South Afr J Gynaecol Oncol. 2026;18:7-12
https://doi.org/10.36303/SAJGO.418

South Afr J Gynaecol Oncol
ISSN 2074-2835 EISSN 2220-105X

ORIGINAL RESEARCH

Multizonal intraepithelial neoplasia (MUZIN) of the lower genital tract: a descriptive review of the management of women with MUZIN at a single institution

H Minter-Brown,[1] R Saidu,[1,2] T Adams[1,2,3]

[1] *Department of Obstetrics and Gynaecology, Groote Schuur Hospital, University of Cape Town, South Africa*
[2] *University of Cape Town Gynaecological Cancer Research Centre, South Africa*
[3] *Division of Global Surgery, Department of Surgery, University of Cape Town, South Africa*
Corresponding author, email: hayleyminterbrown@gmail.com

Background: Multizonal intraepithelial neoplasia (MUZIN) of the lower genital tract occurs when women present with more than one intraepithelial neoplasia lesion associated with human papilloma virus (HPV). This study reviews the management of women diagnosed with MUZIN at Groote Schuur Hospital (GSH) in 2018.
Methods: A retrospective analysis of 104 women diagnosed with MUZIN at the colposcopy clinic was performed. Patient demographics, disease areas, management, histology, follow-up, and recurrences were recorded.
Results: In 2018, 653 women attended the colposcopy clinic at GSH. Of these, 104 women had evidence of MUZIN, providing an incidence of 16%. A total of 90 folders were analysed. Multiple anatomical areas were affected, with the cervix and vulva as the most frequent combination (n = 26, 28.9%). Initial management of women with MUZIN was as outpatients (n = 46, 51.1%), as inpatients (n = 16, 17.8%), or as out- and inpatients (n = 23, 25.6%). Large loop excision of the transformation zone (LLETZ) was the most common outpatient procedure (45.6%), and vulval excision was the most common inpatient procedure (14.4%). Of the 72 histological specimens, 58 (80.6%) were premalignant, and 13 (18%) were malignant. Of the women, 16 had recurrences, and 64.4% were lost to follow-up.
Conclusion: Multiple procedures are often needed, and long-term follow-up is imperative to diagnose and treat recurrences. In this study, we acknowledge that many women may have been lost to follow-up due to the COVID-19 pandemic.
Keywords: multizonal intraepithelial neoplasia, multifocal disease, human papilloma virus, lower genital tract, human immunodeficiency virus

Introduction

Little data is published on MUZIN. Traditionally, clinicians focus on a single organ affected by HPV disease (e.g. the cervix, vulva, perianal area, or oropharynx). We observed an increasing number of women with disease of more than one zone of the lower genital tract, especially in our setting in South Africa, with our high HIV prevalence and its association with HPV.[1,2] MUZIN occurs when patients present with more than one intraepithelial neoplasia lesion associated with HPV.[3,4]

Immune-deficient patients have a higher chance of developing subsequent invasive malignancies from their precancerous lesions. This is due to their inability to clear the HPV infection, leading to persistent HPV infection and increased lower genital tract malignancies.[5] Patients with MUZIN require long-term surveillance and often more extensive surgical procedures. Management options aim to eradicate the precancerous lesions, which are often mutilating and can lead to an altered self-image. Even after surgery, the risk of recurrence remains high.

The women who most often present with MUZIN are young, sexually active, and in their reproductive years. Consequently, management is frequently complicated, as these women mainly desire future fertility, which should be considered when surgery is necessary. Other considerations include hospitalisation time, days off work, and follow-up intervals, as these women are often caregivers or primary breadwinners in their families.

The MUZIN entity requires more description, and this study aims to contribute to this knowledge, especially in a middle-income setting such as South Africa. Adams et al.[6] previously published on the demographic characteristics of women attending the colposcopy clinic in 2018. This study aims to perform a retrospective analysis of these participants' clinicopathological data, specifically reviewing their management and follow-up course.

