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Peer Review

Review of: "Computationally Optimized ctDNA Surveillance for Recurrence Detection in HPV-Positive Head and Neck Squamous Cell Carcinoma"

Tijl Vermassen[1,2,3]

1. Dept. Medical Oncology, Universitair Ziekenhuis Ghent, Gent, Belgium; 2. Biomarkers in Cancer, Dept. Basic and Applied Medical Sciences, Ghent University, Gent, Belgium; 3. Cancer Research Institute Ghent, Ghent, Belgium

Dear authors,

I have carefully read the manuscript "*Computationally Optimized ctDNA Surveillance for Recurrence Detection in HPV-Positive Head and Neck Squamous Cell Carcinoma*."

I find the article very interesting and an important step towards more personalized medicine in HPV+ HNSCC.

Herewith, I provide you with some considerations to improve the manuscript.

1. GENERAL
    a. The article is sometimes hard to follow, especially if you do not have a more 'computational' background. Therefore, I fear that pure clinicians might find the article difficult to understand. It might therefore be an idea to have the manuscript proofread by a non-academic clinician?
2. INTRODUCTION
    a. You state that "human papillomavirus (HPV)-positive HNSCC constitutes over 70% of newly diagnosed HNSCC cases in the United States and that the prevalence of HPV-positive HNSCC has increased dramatically, from 16% in the 1980s to 72% in the 2000s." This is not entirely correct. This statement is true for OPSCC, a subset of HNSCC, which accounts for approximately 30% of all HNSCC in the US.
3. MATERIALS AND METHODS

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a. Be careful not to give results in the Materials and Methods section. For instance, in the paragraph on 'Input parameters and recurrence pattern model parameterization', you indicate that "this analysis accounted for differences in sample sizes across stages and years. The results indicated no statistically significant difference between the two models (p-value = 0.35), suggesting that both models produce comparable disease trajectories (see Figure 1 (b))". This is a result and should be given in the Results section.

b. You indicate that "the cost of ctDNA testing has been reported between $500 and $1,800. For our analysis, we selected the lower end of this range ($500) to ensure consistency with the cost reference used for imaging and biopsy in comparable studies." Would it not be more prudent to 1) perform a similar analysis using the higher cost, or 2) use a median cost? This is because it cannot be predicted which test will become available on the market. In addition, the respective costs used for the PET/CT ($8,240) and the Joint CT neck and chest ($2,510) are also median costs from the article by Kowalchuk et al.

c. In the paragraph 'Disease progression and simulation model': line 9: duplication of the word "*and*". Please omit.

d. It is still not entirely clear to me why you would use various detection delay targets. Is it not more logical to use a single target of three months? In this way, the ctDNA detection and imaging will be more aligned, and a more personalized treatment can be initiated. If not, patients will live in anxiety for several months prior to being able to start a correct treatment course that is guided by imaging.

4. FIGURES

a. Please refer to figures in chronological order. First, you refer to figure 1b, and later to figure 1a. Please adapt.

b. Please provide a legend for not-commonly used abbreviations in each figure (for instance, figure 1: N = negative; P = positive).

c. Figure 1: Would it not be more logical in figure 1 to place the proposed personalized ctDNA-based schedule at the end (=1e and not 1c)?

d. Figure 4: Why is there no confirmatory CT added to the adapted models (at least one)? In my opinion, this is needed as this will guide further treatment (systemic versus locoregional approach). Was an additional CT scan included in the cost-saving calculation?

5. TABLES

a. There is no reference to table 1 in the main text of the manuscript.

Declarations

Potential competing interests: No potential competing interests to declare.