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PROGNOSTIC VALUE OF PERSISTENT CIRCULATING HPV DNA AFTER CERVICAL CANCER CHEMORADIOTHERAPY: A SYSTEMATIC REVIEW

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Abstract

Cervical cancer remains one of the leading causes of gynecologic cancer death worldwide, particularly in low- and middle-income countries. Circulating HPV DNA (cHPV-DNA) is a promising non-invasive biomarker for detecting residual disease and predicting recurrence, but differences in detection methods, specimen types, and post-treatment sampling times have produced variable findings. This study aimed to systematically evaluate and synthesize the evidence on the prognostic value of persistent post-treatment cHPV-DNA in patients with cervical cancer after definitive chemoradiotherapy. This systematic review followed the PRISMA 2020 guidelines, searching PubMed/MEDLINE, Europe PMC, OpenAlex, and ScienceDirect for primary studies published from 2006 to 2026 that assessed HPV DNA in peripheral blood (plasma or serum) after chemoradiotherapy and reported clinical prognostic outcomes. Seven studies met the inclusion criteria. Persistent cHPV-DNA at the end of treatment or during surveillance independently predicted worse progression-free survival (multivariable HR 2.44–14.25) and worse overall survival (HR = 25.4; clearance versus detection HR 0.04–0.20). Persistent cHPV-DNA detected subclinical recurrence with a median lead time of 5.5–10.0 months before radiological progression, whereas post-treatment clearance was consistently associated with durable disease-free survival and a negative predictive value of 87–95%. Persistent post-treatment cHPV-DNA is therefore an independent prognostic biomarker of recurrence, disease progression, and mortality, and liquid biopsy surveillance enables early identification of minimal residual disease.

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INTRODUCTION

Cervical cancer is a major global health burden with high morbidity and mortality among women, occurring most frequently in low- to middle-income countries. More than 99% of carcinomas of the uterine cervix are caused by high-risk *Human Papillomavirus* (HR-HPV) infection, with HPV-16 and HPV-18 responsible for more than 70% of invasive cases globally. Most women present with locally advanced cervical cancer (LACC), categorized according to the revised staging criteria of the International Federation of Gynaecology and Obstetrics (FIGO) (Chen et al., 2025).

The standard definitive regimen for patients with locally advanced cervical

cancer is primary concurrent chemoradiotherapy (CCRT). The standard definitive protocol combines external-beam radiation therapy (EBRT) to the pelvis and involved lymphatic basins, concurrent radiosensitizing chemotherapy (usually weekly cisplatin 40 mg/m^2), and sequential high-dose-rate (HDR) intracavitary brachytherapy or image-guided adaptive brachytherapy (IGABT). This approach aims to maximize local tumor control with a total equivalent dose in 2 Gy fractions (EQD2) of ≥ 85 Gy to the high-risk target volume. Despite high initial clinical response rates, approximately 30% to 40% of patients experience treatment failure, either as persistent locoregional pelvic disease or distant metastasis, most often within the first two years after treatment (Kumar et al., 2018; Kumar & Gupta, 2016).

During cervical carcinogenesis, the HR-HPV viral genome integrates into host cell chromosomes or persists as high-copy-number episomes within malignant epithelial cells. When cervical carcinoma cells undergo turnover, apoptosis, necrosis, or active secretion, cell-free viral DNA fragments physically linked to host genomic sequences are released into the systemic circulation. Because non-malignant somatic host tissues do not contain integrated HR-HPV viral oncogenes (such as E6 and E7), circulating HPV DNA (cHPV-DNA) and circulating HPV tumor DNA (HPV ctDNA) serve as highly specific, non-invasive liquid biopsy biomarkers. Detection of persistent circulating viral DNA after definitive treatment is a direct indicator of remaining subclinical malignant disease (Sabeena et al., 2020).

Although many studies have investigated circulating HPV DNA in cervical cancer, the reported findings come from diverse primary cohorts, heterogeneous assay methodologies (ranging from conventional PCR to ultrasensitive next-generation sequencing [NGS]), different blood specimen matrices (plasma versus serum), and non-standardized post-treatment sampling intervals (end of treatment, 4–6 weeks, 3 months, or routine surveillance). In addition, primary studies have assessed varying clinical endpoints, including overall survival (OS), progression-free survival (PFS), disease-free survival (DFS), recurrence-free survival (RFS), recurrence rates, and subclinical detection lead time. A systematic synthesis is therefore needed to evaluate the prognostic value of post-treatment circulating HPV DNA persistence, assess its independence from clinical stage in multivariable analyses, and determine its potential role in risk stratification.

