

## NARRATIVE REVIEW

## The discerning influence of dynamic contrast-enhanced MRI in anticipating molecular subtypes of breast cancer through the artistry of artificial intelligence – a narrative review

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### Abstract

Radio genomics is an exciting new area that uses diagnostic imaging to discover genetic features of diseases. In this review, we carefully examined existing literature to evaluate the role of artificial intelligence (AI) and machine learning (ML) on dynamic contrast-enhanced MRI (DCE-MRI) data to distinguish molecular subtypes of breast cancer (BC). Implications to non-invasive assessment of molecular subtype include reduction in procedure risks, tailored treatment approaches, ability to examine entire <sup>lesion</sup>, follow-up of tumour biology in response to treatment and evaluation of treatment resistance and failure secondary to tumour heterogeneity. Recent studies leverage radiomics and AI on DCE-MRI data for reliable, non-invasive breast cancer subtype classification. This review recognizes the potential of AI to predict the molecular subtypes of breast cancer non-invasively.

**Keywords:** Artificial Intelligence, Radiomics, Magnetic Resonance Imaging, Machine Learning, Genomics, Neoplasms, Molecular Subtypes, Breast Cancer.

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### Introduction

Breast cancer (BC) stands out as the most commonly diagnosed cancer, affecting women worldwide, and unfortunately, it also holds the grim distinction of being the leading cause of cancer-related fatalities in the female population across the globe. During the year 2020, BC claimed the lives of 685,000 individuals worldwide, underscoring the significant impact of this disease on a global level.<sup>1</sup> Among Asian nations, Pakistan exhibits the highest occurrence of BC, with a one-in-nine chance for

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women to be diagnosed with this disease throughout their lifetime.<sup>2</sup> During the year 2020, a total of 178,388 new cases of BC were diagnosed in Pakistan.<sup>3</sup> This number highlights the disease's high national incidence and acts as a worrisome warning flag for the problems with healthcare that need to be addressed.

BC are highly heterogeneous lesions, showcasing numerous subtypes characterized by a broad range of intrinsic biological variations. These variations are closely linked to diverse biological responses, and prognosis and consequently necessitate tailored treatment approaches.<sup>4</sup> Cancer cells express different receptors, including the human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and estrogen receptor (ER), depending on the expression of their genes.<sup>4</sup> There are four main subtypes of breast cancers outlined in scientific literature, categorised based on the expression of molecular receptors. These subtypes include Luminal A: Characterised by hormone receptor positivity and HER2 negativity, Luminal B: Exhibiting hormone receptor positivity and HER2 positivity, HER2-enriched type: Marked by hormone receptor negativity and HER2 positivity and Triple-negative subtype: Identified by hormone receptor negativity and HER2 negativity.<sup>4,5</sup> Luminal and HER2-enriched cancers are frequently seen as promising candidates for targeted antibody treatment and endocrine therapy, respectively.<sup>6,7</sup> The prognosis and treatment response are poorest for TN tumours.<sup>8</sup>

Tissue sampling, a venerable method considered the standard of care, remains the conventional approach for delineating BC subtypes.<sup>4</sup> Nevertheless, this technique's intrinsic limitations, stemming from invasiveness, anaesthesia requirements, and the inherent inability to encapsulate the entirety of tumour heterogeneity, prompt exploration into non-invasive alternatives.<sup>9</sup> Heterogeneity within a tumour can also lead to treatment resistance and failure.<sup>10,11</sup>

Medical imaging, a multifaceted array of non-invasive techniques, emerges as a promising avenue for

preoperative BC assessment and continuous monitoring throughout therapeutic interventions.<sup>12</sup> Mammography and ultrasonography (US) are the primary imaging techniques for BC screening, diagnosis, therapy response evaluation, and follow-up,<sup>13</sup> however among these, dynamic contrast-enhanced Magnetic Resonance Imaging (DCE-MRI) stands out as a particularly sensitive modality for BC detection. The conventional focal point of clinical radiologists on qualitative and semi-quantitative characteristics, employing the Breast Imaging Reporting and Data System (BI-RADS) descriptors, underscores the traditional paradigm.<sup>14,15</sup>

