

# DCE-MRI and Mammography integrated radiomic analysis in triple negative ductal invasive breast cancer patients. Comparison between BRCA and not BRCA mutated patients: preliminary results

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## HIGHLIGHTS

- Integrating MRI-mammographic model improves genetic breast cancer profiles
- Glandular tissue contributes to stable radiomic profile in detecting BRCA-cancer
- Texture analysis features are relevant for genetic BRCA-cancer detection

## ARTICLE INFO

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## ABSTRACT

**Purpose:** We propose a combined radiomic model based on features extracted from DCE-MRI and mammographic images (MG) to discriminate the mutational status of BRCA genes in patients with TNBC.

**Material and methods:** This retrospective study included patients histologically diagnosed with TNBC who performed a mammography followed by a DCE-MRI between 2010 and 2021.

A manual segmentation was performed on the entire tumor volume on both imaging modalities. Subsequently, a 5-mm ROI was placed within the segmented tumor volume and the contralateral healthy gland. Radiomic features were extracted from these ROIs using Pyradiomics and selected with Maximum Relevance Minimum Redundancy algorithm to fit different classifiers.

A final model was developed by integrating the most predictive features extracted from lesion and healthy gland from both modalities into a single multivariate framework. Finally, the added value of an integrated approach was assessed by comparing the performance with single-modality radiomic models.

**Results:** The population included 52 patients for a total of 53 lesions (13 BRCA-mutated, 40 non BRCA-carriers). The highest classification performance for BRCA mutational status was achieved by Random Forest that integrated both MRI and mammography features, yielding an Area Under the Curve (AUC) of 0.91. Most predictive features were extracted from healthy gland regions and from MR wash-in/wash-out maps. Multimodal imaging analysis outperformed the best models of single-modality approaches (AUC<sub>MG-gland</sub> 0.827, AUC<sub>MR-gland+lesion</sub> 0.80).

**Conclusions:** This study reinforces the feasibility of radiomics to predict BRCA mutation in patients with TNBC, highlighting the possibility of integrating different imaging modalities to enhance model accuracy.

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## 1. Introduction

Triple-negative breast cancer (TNBC) accounts for approximately 8–13% of all breast malignant tumors and it is characterized by the absence of immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER-2) [1].

Triple-negative breast cancer (TNBC) exhibits an aggressive phenotype and is associated with a poorer prognosis compared to luminal subtypes. However, TNBC constitutes a heterogeneous group of tumors, characterized by distinct clinical presentations, biological behaviors, and responses to treatment [2,3].

Due to its rapid growth, increased mammographic breast density in young women, and the lack of traditional malignancy indicators in imaging exams, the detection of early stage TNBC through mammography can be challenging [4].

Magnetic resonance imaging (MRI) still remains the most sensitive imaging modality to identify TNBC, that most commonly appears as an enhancing mass with either irregular or well-defined margins, often exhibiting rim enhancement after contrast administration [5,6].

Given the advantages of mammography as a rapid, generally well-tolerated, and widely accessible imaging modality, and the strengths of MRI in offering multiparametric assessment and higher spatial resolution, the two techniques can provide complementary and synergistic information on the same regions of breast lesions, thereby enhancing diagnostic performance when integrated [7].

Regarding the genetic aspect, TNBCs are more frequently associated with germline BRCA mutations accounting for nearly 60% of breast cancers diagnosed in premenopausal women carrying BRCA1 mutations and approximately 16% of BRCA2-associated breast cancers [8,9].

The use of genetic testing in clinical practice is growing quickly as a result of the impact that gene variants have on BC surveillance, prevention, and treatment choices [10]. Furthermore, with the introduction of poly-ADP-ribose polymerase (PARP) inhibitors as a targeted therapy for hereditary breast and ovarian cancer (HBOC) associated with BRCA1/2 mutations, distinguishing between hereditary and sporadic breast cancers has become crucial for developing personalized treatment strategies [11]. While current guidelines recommend genetic testing for specific individuals, recent studies suggest that expanding BRCA genetic screening to a broader population could provide substantial benefits in terms of cost-effectiveness, prevention, and survival rates [12]. However, a considerable number of high-risk breast cancer cases still miss genetic screening, as eligibility criteria are primarily based on subjective factors such as family history [13]. This limitation leads to an underestimation of the true burden of hereditary cancers and may result in suboptimal therapeutic choices [14].

Radiomics represents an innovative approach in the analysis of medical imaging, facilitating the non-invasive extraction of precious information regarding tumor histopathology, genetic expression and microenvironment [15].

In particular, radiogenomics investigates the relationships between imaging features and biological information, including gene mutations, gene expression, and molecular subtypes, based on the principle that complex genetic and molecular interactions are reflected in medical images [16]. This approach can enhance our understanding of tumor pathophysiology by providing biological interpretability to radiomic models, ultimately contributing to precision medicine in breast cancer management [17].

Although radiomics has been extensively explored in breast cancer research [18–20], studies investigating the relationship between imaging features and BRCA mutational status remain few. In particular, single-modality approaches using ultrasound [21,22] or MRI [23,24] have been proposed for the identification of BRCA mutations in breast cancer patients, highlighting the potential of radiomics as a non-invasive and widely accessible tool for genetic characterization.

