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Radiation Medicine and Protection

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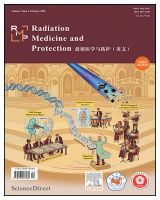

Letter

# Comment on "Normal cell responses to 3D-CRT, VMAT, and helical tomotherapy: A comparative study"

*Dear Editor,*

In a recent article in *Radiation Medicine and Protection*, the authors compared responses of HaCaT and BEAS-2B cells irradiated with 2 Gy using three techniques 3D-CRT, VMAT and helical tomotherapy in a water phantom, reporting technique- and cell type–dependent differences in clonogenic survival, γ-H2AX, cell cycle and bystander viability despite broadly similar target dosimetry.[1] We commend the focus on normal-tissue biology across contemporary delivery modalities.

Study design and dosimetry merit clarification. Although the premise is identical 2 Gy irradiation, planning and verification show differences in $D_{95}$, Dmean and measured dose between techniques, with helical tomotherapy closest to prescription and 3D-CRT/VMAT tending to underdose. This variation, plus intra-flask heterogeneity, could contribute to the survival differences. Furthermore, immortalised HaCaT and BEAS-2B lines are treated as surrogates for early- and late-responding tissues without demonstration of distinct fractionation or α/β behaviour. While endpoints are described as being assessed immediately after irradiation (a single acute time point), the exact post-irradiation intervals for assays (e.g., γ-H2AX) and the timing of conditioned-medium transfer should be explicitly reported; future work should also consider multiple post-irradiation time points to capture time-dependent repair and signalling dynamics.

Statistical interpretation also warrants caution. One-way ANOVA with post hoc testing found no statistically significant differences in clonogenic survival between techniques for either cell line, yet the abstract and discussion repeatedly describe helical tomotherapy and VMAT as inducing the "most pronounced" damage. A clearer separation between non-significant trends and robust inter-technique effects, ideally supported by effect sizes and confidence intervals, would improve interpretability.

Non-targeted effects and immune signalling can modulate normal-tissue responses beyond direct DNA damage. For example, mitochondrial DNA damage has been linked to activation of cGAS/AIM2 pathways and immune-related non-targeted effects.[2] Therefore, conclusions drawn from a single cell line and a single early time point may not capture bystander signalling or inflammatory cascades.

From a clinical perspective, technique choice often involves trade-offs between conformity and integral/low-dose exposure. Patient-based planning comparisons that directly evaluate 3D-CRT, VMAT and helical tomotherapy have reported differences in dose conformity, integral dose and low-dose exposure to organs at risk.[3,4] Higher integral dose and larger low-dose volumes have been associated with post-radiotherapy lymphocytopaenia and adverse outcomes in solid tumours.[5] In a randomized stage III lung cancer trial, IMRT was associated with lower rates of severe pneumonitis and lower cardiac doses compared with 3D-CRT.[6] Together, these data support caution when extrapolating in vitro technique-dependent differences to clinical decision-making.

Addressing these design, reporting and translational issues particularly by accounting for delivered dose, specifying assay timing and tempering clinical extrapolation in light of prospective data would strengthen the contribution of this work to radiotherapy optimisation and normal-tissue protection.

## Conflicts of interest

None.

## References

1. Phumsankhot R, Kasetthamrongrat P, Duangya A, et al. Normal cell responses to 3D-CRT, VMAT, and helical tomotherapy: a comparative study. *Radiat Med Prot.* 2025;6(5):259–266. https://doi.org/10.1016/j.radmp.2025.09.002.
2. Zhang W, Chen S, Guan H, et al. Radiation-induced non-targeted effect of immunity provoked by mitochondrial DNA damage triggered cGAS/AIM2 pathways. *Radiat Med Prot.* 2022;3(2):47–55. https://doi.org/10.1016/j.radmp.2022.05.002.
3. Liu X, Huang E, Wang Y, et al. Dosimetric comparison of helical tomotherapy, VMAT, fixed-field IMRT and 3D-conformal radiotherapy for stage I-II nasal natural killer T-cell lymphoma. *Radiat Oncol.* 2017;12(1). https://doi.org/10.1186/s13014-017-0812-1.
4. Myers PA, Mavroidis P, Papanikolaou N, et al. Comparing conformal, arc radiotherapy and helical tomotherapy in craniospinal irradiation planning. *J Appl Clin Med Phys.* 2014;15(5):12–28. https://doi.org/10.1120/jacmp.v15i5.4724.
5. Joseph N, Alagiyawanna L, Ruwanpura T, et al. Whole-body integral dose and post-radiotherapy lymphocytopaenia in solid tumours. *BMJ Oncol.* 2025;4(1). https://doi.org/10.1136/bmjonc-2024-000522.
6. Chun SG, Hu C, Komaki RU, et al. Long-term prospective outcomes of intensity modulated radiotherapy for locally advanced lung cancer. *JAMA Oncol.* 2024;10(8). https://doi.org/10.1001/jamaoncol.2024.1841.

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https://doi.org/10.1016/j.radmp.2025.12.007
Received 15 December 2025; Received in revised form 29 December 2025; Accepted 31 December 2025
Available online 3 January 2026