In the vanguard of innovation, radiomics capitalizes on the premise that a tumour's intricate biological features manifest as subtle microstructural patterns discernible through medical imaging. These patterns, often imperceptible to the human eye, undergo computational scrutiny, unravelling valuable insights into tumour behaviour and potential treatment responses.<sup>16,17</sup> The burgeoning field of radio genomics, establishing a nexus between radiomics and the concealed genotypic makeup of tumours, assumes prominence, particularly in the context of BC management with DCE-MRI radiomics data.<sup>18-20</sup>

The advent of computer technology propels machine learning to the forefront, affording solutions to intricate clinical challenges. Preliminary machine learning methods applied to radiogenomics in breast MRI yield promising findings.<sup>21-23</sup> Within this landscape, Convolutional Neural Networks (CNN), a specialized branch of machine learning, burgeons, pioneering significant advancements in medical imaging analysis. In stark contrast to conventional methods reliant on human-extracted features, CNN autonomously processes raw data, progressively constructing predictive statistical models through intricate layers and self-optimization processes. This synergy of radiogenomics and CNN heralds a transformative trajectory, promising precision, cost-efficiency, and automation in the nuanced characterisation of BC.<sup>24</sup>

This narrative review delves into the intricate utilisation of AI, specifically ML, Deep Learning (DL), and CNN, for predicting tumour subtypes in BC patients. We anticipate that this review will provide a comprehensive understanding of the current state of AI in the context of BC, particularly in assessing tumour subtypes. It aims to shed light on the potential impact on clinical decision-making, future research, and overall patient care. Our primary goal is to play a pivotal role in advancing the field of BC care. We aim to achieve this by leveraging the capabilities of AI to refine and optimise treatment

strategies, with the ultimate focus on enhancing the overall outcomes and well-being of BC patients. Our mission involves utilising the potential of AI to provide more tailored, effective and efficient healthcare solutions that can lead to improved patient experiences, better quality of life and ultimately, a positive impact on the trajectory of BC as a whole.

## Materials and Methods

The process of identifying pertinent literature involved systematic query of various electronic databases, namely PubMed, Medline, Scopus, Web of Science, and Google Scholar. The search strategy incorporated a blend of keywords and Medical Subject Headings (MeSH) terms associated with breast cancer, such as "breast cancer," "breast MRI," "molecular subtypes," "artificial intelligence," "convolutional neural networks," "machine learning," and "radiomics." The search was not constrained by publication dates, encompassing the most recent articles available. The review was conducted and written in September 2023 – October 2023. This comprehensive approach aimed to ensure a thorough and up-to-date review of relevant research in the field

### Inclusion criteria

- Investigations exploring the application of AI in predicting the molecular subtype in BC patients.
- Articles concentrating on Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) focussed on assessing the molecular subtypes of BC.
- Research articles and clinical studies published in peer-reviewed journals.
- Studies conducted and documented in the English language.
- Relevance to the specific objectives outlined in this narrative review.

### Exclusion criteria

- Publications that did not correspond to the topic of interest
- Studies that were duplicates of previously recognised publications.
- Articles that were not accessible through our electronic database search
- Articles not available in English language.

Selected articles underwent thorough critical review, from which pertinent information was extracted, including study details, patient characteristics, imaging techniques, AI methodologies, and outcomes.

## Results

The amalgamated findings from these studies, shown in Table, offer an overview of the current status of AI-

**Table:** Studies inquiring into Artificial Intelligence Infused Modalities for Prediction of Molecular Subtypes in Breast Cancer Studies.