Methodology

Study design

This was a retrospective descriptive analysis of patients diagnosed with MUZIN who attended the colposcopy clinic at GSH in 2018.

Study population

All women who attended the colposcopy clinic at GSH were entered into a database. Patients diagnosed with MUZIN with evidence of HPV disease based on clinical findings, cytology, histology, or a combination of these, were selected. Patients were excluded if their colposcopy data were missing, if their

medical records were incomplete, or if they had obvious cancers at presentation.

Data collection

The University of Cape Town Gynaecological Cancer Research Centre houses a colposcopy database (reference 344/2011) of women attending the colposcopy clinic. This database documents all anatomical areas involved with HPV-associated lower genital tract disease. A medical record review was performed, and all collected data were entered into a data collection sheet and an Excel spreadsheet.

Ethical considerations

Permission to conduct the study was granted by the University of Cape Town Human Research Ethics Committee (reference 720/2023). This review was in keeping with the Declaration of Helsinki.[7]

Objectives

The study objectives were to describe the anatomical areas of the lower genital tract affected at initial presentation and patient management. We documented how many women had outpatient management compared with those who required inpatient management, and the type of intervention they received. We reviewed the histology of the lesions and each patient's follow-up course, including any lesion recurrences, to June 2023. We also documented whether any women were lost to follow-up during this time.

Statistical analysis

Data analysis was performed with IBM SPSS Statistics version 29.0.2.0 for Windows (released 2023, International Business Machines Corporation, Armonk, United States). Continuous data were presented as medians and interquartile ranges (IQR), and categorical data were presented as frequencies and percentages. Tables and charts were used for data visualisation.

Results

A total of 653 women attended the colposcopy clinic at GSH in 2018. Of these, 104 women had evidence of MUZIN (16% prevalence). We excluded 14 women: two patient records were missing, four women had obvious malignancies and were referred to oncology clinics, and eight were excluded due to missing information in their medical records. Therefore, 90 cases were analysed.

The women's median age was 33.0 years (IQR 28.0–40.8), with a minimum of 18 and a maximum of 68. The median parity was 2.0 (IQR 1.0–3.0), with a minimum of 0 and a maximum of 7. Table I describes the demographics and income status of the 90 women in the study. Most women were HIV positive (n = 77, 85.6%).

Table I: Demographic and clinical characteristics of women with multizonal intraepithelial neoplasia

Variable	n = 90 n (%)
Age group	
< 20	3 (3.3)
21–30	28 (31.2)
31–40	36 (40.0)
41–50	19 (21.1)
51–60	3 (3.3)
> 60	1 (1.1)
Human immunodeficiency virus	
Negative	13 (14.4)
Positive	77 (85.6)
Income	
Employed	34 (37.8)
Self-employed	3 (3.3)
Unemployed	29 (32.2)
Student	6 (6.7)
Others (grant, pension)	12 (13.3)
Unknown	6 (6.7)
Smoking	
No	68 (75.6)
Yes	19 (21.1)
Unknown	3 (3.3)
Menopause	
No	80 (88.9)
Yes	9 (10.0)
Unknown	1 (1.1)
Contraception	
None	26 (28.9)
Injectable	29 (32.2)
Combined oral contraceptive	2 (2.2)
Implant	3 (3.3)
Condoms	10 (11.1)
Sterilisation	5 (5.6)
Intrauterine contraceptive device	2 (2.2)
Not applicable (menopausal)	9 (10)
Unknown	4 (4.5)

Anatomical sites affected by multizonal intraepithelial neoplasia

Multiple anatomical areas were affected in differing combinations, with the cervix and vulva as the most frequent combination in 26 cases (28.9%). Figure 1 illustrates the number of anatomical site combinations in the study population.

Management

Initial management of the women with MUZIN was mostly as outpatients (n = 46, 51.1%), some as inpatients (n = 16, 17.8%), and others as out- and inpatients (n = 23, 25.6%). Five women (5.5%) had no record of management, primarily because they were lost to follow-up before definitive management was received.

