Editors' pick

Mathematical modeling to simulate the effect of adding radiation therapy to immunotherapy and application to hepatocellular carcinoma

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What was your motivation for initiating this study?

The role of radiation in the treatment of advanced cancer is expanding and there is growing evidence that radiation therapy can exhibit immuno-stimulatory effects. Therefore, radiation is being investigated as a treatment option for metastatic disease in combination with systemic agents, particularly immune checkpoint inhibitors (ICIs). However, the increasing number of trials that have combined the use of radiotherapy and ICIs have produced negative and positive results, and concerns persist that this approach might be limited by the occurrence of radiation-induced immunosuppression. As physicists, we were excited to build the first model that would describe the tumour-immune system and would include both the immune-stimulatory and the immune-suppressive effects of radiotherapy, in order to help with the interpretation of trial outcomes and with the design of future combination trials.

What were the main challenges during the work?

A dynamic model that describes the evolution of tumour burden and immune-cell populations requires time-series data for both tumour volume and lymphocyte counts in patients. The main challenge we faced was to find data that enabled us to fit our model, which required both radiotherapy-only and ICI-only treatment outcomes.

In the end, we built the model based on outcomes of hepatocellular carcinoma (HCC) patients, for whom we had good longitudinal data and well-established population estimates of local control, distant progression, and lymphocyte depletion in patients with HCC during and after radiotherapy. The ICI-related parameter was fitted separately to clinical trial data for patients with HCC who had received durvalumab monotherapy, for whom longitudinal tumour volume data were well described.

What is the most important finding of your study?

The irradiated tumour burden, i.e. the fraction of visible tumour that was irradiated, was shown to be the most relevant parameter to measure the effectiveness of combined ICI-radiotherapy treatment regimens. This finding shows that already the immense clonogen reduction that is caused by the use of radiotherapy can produce a synergy with immunotherapy, which is important for the interpretation of ongoing clinical trials.

We also used the model to predict estimated progression-free survival curves for ongoing clinical trials, and to show that, due to the underlying heterogeneous responses to ICIs, the cohort size that is required to show improvement can be large, even if the effect size is substantial.

What are the implications of this research?

We have established a framework that enables the simulation of combination strategies through the inclusion of radiotherapy and ICI treatment effects on both the tumour and the immune system. The simulations predict that a significant amount of the benefit

from radiotherapy treatment given in combination with ICIs stems from the reduction in irradiated tumour burden and associated immune suppression. This aspect should be taken into account when results are interpreted and novel combination trials are designed.

Especially for large-volume metastatic disease, new trade-offs will emerge when patients are treated with radiotherapy. For example, if not all disease can be irradiated to an ablative dose level, should we restrict the target volume or rather irradiate all visible disease to a lower dose? Or if we plan to implement lymphocyte-sparing treatment strategies, how much are they expected to boost response to the ICI component of treatment? If we change from immune checkpoint inhibition to a different approach, i.e. chimeric antigen receptor T-cells, does the best radiotherapy regimen change as well?

Integrated models such as ours that show responses to both radio- and immunotherapy will give us a framework to explore these questions quantitatively and to guide trial design or to personalise treatment for individual patients.

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