Author and year	Study Type	Study Goal	AI Approach Utilized	Findings	Conclusion
Haolin Yin, et al. (2022) (25)	Retrospective study	Establishing CNN algorithm based on DCE-MRI to predict the molecular subtypes of BC.	CNN with CE T1, ADC and T2 weighted sequences data.	Yielded an AUC of 0.762 to 0.920 for CE T1, 0.686 to 0.851 for ADC and 0.639 to 0.697 for T2 based models respectively.	CE T1 based model shows most promising outcomes in prediction of molecular subtypes of breast cancer.
Doris Leithner, et al. (2020) (26)	Retrospective study	Evaluate the performance of radiomics and AI based on DCE-MRI for prediction of molecular subtypes of BC.	Employed multi-layer perceptron feed-forward artificial neural network based on initial DCE-MRI and ADC maps features.	Achieved an AUC of 0.86 for prediction of TN from other cancers and AUC of 0.8 for prediction of luminal A and TN cancers.	DCE- MRI may provide non-invasive prediction of luminal A and TN BC.
Richard Ha, et al. (2019) (27)	Retrospective study	Create and test a CNN algorithm that can identify breast cancer's molecular subtype based on DCE-MRI characteristics.	14 layered CNN algorithm for analysis of radiomics features based on first post contrast phase of DCE-MRI.	Attained an AUC of 0.853 for class normalized macro and AUC of 0.871 for non-normalized micro aggregated data. Aggregated sensitivity and specificity turned out to be 0.603 and 0.958 respectively.	DCE-MRI analysis of BC using an innovative approach CNN is capable of predicting the molecular subtype of BC.
Ming Fan, et al. (2017) (28)	Retrospective study	Investigate features from DCE-MRI and incorporation of clinical information in prediction of molecular subtypes of BC using an evolutionary algorithm.	Employed a multi-class logistic regression classifier with DCE-MRI and clinical data.	Achieved an AUC of 0.867, 0.786, 0.888, and 0.923 for differentiation between luminal A, luminal B, HER2 enriched, and basal-like subtypes.	Clinical data and 3D imaging characteristics from DCE-MRI can be used as potential biomarkers for distinguishing between four molecular subtypes of BC.
Elizabeth J. Sutton, et al. (2016) (29)	Retrospective study	Differentiation of BC molecular subtypes by using features collected from DCE-MRI images and a machine-learning approach.	Radiomic Feature Extraction and SVM modelling with employment of LOOCV to avoid over fitting.	Achieved an overall accuracy of 83.4% and 71.2% after inclusion of top nine pathological and imaging variables and only top 9 imaging variables respectively.	Machine-learning-based prediction model based on DCE-MRI characteristics can differentiate BC subtypes with substantial predictive ability.

Abbreviations: AUC: Area Under the Curve, AI: Artificial Intelligence, HER2: Human Epidermal Growth Factor Receptor 2, DCE-MRI: Dynamic Contrast Enhanced Magnetic Resonance Imaging, CE T1: Contrast-Enhanced T1 Sequence, SVM: Support Vector Machine, CNN: Convolutional neural network, BC: Breast Cancer, ADC: Apparent Diffusion Coefficient, TN: Triple Negative, 3D: Three Dimensional, LOOCV: Leave-one-out cross validation.

enhanced imaging for prediction of molecular subtypes in patients with BC. The methodological quality of these selected studies was assessed to gauge the rigor and validity of the research. It's important to note that this narrative review does not involve primary research or human subjects, and, as such, did not require ethical approval or consent. Furthermore, the quality and data availability in the selected articles may vary, potentially influencing the depth of analysis and the generalisability

of the findings. The ensuing sections of this narrative review will present and deliberate on the role of AI in the evaluation and prediction of molecular subtypes undergoing DCE-MRI and its potential influence on clinical decision-making and patient outcomes.

## Discussion

Tissue sampling remains the preferred method, considered the standard of excellence, while immunohistochemistry (IHC) is used to establish the

subtype of BC.<sup>4</sup> This method has several drawbacks since the limited quantity, size, and distribution of the samples cannot capture tumour heterogeneity in its entirety. Moreover, the biology of breast tumours can exhibit alterations over time and in response to different therapeutic interventions.<sup>9</sup> Treatment resistance and failure may result from heterogeneity within a single tumour.<sup>10,11</sup> Tissue biopsy, despite its invasiveness and reliance on anaesthesia, provides limited insights into tumours due to sampling constraints.

