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MODERN APPROACHES TO TREATMENT AND POST-TREATMENT MONITORING OF HPV-POSITIVE WOMEN WITH CERVICAL PATHOLOGY

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Abstract: Cervical pathology in HPV-positive women remains a key problem in modern gynecology and gynecologic oncology, as it is in this group that the transition from virus carriage to clinically significant precancerous lesions and invasive cervical cancer occurs. In recent years, primary HPV screening, molecular triage, and risk stratification have significantly changed early diagnosis. However, the selection of optimal treatment strategies and the development of effective post-treatment monitoring remain the subject of active clinical debate. The main difficulty stems from the heterogeneity of the HPV-positive population: some patients have transient infection and lesions with a high probability of regression, while others develop HSIL/CIN2+ lesions, requiring timely and oncologically adequate intervention. The aim of this review article is to analyze current literature on the treatment of cervical pathology in HPV-positive women and the organization of post-treatment follow-up. This review focuses on the individualization of treatment strategies, the problem of overtreatment, the reproductive consequences of excisional procedures, the importance of follow-up hrHPV testing, and prospects for further personalization of the patient's care pathway. This paper examines current approaches to choosing between surveillance, ablative methods, LEEP/LLETZ, and conization, highlighting their advantages and limitations, and emphasizing the need to balance oncological safety with reproductive preservation. Special attention is paid to post-treatment surveillance, where follow-up hrHPV testing plays a key role as the most informative tool for the early detection of treatment failure. Factors predicting an unfavorable prognosis are discussed, including persistent hrHPV positivity, resection margin status, age, and initial lesion severity. The final section presents promising areas related to artificial intelligence, therapeutic HPV vaccines, and molecular personalization of treatment algorithms. It is concluded that treatment and follow-up of HPV-positive women should not be based on a one-size-fits-all approach, but on a step-by-step, individualized risk assessment. This allows for a simultaneous reduction in the likelihood of missing clinically significant lesions, a reduction in overtreatment, and an improvement in oncologic and reproductive outcomes.

Keywords: Human Papillomavirus, HPV, Cervical Pathology, CIN2+, HSIL, LEEP, LLETZ, Conization, Ablation, Post-Treatment Follow-Up, hrHPV, Risk Stratification, Overtreatment, Reproductive Outcomes

Introduction

Cervical pathology in HPV-positive women remains one of the most significant problems in modern gynecology, gynecologic oncology, and reproductive medicine. This is due not only to the high prevalence of human papillomavirus infection but also to its decisive role in cervical carcinogenesis. According to WHO and GLOBOCAN, cervical cancer remains a leading cause of cancer morbidity and mortality among women, and the main burden of the disease still falls on low- and middle-income countries, where vaccination coverage, organized screening, and timely treatment of precancerous lesions remain limited [1–7]. However, the very concept of "HPV-positive woman" can no longer be

perceived as a single clinical category. Most HPV infections in immunocompetent patients are transient and resolve naturally, while only a minority of cases develop into long-term persistence with the risk of developing HSIL/CIN2+, CIN3+, and, ultimately, invasive cancer. Therefore, the clinical significance of a positive HPV test is determined not by the fact of virus carriage itself, but by a combination of genotype, duration of persistence, cytological and colposcopic findings, characteristics of the transformation zone, immune status, and the patient's reproductive context [8–11, 17–20].

Modern therapeutic strategies for HPV-positive women are shaped by two objectives. On the one hand, it is essential to promptly identify and treat truly dangerous lesions, preventing progression to invasive cancer. On the other hand, it is equally important to avoid unnecessarily aggressive interventions in women with limited lesions, a high probability of regression, and significant reproductive plans. It is at this juncture that the main shortcomings of previous approaches have become apparent: formulaic solutions, an overestimation of radicality as a synonym for safety, insufficient consideration of the characteristics of the transformation zone and endocervical component, and a formal attitude toward post-treatment surveillance [12, 13, 21–23, 24–29].

While previously the main discussion centered on the question of "when to treat," today, equally important are the questions of "how to treat," "how much to treat," and "how to monitor after treatment." It is becoming clear that effective management of HPV-positive women requires a continuous process: from an accurate pre-treatment assessment—through the selection of an oncologically sufficient but functionally gentle tactic—to long-term post-treatment monitoring, based primarily on hrHPV testing [14, 28–34].