The women received various forms of management, including surgical, ablative, and medical procedures (Table II). These procedures were performed either as a single modality or

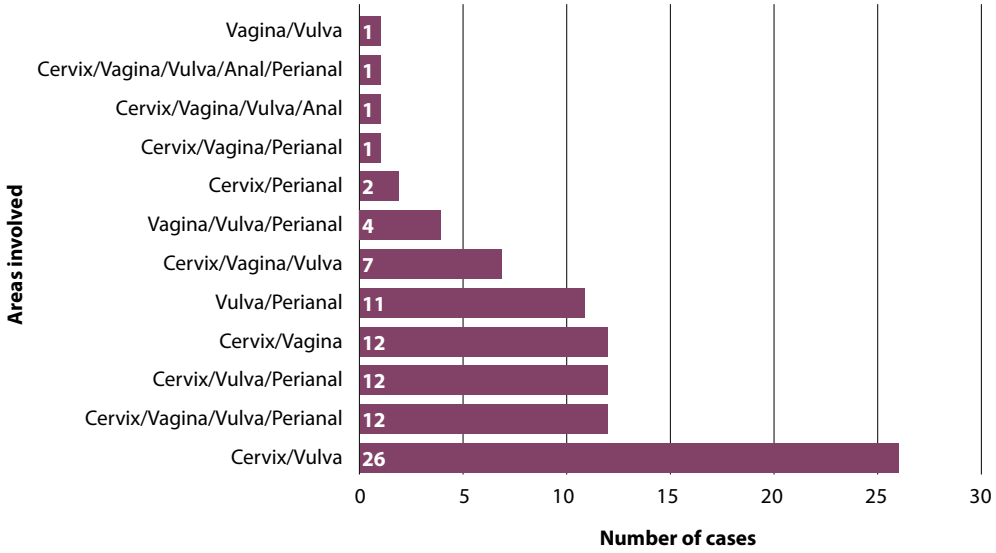

Figure 1: The anatomical sites involved with multizonal intraepithelial neoplasia

Table II: Main management combinations given to patients at different settings

Management		Outpatient *n* = 46	Inpatient *n* = 16	Out- and inpatient combination *n* = 23
Surgical	LLETZ	22	3	7
	Cervical biopsy	8	0	2
	LLETZ/vaginal biopsy	3	0	0
	Vulval excision	2	4	1
	Cervical biopsy/LLETZ	1	0	0
	Perianal biopsy	1	2	0
	LLETZ/vulval excision	0	1	5
	Vulval biopsy	0	1	4
	LLETZ/perianal biopsy	0	1	0
	Cervical biopsy/hysterectomy	0	0	1
	LLETZ/vulval biopsy	0	0	2
	Vulval biopsy/vulval excision	0	1	0
	Hysterectomy	0	1	0
	LLETZ/vulval RWLE	0	0	1
Medical	Podophyllin	3	1	1
	TCA	2	0	2
	Imiquimod	1	0	1
Ablative	Laser	2	2	2
	Cautery	1	6	7

LLETZ – large loop excision of the transformation zone, RWLE – radical wide local excision, TCA – trichloroacetic acid

in combination. The management was aimed at their initial presenting diagnosis and may have occurred over numerous visits or admissions until June 2023. Some patients received a combination of out- and inpatient management, and others had an initial biopsy before definitive management.

Among women managed at the outpatient clinic (n = 46), the most common procedure was LLETZ (n = 26, 56.5%), followed by cervical biopsy (n = 9, 19.6%). For the women who required inpatient management (n = 16), vulval excision was the most common surgical procedure (n = 6, 37.5%), as well as eight (50%) ablative procedures. The out- and inpatient management of 23 women comprised 15 LLETZ (65.2%), seven cautery (30.4%), one hysterectomy (4.3%), and one radical wide local excision (4.3%). These management modalities were often combined (Table II).

Histology

Histological specimens were obtained from 72 women, of whom 58 (80.6%) were diagnosed as premalignant, 13 (18%) as malignant, and one (1.4%) as a benign lesion (Figure 2). No histology was taken for 18 women.

