 17/SC/0487.

Statistics

Outcome frequencies were compared between the EO and the CRT groups. Fisher exact 2-tailed test was used for comparison of categorical nominal values considering $p \leq 0.05$ as significant; 2-sample t test and Wilcoxon rank sum test were used for continuous data (parametric and nonparametric). Time to HSIL diagnosis was analyzed using Kaplan-Meier estimates with the log-rank test for significance between curves. Data were analyzed using SPSS (IBM, SPSS Software, version 19) and R (R Foundation for Statistical Computing, Vienna, Austria. ISBN 3-900051-07-0, URL http://www.R-project.org/).

RESULTS

Cohort Characteristics

Seventy-six cases of ASCC diagnosed between June 1998 and February 2018 were assessed for inclusion in the HRA surveillance program. Three (4%) were excluded because of nonsquamous histology and 10 (13%) because of persistent symptomatic primary tumor still present ≤6 months after CRT. Thus, 63 (83%) patients were identified as suitable for the program. Of these, 2 refused HRA surveillance and were followed up by their local team. Therefore, 61 of 63 (97%) patients underwent at least 1 HRA surveillance visit. One of 61 was found to have an asymptomatic persistent ASCC at initial HRA assessment 4 months after CRT and was sent for palliative chemotherapy. Thus, 60 patients were entered in the surveillance program (Fig. 1).

Seven patients were found to already have had a LR before the commencement of surveillance. These patients were thought likely to have a different risk of LR and are considered separately within this article.

Of the 53 remaining patients, 31 (58%) were men, of whom 18 (58%) identified as men who have sex with men. Thirteen of 22 women (59%) had diagnoses of HSIL/cancer at other lower anogenital tract sites either before or after ASCC diagnosis (9 HSIL, 4 cancer; Table 2). Fifteen of 53 (28%) patients were HIV positive, and 14 were otherwise immunocompromised. Data on immune status were missing in 10 presumed immunocompetent patients.

Thirty-three of 53 (62%) of the cancers were located in the perianus. Twenty-one of 33 (64%) of perianal lesions were treated with EO. All AC lesions were treated with CRT apart from 2 (10%) that were in the EO group, being fully excised ASCCs within a hemorrhoid specimen.

Outcomes of Surveillance Program

Of 30 patients who underwent chemoradiotherapy (including 1 who received radiotherapy alone), 4 (13%) were found to have at least 1 occurrence of anal HSIL on subsequent HRA during a median 46-month follow-up. The patient with radiotherapy alone was 1 of those subsequently found to have HSIL but did not develop LR. Seventeen (74%) of 23 patients in the EO group developed HSIL over a median of 39 months of HRA follow-up (Table 3). Time to first HSIL was significantly different by log rank test (Fig. 2).

The LR rate within the CRT group was 0.56/1000 person-months. This represented 1 perianal case (1/30, 3%, 46 months median follow-up), with LR 39 months after CRT for an unusual multifocal invasive perianal squamous cell carcinoma (SCC). High-grade squamous intraepithelial lesion was first detected in the perianus at 15 months after CRT but resolved. High-resolution anoscopy was negative for HSIL until 28 months, and HSIL was CO_2 laser-ablated in the right posterior and left anterior perianus at 30 months; biopsies were low grade at 35 months, but a right posterior perianal ulcer at 39 months contained ASCC (0.6-mm depth invasion). Excision showed no further invasive disease. The only risk factors were smoking and obesity (BMI 43). Difficulties included large surface area, multiple erythematous patches postradiotherapy, multiple warts, and patient tolerance of both local and general anesthetic because of size. A staged program of laser ablation of the entire perianus has been performed since. AC HSIL has also been ablated. There has been no further LR in 23 months of subsequent follow-up. There was no LR in the EO group.

High-grade squamous intraepithelial lesion was treated in 20 of 21 (95%) cases in the 53 patients with no prior LR. One (4%) patient underwent excision; the other 19 (85%) had laser ablation. One case resolved spontaneously. All 3 LR cases occurred after detection and treatment of HSIL by HRA.

To date, 2 patients have died within the HRA surveillance program (3.3%). Neither death was due to ASCC: one patient died of a midgut neuroendocrine tumor, and 1 patient with innate immunosuppression died of vaginal SCC.

