LETTER to the EDITOR **Editorial Process:** Submission:01/22/2026 Acceptance:07/13/2026 Published:07/28/2026

Comment on Dosimetric Determinants of Locoregional Failure in Nasopharyngeal Carcinoma Treated with Definitive Intensity-Modulated Radiotherapy with or without Concomitant Chemotherapy

Asian Pac J Cancer Prev, **27 (7),** 2357-2358

Dear Editor

We read with interest the study by Kalantari Khandani et al. [1], which reports 5-year patterns of locoregional failure in nasopharyngeal carcinoma (NPC) treated with definitive intensity-modulated radiotherapy (IMRT) with or without chemotherapy. The authors should be commended for providing long-term outcome data from a non-endemic, resource-limited region and for attempting to classify recurrence patterns as in-field, marginal, or out-of-field. Such analyses remain clinically relevant, as radiotherapy remains the cornerstone of curative treatment for NPC [2, 3]. Nevertheless, three interrelated methodological issues substantially limit the interpretability, causal attribution, and clinical translatability of the findings.

First, the authors do not unequivocally substantiate their central claim of identifying the specific dosimetric determinants of locoregional failure, despite presenting the study as a dosimetric analysis. This limitation arises because the methodology relies primarily on near-minimum dose metrics (D98% or D95%) calculated for predefined clinical target volumes (CTV1–CTV3) [1]. Although these parameters are standard for plan evaluation, they mainly indicate compliance with general acceptability criteria rather than the biologically relevant dose delivered to tumor subvolumes that ultimately recurred. Recent failure-pattern analyses increasingly emphasize recurrence-subvolume-based or voxel-level dosimetry, including Dmax, D1cc, and assessment of high-dose subvolume coverage, mapped directly to the site of recurrence [4–6]. These approaches enable more robust discrimination among failures related to intrinsic tumor radioresistance, systematic underdosage, intratarget dose heterogeneity, or geometric uncertainty. Without such analyses, the dominant mechanism underlying recurrence cannot be reliably determined. Consequently, while the study delineates the spatial relationship between recurrences and planned target volumes, it does not convincingly identify which specific dosimetric factors contributed to failure or clarify whether these events reflect biological resistance or suboptimal dose delivery.

Second, the interpretation of in-field recurrence as evidence of intrinsic tumor radioresistance is insufficiently supported and warrants a more nuanced analysis. Approximately 60% of locoregional failures were classified as in-field, leading the authors to infer radioresistance as the dominant mechanism [1]. However, defining in-field recurrence solely by V95% ≥95% coverage of the recurrence volume fails to account for several factors that influence dose distribution and local control. This threshold does not capture clinically meaningful intrafield dose heterogeneity or localized cold spots within the recurrence volume. Even when most of the recurrent region receives the prescribed dose, small underdosed subvolumes may persist because of plan complexity, steep dose gradients, or technical constraints. Dosimetric studies have shown that such focal cold spots, even when limited in volume, can disproportionately compromise tumor control. In addition, reliance on the initial treatment plan ignores temporal anatomical changes during radiotherapy. Tumor regression, weight loss, and soft-tissue deformation can alter the spatial relationship between the target and delivered dose, resulting in biologically relevant underdosage despite apparently adequate initial coverage [7, 8]. Without mid-treatment imaging, adaptive replanning, or deformable dose accumulation, the actual dose received by the recurrence site cannot be reliably determined. In this context, attributing in-field failure primarily to tumor biology risks oversimplifying a multifactorial process involving geometric uncertainty, setup variability, and technical limitations. This distinction is clinically important, as misclassifying dosimetric or geometric inadequacies as biological resistance may encourage indiscriminate dose escalation, increasing toxicity without addressing the true cause of failure.

Third, the inferential strength of the conclusions is constrained by the small number of evaluable locoregional failures. Only about 10 patients with locoregional recurrence had analyzable treatment plans, including three marginal failures and one out-of-field failure [1]. Proportion-based conclusions derived from such limited event numbers are inherently unstable, as the inclusion or exclusion of a single case could materially alter the reported failure distribution. Although sample size is acknowledged as a limitation, the discussion nevertheless advances relatively strong recommendations regarding dose escalation and target delineation. Given the limited event count and heterogeneity in tumor stage and nodal

burden, these findings are more appropriately interpreted as hypothesis-generating, consistent with prior cautions in IMRT failure-pattern research [9, 10].

Taken together, these issues substantially temper the clinical implications of the study. While the data confirm that locoregional failure remains a clinically relevant challenge in the IMRT era, the current analysis does not permit definitive attribution of recurrence to specific dosimetric mechanisms or clear separation of biological resistance from technical or geometric contributors. Future investigations incorporating multicenter collaboration, recurrence-subvolume dosimetric mapping, functional imaging, and adaptive radiotherapy strategies will be essential to translate failure-pattern analyses into rational and generalizable treatment intensification approaches for NPC.

Conflict of interest

The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

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