Point-by-Point Response to Reviewers' Comments

We would like to thank the reviewers and the editorial board for the favorable review of our manuscript. We have made the two changes as suggested by the reviewers:

Reviewer 1

This is an excellent review article on the role of Deep learning in the management of hepatocellular carcinoma. It is well-written and comprehensive. I only have 2 small suggestions:

1. Please define "multi-omics" in the manuscript as I don't know if most readers of our journal will know to what you are referring.

    a. We thank the reviewer for the kind suggestion. We have defined multi-omics as following: "Multi-omics refers to an approach to biological analysis which utilizes data sets from multiple "omes", such as the genome, epigenome, transcriptome, proteome, metabolome, and microbiome." (Page 7, Paragraph 2)

2. Many readers are interested in robotics and autonomous actions. It is a controversial topic, with some authors thinking that we are far away from autonomy and other authors thinking that there are already examples of autonpomous actions in surgery. Hashimoto DA, Rosman G, Rus D, Meireles OR. Artificial Intelligence in Surgery: Promises and Perils. Ann Surg. 2018 Jul;268(1):70-76. doi: 10.1097/SLA.0000000000002693. PMID: 29389679; PMCID: PMC5995666. Gumbs AA, Perretta S, d'Allemagne B, Chouillard E. What is Artificial Intelligence Surgery?. Art Int Surg 2021;1:1-10. http://dx.doi.org/10.20517/ais.2021.01 What do you think of these diverging opinions? And more importantly, what is the future role of Deep learning in getting us towards autonomous actions? Evaluation of Surgical Skills during Robotic Surgery by Deep Learning-Based Multiple Surgical Instrument Tracking in Training and Actual Operations J. Clin. Med. 2020, 9, 1964; doi:10.3390/jcm9061964 Evaluation of Deep Learning Models for Identifying

Surgical   Actions   and   Measuring   Performance
ShujaKhalid,MSc;MitchellGoldenberg,MBBS,PhD;TeodorGrantcharov,MD,PhD;BabakTaati,PhD;FrankRudzicz,PhD Is it limited to evaluating surgical skills only, or will it lead us towards autonomous robotics? Degrave J, Hermans M, Dambre J, Wyffels F. A Differentiable Physics Engine for Deep Learning in Robotics. Front Neurorobot. 2019 Mar 7;13:6. doi: 10.3389/fnbot.2019.00006. PMID: 30899218; PMCID: PMC6416213.

a. We appreciate the reviewer for their thoughtful question on the topic of robotics and autonomous actions. We have added the following paragraph about autonomous robotics in the "Future Direction" section of our Discussion:

"A currently under-explored, but highly promising and exciting area for the application of deep learning is the field of autonomous robotics. In a recent editorial, Gumbs et al state that while the current form of robotic surgery seems like a form of minimally invasive surgery, the true power of robotic surgery exists in its potential to create autonomous actions[67]. Recently, a deep learning-based surgical instrument tracking algorithm was able to closely track the instruments during robotic surgery and evaluate the surgeons' performance, demonstrating that deep learning algorithms can learn the correct steps of robotic surgery[68]. With the help of deep learning and other AI technologies, it may be possible to imagine a future where fully autonomous robots perform resection of large, complex HCC in ways that no human surgeons can mimic. However, there are significant barriers before the idea of fully autonomous robotic surgery can become a reality, including the current technical limitations of autonomous surgical robotics, as well as the hesitation of patients and providers to trust fully autonomous robots to perform invasive operations. "Explainability" of the deep learning algorithms will be critical here, as humans would need to be able to understand and correct every single

mistake that an autonomous robot makes during surgery. Therefore, for the foreseeable future, deep learning will most likely remain as a helpful, adjunctive tool to assist human surgeons." (Page 13, Paragraph 2)

Reviewer 2

1. Title is good and relevant.

    a. We thank the reviewer for finding our title adequate. As in the title, we sought to provide a comprehensive overview of deep learning in hepatocellular carcinoma.

2. Table 1 actually depicts all the previous study been done on the relevant problem of applying deep learning on hepatocellular carcinoma currently and in future.

    a. We appreciate the reviewer for their comment on our Table 1. We put in a significant amount of effort to organize most of the relevant studies performed to date which applied deep learning on hepatocellular carcinoma.

3. Emphasis is seen in the paper but the paper discusses more on the disease and its diagnostic measures rather explaining the AI and deep learning expect of it. I would recommend to incorporate some technical expertise related information and details related to the application of deep learning in past, present and future.

    a. We thank the reviewer for their interest in the technical aspects of AI and deep learning. It is true that we primarily focused on the clinical applications of deep learning for an audience with mostly healthcare-related background. We did define and explain the major terminologies such as artificial intelligence, machine learning, artificial neural networks, and deep learning in the section "AI, Machine Learning, and Deep Learning" and we hope that the reviewer finds this acceptable for the scope of this review. (Page 4, Paragraph 3 – Page 6, Paragraph 1)

Revised-review:

Paper is good as a mini-review paper of how deep learning would leverage the diagnosis and prognosis of HCC in future. The paper holds significance for the field of recent advancements in SmartHealth. As a review paper is limited to identify the connection of deep learning to diagnose HCC in future but would require the intervention of technology experts to take it forward for implementation.

Thanks for your comments.