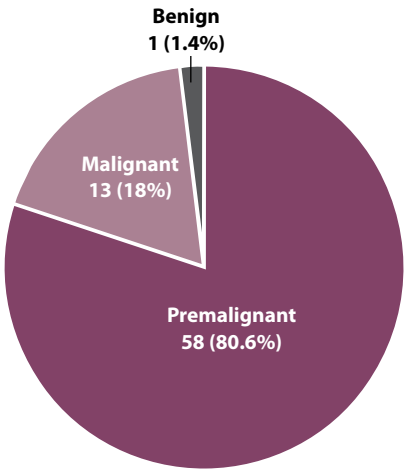

Figure 2: Histology of samples collected (n = 72)

Recurrences and follow-up

Of the 16 women with recurrences over four years, 14 (87.5%) had premalignant lesions and two (12.5%) had malignant lesions. Recurrence sites included the cervix (n = 7), vulva (n = 6), and vagina (n = 1). For recurrence management, six women had LLETZ procedures, four had vulval excisions, one had a hysterectomy, two had a vulval biopsy, and one had a vaginal biopsy. Two women with recurrence had no evidence of management.

Over the four years until June 2023, 58 women (64.4%) were lost to follow-up, 11 (12.2%) were discharged, 16 (17.8%) had recurrences, and five (5.6%) had no recurrences but were still being followed up. Follow-up loss resulted from four women passing away, COVID-19 in two, pregnancy in four, and eight did not receive their planned management and were lost to follow-up before definitive management.

After our analysis, we noted through the National Health Laboratory Service that 16 patients have been following up at other hospitals, and their Pap smears and biopsies were retrieved. One of these patients had vulval squamous cell carcinoma, four had Pap smears indicating high-grade squamous intraepithelial lesion (HSIL), one had low-grade squamous intraepithelial lesion, and 10 were negative for intraepithelial lesion or malignancy. Unfortunately, we are not able to retrieve any further data for these women.

Discussion

The prevalence of MUZIN was 16% at the GSH colposcopy clinic in 2018, as determined in a retrospective review by Adams et al.[6] There are no other local studies to compare this data; however, it is consistent with findings from a study by Zhang et al.,[8] who reported a 15.7% prevalence. Zhang et al.[8] reviewed 1 950 women attending the Cervical Disease Clinic at the Liaoning Cancer Hospital and Institute in China.

In our study, the women's median age was 33 years. Most women (70%) were under 40, and 88.9% were premenopausal. Zhang et al.[8] report 50 as the median age of women with multicentric lesions, and the risk factors in their study were menopause, a history of malignant tumours beyond the lower genital tract, high-risk HPV viral load > 1 000, and multiple HPV infections. They further explain that menopause is one of the two peaks of high-risk HPV infection, due to the low oestrogen level and thinner vaginal epithelium, as well as immune system disturbances from hormonal fluctuations.

We postulate that women presenting with MUZIN were younger in our study due to the high HIV prevalence in South Africa. In 2018, HPV deoxyribonucleic acid (DNA) testing was not available in the public sector, so we could not compare it with Zhang's study. According to the Statistics South Africa 2024 mid-year population estimates, 16.7% of adults aged 15–49 are HIV-positive.[9] The Sixth South African National HIV Prevalence, Incidence and Behaviour Survey found that HIV prevalence peaks at 34.2% for females aged 35–39 years, showing higher HIV prevalence in younger patients in South Africa, and, therefore, they have a higher chance of developing MUZIN.[10] This could explain differences between international cohorts. This is an important finding, as these are mostly women in the prime of their lives, either working to earn an income or caring for their children.

Contraception was not used by 28.9% of women at MUZIN diagnosis. These women risk conceiving during treatment, which would delay treatment further and risk cancerous transformation. Despite the high HIV rate, only 11.1% of women were documented to be using condoms. This could be skewed if women were using dual contraception but chose only to document their primary form of contraception. Contraception may have been offered during their follow-up visits, but this was not reported in the data collection.

