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HPV Vaccine as Adjuvant Therapy in HPV Lesions

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Persistent infection with HPV is responsible for nearly 70% of vulvar/vaginal cancers, 90% of cervical and anal cancers, 70% of oropharyngeal cancers, and 60% of penile cancers (1). It has been observed that the use of prophylactic HPV vaccines can lead to a significant reduction in these cancers (2). Eradication of the virus depends primarily on cell-mediated immunity, after which antigen-presenting cells present mainly E2 and E6 proteins of HPV to T helper cells, ending with the activation of cytotoxic T cells. To a lesser degree, humoral responses of the immune system to the L1 protein are also significant. However, in natural HPV infection, the antibody response is considerably weaker than in vaccinated individuals (3). U.S. Food and Drug Administration (FDA) licensed three types of HPV. After the year of 2016, the 9-valent form of HPV vaccine was administered as the primary one in the United States. After 2018, this vaccine was approved for use between the ages of 9-45 (1).

The primary protection mechanism provided by HPV vaccines is through neutralizing antibodies formed against L1/HPV-like particles—the high amounts of neutralizing antibodies formed by the vaccine act before the virus enters the cell. Therefore, the vaccine is not therapeutic and is not expected to affect the virus in patient cells. In current practices, it is recommended that individuals be vaccinated before they become infected for the best protection. However, HPV screening is not recommended before vaccination (3,4).

Nevertheless, if someone who has previously been exposed to HPV is vaccinated, the vaccine is likely to provide an advantage to the patient through the following mechanisms:

- **Prevention of reinfection/reactivation:** Although the new infection rate decreases with age, reinfections can occur. Randomized controlled trials have shown that vaccination in women aged 24 to 45 prevents new HPV infections and disease (4,5).
- **Broder protection:** While the vaccine targets specific HPV types, it may provide some cross-protection against other types, which could be beneficial for individuals with multiple HPV infections (2,6).
- **Immune modulation**: The vaccine may enhance the immune response against HPV, potentially aiding in the regression of existing lesions (3,4).

Recently, there has been increasing interest in utilizing the HPV vaccine as an adjuvant treatment for HPV-related genital lesions, including genital warts and precancerous lesions. A meta-analysis examined the effects of HPV vaccination after primary therapy in different organs. In this study, the recurrence rates of CIN 1+ (OR: 0.45, 95% CI 0.27-0.73; P = 0.001), CIN 2+ (OR: 0.33, 95% CI: 0.20-0.52; $P < 0.0001$), and CIN 3 (OR: 0.28, 95% CI: 0.13-0.59; $P = 0.0009$) were lower in the group vaccinated when compared to the unvaccinated one. Similarly, the risk of anal intraepithelial neoplasia development was also reduced by vaccination ($P = 0.005$). However, the rates of recurrence for vulvar intraepithelial neoplasia and anogenital warts did not change (7,8).

In addition, the efficacy of HPV vaccination as an adjuvant in early-stage cervical cancer was investigated in a prospective case-control study. In stage 1A1 cervical cancer patients treated with conization, recurrence rates were 1.2% in the HPV vaccine group, while this rate was five times higher (6.4%) in the unvaccinated group (P 0.01) (9).

The usage of HPV vaccines as adjuvants in the treatment of HPV lesions is a hot topic, but data in this area are very limited. Comprehensive, high-quality publications are needed on this subject. Moreover, details such as

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patient selection, vaccination timing, and safety need to be investigated, and application schemes need to be established.

Competing Interests
None declared.

Ethical Issues
Not applicable.

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