Based on the above, the research question of this review is: in patients with cervical cancer undergoing definitive chemoradiotherapy, is persistent post-treatment circulating HPV DNA associated with worse clinical outcomes compared with undetectable or cleared circulating HPV DNA? The primary objective of this study was to systematically evaluate the prognostic value of persistent post-treatment circulating HPV DNA in patients with cervical cancer after definitive chemoradiotherapy. Specifically, this review aimed to assess the association between persistent circulating HPV DNA and overall survival, progression-free survival, and disease-free or recurrence-free survival; to evaluate the prognostic significance of post-treatment HPV DNA clearance; and to describe circulating HPV DNA detection methodologies and post-treatment blood sampling time points.

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RESEARCH METHODS

Study Design and Framework

This study is a systematic review conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. A structured narrative synthesis was chosen *a priori* because clinical and technical heterogeneity was anticipated in biomarker assay methods, sampling intervals, operational definitions of biomarker persistence, and clinical outcome measures. Study selection followed the Population, Exposure, Comparator, and Outcome (PECO) framework. The Population (P) was patients diagnosed with primary cervical cancer undergoing definitive concurrent chemoradiotherapy. The Exposure (E) was persistent or detectable circulating HPV DNA (cHPV-DNA or HPV ctDNA) in peripheral blood samples collected after treatment or during post-treatment surveillance. The Comparator (C) was patients with undetectable or cleared circulating HPV DNA after completion of treatment. The Outcomes (O) were clinical prognostic endpoints, including OS, PFS, DFS, RFS, disease recurrence, disease progression, diagnostic lead time, and diagnostic accuracy parameters.

Eligibility Criteria

The inclusion criteria were: (1) original primary clinical research studies involving patients diagnosed with cervical cancer; (2) patient cohorts treated with primary definitive chemoradiotherapy; (3) studies evaluating circulating HPV DNA or HPV ctDNA from peripheral blood specimens (plasma or serum); (4) studies assessing circulating HPV DNA status after completion of chemoradiotherapy or during post-treatment surveillance; and (5) studies reporting at least one objective clinical prognostic outcome (OS, PFS, DFS, RFS, recurrence, or progression).

The exclusion criteria were: (1) studies of non-cervical malignancies, unless cervical cancer data could be extracted separately; (2) studies evaluating only tumor tissue HPV DNA or HPV DNA from cervical swabs/exfoliated cells without evaluation of cell-free DNA in blood; (3) studies assessing only pre-treatment circulating HPV DNA without post-treatment biomarker assessment; (4) patient cohorts treated only with primary radical surgery followed by adjuvant therapy; (5) studies without relevant clinical prognostic endpoints; and (6) narrative reviews, systematic reviews, meta-analyses, editorials, letters, case reports, and non-peer-reviewed conference abstracts lacking sufficient clinical data.

Search Strategy and Study Selection

A literature search was conducted in four electronic databases, namely PubMed/MEDLINE, Europe PMC, OpenAlex, and ScienceDirect, for primary research published between 2006 and 2026. The search strategy combined Medical Subject Headings (MeSH) and free-text terms using Boolean operators. The search concepts consisted of three main groups. Concept 1 (disease): ("cervical cancer" OR "cervical carcinoma" OR "cervix neoplasm" OR "locally advanced cervical cancer" OR "LACC"). Concept 2 (biomarker): ("circulating HPV DNA" OR "cHPV DNA" OR "HPV ctDNA" OR "cell-free HPV DNA" OR "liquid biopsy" OR "circulating tumor DNA"). Concept 3 (intervention): ("chemoradiotherapy" OR "chemoradiation" OR "radiotherapy" OR "CCRT" OR "CRT"). The search syntax was adapted for each database platform.

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Titles and abstracts were screened to exclude irrelevant studies. Potentially eligible records were then retrieved in full text and independently evaluated against the predefined eligibility criteria. Ultimately, seven primary research studies met all eligibility criteria and were included in this systematic review. The study selection process is presented in Figure 1.

