



## Comments on: Value and role of surgical margins in transoral laser microsurgery of the larynx, literature review and clinical considerations

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Dear Editor,

We read with great interest the recent article published by Reale and colleagues [1] about the influence of surgical margins in patients who underwent transoral laser microsurgery (TLM). We particularly appreciate the authors' effort to address such a relevant topic that lacks solid evidence in the literature.

While we acknowledge the efforts made by the authors in conducting their meta-analysis, we believe that some important nuances and considerations deserve attention.

The paper's conclusion suggests that positive margins represent a risk factor for overall survival (OS), disease free survival (DFS), disease specific survival (DSS), and laryngeal preservation (LP). However, we have identified several

notable methodological shortcomings after carefully reviewing the study.

A survival analysis is a particular statistical analysis designed to handle time-related events and the phenomenon of censoring [2]. A meta-analysis of proportions that computes odds ratios (OR) without considering the timing of events is inherently inadequate for making direct comparisons between the mentioned survival outcomes. This often entails combining studies reported at various stages of maturity, yielding an estimate that is not only unreliable but also challenging to interpret. This statistical approach can be appropriate when defining a survival outcome within a specific time frame (e.g., a 2-year period). However, this aspect was not clarified in the analysis, resulting in the merging of different follow-up times across studies and yielding a

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mixed, and ultimately incorrect, pooled value. Furthermore, the authors employed conventional statistical approaches to compare averages between the two groups (positive and negative margins) in terms of recurrence rates. This approach is fundamentally flawed when merging data from different studies because meta-analytic methods require pooling the single-study effect sizes through more complex statistical models. These models involve a weighted average of the effect estimates from the different studies, accounting for variations across studies and their heterogeneity.

In a meta-analysis, it is essential to consider the consistency of the included studies. As the authors report, there was considerable heterogeneity in the definition of a negative resection margin (ranging from 2 mm to less than 1 mm). Regarding this topic, we would like to remind the readers that, considering several factors including charring of the monopolar cut, the post-resection shrinkage, and the formalin fixation process, only “ink-on-tumor” margins seem to hold enough evidence to be considered positive margins in transoral surgery, especially for the larynx [3–5].

Finally, the authors concluded that a surgical second look in case of positive margin seems to be the best option for the patient in terms of lower risk of recurrence and better oncological results. However, this statement is not supported by the results of the present meta-analysis, and a more comprehensive discussion of this topic would be required taking into account multiple factors (e.g. number of positive margins, deep vs. superficial margins) before recommending a second look surgery indiscriminately considering the economical and functional cost of this procedure.

Unfortunately, conducting meta-analyses on survival data is not always straightforward, particularly when dealing with retrospective studies. In such scenarios, improperly conducted statistical analyses can lead to erroneous conclusions, with adverse effects on future research endeavors. In light of these points, we implore an abundance of caution in using these findings to derive clinical decisions such as adjuvant therapy or re-resections.

Although we find the current subject matter to be highly important, the current work falls short of significantly

enhancing the existing literature due to limitations in data analysis. Therefore, we appreciate the opportunity to share this perspective and hope that it may contribute to a more comprehensive discussion on the subject of surgical margins in TLM.

## Declarations

**Conflict of interest** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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