There were no distant metastases and no deaths from ASCC in the HRA surveillance program. One further patient, still alive, was diagnosed with primary lung cancer during ASCC follow-up. No patient has undergone abdominoperineal excision.

Patients With Prior Local Recurrence

Seven patients had had a prior LR before entry into HRA surveillance. These were analyzed separately because of a higher risk of further LR.

Three of the 7 had had prior CRT treatment and excision of an LR before study entry. All 3 had further HSIL, and of these, one had a second LR treated with excision 8 months later in an adjacent site (Table 4).

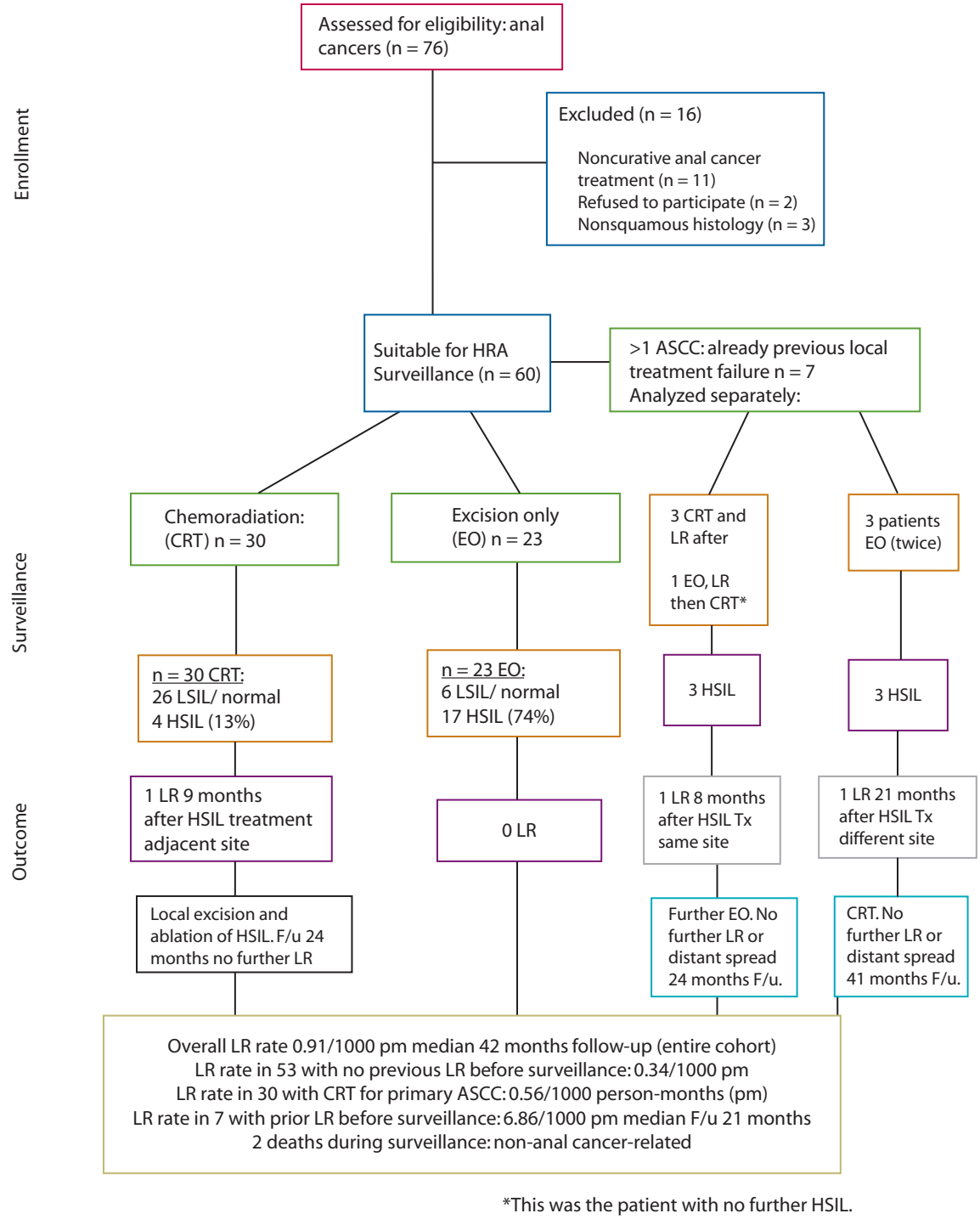

FIGURE 1. Flow chart for HRA after anal SCC. CRT = chemoradiation; EO = excision only; F/u = follow-up; HRA = high-resolution anoscopy; HSIL = high-grade squamous intraepithelial lesion; LR = local recurrence; LSIL = low-grade squamous intraepithelial lesion; pm = person-month; SCC = squamous cell carcinoma; Tx = treatment.

