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Does radiation-induced lymphocytopenia matter? Developing a radiotherapy dosimetric strategy for immune preservation and improved survival

Mohammed Abdul-Latif ,[1] John Conibear,[2] Niluja Thiruthaneeswaran,[3,4] Yat Man Tsang [5,6]

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For numbered affiliations see end of article.

Correspondence to
Dr Yat Man Tsang;
Yat.Tsang@uhn.ca

Globally, around half of all patients with cancer require radiotherapy as a part of their multimodality cancer treatment.[1] Despite its important role in optimising cancer outcomes, its systemic immunological consequences, particularly radiation-induced lymphocytopenia, can pose a significant challenge and be associated with poorer treatment outcomes that impact the overall survival.

The immune response to cancer is most relevant during carcinogenesis, but also in the maintenance of cancer remission. Immune evasion is a hallmark of cancer, in which tumour cells proliferate while avoiding immune stimulation and destruction. This is equally relevant in patients who have completed radical cancer treatments and who rely on intact immune surveillance to keep them in remission.[2] The significance of immune competence in cancer surveillance is best observed in immunosuppressed patients, who are more likely to develop cancer and have suboptimal responses to traditional cancer treatments.[3]

Radiation-induced lymphocytopenia in particular has been demonstrated in multiple studies to be linked to larger radiation volumes, higher radiation doses and anatomical sites near to great vessel or significant volumes of bone marrow, for example, the chest and mediastinum, head and neck and pelvis.[4] Radiation doses required to cause lymphocyte cell death are low and are easily exceeded by standardised radiation regimes. Radiation volumes often overlap with great vessels, lymphoid tissue and bone marrow, sites containing or involved in lymphocyte production and sequestration. Modern radiation techniques, such as intensity-modulated radiotherapy (IMRT), are more conformal; however, they deliver a 'low-dose bath' of radiation dose in large volumes to achieve that conformality.[5]

This can influence immunotherapy drug response, as these therapies require a functional immune system for optimal effect. Poorer response rates to immunotherapy are seen in patients with lymphocytopenia secondary to radiotherapy, especially in patients receiving significant doses of radiation to large volumes of tissue.[6] To mitigate this, the development of radiotherapy dosimetric strategies that prioritise immune preservation for reducing radiation-induced lymphocytopenia is needed. There are, however, persisting challenges in achieving this, such as how to relate radiotherapy dosimetry to the development of lymphocytopenia. One approach can be simply using dose-volume parameters, such as V5, the volume of tissue receiving at least 5Gy,[7] while another could be using the 'integral dose' as a surrogate marker for likely radiation-induced lymphocytopenia. Integral dose is the product of the mean body dose and the whole body volume as demonstrated in Joseph *et al*'s study.[8] A further approach involves identifying and outlining lymphatic tissue and bone marrow as organs at risk (OAR). Functional bone marrow can be identified using single-photon emission computed tomography (SPECT) techniques, which aids in identifying bone marrow as a potential OAR.[9] With further research, it may be possible to establish dose constraints for these lymphocyte-containing OARs, which, in turn, could help minimise the risk

of developing lymphocytopenia during radiotherapy treatments.[10]

Joseph *et al*'s retrospective analysis of 116 patients aimed to examine the significance of lymphocytopenia in the context of integral body dose for patients with different cancers receiving radiotherapy.[8] Their study demonstrates that integral dose serves as a robust predictor of post-treatment lymphocytopenia. Subgroup analysis of patients with head and neck cancer revealed that severe lymphocytopenia ($<0.72 \times 10^9$/L) correlated with markedly reduced 1-year disease-free survival (36% vs 67%, p=0.05). Notably, lymphocytopenia emerged as the most consequential haematological parameter, surpassing neutropenia or anaemia in its association with survival outcomes. However, it is important to acknowledge that this effect of integral dose may be limited to chemoradiation only as the subset analysis was only performed on patients with head and neck cancer receiving combined modality treatment.

Several limitations of Joseph *et al*'s study[8] should be noted. As a retrospective analysis, the radiotherapy treatment protocols did not include specific dose constraints for lymphatic organs, such as bone marrow, spleen and thymus gland. These structures were not contoured as organs, preventing analysis of the dosimetric impact of individual lymphatic organs on post-treatment lymphocytopenia. Additionally, while IMRT did not show significance in univariate analysis, future work should consider additional radiotherapy technical factors. These include bone marrow sparing techniques, constraints for high-risk organs and integration of alternate modalities like proton or carbon ion therapy, which is particularly relevant for head and neck cancers.

In conclusion, Joseph *et al*'s work[8] highlights the importance of considering chemoradiation-induced lymphocytopenia during the radiotherapy planning process through the lens of immune preservation. Prospective trials comparing integral dose-constrained radiotherapy plans versus unconstrained plans are needed to validate these findings, particularly in patients receiving immunotherapy as a part of their overarching management plan. As immunotherapy becomes increasingly integral to multidisciplinary cancer care, preserving immune competence through radiotherapy dosimetric innovation is no longer optional, but essential. Now is the time to redefine the future of cancer treatment by prioritising the development and implementation of innovative radiotherapy strategies that safeguard immune function.

Author affiliations
[1]Mount Vernon Cancer Centre, Northwood, UK
[2]Barts Cancer Centre, St. Bartholomew's Hospital, London, UK
[3]Radiation Oncology Network, Western Sydney Local Health District, Wentworthville, New South Wales, Australia
[4]Faculty of Health and Medicine, The University of Sydney, Sydney, New South Wales, Australia
[5]Radiation Medicine Program, Princess Margaret Cancer Centre, Toronto, Ontario, Canada
[6]Department of Radiation Oncology, University of Toronto, Toronto, Ontario, Canada

X Yat Man Tsang @YatTsang

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ORCID iDs
Mohammed Abdul-Latif http://orcid.org/0000-0001-7206-7210
Yat Man Tsang http://orcid.org/0000-0002-5369-3299

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