［課程－２］

審査の結果の要旨

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ABSTRACT

Objective: To propose modifications of orthotopic rat lung transplantation (LTx) and construct machine learning (ML)-based positron emission tomography (PET) radiomics models for predicting AR in rat LTx.

Methods: Initially, 180 consecutive rat LTx were performed using the modified technique. Twenty-eight recipient rats were served in the PET experiment and set in four groups: isograft, allograft-cyclosporine$_{continuous}$ (CsA_{cont}), allograft-$CsA_{delayed}$, and allograft-CsA_{1week}. 18F-fluorodeoxyglucose PET was acquired at weeks 3 and 6 post-transplant, and the maximum standardized uptake value (SUV_{max}) and radiomics features were extracted from PET images. The least absolute shrinkage and selection operator algorithm was used to calculate a radiomics score (Rad-score). Eight modeling algorithms (seven ML algorithms and one logistic regression) with six feature selection methods were performed to develop 48 radiomics models for monitoring AR, validated using leave-one-out cross-validation.

Results: I modified a rat LTx model with easy mastery, expeditiousness, no intraoperative complication or death. In total, 837 radiomics features were extracted from each PET image. The SUV_{max} and Rad-score showed significant positive correlations with histopathology ($P < 0.05$). The median area under the curve (AUC) of 42 ML models was 0.944, superior to that of 6 logistic regression models (AUC, 0.794). The optimal ML model using a random forest modeling algorithm with random forest feature selection method exhibited the highest AUC of 0.978 in all models.

Conclusion: I modified the rat LTx model and demonstrated SUV_{max} provided a good correlation with AR, but ML-based PET radiomics further strengthened the power of 18F-fluorodeoxyglucose PET functional imaging for monitoring AR in LTx.

ACHIEVEMENTS

Using this modified technique, I have supervised two Doctoral Program students who achieved the first rat LTx success in one week with less than ten attempts. In addition, I was invited to introduce this technique in China and supervised researchers from more than ten institutes. All of them mastered this modified rat LTx in less than one week. The most significant honor for this modified technique was that the International Society for Heart and Lung Transplantation (ISHLT) invited me to present this technique at the Annual Meeting (April 27, 2022; Boston, USA). This further indicated the modified rat LTx had been internationally recognized. The advantages of this modified cuff technique include its expeditiousness, low complication rate, and high success rate. A high success rate not only saves cost and time but can also strengthen the operator's confidence during surgery. Based on this modified model, further preclinical research can be achieved with stable and reproducible results.

Furthermore, using the modified rat LTx model, I introduced a noninvasive method of machine learning-based 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) radiomics to monitor allograft rejection with excellent performance. This study first reported the application of machine learning-based radiomics to detect allograft rejection in LTx and was invited to present at the 41st ISHLT (2021) Annual Meeting. This noninvasive method will further enhance the value of radiological imaging in clinical practice, and radiomics based on 18F-FDG PET and machine learning algorithms may serve to decrease biopsy and potentially serve as a useful noninvasive method for postoperative lung allograft rejection. With this noninvasive method, patients with contraindications of biopsy may be applied.

よって本論文は博士（医学 ）の学位請求論文として合格と認められる。