To the best of our knowledge this is the first study to propose a multi-

modality method integrating mammographic and MRI data to investigate the association between BRCA status and radiomic features. Therefore, in this study we present a combined radiomic model based on features extracted from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and mammographic images to build a radiomic signature capable of discriminating BRCA mutational status in patients with invasive ductal TNBC.

## 2. Methods

### 2.1. Study design

We used the CLEAR checklist (CheckList for Evaluation of Radiomics research) endorsed by ESR and EuSoMII to design and report this manuscript [25].

The research was approved by the Vasta Emilia Nord Ethical Committee and informed consent was obtained from all subjects.

Patients with a histological confirmed diagnosis of triple-negative breast cancer (TNBC) were selected from the total number of breast cancer diagnoses admitted to the Oncology Division in the period 2010–2021. Of these, only patients with BRCA genetic test and both diagnostic radiological tests (MRI and digital mammography) available were included in the final dataset.

The exclusion criteria were: the absence of clinical or pathological data, unavailability of MRI or mammography images, the presence of MRI artifacts and non-standardized acquisition protocols, particularly the protocols in which the dynamic contrast sequence presented variations with respect to the standard protocol

### 2.2. Radiological data

Breast MRI scans were acquired on a 1.5 Tesla scanner (Philips Achieva software version 2.6 and 3.2) using a 7-channel dedicated surface breast coil. Dynamic sequences were obtained in the axial plane with a fat-suppressed 3D-T1-weighted sequence, namely T1 High Resolution Isotropic Volume Excitation (THRIVE) (TR 7 s, TE 3 ms, FA 12°, pixel dimensions  $0.7 \times 0.7 \times 1$  mm<sup>3</sup>, using Spectral Attenuated Inversion Recovery - SPAIR - for fat suppression) or Water Selective Excitation (WATS) (TR 15 s, TE 5 ms, FA 20°, pixel dimensions  $0.7 \times 0.7 \times 1$  mm<sup>3</sup>). One pre-contrast phase and five post-contrast phases (each lasting 90–120 s) were acquired following the intravenous administration of a gadolinium-based contrast agent (Dotarem, 0.2 mL/kg) at an injection rate of 2 mL/s, covering a total duration of 10 min.

Mammographic examinations were performed with digital acquisition techniques in standard projections (LCC, LMLO, RCC, RMLO) primarily using a Hologic Selenia Dimensions system.

Non-radiomic data were collected for both mammographic and MRI examinations in accordance with the American College of Radiology (ACR) BI-RADS atlas. The main data included breast composition (A - almost entirely fatty, B - scattered areas of fibroglandular density, C - heterogeneously dense breasts, D - extremely dense breast), mammographic pattern of the lesion (nodule with or without microcalcifications, distortion and isolated microcalcifications), MRI shape of the lesion (mass-like/non mass-like), extent of disease in mammographic projections (single or multiple lesions) and MRI (single lesion, multifocal and multicentric), background parenchymal enhancement (BPE - minimal, mild, moderate, or marked) and enhancement kinetics curves (type 1: progressive or persistent enhancement pattern, type 2: wash in - plateau pattern, type 3: wash in - wash out pattern).

### 2.3. Radiomic analysis

Breast MRI and mammographic studies were retrospectively reviewed to extract radiomic data from both the tumor and the contralateral gland which were manually segmented. Radiomic data were compared between tumors and contralateral glands of BRCA-

mutated and non-BRCA mutated women and different radiomic classifiers were tested to predict mutational status.

## 2.4. Segmentation

Segmentation was manually performed by two radiologists in consensus using a contouring tool in Advantage Workstation 4.7 (GE Healthcare) for both imaging modalities. Tumor segmentation included the entire lesion, identified in the mammographic projection where lesion margins were best visualized and in the second post-contrast MRI phase (approximately two minutes after contrast administration). Two round-shaped 5 mm-diameter Regions of Interest (ROIs) were drawn respectively inside the volume of the segmented tumor and inside the normal glandular tissue of the contralateral breast, in the most homogeneous area, avoiding necrotic tissue, blood vessels and prosthesis (Fig. 1). When multiple tumors were present in a single patient, all tumors of at least 5 mm diameter were segmented. When at the time of diagnosis, the mammographic projection of the healthy contralateral gland was not available, we considered the most temporally closest bilateral mammographic examination (typically performed 6–12 months apart).

## 2.5. Pre-processing

MR images were pre-processed as reported in previous work [24]: briefly, wash-in and wash-out maps were calculated by taking the percentage difference voxel-by-voxel of respectively the dynamic with peak contrast and the first dynamic (contrast-free), and the last dynamic and the dynamic with the peak contrast.

Concerning MG images, they were normalized to the 99th percentile to consider scanner differences.

