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Original Article

Long-term efficacy of surgical excision followed by delayed adjuvant imiquimod in the treatment of perianal condyloma acuminata

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Abstract

Aim: Perianal condyloma acuminata (CA) is a common sexually transmitted disease caused by human papillomavirus (HPV), characterized by high recurrence rates following monotherapies. While surgical modalities provide rapid clearance, they often fail to eliminate subclinical viral reservoirs in surrounding tissue. This study evaluates the long-term efficacy and recurrence outcomes of a combined therapeutic protocol involving surgical excision followed by delayed adjuvant topical imiquimod.
Materials and Methods: In this single-center retrospective cohort study, 31 patients treated for perianal CA between 2014 and 2022 were analyzed. The treatment protocol consisted of surgical excision and electrocauterization of all macroscopic lesions, with wounds left for healing by secondary intention. Delayed adjuvant 5% imiquimod cream was initiated on postoperative day 15 and applied once daily for 16 weeks. Recurrence was assessed at two levels: clinical recurrence (new visible lesions on examination) and virological recurrence (positive HPV DNA detection).
Results: Thirty-one patients (24 males, 7 females; mean age 38.5±17.7 years) were included. Lesions were confined to the perianal region in 80.6%. The mean follow-up duration was 29.4 months (range: 12–72 months). All patients completed the protocol without major complications or treatment discontinuation. Among 20 patients (64.5%) with regular clinical follow-up, no clinical recurrence was observed (0/20). Among 10 patients with complete follow-up including HPV DNA screening, virological recurrence was detected in 2 patients (20%).
Conclusion: Surgical excision followed by delayed adjuvant imiquimod therapy appears to be a safe and effective strategy for the management of perianal CA, yielding 0% clinical recurrence and 20% virological recurrence over a median follow-up of 22 months. These findings should be confirmed by prospective studies with larger cohorts.

Keywords: Condylomata acuminata, surgical excision, imiquimod, recurrence, human papillomavirus, anogenital warts

INTRODUCTION

Condyloma acuminata (CA), primarily caused by human papillomavirus (HPV) types 6 and 11, is one of the most common sexually transmitted infections worldwide, with a significant impact on quality of life due to its recurrent nature and psychosocial burden (1). Although the global incidence varies, it is estimated to range from 160 to 289 cases per 100.000 person-years, with a peak prevalence in sexually active young adults (2).

The management of perianal CA—a subset of anogenital CA localized to the perianal region—presents a therapeutic challenge because no single treatment modality has been proven to be uniformly effective in preventing recurrence. Current treatment guidelines categorize interventions into patient-applied therapies (e.g., imiquimod, podophyllotoxin) and provider-administered therapies (e.g., cryotherapy, electrosurgery, surgical excision) (1,3). While ablative techniques are highly effective for the rapid clearance of visible lesions, they are associated with high clinical recurrence rates ranging from 19% to 77% in the long term (4,5).

This high recurrence is largely attributed to subclinical viral persistence in the clinically normal-appearing skin surrounding treated lesions, which ablative methods fail to eradicate (2).

Unlike ablative methods that target only visible lesions, topical immunomodulators such as imiquimod stimulate the local production of cytokines—including interferon-alpha (IFN-α), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α)—thereby enhancing the host's cellular immunity against the virus (6). In a recent comprehensive review, Bıyık Özkaya et al. reported that imiquimod 5% monotherapy achieves approximately 50% complete clearance with a 13% recurrence rate, noting that three-times-weekly application is a commonly used regimen, although daily dosing has also been employed in clinical practice (7). However, monotherapy with immunomodulators may have slower clearance rates for large or keratinized lesions compared to surgical methods (8).

Recent evidence, including randomized controlled trials and observational studies, supports a multimodal approach for superior disease control. A comprehensive network meta-analysis demonstrated that surgical excision and electrosurgery are superior to other monotherapies in achieving initial complete clearance (9). Furthermore, a systematic review of 37 randomized controlled trials indicated that combining ablative therapy with adjuvant self-administered immunotherapy, including imiquimod, yields significantly higher sustained clearance rates compared to ablation alone (10). The biological rationale for this combination is that surgical debulking eliminates macroscopic disease while subsequent immune activation targets residual subclinical viral reservoirs.

