

Purpose: To predict radiation-induced cardiac perfusion defects using a fusion model that combines the results of four separate models: feed-forward neural networks (NNET), self-organizing maps (SOM), support vector machines (SVM), and multivariate adaptive regression splines (MARS). **Methods and Materials:** The database comprised 111 patients with left-sided breast treated with radiotherapy (56 diagnosed with cardiac perfusion defects post-radiotherapy). The four independent models (NNET, SOM, SVM, and MARS) were constructed using a small number of independently selected features. The four models were then fused to a final model by averaging their patient predictions. Patient predictions were generated by testing the models using ten-fold cross-validation, wherein 1/10th of the data were tested, in turn, using models built with the remaining 9/10th of the data. To account for the variance in patient predictions caused by the effect of data splitting, 10-fold cross validation was repeated 100 times with random data splitting. **Results:** For the fused model, the area under the Receiver Operating Characteristics (ROC) curve for cross-validated testing was 0.890±0.012 (sensitivity = 80.6±1.7%, specificity = 80.2±1.7%). It was superior to the individual models (NNET: ROC = 0.764±0.015, sensitivity = 72.9±1.5%, specificity = 72.4±1.6%; SOM: ROC = 0.769±0.013, sensitivity = 73.0±1.4%, specificity = 72.2±1.5%; SVM: ROC = 0.900±0.048, sensitivity = 87.3±6.2%, specificity = 86.0±6.1%; MARS: ROC = 0.802±0.009, sensitivity = 76.1±1.1%, specificity = 75.6±1.1%) either in regard to higher predictive capability or lower variance. The fused model identified the following features as most important in predicting radiation-induced perfusion defects: generalized equivalent uniform dose (EUD) with exponent $a = 0.7$, 1.0, and 3.6, and hypertension. Other features such as V46, V47, obesity, pack years, and chemotherapy played a less important role. **Conclusions:** The fused model provides promise for prospectively predicting radiation-induced cardiac perfusion defects with high accuracy and confidence (low variance).