In contrast, non-invasive medical imaging techniques offer comprehensive preoperative breast cancer assessment and therapy monitoring.<sup>12,13</sup> Radiomics, an emerging field, analyses subtle microstructural patterns in medical images using computational methods to reveal valuable information about tumour behaviour and treatment responses.<sup>16</sup> Owing to swift progress in quantitative radiology techniques, notably in the field of radiomics, it is now possible to assess tumour biology and genetics with a greater degree of precision, predictability, and cost-efficiency. Quantitative radiomics involves the extraction of data from routine medical imaging, followed by the analysis of intricate and high-fidelity imaging features that may escape human visual perception. This innovative approach offers an avenue for more accurate and cost-effective evaluation of tumour characteristics and genetic profiles.<sup>17</sup> Radiogenomics is establishing a connection between radiomics and the concealed genotypic makeup of a tumour or tissue.<sup>18</sup> In essence, when applied to BC with MRI, radiogenomics involves the examination of intrinsic characteristics, such as dynamic contrast enhancement (DCE) kinetics. These characteristics are instrumental in defining tumour heterogeneity and are leveraged to make predictions about the molecular subtype of the cancer.<sup>19,20</sup>

The rapid progress in computer technology has catapulted machine learning to the forefront, empowering it to address intricate clinical challenges effectively. The use of preliminary machine learning methods to analyse radiogenomics in breast MRI has yielded encouraging findings.<sup>21-23</sup> In recent times, a specific domain of machine learning known as Convolutional Neural Networks (CNN) has achieved significant progress in the realm of diagnostic imaging assessment. In contrast to conventional machine learning, which heavily depends on features extracted by humans, neural networks like CNN operate by processing unprocessed information and enable the computer to autonomously construct predictive statistical models through progressively intricate layers and self-adjustment processes.<sup>24</sup> The tabulated data herein encapsulates the

encompassed studies (Table)

A retrospective study performed by Haolin Yin, et al (2022)<sup>25</sup> assessed the effectiveness of CNNs on DCE-MRI data for preoperative identification of BC molecular subtypes. A total of 136 lesions from 136 patients were enrolled in the study and were segregated into training, validation and testing subsets with ratio of 6:2:2. All DCE-MRI examinations were performed on 3T machine with T2, DWI and dynamic post contrast sequences and region of interest was drawn manually on T2, Apparent diffusion coefficient (ADC) and post contrast T1 sequences. Image data set was augmented and one molecular subtype vs all other subtypes technique was employed. Pre-trained CNNs with multiple modifications were used for predictive models using transfer learning. The results were categorized separately for each subtype with separate evaluation of area under curve (AUC), sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and an overall Accuracy for each sequence. The post contrast T1 model yielded better performance than ADC or T2 weighted sequences. In characterising breast cancer subtypes, the post-contrast T1 model displayed distinctive performance metrics. When identifying the luminal A subtype, it achieved an AUC of 0.817, with sensitivity, specificity, PPV, NPV, and accuracy values of 0.673, 0.886, 0.875, 0.696, and 0.771, respectively. In the context of distinguishing the luminal B subtype, the AUC was 0.762, accompanied by sensitivity, specificity, PPV, NPV, and accuracy values of 0.690, 0.795, 0.714, 0.775, and 0.750. For HER2-enriched subtype differentiation, the post-contrast T1 model showcased an AUC of 0.885, along with sensitivity, specificity, PPV, NPV, and accuracy values of 0.800, 0.895, 0.889, 0.811, and 0.847, respectively. Lastly, in discerning the Triple-negative (TN) subtype, the post-contrast T1 model exhibited a robust AUC of 0.920, complemented by sensitivity, specificity, PPV, NPV, and accuracy values of 0.800, 0.930, 0.936, 0.784, and 0.857. In conclusion, post contrast T1 weighted imaging data set accomplished better results than ADC and T2 weighted data sets. The differentiation power of this CNN was better for HER2 enriched and TN BC.<sup>25</sup>

Identically relating the microstructural differences in the tumour subtypes using radiomics and AI, Doris Leithner, et al. (2020)<sup>26</sup> performed a retrospective study inclusive of 91 patients who underwent DCE-MRI prior to the initiation of therapy with the postsurgical histopathology record available. Similar to the previous study, all scans were performed on a 3T MRI unit with data available for T2, DWI and DCE-MRI sequences. The first post-contrast phase and ADC maps were used for radiomics analysis,

