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# Correlation of Contrast Enhancement Patterns with Molecular Subtypes in Dynamic Contrast-Enhanced Magnetic Resonance Imaging of Breast Malignancies

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**Abstract**

**Objective:** This study aimed to evaluate the use of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to predict the molecular subtypes of breast cancer, with a focus on receptor status.

**Methods:** The authors retrospectively reviewed breast MRI scans of 154 patients with histopathologically confirmed invasive breast carcinoma who underwent preoperative DCE-MRI between January 2010 and January 2015. Tumors were classified as Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, or triple-negative based on IHC for ER, PR, and HER2. Contrast-enhanced magnetic resonance imaging findings included time–signal intensity curve patterns and enhancement characteristics. The axillary nodal status and background parenchymal enhancement (BPE) were also recorded.

**Results:** In total, 154 patients (mean age: 51.4 years; range, 24-80 years) were evaluated. Magnetic resonance imaging findings demonstrated homogeneous internal contrast in 31%, heterogeneous contrast in 40%, and rim enhancement in 29% of the tumors. Regarding molecular markers, ER positivity was observed in 39.4% of patients, PR positivity in 43.5%, and HER2 positivity in 36.4%. The tumor subtype distribution included Luminal A (17.4%), Luminal B (36.8%), and triple-negative (44.5%). Type 1 enhancement was observed in 37.7% of patients, type 2 in 36.4%, and type 3 in 26.0%. A significant relationship was identified between Luminal A subtype and type 3 contrast enhancement ($P < .05$). Luminal B subtype was significantly associated with increased BPE (types 1 and 2) and contralateral breast enhancement ($P < .05$). No significant associations were observed between molecular markers or subtypes and lymph node positivity.

**Conclusion:** Human epidermal growth factor receptor 2-positive tumors have a plateau perfusion pattern and washout kinetics, and triple-negative tumors often exhibit rapid washout. These findings support the continued investigation of DCE-MRI for early subtype prediction and personalized treatment planning.

**Keywords** Breast cancer, contrast-enhanced magnetic resonance imaging, imaging, magnetic resonance imaging, molecular subtypes

## INTRODUCTION

Breast cancer remains a leading cause of cancer-related mortality among women worldwide, and its clinical and biological heterogeneity necessitates precise molecular subtyping to guide personalized treatment strategies.[1] Breast cancer is classified into Luminal A, Luminal B, human epidermal growth factor receptor 2 (HER2)-enriched, and triple-negative subtypes, based on estrogen receptor (ER), progesterone receptor (PR), and HER2 status, and has revolutionized therapeutic decision-making and prognostication.[1] Although immunohistochemistry (IHC) and genomic profiling are the current standards for subtyping, these methods are invasive and time-consuming, highlighting the need for noninvasive predictive tools.[2]

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) has emerged as a pivotal modality for breast cancer diagnosis, offering high sensitivity for lesion detection and characterization through perfusion and kinetic analyses.[3] Contrast-enhanced magnetic resonance imaging parameters, such as time–signal intensity curves (TIC) and enhancement patterns, reflect tumor angiogenesis and vascular permeability, which are influenced by molecular pathways.[4] Previous studies have explored the associations between MRI features and receptor status; for instance, HER2-positive and triple-negative tumors often exhibit rapid washout kinetics, while luminal subtypes may demonstrate persistent or plateau enhancement.[5,6] However, inconsistencies persist regarding specific correlations, particularly for Luminal A/B differentiation and background parenchymal enhancement (BPE) implications.[7,8]

Recent radiogenomic investigations suggest that DCE-MRI phenotypes may mirror the underlying genetic expression, with rim enhancement linked to high-grade tumors and heterogeneous internal enhancement associated with proliferative markers.[9,10] Despite these advances, comprehensive

analyses correlating TIC patterns, BPE, and axillary nodal status across all the molecular subtypes remain limited. This gap impedes the integration of MRI biomarkers into clinical subtype algorithms.

This study evaluated the potential of DCE-MRI to predict molecular subtypes of invasive breast carcinoma, focusing on enhancement kinetics, BPE, and nodal involvement. By elucidating subtype-specific imaging signatures, the authors aim to advance noninvasive stratification, potentially reducing the dependency on biopsy for treatment planning.