Despite these findings, data on the optimal timing of adjuvant imiquimod initiation following surgical excision remain scarce. This study evaluates the long-term efficacy of a conceptual "debulk and defend" protocol—surgical excision of all macroscopic lesions followed by daily 5% imiquimod initiated on postoperative day 15, after initial wound epithelialization—in patients with perianal CA. We aimed to assess both clinical and virological recurrence outcomes over long-term follow-up.

MATERIALS AND METHODS

Study Design and Patient Selection

This single-center retrospective cohort study was conducted at the Proctology Clinic of the Department of General Surgery of a tertiary university hospital, between 2014 and 2022. The study was approved by the İnönü University Health Sciences Scientific Research Ethics Committee (Decision Date: 16.06.2020, Decision No: 2020/803) and was conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent regarding the surgical procedure and the long-term follow-up process was obtained from all patients.

The study included 31 consecutively enrolled adult patients (aged ≥18 years) diagnosed with perianal CA who underwent a combined treatment protocol comprising surgical excision followed by adjuvant topical imiquimod therapy. Inclusion criteria were: (1) histopathologically confirmed diagnosis of CA; (2) lesions localized to the perianal region, with or without extension to adjacent genital areas; (3) age ≥18 years; and (4) availability of follow-up data. Exclusion criteria were: (1) immunocompromised status or active immunosuppressive drug use (Human immunodeficiency virus (HIV)-positive patients were not excluded, as CA is highly prevalent in this population and their inclusion was considered relevant to recurrence outcomes); (2) concurrent anogenital malignancies; (3) pregnancy or lactation; and (4) known allergy to imiquimod.

Demographic data (age, sex), clinical characteristics (lesion localization), HIV serostatus, previous treatment history, and recurrence outcomes were systematically extracted from the hospital database by three investigators (E.Ş., A.T., E.K.). Patients for whom follow-up data were unavailable were analyzed only within the subset for which data existed; no imputation was performed for missing values. Lesion localization was categorized as "perianal only" or "multiple localizations" (perianal plus adjacent genital involvement).

Surgical Technique

All surgical procedures were performed by two experienced colorectal surgeons under spinal anesthesia, following a standardized protocol, with the patient in either the lithotomy or jackknife position. The anal canal was examined in detail using an anoscope to identify and map all lesions, including those extending into the dentate line. Visually prominent condylomatous lesions (>5 mm) were surgically excised using electrocautery; smaller, millimetric lesions (≤5 mm) were treated with electrocoagulation. Hemostasis was achieved using electrocautery. Excision sites were not sutured and were left to heal by secondary intention to minimize infection risk, facilitate drainage, and reduce the risk of burying residual HPV-infected epithelium. Subclinical lesion mapping with acetic acid was not performed, as this was not part of the routine clinical protocol. All excised tissue samples were sent for histopathological verification, including screening for dysplasia or malignancy.

Postoperative Management and Follow-up Protocol

To allow for initial wound epithelialization—typically completed within two weeks following perianal surgery—adjuvant therapy was initiated on postoperative day 15 as a standardized time point. All patients were prescribed 5% imiquimod cream applied once daily to the affected area for 16 weeks. Although the commonly recommended regimen is three times per week, daily application was employed based on clinical experience and the aim of maximizing local immune stimulation in the moist perianal environment, where drug retention may be reduced; this rationale is hypothesis-based rather than pharmacokinetically validated.

Patients were evaluated clinically at the first postoperative month to assess wound healing and review pathology results. To monitor for recurrence, patients underwent physical examination at 3-month intervals during the first year and at 6-month intervals in subsequent years. At the end of the first year, HPV DNA screening was performed via polymerase chain reaction (PCR)-based swab sampling from the anal canal and perianal tissue in patients who consented and completed the minimum 12-month follow-up. Compliance was assessed through patient self-report and clinical evaluation at scheduled follow-up visits. Postoperative complications were monitored at each visit.

