Qeios

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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Manuscript Title: Monitoring of Cell-free Human Papillomavirus DNA in

Metastatic or Recurrent Cervical Cancer: Clinical

Significance and Treatment Implications

Author: Hanmei Lou

General comments:

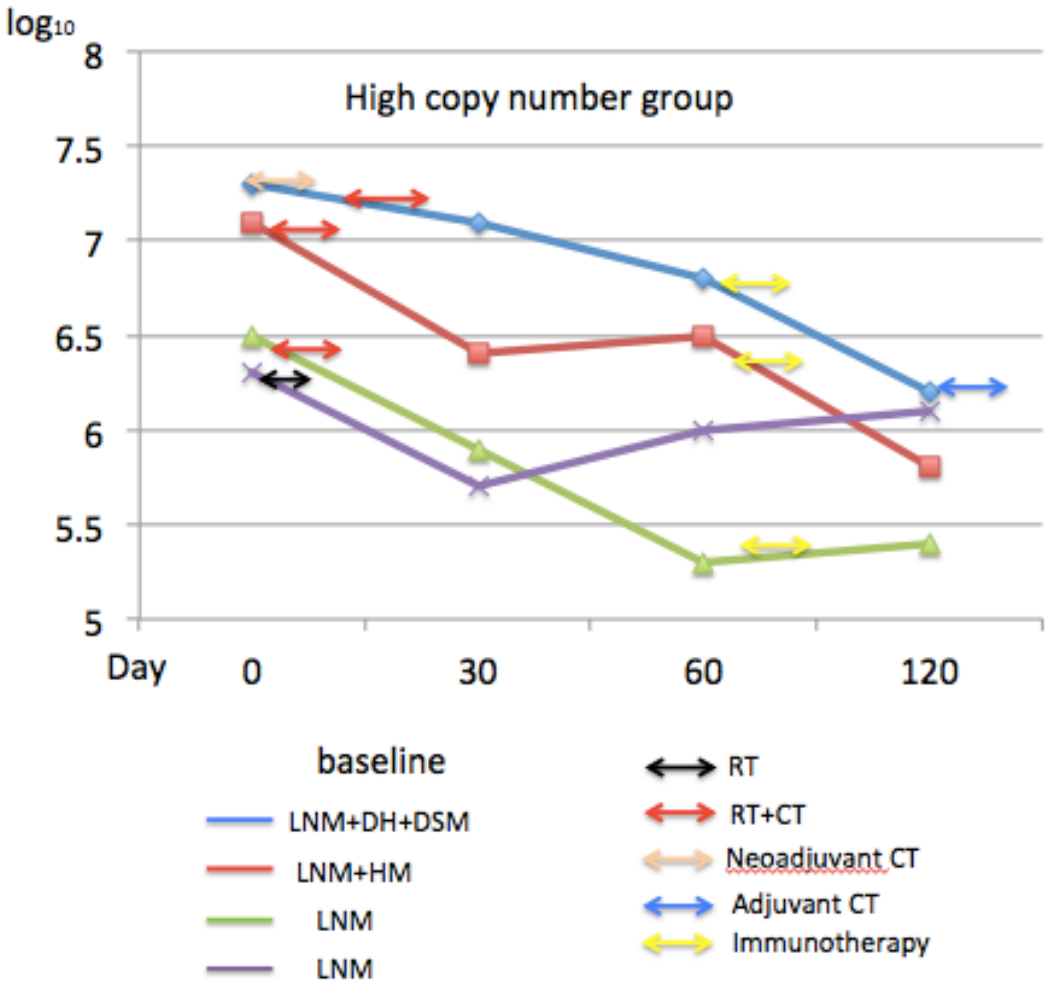
This manuscript addresses an issue regarding the diagnostic and therapeutic values of ddPCR detection of HPV cell-free DNA (cfDNA) from patients with advanced (recurrent or metastatic) HPV-positive cervical cancer. The author concludes that 1) the baseline copy number of HPV cfDNA correlates with baseline recurrence/metastatic patterns (Fig. 2B), 2) HPV cfDNA can predict treatment response earlier than imaging assessments (Fig. 3A1, B1, C1 and D1), and 3) ddPCR outperforms SCC-Ag as a biomarker (Fig. 3). Although several related studies have been published (as reviewed by Andrioaie et al. Pathogens (2023) 12, 908) and the author admits some weak points (e.g., relatively small sample size and inconsistency of sampling protocol), this report with samples of distinct ethnicity should contribute to a deeper understanding of the issue. Unfortunately, however, data presentation is not sufficiently comprehensive.

Specific points:

doi.org/10.32388/XKYO4Q

1. The author mentions in the bottom paragraph on p. 8, “Six patients with clinically progressive disease (as per RECIST) exhibited elevation of HPV cfDNA copy number---,” and showed results for 3 patients in Fig. 3A1. I think it would be better to show more information on all 6 patients.

In Figure 3, especially F1 and F2, what can be obtained from this graph at a glance is that HPV cfDNA changes fluctuate, whereas SCC-Ag changes decline rapidly in the early days. This fluctuation is probably due to recurrent/metastatic status and therapeutic intervention. In addition, high-density plots can cause difficulty in data interpretation. To make the data more informative and comprehensive, I would suggest dividing the data into three categories by copy number (high, medium, and low) and preparing figures like the one attached below. Information on patient death should also be included. Alternatively, just a comprehensive table would be helpful. Then readers can better understand the relationships between baseline status, conducted therapies, outcome, and the cfDNA amounts.



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1. Also related to Fig. 3, the author mentions in the upper paragraph on p. 11, “HPV cfDNA exhibited dynamic fluctuations, while serum SCC-Ag levels in the majority of patients rapidly decreased near or below the normal levels ----,” and concludes that HPV cfDNA can predict treatment response better than SCC-Ag. However, the very rapid (in 30~60 days) response of SCC-Ag to therapies can also be useful for early assessment of treatment response. It is possible that SCC-Ag reflects a more dynamic or transcriptionally active state of DNA and that inactive or fragmented HPV cfDNA contributed to the more sensitive and persistent detection. Do persistent HPV cfDNA levels correlate with poor long-term prognosis, such as death? The author needs to discuss these possibilities.
2. In Fig. 3C1/C2, the author showed just one case of double infection of HPV subtypes. Six patients had a different subtype (58, 18, and 31). How was the clinical efficacy or cfDNA change in these patients compared to patients with subtype 16?
3. The author mentions that HPV cfDNA levels between $\geqq 3.9\times10^4$ and $<3.9\times10^4$ did not show an OS difference. In fact, the $\geqq 3.9\times10^4$ group has rather preferable survival, although statistically not significant. If more information on the therapies is included, this apparent paradox might be explained; the $\geqq 3.9\times10^4$ group might have received more extensive therapies, and it benefited their survival. It would be better to discuss this as well.

Declarations

Potential competing interests: No potential competing interests to declare.