## 2.6. Features extraction

For each ROI, features extraction was performed using Pyradiomics package of Python 3.8 with normalized data, 20 bins and a symmetrical Gray Level co-occurrence matrix, including features from tumor wash-in and wash-out maps, as well as features from the healthy contralateral gland on DCE-MRI. Similarly, radiomic features were extracted from both the lesion and the contralateral gland using the corresponding mammographic projection.

## 2.7. Features selection and data preparation

The processing of the extracted features and the statistical analyses were performed through a Stata 17 code with Python 3.8 integration, using the Python libraries SK-learn v. 1.0.2, and Numpy v. 1.24.4. The extracted features were standardized by subtracting the mean value and

dividing by the standard deviation. Overall, the analysis was performed separately by considering 7 different datasets: all features from MR and MG, only gland features from MR and MG, only tumor features from MR and MG, only gland features from MG, only gland features from MR, only tumor features from MG and only tumor features from MR.

Features selection was conducted using the Maximum Relevance Minimum Redundancy (MRMR) algorithm on the full dataset, with the final number of features determined from correlation heatmaps of all features, showing the Spearman correlation matrix in color scale, with rows and columns sorted by similarity via hierarchical clustering. We performed a Principal Component Analysis (PCA) on the Spearman correlation matrix and determined the number of components explaining 75% of the total variance. Starting from this number of features, we progressively reduced the dimensionality until achieving the best AUC scores through cross-validation [26].

## 2.8. Modelling

Given the exploratory nature of the study, the limited sample size, and the absence of external validation, multiple modeling strategies were evaluated to investigate potentially informative predictive patterns rather than to define a single final model. In particular, the most relevant features were used to train four machine learning classifiers: Logistic Regression (linear), Support Vector Classifier (SVC), Random Forest and Decision Tree (non-linear). The setting parameters were left as default, i. e. SVC with 1 as regularization parameter; Random Forest with 100 estimators and no maximum depth, as well as for Decision Tree.

## 2.9. Evaluation

Models performance was internally assessed through a stratified 5-fold cross validation, with the train-test split that remained consistent across all models. The stratified validation was used to ensure that the training and testing sets had the same proportion of positive and negative outcomes, thereby reducing the bias introduced by the original dataset imbalance. Performance metrics included the Area Under the ROC Curve (AUC), accuracy, sensitivity and specificity, with results reported as mean values and standard deviations across permutations. AUC was considered the main performance metric. To determine statistical significance in AUC differences across datasets, DeLong's test was applied [27]. In particular, the best AUC for each dataset was tested to know if there was a significant difference in considering the gland and/or the lesion for the outcome prediction. This analysis was intended to provide a descriptive comparison of relative trends in model performance, acknowledging that applying the DeLong test to cross-validated AUCs has methodological limitations because the folds are not fully independent.

Given the small sample size and the limited number of BRCA-mutated cases, which increased the risk of overfitting, the results were considered exploratory. Accordingly, p-values were treated as descriptive rather than inferential, and no correction for multiple comparisons was applied.

We did not perform feature selection within each cross-validation fold, which may have introduced information leakage. While this approach may enhance consistency in the selected features, it could also have resulted in optimistic estimates of model performance.

## 3. Results

Among patients with a histological diagnosis of triple-negative breast cancer (TNBC) between February 2010 and August 2021, we retrospectively identified 69 individuals with an available baseline breast MRI and known BRCA mutational status. A flow diagram summarizing patient selection is provided in Fig. 2.

Only patients with a diagnostic mammogram available at the time of initial evaluation were included in the final study population. This

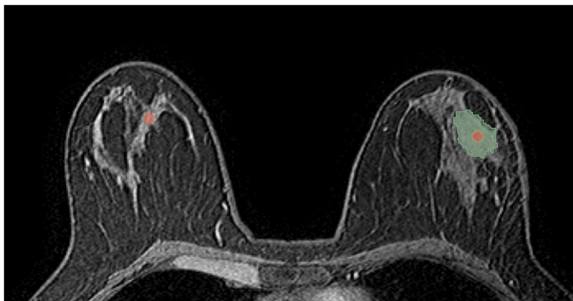


**Fig. 1.** Manual segmentation workflow on contrast-enhanced breast MRI. Volumetric tumor segmentation was performed on the second post-contrast phase (green area), followed by placement of 5-mm circular ROIs within the lesion and the contralateral normal glandular tissue for radiomic analysis (red circle).

