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LETTER TO EDITOR

Cisplatin-based chemoradiotherapy trumps cetuximab-based bioradiotherapy in p16/HPV-positive oropharyngeal cancers

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Sir,

We read with interest the recently updated pooled meta-analysis of 1665 patients from 5 retrospective studies, 1 secondary analysis of a small phase II study, and 2 large phase III randomized controlled trials (RCTs) published in your prestigious journal by Suton et al. [1] on a relevant issue of therapy de-intensification in p16/human papilloma virus (HPV)-positive oropharyngeal cancers. The main aim of the meta-analysis was to directly compare the efficacy of cisplatin (CDDP) versus cetuximab (C225) delivered concurrently with definitive radiotherapy for p16/HPV-positive non-metastatic, locally advanced/unresectable oropharyngeal cancers. The reported pooled odds ratio (OR) for 2-year overall survival (OS) and 2-year loco-regional recurrence (LRR) was 0.45 ($p < 0.0001$) and 0.35 ($p < 0.0001$), respectively, in favor of CDDP. Patients treated with CDDP-based chemoradiotherapy had a 2.2- and 2.9-fold decreased risk of death and loco-regional relapse, respectively, compared to C225-based bioradiotherapy confirming that replacing cisplatin with cetuximab is associated with detrimental outcomes. Although we strongly believe that C225-based bioradiotherapy is significantly inferior to CDDP-based chemoradiotherapy even in the favorable subset of p16/HPV-positive oropharyngeal cancers, there are several shortcomings associated with the reported meta-analysis that merit further discussion.

The current meta-analysis inappropriately pools data from prospective RCTs as well as retrospective studies in clear deviation of the recommendations from the Cochrane handbook for systematic reviews of interventions [2]. The inclusion of non-randomized, retrospective studies in any meta-analysis potentially introduces bias that could influence the interpretation and outcomes, with resultant downgrading of the quality of evidence. The use of OR for reporting pooled analysis of 2-year OS and LRR is also not recommended; a more appropriate measure of relative effect would be the hazards ratio (HR) for such time-to-event outcomes. For the purpose of this meta-analysis, data from the study by Riaz et al. were extracted only from an abstract (reported as a correspondence) which had not provided information on survival, despite the availability of full-text publication with survival outcomes reported at a later date [3]. Apart from efficacy of treatment, comparison of toxicity and quality-of-life (QOL) between two regimens assumes importance in patients with good prognosis and favorable biology disease such as p16/HPV-positive oropharyngeal cancer. However, the authors did not attempt to pool data pertaining to toxicity or QOL in their meta-analysis. Both the prospective randomized trials—RTOG 1016 [4] and DeESCALaTE [5] had provided details of acute and late toxicity, concluding that it did not differ significantly between the two treatment arms (CDDP versus C225). Pooling toxicity data from both these trials would have provided further value addition to their results. Finally, the authors did not follow the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for reporting such meta-analysis. The lack of a formal risk-of-bias assessment, integral to quality assessment for grading the strength of recommendation raises further questions regarding the robustness of interpretation of results and conclusions in such pooled analysis.

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Compliance with ethical standards

Conflict of interest None of the authors have any conflicts to declare.

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Informed consent Not applicable, this is a comment on a recent article in the journal and does not involve research on human participants.

Institutional ethics committee approval Not applicable.

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