## MATERIAL AND METHODS

### Patient Selection and Inclusion Criteria

Ethical approval for the study was obtained from the Konya Necmettin Erbakan University institutional review board (Approval No. 2214/5, dated 20.01.2016). This retrospective study included 154 female patients (age range: 24-80 years; mean age: 52 years) who underwent preoperative DCE-MRI between January 2010 and January 2015. All patients had histopathologically confirmed invasive breast cancer based on core needle biopsy and subsequent surgical specimen analysis. Demographic data and pathological findings were collected from the hospital information system. Patients who had received neoadjuvant therapy before MRI or had premalignant breast cancer were excluded. Contrast-enhanced magnetic resonance imaging examinations that were unavailable for review and cases without definitive pathology results for ER, PR, and HER2 status were also excluded. Given the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

### Magnetic Resonance Imaging Acquisition Protocol and Image Analysis

All breast MRI examinations were performed using a 1.5 Tesla scanner (Siemens Magnetom Avanto, Erlangen, Germany) with a dedicated 16-channel bilateral breast coil. Patients were imaged in the prone position. The MRI protocol included high-resolution morphological sequences, followed by dynamic contrast-enhanced imaging, as presented below.

**Precontrast Sequences:** Axial and sagittal localizer images were obtained, followed by T1-weighted spin-echo sequences without fat suppression in the coronal plane (TR, 313 ms; TE: 4.5 ms, slice thickness, 3 mm) and T2-weighted fast spin-echo sequences in the axial plane (TR: 9710 ms, TE: 190 ms, slice thickness 3 mm). An axial STIR sequence (Turbo Inversion Recovery Magnitude, TRIM) was also acquired for additional lesion characterization.

**Dynamic Contrast-Enhanced Sequence:** A 3D T1-weighted gradient-echo sequence (TR: 4.4 ms, TE: 1.3 ms, flip angle as per protocol, slice thickness: 1 mm) was performed in the axial plane. First, a baseline (precontrast) image was acquired. A standard dose of gadolinium contrast (0.1 mmol/kg gadopentetate dimeglumine) was injected intravenously at 2 mL/s, followed by a saline flush. Serial post-contrast images were obtained immediately after injection, with at least 3-5 sequential acquisitions covering up to 7-8 minutes. All post-contrast images were automatically subtracted from the precontrast image using MRI system software to highlight contrast uptake and produce multiple time points for dynamic analysis.

**Image Analysis:** All MR images were reviewed on a workstation by a radiologist with at least 10 years of experience in breast imaging. The lesions were identified and characterized according to the BI-RADS MRI lexicon.[9] For each lesion, morphology and enhancement features were recorded.

1-The lesion shape was categorized (e.g., round, oval, lobulated, irregular stellate, or linear forms).

2-The lesion margin was defined as well-defined or poorly defined/spiculated.

The internal enhancement pattern of each mass on post-contrast images was classified as homogeneous (uniform enhancement), heterogeneous (mixed enhancement), or rim enhancement (peripheral enhancement with a central low signal), according to standard BI-RADS descriptors. These 3 contrast enhancement patterns were used to describe the spatial distribution of the contrast within the tumor.

Time–signal intensity curves to evaluate kinetic characteristics for each lesion were generated using a dedicated software platform (Siemens Syngo.via, Siemens Healthineers). A region of interest (ROI) with standardized dimensions (approximately 5-10 mm$^2$, adjusted based on lesion size and image resolution) was manually placed on the area of the tumor demonstrating the strongest early enhancement, carefully avoiding necrotic, cystic, or nonenhancing regions. In patients with multiple lesions, the largest or most clinically significant lesion was used for kinetic analysis. Signal intensities within the ROI were recorded across sequential dynamic contrast-enhanced phases to plot the enhancement curve. The kinetic curves of each lesion were then categorized into 1 of the 3 standard kinetic patterns based on their shape:[9]

**Type 1 (Persistent):** Signal intensity continuously increases over time (progressive enhancement with no plateau or washout) (Figure 1).

**Type 2 (Plateau):** Signal intensity rises initially and then levels off (plateaus) in later phases (suggesting intermediate kinetics) (Figure 2).

**Type 3 (Washout):** Signal intensity increases rapidly and then decreases in the late phase (initial enhancement followed by washout, often indicating more aggressive behavior) (Figure 3).

In addition to lesion analysis, BPE was also evaluated. Two ROIs of similar size were placed in visually normal fibroglandular tissue: 1 in the ipsilateral breast (outside the tumor area) and 1 in the corresponding location of the contralateral breast. Time–signal intensity curves

### MAIN POINTS

- Luminal A breast tumors show a significant association with washout-type contrast enhancement kinetics on dynamic DCE-MRI.
- Luminal B tumors frequently exhibit moderate-to-marked BPE and contralateral breast enhancement, reflecting their aggressive biological characteristics.
- Human epidermal growth factor receptor 2-positive and triple-negative breast cancers predominantly demonstrate rapid washout kinetics, though HER2-positive tumors may also exhibit plateau-type enhancement, highlighting molecular complexity.
- Contrast-enhanced magnetic resonance imaging features alone are not reliable predictors for axillary lymph node involvement across breast cancer molecular subtypes.
- Contrast-enhancement kinetics on DCE-MRI could support non-invasive molecular subtyping, potentially reducing reliance on invasive biopsy procedures for personalized treatment decisions.