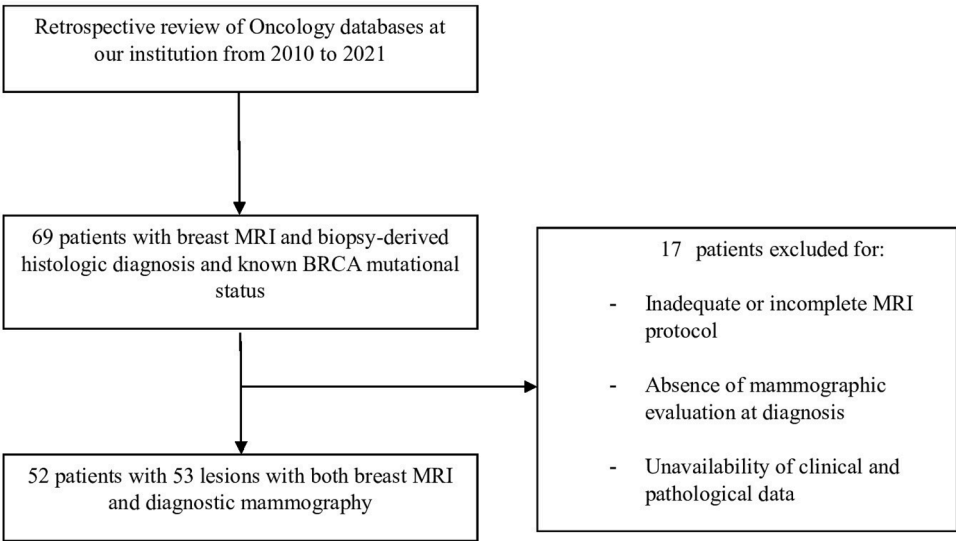


Fig. 2. Flow diagram of patients selection.

resulted in a cohort of 52 patients (13 in BRCA1/2-mutated and 39 in non-BRCA-mutated patients), from whom a total of 53 breast lesions were analyzed, as one individual presented with multifocal disease.

Characteristics of study population are shown in Table 1. Features extracted from lesion ROIs were 107 for each image type (wash-in, wash-out and MG), while features of the gland were 93 for each image type, since the shape features were irrelevant and not considered.

The visual inspection and PCA of the feature Spearman correlation matrix (FigS1, S2 and S3) guided the identification of independent radiomic features, from which 6 were chosen for inclusion in the predictive model with dimensionality reduction. These features were selected based on their statistical significance using the Minimum Redundancy Maximum Relevance (MRMR) algorithm, ensuring the most informative and non-redundant variables were retained. The selected features of integrated model (MG and MR- lesion and gland) comprised a combination of first-order statistical descriptors and texture-based characteristics, specifically:

- 10th percentile (first order) from lesion ROI of MR wash-out map ( $p < 0.01$ , lower in BRCA-mutated patients)
- Total Energy (first-order) from gland ROI of MR wash-out map ( $p < 0.05$ , higher in BRCA-mutated patients);
- Correlation (GLCM) from gland ROI of MR wash-in map ( $p < 0.05$ , higher in BRCA-mutated patients);

Table 1  
Characteristics of study population.

| Characteristic               | BRCA-mutated (n = 13) | Non-BRCA-mutated (n = 39) | Overall (n = 52) |
|------------------------------|-----------------------|---------------------------|------------------|
| Breast density               |                       |                           |                  |
| A                            | 2 (15.4%)             | 5 (12.8%)                 | 7 (13.5%)        |
| B                            | 7 (53.8%)             | 13 (33.3%)                | 20 (38.5%)       |
| C                            | 2 (15.4%)             | 15 (38.5%)                | 17 (32.7%)       |
| D                            | 2 (15.4%)             | 6 (15.4%)                 | 8 (15.4%)        |
| Number of lesions            | 13                    | 40                        | 53               |
| Lesion type                  |                       |                           |                  |
| Mass (nodule)                | 9 (69.2%)             | 27 (67.5%)                | 36 (67.9%)       |
| Mass + microcalcifications   | 4 (30.8%)             | 11 (27.5%)                | 15 (28.3%)       |
| Isolated microcalcifications | 0 (0%)                | 2 (5.0%)                  | 2 (3.8%)         |
| Extent of disease            |                       |                           |                  |
| Single lesion                | 13 (100%)             | 38 (97.4%)                | 51 (98.1%)       |
| Multiple lesions             | 0 (0%)                | 1 (2.6%)                  | 1 (1.9%)         |
| Age (years)                  | 44.9 ± 10.4           | 49.0 ± 8.9                | 48.0 ± 9.4       |

- Sum Entropy (GLCM) from gland ROI of MG image ( $p < 0.01$ , higher in BRCA-mutated patients);
- MCC (GLCM) from gland ROI of MR wash-in map;
- Size Zone non Uniformity Normalized (GLSZM) from gland ROI of MG image.

These features were subsequently used to train four machine learning classifiers: Logistic Regression, Random Forest, Decision Tree, and Support Vector Classifier (SVC). Model performance was assessed through a 5-fold stratified cross-validation approach to ensure robustness and minimize potential biases associated with the limited sample size.

The best classifier for the dataset including both gland and lesion features (Fig. 3) from MG and MR images was Random Forest (mean AUC 0.91, SD 0.11) (Table 2), significantly different from decision tree ( $p < 0.001$ ), but not from Logistic Regression and SVC. The selected features were mainly from gland ROI (5/6) and MR wash-in and wash-out maps (4/6). For the dataset including only gland features (Fig. 4) the best classifier was Random Forest (mean AUC 0.88, SD 0.18) (Table 3), which differed significantly from Decision Tree ( $p < 0.01$ ). The selected features were both from MR maps and MG images. The standard deviations were relatively high, reflecting a variability across folds due to the limited sample size.

Considering only the lesion features (Fig. 5), the best classifier was Random Forest (AUC 0.83, SD 0.1) (Table 4).

