ejpmr, 2022, 9(5), 518-525

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

APPLICATION OF MAMMOGRAPHY PLUS ULTRASOUND BASED RADIOMICS IN THE IDENTIFICATION OF BENIGN AND MALIGNANT BREAST TUMORS

Hezam Mohammed Ahmed Mohammed[1], Wei Wang[1]*, Hang Qu[1], Han Yu[2], Yifan Du[2] and Prosenjit Paul[3]*

[1,2]Department of Radiology, Medical Imaging Center, The Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China.

[3]Negenome Bio Solutions Pvt Ltd, Jorhat, Assam-785001.

***Corresponding Author: Wei Wang**

Department of Radiology, Medical Imaging Center, The Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China.

Article Received on 21/03/2022 **Article Revised on 11/04/2022** **Article Accepted on 01/05/2022**

ABSTRACT

The aim of the work was to develop and evaluate machine learning models based on characteristics retrieved by conventional radiomics. A total of 92 patients with breast tumors who underwent mammography and ultrasonography were included in the study. Tumors were confirmed by pathological biopsy. The CC and ROI regions were mapped independently by two highly experienced surgeons using ITK-snap software. Data were randomly assigned in a 7:3 ratio to the training cohort and test cohort. LASSO (Least absolute relevance and selection operator) were used to screen, select the features, and develop the radiomics signature. Four machine learning models (RandomForest, DecisionTrees, KNN and Bayes) performance were evaluated with ROC (Receiver Operating Characteristic Curve), and decision curves. The AUC (Area under the ROC curve) of the model, RandomForest, DecisionTrees, KNN and Bayes in the training set and test set were 1.0, 0.969; 0.996, 0.87; 1.0, 0.857; 0.897, 0.895, respectively. AUC values of Tree and Forest model are statistically different at $p<0.05$. Forest model showed a statistically significant difference with Bayes and Tree model at $p<0.05$. Our analysis confirms that Forest model outperforms the other three models in terms of AUC score for breast tumor prediction.

KEYWORDS: Breast cancer; machine learning; mammography; features.

INTRODUCTION

Breast cancer (BC) is a common malignancy in women worldwide (2.3 million in 2020).[1] BC has been identified in 7.8 million living women in the previous five years, according to a WHO report published in 2020. According to Waks and Winer 2019, about 12% of all women in the United States will be diagnosed with the condition at some time in their life.[2] BC is risking the lives of Chinese women, as it is in other nations. China accounts for 12.2 percent of all newly diagnosed BC cases and 96 percent of all global fatalities, respectively.[3] China has a higher age-standardized incidence rate of breast cancer (49–55 years) than other developing nations like Niger and Tanzania.[4] Breast cancer was most common in China's metropolitan or eastern districts, which were more socioeconomically developed.[5] The age-specific incidence rate climbed fast after the age of 25 years and peaked at the age of 45–59 years, according to a study done by Lei et al 2021.[4] Breast cancer in young women is more likely to be discovered at a later stage than in older women, according to previous research.[6] According to one study, having more children per woman was linked to a lower incidence of breast cancer (OR = 0.69, 95 percent CI: 0.52–0.91).[7] Chinese women with a higher BMI (greater than 24 kg/m2) and type 2 diabetes were also shown to have a higher risk of breast cancer (OR = 1.696).[8,9]

Mammography, ultrasound, and magnetic image resonance have all been combined into various screening programs around the world to improve early detection, with mammography alone or in combination with ultrasound showing the best results in terms of early diagnosis and overall survival for breast cancer patients.[10] Mammography has a few drawbacks, such as being less efficient in patients under the age of 40 and in subjects with thick breasts, as well as being less sensitive to tumors less than 1mm.[11,12] Medical imaging has evolved dramatically as a result of recent technological advancements. Radiomics is a new and fast-expanding field of research that uses high-throughput computer power to extract enormous numbers of visual attributes and turn them into measurable data.[13] Radiomics is a non-invasive and cost-effective method of analyzing the characteristics of cancer lesions.[14] The radiomic features correctly represent the lesions' morphological and functional characteristics.[15] Marino et al.[15] evaluated 100 individuals who had contrast-enhanced mammography pictures in a retrospective investigation.

