

Comment on: Treatment-related mortality in head and neck cancer patients receiving chemotherapy and radiation: results of a meta-analysis of published trials

Donato Pezzulla^{ID}, Elisa D'Angelo^{ID}, Daniela Musio^{ID}, Francesco Deodato^{ID}
and Elvio Russi^{ID}

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Dear Editor,

We comment on Gurizzan et al.¹ for their insightful meta-analysis of treatment-related mortality (TRD) in head and neck cancer patients undergoing chemoradiotherapy (CRT). Their work highlights a crucial clinical issue and the challenges in balancing treatment efficacy and toxicity. However, we believe that the role of radiotherapy (RT) in TRD warrants further nuance, particularly regarding fractionation strategies in the era of precision RT.

By necessity, the meta-analysis classifies RT into “standard” or “altered” fractionation; however, this categorization was the sole criterion used to assess toxicity, potentially masking the influence of other critical parameters. Historically, fractionation has played a pivotal role in both tumor control and toxicity modulation,² particularly when RT techniques lacked the precision available today.^{3–5} However, in the context of TRD, the impact of fractionation has likely diminished compared to factors such as:

- RT delivery techniques (Intensity-Modulated Radiation Therapy (IMRT), 3D-CRT, proton therapy),^{4,5}
- The extent of treatment volumes and the ability to parameterize doses to critical structures (e.g., dose–volume histograms),^{3,6}
- Therapeutic intent (curative vs postoperative).

These parameters are now more influential in determining toxicity and mortality risks than fractionation alone is. Modern RT techniques have revolutionized treatment precision by reducing the irradiation of normal tissues and mitigating toxicity, independent of fractionation.⁷ The historical relevance of altered fractionation, particularly its radiobiological impact on tumor control, remains undeniable. However, in the era of advanced treatment planning, image guidance, intensity modulation, and adaptive RT, fractionation per se may no longer be the dominant factor in TRD.^{2,8,9}

Thus, while we acknowledge the valuable contribution of Gurizzan et al., we encourage the interpretation of their findings in the context of the evolving RT paradigms. Future analyses incorporating granular RT parameters are essential to accurately define the determinants of TRD.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Author contributions

Donato Pezzulla: Conceptualization; Formal analysis; Investigation; Writing – review & editing.

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Correspondence to:

Donato Pezzulla
Radiation Oncology Unit,
Responsible Research
Hospital, Largo A. Gemelli
1, Campobasso 86100, Italy
donato.pezzulla@responsible.hospital

Elisa D'Angelo
Radiation Oncology
Department, Bellaria
Hospital, AUSL of Bologna,
Bologna, Italy

Daniela Musio
Radiation Oncology Unit,
University Hospital La
Sapienza, Rome, Italy

Radiation Oncology Unit,
Santa Maria Addolorata
Hospital, Rome, Italy

Francesco Deodato
Radiation Oncology Unit,
Responsible Research
Hospital, Campobasso,
Italy

Istituto di Radiologia,
Università Cattolica del
Sacro Cuore, Rome, Italy

Elvio Russi
Struttura Complessa di
Radioterapia, Azienda
Sanitaria Ospedaliera S.
Croce e Carle, Cuneo, Italy

Elisa D'Angelo: Conceptualization; Formal analysis; Investigation; Methodology; Writing – review & editing.

Daniela Musio: Conceptualization; Formal analysis; Methodology; Writing – review & editing.

Francesco Deodato: Conceptualization; Investigation; Writing – review & editing.

Elvio Russi: Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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ORCID iDs

Donato Pezzulla  <https://orcid.org/0000-0001-6676-1169>

Elisa D'Angelo  <https://orcid.org/0000-0002-5954-0939>

Daniela Musio  <https://orcid.org/0000-0003-1373-281X>

Francesco Deodato  <https://orcid.org/0000-0003-1276-5070>

Elvio Russi  <https://orcid.org/0000-0003-1278-2313>

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