PREVENTION OF HPV RECURRENCE WITH HPV VACCINATION AFTER LASER VAPORIZATION AND CONIZATION IN REPRODUCTIVE-AGE PATIENTS WITH HSIL-CIN 2

***NINO MUSERIDZE**, MD, PhD;[2] **MADONA JUGHELI**, MD, PhD;[1] **ANA CHOKHONELIDZE**;[2] **BELA JUGHELI**, MD;[1] **NANI TATISHVILI**[2]*

[1] *Caraps Medline Clinic, Tbilisi, Georgia*

[2] *Georgian-German Reproduction Center, Tbilisi, Georgia*

DOI: https://doi.org/10.71419/mtggrc.2025.28

ABSTRACT

Background: Persistent infection with high-risk human papillomavirus (HPV) after surgical management of high-grade squamous intraepithelial lesions (HSIL-CIN 2) is recognized as a major driver of recurrence and progression to cervical cancer.[6 10] Despite advances in screening and surgical techniques, recurrence rates remain clinically significant.[5 9 10] Globally, cervical cancer continues to be one of the most common cancers affecting women, particularly in low- and middle-income countries.[6] Although prophylactic HPV vaccines such as Gardasil® and Gardasil 9® were initially developed for primary prevention,[3 7 8] emerging evidence suggests that they may also serve a secondary preventive role when administered after surgical treatment by reducing reinfection and supporting clearance of residual viral particles.[1 2 4 5 9]

Objective: This study aimed to assess whether postoperative administration of the quadrivalent HPV vaccine (Gardasil®) in reproductive-age women treated with CO_2 laser conization and vaporization for HSIL-CIN 2 could reduce recurrence of HPV infection and associated cytological abnormalities, thereby improving recurrence-free survival.

Methods: A prospective cohort study was conducted from January 2019 to December 2023 in two tertiary centers in Tbilisi, Georgia. A total of 145 women aged 20-45 years with histologically confirmed HSIL-CIN 2 underwent CO_2 laser conization and vaporization. Fifty-three women received Gardasil® within 14 days postoperatively according to the 0-2-6 month vaccination schedule, while ninety-two women remained unvaccinated. Follow-up was performed at 3, 6, 9, and 12 months post-treatment, including Pap smear cytology (Bethesda system), colposcopy (Reid's colposcopic index), and HPV DNA PCR testing for types 6, 11, 16, 18, and 31.[7] Histological reassessment with p16 immunohistochemistry was performed when clinically indicated. Recurrence was defined as histologically confirmed LSIL/HSIL or persistent HPV DNA positivity combined with abnormal cytology.[5 9]

Results: At 12 months, recurrence-free survival was 90.6% among vaccinated women compared with 75.0% in the unvaccinated cohort. HPV DNA PCR positivity was also significantly lower in the vaccinated group (11.3% vs. 28.3%, p=0.01). Abnormal cytology rates followed the same pattern, with vaccinated women experiencing fewer abnormalities throughout follow-up. Kaplan-Meier analysis demonstrated significantly higher recurrence-free survival among vaccinated patients (HR for recurrence: 0.41, 95% CI 0.20-0.85).

Conclusions: Postoperative HPV vaccination significantly reduces recurrence of HPV infection and intraepithelial lesions after CO_2 laser conization for HSIL-CIN 2.[1 2 5 9] These findings support the inclusion of HPV vaccination as part of standard postoperative protocols in reproductive-age women. Broader adoption of this strategy could improve long-term outcomes, reduce the burden of cervical cancer, and align with the World Health Organization's global call for cervical cancer elimination.[6]

Keywords: HPV vaccination; HSIL-CIN 2; CO_2 laser conization; recurrence prevention; gardasil; reproductive-age women; cervical cancer

Introduction

Cervical cancer is a preventable malignancy, yet it remains a significant contributor to morbidity and mortality in women worldwide. According to the World Health Organization (WHO, 2023), cervical cancer is the fourth most common cancer in women globally, with an estimated 600,000 new cases and over 340,000 deaths annually.[6] The burden is disproportionately high in low- and middle-income countries, where access to screening, HPV vaccination, and timely treatment of precancerous lesions is limited.[6 10] In Eastern Europe and the Caucasus region, including Georgia, cervical cancer rates are higher than in Western Europe, reflecting disparities in healthcare infrastructure and preventive strategies.[10]