Their radiomics investigation revealed that it is capable of classifying tumor form, degree, and hormone receptor status.

Till date a few machine learning models have been used on radiomics features to classify benign and malignant breast cancer. Among them the most commonly used models are Native Bayes Classifier, Support Vector Machine (SVM) classifier, random forest (FR), K-Nearest neighbor (KNN) and decision tree (tree). Most of the available publications on radiomics.[16-18] identified only one or two models to compare for the prediction of breast cancer. As a result, the current research work intends to not only extract essential characteristics from radiological pictures, but also to construct and compare four unique ML models (Forest, Bayes, KNN and Tree).

MATERIALS AND METHODS

Clinical data

We retrospectively reviewed data for 92 patients with breast cancer who underwent surgery at the Northern Jiangsu People's Hospital, Affiliated Hospital of Yangzhou University, China. Here we considered those patients who underwent breast mammography imaging and ultrasonography before the pathological biopsy from October 2019 to September 2021. The average age of the patients was found to be 55.11. In this study, BI-RADS 4A was used as the best segmentation point. Class 3 and 4A breast tumors were recorded as benign, and class 4b, 4C and 5 breast tumors were recorded as malignant.

Mammography

GE Senographe Essential was used to take standard head and tail (CC) and internal and external oblique (MLO) films (GE Healthcare, Milwaukee, Wisconsin). The CC and MLO positions should encompass as much of the focus and breast parenchyma as feasible, and specific photographic techniques, such as local pressure magnification photography, should be used when necessary.

Ultrasonography

Images were acquired using a Sonix RP clinical research system (Analogic Medical Corp., Vancouver) with a linear array transducer (L14-5/60, Analogic Medical Corp., Vancouver) having a central frequency of 7 MHz (bandwidth 4–9 MHz).

Image processing

Image export and ROI selection

The radiological pictures of all breast cancer patients were manually segmented first. Two expert imaging specialists utilized ITK-snap software to map the CC and ROI areas. Each patient's ROI was processed separately by both surgeons. When there is a disagreement on the ROI selection range, the two parties must work together to define the ROI outline range.

Data preprocessing

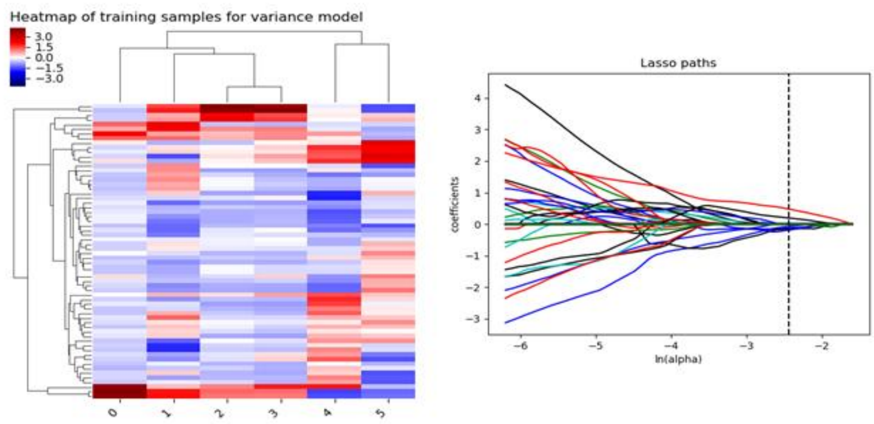
The dataset was randomly assigned in a 7:3 ratio to either the training cohort or test cohort. All cases in the training cohort were used to train the predictive model, while cases in the test cohorts were used to independently evaluate the model’s performance. Before analyses, variables with zero variance were excluded from analyses. Then, the missing values and outlier values were replaced by the median. Finally, the data were standardized by standardization.

Feature selection

Feature selection was performed by using LASSO. Lasso compresses the coefficients of all variables by constructing a penalty function, so that some regression coefficients become 0, so as to achieve the purpose of variable selection. In this study, we use the tenfold feature of the regularization function to further verify the classification ability of the most benign and malignant data.