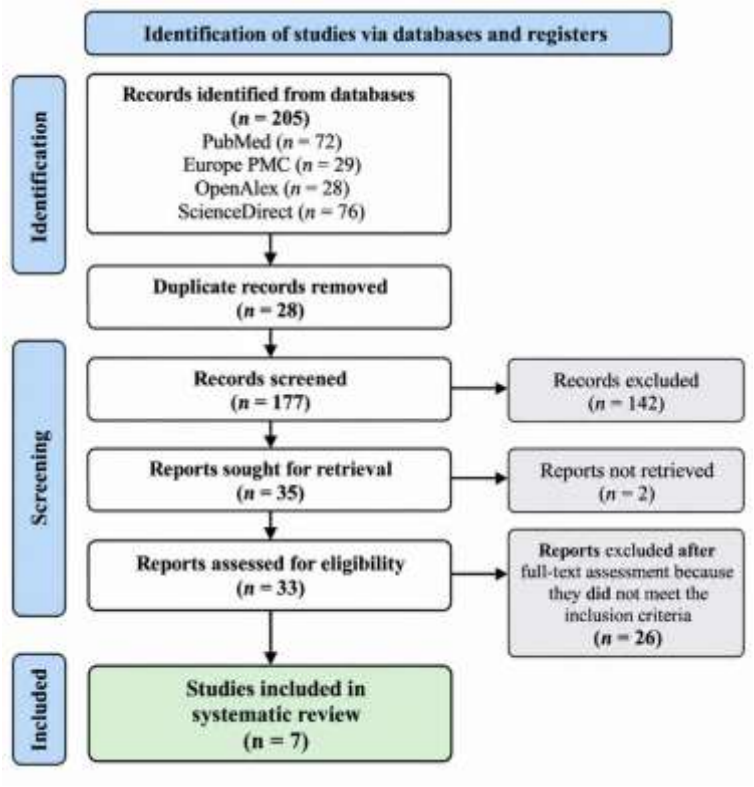

Figure 1. PRISMA flow diagram of study selection

The seven included studies evaluated a total of 500 patient samples from various countries, including India, the United Kingdom, France, Canada, the United States, Mexico, Peru, Chile, Brazil, China, Israel, and other European countries.

RESULTS AND DISCUSSION

Characteristics and Findings of the Included Studies

Singh et al. (2006) reported a retrospective cohort of 56 patients with stage IB–IVB cervical cancer treated with definitive radical radiotherapy in India. Post-treatment plasma HPV DNA positivity (5–224 months after radiotherapy), detected in 20% of samples (11/56), was strongly associated with disease recurrence ($p = 0.0002$; recurrence occurred in 72.7% of HPV DNA-positive patients versus 13.3% of HPV DNA-negative patients) and significantly associated with reduced disease-free survival (log-rank $p = 0.04$).

Mayadev et al. (2025) performed an exploratory biomarker analysis of the global phase III randomized controlled CALLA trial (NCT03830866). The study included 186 biomarker-evaluable patients with FIGO 2009 stage IB2–IVA cervical cancer who underwent definitive chemoradiotherapy with or without durvalumab (1500 mg every 4 weeks) at multiple international centers. Persistent plasma ctDNA was detected in 35.5%–39.8% of patients after chemoradiotherapy (C3D1)

and in 23.4%–36.4% of patients 3 months after treatment (C6D1). Post-treatment ctDNA positivity was a strong independent prognostic factor for both progression-free survival (multivariate HR = 5.27; 95% CI: 2.95–9.40; p < 0.001) and overall survival (p < 0.001), whereas complete ctDNA clearance at 3 months conferred a very large survival benefit (C6D1 PFS and OS HR = 0.04; 95% CI: 0.01–0.17; p < 0.001).

Lalondrelle et al. (2023) conducted a prospective cohort study at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (United Kingdom) involving 22 patients with FIGO 2019 stage IB2–IVA cervical cancer who underwent radical chemoradiotherapy with image-guided adaptive brachytherapy. Plasma cHPV-DNA evaluated with an ultrasensitive amplicon-based NGS assay (panHPV-detect) accurately stratified recurrence risk. At 3 months after chemoradiotherapy, persistent cHPV-DNA was detected in 3 patients, all of whom (100%) experienced recurrence or persistent active disease, whereas 92.3% (12/13) of patients with cleared cHPV-DNA remained recurrence-free. Overall, cHPV-DNA monitoring at 3 months after treatment achieved a diagnostic accuracy of 93.8% (15/16 samples) in predicting residual or recurrent disease and clarified equivocal post-radiation MRI and PET-CT findings in four patients who did not experience recurrence.