One patient who was referred for surveillance after EO of an AC ASCC was found to have LR at first HRA and was entered into surveillance after subsequent CRT. This patient had no further HSIL.

Of the 3 with no previous CRT, one had had EO of a primary ASCC, underwent laser ablation for a diffuse T2 perianal recurrence 4 years later (considered unfit for CRT because comorbidities), and then developed LR in the AC after 21 months and underwent CRT. The 2 others had an excision for T1 SCC with a further excision for LR before study entry.

In our surveillance program, 6 of the 7 patients had a mean of 2.5 HSIL episodes (1–4). All patients were treated

TABLE 2. Demographics and risk factors: follow-up after primary ASCC treatment

Demographics	*Chemoradiation*[a]	*Excision only*	*Overall*	*p value*
Number	30	23	53	
Mean age, y (range)	55 (39–72)	51 (27–75)	53	0.19
Sex M:F	19:11	12:11	31:22	0.57
MSM	12	6	18	0.222
Other genital HSIL/cancer (women)	4 HSIL, 1 cancer as well as HSIL	5 HSIL, 3 cancers as well as HSIL	9 HSIL, 4 cancers	0.328 (HSIL) 0.104 (cancer)
Persons living with HIV (all men), n (%)	10 (33)	5 (22)	15 (28)	0.28
Other immune compromise,[b] n (%)	7 (23)	7 (30)	14 (26)	0.75
Initial AJCC site and stage				
Site of anal cancer: anal vs perianal	18:12	2:21	20:33 (38% AC)	0.0006
Stage unknown, n (%)	1 (3)		1/53 (2)	
Stage 1, n (% total)	10 (33)	22 (96)	32/53 (60)	<0.0001
Stage 2, n (% total)	8 (27)	1 (4)	9/53 (17)	0.034
Stage 3 or 4, n (% total)	11 (37)	0	11/53 (21)	0.001

AC = anal canal; AJCC = American Joint Committee on Cancer; ASCC = anal squamous cell carcinoma; HRA = high-resolution anoscopy; HSIL = high-grade squamous intraepithelial lesion; MSM = men who have sex with men.
[a]One patient radiotherapy only.
[b]Other conditions causing immune compromise included liver transplant, connective tissue disease, rheumatoid arthritis, collagenous colitis, Kaposi sarcoma, diabetes mellitus, Crohn's disease, Churg-Strauss syndrome, renal transplant, lymphoma, severe combined immune deficiency, and innate CD4 lymphopenia.

with ablation. In 2 patients, there was a delay to treatment, leading to 9 months of delay in each case. The first, due to patient nonattendance, did not impact outcome. The second, due to patient treatment for vulval cancer at another hospital, may have contributed to the LR.

All 7 patients were still alive with no lymph node metastases or further LR at the end of the study. The rate of cancer in this group was 6.86/1000 person-months calculated from the time of most recent LR treatment before study entry until either the date of LR or their most recent HRA to December 2018. Follow-up was a median of 21 months (range 8–121).

DISCUSSION

High-grade squamous intraepithelial lesion is recognized as the likely precursor lesion for ASCC, and HRA is the standard technique for its detection.[3,13–16] However, little is known about the use of HRA in the post-ASCC setting, and no international standards exist for its use.

Because HSIL is potentially precancerous, it is likely that significant areas of concomitant HSIL were present in the patients with cancer and regressed or responded to CRT. Decreased HSIL occurrence following CRT supports this assumption. Furthermore, given the number of HSILs that developed in the EO group, which in some[19] but not all[20] studies is associated with a higher rate of LR, there may be a benefit from HRA and ablation influencing the relatively low LR rate.[21]

Interestingly, the CRT group originally had significantly worse prognosis, higher-stage ASCCs than the EO group, but developed fewer HSILs.