Feature screening

To discover the independent variables with statistical differences, the t-test and rank-sum test were utilised. Then, using Lasso, the dimension was reduced, the number of features was automatically retained according to the appropriate truncation point, and six feature parameters were added. As seen in Figure 1



(A) **(B)**

Figure 1: (A) 6 features retrieved after lasso dimensionality reduction, (B) figure depicts the lasso feature coefficients convergence diagram, where significant features were represented by the vertical dotted line

Machine learning models

Random Forest is a well-known machine learning algorithm that uses the supervised learning method. A Forest model was built from the established optimal feature subsets of the training dataset. The parameter settings used for model building was as follows 'max_depth': 5, 'min_samples_split': 2, 'n_estimators': 20. The parameter settings used for DecisionTree model building was as follows, 'max_depth': 5, 'min_samples_split': 2. KNN works by calculating the distances between a search and all of the instances in the data, picking the K closest instances to the inquiry, and then voting for the most common label (in the case of classification) or averaging the labels (in the case of regression). The parameter settings used for model building was as follows, 'n_neighbors': 1. In applied machine learning, the Bayes Theorem is a helpful tool. It offers a framework for considering the link between data and a model. The parameter settings used for model building was as follows, 'Model': 'BernoulliNB', 'alpha': 0.1, 'binarize': 0.2

Statistical analysis

Receiver operating characteristic (ROC) curve was used to compare the performance of supplementary machine learning model; and accuracy, sensitivity, specificity and area under curve (AUC) were calculated. All statistical analyses for the present study were performed with R 3.5.1 and Python 3.5.6. A two-tailed p-value <0.05 indicated statistical significance.

RESULTS

A total of six features were finally selected after lasso dimensionality reduction are morphological features. These features were: first-order feature Kurtosis, grey-level dependency matrix (gldm): Dependence variance.

Gray-Level Size Zone Matrix (GLSZM): Gray Level Variance, neighborhood gray-tone difference matrix (NGTDM): Complexity, Shape: Elongation, and Maximum2DDiameterRow. The six feature parameters obtained after feature dimensionality reduction are used in machine learning algorithms Forest, Tree, KNN and Bayes for classification learning. The accuracy, area under ROC (AUC), sensitivity and specificity are cross verified, and the average value is taken as the final classification result. The efficiency parameters are as follows:

Table 1; Evaluation report of the Forest model in the training and testing samples.

Item	Train	Test
Accuracy	1.0	0.857
f1_score	1.0	0.846
Recall	1.0	0.786
Precision	1.0	0.917
AUC	1.0 (1.0, 1.0)	0.969 (0.922, 1.0)
Sensitivity	1.0	0.786
Specificity	1.0	0.929
positive prediction	1.0	0.917
negative prediction	1.0	0.812
positive llr	inf	11.0
negatice llr	0.0	0.231

Table 2: Evaluation report of the Tree model in the training and testing samples.

Item	Train	Test
Accuracy	0.969	0.893
f1_score	0.968	0.88
Recall	0.938	0.786
Precision	1.0	1.0
AUC	0.996 (0.989, 1.0)	0.87 (0.744, 0.967)
Sensitivity	0.938	0.786
Specificity	1.0	1.0
positive prediction	1.0	1.0
negative prediction	0.941	0.824
positive llr	inf	inf
negatice llr	0.062	0.214

Table 3: Evaluation report of the KNN model in the training and testing samples.

Item	Train	Test
Accuracy	1.0	0.857
f1_score	1.0	0.846
Recall	1.0	0.786
Precision	1.0	0.917
AUC	1.0 (1.0, 1.0)	0.857 (0.741, 0.962)
Sensitivity	1.0	0.786
Specificity	1.0	0.929
positive prediction	1.0	0.917
negative prediction	1.0	0.812
positive llr	inf	11.0
negatice llr	0.0	0.231

Table 4: Evaluation report of the Bayes model in the training and testing samples.