Jeannot et al. (2021) was a prospective multicenter observational cohort study evaluating 94 patients with FIGO 2018 stage I–IV cervical cancer treated with chemoradiotherapy at several European centers. Baseline (pre-treatment) serum ctDNA positivity was not prognostic for PFS (p = 0.19). In contrast, persistent serum ctDNA at the end of treatment, detected in 27.5% of samples, was a strong independent predictor of worse PFS in multivariable Cox regression (HR = 14.25; 95% CI: 3.10–61.57; p = 0.001; univariable HR = 10.95; 95% CI: 2.94–40.7; p < 0.0001). Undetectable serum ctDNA at the end of treatment yielded a negative predictive value of 95% for recurrence-free survival.

Han et al. (2024) conducted a prospective multicenter validation cohort study at four Canadian centers evaluating 70 HPV-positive patients with FIGO 2018 stage IB–IVA cervical cancer treated with definitive chemoradiotherapy and MRI-guided adaptive brachytherapy. The study used digital PCR (dPCR) and an ultrasensitive NGS assay (HPV-seq) targeting 38 high-risk and low-risk HPV genotypes. Persistent plasma HPV ctDNA detected after chemoradiotherapy was identified as an independent predictor of significantly worse PFS at several post-treatment time points. In multivariable Cox regression adjusted for FIGO 2018 stage, post-treatment dPCR and HPV-seq ctDNA positivity predicted worse PFS at the end of chemoradiotherapy (dPCR HR = 2.44; 95% CI: 1.02–5.82; p = 0.045; HPV-seq HR = 4.13; 95% CI: 1.38–12.34; p = 0.010), increased significantly at 4–6 weeks after chemoradiotherapy (dPCR HR = 6.79; 95% CI: 2.66–17.34; p < 0.001; HPV-seq HR = 3.86; 95% CI: 1.61–9.22; p = 0.002), and remained highly predictive of progression at 3 months after chemoradiotherapy (dPCR HR = 5.50; 95% CI: 2.32–13.04; p < 0.001; HPV-seq HR = 7.78; 95% CI: 3.15–19.24; p < 0.001). In addition, serial post-treatment plasma ctDNA detection preceded clinical or radiographic recurrence by a median lead time of 5.9 months (range 0–28 months).

Cabel et al. (2021) was a French cohort study of 55 patients with FIGO 2018

stage I–IVA cervical cancer, primarily treated with definitive chemoradiotherapy and evaluated using genotype-specific ddPCR for 9 high-risk HPV types. Pre-treatment ctDNA detection showed no significant prognostic association with disease-free survival (HR = 0.85; 95% CI: 0.4–2.0; p = 0.71) or overall survival (HR = 1.4; 95% CI: 0.4–4.4; p = 0.57). In contrast, circulating HPV ctDNA persisting at the end of chemoradiotherapy or during post-treatment surveillance in the prospective cohort was significantly associated with worse disease-free survival (HR = 5.1; 95% CI: 0.85–31; log-rank p = 0.048) and worse overall survival (HR = 25.4; 95% CI: 2.4 to >100; log-rank p = 0.0013). In the retrospective cohort, all patients with residual ctDNA at the end of treatment (2/2; 100%) experienced recurrence.

Leung et al. (2021) conducted a retrospective proof-of-principle biomarker study within a prospective multicenter clinical trial cohort evaluating 17 patients with locally advanced cervical cancer treated with definitive chemoradiotherapy in Canada. Pre- and post-treatment plasma ctDNA was analyzed quantitatively using ultrasensitive HPV-seq. At the end of chemoradiotherapy (evaluated in 16 samples), persistent plasma HPV ctDNA was detected in 56.3% of patients (9/16), with significantly higher concentrations in patients who subsequently relapsed than in those who remained disease-free (Mann–Whitney p = 0.0005). Detectable plasma ctDNA at the end of treatment was associated with worse PFS (log-rank p = 0.051), with 100% sensitivity (4/4 recurrences detected) and a 100% negative predictive value for complete ctDNA clearance.

