Manuscript NO: 55140

Title of manuscript: Multiphase Convolutional Dense Network for the Classification of Focal Liver Lesions on Dynamic Contrast-Enhanced CT

Response Letter

Dear Editors,

We would like to submit our revised attached manuscript to World Journal of Gastroenterology.

Thank you for your feedback and thorough reviews.

Thank the reviewers for their valuable and constructive comments.

We have carefully considered the valuable comments and tried our best to revise the manuscript. The point-to-point responses to editors and reviewers' comments are listed as follows.

The revised manuscript was edited for proper English language, grammar, punctuation, spelling, and overall style by one or more of the highly qualified native English-speaking editors at AJE.

All authors have read and approved the final revised version.

We hope the manuscript can be accepted for publication in World Journal of Gastroenterology.

Yours sincerely,
Jin Wang

Reviewers' Comments to Author

Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors:

1 Title. Good

2 Abstract. Good

3 Key words. Good

4 Background. Good

5 Methods. See comments below:

- How could the classification of the lesion by the home-developed lesion annotation module in 3D Slicer trusted? -

Response: Thank you for your valuable advice. The classification of the type of each lesion was manually and independently annotated by four radiologists (all had at least four years of imaging experience), and the results were reviewed by a radiologist with 20 years of imaging experience. We numbered the same type of lesions and placed them in the same folder, then manually loaded each lesion into 3D Slicer (https://www.slicer.org) for labeling using a home-developed lesion annotation module.

- Section: Input Data: CT Imaging Annotation: How did the authors define the 3D bounding box surrounding the lesion's boundary used to crop the four-phase lesion volumes? Manually, etc.? Please discuss.

Response: Thank you for your valuable advice. The means of cropping is described below. The boundary of each lesion was manually drawn slice-by-slice along the visible borders of the lesion using the annotation module available in 3D Slicer. Then, a 3D bounding box was generated to cover the lesion boundary and extended with a spare boundary of 10 mm along each direction using the python library scikit-image 0.15.0 (https://scikit-image.org/ scikit-image 0.15.0). After extracting the bounding

box of the lesion, ROIs were cropped from the portal venous phase (PVP). The ROI was a square on each axial plane, the length of side was 1.5 times the value of the longest side of bounding box on the axial plane, and the center point was the projection of the center point of the bounding box on each axial plane. The bounding boxes were then propagated on other phases to crop the lesion. Following lesion cropping, each cropped ROI was resized into an identical shape in the size of 128 x 128. ROIs from five slices centered at the lesion were extracted and stacked together to form a [128, 128, 5] tensor as the input data for each phase.

(The means of cropping has addressed in the revised manuscript and marked in red color).

- Section: Input Data: CT Imaging Processing Pipeline: Authors doesn't explain how the cropping was achieved. Is it manually?

Response: Thank you for your valuable advice. No, the cropping was achieved by using the python library scikit-image 0.15.0(https://scikit-image.org/ scikit-image 0.15.0). The means of cropping is as above response.

-The following text should be in Section: Deep Convolutional Network Architecture "The deep convolutional network was a 2.5D MP-CDN with the four phases of resized multichannel images as the input (slice was used as the channel dimension in this network). The classification tasks consisted of training and testing, where the training task was executed with a batch size of 100, and the test task was executed once for each lesion."

Response: Thank you for your valuable advice. We have moved the text to the section "Deep Convolutional Network Architecture" as you suggested

- Section: Deep Convolutional Network Architecture: Did the authors evaluate the effect of data augmentation on the training. I mean, does data augmentation improve the results or not?

Response: Thank you for your valuable advice. No, we did not evaluate the effect of data augmentation on the training. Data augmentation is one important preprocessing method that has been shown to be effective in training highly discriminative deep learning models. Since a slight difference in position may lead to the inconsistency between examinations, which can help preempt overfitting. In our study, data augmentation strategies such as rotation and scaling have been adapted. Although, we didn't further evaluate the effect on the training, the previous study[1, 2] shows that augmentation options such as rotation and scaling can increase accuracy and generalization of CNNs.