Item	Train	Test
Accuracy	0.797	0.857
f1_score	0.8	0.846
Recall	0.812	0.786
Precision	0.788	0.917
AUC	0.897 (0.835, 0.951)	0.895 (0.779, 0.979)
Sensitivity	0.812	0.786
Specificity	0.781	0.929
positive prediction	0.788	0.917
negative prediction	0.806	0.812
positive llr	3.714	11.0
negatice llr	0.24	0.231

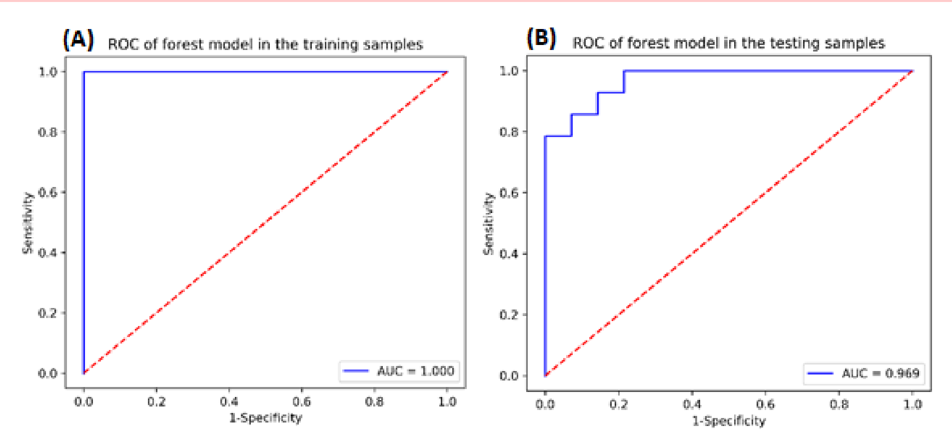


Figure 1: ROC of the forest model with (A) Training dataset; (B) Test dataset.

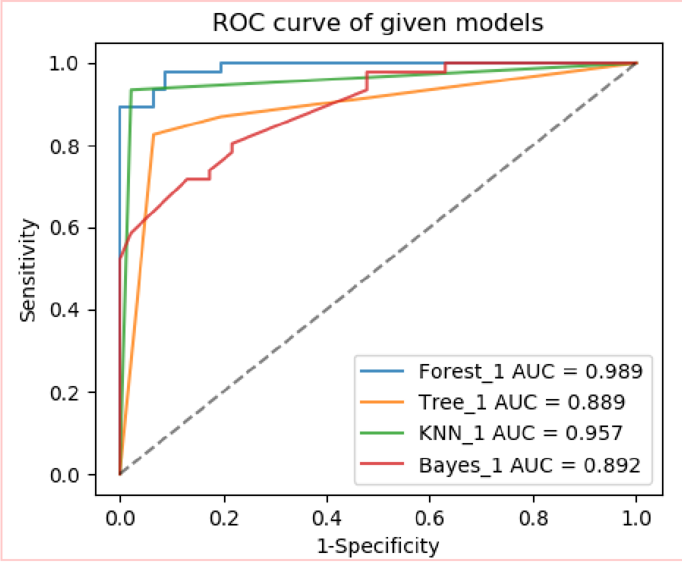


Figure 2: Comparison of ROC curve of four ML models studied.

From the heat map (Figure 4), it is evident that the AUC values retrieved from the Tree and Forest model are statistically different at $p<0.05$. A similar finding was also observed between Bayes and Forest model ($p=0.0018$). In this case, we found that Forest outperformed the other three models in terms of AUC.

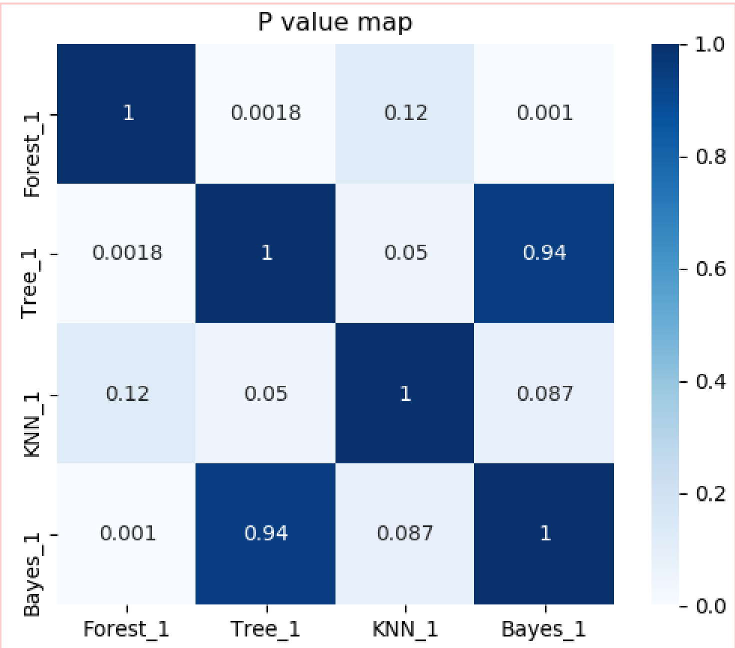


Figure 3: Heat map showing the difference in AUC values between the four ML methods.