Excision alone of small anal/perianal cancers has had variable success,[19,20,22,23] but the use of EO is rising.[5] A population study of EO vs CRT showed reduced survival for EO after 80 months, despite the early stage; however, LR was not measured.[22]

A further study found a higher LR rate for EO vs CRT,[23] with 37% (of 52) EO cases recurring locoregionally within a 41-month median follow-up, which is a much higher rate than we observed. High-resolution anoscopy was not used, and HSIL was neither detected nor treated. Higher HSIL has previously been noted after the excision of 5 T1 cancers without vs 12 with adjuvant CRT.[24]

This evidence and our own study provide support for EO of <2 cm diameter node-negative lesions. Whether

TABLE 3. Outcome of surveillance: follow-up after primary ASCC treatment

Outcome	*Chemoradiation (n = 30)*	*Excision only (n = 23)*	*Overall (n = 53)*	*p value*
Median follow-up since cancer treatment, months (range)	45.6 (8–240)	38.6 (7–193)	41.8 (7–240)	0.484
HSIL since cancer treatment, n (%)	4 (13)	17 (74)	21/53 (40)	0.00001 log rank test, time to first HSIL (Fig. 2)
Treatment of HSIL, [a]n (%)	4/4 (100)	16/17 (94)	20/21 (95)	1.0
Local recurrence during HRA surveillance, n (%)	1 (3) 0.56/1000 p-m	0 0	1/53 (2) 0.34/1000 p-m	1.0

ASCC = anal squamous cell carcinoma; HRA = high-resolution anoscopy; HSIL = high-grade squamous intraepithelial lesion; p-m, person-months.
[a]1 resolved spontaneously.

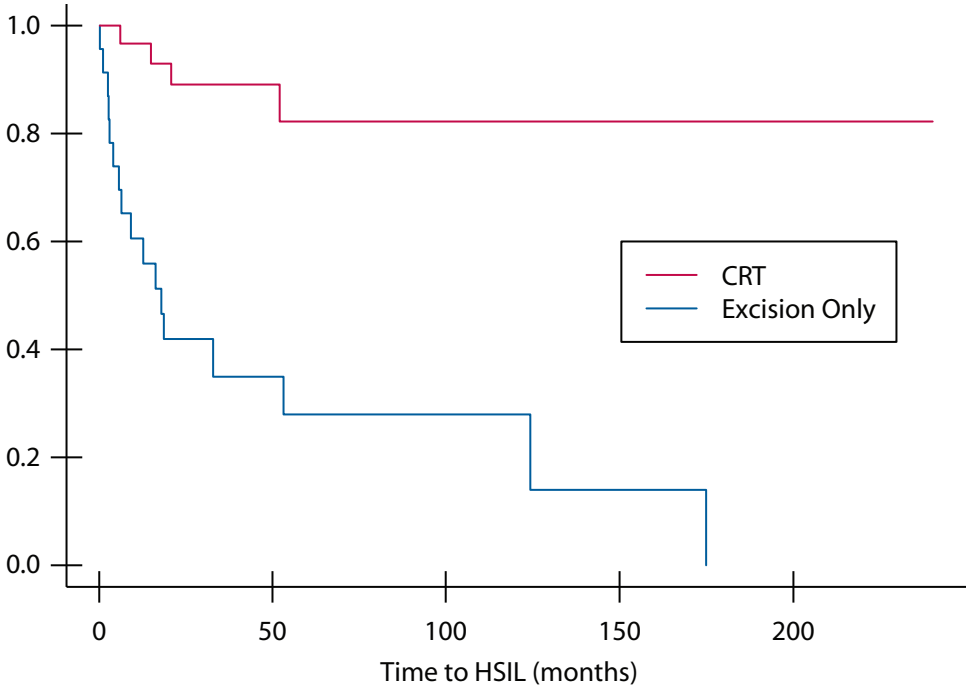

FIGURE 2. Time to first HSIL diagnosis by type of ASCC treatment, CRT or excision only of ASCC. ASCC = anal squamous cell carcinoma; CRT = chemoradiation; HSIL = high-grade squamous intraepithelial lesion. Log rank test $p < 0.0001$.

HRA with close follow-up and ablation of HSIL may reverse the concerning recurrence rates in EO cases in some articles[19,23] requires further study in clinical trials, but the data from our study are encouraging.