Overall Survival

Overall survival outcomes were reported in three primary studies. Mayadev et al. (2025) showed that ctDNA clearance at C3D1 after chemoradiotherapy was associated with an 80%–82% reduction in the risk of death (HR = 0.18; 95% CI: 0.08–0.38 in the chemoradiotherapy arm; HR = 0.20; 95% CI: 0.09–0.47 in the durvalumab + chemoradiotherapy arm; p < 0.001). At C6D1 (3 months after chemoradiotherapy), ctDNA clearance conferred a 96% reduction in mortality risk (HR = 0.04; 95% CI: 0.01–0.19; p < 0.001), establishing post-treatment ctDNA as an independent predictor of overall survival. Similarly, Cabel et al. (2021) showed significantly reduced overall survival in patients with persistent post-treatment ctDNA (HR = 25.4; 95% CI: 2.4 to >100; p = 0.0013). In contrast, neither the presence nor the concentration of pre-treatment ctDNA was significantly associated with overall survival (HR = 1.4; 95% CI: 0.4–4.4; p = 0.57).

Progression-Free Survival

Progression-free survival was evaluated as a primary endpoint in four studies. According to Jeannot et al. (2021), persistent serum HPV ctDNA at the end of treatment was associated with worse PFS (HR = 14.25; 95% CI: 3.10–61.57; p = 0.001). Han et al. (2024) confirmed an independent prognostic association at multiple post-chemoradiotherapy time points using dPCR and NGS platforms, with multivariable HRs for PFS ranging from 2.44 (p = 0.045) at the end of treatment to 7.78 (p < 0.001) at 3 months after chemoradiotherapy. Mayadev et al. (2025) reported that ctDNA clearance at C3D1 conferred a 77%–85% reduction in the risk of disease progression (HR = 0.15–0.23; p < 0.001), increasing to a 96% risk reduction at C6D1 (HR = 0.04; p < 0.001). Leung et al. (2021) further supported

these findings by showing a strong trend toward worse PFS in patients with detectable plasma ctDNA at the end of treatment (p = 0.051).

Disease-Free and Recurrence-Free Survival

Disease-free and recurrence-free survival endpoints were reported in three studies. Singh et al. (2006) showed that post-radiotherapy plasma HPV DNA positivity was significantly associated with shorter DFS (p = 0.0445/log-rank p = 0.04). Cabel et al. (2021) also showed that ctDNA persisting during post-treatment surveillance yielded an HR of 5.1 (95% CI: 0.85–31; p = 0.048) for DFS.

Recurrence Rates and Detection Lead Time

Across all studies, persistent post-treatment circulating HPV DNA was highly predictive of recurrence, with recurrence rates ranging from 72.7% to 100%. In Singh et al. (2006), recurrence occurred in 72.7% of plasma HPV DNA-positive samples compared with 13.3% of plasma HPV DNA-negative samples. In Jeannot et al. (2021), the recurrence rate with persistent ctDNA at the end of treatment was 81.8%, while with prospective longitudinal persistence it reached 100%. In Lalondrelle et al. (2023) and Cabel et al. (2021), all samples (100%) with persistent viral DNA during post-chemoradiotherapy surveillance experienced recurrence.

Furthermore, persistent circulating HPV DNA was able to detect subclinical minimal residual disease (MRD) much earlier than standard anatomical or metabolic imaging. The median diagnostic lead time from molecular detection of persistent cHPV-DNA/ctDNA to clinical or radiological confirmation of recurrence ranged from 5.5 to 10 months. Jeannot et al. (2021) reported a median lead time of 10.0 months (range 2–15 months), Han et al. (2024) reported a median of 5.9 months (range 0–28 months), and Mayadev et al. (2025) obtained a median of 5.5 months (164 days; range 46–497 days).

Prognostic Value of Circulating HPV DNA Clearance

Complete clearance of circulating HPV DNA after chemoradiotherapy was consistently associated with long-term recurrence-free survival. The negative predictive value (NPV) of post-treatment cHPV-DNA clearance ranged from 87% to 95% across the main studies, namely 87% in Singh et al. (2006), 94% at 3 months after chemoradiotherapy in Mayadev et al. (2025), and 95% in Jeannot et al. (2021), reaching 100% in the pilot NGS cohort of Leung et al. (2021). In Lalondrelle et al. (2023), cHPV-DNA clearance clarified equivocal post-radiation MRI/PET-CT findings in 100% (4/4) of cases in which imaging suggested residual tumor, confirming complete molecular remission without clinical recurrence.