Forest model showed a statistically significant difference with Bayes and Tree model at $p<0.05$.

DISCUSSION

Breast cancer is the most often diagnosed cancer among women and the main cause of cancer mortality.[1] In China, like in other nations, the incidence rate has risen year after year, with more than 16 million Chinese women being diagnosed each year and 12 million dying from the disease.[3] The importance of early diagnosis in the treatment of breast cancer cannot be overstated. Mammography is the most essential breast cancer screening test. However, it is impossible to extract all of the information from a radiogram with the naked eye. Computer-Aided Detection (CAD) and Digital Mammography are two recent technological innovations that have shown promising results in hidden feature extraction from radiological images.[19] With more synchronization and machine learning, a new route for improved breast cancer diagnosis has opened up.[20-22]

In this study, six radiomics features were extracted after lasso dimensionality reduction, including first order feature Kurtosis, gray-level dependency matrix (gldm):

Dependence variance,

Gray-Level Size Zone Matrix (GLSZM): Gray Level Variance, neighborhood gray-tone difference matrix (NGTDM): Complexity, Shape: Elongation, and Maximum2DDiameterRow. All these six feature are difficult to extract with the naked eye without the help of computer programs. Kurtosis is a measure of a distribution's 'peakedness.' A greater kurtosis indicates that the distribution's bulk is concentrated around the mean and the tails are fatter. A lower kurtosis indicates that the distribution's mass is broadly dispersed around the mean.[23] Higher kurtosis is assumed to indicate more heterogeneity and an even worse prognosis.[24,25] Earlier reports confirm that the kurtosis coefficients in the malignant lesions (grade 3 breast cancer) are substantially greater than in the benign lesions.[26] Gray-level dependency matrix (gldm) contains 14 unique features. We chose dependency variance as one of them, as it assesses the variation in dependence size in the images. Increased dependence Variance indicates a greater degree of variety in the size of local zones. The GLDM (gray-level dependency matrix) feature performed well in predicting the level of Tumor-Infiltrating Lymphocytes in Breast Cancer Patients.[27] Gray Level Size Zone Matrix (GLSZM) consist of 16 features. Gray level variance (GLV) is one of them, and it quantifies the variation in grey level strengths for the regions. Fusco et al. recently demonstrated that the Gray-Level Size Zone Matrix feature extracted from dual-energy contrast-enhanced mammography (CEM) images has a strong power in breast lesions classification using univariate and multivariate statistical analyses, including artificial intelligence approaches.[28] The difference between a grey value and the average grey value of its neighbors within a distance is quantified by a Neighboring Gray Tone Difference Matrix (NGTDM). When a picture is non-uniform and has many quick shifts in grey level intensity, it is termed complicated. Hence, the complexity feature play a key role in diagnosis. Employing a backpropagation neural network classifier, textural analysis of breast thermograms utilising Neighborhood gray-tone difference matrix (NGTDM) features yielded an average accuracy of 80 percent, sensitivity of 94 percent, and specificity of 71.4 percent.[29] The biggest pairwise distance between tumor surface mesh vertices in the sagittal plane is defined as the maximum 2D diameter (Row). The link between the two greatest major components in the ROI shape is shown by the radiomics feature elongation (shape). It has a value of 0 to 1. A few studies found it to be an independent predictor of Ki67 PI(AUC= 0.61).[30]