ROI drawn manually and radiomics feature extraction was performed using a semi-automated software. The sample was divided in 70:30 for training and validation. A multi-layer perceptron feed-forward artificial neural network (MLP-ANN) was employed for groups of more than twenty patients. Leave-one-out cross validation (LOOCV) was utilized to separate two groups with less than twenty patients each. The MLP-ANN was utilized in four pairwise classifications since the group sizes were big enough, i.e., more than 20 patients in each group, whereas LOOCV was employed in all other examinations. The data revealed best results for differentiation of TN and luminal A subtypes from others. MLP-ANN achieved an overall median AUC of 0.86 for distinguishing TN from all other subtypes, with 85.9% accuracy in the training and 85.2% accuracy in the validation datasets. Median AUC for distinguishing luminal A from TN tumours was 0.8, with median accuracies of 74% in the training and 68.2% in the validation datasets pointing to promise towards evaluation of BC subtypes on DCE-MRI.<sup>26</sup> Adding to the prior detailed studies, a retrospective study including 216 patients performed by Richard Ha, et al. (2019)<sup>27</sup> for evaluation of molecular subtypes using CNN on DCE-MRI data showed promising results. This study made use of post contrast MRI data on which ROI was drawn manually by fairly experienced breast radiologists and the data was augmented and underwent several real time modifications. Subsequently on the acquired data a custom made 14 layered CNN was applied and additionally several other CNN architectures were tested. The results showed accuracy of the testing set to be 70%. Class normalized macro-AUC to be 0.853. AUC for non-normalized micro-aggregated data was 0.871, indicating better prediction power for the largely represented Luminal A and B subtypes. The combined sensitivity and specificity were 0.603 and 0.958, respectively.<sup>27</sup>

Role of DCE-MRI breast characteristics with addition of clinical data to predict the molecular subtypes of BC was examined in retrospective fashion including a total of 96 patients by Ming Fan, et al. (2017).<sup>28</sup> The patients in this study were divided into two cohorts, one for training including 60 patients and other cohort was made to testing and validity including 36 patients. The lesion on DCE-MRI were segmental automatically using an algorithm and was manually corrected if needed by experienced breast radiologists. Subsequently computerized techniques were applied on segmented DCE-MRI data for extraction of imaging characteristics. The study employed Weka (30) for analysing molecular subtypes using multi-class logistic regression. Feature selection was optimized with Evolutionary Search, and classifier performance was evaluated using ROC analysis

and LOOCV. The overall AUC for the multi-class classifier based on 24 chosen characteristics was 0.869 for the first cohort. The classifier for luminal A subtype yielded an AUC of 0.867, demonstrating a sensitivity of 88.2% and specificity of 76.9%. Luminal B classifier achieved an AUC of 0.786, with 86.5% sensitivity and 62.5% specificity. The HER2 subtype exhibited an AUC of 0.888, featuring 81.1% sensitivity and 100% specificity. Meanwhile, the basal-like subtype displayed an AUC of 0.923, with sensitivity and specificity both at 81.1%. In the context of a multi-class classifier encompassing 15 chosen characteristics, the overall AUC for the reproducibility cohort was 0.872. Delving into individual subtypes, the luminal A classifier achieved an AUC of 0.905, boasting 87.5% sensitivity and 92.9% specificity. Luminal B, with an AUC of 0.835, demonstrated 59.3% sensitivity and 100% specificity. The HER2 subtype excelled with an AUC of 0.947, showcasing optimal sensitivity and specificity at 88.9%. Conversely, the basal-like subtype revealed an AUC of 0.802, with sensitivity at 88.9% and specificity at 63.0%. The study suggests that the combination of DCE-MRI imaging and clinical characteristics allows for a confident determination of the molecular subtype of breast cancer.<sup>28</sup> Likewise Elizabeth J Sutton, et al. in 2017<sup>29</sup> performed a study investigating the role of ML algorithms for prediction of BC molecular subtypes non-invasively on DCE-MRI data. Their study included a total of 178 patients with all patients undergoing MRI examinations of either 1.5T or 3T MRI systems. The radiomics imaging characteristics were fetched after drawing the ROI manually on post contrast T1 MRI sequences using in-house open-source software. The imaging characteristics along with clinical and pathological data were analysed using multiclass support vector machine (SVM) models using LOOCV approach. The highest accuracy on LOOCV was found utilising nine characteristics across all tumours examined. When incorporating the top nine pathologic and imaging variables, the prediction model distinguished IDC subtypes with an overall accuracy of 83.4%. The combined pathologic and imaging model exhibited subtype-specific accuracies of 89.2% for luminal type, 63.6% for HER2+ enriched, and 82.5% for TN. Alternatively, when considering solely the top nine imaging characteristics, the prediction model achieved an overall accuracy of 71.2% in distinguishing IDC subtypes. The accuracy of integrated pathologic and imaging models was 69.9% (luminal type), 62.9% (HER2+ enriched), and 81.0% (TN). In this study, the authors have a fashioned sophisticated predictive model based on ML, leveraging features derived from DCE-MRI to discern molecular subtypes of BC with notable predictive efficacy.<sup>29</sup>