Detection Methods and Sampling Time

Comparative analysis of detection technologies showed that the conventional PCR–Southern blot method in Singh et al. (2006) achieved a clinical sensitivity of only about 57% (8/14 recurrences detected), whereas modern quantitative digital PCR (dPCR/ddPCR) and targeted NGS (HPV-seq, panHPV-detect, NeXT Personal®) achieved sensitivities of 88% to 100% and specificities of 67% to 100%. Cell-free DNA from plasma showed greater consistency and yield than serum. In addition, panels targeting 8 to 38 high-risk/low-risk genotypes prevented false-negative results in cervical carcinomas not caused by HPV-16/18.

Biomarker kinetics showed that although pre-treatment circulating HPV DNA reflects baseline tumor burden, its level did not independently predict survival after definitive chemoradiotherapy (p = 0.19 to 0.841). In contrast, post-treatment evaluation captures tumor sensitivity to therapy. Sampling at the end of treatment provides an initial reference point for MRD risk assessment (HR = 2.44–14.25). However, testing at 4–6 weeks and 3 months after chemoradiotherapy showed higher HRs (HR = 5.50–7.78) and better diagnostic specificity, because the clearance kinetics of DNA from early post-radiation cell death have subsided.

Synthesis of Findings

This systematic review shows that persistent post-treatment circulating HPV DNA (cHPV-DNA/HPV ctDNA) is a strong prognostic biomarker in patients with cervical cancer undergoing definitive chemoradiotherapy. Across seven primary studies involving diverse geographic populations, analytical platforms, and post-treatment sampling schedules, persistent post-treatment circulating HPV DNA was consistently associated with disease recurrence, shorter disease-free survival, worse progression-free survival, and worse overall survival. Persistent circulating HPV DNA also identified subclinical MRD with a median lead time of 5.5 to 10.0 months before radiological progression. Conversely, complete biomarker clearance after chemoradiotherapy was consistently associated with durable recurrence-free survival and a high negative predictive value. The strength of this review lies in its specific focus on post-treatment (rather than pre-treatment) biomarker assessment in a population undergoing definitive chemoradiotherapy, making its findings directly relevant to post-treatment surveillance strategies.

Limitations

Several limitations should be considered. First, some studies had relatively small sample sizes (n = 17 to 55), which may limit statistical power and the reliability of the results. Second, detection technologies differed between studies (PCR, ddPCR, dPCR, amplicon NGS, HPV-seq, and tumor-informed whole-genome sequencing), making direct comparisons difficult. Post-treatment blood sampling schedules also varied between studies (from the end of treatment to diverse surveillance intervals). In addition, several older studies tested only for HPV-16 and HPV-18 and may therefore have missed other high-risk HPV types. Finally, some studies did not provide complete statistical data, such as hazard ratios and confidence intervals, limiting further analysis.

Implications for Future Research

Future research should focus on assay standardization by harmonizing analytical protocols, establishing standardized positivity thresholds, and building consensus reference panels for dPCR- and NGS-based cHPV-DNA testing. Blood sampling schedules should also be harmonized, for example at baseline, mid-chemoradiotherapy, end of treatment, and 4–6 weeks, 3 months, 6 months, and 12 months after chemoradiotherapy.

CONCLUSION

Persistent post-treatment circulating HPV DNA is a strong independent prognostic biomarker of disease recurrence, worse progression-free survival, and reduced overall survival in patients with cervical cancer treated with definitive

chemoradiotherapy. Molecular detection of persistent viral DNA can identify minimal residual disease before clinical or radiological manifestation, with a diagnostic lead time of 5.5 to 10.0 months ahead of conventional imaging. Standardization of assay platforms and prospective validation through biomarker-driven interventional trials are recommended to support the integration of circulating HPV DNA liquid biopsy into routine clinical practice.

Statement on the Use of Artificial Intelligence

AI was used in the preparation of this manuscript. The authors used artificial intelligence tools solely to assist with language improvement, grammar checking, and editing for clarity and readability. The authors remain fully responsible for the accuracy, originality, integrity, and academic content of the manuscript. All AI-assisted content was reviewed and verified by the authors before submission.

Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization, C.A. and D.K.; literature search and selection, C.A.; data extraction, C.A.; data validation, D.K.; formal analysis, C.A. and D.K.; writing—original draft preparation, C.A.; writing—review and editing, D.K.; supervision, D.K. All authors have read and approved the final version of the manuscript.

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