The purpose of this review article was to analyze current literature on the treatment of cervical pathology in HPV-positive women and the organization of post-treatment follow-up, with an emphasis on individualizing treatment strategies, identifying deficiencies in previous practices, preventing overtreatment and treatment failure, and prospects for further personalization of the patient's care pathway [24–29, 35–46].

Methodology

This study was conducted as a narrative review aimed at synthesizing current evidence on the treatment and post-treatment monitoring of HPV-positive women with cervical pathology. A comprehensive literature search was performed using major medical and scientific databases, including PubMed, Scopus, Web of Science, and WHO guideline repositories, focusing on publications from recent years to ensure relevance to contemporary clinical practice. Keywords such as “human papillomavirus,” “HPV,” “cervical pathology,” “CIN2+,” “HSIL,” “LEEP,” “LLETZ,” “conization,” “ablation,” and “post-treatment follow-up” were used in various combinations. Priority was given to systematic reviews, meta-analyses, randomized and cohort studies, as well as international clinical guidelines. Articles were selected based on their relevance to treatment decision-making, risk stratification, reproductive outcomes, and surveillance strategies in HPV-positive populations. Studies focusing on both diagnostic and therapeutic aspects, including hrHPV testing, cytology, colposcopy, and emerging technologies such as artificial intelligence and molecular biomarkers, were included to ensure a comprehensive perspective. Data extraction was performed through critical analysis of study objectives, methodologies, and outcomes, with particular attention to factors influencing treatment selection and prediction of residual or recurrent disease. The collected data were qualitatively synthesized to identify consistent patterns, clinical controversies, and gaps in current practice. Emphasis was placed on integrating findings into a risk-based, individualized care framework, reflecting the shift from standardized approaches toward personalized management of HPV-associated cervical pathology.

Result

Modern Principles of Treatment Tactics in HPV-Positive Women

One of the most important clinical advances in recent years has been a change in the philosophy of treatment itself. While safety was previously often equated with the most radical intervention, modern practice increasingly relies on the principle of oncological sufficiency with functional sparing. This means that the physician's task is not to select the largest possible treatment, but to choose an intervention that, in a specific clinical situation, ensures disease control without excessive trauma to the cervix [24, 25, 28, 29]. This shift has been made possible by the development of risk stratification and a more precise understanding of the natural history of HPV-associated lesions. Genotyping, dual staining, clarification of the role of the transformation zone, more careful assessment of the endocervical component, and the accumulation of data on the natural history of CIN2 in young women have shown that clinically different situations cannot be treated identically [8–11, 15–18, 21–23]. In essence, modern tactics are designed to correct two opposing shortcomings of previous practice: underestimation of lesions requiring active treatment and overtreatment of those patients for whom intervention is more traumatic than the underlying biology of the process.

Surveillance as an Active Treatment Strategy

One of the most fundamental changes has been the recognition that not every histologically confirmed CIN2 in an HPV-positive woman requires immediate excision. In some patients, particularly young women with satisfactory visualization of the transformation zone and no signs of a more severe process, active surveillance has come to be considered a clinically acceptable and, in some cases, preferable strategy [15, 16, 28, 29].

It is important to emphasize that surveillance is not synonymous with inaction. Instead, it is an organized clinical approach based on the understanding that some CIN2 can regress, especially in young women. Its primary goal is to avoid missing progression while simultaneously avoiding unnecessary cervical trauma in those patients for whom immediate excision does not provide a significant benefit [15, 16, 17].

The practical significance of this approach is particularly significant for patients with high reproductive priorities. Excessive excisional treatment may be associated with an increased risk of preterm birth, cervical insufficiency, and other obstetric complications, whereas properly managed surveillance allows for cervical preservation without reducing oncological suspicion [16, 24, 29, 30].

However, active surveillance requires strict conditions. It is only justified in cases where a comprehensive colposcopic assessment has been performed, there is no suspicion of an occult endocervical component, morphological verification inspires confidence, and the patient is prepared for disciplined follow-up. If these conditions are not met, surveillance ceases to be an organ-preserving strategy and can become a form of delayed undertreatment [12, 13, 21–23, 28]. Therefore, the value of surveillance lies not in its "gentleness," but in the proper selection of patients.

Ablative Methods: Potential and Limitations

Ablative methods still retain their place in the treatment of HPV-associated cervical pathology, but this role has become much more clearly defined. Their primary advantage is the tissue-preserving nature of the intervention and the potentially more favorable impact on future reproductive outcomes. Therefore, in appropriately selected patients, ablation remains an important treatment option [24, 25].