The high number of early-stage and perianal cancers in this cohort was because patients were referred for HRA surveillance after excision of small ASCC, which is primarily a perianal treatment modality, and because of our detection of unexpected small invasive ASCCs with HRA after referrals for HSIL treatment. In a number of cases, LR was found at first HRA after having been missed by the referring clinician who had not had HRA available. Finding early SCCs is a useful function of HRA in addition to identifying HSIL and is a further reason to consider HRA as part of post-ASCC surveillance.[3]

The overall LR rate of 0.91/1000 person-months is low compared to the expected LR rate from a 2005 UK article[8] of 9.89/1000 person-months calculated by Goon et al.[9] They contrasted this with their own LR rate of 1.98/1000 person-months in a pilot study of HRA and HSIL treatment after CRT for ASCC in 19 HIV-negative patients over a median of 19 months follow-up. Neither HSIL incidence nor treatment was reported. Their LR rate represented a 5-fold improvement from the 2005 data, albeit those data were from an era before modern radiotherapy techniques that have reduced LR rates.[10] Randomized controlled trial evidence often combines regional and local recurrence and is quoted as 25% at 5 years.[25] The overall LR rate of 0.91/1000 person-months in our cohort of 60 patients over 42 months follow-up represents a further 2-fold reduction over the Goon et al[9] figure, with over half having an immune compromise. This represents a 10-fold improvement from the 2005 LR rate.[8] These improvements in LR rate in both ours and Goon et al's figure may be due at least in part to HRA surveillance and HSIL treatment. The high-quality prospective cohort study in the PLATO umbrella series of trials, ACT 3, will provide interesting comparative data, because small fully excised cancers are being closely observed but without HRA or HSIL treatment.[26]

Within this study, there was only 1 de novo LR. This case occurred in a middle-aged heterosexual man whose unusual multifocal perianal invasive lesion had resulted in a wide radiotherapy field. His LR arose despite treatment but was excised at a microinvasive stage. This patient has been referred for immunological assessment. The other 2 cases were in patients who had already had 1 recurrence and appear to have been at higher risk of a second LR. All 3 have had further HSIL on surveillance that has been treated with no distant recurrence and no abdominoperineal excision. These numbers are too small to draw any further specific conclusions; however, the LR cases in this study were all T1N0M0. High-resolution anoscopy may downstage LR even if HSIL treatment does not prevent it. Further studies may determine potentially modifiable factors to improve the prevention of LR, such as closer follow-up intervals every 3 to 4 months or more intensive ablation.

TABLE 4. Patients with prior LR of ASCC at entry into HRA surveillance program

Patients with prior LR of ASCC	*Successful excision of LR after primary CRT*	*Excision only, LR, CRT*	*Excision only, excision of LR, then sent for surveillance*
Total number of patients	3	1	3
Further LR during surveillance	1	0	1
Details	Original ASCC: T2 AC 10 y before referral Risk factors: smoker; obesity Age: 50s. First LR: at referral for HRA: excision 1.1-mm depth 10-mm ASCC perianal "4 o'clock" HSIL treatment since: a) Ablation perianal HSIL at excision b) Five months later AC ablation HSIL Biopsy perianal left lateral: AIN2 Second LR: 2 mo later, left lateral perianal 3-mm horizontal, 1.5-mm depth. Treatment: excision Outcome: Since then HSIL laser ablation; no ASCC recurrence.		Original ASCC: T1N0M0 ASCC excised 4 y before referral Risk factors: obesity, diabetes mellitus Age: 40s Vulval SCC (excised) First LR: T2 perianal ASCC referred for laser; CRT not given due to comorbidities HSIL treatment since: a) Widespread HSIL staged laser ablation over 1 y b) Excision of second vulval SCC with perineal HSIL 1 y later. Delay to HRA surveillance. Second LR: 21 mo from previous, AC ASCC Treatment: CRT Outcome: HSIL laser ablation since; no ASCC recurrence.
No further LR during surveillance	2	1	2
Details	Original ASCC: CRT LR: at 6 and 1.5 y respectively Treatment: excision only and major excision with plastic surgical reconstruction Entered into program: Outcome: mean 3.5 HSILs treated Follow-up: 121 and 74 mo	Original ASCC: excision of anterior anorectal junction ASCC LR: first HRA: anal margin lesion referred for GA biopsy excision; LR also at anterior anorectal junction diagnosed. Treatment: CRT Entered into program: Outcome: no further HSIL 8 mo follow-up	Original ASCC: excision LR: 5 and 2 y after excision respectively Treatment: further excision with clear margins Outcome: both 1 HSIL treated Follow-up: 10 and 48 mo

AC = anal canal; AIN = anal intraepithelial neoplasia; ASCC = anal squamous cell carcinoma; CRT = chemoradiation; HRA = high-resolution anoscopy; HSIL = high-grade squamous intraepithelial lesion; LR = local recurrence.