Persistent infection with high-risk HPV types is the necessary cause of cervical cancer.[6 7] Among over 200 known HPV types, at least 14 are classified as oncogenic, with HPV 16 and 18 alone accounting for ~70% of cervical cancers.[7] HSIL, corresponding histologically to CIN 2 or CIN 3, represents a precancerous stage that, if untreated, carries a high risk of progression to invasive disease.[10] Women diagnosed with HSIL-CIN 2 typically undergo surgical excision procedures such as a loop electrosurgical excision procedure (LEEP), cold knife conization, or CO_2 laser conization.[5]

Surgical treatment is effective in removing dysplastic tissue. Yet, it does not eradicate the underlying HPV infection.[7 8] Viral particles can persist in the basal epithelial layers of the transformation zone or be reintroduced via reinfection from sexual partners.[3 7] As a result, recurrence rates remain considerable, ranging from 5% to 30% within 2 years depending on patient characteristics, surgical margins, HPV genotype, and immune competence.[5 9]

HPV vaccination has revolutionized primary prevention by inducing high titers of neutralizing antibodies against the L1 capsid protein, thereby blocking infection.[7 8] The quadrivalent vaccine (Gardasil®) targets HPV types 6, 11, 16, and 18, while the nonavalent formulation (Gardasil 9®) extends protection to five additional oncogenic types.[7 8] Although initially intended for use before sexual debut,[3] growing evidence suggests that HPV vaccination may also play a role in secondary prevention, particularly when administered after surgical treatment of precancerous lesions.[1 2 4 5 9]

The hypothesized mechanisms include:

- Induction of robust systemic immunity that facilitates clearance of residual HPV particles.[7 8]
- Prevention of reinfection with vaccine-covered HPV types from sexual partners.[3]
- Potential cross-protection against phylogenetically related non-vaccine HPV types (e.g., HPV 31, 33, 45).[7]

Recent observational studies and meta-analyses have supported this hypothesis. For example, Del Pino et al. (2023) demonstrated that postoperative vaccination reduced recurrence rates of cervical intraepithelial neoplasia,[1] while Brzeziński et al. (2023) reported a 57% risk reduction.[2] Meta-analyses by Arbyn et al. (2020) and Nasioutziki et al. (2020) similarly confirmed a protective effect.[4 9] These findings have prompted international discussions on whether postoperative vaccination should be routinely incorporated into management guidelines.[5]

Given the absence of national HPV vaccination programs in Georgia during the study period and the limited availability of prospective cohort data from the Caucasus region, our study sought to evaluate the effect of postoperative quadrivalent HPV vaccination in preventing HPV reinfection and recurrence after CO_2 laser conization for HSIL-CIN 2 in Georgian women of reproductive age.

Methods

Study Design and Setting: This was a prospective cohort study conducted between January 2019 and December 2023 in two tertiary gynecologic centers in Tbilisi, Georgia: Caraps Medline Clinic and the Georgian-German Reproductive Center. Both centers serve as referral institutions for the management of cervical precancerous lesions.[6]

Ethical approval was obtained from the institutional review boards of both centers, and all participants provided written informed consent.

Study Population: A total of 145 women aged 20-45 years were enrolled. All had histologically confirmed HSIL-CIN 2 and tested positive for high-risk HPV DNA by PCR (types 6, 11, 16, 18, or 31).[7]

Inclusion criteria:

- Age 20-45 years
- Histologically confirmed HSIL-CIN 2
- High-risk HPV PCR positivity
- No prior HPV vaccination[7]

Exclusion criteria:

- Pregnancy at the time of enrollment
- Immunosuppressive conditions (e.g., HIV, chronic corticosteroid use)
- Prior radical cervical surgery or invasive cervical cancer[6]
- Known allergy to HPV vaccine components[7]

Surgical Intervention: All patients underwent CO_2 laser conization combined with vaporization under colposcopic guidance.[5] Conization specimens were sent for histopathologic evaluation, with margin status documented.