However, modern clinical logic no longer allows for the perception of ablation as a simple "easy alternative" to excision. Its effectiveness directly depends on the quality of pre-treatment diagnostics. If the lesion is not fully visualized, endocervical spread is suspected, discrepancies between morphology and colposcopy persist, or a more severe process is likely, ablative tactics become less justified [12, 13, 21–23]. Consequently, the place of ablation in modern practice is determined not only by the biology of

the lesion but also by the reliability of the diagnosis. From this perspective, ablative methods particularly clearly demonstrate an important principle: sparing treatment is permissible only where diagnostic uncertainties are eliminated. Otherwise, attempts to reduce the trauma of the procedure may result in undertreatment of the patient.

LEEP/LLETZ as the Primary Excisional Method

In most clinical scenarios, LEEP/LLETZ occupies a central place among excisional procedures. Its importance stems from the fact that the method simultaneously serves both therapeutic and diagnostic functions: it removes the affected tissue and allows for morphological assessment of the lesion depth, the status of the resection margins, and the presence or absence of a more severe component [28, 29]. It is precisely because of this dual role that LEEP/LLETZ has become one of the key tools in modern cervical pathology. However, in recent years, the approach to the extent of intervention has changed. While previously, wider excision was often perceived as a priori safer, today it is becoming increasingly clear that excessive depth and breadth of resection can reduce the risk of residual disease at the cost of increased reproductive loss [16, 24, 29, 30].

This leads to one of the most important practical conclusions: improving LEEP/LLETZ lies not only in technique but also in the correct pre-treatment route. Insufficient risk stratification, ignoring the characteristics of the transformation zone, incomplete assessment of the endocervical component, and a formulaic approach to choosing the extent of intervention remain among the main causes of both overtreatment and insufficient radicality. Consequently, the question is not whether LEEP/LLETZ is needed, but rather which patient, to what extent, and after what diagnostic test it is truly needed.

Conization and its special clinical significance

Conization retains a special place in the treatment of cervical pathology in HPV-positive women, particularly in cases requiring a deeper and more anatomically complete specimen. The most typical indications for conization remain suspected glandular lesions, AIS, a prominent endocervical component, incomplete visualization of the transformation zone, discrepancies between cytology, colposcopy, and biopsy, as well as the need to exclude a microinvasive process [26, 27].

Modern practice has also become more flexible in this regard. Even with AIS, the possibility of organ-preserving treatment in carefully selected patients with reproductive plans, provided reliable follow-up, is increasingly being discussed. This once again underscores the main thrust of modern treatment evolution: a shift away from reflexive radicalism and a transition to precise, clinically proven tactics [26, 27].

The Problem of Overtreatment and Reproductive Consequences

Overtreatment has become one of the most serious problems in modern cervical pathology. Essentially, this is the price of a previous era, when the fear of missing a serious lesion pushed for expanded indications for excisional procedures. However, accumulated data has convincingly demonstrated that more radical treatment does not always mean more appropriate treatment [16, 24, 29, 30].

This is especially true for young and nulliparous women. In this group, excessive excision can be associated with worse obstetric outcomes, including an increased risk of preterm birth. Therefore, one of the central goals of modern tactics is to eliminate not only the risk of progression but also the risk of unnecessary harm caused by treatment [16, 24, 29, 30].

In practice, this means that physicians should think not in terms of "maximal treatment" or "minimal treatment," but rather in terms of "sufficient and precise treatment." This is the essence of a mature risk-based approach: not to lower oncological suspicion, but also not to turn every dysplasia into a reason for excessive excision.

Post-treatment surveillance as an independent stage of care

Post-treatment surveillance in HPV-positive women is not a formal final step after excision or ablation, but an independent and clinically critical part of the entire cervical cancer prevention strategy. Even after

technically correct treatment, the risk of residual or recurrent CIN2+ does not disappear immediately and does not become low in the general population. According to current data, treatment failure in the form of residual/recurrent HSIL occurs in approximately 5–10% of patients, and in some women, invasive cancer may be detected in the immediate post-treatment period [14, 28, 29, 34].

Furthermore, the long-term risk does not disappear. Women with previous CIN3 retain an increased risk of cervical cancer compared to the general population, especially at an older age and with recurrent disease [33]. These data eliminate one of the most dangerous misconceptions of previous practice—the idea that after technically successful treatment, the patient automatically returns to the general population risk group.

