Qeios

Peer Review

Review of: "Monitoring Circulating Cell-Free HPV DNA in Metastatic and Recurrent Cervical Cancer: Clinical Importance and Implications for Treatment – A Pilot Study"

Jonas Michel Wolf[1]

1. Hospital Moinhos de Vento, Porto Alegre, Brazil

This prospective pilot observational study explores the utility of monitoring circulating human papillomavirus cell-free DNA (HPV cfDNA) as a tumor marker for disease surveillance and guiding clinical treatment decisions in patients with recurrent or metastatic HPV-positive cervical cancer. Given the significant challenges in effectively managing advanced cervical cancer, particularly in terms of early detection of recurrence and monitoring treatment response, a minimally invasive and highly accurate tumor marker is desperately needed. This research addresses a critical gap in current clinical practice and holds substantial promise for advancing precision medicine in oncology.A major strength of this study is its clear focus on recurrent or metastatic HPV-positive cervical cancer, a patient population with high unmet needs for effective surveillance tools. By concentrating on this specific group, the study directly addresses a clinically relevant problem, aiming to provide a more precise and timely method for monitoring disease progression and treatment efficacy beyond conventional imaging and less sensitive tumor markers like SCC-Ag.The high detection rate of HPV cfDNA (100% in all 28 patients) at baseline is a compelling finding. This indicates the strong sensitivity of the digital droplet polymerase chain reaction (ddPCR) method for detecting circulating tumor DNA in this patient cohort, suggesting that HPV cfDNA could be a universal marker for HPV-positive cervical cancer patients with advanced disease, regardless of their metastatic pattern.The study provides valuable insights into the correlation between baseline HPV cfDNA levels and metastatic patterns. The observation that patients with a combined multi-metastatic pattern exhibit significantly higher median baseline HPV cfDNA levels compared to those

 doi.org/10.32388/2BNZBQ

with a single-metastasis pattern is highly significant (P=0.003). This suggests that HPV cfDNA levels may not only indicate the presence of disease but also correlate with disease burden or aggressiveness, offering a potential prognostic indicator.Furthermore, the longitudinal monitoring aspect, demonstrating changes in HPV cfDNA levels over a median period of 2 months, is crucial. This indicates the dynamic nature of HPV cfDNA as a real-time reflection of tumor activity. More importantly, the high concordance (90%) between changes in HPV cfDNA levels and changes in disease status, compared to SCC-Ag (50%), strongly positions HPV cfDNA as a superior tumor marker for monitoring treatment efficacy and disease progression in squamous cell cervical cancer. The statistical significance of this difference (P = 0.014) is particularly impactful.However, despite its promising findings, this pilot study has several opportunities for improvement that, if addressed, could significantly strengthen its conclusions and pave the way for broader clinical implementation. The most prominent limitation, acknowledged by the term "pilot observational study," is the small sample size (n=28 patients). While the initial findings are compelling, a larger cohort is essential to confirm these results, increase statistical power, and establish the generalizability of HPV cfDNA's utility across a more diverse patient population.The median monitoring period of 2 months, although providing initial longitudinal data, is relatively short for a chronic disease like cancer, particularly for assessing long-term treatment efficacy and recurrence. Extending the follow-up duration would provide more robust evidence on the sustained utility of HPV cfDNA as a surveillance marker and its ability to predict long-term outcomes, such as progression-free survival and overall survival.While the study matched HPV cfDNA levels to clinical outcomes, a more detailed breakdown of these "clinical outcomes" would be beneficial. Specifying the criteria used for defining "treatment response" (e.g., RECIST criteria, clinical improvement) and "disease progression" would add rigor and allow for a more precise understanding of the concordance observed.The study primarily focuses on squamous cell cervical cancer (26 out of 28 patients). While this is the most common histological type, further investigation into the utility of HPV cfDNA in other less common HPV-associated cervical cancer types, such as adenocarcinoma, would broaden the clinical applicability of this biomarker.Finally, while the conclusions emphasize the potential of HPV cfDNA in guiding clinical decisions within precision medicine, the study does not explicitly detail how HPV cfDNA levels were used to *guide* such decisions in this pilot cohort. Providing specific examples or a framework for how these measurements influenced treatment adjustments, initiation of new therapies, or changes in surveillance frequency would demonstrate the translational impact more directly and foster greater understanding among clinicians.In conclusion, this pilot study presents compelling evidence that circulating HPV cfDNA is a highly promising, minimally invasive tumor marker for the surveillance of

recurrent or metastatic HPV-positive cervical cancer. Its strengths lie in the high detection rate, correlation with metastatic burden, and superior concordance with disease status compared to SCC-Ag. To fully realize its potential in guiding clinical decisions and advancing precision medicine, future research should transition to larger, multi-center studies with extended follow-up periods, provide more detailed definitions of clinical outcomes, explore its utility across different histological subtypes, and clearly articulate the practical application of cfDNA levels in clinical decision-making.

Declarations

Potential competing interests: No potential competing interests to declare.