### Limitations and Prospects

While the foregoing analyses offer profound insights into the potential synergy between AI and DCE-MRI for prognosticating molecular subtypes in BC patients, it is imperative to conscientiously acknowledge the inherent limitations encapsulated within this corpus of literature. Foremost among these considerations is the retrospective nature of the discussed studies, which inherently introduces bias and the potential for confounding variables. To validate the clinical applicability and broaden the scope of generalizability for these AI models, prospective studies boasting more expansive and diversified patient cohorts become imperative.

Moreover, the presence of disparities in imaging protocols, AI model architectures, and data preprocessing methodologies across the extant studies introduces a notable challenge to achieving consistency and comparability in outcomes. Addressing this challenge necessitates a standardised approach to these variables, thereby fostering seamless cross-study comparisons and facilitating the eventual clinical implementation of AI-enhanced methodologies.

Finally, the incorporation of diverse AI modalities, such as DL and CNNs, though brimming with promise, requires more extensive validation and direct comparative analyses. A comprehensive understanding of the efficacy and robustness of these diverse methodologies can only be gleaned through rigorous head-to-head comparisons.

The encouraging outcomes of recent studies arising from the convergence of AI and imaging methods in predicting molecular subtypes in BC patients hold substantial implications for the future of oncology. AI-based models possess the capacity to transform clinical decision-making by facilitating early non-invasive identification of molecular subtypes, thereby aiding in the formulation of tailored personalized treatment plans and ultimately ameliorating overall outcomes and quality of life. With the incessant surge in healthcare data and technological progress, the role of AI in BC care is set for continuous expansion, introducing a phase of precision medicine.

Moreover, the implementation of AI-driven screening and diagnostic tools could play a pivotal role in mitigating healthcare disparities in low- and middle-income countries (LMICs). These nations, confronting impediments in accessing specialised healthcare services, including BC treatment, might benefit from cost-effective and scalable AI-driven solutions. By enhancing early detection, treatment planning, and patient outcomes in resource-constrained settings, AI has the potential to

alleviate the global burden of BC. Collaborative endeavours and global alliances are indispensable to guarantee that AI technologies are accessible and advantageous for LMICs, thus contributing to a more just landscape in global healthcare.

These nuanced limitations and high prospects underscore the exigency for continual research initiatives, collaborative endeavours, and the establishment of standardised protocols within the realm of AI-assisted BC management. Such endeavours are paramount to optimising the benefits afforded to both patients and clinicians alike.

### Conclusion

The findings derived from this review lend credence to the efficacy of radiomic analyses in discerning molecular subtypes of BC through DCE-MRI in the early stages of the disease. Nevertheless, the observed constraints in sensitivity and specificity, with levels scarcely exceeding 90%, curtail the feasibility of its integration as a supplementary component in the existing diagnostic workup for BC patients. This underscores the imperative need for refinement in radiomic techniques to enhance their diagnostic accuracy. Furthermore, within the ambit of Low- and Middle-Income Countries (LMICs), the judicious application of AI emerges as a beacon of potential, offering not only cost-effective but also scalable solutions to redress prevailing healthcare disparities in BC management. Realising the zenith of AI's potential in BC care mandates harmonious collaborative endeavours, forging a global alliance to disseminate its beneficent impact expansively.

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