HrHPV surveillance testing as the basis of a test of cure

HrHPV surveillance testing occupies a central place in the modern post-treatment surveillance system. Current recommendations assume that HPV-based testing has the highest prognostic value for residual/recurrent disease. Following treatment for HSIL, HPV-based testing is preferable after six months, with subsequent patient management based on the results of virological monitoring and subsequent repeat testing [28, 29].

This prioritization of HPV testing is not accidental. A systematic review and meta-analysis demonstrated that hrHPV testing after excisional treatment has high sensitivity and sufficient specificity for predicting treatment failure, and a negative hrHPV result most reliably reduces the post-test risk of residual/recurrent CIN2+ [14]. A study by Håstad et al. demonstrated that HPV testing alone as a “test of cure” is comparable to cotesting in its ability to detect HSIL+ for up to three years after treatment, but has higher specificity [30]. Consequently, the hrHPV follow-up test has become the primary tool for distinguishing women with ongoing biological risk from those with truly low risk after treatment.

Limitations of Cytology Alone

Against this backdrop, the limitations of isolated cytology become particularly apparent. Cytological examination remains valuable as an additional morphological component of surveillance, but is no longer considered the optimal sole post-treatment test. According to a meta-analysis, cytology is inferior to hrHPV testing in sensitivity, and the addition of cytology to virological testing only slightly increases sensitivity while reducing specificity [14, 30].

This means that cytology alone is less able to detect ongoing viral persistence and the early risk of recurrence. This is where the modern approach addresses another significant shortcoming of previous practice—overestimating morphological control while underestimating the biological activity of the process.

Predicting Residual/Recurrent CIN2+

The key task of the post-treatment phase is not simply to determine whether a patient is "normal" or "not normal," but to predict whether CIN2+ will develop residual or recurrent. Current data show that persistent post-treatment hrHPV positivity remains the most informative predictor of treatment failure [14, 30–32]. However, in real-world practice, a combined assessment of several parameters is most valuable: virological status, resection margin status, age, and initial lesion severity [14, 31, 32]. Thus, the risk of recurrence after conization is significantly higher in HPV-positive women than in HPV-negative ones, and taking margin status into account further improves risk stratification [31]. Other observations have shown that post-treatment hrHPV positivity, involved or indeterminate resection margins, and age 35 years and older are significant predictors of persistent/recurrent CIN2-3, while the combination of negative hrHPV and clear margins provides an extremely high negative predictive value [32]. Therefore, modern clinicians should evaluate post-treatment prognosis not by a single marker, but by a combination of several clinically significant factors.

Post-treatment Surveillance as Risk Re-Stratification

From a practical perspective, post-treatment surveillance should be considered a step in risk re-

stratification. A woman with negative hrHPV after treatment, especially with clean resection margins, moves into the very low-risk category but still does not automatically return to standard population screening [28, 29, 31, 32]. In contrast, a patient with persistent hrHPV, abnormal cytology, positive resection margins, baseline CIN3, AIS, or advanced age requires more vigilant and sometimes longer-term monitoring [14, 30–34].

The key clinical implication here is simple: post-treatment surveillance after CIN2+/HSIL is no longer a cytological process, but primarily an HPV-focused one, in which negative virological testing has the greatest "reassuring" value, and ongoing hrHPV positivity serves as an early signal of ongoing neoplastic risk.

Promising Directions: How to Prevent New Diagnostic and Treatment Errors

Artificial Intelligence as a Standardization Tool

One of the most notable future directions is the implementation of artificial intelligence in cytology and colposcopy. The practical value of AI stems from the fact that both methods remain sensitive to the specialist's experience, the quality of sample preparation, the completeness of visualization, and interobserver variability [35–37]. This largely explains one of the persistent shortcomings of clinical practice—variability in interpretation quality and the dependence of the patient's path accuracy on the skill of the individual specialist.

Current data show that AI can reduce this variability, standardize interpretation, and improve the reproducibility of the initial assessment [35, 36]. In the context of treatment and follow-up, this is particularly important, as eliminating variability at the diagnostic stage automatically reduces the risk of both overtreatment and undertreatment. The most realistic scenario for the near future is not a replacement of physicians, but a hybrid "human + AI" model, where algorithms help triage medications, highlight suspicious areas, and support clinical decisions.