Multiple anatomical areas were affected in varying combinations; the most frequent combination was the cervix and vulva (26 women, 28.9%). The cervix was involved in combination with the top four most frequent sites and overall in 78 cases. Zhang et al.[8] report the most frequent combination as the cervix and vagina in 288 patients (93.8%), followed by the cervix and vulva in eight (2.6%). At a colposcopy clinic in France, a retrospective review by Menguellet et al.[11] reported a 4.4% incidence of multicentric lesions among 998 patients referred with cervical intraepithelial neoplasia (CIN). The combination of CIN and vulval intraepithelial neoplasia was diagnosed in 45.5% of patients, and CIN and vaginal intraepithelial neoplasia (VAIN) in 45.5%.[11]

These geographical differences may result from the high HIV prevalence in South Africa and its association with increased HPV infections. In a country-based analysis of cancer registries, Huang et al.[12] examined trends in vulval cancer. They found that young females aged 15–49 years in South Africa had the highest incidence of vulval cancer in 2020.[12] They also found a high disease burden among older females in Western Europe and in countries with a very high Human Development Index.[12]

A retrospective study by Butt et al.[13] in 2017 found that women in South Africa with vulval cancer were on average 10–15 years younger than those in high-income countries. They hypothesised that the reason was the high incidence of HPV in our country.[13] This is supported by a review by Loggenberg et al.[14] of women diagnosed with vulval carcinoma at GSH in 2002–2012, in which

82.4% of women diagnosed with squamous cell carcinoma had evidence of HPV disease. Only 15.1% of women had lichen sclerosus.[14]

Regarding the management women received, 43.4% required inpatient management at some point, and vulval excision was the most common surgical procedure. The most common procedure was LLETZ for women managed at the outpatient clinic. In the study by Menguellet et al.,[11] the most common procedure was loop electrosurgical excision in 70.4% of patients, followed by CO_2 (carbon dioxide) laser in 18.2%, and hysterectomy for CIN in 4.5%, which aligns with our findings. For vaginal lesions, Menguellet et al.[11] reported that 33.3% of patients were treated with CO_2 laser, 12.5% with surgical excision, and surgery for vulval lesions was performed in 41.7%. This is also consistent with our study and aligns with the American College of Obstetricians and Gynecologists' (ACOG) statement, which recommends a wide local excision to be performed for all women with suspected cancer or confirmed biopsies of vulval HSIL.[15]

In our cohort, only two women were treated with imiquimod for vulvovaginal warts. Chen[16] reported a 76.3% HPV clearance rate in women with persistent HPV after surgical therapy for CIN or VAIN who were treated with imiquimod. Lin et al.[17] showed a 51.4% regression of persistent HPV. According to the consensus statement on VAIN management, imiquimod is associated with the lowest recurrence rate and the highest HPV clearance and is considered the best topical treatment option.[18] Per the 2024 Government Employees Medical Scheme (GEMS) drug reference price list, imiquimod cream costs between R900 and R1 040 for 12 sachets.[19] In our setting, where patients often present with large lesions, this may not be an affordable option.

Histology was taken for 72 women, and 18% of these, initially considered premalignant, revealed malignancy. It is expected that most histologies will be premalignant in MUZIN; however, the high malignancy rate underscores the need to biopsy these lesions and provide long-term surveillance. Of the 14 women who had vulval excision, two (14.3%) had histology reports showing malignancy, nine (64.3%) had premalignancy, and three (21.4%) had no evidence of histology. These three had obvious warts without suspicious lesions, and the tissue was not sent for histology.

Follow-up loss occurred in 64.4% of women. Only 16 women had recurrences over the four years; however, due to the high follow-up loss, this is not a true representation. Menguellet et al.[11] concluded that multicentric dysplasias are associated with a high rate of residual lesion and recurrence. They observed recurrences in 43.5% of women who had at least two negative controls after treatment.[11] Dodge et al.[20] also concluded that multifocality was a significant risk factor for recurrence. Their study and ours highlight the importance of counselling women on the need for long-term surveillance.

