Editorial Commentary

In silico trials of combination immuno-radiation for unresectable hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is rising in incidence and is poised to be one of the leading causes of cancer-related deaths worldwide (1,2). While ablation, resection, and liver transplant are potentially curative therapies, at least 60% of patients are not surgical candidates. In patients with locally advanced unresectable disease, immunotherapy has become the standard of care (3-6). There are multiple ongoing clinical trials evaluating HCC response to various immune checkpoint inhibitors (ICIs), either monotherapy or combination therapy, as well as tyrosine kinase inhibitor (TKI) therapy, often in combination with ICI. Many studies have shown varying overall response rates (ORR) from less than 12% to greater than 35%, depending on the type of monotherapy or combination therapy with ICIs and TKIs (3,5,7,8). Although ICIs show improved efficacy in ORR in patients with advanced stage HCC, further enhancing the effectiveness of ICI therapy has been an emerging area of clinical research in the management of patients with advanced stage HCC.

External beam radiotherapy (EBRT) has also been shown to be an effective treatment for unresectable locally advanced HCC in patients who are not candidates for ablation, with acceptable safety profile and excellent local control (9). Numerous studies have demonstrated excellent local control with the combination of EBRT with other locoregional therapies such as transarterial chemoembolization or thermal ablation in intermediate and advanced stage HCC (10). However, in patients with advanced stage HCC, particularly those with extrahepatic disease, combination therapies with systemic agents (ICIs or TKIs) plus EBRT may improve ORR and progression-free survival (PFS). Recently, a randomized trial of stereotactic body radiation *vs.* sorafenib (RTOG 1112) showed an overall survival benefit to radiotherapy (RT) compared to sorafenib (ASTRO 2022). There is emerging interest in harnessing the combination of immunotherapy and radiation in pursuit of the abscopal effect (11). There have already been published phase I trials on combination immunotherapy and RT for HCC with promising results (12,13). Given the low ORR with systemic therapy alone and the low rates of PFS seen in patients treated with EBRT alone, there is an unmet need for combination therapies which can provide excellent local control (EBRT) in combination with systemic control (ICI therapy) in patients with advanced stage HCC.

Emerging evidence on the role of effector T-cell efficacy on stimulating the immune system to promote tumor cell destruction has been the mainstay of ICI therapy. Numerous pre-clinical trials have shown the synergistic interaction between ICI therapy and radiation therapy (14). Radiation-induced cell death exposes tumor-specific antigens to the immune system, which sparks

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a cytokine cascade resulting in activation of normally suppressed tumor-specific T-lymphocytes, thus facilitating activated T-lymphocyte recruitment to the tumor (14). Thus, the combination of radiation and ICI therapy allows for further enhancement of anti-tumor effects.

The current *in silico* trial postulates on modeling the mechanism behind the interaction of durvalumab monotherapy and radiation in treatment of HCC. While recent studies combine durvalumab and tremelimumab, there is evidence that single agent durvalumab has some activity against HCC and that radiation may potentiate its effects (4,15,16). In the proposed mathematical model, the authors utilize a cell compartment approach as described by ordinary differential equations and represent irradiated and nonirradiated tumor cells and lymphocytes. The model simulates radiation kill via the linear quadratic model, while the effects of immunotherapy (immune-check point inhibition) is modeled via an immune activation term that is based on tumor size changes. In order to encompass observable information from clinical data, the design of the model has been restricted to phenomenological information rather than mechanistic underpinning, which may still be valuable for clinical trial design but may limit the ability to make radiobiological inferences. The current model incorporates baseline immune features such as lymphocyte count, radiation fraction size, and sequencing of immunotherapy and radiation. The mathematical model attempts to provide a framework for designing trials with this combination therapy and for evaluating objective response.

Given the heterogeneity of radiation treatment parameters in everyday clinical practice, such as radiation dose, fractionation, sequencing and patient selection, the current mathematical model can incorporate these differences to guide treatment combinations. The current mathematical model adjusts for the aforementioned RT parameters that we can control, not the underlying biological heterogeneity in patient population, in order to best predict optimal treatment outcomes. The current study compares PFS in patients with ICI and differing percentage of RT volumes to ICI alone, as well as differing times of ICI therapy with RT (concomitant versus RT with ICI treatment break).

The current mathematical model predicts that the response rates based on PFS were maximized when ICI-RT combination regimen was with an irradiated tumor fraction of 90% as opposed to 50%. Furthermore, the mathematical model suggests improved response rates when durvalumab and EBRT were simultaneously given, and decreasing efficacy with an ICI and radiation gap, results which are concordant with the PACIFIC trial evaluating durvalumab with chemo-radiation in lung cancer (17,18). Finally, the mathematical model predicts that baseline lymphocyte counts strongly predict outcomes, such that patients with higher baseline lymphocyte counts and lower tumor burden have better response rates. These results are corroborated by other studies evaluating lymphocyte count in non-small cell lung cancer and tumor burden to ICI monotherapy response (19,20).

There has been interest in applying more data driven techniques with artificial intelligence (AI) to learn directly from clinical data and subsequently optimize outcome prediction and decision making. Examples of such approaches are using quantitative image analysis (radiomics), for instance (21,22). However, it is recognized that AI methods may require large datasets and the combination with mathematical modeling may alleviate such requirements in outcome modeling of cancer response in general and radio-immunotherapy in particular (23).

