Letter to the Editor

Letter to the Editor-in-Chief regarding "Adjuvant pulse-dose-rate brachytherapy for oral cavity and oropharynx carcinoma: Outcome and toxicity assessment of 66 patients"

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J Contemp Brachytherapy 2024; 16, 3: 171–172
DOI: https://doi.org/10.5114/jcb.2024.141188

Dear Editor-in-Chief,

Renard *et al*. should be congratulated for their informative analysis of adjuvant pulse-dose-rate brachytherapy (BT) with or without external beam radiotherapy (EBRT) in 66 patients with early-stage oral cavity (OCC) or oropharynx cancers (OPC) [1]. The study's primary objective was local control, while regional control and toxicity rates were the secondary outcome measures. The authors found that 11% and 20% of patients had local and regional recurrences, with no significant factor identified for predicting these recurrences. Notably, soft tissue necrosis (STN) was found in 5 (7.6%) patients, necessitating medical treatment. No predictive factors were identified for STN risk. Osteoradionecrosis (ORN) was diagnosed in 2 (3.0%) patients. Consequently, Renard and colleagues concluded that oral and oropharyngeal BT as adjuvant treatment is safe and effective for well-defined indications [1]. While the current findings provide valuable insights, it is essential to address two relevant issues to gain a more dedicated understanding of the research outcomes.

Firstly, although the authors prescribed comparable total equivalent dose in 2 Gy fractions (EQD_2) doses for BT-only and EBRT + BT groups, the two treatments' lower and upper limits ranges show a significant divergence. The prescribed doses for BT-only and EBRT + BT were 58.4 (range, 53.6-63.3 Gy) and 60.0 (range, 60.0-68.3 Gy), respectively [1]. Namely, the lower and upper limits of the EBRT + BT group were 6.4 Gy (11.2%) and 5.0 Gy (7.9%), respectively, higher than those of the BT-only group. Notably, these dosage discrepancies may influence STN and ORN yields, favoring the BT-only group, given the commonly well-appreciated critical dosages of 56.8 Gy and > 60 Gy required for STN and ORN development, respectively [2-4]. García-Consuegra and colleagues from the Head and Neck and Skin GEC-ESTRO working group conducted a study to examine the dosimetric risk factors associated with STN and ORN in a cohort of 227 patients with head and neck cancers who had adjuvant surgery, and received BT-alone or in combination with other treatments [5]. This study observed STN and ORN in 28 (12.3%) and 13 (5.7%) cases. Confirming our remark, the authors reported that the larger the clinical target volume (CTV ≥ 15 cm^3), the higher the EQD_2 dose (≥ 87 Gy). Specifically, the risk of STN was 2% in the absence of both factors, 15.7% with either factor present, and 66.7% with both factors identified (p = 0.001). Similarly, patients receiving total physical doses greater than 61 Gy had a 20-fold increased risk of ORN. These results are consistent with other studies conducted on BT, which reported similar conclusions, though with different cut-off values for increased STN and ORN risks [2, 6]. Therefore, it is advisable to search for cut-offs associated with the increased risk of these complications using receiver operating characteristic (ROC) curve analysis or a cut-off finder. Alternatively, providing information on individual dose-volume parameters can also be helpful. Such analytic information will allow us to more reliably determine patients who are more susceptible to these debilitating complications.

Secondly, the study's authors presented the rates of STN and ORN as 7.6% (5/66) and 3.0% (2/66) in the study's overall population. However, there is no firm emphasis on their respective rates within the two fundamentally distinct treatment groups. Such an omission can either overestimate or underestimate the true impact of these detrimental conditions on one of the study groups. To better explain, let's consider two possible scenarios. In the first scenario, if both ORNs were observed in the same group, the respective ORN rates would be 2/43 (4.7%) vs. 0/23 (0%) or 0/43 (0%) vs. 2/23 (8.7%), which are considerably different from the reported overall ORN rate of 3.0% and from each other. In the

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Received: 30.04.2024
Accepted: 12.06.2024
Published: 28.06.2024

second scenario, even if each of the two ORNs was distributed equally to the two treatment groups (1 case for each), the respective ORN rates would be 1/43 (2.3%) and 1/23 (4.3%), still representing different levels of ORN risk among the groups studied. Moreover, it is probable that the discrepancy in STN rates between the two groups could be more pronounced than the variation in ORN rates if the same scenario is employed. Based on their results observed in the whole study cohort, the authors of the study reported that their STN and ORN rates of 7.6% and 3.0%, respectively, are comparable to recent studies that employed 3 to 4 Gy per fraction BT doses, and reported STN rates of 9.3-16.0% and ORN rates of 2.0-4.0% [7, 8]. However, the outcomes for each group may diverge significantly from the literature either way, as exemplified by the potential STN and ORN rates above. Hence, to gain a comprehensive understanding of the precise occurrence rates on a per-treatment modality basis, it is recommended that the authors provide comparative rates of STN and ORN in both BT-only and EBRT + BT groups. By doing so, it may be possible to stratify the patients into distinctive STN and ORN risk groups, allowing for the timely initiation of preventive measures in high-risk groups through stringent cooperation between radiation and dental oncologists.

Funding

This research received no external funding.

Disclosures

Approval of the Bioethics Committee was not required.
The authors report no conflict of interest.

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