Of the women in our study, 32.2% were unemployed. Travelling to the hospital for multiple follow-up visits or admissions may not be affordable, and women may default on their follow-up as a result. The impact of the COVID-19 pandemic is also recognised. We suspect that more women were lost to follow-up, either directly or indirectly, due to COVID-19 than those documented. Clinics were closed or postponed, and a "telemed" system was used to inform women of their histology results or follow-up dates.

Study limitations and strengths

The retrospective study design compromised data quality, as we relied on medical records. The high loss to follow-up significantly limits our ability to estimate true recurrence rates and long-term outcomes. While some losses were documented, most had undocumented reasons, likely reflecting systemic barriers to care, including financial constraints and transport difficulties. The absence of HPV DNA testing in the public sector in 2018 prevented the characterisation of specific genotypes and viral loads, limiting our understanding of the molecular epidemiology of MUZIN in this population. Folder-based data collection may have failed to capture management complications, patient-reported outcomes, and psychosocial impacts. The relatively small sample size from a single tertiary centre limits generalisability.

Despite these limitations, the study provides valuable insights into MUZIN management in an HIV-endemic, resource-limited setting with scarce global data. We suggest the following focus points for future research:

- Prospective studies wherein women with MUZIN are identified and seen regularly, with recorded treatment and recurrence rates.
- Prospective HPV DNA genotyping in our population.
- Prospective immunological studies on these women.
- Qualitative research of MUZIN's effect on these women's body image post-treatment, and financial and family impact.
- Economic studies of the hospital's financial burden.

Conclusion

In South Africa, we have a significant MUZIN disease burden, especially in younger women, likely due to the high HIV prevalence and its association with HPV. Nearly half of the women required inpatient management at some point, with extensive cost implications for the woman, her family, and the hospital.

Acknowledgements

The author expresses their gratitude to their supervisor, Prof. Tracey Adams, for consistently offering guidance and being available whenever assistance was needed. She encouraged research presentation at the departmental research day and the international FIGO (International Federation of Gynaecology and Obstetrics) conference. The author acknowledges Dr Rakiya Saidu for assisting with statistical analysis and Joseph Auffray for assisting with folder retrieval.

Conflict of interest

The authors declare no conflict of interest.

Funding source

No funding source to be declared.

Ethical approval

Permission was granted from the University of Cape Town Human Research Ethics Committee (reference 720/2023).

ORCID

H Minter-Brown https://orcid.org/0009-0008-8894-5231
R Saidu https://orcid.org/0000-0003-4959-8157
T Adams https://orcid.org/0000-0002-3686-3540