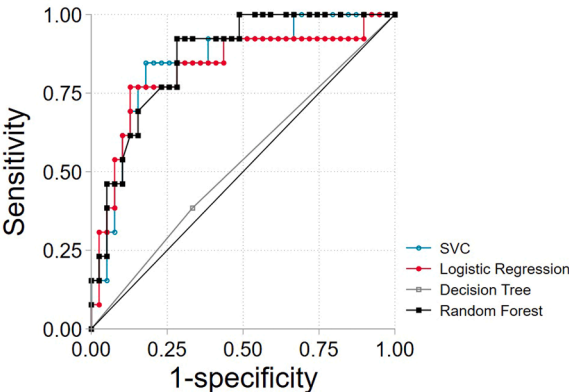


Fig. 3. AUC scores of ROC curves of models fitted with both gland and lesion features from MG and MR images.

**Table 2**

Performance metrics of the models obtained using features listed below\* from gland and lesion ROIs of MG image and MR wash-in and wash-out maps.

| Model               | AUC<br>Mean (SD) | Accuracy<br>Mean (SD) | Sensitivity<br>Mean (SD) | Specificity<br>Mean (SD) |
|---------------------|------------------|-----------------------|--------------------------|--------------------------|
| SVC                 | 0,89 (0,09)      | 0,89 (0,07)           | 0,93 (0,13)              | 0,87 (0,14)              |
| Random Forest       | 0,91 (0,11)      | 0,83 (0,1)            | 0,93 (0,13)              | 0,88 (0,11)              |
| Decision Tree       | 0,59 (0,07)      | 0,66 (0,09)           | 0,47 (0,12)              | 0,71 (0,11)              |
| Logistic Regression | 0,83 (0,17)      | 0,85 (0,11)           | 0,93 (0,13)              | 0,85 (0,18)              |

\* 10th percentile (first-order) from lesion ROI of MR wash-out map; Total Energy (first-order) from gland ROI of MR wash-out map; Correlation (GLCM) from gland ROI of MR wash-in map; Sum Entropy (GLCM) from gland ROI of MG image; MCC (GLCM) from gland ROI of MR wash-in map; Size Zone non Uniformity Normalized (GLSZM) from gland ROI of MG image

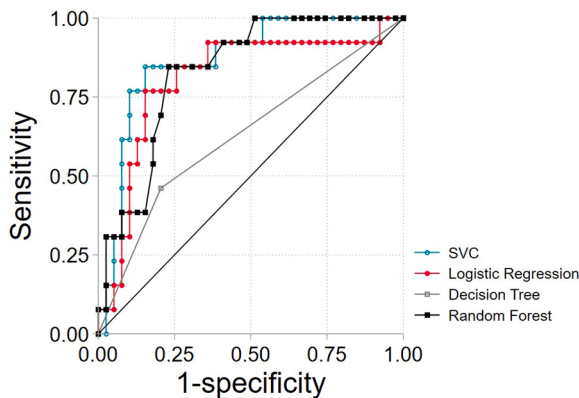


**Fig. 4.** AUC scores of ROC curves of models fitted with only gland features from MG and MR images.

**Table 3**

Performance metrics of the models obtained using features listed below\* from gland ROI of MG image and MR wash-in and wash-out maps.

| Model               | AUC<br>Mean (SD) | Accuracy<br>Mean (SD) | Sensitivity<br>Mean (SD) | Specificity<br>Mean (SD) |
|---------------------|------------------|-----------------------|--------------------------|--------------------------|
| SVC                 | 0,87 (0,11)      | 0,77 (0,13)           | 1 (0)                    | 0,79 (0,17)              |
| Random Forest       | 0,88 (0,18)      | 0,81 (0,15)           | 1 (0)                    | 0,85 (0,24)              |
| Decision Tree       | 0,66 (0,17)      | 0,75 (0,1)            | 0,5 (0,33)               | 0,84 (0,1)               |
| Logistic Regression | 0,82 (0,21)      | 0,81 (0,14)           | 0,93 (0,13)              | 0,82 (0,23)              |

\* Sum Entropy (GLCM) from MG image; Correlation (GLCM) from MR wash-in map; Total Energy (first-order) from MR wash-out map; MCC (GLCM) from MR wash-in map; Size Zone non Uniformity Normalized (GLSZM) from MG image; Median (first-order) from MG image.

SVC was the best classifier for the individual MR subsets ( $AUC_{gland}$  0.82, SD 0.16;  $AUC_{lesion}$  0.82, SD 0.04) (Table S1-S2), while for the MG subsets Logistic Regression was the best for lesion (AUC 0.73, SD 0.13) (Table S3) and for gland (AUC 0.83, SD 0.16) (Table S4).

The Random Forest model for the dataset including both gland and lesion features from MG and MR images did not differ significantly from models including only lesion and only gland features and both MR and MG features. However, it differed from the Logistic Regression model of lesion MG ( $p < 0.01$ ).