Recurrence Assessment

Recurrence was assessed at two levels: (1) clinical recurrence, defined as new visible condyloma lesions detected on physical examination by the treating surgeon during scheduled follow-up visits; and (2) virological recurrence, defined as positive HPV DNA detection (any HPV subtype, as genotyping was not available).

Patients were stratified into two groups: the clinical follow-up group (regular physical examinations without HPV DNA screening) and the complete follow-up group (clinical visits plus HPV DNA screening at ≥12 months). Of the 31 patients, 20 constituted the clinical follow-up group. Among these, 12 met the ≥12-month criterion with clinical visits; however, two did not undergo HPV DNA screening. The remaining 10 patients constituted the complete follow-up group.

Statistical Analysis

Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were expressed as mean±standard deviation (SD) and compared using the Independent Samples t-test; non-normally distributed variables were expressed as median (minimum–maximum) and compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the Chi-square or Fisher's Exact test. All tests were two-tailed, and a p-value of <0.05 was considered statistically significant. The analysis was descriptive and exploratory in nature; confidence intervals were not calculated due to the small sample size.

RESULTS

A total of 31 patients were included. The mean age was 38.5±17.7 years (range: 18–79), with a median of 34 years. The study population consisted of 24 males (77.4%) and 7 females (22.6%), with a male-to-female ratio of 3.4:1. The highest incidence was observed in the 18–30 age group (n=14, 45.2%), followed by 31–50 (n=10, 32.3%) and 51–80 (n=7, 22.6%). In an exploratory analysis, there was no statistically significant difference in mean age between male (37.1±15.8) and female (43.1±23.9) patients (p=0.435). Demographic and clinical characteristics are summarized in Table 1.

Table 1. Demographic and clinical characteristics of the patients (n=31)

Characteristic	Value
Total patients, n	31
Gender, n (%)	
Male	24 (77.4%)
Female	7 (22.6%)
Male/Female ratio	3.4:1
Age (years)	
Mean±SD	38.5±17.7
Median (range)	34 (18–79)
Age groups, n (%)	
18–30 years	14 (45.2%)
31–50 years	10 (32.3%)
51–80 years	7 (22.6%)
Lesion localization, n (%)	
Perianal only	25 (80.6%)
Multiple localization	6 (19.4%)
HIV status (n=29 tested)	
Positive	2 (6.9%)
Negative	27 (93.1%)
Histopathology (n=29 available)	
Condyloma acuminata	26
Buschke–Löwenstein tumor	1
Anal intraepithelial neoplasia	2
Follow-up (months)	
Mean±SD	29.4±19.3
Median (range)	22 (12–72)

HIV: Human immunodeficiency virus; SD: Standard deviation. Two patients were not tested for HIV and two had unavailable pathology reports

Lesions were confined to the perianal region in 25 patients (80.6%). Multiple localizations were observed in 6 patients (19.4%), including perianal with concomitant scrotal and penile involvement (n=2), perianal with penile (n=1), perianal with pubic (n=1), perianal with scrotal (n=1), and perianal with vaginal involvement (n=1). Histopathological examination was available for 29 of 31 patients. Among confirmed cases, CA was identified in 26 specimens, Buschke–Löwenstein tumor in one, and anal intraepithelial neoplasia (AIN) in two cases (AIN 1 in one; AIN 3 in one). All patients, including those with non-CA histopathological diagnoses, were included in the outcome analysis, as the same treatment protocol was applied; however, differential outcome analysis by histopathological subtype was not performed due to the small numbers. HIV testing was performed in 29 patients; 2 patients (6.9%) were HIV-positive, both male.

All 31 patients successfully completed the surgical excision followed by the 16-week adjuvant imiquimod therapy protocol

without major complications or treatment discontinuation. Minor local side effects, including transient erythema and irritation, were observed in a subset of patients, for whom brief treatment interruptions of 4–5 days were permitted before resuming the full course. The mean follow-up duration was 29.4±19.3 months (median: 22 months; range: 12–72 months).