None of our cohort has required abdominoperineal excision or developed metastatic disease. However, persistent HSIL was aggressively treated. High-grade squamous intraepithelial lesion cannot be reliably detected or targeted for treatment without HRA. In patients in whom radiotherapy is not an option because of prior treatment or other contraindications, EO of a perianal recurrence with close follow-up may be a viable alternative to abdominoperineal excision. However, great care needs to be taken in fully informing patients of the risks of this conservative approach.[1] Excision of LR is only feasible if it is found early and is excised with >1 mm clear margins, which is easiest to achieve in the perianus.

Limitations

This is a retrospective analysis of a prospectively collected data set. The retrospective nature of the data meant a power calculation a priori was not possible, and, hence, the study is likely underpowered. Because of the tertiary referral nature of the practice, our cohort may not be representative. There are notable background differences between groups brought out in the text.

CONCLUSIONS

Given that radiotherapy is highly morbid with negative effects on quality of life,[27] it is desirable to have a safe alternative technique to treat small ASCC. We have presented HRA surveillance with HSIL detection and treatment and the excision of appropriately selected LR. Early-stage diagnosis of LR and a low LR rate were observed.

Because of the high rate of observed HSIL after EO, we propose that HRA-led surveillance is required in these ASCCs with a good prognosis. More surgical units should consider training in HRA to detect and treat HSIL after ASCC treatment.

This is the largest study, to our knowledge, of patients after ASCC followed up with HRA. Further prospective studies of HRA in this population are needed to understand the optimal follow-up after CRT and EO, and to

evaluate the impact of HSIL treatment on LR, and ultimately survival.

