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Peer Review

Review of: "Monitoring of Cell-free Human Papillomavirus DNA in Metastatic or Recurrent Cervical Cancer: Clinical Significance and Treatment Implications"

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The aim of this research is to contribute to a better clinical assessment of patients with cervical cancer. The Author monitored circulating HPV cfDNA levels during treatment and follow-up.

The rationale for the research is based on the continuous release into the bloodstream of tumor cell-free DNA, the amount of which is related to the extent of cancer spread. Circulating DNA can be precisely measured via digital droplet polymerase chain reaction or next-generation sequencing technology. Therefore, the variations in serum levels of cancer DNA over time provide a precise evaluation of the evolution of the disease in response to treatment. The Author emphasizes the need to explore clinically effective markers for cervical cancer because the one currently adopted, i.e., the squamous cell carcinoma antigen, has proven to be of little use.

Based on the above criteria, 28 patients with recurrent or metastatic HPV+ cervical cancer were monitored via digital droplet polymerase chain reaction. In addition, Squamous-Cell Carcinoma Antigen testing was conducted for patients with squamous cell cancer.

As usual, the data were correctly analyzed by Fisher's exact test, Kaplan-Meier analysis, and the Cox model.

The study provided the following results, consistent with the theoretical premises:

- no significant correlation between Squamous Cell Carcinoma Antigen and HPV cfDNA levels;

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- HPV cfDNA dynamic fluctuations during treatment, while the Squamous Cell Antigen levels rapidly decrease towards the normal range;
- correlation between baseline HPV cfDNA copy number and recurrence/metastasis;
- faster cell-free DNA prediction of disease regression and progression compared to imaging assessment;
- superiority of serum HPV cell-free DNA over Squamous Cell Cancer Antigen in monitoring metastatic or recurrent cervical cancer.

Several relevant observations are highlighted in the discussion, among which:

- 100% agreement of HPV typing results between exfoliated cervical cells and serum samples;
- positive correlation of HPV+ cancer cells with tumor stage, tumor load, and lymph node status;
- enhancement of tumoral cell death and clearance of HPV cell-free DNA by the combination of immunotherapy and targeted therapy along with cytotoxic chemotherapy, compared to cytotoxic chemotherapy alone.

The small sample size and the heterogeneous sequential sampling protocol are mentioned as limitations of the research.

I read the manuscript with interest. It clearly expresses logical concepts from a clinical perspective. The research results constitute a solid basis for better diagnostic, therapeutic, and prognostic assessment of patients affected by advanced cervical cancer.

I don’t believe that the small number of patients and the heterogeneous sequential sampling limit the meaning or the value of the results: in my opinion, when a large study population is required to achieve statistical significance, this means that the truth to be discovered is very small!

HPV testing as a primary screening is a more complex issue that requires a different experimental approach; it is not reasonable to think that it can replace cytology at the moment. However, the hypothesis that direct HPV DNA testing on cervical scrapings may enhance the efficacy of cytology cannot be disregarded.

The different behavior of HPV cfDNA compared to squamous cell carcinoma antigen is very interesting. I do not have an explanation for this, and it would be very kind of the Author to enrich the discussion with their opinion on this matter.

Overall, however, the manuscript can be published even in its present form.

Declarations

Potential competing interests: No potential competing interests to declare.