Of the 31 patients, 20 (64.5%) attended regular clinical follow-up examinations. No clinical recurrence—defined as new visible condyloma lesions—was observed in any of these 20 patients (0%, 0/20). The remaining 11 patients (35.5%) were lost to follow-up due to phone disconnection, relocation, or emigration; this differential attrition may introduce selection bias.

Among the 20 patients with clinical follow-up, 10 also completed HPV DNA screening, constituting the complete follow-up group. Virological recurrence (positive HPV DNA detection) was detected in 2 of these 10 patients (20%). One female patient had virological recurrence at 7 months postoperatively, was successfully treated with a second excision and imiquimod course, and showed no further recurrence during subsequent follow-up. The second virological recurrence was documented in a male patient during the observation period. In both patients, no visible clinical lesions were present at the time of HPV DNA positivity. HPV subtype data were not available, as genotyping was not part of the routine protocol. Recurrence and follow-up outcomes are detailed in Table 2.

Table 2. Treatment outcomes and recurrence rates

Parameter	Value
Total patients treated	31
Treatment regimen	Surgery+Imiquimod (16 weeks)
Follow-up, mean±SD (months)	29.4±19.3
Follow-up, median (range)	22 (12–72)
Tier 1: Clinical follow-up (physical examination)	
Patients with clinical follow-up	20/31 (64.5%)
Clinical recurrence (new visible lesions)	0/20 (0%)
Lost to follow-up	11/31 (35.5%)
Tier 2: Complete follow-up (clinical + HPV DNA)	
Patients with complete follow-up	10/31 (32.3%)
Virological recurrence (HPV DNA positive)	2/10 (20%)
No recurrence	8/10 (80%)
Complications	
Wound infection	0
Anal incontinence	0
Anal stenosis	0
Severe bleeding	0

HPV: Human papillomavirus. Tier 1 (Clinical follow-up): patients who attended scheduled physical examinations. Tier 2 (Complete follow-up): patients who completed both clinical visits and HPV DNA screening at ≥12 months of follow-up

Regarding safety, no wound infections, anal incontinence, anal stenosis, or major bleeding complications were reported. Minor wound-related issues were managed conservatively with local care. Imiquimod-related side effects were not systematically recorded in the retrospective dataset; however, the absence of treatment discontinuations suggests overall tolerability.

DISCUSSION

The primary challenge in managing perianal CA is not initial clearance but preventing recurrence—the main determinant of long-term treatment success—which places a significant psychological and economic burden on patients (1). In this study, our "debulk and defend" strategy yielded 0% clinical recurrence among 20 patients with regular follow-up and 20% virological recurrence among 10 patients who completed HPV DNA screening, over a mean follow-up of 29.4 months (median: 22 months). These findings should be interpreted with caution given the limited subgroup sizes.

The distinction between clinical and virological recurrence is clinically meaningful and represents the core contribution of this study. Literature indicates that most visible recurrences occur within the first 3–6 months, with approximately 83% manifesting within 12 months (11). The absence of new visible lesions in all 20 monitored patients after a median of 22 months suggests durable macroscopic disease clearance. The two virological recurrences, detected only by HPV DNA screening in the absence of visible lesions, likely represent subclinical viral persistence rather than true treatment failure—a well-recognized phenomenon in HPV biology (2). Isolated HPV DNA positivity does not necessarily predict future clinical recurrence, as immune-mediated viral clearance without overt disease manifestation has been documented. However, virological outcomes in this study are based on a very small subset (n=10), substantially limiting their interpretability.

Current guidelines and meta-analyses indicate that surgical excision and electrosurgery achieve the highest initial clearance rates (94–100%) but carry clinical recurrence rates of 19–29% as monotherapies (9,12). Some long-term studies report rates as high as 77% (2,4). However, these figures should be interpreted in the context of considerable heterogeneity across studies regarding patient populations, follow-up durations, and treatment protocols. Our combined approach, yielding 0% clinical recurrence, compares favorably with the 20–50% rates typically reported for surgical monotherapy (5,13), although this comparison is limited by our retrospective design, small sample size, and incomplete follow-up.

