PCM PRECISION CANCER MEDICINE
A JOURNAL AIMING TO DELIVER A LASTING BLOW TO CANCER

Peer Review File

Article information: https://dx.doi.org/10.21037/pcm-22-28

Reviewer comments

Very interesting viewpoint. This manuscript is clear and organized. Just have a few formatting issues or clarifying questions:

1.About the format of citing, consider using "et al." for works done by multiple authors.

[R] Thank you for your comment. We have corrected the formatting of multiple authors' articles with "et al.

2.For works that focus on specific treatment sites, please add this to the main text as well.

[R] Thank you for your comment . We added some results related to specific treatment sites.

(Page 16 Line 342)

"Among the included studies, in terms of treatment sites, the majority focused on the head and neck (10/23). This was followed by the abdomen (8/23) and the thorax (5/23). "

3. Line 128, the word "connection" was confusing at the first look. Maybe it means "transferring"?

[R] Thank you for your comment. You are right, 'transferring' is much clear than 'connection'. We changed it to transferring.

(Page 5 Line 111)

"However, the basic GAN generates data from noise so there are still some shortcomings: first, the class of the generated data cannot be controlled and, secondly, the transferring between two different clinical imaging modalities cannot be done by a basic GAN. To overcome these problems, some improvements to GAN based model were made."

4.Lines 130-138, not sure about the term "supervised" here. My understanding of supervised learning was that every input is paired with an output. Whereas the difference between cGAN and GAN is that cGAN is conditioned, with an additional block "c" in figure 1b. Please correct me if this is not the case.

[R] Thank you for your comment. The original GAN only needs input data to generate images. While cGAN changes the input of GAN so that it also needs input labels, so CGAN can be considered as input supervised learning.

5.Lines 300-303, "real-time generate dose distribution" and "predict a fluence map without statistical significance from the real one" might be different from the conclusions in the original study. This study generates fluence maps (or plans) and evaluated results using dosimetric merits. Please make sure the other works were also described accurately.

[R] Thank you for your comment. We agree with your comment, it should be generate fluence map. I corrected it.

(Page 13 Line 269)
"In another work, Xinyi Li et al. (2021) designed a CGAN-based model which can real-time generate fluence map from CT."

6.Line 359 says no significant difference as well as p<0.01, which sounds contradictory.

[R] Thank you for your attentive comment. We checked the reference again and corrected the 'no significant difference' to 'significantly outperformed performance'.

(Page 15 Line 316)
"The performance of the model has significantly outperformed performance in the 14 patients' test set (47 ± 7 HU versus 51 ± 8 HU; paired Wilcoxon signed-rank test, P < 0.01). "

7.Could you please discuss how to deal with different contrasts among different scanners or even different patients? Especially for MR images, image contrast, or absolute image pixel values highly rely on scanning parameters and scanners. These parameters are often not included during training. How will this affect model training, prediction accuracy, robustness, and application?

[R] Thank you for your comment. We added the discussion about your comment.

(Page 18 Line 380)

"And, It is worth noting that, addition to the hyper parameters of the GANs model, the physical difference (contrasts, scanners, and patients etc.) which often not included during training also have a significant impact on the performance of the generated images. Especially for MR images, image contrast, or absolute image pixel values highly rely on scanning parameters and scanners, which makes the algorithm more difficult to train, less robustness , harder to migrate the model to data generated by other scanners, making it difficult to be widely used. Fortunately, there are many traditional and deep learning based image harmonization methods (adjusting the distribution of images from different sources so that they are close to each other) can overcome the above problem(28-30)."

28. Song S, Zhong F, Qin X, Tu C, editors. Illumination harmonization with gray mean scale. Computer Graphics International Conference; 2020: Springer.
29. Pinto MS, Paolella R, Billiet T, Van Dyck P, Guns PJ, Jeurissen B, et al. Harmonization of Brain Diffusion MRI: Concepts and Methods. Frontiers in neuroscience. 2020;14:396.
30. Jiang Y, Zhang H, Zhang J, Wang Y, Lin Z, Sunkavalli K, et al., editors. Ssh: A self-supervised framework for image harmonization. Proceedings of the IEEE/CVF International Conference on Computer Vision; 2021.

8.Is any of the synthetic CT images accurate enough for clinical application?

[R] Thank you for your comment. We added some discussion according to your comment.

(Page 19 Line 399)

"Although many studies (9, 13, 15, 25, 31-33) have conducted distribution comparison between synthetic and real one or validated their models in simulated clinical settings and have shown great potential to apply it in the real world. It still needs more evidence to apply it in the clinic, such as conducting clinical trials or embedding it into treatment planning systems to validate its application in daily clinical practice. Setting these exciting results aside, there are still some technical barriers that need to be overcome. For example, for MRI-based generation of synthetic CT, organ effects such as organ motion (13, 33) and organs containing cavities (15) will have an impact on the accuracy of the results or require manual intervention (11, 13), which needs to be supported by more relevant studies, such as advances in deformable alignment techniques. Therefore, we consider that the application of GANs techniques requires a series of synergistic developments from a technical point of view to be accomplished."

9.Liu Y, Lei Y, Wang Y, Shafai-Erfani G, Wang T, Tian S, et al. Evaluation of a deep learning-based pelvic synthetic CT generation technique for MRI-based prostate proton treatment planning. Physics in medicine and biology. 2019;64(20):205022.

