



## Letter to the editor

## Clinical validity and conceptual interpretation of systematic review and meta-analysis on elective neck dissection (END) versus observation for early-stage oral squamous cell carcinoma (OSCC)



To the Editor,

A systematic review and meta-analysis study was recently published by Oh et al. in the Oral Oncology journal, comparing the effects of elective neck dissection versus observation in early-stage oral squamous cell carcinomas [1].

**High quality of the study:** The study put forward by Oh et al. is of high academic quality, logically structured and presented well and provides valuable insights into factors contributing to prognosis in OSCC. After the issues presented here are addressed, this study may also serve to inform clinical decision making. Patient prognosis in OSCC is an issue of considerable clinical interest, especially with studies suggesting that observation can help reduce unnecessary surgical interventions that may place an undue burden on the patient or lead to worse prognosis or quality of life issues. However, we propose that the study by Oh et al. could be improved by addressing a few issues in its methodology to be addressed before being sufficiently robust to inform clinical decision making.

**A discordance in the title:** There is a discordance in the title which compares the treatment of elective neck dissection with watchful waiting in early oral cancers. At the same time, the aim of the study constricts its comparison to early-stage tongue cancers, which is a discrete oral cavity subsite [2]. Albeit, cancers of the oral tongue and the floor of the mouth are more likely to metastasise to the cervical lymph nodes [3].

**Debulking surgery of neck nodes:** Debulking surgery or berry picking of neck nodes in head and neck cancer has no role as it is an all or none phenomenon. Neck dissection regimen can be a prophylaxis for future regional metastasis, is the best staging modality and also addresses the removal of a gross disease with an improved clinical outcome. The utility of neck dissection has often remained a contention issue over that past decades in relation to early-stage oral cancers where there is a probability of imperceptible neck metastasis, despite clinical and imaging surveillance. Besides, the significant impact of neck dissection on the disease-specific survival, overall survival, and the augmented nodal status following observation often eclipse the morbidity associated with it.

**Interpretation of statistical significance on determining the effectiveness of the interventions:** A primary issue in this study is the emphasis on determining the effectiveness of the interventions using statistical significance. The authors give clinical recommendations in the results based on the “significance” in the difference between the recurrence rates and survival rates between the two interventions. Statistical significance has been shown to be an imprecise parameter for determining the value of results obtained in meta-analysis. Consequently, the recommendations given here are misleading [4]. We recommend that in its stead, the focus be placed on presenting the results purely through the effect size values of OS and DFS, with clinical

relevance and recommendations open to interpretation by clinicians and peers, who can apply the data depending on the context.

**Summary statistics of effect size:** Furthermore, for analysis of prognosis in systematic reviews and meta-analysis, the Odds Ratio (OR) is not the appropriate effect size metric in the instance. Systematic review and meta-analysis studies on prognosis in cancer, has historically pooled from multiple different studies, should use the effect size metric of Hazard Ratios (HR), which we would like to recommend. The pooling of HR in meta-analysis studies is derived from the three endpoints of survival, i.e., Overall Survival (OS), Disease-Free Survival (DFS), and Disease-Specific Survival (DSS). For this reason, each of these endpoints should have been assessed as different subgroups and should not have been pooled into a single meta-analysis [5,6]. We wish to highlight this limitation and suggest Oh et al. to reconsider their use of OR as their effect size metric.

**Publication bias:** Additionally, meta-analysis guidelines require that publication bias analysis be conducted and the results explicitly presented in the study [7]. Oh et al. have not conducted any publication bias analysis, which also affects the clinical applicability of the study, as the extent that bias affects the study results is not currently known. We recommend the use of the Egger's bias indicator test for analysis of publication bias in the meta-analysis. In addition, it is recommended to consider the classical publication indicators such as Orwin and Classic Fail-Safe N tests, Begg and Mazumdar Rank Correlation tests, and Duval and Tweedie's Trim and Fill test. These indicators should be used to investigate any possible bias due to missing studies or small studies.

**Type of recurrence:** The current meta-analysis does not explore the type of recurrence, incidence of node capsule rupture in the wait and watch arm, and its impact on the disease-specific survival.

**Inclusion of previous meta-analysis:** Some of the studies included in the meta-analysis are obsolete, for example, a 40-year-old study by Vandembrouck et al., which we feel may undermine the power of analysis [8]. In contrast, the authors fail to include the recent meta-analysis by Ding et al. done on similar lines [9]. The approach of Nalluri could also be considered [10].

These points presented are in service to the advancement and quality of research in this field. We hope this commentary will provide valuable insight into future studies in this field as well as help this study reach clinical and practical relevance and contribute to refinement in treatment and prognosis in OSCC.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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**Declaration of Competing 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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