#### 4. Discussion

In clinical practice, the genetic characterization of BRCA mutations has a high impact on the surveillance, diagnosis and treatment pathways of breast cancer, in particular the distinction between sporadic and hereditary breast cancers is fundamental in the treatment pathway of patients. However, despite this, screening to access the genetic test is

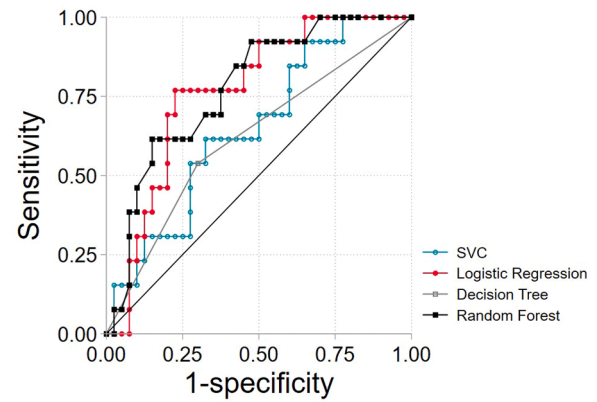


**Fig. 5.** AUC scores of ROC curves of models fitted with only lesion features from MG and MR images.

**Table 4**

Performance metrics of the models obtained using features listed below\* from lesion ROI of MG image and MR wash-in and wash-out maps.

| Model               | AUC<br>Mean (SD) | Accuracy<br>Mean (SD) | Sensitivity<br>Mean (SD) | Specificity<br>Mean (SD) |
|---------------------|------------------|-----------------------|--------------------------|--------------------------|
| SVC                 | 0,79 (0,11)      | 0,72 (0,06)           | 0,93 (0,13)              | 0,73 (0,2)               |
| Random Forest       | 0,83 (0,1)       | 0,79 (0,09)           | 0,87 (0,16)              | 0,8 (0,13)               |
| Decision Tree       | 0,72 (0,13)      | 0,76 (0,09)           | 0,63 (0,22)              | 0,8 (0,06)               |
| Logistic Regression | 0,82 (0,08)      | 0,81 (0,01)           | 0,87 (0,16)              | 0,85 (0,09)              |

\* 10th percentile (first-order) from MR wash-out map; Dependence Variance (GLDM) from MR wash-out map; Low Gray Level Zone Emphasis (GLSZM) from MG image; 90th percentile from MG image; Gray Level Non Uniformity (GLRLM) from MG image; Maximum (first-order) from MR wash-out map.

limited as in healthy women it is essentially based on family history criteria. Consequently, many mutations remain unrecognized until the diagnosis of breast cancer, excluding the possibility of risk reduction strategies with a view to the prevention of hereditary breast and/or ovarian cancer. It is necessary to improve the systems for analyzing the risk of developing breast cancer by introducing non-invasive tools in order to identify early on women who are carriers of genetic mutations [28].

Radiomics is an emerging approach for in-depth digital image analysis that has rapidly developed in recent years. It goes beyond visually assessed descriptors by enabling the non-invasive extraction of quantitative imaging features, which can be correlated with clinical outcomes or pathological characteristics in oncology.

The features extracted with radiomic analysis demonstrate high performance in diagnosis, characterization and follow-up of patients during treatment. Therefore, radiomics can be utilized as a non-invasive clinical tool in the future direction of personalized medicine [29,30].

In particular, radiogenomics provides the opportunity to investigate the relationships among imaging features, genomics, and clinical data [31].

The aim of this study is to evaluate the feasibility of an integrated radiomic model that combines the complementary information obtained from radiomic analyses of breast MRI and mammography in a cohort of patients with histologically confirmed triple-negative breast cancer (TNBC), with the goal of predicting BRCA genetic mutation status. Since the sample size was small and there was no external validation, the results were considered explorative.

After independently evaluating radiomic models derived from MRI and mammography in previous studies conducted within the same broader radiomics research project, [24,32], we aimed to assess the feasibility of an integrated radiomic model combining both modalities by re-running the same analytical pipeline from scratch, including feature selection.

We then evaluated seven different integrated analysis and the best overall discriminative performance in terms of AUC was obtained by combining all radiomic data from MRI and mammography, using features from both glandular and tumoral locations.

The AUC values of this integrated complete model (AUC 0.91) exceed the best performance that emerged in the separate independent analyses on the two methods, namely the model built on the analysis of the healthy gland alone in mammographic examination (AUC 0.827) [32] and the model built on the radiomic analysis of the lesion and gland in MR examination (AUC 0.80) [24].

This suggests that integrating the radiomic information extracted from the two methods may allow to obtain better performance in mutation prediction. These findings should be interpreted with caution, as the AUC values showed high variability due to the limited sample size.

Analyzing separately models based on radiomic analysis of the gland and the lesion alone which integrated both MR and mammography, the model with the highest AUC is the one built on the gland with AUC values of 0.88 (vs AUC of 0.83). This result may confirm the role of normal glandular tissue in the mutation predictivity that emerged in the analysis conducted both in mammography, where the best model was the one built on the gland [32], and in MR where the best model was the one built on the gland and lesion with AUC values not too different from those obtained in the model with only the gland [24]. This supports the hypothesis that normal glandular tissue may harbor information closely related to genetic makeup.