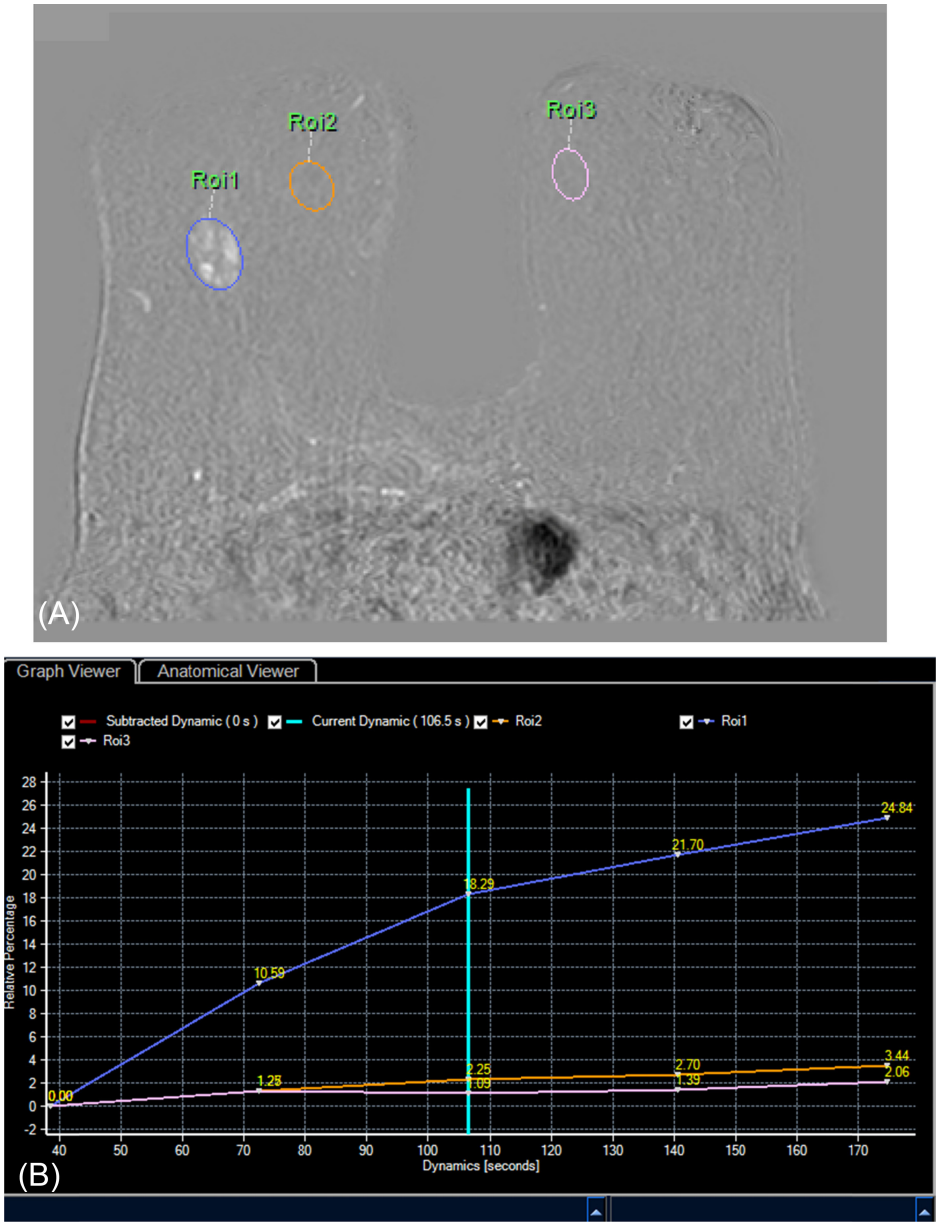


**Figure 1** A 70-year-old patient is presented with an oval shaped and spiculated margin mass measuring 9 × 8 mm on the right breast at 11 o'clock, which is followingly diagnosed as invasive ductal carcinoma. Histopathological examination reveals estrogen receptor (−), progesterone receptor (+), and c-erbB2 (−). A) The mean curve measurement of mass enhancement, non-mass enhancement, and parenchymal enhancement in the contralateral breast on dynamic contrast-enhanced breast MRI using ROI, (B) the time–intensity curve displays type 1 pattern of mass enhancement, non-mass enhancement, and the parenchymal enhancement of the contralateral breast.

were also generated for these ROI locations to evaluate parenchymal enhancement characteristics.

**Histopathological Assessment and Receptor Status Classification**

All patients underwent breast surgery (mastectomy or lumpectomy with axillary evaluation) after the breast MRI. The tumor type and grade were recorded.

