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Comment

Comment on Russo et al. Does Tumor Volume Have a Prognostic Role in Oropharyngeal Squamous Cell Carcinoma? A Systematic Review and Meta-Analysis. *Cancers* 2022, *14*, 2465

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I read the article by Russo et al. [1] with great interest and acknowledge the authors' attempt to investigate the prognostic role of tumor volume in oropharyngeal squamous cell carcinoma. The authors performed a meta-analysis and included data from 10 studies where some studies used dichotomized tumor volume (such as in [2,3]), and others used tumor volume as a continuous variable (such as in [4,5]) in their original analyses. The separate studies have shown significant importance of tumor volume both as dichotomized variable in [2,3] ($p < 0.0001$ and $p = 0.0003$, respectively) and as continuous variable in [4] ($p < 0.001$ (hazard ratio (HR) per unit tumor volume)). In the current meta-analysis, the authors calculated an HR of 1.02 for overall survival and 1.07 for loco-regional control. The authors claim that the effect size is too small to be clinically relevant.

As a reader, it is hard to fully comprehend how the pooled analyses were conducted and how to interpret the results. Firstly, the authors seem to have mixed HR for tumor volume as a continuous variable ($HR_{continuous}$, i.e., the increased risk per cm^3 tumor volume) and dichotomized tumor volumes ($HR_{dichotomized}$, i.e., large compared with small tumor separated at a specific tumor volume). For instance, in Figure 2A the $HR_{continuous}$ for Carpen et al. [5] denotes the risk per unit increase in tumor volume (e.g., 1.02 for p16-negative), which corresponds to an increased risk of 1.02 *per cm^3 increase in tumor volume.* Thereby, comparing a tumor that is 40 cm^3 to a tumor of 10 cm^3, the estimated risk for OS-event increases by 1.02^30 = 1.81 (i.e., 81% increased risk). The Lok et al. [3] report used dichotomized data and found an $HR_{dichotomized}$ of 3.74 for large vs. small tumors (threshold 32.79 cm^3) among the 340 studied patients (who were assigned a weight of 0.2% despite constituting 45% of all included patients).

Secondly, and perhaps a consequence of the first issue, the pooled analyses were weighted in an ambiguous manner. As depicted in Figure 4A, a weight of 35.7% was assigned to the 19 patients with p16-negative patients in Carpen et al. [5], whereas the 160 patients in the CF-arm of Adrian et al. [2] received a weight of 0.9%. Perhaps the authors relied on the absolute value of the standard error (SE) to assign weights to the cohorts? If that is the case, the weight for the studies using $HR_{continuous}$ will be falsely inflated (since the numerical value of $HR_{continuous}$ and corresponding SE are lower compared with $HR_{dichotomized}$). The authors calculated a pooled HR of 1.02 for overall survival based on data from 760 patients. Additionally, 99.2% of the weights were assigned to the 278 patients reported by Panje et al. [4] and Carpen et al. [5], who both used $HR_{continuous}$ in their analyses (with $HR_{continuous}$ in the range 1.01–1.02 per cm^3). An $HR_{continuous}$ in that range could be highly clinically relevant, as exemplified above.

In summary, the intention of the performed meta-analysis is of high relevance to the community, but the presented analyses are difficult to interpret. In fact, if the authors re-do the calculations separately for studies using $HR_{continuous}$ and $HR_{dichotomized}$, the conclusion may very well be that tumor volume is a reliable prognostic factor for oropharyngeal squamous cell carcinoma with high clinical significance.

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References

1. Russo, E.; Accorona, R.; Iocca, O.; Costantino, A.; Malvezzi, L.; Ferreli, F.; Franzese, C.; Scorsetti, M.; Capaccio, P.; Mercante, G.; et al. Does Tumor Volume Have a Prognostic Role in Oropharyngeal Squamous Cell Carcinoma? A Systematic Review and Meta-Analysis. *Cancers* **2022**, *14*, 2465. [CrossRef] [PubMed]
2. Adrian, G.; Gebre-Medhin, M.; Kjellén, E.; Wieslander, E.; Zackrisson, B.; Nilsson, P. Altered fractionation diminishes importance of tumor volume in oropharyngeal cancer: Subgroup analysis of ARTSCAN-trial. *Head Neck* **2020**, *42*, 2099–2105. [CrossRef] [PubMed]
3. Lok, B.H.; Setton, J.; Caria, N.; Romanyshyn, J.; Wolden, S.L.; Zelefsky, M.J.; Park, J.; Rowan, N.; Sherman, E.J.; Fury, M.G.; et al. Intensity-modulated radiation therapy in oropharyngeal carcinoma: Effect of tumor volume on clinical outcomes. *Int. J. Radiat. Oncol. Biol. Phys.* **2012**, *82*, 1851–1857. [CrossRef] [PubMed]
4. Panje, C.; Riesterer, O.; Glanzmann, C.; Studer, G. Neutrophil-lymphocyte ratio complements volumetric staging as prognostic factor in patients treated with definitive radiotherapy for oropharyngeal cancer. *BMC Cancer* **2017**, *17*, 643. [CrossRef] [PubMed]
5. Carpén, T.; Saarilahti, K.; Haglund, C.; Markkola, A.; Tarkkanen, J.; Hagström, J.; Mattila, P.; Mäkitie, A. Tumor volume as a prognostic marker in p16-positive and p16-negative oropharyngeal cancer patients treated with definitive intensity-modulated radiotherapy. *Strahlenther. Onkol.* **2018**, *194*, 759–770. [CrossRef] [PubMed]