Comparing the results of radiomic analysis performed with features extracted from lesion ROIs on both MR and mammography, the winning model was that of MR with AUC results of 0.82, while for the glands the performances of the two models based on mammography and MR are superimposable with AUC values of respectively 0.83 and 0.82.

This underlines the possible superiority of the lesion radiomic analysis performed on MR compared to mammography, reflecting the additional diagnostic value of dynamic vascular information compared with the predominantly morphological information available from mammography.

Among all the features considered, the most significant ones in the tested models are 6, all related to texture analysis, 5 extracted from gland and 1 extracted from lesions, all belong to first, second and higher order texture analysis.

In brief, First-order features provide the simplest level of information and are based on the distribution of individual pixel/voxel-values within the lesions without emphasis on their spatial relationships. Second-order features contain more information about texture by considering relationships between intensity of pairs of neighboring pixels/voxels. Higher-order features go one step further and provide sophisticated patterns and textural information by emphasizing relationships between multiple pixels/voxels [29].

Four out of six features showed statistically significant differences in both BRCA mutated and non-mutated patient populations.

Two out of four statistically significant features belonged to the first order ones, namely 10th percentile extracted from the ROI in the lesion under MR examination in wash-out map and total energy extracted from the ROI in the gland under MRI examination in wash-out map. In our cohort, the 10th percentile displayed lower values in BRCA-mutated patients, while Total Energy exhibited higher values in the mutated group.

Two of the most significant features in our work belong to the second-order texture analysis features particularly GLCM (gray-level co-occurrence matrix), all two, correlation and sum entropy, extracted from the ROI positioned in the gland, one, correlation, in the MRI examination in the wash-in map and one, sum entropy in the mammographic examination. The features identified analyze the intensity, contrast and homogeneity between the pixels of the image. Both correlation and sum entropy were higher in BRCA mutated patients.

Notably, total energy, correlation, and sum entropy not only were selected in the combined model, but also showed relevant contributions

in single-modality radiomic analyses. Specifically, total energy and correlation emerged as discriminative features in the MRI-based model, while sum entropy contributed to the best-performing model trained on mammographic images.

Although the limited sample size raises the possibility of overfitting, the consistency of these features across radiomic analyses, both single-modality and integrated model, suggests a degree of reliability and supports their association with imaging patterns possibly linked to the underlying biology of healthy versus BRCA-mutated breast tissue. These characteristics may therefore represent reliable imaging markers with meaningful discriminative potential.

In brief, Total Energy quantifies the overall magnitude of voxel intensities scaled by voxel volume; GLCM Correlation captures the linear dependency between a voxel's intensity and that of its neighbors, with higher values indicating greater local homogeneity in gray-level patterns.

Higher values of Total Energy in wash-out and GLCM Correlation in wash-in maps may be associated with a more homogeneous early enhancement pattern and a slower contrast wash out and potentially reflect differences in contrast dynamics in the healthy gland.

GLSZM Sum Entropy, a higher-order texture feature, quantifies the degree of randomness in image intensity values, suggesting that higher Sum Entropy values may reflect greater complexity and heterogeneity in the intensity patterns of mutated breast tissue. Collectively, these findings may suggest underlying biological differences that warrant further investigation. However, it should be emphasized that such interpretations remain speculative, as they are inferred from the mathematical definitions of radiomic features rather than supported by direct biological or histopathological validation.

Given these considerations, it is crucial to stress that the two imaging modalities capture different biological aspects: mammography provides static information on tissue density, whereas DCE-MRI reflects dynamic perfusion patterns and functional vascular behavior. Accordingly, the radiomic features extracted from these modalities describe complementary rather than overlapping tissue characteristics.

Further studies integrating radiomic data with clinicopathological and histomolecular features in larger cohorts are needed to better understand the relationship between imaging phenotypes and the underlying genetic background.

In the literature, these features consistently demonstrate strong predictive and/or discriminative performance and are among the most frequently selected variables in radiomic models developed for tasks such as breast cancer risk assessment, therapy response prediction, evaluation of tumor-infiltrating lymphocytes, and molecular subtype discrimination [33–35]. The potential benefit of incorporating texture analysis into the breast imaging workflow is highlighted by the fact that the combined use of several texture features, such as entropy and correlation, provides significantly higher prediction accuracy than simpler qualitative descriptors like mammographic density [33].

The only characteristic chosen from the tumor-derived radiomic set, the 10th percentile, is a unique imaging descriptor that has not been documented in our earlier radiomic studies of BRCA-related breast cancer. In the present analysis, the 10th percentile, a first-order statistic, corresponds to the intensity value below which 10% of the tumor voxels fall. This measure represents the amount of wash-out in the voxel subset showing the biggest signal drop from peak to late post-contrast phases since it captures the lesion's lowest-intensity component, suggesting that significantly lower 10th percentile seen in BRCA-mutated tumors indicates a population of voxels with noticeably stronger wash-out. This finding could be consistent with the intense neo-angiogenesis of the tumoral bed, and therefore a more aggressive pattern, commonly associated with BRCA-related triple-negative breast cancers.

