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Osteoradionecrosis and Proton Therapy—Reply

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Thank you for your interest in our recent publication on osteoradionecrosis (ORN) of the jaw following proton radiation therapy (PRT) for head and neck cancer.[1] We provide below the response to your comments.

Surgical management of head and neck cancer prior to radiation therapy (RT), especially involving mandibular and/or maxillary resection, is a known risk factor for ORN.[2] A systematic review reported a similar risk of developing ORN when curative-intent RT treatment was compared with adjunctive RT treatment following surgery.[3] The primary aim of our observational nonconsecutive case series was to report the prevalence and clinical characteristics in 13 of 122 patients who developed ORN following PRT. In the ORN group, 8 of 13 (60%) patients had prior surgery, including 4 of 13 (30%) patients who underwent mandibulectomy and/or and maxillectomy, 1 of 13 (7%) patients with mandibulotomy, and 3 of 13 (23%) patients who underwent wide local excision of the primary tumor without any bony surgery.

In the ORN group, 5 of 13 (38%) patients were treated with single uniform scanning (US), a passive scattering technique. In addition, 2 of 13 (15%) received a proton boost with US technique, in addition to photons. Overall, 5 of 13 (38%) patients were treated using pencil-beam scanning (PBS) technique, whereas 1 of 13 (8%) patients received PRT using both techniques. The dose proximal to the target is generally higher with US than with PBS. However, ORN was generally seen within the target areas prescribed full dose, which would have similar homogeneity. Similarly, the areas of significantly higher linear energy transfer (LET), leading to hypothetically increased relative biological effectiveness in vivo, are primarily the lateral and distal edges of the target for a given beam path, whereas ORN developed primarily within the targets, where the LETs from a US and single-field–optimized PBS plan are similar. The development of ORN in areas receiving less than the photon equivalent threshold dose of 60 Gy would be evidence for an enhanced RBE higher than 1.1.[4] We agree that PBS should reduce the risk of ORN, primarily through the ability to dose paint, thereby reducing dose to the organs at risk for ORN below the threshold.

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Currently, there exists conflicting evidence regarding treatment with chemotherapeutic agents as an associated risk factor for ORN.[2,3] In our study,[1] 6 of 13 (54%) patients received concurrent chemotherapy, mostly with cisplatin derivatives (4/13 [31%]), resulting in an odds ratio of 1.17 (95% CI, 0.36–3.76) that was not considered a statistically significant risk factor for ORN. There are also limited direct comparisons of ORN rates between concurrent and induction chemotherapy regimens, especially in the setting of PRT.[5] Only 1 of 13 (8%) patients in our ORN study group received induction chemotherapy.

Our study was a preliminary reporting of ORN as a significant toxic effect following PRT in a heterogeneous population of patients with head and neck cancer treated with different delivery techniques. Future studies will be required to further investigate potential risk factors including prior surgical interventions, such as mandibular surgery and different chemotherapy regimens, to improve our understanding of ORN in the setting of PRT.

Conflict of Interest Disclosures:

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