11. Kazemifar S, Barragán Montero AM, Souris K, Rivas ST, Timmerman R, Park YK, et al. Dosimetric evaluation of synthetic CT generated with GANs for MRI-only proton therapy treatment planning of brain tumors. Journal of applied clinical medical physics. 2020;21(5):76-86.

13. Olberg S, Zhang H, Kennedy WR, Chun J, Rodriguez V, Zoberi I, et al. Synthetic CT reconstruction using a deep spatial pyramid convolutional framework for MR-only breast radiotherapy. Medical physics. 2019;46(9):4135-47.

15. Maspero M, Savenije MHF, Dinkla AM, Seevinck PR, Intven MPW, Jurgenliemk-Schulz IM, et al. Dose evaluation of fast synthetic-CT generation using a generative adversarial network for general pelvis MR-only radiotherapy. Physics in medicine and biology. 2018;63(18):185001.

25. Liu Y, Lei Y, Wang T, Fu Y, Tang X, Curran WJ, et al. CBCT-based synthetic CT generation using deep-attention cycleGAN for pancreatic adaptive radiotherapy. Medical physics. 2020;47(6):2472-83.

31. Babier A, Mahmood R, McNiven AL, Diamant A, Chan TCY. Knowledge-based automated planning with three-dimensional generative adversarial networks. Medical physics. 2020;47(2):297-306.

32. Maspero M, Savenije Mhf Fau - Dinkla AM, Dinkla Am Fau - Seevinck PR, Seevinck Pr Fau - Intven MPW, Intven Mpw Fau - Jurgenliemk-Schulz IM, Jurgenliemk-Schulz Im Fau - Kerkmeijer LGW, et al. Dose evaluation of fast synthetic-CT generation using a generative adversarial network for general pelvis MR-only radiotherapy. (1361-6560 (Electronic)).

33. Liu Y, Lei Y, Wang Y, Wang T, Ren L, Lin L, et al. MRI-based treatment planning for proton radiotherapy: dosimetric validation of a deep learning-based liver synthetic CT generation method. Physics in medicine and biology. 2019;64(14):145015.

9. A few manuscripts that might be related to the topic (sorry if any of these are already included or irrelevant to the topic):

https://pubmed.ncbi.nlm.nih.gov/34242852/
https://pubmed.ncbi.nlm.nih.gov/34741702/
https://pubmed.ncbi.nlm.nih.gov/33802499/
https://pubmed.ncbi.nlm.nih.gov/32989773/
https://pubmed.ncbi.nlm.nih.gov/34350052/
https://pubmed.ncbi.nlm.nih.gov/32632116/
https://pubmed.ncbi.nlm.nih.gov/34552709/
https://pubmed.ncbi.nlm.nih.gov/31131901/
https://pubmed.ncbi.nlm.nih.gov/32365088/
https://pubmed.ncbi.nlm.nih.gov/28574346/
https://pubmed.ncbi.nlm.nih.gov/29870364/
https://pubmed.ncbi.nlm.nih.gov/29464432/
https://pubmed.ncbi.nlm.nih.gov/34649572/
https://pubmed.ncbi.nlm.nih.gov/31610527/
https://pubmed.ncbi.nlm.nih.gov/34990905/
https://pubmed.ncbi.nlm.nih.gov/35184310/
https://pubmed.ncbi.nlm.nih.gov/31733164/
https://pubmed.ncbi.nlm.nih.gov/31675444/

[R] Thank you for your comment. Though not all of the above manuscripts exactly match our search strategy, we think they are match our research area and worthwhile to share with readers . In this way, we added the relevant articles mentioned in the comments to our manuscript.

(Page 18 Line 380)

"Vincent Bourbonne (2021) was the first study which demonstrate the GAN-generated CT from diagnostic brain MRIs have comparable performance to initial CT for the planning of brain stereotactic RT. In their study , the 2D-UNet was selected as the backbone of generator. Through experiments on a dataset of 184 patients, there were no significant statistical differences regarding ICRU 91s endpoints, which means the synthetic CT and initial CT has high similarity for both the organs at risk and the target volumes(14)."

(Page 15 Line 328)

"Except self-attention, Liugang Gao (2021) proposed an attention-guided Cycle-GAN which contains two equipped with attention module generators to generate attention mask. It can make generator pays attention to the important part of images to eliminate numerous artifacts. By training and testing on a dataset of 170 patients, the proposed method has similar quality with real CT in MAE (43.5 ± 6.69), SSIM(93.7 ± 3.88), PSNR(29.5 ± 2.36), mean and standard deviation (SD) HU values ($P < 0.05$). Besides that, sCT provided the highest gamma passing rates (91.4 ± 3.26) in dose calculation compared with GAN methods. These demonstrate that the proposed method can trained by unpaired data to generate high-quality CT from CBCT(26)."

14. Bourbonne V, Jaouen V, Hognon C, Boussion N, Lucia F, Pradier O, et al. Dosimetric Validation of a GAN-Based Pseudo-CT Generation for MRI-Only Stereotactic Brain Radiotherapy. Cancers. 2021;13(5).
26. Gao L, Xie K, Wu X, Lu Z, Li C, Sun J, et al. Generating synthetic CT from low-dose cone-beam CT by using generative adversarial networks for adaptive radiotherapy. Radiation oncology (London, England). 2021;16(1):202.