Therapeutic HPV vaccines

The second major area involves therapeutic HPV vaccines. Unlike prophylactic vaccines, they are aimed not at preventing primary infection, but at women who already have infection and/or precancerous lesions [38–41]. This makes them particularly important for future organ-preserving treatment.

Their particular appeal lies in the fact that they could potentially eliminate one of the key shortcomings of current practice—the need for mechanical removal of diseased tissue, even in some young women with high reproductive priorities. The ability to immunologically influence persistent HPV-associated neoplasia opens a new model of organ-preserving management. However, at this stage, therapeutic vaccines should be viewed as a rapidly developing area, rather than a real alternative to approved treatments for HSIL/CIN2+.

Molecular Personalization of Algorithms

Molecular personalization of risk algorithms remains the most strategically important area. This approach combines genotyping, dual staining, self-sampling, methylation, mRNA and oncoprotein testing, information on the transformation zone type, post-treatment margin status, age, and clinical context [42–46]. It is becoming increasingly clear that the future of HPV-positive women's care does not lie with a single "perfect" test. Instead, the most powerful algorithms are those that integrate multiple risk levels into a single clinical model.

This approach can address another fundamental shortcoming of previous practice: the linearity of the pathway, where clinical decisions were made based on one or two indicators. Molecular personalization enables truly dynamic prognostication: not only recording the current state of the cervix, but also predicting which patients are likely to regress, which to persist, and which to progress. In the future, this will allow for the selection of the optimal observation interval, the depth of follow-up testing, and the extent of treatment, not just based on a "group average," but on a specific woman's specific needs.

Discussion

The analysis shows that treatment of cervical pathology in HPV-positive women can no longer be based on a one-size-fits-all approach, where a single virological status automatically leads to the same intervention. Modern clinical practice increasingly demonstrates that the optimal strategy should be determined by the biology of the lesion, the completeness of its visualization, the likelihood of an endocervical component, the patient's age, her reproductive plans, and the risk of subsequent adverse outcomes. Surveillance, ablation, LEEP/LLETZ, and conization are not competing approaches, but rather elements of a unified, risk-based and functionally-sparing system of care.

Equally important is the fact that post-treatment surveillance in the modern model has become an active continuation of treatment. Follow-up hrHPV testing has proven to be the most informative tool for the early detection of residual/recurrent CIN2+, while cytology alone no longer provides sufficient sensitivity. A negative post-treatment hrHPV result has high prognostic value, and its persistence serves as an early signal of ongoing risk. Therefore, the HPV-positive woman's journey does not end after intervention; instead, after treatment, a new stage of individualized risk-based surveillance begins.

Prospects for further development are linked to artificial intelligence, therapeutic HPV vaccines, and the molecular personalization of algorithms. The overall meaning of these changes is already clear: the future of treatment and surveillance for HPV-positive women lies not in standardized schemes, but in a flexible system in which clinical decisions are based on a comprehensive risk assessment, and the care itself becomes more precise, more gentle, and more personalized.

Conclusion

1. Treatment of cervical pathology in HPV-positive women should be strictly individualized.

Observation, ablative methods, LEEP/LLETZ, and conization represent elements of a differentiated strategy, the choice of which is determined by the biology of the lesion, the completeness of visualization of the transformation zone, the likelihood of an endocervical component, the patient's age, and her reproductive priorities.

2. One of the main drawbacks of previous practice was overtreatment, especially in young and nulliparous women.

More radical excisional interventions reduce the risk of treatment failure but are associated with a higher risk of preterm birth and other reproductive complications; therefore, modern strategies should be oncologically adequate but as gentle as possible.

3. Post-treatment surveillance should be considered an independent and long-term stage of management.

Even after technically correct treatment, the risk of residual/recurrent CIN2+ does not immediately disappear, and therefore the patient should not automatically return to the standard population-based screening regimen.

4. Follow-up hrHPV testing is a key tool in modern post-treatment surveillance.

HPV-based testing has the highest predictive value for treatment failure, while isolated cytology is less sensitive. A negative post-treatment hrHPV result most reliably reduces subsequent risk, while its persistence requires more vigilant monitoring.

5. The future of care for HPV-positive women is associated with eliminating the variability and linearity of clinical decisions.

Artificial intelligence, therapeutic HPV vaccines, and molecular personalization of algorithms offer opportunities for a more accurate, reproducible, and patient-centered treatment and monitoring model, but their implementation must be based on rigorous clinical validation and integration into risk-based algorithms.

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