The rationale for this combined approach is supported by systematic reviews. Feng et al. analyzed 37 randomized controlled trials and concluded that combining ablative therapy with self-administered treatment yields significantly higher sustained clearance compared to ablation alone (10). Imiquimod stimulates the release of interferon-alpha, IL-6, and TNF-alpha, inducing a T-cell memory response that targets residual

microscopic disease and may thereby reduce recurrence risk (6,14). However, the magnitude of this immune response is subject to individual variability, which may partly account for the virological recurrences observed in our cohort.

The dependence of imiquimod efficacy on intact cellular immunity was illustrated in a case report by Kennoki et al., who demonstrated that Janus kinase 1 (JAK1) inhibitor therapy appeared to impair imiquimod's ability to clear anogenital warts (15). While this single observation cannot be directly generalized, it underscores the broader principle that immune status is a key determinant of treatment success—a relationship relevant to our cohort, which included two HIV-positive patients who nonetheless completed the protocol without recurrence.

A distinctive and less-studied feature of our protocol was delayed imiquimod initiation on postoperative day 15, allowing wound epithelialization prior to immune modulation. Applying immunomodulators to fresh surgical wounds can cause systemic absorption and severe local inflammatory reactions, potentially compromising compliance (16). The delayed strategy in our cohort was associated with 100% treatment completion, suggesting improved tolerability compared to immediate-start protocols, though direct comparative data are lacking. This approach is supported by a prospective study by Hoyme et al., who reported 11.8% recurrence with adjuvant imiquimod initiated after wound healing following laser ablation in 211 patients with external anogenital warts, using a three-times-weekly regimen over 12 weeks (17)—differing from our perianal-specific cohort, daily dosing, and 16-week duration.

Our once-daily regimen represents a non-standard schedule compared to guideline-recommended three-times-weekly dosing (7,18). This frequency was selected to maximize local immunostimulatory exposure in the perianal region, where the moist environment may reduce drug contact time; this rationale is hypothesis-based and dose-optimization studies are warranted. The delayed start likely mitigated adverse reactions, as all patients tolerated daily application without discontinuation.

The study included one histopathologically confirmed Buschke–Löwenstein tumor. This represents a single case observation; the absence of recurrence during 51 months of follow-up does not allow conclusions regarding efficacy, and prospective studies are needed to evaluate adjuvant imiquimod in aggressive variants (19).

Limitations

This study is limited by its retrospective design, small sample size (n=31), and lack of a control group. Virological recurrence outcomes are based on only 10 patients, substantially limiting interpretability. The 35.5% attrition rate, while consistent with sexually transmitted infection research literature, may bias outcomes toward lower recurrence in retained patients (5). The once-daily dosing differs from the standard three-times-weekly protocol, limiting external comparability and guideline alignment. The inclusion of histopathologically heterogeneous entities—AIN and Buschke–Löwenstein tumor—alongside CA may affect outcome interpretation. Despite these limitations, the median follow-up of 22 months provides valuable preliminary data on the durability of the therapeutic response.

CONCLUSION

Perianal CA should be managed as a chronic viral condition rather than a simple surgical problem. Our results suggest that a combined protocol of surgical excision followed by delayed adjuvant imiquimod therapy (starting day 15) appears to be a safe and effective strategy. This protocol yielded 0% clinical recurrence among patients with regular follow-up and 20% virological recurrence among those with complete HPV DNA screening—a distinction that represents the core contribution of this study—over a median follow-up of 22 months. These findings may not be generalizable given the retrospective design and small sample size; patients with recurrent or extensive disease may represent the subgroup most likely to benefit. Prospective, randomized controlled trials with standardized follow-up protocols are needed to validate these findings.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that there is no financial support.

Ethical Approval
The study protocol received approval from the İnönü University Health Sciences Scientific Research Ethics Committee (Decision Date: 16.06.2020, Decision No: 2020/803).

Patient Consent
Not necessary for this manuscript.

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