References:

1 Hussain Z, Gimenez F, Yi D, Rubin D. Differential Data Augmentation Techniques for Medical Imaging Classification Tasks. AMIA Annu Symp Proc 2017 2017-01-20; 2017: 979-984[PMID:29854165]

2 Lakhani P, Gray DL, Pett CR, Nagy P, Shih G. Hello World Deep Learning in Medical Imaging. J DIGIT IMAGING 2018 2018-06-01; 31: 283-289 [PMID:29725961 DOI:10.1007/s10278-018-0079-6]

6 Results. Good

7 Discussion. Good

8 Illustrations and tables. Good

9 Biostatistics. Good

10 Units. Good

11 References. Good

12 Quality of manuscript organization and presentation. Good

13 Research methods and reporting. Good 14 Ethics statements. OK

Response: Thank you for your valuable advice. The details addressing the reviewers' comments have been provided in the revised manuscript.

Editorial Office's comments

The author must revise the manuscript according to the Editorial Office's comments and suggestions, which listed below:

Science Editor**:**

1 Scientific quality: The manuscript describes a retrospective study of the classification of focal liver lesions. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: This is a well-written paper. Reviewer#02708249 thinks the writing of "title", "abstract" and "method" section all good. Quality of manuscript organization and presentation is good. However, there are some points need to be addressed. The questions raised by the reviewers should be answered; and (3) Format: There are 3 tables and 5 figures. A total of 31 references are cited, including 16 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A. A language editing certificate issued by AJE was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement, the Institutional Review Board Approval Form, and informed consent. No academic misconduct was found in the Bing search.

CrossCheck detection showed a high similarity with other articles, our editorial policy states the overall similarity should be less than 30%, the overlapped section should be less than 5% in single papers, including author's own work. The authors need to rephrase these repeated sentences.

Response: Thank you for your valuable advice. The repeated sentences have been rephrased. The current similarity index is 17% and the two papers with a relative high degree of overlap with this paper are our own articles. The similarity report obtained from CrossCheck (https://app.ithenticate.com/) have been uploaded in the Supplementary Material.

4 Supplementary comments: This is an unsolicited manuscript. The study was supported by the National Natural Science Foundation of China grant 91959118 (JW), Science and Technology Program of Guangzhou, China 201704020016 (JW), SKY Radiology Department International Medical Research Foundation of China Z-2014-07-1912-15 (JW), and Clinical Research Foundation of the 3rd Affiliated Hospital of Sun Yat-sen University. The topic has not previously been published in the WJG. The corresponding author has not published articles in the BPG.

5 Issues raised:

(1) I found there is no "Author contribution" section. Please provide the author contributions;

Response: Thank you for your valuable advice. The "Author contribution" section has been added in the revised manuscript. (marked in red color in the revised manuscript)

The author contribution are shown below.

Author contributions: Cao SE, Zhang LQ, Shi WQ, Chen YN, Liu H and Ye M contributed to the conception and design of the study. Cao SE, Kuang SC, Shi WQ, Hu B, Jiang T, Chen SM and Zhang HX collected the patients' data, analyzed and interpreted the data. Cao SE wrote original draft and revised the manuscript. Wang J contributed to the conception of the study and provided final approval of the version to be submitted and any revised versions.

(2) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Response: Thank you for your valuable advice. The approved grant application forms have been uploaded.

(3) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

Response: Thank you for your advice. The arranged original figures using PowerPoint have been provided.

and (4) I found the authors did not write the "article highlight" section. Please write the "article highlights" section at the end of the main text.

Response: Thank you for your valuable advice. The "article highlight" section has been added at the end of the revised manuscript. (marked in red color in the revised manuscript)

The article highlights are shown below.

