Peer Review File

Article Information: https://dx.doi.org/10.21037/atm-22-2647

Reviewer Comments

1. The authors extracted a total of 157 radiomics features including 100 PET radiomics and 57 CT radiomics by using an open-source software, the Chang Gung Image Texture Analysis (CGITA). They appear to have extracted radiomics features from original PET/CT images without also extracting those from filtered images such as wavelet or Laplacian-of-Gaussian, and so on. Furthermore, extracted CT radiomics features were nearly half the size of PET radiomics features. They may need to employ filtered images for extracting additional PET/CT radiomics features because radiomics features from filtered images have frequently been selected as prognostic and diagnostic markers (Aerts HJ et al. Nat Commun 2014;5:4006; Huynh E et al. Radiother Oncol 2016;120(2):258-266; Jing R et al. Sci Rep 2021;11, 22330). They would also need to extract texture features from CT and PET as closely as possible, though shape features could be extracted from either CT or PET depending on which image was used as a reference for segmenting/contouring BPNs or MPNs.They would also need to extract texture features from CT and PET as closely as possible, though shape features could be extracted from either CT or PET depending on which image was used as a reference for segmenting/contouring BPNs or MPNs.

Reply: Thank you for your kind suggestion. In this study, the radiomics features were calculated using the Chang-Gung Image Texture Analysis (CGITA), an open-source software package for academic use (Fang, Y et al. BioMed Res. Int. 2014). These radiomics features were extracted based on morphological characteristics (shape, volume, surface area, density and mass), statistics (attenuation histogram) and regional (intra-tumor neighborhood analysis) in the ROI. In addition, part of radiomics features from original PET/CT images have been selected as diagnostic markers and have an excellent performance in this study and our previous work (Ren C et al. Eur J Nucl Med Mol Imaging 2021;48(5):1538-1549).

As shown in Table S1 of supplementary data, 43 of the 157 radiomics features were calculated from SUV Statistics, which were only for PET images. Among the remaining 114 radiomics features, there were 57 PET radiomics features and 57 CT radiomics features, respectively. The number of radiomics features extracted from PET and CT images was equal. However, as your suggestion, we will try to employ filtered images for extracting additional PET/CT radiomics features in the future works.

2. In this study, the tumor area was delineated/segmented on PET images using a threshold of 40% of SUVmax, and PET and CT radiomics features were extracted. If the segmented tumor

contours from PET scans are not refined using CT images, they may not fully reflect the accurate anatomical tumor borders. PET images are typically over-segmented due to the partial volume effect. If they used partial volume correction on PET images, they should also explain how they did it.

Reply: Thank you for your suggestion. We delineated the tumor area on PET images using a threshold of 40% of SUVmax, and refined the segmented tumor contours from PET scans using CT images to avoid the inclusion of areas with physiological ^{18}F-FDG uptake within the regions of interest and ensure that the accurate anatomical tumor borders were fully reflected. We have added the details in the Materials and Methods section of the revised manuscript.

The text now reads as follows: "To avoid the inclusion of areas with physiological ^{18}F-FDG uptake within the regions of interest and ensure that the accurate anatomical tumor borders were fully reflected, a joint reading of both the CT and PET scans was performed side by side".

Changes in the text: Page 9, lines 135 to 138.

3. Utilizing a large number of radiomics features may not always improve predictive performance because it is prone to overfitting. Furthermore, even if they used LASSO for feature selection, the performance of LASSO might have been hampered by collinearity between features and their high dimensionality (). To mitigate this issue, they could conduct multiview radiomics analysis, which aims to identify a suitable set of input radiomics classes by subcategorizing radiomics features and improve the performance of a radiomics model. (Lee et al. Phys Med Biol 2020;65:195015).

Reply: Thank you for your suggestion. To date, most radiomics studies have concatenated the multiple feature groups all together to form a single-view feature vector. Radiomics feature selection and classifier performance are based on the single-view data analysis scenario (Parmar C, et al. Front. Oncol.2015). In this study, the feature selection was performed by the single-view analysis (LASSO algorithm) which could address multiple cross-related covariates and reduce the risk of overfitting of the data. Finally, we successfully developed and validated an integrated model consisting of clinico-biological factors, tumor markers and ^{18}F-FDG PET/CT radiomics features, which held an excellent performance in noninvasively distinguishing between BPN and MPN patients (AUCs of 0.91 and 0.94, respectively). However, as you pointed out, multi-view learning approaches have been increasingly adopted to handle machine learning problems with high-dimensional data represented by multiple distinct feature sets. We will try these approaches in subsequent studies.

4. The authors may perform an integrative approach for identifying key signatures by addressing correlated nature of different feature types while also predicting a target variable (Lee SH et al. Int J Radiat Oncol Biol Phys 2021;110(5):1451-1465). If this strategy cannot be used in the current study, it should be mentioned as one of the study's limitations in the

discussion.

Reply: Thank you for making this point. We have added this limitation in the Discussion section of the revised manuscript according to your suggestion.

The text now reads as follows: “Thirdly, the supervised classification approach was used to identify the key features for predicting the target variable in this study. However, the latent relations between different feature types did not been explored. How to integrate features obtained across imaging, molecular and clinical modalities more reasonably to improve the differentiation ability and clarify the potential biological characteristics of tumor will be an important direction for future work”.

Changes in the text: Page 20, lines 308 to 313.