Vaccination Protocol: The intervention group (n = 53) received the quadrivalent HPV vaccine (Gardasil®) within 14 days after surgery, following the standard 0-2-6 month schedule.[7] Vaccination was offered free of charge through a study support program.

The control group (n = 92) declined vaccination, mainly due to lack of insurance coverage or personal preference.

Follow-Up Assessments: Patients were followed at 3, 6, 9, and 12 months postoperatively.[7] Each visit included:

- Pap smear cytology interpreted using the Bethesda system.[6]
- Colposcopic examination scored using Reid's colposcopic index.[6]
- HPV DNA PCR testing for types 6, 11, 16, 18, and 31.[7]
- Histologic biopsy with p16 immunohistochemistry when cytologic or colposcopic abnormalities were present.[5]

Definition of recurrence: Either histologically confirmed LSIL/HSIL or persistent HPV DNA positivity with concurrent abnormal cytology.[4 9]

Laboratory Procedures: HPV DNA was extracted from cervical swab samples and amplified via PCR targeting L1 region-specific primers.[7] Positive samples were genotyped for HPV types 6, 11, 16, 18, and 31. Immunohistochemistry for p16 was performed using CINtec® p16 histology kit.[5]

Statistical Analysis: Data were analyzed using SPSS v.26. Recurrence-free survival was evaluated using Kaplan-Meier curves with log-rank tests. Cox regression was used to calculate hazard ratios (HR) with 95% confidence intervals (CI). A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics: The mean age was 32.6 years (range 20-45). No significant differences were noted between vaccinated and unvaccinated groups in terms of age, smoking status, parity, baseline HPV genotype, or margin positivity.[5]

Recurrence Rates: At 3 months, recurrence rates were similar between groups (vaccinated 3.8% vs. unvaccinated 5.4%, p = 0.65). Divergence emerged by 6 months:

- 6 months: Vaccinated 5.7% vs. unvaccinated 15.2% (p = 0.04)
- 9 months: Vaccinated 7.5% vs. unvaccinated 21.7% (p = 0.02)
- 12 months: Vaccinated 9.4% vs. unvaccinated 25.0% (p = 0.01)

Overall, recurrence-free survival at 12 months was 90.6% in the vaccinated group versus 75.0% in the unvaccinated group. Kaplan-Meier survival analysis confirmed significantly higher recurrence-free survival in vaccinated women (HR 0.41, 95% CI 0.20-0.85).[1 2 5 9]

HPV DNA Positivity: By 12 months, HPV DNA positivity was observed in 11.3% of vaccinated women compared with 28.3% of unvaccinated women (p = 0.01).

Cytological Findings: Cytological abnormalities (ASC-US or higher) were lower among vaccinated patients at all time points. At 12 months, abnormal cytology was observed in 13.2% of vaccinated patients compared with 30.4% of unvaccinated patients.[1 2 5]

Subgroup Analysis

- Smoking status: Smokers in the unvaccinated group had particularly high recurrence rates (29.6%) compared with nonsmokers (21.2%). In vaccinated women, smoking did not significantly affect recurrence rates.[5]
- Margin status: Women with negative surgical margins still benefited from vaccination, with recurrence rates of 7.8% versus 20.4% in unvaccinated counterparts.[5]

Discussion

Our prospective cohort study demonstrates that administration of the quadrivalent HPV vaccine within 14 days after CO_2 laser conization for HSIL-CIN 2 significantly reduces recurrence of HPV infection and associated cytological abnormalities. Vaccinated women experienced nearly a 60% reduction in recurrence risk over 12 months, consistent with previous studies from other populations.[1 2 5 9]

Comparison with Previous Literature: Our findings echo those of Ghelardi et al. (2018), who conducted a randomized controlled trial showing a 46% reduction in recurrence with HPV vaccination after CIN 2+ treatment.[5] Brzeziński et al. (2023) reported a 57% reduction in recurrence,[2] while Del Pino et al. (2023) confirmed lower recurrence risk in a Spanish cohort.[1] A meta-analysis by Arbyn et al. (2020) estimated an overall 60% reduction in recurrence following vaccination.[9]

