LETTER to the EDITOR

Editorial Process: Submission:01/16/2024 Acceptance:02/16/2024

Comment on Prospective Study to Compare Efficacy of Conventional Chemoradiotherapy with Hypofractionated Chemoradiotherapy in Locally Advanced Carcinoma of Oropharynx

Asian Pac J Cancer Prev, **25 (2),** 367-368

Dear Editor

We applaud Dwivedi et al. [1] for their valuable research on a critical head and neck oncology issue. In this prospective study, the authors compared two radiotherapy (RT) schedules: hypofractionated RT (HFRT) and standard fractionation RT (SFRT) in stage III and IV oropharyngeal squamous cell carcinoma (OPSCC) patients. The HFRT (n=34) schedule involved 64 Gy in 25 fractions of 2.56 Gy per fraction, while the SFRT (n=34) schedule involved 70 Gy in 35 fractions of 2.0 Gy per fraction. Both treatment groups received concurrent RT during the course of their treatment. All patients had a minimum follow-up time of six months (range: 6-18 months). At 3 months, both treatment groups had outstanding complete response rates, with 100% and 96.7% for HFRT and SFRT, respectively. Also, the disease-free survival (DFS) and overall survival (OS) rates were similar across the two groups at 3 months, 6 months, and 12 months. According to the research results, SFRT was more harmful regarding long-term toxic effects than the HFRT protocol employed in this investigation. Furthermore, demonstrating that patients with a significant nodal load are less likely to benefit from HFRT, most patients who encountered loco-regional failures had a bulky nodal status at the first presentation. The results of this study are significant for hypofractionated 2D-RT literature, but one concern needs to be addressed to interpret them more reasonably.

Dwivedi and colleagues [1] employed two-dimensional RT (2D-RT) in their OPSCC patients who were either receiving SFRT or HFRT, and both groups had acceptable survival results. However, the relevance of major toxicity concerns in this kind of research is equivalent to the value of survival outcomes due to their detrimental influence on practically all areas of quality of life (QoL) assessments [2]. Current advanced intensity-modulated RT (IMRT) techniques offer significant advantages over other RT techniques, including 2D-RT and 3D-RT. Unfortunately, with 2D-RT, the entire volume in the path of opposing parallel fields is irradiated without distinguishing between the tumor and surrounding tissues. In contrast, IMRT allows the RT dose intensity to be matched to the tumor's shape, which helps minimize radiation exposure to surrounding organs at risk (OAR) [3]. As a result, the total dose prescribed for the tumor was likely the same as that received by some parts of the parotid glands, masticatory apparatus, mandible, and teeth in Dwivedi and colleagues' study due to the inability of 2D-RT to spare OAR in most patients. For example, salivary hypofunction, often manifested as xerostomia, is a prevalent toxicity that affects more than 80% of patients in this context [4]. Furthermore, even with the use of advanced IMRT and proton treatment techniques, osteoradionecrosis (ORN) of the jaw may still impact as many as 10% of patients [5]. Another common progressive complication seen in these individuals is radiation-induced trismus (RIT), which affects 6 to 86% of patients [6].Up to 80.0 % of patients undergoing RT and chemoradiotherapy may also have at least one tooth loss, another notable severe side effect [7]. Surprisingly, the authors did not report any of these severe toxicities despite the fact that the typical 2D-RT portal design for advanced OPSCC patients encompasses a significant portion of the parotids, posterior half of the mandible, masticatory apparatus, and molar and premolar teeth, delivering nearly 100% of the prescribed tumor dose. However, these toxicities are not negligible given their adverse influences on the affected patients' chance for longer life expectancies, all domains of quality-of-life metrics, and excess economic burden on the health care system [8]. To illustrate, severe RIT can threaten a patient's survival in emergencies where a patent airway is necessary. Similarly, teeth loss, especially when excessive, can significantly impact nutritional patterns and hasten the progression of fatal cancer cachexia [9].

Finally, due to the lack of comprehensive toxicity data, it may be incorrect to conclude that the two-dimensional HFRT schedule with concurrent chemotherapy is a tolerable treatment option for advanced OPSCC patients. Because relying solely on the DFS and OS outcomes comparable with those achieved with SFRT and concurrent chemotherapy may not be sufficient to justify its use for all OPSCC patients. Our concerns expressed herein may help in planning more comprehensive future study designs, such as the one currently being planned by the authors. These concerns may also prevent the misinterpretation of the study results as solid evidence for the use of two-dimensional HFRT and concurrent chemotherapy for all head and neck cancer patients, including those with

advanced OPSCC.

Keywords: oropharyngeal squamous cell carcinoma- osteoradionecrosis- hypofractionated radiotherapy- radiation induced trismus.

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