References

1. Tayib S, Allan B, Williamson A-L, Denny L. Human papillomavirus genotypes and clinical management of genital warts in women attending a colposcopy clinic in Cape Town, South Africa. S Afr Med J. 2015;105(8):679-84. https://doi.org/10.7196/SAMJnew.7890.
2. Women with HIV are more commonly infected with non-16 and -18 high-risk HPV types [Internet]. ClinicalKey. Available from: https://www-clinicalkey-com.ezproxy.uct.ac.za/#!/content/playContent/1-s2.0-S0090825809008622. Accessed 24 May 2023.
3. Adams TS, Mbatani NH. Clinical management of women presenting with field effect of HPV and intraepithelial disease. Best Pract Res Clin Obstet Gynaecol. 2018;47:86-94. https://doi.org/10.1016/j.bpobgyn.2017.08.013.
4. Adams TS, Mbatani NH, Rogers LJ. Management of women with field effect of anogenital human papillomavirus infection. Curr Obstet Gynecol Rep. 2016;5(3):203-9. https://doi.org/10.1007/s13669-016-0170-2.
5. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. Lancet. 2019;393(10167):169-82. https://doi.org/10.1016/S0140-6736(18)32470-X.
6. Adams TS, Mhembere M, Mbatani NH, Rogers L. The demographics of women with multizonal anogenital HPV disease: a retrospective cohort study in Cape Town, South Africa. South Afr J Gynaecol Oncol. 2025;17(1):29-34.
7. wma.net [Internet]. Declaration of Helsinki. World Medical Association. Available from: https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/. Accessed 22 June 2025.
8. Zhang J, Liu G, Cui X, Yu H, Wang D. Human papillomavirus genotypes and the risk factors associated with multicentric intraepithelial lesions of the lower genital tract: a retrospective study. BMC Infect Dis. 2021;21(554). https://doi.org/10.1186/s12879-021-06234-0.
9. statssa.gov.za [Internet]. 2024 mid-year population estimates. Statistics South Africa; 2024. Available from: https://www.statssa.gov.za/?p=17440. Accessed 3 July 2025.
10. Zuma K, Zungu NP, Moyo S, et al. The Sixth South African National HIV Prevalence, Incidence and Behaviour Survey, 2022: a summary report [Internet]. Cape Town: HSRC Press; 2024. Available from: https://hsrc.ac.za/wp-content/uploads/2024/07/SABSSM_VI_EXEC_REPORT_2PP.pdf. Accessed 20 August 2025.
11. Menguellet SA, Collinet P, Debarge VH, et al. Management of multicentric lesions of the lower genital tract. Eur J Obstet Gynecol Reprod Biol. 2007;132(1):116-20. https://doi.org/10.1016/j.ejogrb.2006.04.011.
12. Huang J, Chan SC, Fung YC, et al. Global incidence, risk factors and trends of vulvar cancer: a country-based analysis of cancer registries. Int J Cancer. 2023;153(10):1734-45. https://doi.org/10.1002/ijc.34655.
13. Butt JL, Botha MH. Vulvar cancer is not a disease of the elderly: treatment and outcome at a tertiary referral centre in South Africa. S Afr Med J. 2017;107(11):1000-4. https://doi.org/10.7196/SAMJ.2017.v107i11.12497.
14. Loggenberg FE, Adams TS. A review of vulvar carcinoma at Groote Schuur Hospital for the period 2002 to 2012 with particular emphasis on HPV-related disease. South Afr J Gynaecol Oncol. 2020;12(1):17-22. https://doi.org/10.1080/20742835.2020.1763032.
15. Committee Opinion No.675. Management of vulvar intraepithelial neoplasia. Obstet Gynecol. 2016;128(4):e178-82. https://doi.org/10.1097/AOG.0000000000001713.
16. Chen FP. Efficacy of imiquimod 5% cream for persistent human papillomavirus in genital intraepithelial neoplasm. Taiwan J Obstet Gynecol. 2013;52(4):475-8. https://doi.org/10.1016/j.tjog.2013.10.004.
17. Lin CT, Qiu JT, Wang CJ, et al. Topical imiquimod treatment for human papillomavirus infection in patients with and without cervical/vaginal intraepithelial neoplasia. Taiwan J Obstet Gynecol. 2012;51(4):533-8. https://doi.org/10.1016/j.tjog.2012.09.006.
18. Kesic V, Carcopino X, Preti M, et al. The European Society of Gynaecological Oncology (ESGO), the International Society for the Study of Vulvovaginal Disease (ISSVD), the European College for the Study of Vulval Disease (ECSVD), and the European Federation for Colposcopy (EFC) consensus statement on the management of vaginal intraepithelial neoplasia. Int J Gynecol Cancer. 2023;33(4):446-61. https://doi.org/10.1136/ijgc-2022-004213.
19. gems.gov.za [Internet]. Full drug reference price list: October 2024. Government Employees Medical Scheme; 2024. Available from: https://www.gems.gov.za/-/media/Project/Documents/formulary-documents/2024/GEMS-Full-Drug-Reference-Price-List-October-2024.pdf. Accessed 3 July 2025.
20. Dodge JA, Eltabbakh GH, Mount SL, Walker RP, Morgan A. Clinical features and risk of recurrence among patients with vaginal intraepithelial neoplasia. Gynecol Oncol. 2001;83(2):363-9. https://doi.org/10.1006/gyno.2001.6401.