Mechanisms of Protection: Possible mechanisms include:

1. Immune clearance of residual virus – vaccine-induced neutralizing antibodies may aid the immune system in eliminating viral particles.[7 8]
2. Prevention of reinfection – vaccination reduces the risk of acquiring new infections from sexual partners.[3]
3. Cross-protection – the quadrivalent vaccine may offer protection against genetically related high-risk types, such as HPV 31.[7]

Clinical Implications: Routine postoperative HPV vaccination could transform management of HSIL-CIN 2 by reducing repeat surgical procedures, improving quality of life, and lowering healthcare costs. It aligns with WHO's strategy for cervical cancer elimination.[6]

Fertility Considerations: Vaccination can reduce the need for repeat conization, thereby preserving fertility and lowering obstetric risks.[5]

Limitations: Non-randomized design, 12-month follow-up, quadrivalent vaccine only, and geographic specificity limit generalizability.

Future Directions: Future studies should include longer randomized controlled trials, cost-effectiveness analysis, and assessment of nonavalent vaccines.[3 7 8]

Conclusion

Postoperative HPV vaccination with Gardasil® in reproductive-age women undergoing CO_2 laser conization for HSIL-CIN 2 significantly reduces recurrence risk, HPV DNA positivity, and abnormal cytology rates.[1 2 5 9] The protective effect observed in our study is consistent with international evidence, supporting the integration of vaccination into standard postoperative care.[5 6] Adopting this strategy has the potential to reduce cervical cancer incidence, decrease healthcare costs, and preserve fertility in young women.[7 8 10]

References:

1. Del Pino M, Fusté P, Alonso I, et al. HPV vaccination and risk of recurrence after treatment of cervical lesions. *Infect Agent Cancer*. 2023;18(1):15. doi:10.1186/s13027-023-00545-0
2. Brzeziński J, Ciebiera M, Baranowski W, et al. Efficacy of HPV vaccination following surgical treatment of cervical intraepithelial neoplasia. *J Clin Med*. 2023;12(5):1132. doi:10.3390/jcm12051132
3. Moscicki AB, Wheeler CM, Romanowski B, et al. Updating evidence on HPV vaccination in adolescents and adults. *J Low Genit Tract Dis*. 2015;19(1 Suppl 1):S27-S43. doi:10.1097/LGT.0000000000000090
4. Nasioutziki M, Daniilidis A, Kyrgiou M, et al. HPV vaccination in the prevention of cervical lesion recurrence. *Infect Agent Cancer*. 2020;15:56. doi:10.1186/s13027-020-00314-0
5. Ghelardi A, Parazzini F, Martella F, et al. HPV vaccination after treatment for CIN 2+: a randomized controlled trial. *J Clin Oncol*. 2018;36(20):1981-1989. doi:10.1200/JCO.2017.77.5733

6. World Health Organization. Human papillomavirus (HPV) and cervical cancer. Fact sheet. 2023. Accessed August 15, 2025. https://www.who.int/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer
7. Garland SM, Kjaer SK, Muñoz N, et al. Impact and effectiveness of the quadrivalent HPV vaccine: a systematic review of 10 years of real-world experience. *Clin Infect Dis*. 2016;63(4):519-527. doi:10.1093/cid/ciw354
8. Kjaer SK, Nygård M, Dillner J, et al. The impact of HPV vaccination on cervical cancer prevention and elimination efforts: current perspectives. *Papillomavirus Res*. 2022;14:100260. doi:10.1016/j.pvr.2022.100260
9. Arbyn M, Bryant A, Beutels P, et al. Prophylactic HPV vaccination after treatment of CIN: a systematic review and meta-analysis. *Lancet Oncol*. 2020;21(9):1226-1238. doi:10.1016/S1470-2045(20)30445-3
10. Schiffman M, Castle PE. The promise of global cervical-cancer prevention. *N Engl J Med*. 2005;353(20):2101-2104. doi:10.1056/NEJMp058171