This feature has become noteworthy in a number of radiomic analyses utilizing ADC maps in MRI, where it has been linked to tumor locations displaying more aggressive biological behavior, most likely due to increased cellularity or proliferative activity. It has shown particular

relevance in distinguishing IDH1-mutant from IDH1-wildtype gliomas, as well as in assessing pretreatment HPV status in oropharyngeal carcinomas [36,37].

These preliminary results, confirmed by the combined model presented in this study, suggest the feasibility of radiomic analysis on both mammography and breast MRI, with probable superior accuracy observed for MRI. These findings, intended as exploratory given the lack of external validation, suggest that radiomics may provide predictive insights into BRCA mutation status and associated breast cancer risk, supporting the integration of imaging-derived biomarkers into routine clinical workflows and oncological risk assessment models. Overall, our study, fits into the larger context of radiogenomics applications in oncological patient management with the goal of assisting in the creation of increasingly individualized care pathways.

Our study presents several limitations. First, the small sample size raises concerns regarding model overfitting, which could limit generalizability and result in an overly optimistic performance estimate.

Given the preliminary nature of this work, future analyses will require external validation on fully independent datasets to adequately assess the true robustness and reproducibility of the proposed model. Moreover, the limited cohort, composed of a highly selected population of breast cancer patients, although ensuring data homogeneity, may further restrict the applicability of our findings to broader and more heterogeneous clinical populations. Finally, the long observation period represents an additional limitation, as temporal variability in both mammographic and MR acquisition protocols may have introduced heterogeneity in the imaging data.

## 5. Conclusions

The results of this study conclude a series of preliminary radiomic analyses conducted on the same patient population using different methodological approaches, with the primary aim of exploring the potential of applying radiomics for the genetic evaluation of BRCA mutations in patients with triple-negative breast cancer.

Considering the limits reported above, the results of our study suggest that radiomic analysis can be performed on both tumor lesions and healthy tissues, such as mammary glandular tissue. Therefore, radiomics may provide quantitative information from the complex patterns in radiological images that can be integrated in predictive models incorporating clinical and genetic factors.

It is also possible to think of integrated models that combine information from different radiological methods performed on the same patient to improve performance in terms of AUC and accuracy of radiomic models.

Our data supports a future study that prospectively analyses the role of radiomics performed on screening tests in predicting the risk of disease and confirms the possibility of including radiomics itself in broader breast cancer risk estimation systems.

## Ethical statement

The research was approved by the Area Vasta Emilia Nord Ethical Committee (463/2020/OSS/AOUMO SIRER ID 236 - EMENDAMENTO SOSTANZIALE 1.0 (prot. AOU 0008681/22 del 23/03/2022) and informed consent was obtained from all subjects.

## CRedit authorship contribution statement

**Cecilia Beretta:** Writing – review & editing, Investigation. **Annarita Pecchi:** Writing – original draft, Investigation, Data curation, Conceptualization. **Pietro Torricelli:** Writing – review & editing, Supervision, Investigation. **Laura Cortesi:** Writing – review & editing, Investigation, Conceptualization. **Angela Toss:** Writing – review & editing, Investigation, Conceptualization. **Massimo Dominici:** Writing – review & editing, Investigation, Conceptualization. **Gabriele Guidi:** Writing –

review & editing, Software, Methodology, Formal analysis. **Luca Nocetti:** Writing – review & editing, Software, Methodology, Formal analysis. **Erica Balboni:** Writing – review & editing, Software, Methodology, Investigation. **Giulia Sessa:** Writing – review & editing, Investigation. **Chiara Bozzola:** Writing – review & editing, Investigation, Data curation.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.ejro.2026.100810](https://doi.org/10.1016/j.ejro.2026.100810).

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## Glossary

ACR: American College of Radiology  
 AUC: Area Under ROC Curve  
 BI-RADS: Breast Imaging Reporting & Data System  
 BRCA: a gene related to a higher risk of breast cancer  
 CLEAR checklist: CheckList for Evaluation of Radiomics research  
 DCIS: Ductal Carcinoma In Situ  
 ER: estrogen receptors  
 ESR: European Society of Radiology  
 EuSoMI: European Society of Medical Imaging Informatics  
 GLCM: gray level co-occurrence matrix  
 GLDM: Gray Level Dependence Matrix  
 GLRLM: Gray Level Run Length Matrix  
 GLSZM: gray level size zone matrix Heat-plot maps/ Heat maps an image that depicts the values of some variables of interest across two axes as a color-coded matrix  
 HER-2: Human Epidermal growth factor Receptor 2  
 MRI: Magnetic Resonance Imaging  
 NGTDM: neighborhood gray-tone difference matrix  
 PG: progesterone receptors  
 Pyradiomics library: an open-source python package for the extraction of Radiomics features from Medical Imaging  
 Python: A programming language that allow to work quickly and integrate systems more effectively.  
 ROC Curve: Receiver Operating Characteristic curve which is a graphical plot that illustrates the performance of a binary classifier model  
 ROI: region of interest  
 TNBC: triple negative breast cancer