ARTICLE HIGHLIGHTS

Research background

The accurate classification of focal liver lesions (FLLs) is essential to properly guide treatment options and predict prognosis. Dynamic contrast-enhanced computed tomography (DCE-CT) is commonly used for the noninvasive detection and exact classification of FLLs due to its high scan speed and high density resolution. Since their recent development, convolutional neural network (CNN)-based deep learning techniques have been recognized to have high potential for image recognition tasks.

Research motivation

Since the different types of FLLs have different outcomes and require different clinical interventions, the current challenge in determining an accurate diagnosis involves not only effectively differentiating between benign and malignant FLLs according to the medical image but also

accurately recognizing the different types of FLLs. Our purpose was to develop and evaluate a deep learning-based CNN to classify FLLs on multiphase CT. Our CNN model is expect to become an efficient tool to assist radiologists in accurately identifying the different types of FLLs.

Research objectives

The appearances, especially the dynamic enhancement patterns of FLLs on CT imaging, are essential for categorizing lesions. We employed a four-channel input data to preserve the dynamic enhancement properties. The combination of the lesion's dynamic enhancement pattern with a CNN can imitate the image diagnosis of radiologists and is expected to improve diagnostic accuracy.

Research methods

Five hundred seventeen FLLs scanned on a 320-detector CT scanner using a four-phase DCE-CT imaging protocol (including precontrast phase, arterial phase, portal venous phase, and delayed phase) from 2012 to 2017 were retrospectively enrolled. FLLs were classified into four categories (category A, hepatocellular carcinomas [HCCs]; category B, liver metastases; category C, benign non-inflammatory FLLs including hemangiomas, focal nodular hyperplasias [FNHs] and adenomas, and Category D, hepatic abscesses). Each category was randomly split into a training set and test set in an approximately 8:2 ratio, and the variables including the maximum diameter of the lesion were not significantly different between the training and test sets.

The CNN model with a sequential input of the 4-phase CT images was developed to automatically classify FLLs. The classification performance of CNN model was evaluated on the test set: The accuracy, specificity and sensitivity were calculated from the confusion matrix, and the area under the

receiver operating characteristic curve (AUC) was calculated from the softmax probability outputted from the last layer of the CNN model.

Research results

A total of 410 FLLs were used for training and 107 FLLs were used for testing. The accuracy/specificity/sensitivity of differentiating each category from others were 0.916/0.964/0.739, 0.925/0.905/1.0, 0.860/0.918/0.735 and 0.925/0.963/0.815 for HCCs, metastases, benign non-inflammatory FLLs, and abscesses on the test set, respectively. The AUC (95%Confidence Interval (CI)) for differentiating each category from others was 0.92 (0.837-0.992), 0.99 (0.967-1.00), 0.88 (0.795-0.955) and 0.96 (0.914-0.996) for HCCs, metastases, benign non-inflammatory FLLs, and abscesses on the test set, respectively. Also, for this study, we only trained and evaluated the CNN model in a single center setting using a single CT scanner, where there might be a data bias that may lead to model bias. Further evaluation of this model in a multicenter setting is needed to evaluate its clinical utility.

Research conclusions

Overall, Our CNN model showed a high differential diagnostic performance for classification FLLs as HCCs, metastases, benign non-inflammatory FLLs and hepatic abscesses in four-phase CT image and could become an efficient tool to assist radiologists in accurate identification of the different types of FLLs.

Research perspectives

Further multicenter studies are necessary to evaluate the clinical utility of our CNN model. In addition, it's worth to evaluate the clinical information whether can further improve the perform of CNN model.

6 Re-Review: Not required. 7 Recommendation: Conditionally accepted.

(2) Editorial Office Director: I have checked the comments written by the science editor.

(3) Company Editor-in-Chief: I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Response: Thank you for your valuable advice. A revised manuscript answering the comments made by the reviewers have been provided.