In conclusion, the proposed mathematical model provides a framework to identify optimal ICI + RT combinations for advanced stage HCC treatment to maximize treatment efficacy, while accounting for patient heterogeneity. While their results are concordant with literature evaluating ICI + RT in other tumor subtypes, further studies with more clinical data and larger patient sample sizes are needed to understand the true predictive nature of this mathematical model.

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References

1. Wong RJ, Saab S, Konyn P, et al. Rural-Urban Geographical Disparities in Hepatocellular Carcinoma Incidence Among US Adults, 2004-2017. Am J Gastroenterol 2021;116:401-6.
2. Reinders MTM, van Meer S, Burgmans MC, et al. Trends in incidence, diagnosis, treatment and survival of hepatocellular carcinoma in a low-incidence country: Data from the Netherlands in the period 2009-2016. Eur J Cancer 2020;137:214-23.
3. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus Bevacizumab in Unresectable Hepatocellular Carcinoma. N Engl J Med 2020;382:1894-905.
4. Kelley RK, Sangro B, Harris W, et al. Safety, Efficacy, and Pharmacodynamics of Tremelimumab Plus Durvalumab for Patients With Unresectable Hepatocellular Carcinoma: Randomized Expansion of a Phase I/II Study. J Clin Oncol 2021;39:2991-3001.
5. Yau T, Park JW, Finn RS, et al. Nivolumab versus sorafenib in advanced hepatocellular carcinoma (CheckMate 459): a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol 2022;23:77-90.
6. Greten TF, Abou-Alfa GK, Cheng AL, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of hepatocellular carcinoma. J Immunother Cancer 2021;9:e002794.
7. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med 2008;359:378-90.
8. Finn RS, Ryoo BY, Merle P, et al. Pembrolizumab As Second-Line Therapy in Patients With Advanced Hepatocellular Carcinoma in KEYNOTE-240: A Randomized, Double-Blind, Phase III Trial. J Clin Oncol 2020;38:193-202.
9. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. J Clin Oncol 2016;34:452-9.
10. Buckstein M, Kim E, Özbek U, et al. Combination Transarterial Chemoembolization and Stereotactic Body Radiation Therapy for Unresectable Single Large Hepatocellular Carcinoma: Results From a Prospective Phase 2 Trial. Int J Radiat Oncol Biol Phys 2022;114:221-30.
11. Choi C, Yoo GS, Cho WK, et al. Optimizing radiotherapy with immune checkpoint blockade in hepatocellular carcinoma. World J Gastroenterol 2019;25:2416-29.
12. Juloori A, Katipally RR, Lemons JM, et al. Phase 1 Randomized Trial of Stereotactic Body Radiation Therapy Followed by Nivolumab plus Ipilimumab or Nivolumab Alone in Advanced/Unresectable Hepatocellular Carcinoma. Int J Radiat Oncol Biol Phys 2023;115:202-13.
13. Zheng J, Shao M, Yang W, et al. Benefits of combination therapy with immune checkpoint inhibitors and predictive role of tumour mutation burden in hepatocellular carcinoma: A systematic review and meta-analysis. Int Immunopharmacol 2022;112:109244.
14. Wang Y, Deng W, Li N, et al. Combining Immunotherapy and Radiotherapy for Cancer Treatment: Current Challenges and Future Directions. Front Pharmacol 2018;9:185.
15. Bang YJ, Golan T, Dahan L, et al. Ramucirumab and durvalumab for previously treated, advanced non-small-cell lung cancer, gastric/gastro-oesophageal junction adenocarcinoma, or hepatocellular carcinoma: An open-label, phase Ia/b study (JVDJ). Eur J Cancer 2020;137:272-84.
16. Levy A, Massard C, Soria JC, et al. Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: Single centre subset analysis from a phase 1/2 trial. Eur J Cancer 2016;68:156-62.
17. Faivre-Finn C, Spigel DR, Senan S, et al. Impact of prior chemoradiotherapy-related variables on outcomes with durvalumab in unresectable Stage III NSCLC (PACIFIC). Lung Cancer 2021;151:30-8.

18. Antonia SJ. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. Reply. N Engl J Med 2019;380:990.
19. Joseph RW, Elassaiss-Schaap J, Kefford R, et al. Baseline Tumor Size Is an Independent Prognostic Factor for Overall Survival in Patients with Melanoma Treated with Pembrolizumab. Clin Cancer Res 2018;24:4960-7.
20. Tang C, Liao Z, Gomez D, et al. Lymphopenia association with gross tumor volume and lung V5 and its effects on non-small cell lung cancer patient outcomes. Int J Radiat Oncol Biol Phys 2014;89:1084-91.
21. Wei L, Owen D, Rosen B, et al. A deep survival interpretable radiomics model of hepatocellular carcinoma patients. Phys Med 2021;82:295-305.
22. Sun R, Lerousseau M, Briend-Diop J, et al. Radiomics to evaluate interlesion heterogeneity and to predict lesion response and patient outcomes using a validated signature of CD8 cells in advanced melanoma patients treated with anti-PD1 immunotherapy. J Immunother Cancer 2022;10:e004867.
23. El Naqa I. A Guide to Outcome Modeling In Radiotherapy and Oncology: Listening to the Data. 1st edition. Taylor & Francis, 2020.

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