In the present study, we established four machine learning models based on six common features extracted from mammography and ultrasonography. The models were designed to classify benign tumors from a malignant tumor. The name of the models are Forest, Tree, KNN and Bayes. The performance of all four models was compared with respect to their accuracy, sensitivity, AUC and specificity. The best diagnostic efficacy (AUC) was given by the Forest model (0.969), followed by Bayes (0.895), Tree (0.87) and KNN (0.857). Furthermore, the comparison of model effectiveness between Forest and Bayes has significant statistical difference ($p< 0.001$). The model effectiveness of Forest is statistically higher. A significant statistical difference was also observed between Forest and Tree model ($P=0.0018$). Altogether these statistics signify that the Forest model is the best in classifying malignant tumors from the benign type. A few recent comparative research found that the Forest model (97.6% accuracy) outperforms the KNN and SVM models in breast cancer diagnosis.[31] Al-Quraishi et al.[32] used the UCI machine learning repository to collect patient data and evaluated the performance of two models: RF (accuracy: 98.63±2.56 percent) and DNN (accuracy: 77.44±1.22 percent). They also discovered that the RF model performs better than the DNN model. Our findings are in line with the existing findings on breast cancer data.

Furthermore, the Forest model showed highest prediction efficacy (AUC of training set and test sets' accuracy was 1.0 and 0.969, respectively). This suggest, Forest classification learning model has good performance efficiency in cancer diagnosis. All the models showed a unique sensitivity value i.e. 0.786 and a specificity value of 0.929 (except Tree model (1.0)).

Extensive research over the last 5 years has proved the potential of radiomics and machine learning in detecting benign and malignant breast tumours, similar to our work. It has the potential to be used as a noninvasive biomarker for breast cancer. However, there are certain limits. For example, the ROI mapping was done by 2 surgeons separately. For which they showed discrepancy for some patient's images. Therefore semi-automated or even automatic mapping can be employed in future investigations. Second, the sample size in this study is limited, and it is a single-centre study, both of which have limitations and should be confirmed by data from many centres with high sample size.

CONCLUSION

In conclusion, the four classification models developed using radiomics-based characteristics and machine learning approaches are capable of predicting benign and malignant breast lesions, opening up a new avenue for the diagnosis of benign and malignant breast lesions, which requires further validation.

Conflict of interest
None declared.

Funding
Unfunded: The work was not supported by any national or international organization.

Data Availability
Information presented are cited properly.

ACKNOWLEDGEMENTS

We are thankful to Department of Radiology, Medical Imaging Center, The Affiliated Hospital of Yangzhou University, Yangzhou University, Yangzhou, China and also Negenome Bio Solutions Pvt Ltd, India for providing the necessary facilities to carry out this research work.