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REFERENCES

1. Geh I, Gollins S, Renehan A, et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): guidelines for the management of cancer of the colon, rectum and anus (2017) - anal cancer. *Colorectal Dis.* 2017;19(suppl 1):82–97.
2. Darragh TM, Colgan TJ, Cox JT, et al; Members of LAST Project Work Groups. The Lower Anogenital Squamous Terminology Standardization Project for HPV-Associated Lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *J Low Genit Tract Dis.* 2012;16:205–242.
3. Berry JM, Jay N, Cranston RD, et al. Progression of anal high-grade squamous intraepithelial lesions to invasive anal cancer among HIV-infected men who have sex with men. *Int J Cancer.* 2014;134:1147–1155.
4. Gonzalez RS. *Pathologic TNM Staging of Anal Carcinomas (AJCC 8th edition).* PathologyOutlines.com http://www.pathologyoutlines.com/topic/anusstaging.html. Accessed January 1, 2020.
5. Chai CY, Tran Cao HS, Awad S, Massarweh NN. Management of stage I squamous cell carcinoma of the anal canal. *JAMA Surg.* 2018;153:209–215.
6. Renehan AG, Muirhead R, Sebag-Montefiore D. Limitations of the National Cancer Data Base to evaluate early-stage anal cancer treatment outcomes. *JAMA Surg.* 2018;153:691.
7. PLATO - Personalising anal cancer radiotherapy dose. ISRCTN Registry. https://doi.org/10.1186/ISRCTN88455282. Accessed December 29, 2019
8. Renehan AG, Saunders MP, Schofield PF, O'Dwyer ST. Patterns of local disease failure and outcome after salvage surgery in patients with anal cancer. *Br J Surg.* 2005;92:605–614.
9. Goon P, Morrison V, Fearnhead N, et al. High resolution anoscopy may be useful in achieving reductions in anal cancer local disease failure rates. *Eur J Cancer Care (Engl).* 2015;24:411–416.
10. Mitra D, Hong TS, Horick N, et al. Long-term outcomes and toxicities of a large cohort of anal cancer patients treated with dose-painted IMRT per RTOG 0529. *Adv Radiat Oncol.* 2017;2:110–117.
11. Standards for patients diagnosed with anal cancer in the London Cancer Integrated Cancer System (incorporating Operational Policy and Guidelines). May 2014. http://www.londoncancer.org/media/72800/london-cancer-anal-cancer-guidelines-final-v1.1.pdf. Accessed February 3, 2020.
12. Jay N, Berry JM, Miaskowski C, et al. Colposcopic characteristics and Lugol's staining differentiate anal high-grade and low-grade squamous intraepithelial lesions during high resolution anoscopy. *Papillomavirus Res.* 2015;1:101–108.
13. Hillman RJ, Cuming T, Darragh T, et al. 2016 IANS International Guidelines for Practice Standards in the Detection of Anal Cancer Precursors. *J Low Genit Tract Dis.* 2016;20:283–291.
14. Goldstone SE, Johnstone AA, Moshier EL. Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. *Dis Colon Rectum.* 2014;57:316–323.
15. Richel O, de Vries HJ, van Noesel CJ, Dijkgraaf MG, Prins JM. Comparison of imiquimod, topical fluorouracil, and electrocautery for the treatment of anal intraepithelial neoplasia in HIV-positive men who have sex with men: an open-label, randomised controlled trial. *Lancet Oncol.* 2013;14:346–353.
16. Nathan M, Hickey N, Mayuranathan L, Vowler SL, Singh N. Treatment of anal human papillomavirus-associated disease: a long term outcome study. *Int J STD AIDS.* 2008;19:445–449.
17. Topical or Ablative Treatment in Preventing Anal Cancer in Patients with HIV and Anal High-Grade Squamous Intraepithelial Lesions (ANCHOR). ClinicalTrials.gov Identifier: NCT02135419. https://clinicaltrials.gov/ct2/show/NCT02135419?id=NCT02135419&draw=2&rank=1&load=cart. Accessed on January 1, 2020.
18. Glynne-Jones R, Sebag-Montefiore D, Meadows HM, et al; ACT II study group. Best time to assess complete clinical response after chemoradiotherapy in squamous cell carcinoma of the anus (ACT II): a post-hoc analysis of randomised controlled phase 3 trial. *Lancet Oncol.* 2017;18:347–356.
19. Deshmukh AA, Zhao H, Das P, et al. Clinical and economic evaluation of treatment strategies for T1N0 anal canal cancer. *Am J Clin Oncol.* 2018;41:626–631.
20. Alfa-Wali M, Dalla Pria A, Nelson M, Tekkis P, Bower M. Surgical excision alone for stage T1 anal verge cancers in people living with HIV. *Eur J Surg Oncol.* 2016;42:813–816.
21. Gilbert DC, Wakeham K, Langley RE, Vale CL. Increased risk of second cancers at sites associated with HPV after a prior HPV-associated malignancy, a systematic review and meta-analysis. *Br J Cancer.* 2019;120:256–268.
22. Suradkar K, Pappou EE, Lee-Kong SA, Feingold DL, Kiran RP. Anal canal squamous cell cancer: are surgical alternatives to chemoradiation just as effective? *Int J Colorectal Dis.* 2018;33:181–187.
23. Leon O, Hagberg O, Johnsson A. Primary surgery with or without postoperative radiotherapy in early stage squamous cell carcinoma in the anal canal and anal margin. *Acta Oncol.* 2018;57:1209–1215.
24. Arana R, Fléjou JF, Si-Mohamed A, Bauer P, Etienney I. Clinicopathological and virological characteristics of superficially invasive squamous-cell carcinoma of the anus. *Colorectal Dis.* 2015;17:965–972.
25. Northover J, Glynne-Jones R, Sebag-Montefiore D, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). *Br J Cancer.* 2010;102:1123–1128.
26. Renehan AG, Muirhead R, Berkman L, McParland L, Sebag-Montefiore D; PLATO trial management group. Early stage anal margin cancer: towards evidence-based management. *Colorectal Dis.* 2019;21:387–391.
27. Sodergren SC, Johnson CD, Gilbert A, et al; EORTC Quality of Life Group. Phase I-III development of the EORTC QLQ-ANL27, a health-related quality of life questionnaire for anal cancer. *Radiother Oncol.* 2018;126:222–228.