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Comment on: The relevance of dental management prior to radiation therapy with severe oral mucositis in head and neck cancer patients

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Radiotherapy;
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Oral cavity cancer

Dear Editor,

We congratulate Wang and colleagues for their influential study, which sought to examine the potential association between dental management and the incidence of severe radiation-induced oral mucositis (ROM) in 144 head and neck cancer (HNC) patients.[1] In this study, logistic regression analysis showed that the number of extracted teeth ($P = 0.015$) and primary tumor location in the oral cavity ($P = 0.005$) were associated with significantly increased rates of grade 3 ROM. Hence, the authors concluded that more teeth extracted and the primary site in the oral cavity were independent risk factors for developing severe ROM after radiotherapy (RT). Although we admire the authors' efforts, we have one concern that needs to be addressed, which may enhance the better understanding of the presented results.

Wang and colleagues found that tumors in the oral cavity pose a significantly higher risk for ROM compared to other sites.[1] Previously, several contributory factors have been postulated to affect the incidence of ROM, with dosimetric factors associated with the oral mucosa being the most potent determinants.[2,3] Of all HNCs, oral cavity (OCC) and oropharyngeal cancers (OPC) are the most frequently cited tumor locations that are marked to pose the highest ROM risk. This assertion is typically founded on outcomes of multivariate analyses, which often lack the inclusion of dosimetric parameters. However, no preclinical or clinical genetic, physiological, or radiobiological research data has indicated a scientific foundation for these observations so far. Moreover, there is no evidence to assert that OCCs or OPCs generate specific metabolites, chemokines, or cytokines that may specifically increase the rates of ROM compared to other HNC primaries. Instead, the RT technique, modality, and doses to the oral cavity are the primary determinants of rates of ROM.[4] It is firmly established that a cumulative RT dose equal to or exceeding $\geq$50 Gy poses a significant risk of ROM, and this risk is highest with cumulative doses $\geq$65 Gy, independent of the tumor's location.[3] The association between oral cavity doses and the development of ROM was investigated by Narayan and colleagues.[5] Their findings revealed that cumulative point doses below 32 Gy were correlated with mild ROM severity (grade $\leq$1) and a short duration ($\leq$1 week) of mucositis. Conversely, doses exceeding 39 Gy were linked to prolonged mucositis. Consequently, restricting the dose to below 39 Gy or maintaining an average oral mucosa dose below 32 Gy led to milder symptom severity and a shorter duration of ROM in HNC patients. Wang and colleagues conducted a prospective comparative trial focusing on the incidence of ROM in a specific patient cohort receiving less than 32 Gy to the oral cavity.[2] Their trial demonstrated that only 25% of these patients experienced grade 3 ROM and seldom required analgesics and intravenous antibiotics. These research results clearly demonstrate that ROM incidence and severity depend mainly on the oral cavity doses rather than the primary tumor location.

Based on the above data, it is rational to posit that OCCs represent only a relative risk factor for ROM rather than an absolute one, which may be attributed to a larger mucosal volume being unavoidably exposed to higher doses of RT in these tumors. Hence, available scientific data does not

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provide scientific rationales for expecting a higher risk of ROM in OCC patients when the mean oral cavity doses are similar between OCCs and nasopharyngeal or maxillary sinus tumors. The same reasoning also applies to prescription doses, as identical prescription doses may result in different oral mucosa doses when administered using different RT techniques. Advanced RT techniques may result in lower oral cavity doses and reduced risk of ROM and other complications compared to old-fashioned RT techniques, even when significantly higher prescription doses are used on the same target volume.

In conclusion, without relevant dosimetric data such as the mean dose (Dmean) and Vx (the volume exposed to $\geq$ X Gy) of the oral cavity, a multivariate analysis might produce incorrect results concerning the connections between primary tumor sites and other contributing factors. In this context, only well-designed research that exclusively includes propensity score-matched OCC versus other HNCs with similar oral cavity doses (e.g., Dmean $>$50 Gy) might reveal any differences in the risks of ROM if they exist.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

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Erkan Topkan*
Department of Radiation Oncology, Faculty of Medicine, Baskent University, Adana, Turkey

Sibel Bascil
Department of Periodontology, Faculty of Dentistry, Baskent University, Ankara, Turkey

Ugur Selek
Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey

*Corresponding author. Department of Radiation Oncology, Baskent University Medical Faculty, Kazım Karabekir St. Gulhatmi Road. Adana, 01120, Turkey.
E-mail address: docdretopkan@gmail.com (E. Topkan)

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