REFERENCES

1. Bray, F., et al., *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA: a cancer journal for clinicians, 2018; 68(6): 394-424.
2. Waks, A.G. and E.P. Winer, *Breast cancer treatment: a review.* Jama, 2019; 321(3): 288-300.
3. Fan, L., et al., *Breast cancer in China.* The lancet oncology, 2014; 15(7): e279-e289.
4. Lei, S., et al., *Breast cancer incidence and mortality in women in China: temporal trends and projections to 2030.* Cancer biology & medicine, 2021; 18(3): 900.
5. DeSantis, C., et al., *Breast cancer statistics.* CA: a cancer journal for clinicians, 2014; 64(1): 52-62.
6. Winchester, D.P., R.T. Osteen, and H.R. Menck, *The National Cancer Data Base report on breast carcinoma characteristics and outcome in relation to age.* Cancer: Interdisciplinary International Journal of the American Cancer Society, 1996; 78(8): 1838-1843.
7. Bao, P.-P., et al., *Association of hormone-related characteristics and breast cancer risk by estrogen receptor/progesterone receptor status in the shanghai breast cancer study.* American journal of epidemiology, 2011; 174(6): 661-671.
8. Yu, Z.-g., et al., *Risk factors related to female breast cancer in regions of Northeast China: a 1: 3 matched case-control population-based study.* Chinese medical journal, 2012; 125(05): 733-740.
9. Dai, Q. and Y.-k. Du, *Exploration of risk factors of female mammary cance.* Chinese Journal of Woman and Child Health Research, 2007; 18(1): 71-73.
10. Broeders, M., et al., *The impact of mammographic screening on breast cancer mortality in Europe: a review of observational studies.* Journal of medical screening, 2012; 19(1_suppl): 14-25.
11. Hellquist, B.N., et al., *Effectiveness of population‐based service screening with mammography for women ages 40 to 49 years with a high or low risk of breast cancer: Socioeconomic status, parity, and age at birth of first child.* Cancer, 2015; 121(2): 251-258.
12. Onega, T., et al., *Facility mammography volume in relation to breast cancer screening outcomes.* Journal of medical screening, 2016; 23(1): 31-37.
13. Gillies, R.J., P.E. Kinahan, and H. Hricak, *Radiomics: images are more than pictures, they are data.* Radiology, 2016; 278(2): 563-577.
14. Valdora, F., et al., *Rapid review: radiomics and breast cancer.* Breast cancer research and treatment, 2018; 169(2): 217-229.
15. Marino, M.A., et al., *Contrast-enhanced mammography and radiomics analysis for noninvasive breast cancer characterization: initial results.* Molecular imaging and biology, 2020; 22(3): 780-787.
16. Elsayad, A.M. and H. Elsalamony, *Diagnosis of breast cancer using decision tree models and SVM.* International Journal of Computer Applications, 2013; 83(5).
17. Anisha, P., et al. *Early Diagnosis of Breast Cancer Prediction using Random Forest Classifier*. in *IOP Conference Series: Materials Science and Engineering*, 2021. IOP Publishing.
18. Saraswathi, D. and E. Srinivasan. *Performance analysis of mammogram CAD system using SVM and KNN classifier*. in *2017 International Conference On Inventive Systems And Control (Icisc)*, 2017. IEEE.
19. Champaign, J.L. and G.J. Cederbom, *Advances in breast cancer detection with screening mammography.* Ochsner Journal, 2000; 2(1): 33-35.
20. Osareh, A. and B. Shadgar. *Machine learning techniques to diagnose breast cancer*. in *2010 5th international symposium on health informatics and bioinformatics*, 2010. IEEE.
21. Ahmad, L.G., et al., *Using three machine learning techniques for predicting breast cancer recurrence.* J Health Med Inform, 2013; 4(124): 3.
22. Amrane, M., et al. *Breast cancer classification using machine learning*. in *2018 electric electronics, computer science, biomedical engineerings' meeting (EBBT)*, 2018. IEEE.
23. Cook, G.J., et al., *Radiomics in PET: principles and applications.* Clinical and Translational Imaging, 2014; 2(3): 269-276.
24. Davnall, F., et al., *Assessment of tumor heterogeneity: an emerging imaging tool for clinical practice?* Insights into imaging, 2012; 3(6): 573-589.
25. Ganeshan, B., et al., *Texture analysis of non-small cell lung cancer on unenhanced computed tomography: initial evidence for a relationship with tumour glucose metabolism and stage.* Cancer imaging, 2010; 10(1): 137.
26. Sun, K., et al., *Breast cancer: diffusion kurtosis MR imaging—diagnostic accuracy and correlation with clinical-pathologic factors.* Radiology, 2015; 277(1): 46-55.
27. Yu, H., et al., *Predicting the level of tumor-infiltrating lymphocytes in patients with breast cancer: usefulness of mammographic radiomics features.* Frontiers in Oncology, 2021; 11: 393.
28. Fusco, R., et al., *Radiomics and artificial intelligence analysis with textural metrics extracted by contrast-enhanced mammography in the breast lesions classification.* Diagnostics, 2021; 11(5): 815.

29. Sathish, D., et al., *Texture analysis of breast thermograms using neighbourhood grey tone difference matrix.* International Journal of Bioinformatics Research and Applications, 2018; 14(1-2): 104-118.
30. Zhou, B., et al., *Correlation between radiomic features based on contrast‐enhanced computed tomography images and Ki‐67 proliferation index in lung cancer: A preliminary study*. Thoracic Cancer, 2018; 9(10): 1235-1240.
31. Selvathi, D. and A. AarthyPoornila. *Performance analysis of various classifiers on deep learning network for breast cancer detection*. in *2017 International Conference on Signal Processing and Communication (ICSPC)*, 2017. IEEE.
32. Al-Quraishi, T., et al. *Breast cancer recurrence prediction using random forest model*. in *International Conference on Soft Computing and Data Mining*, 2018. Springer.