Estrogen receptor and progesterone receptor status was determined by IHC staining for estrogen and PRs in the tumor tissue. The percentage of cells with strong, moderate, or weak nuclear staining was assessed and weighted; tumors with an IHC score above a defined cutoff (corresponding roughly to >1% of nuclei positive) were considered ER- or PR-positive. Tumors with essentially no nuclear staining or only minimal staining (<1% or below the cut-off score) were considered negative for ER or PR. HER2 status was evaluated by IHC for the HER2/neu (c-erbB2) protein. Staining was scored on a 0-3+ scale, following the ASCO/CAP guidelines.[10] For each case, the ER, PR, and HER2 statuses were recorded as positive or negative. Tumors were categorized into molecular subtypes for further analysis as (1) Luminal A, 2) Luminal B, (3) HER2-enriched, and (4) triple negative.[10]

Axillary lymph node dissection or sentinel node biopsy was performed in all cases, and lymph node involvement (presence of

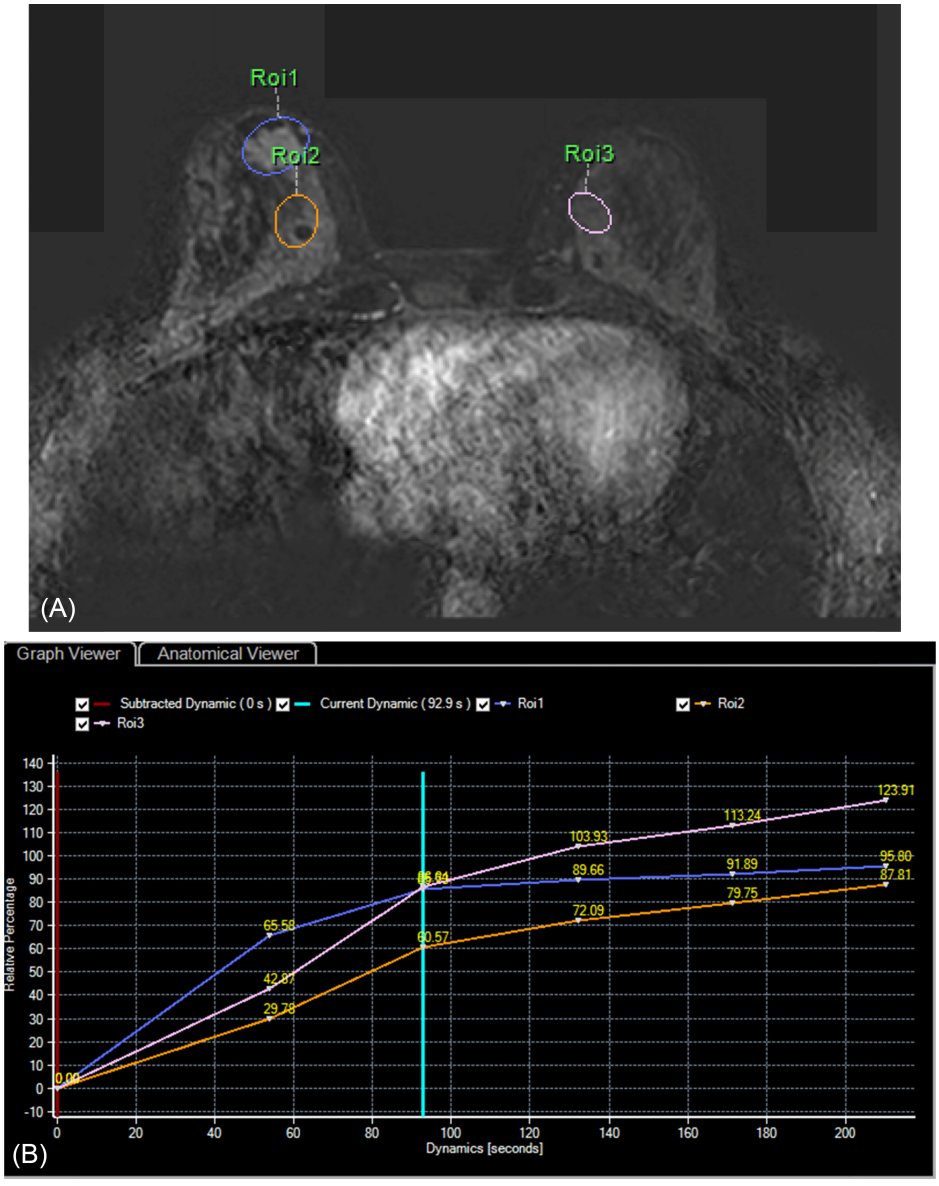


**Figure 2** The patient has a mass measuring 32 × 27 mm with a dendritic shaped and spiculated margins in the middle of the right breast and is followingly diagnosed as invasive ductal carcinoma after the biopsy. Histopathological examination reveals estrogen receptor (+), progesterone receptor (−), c-erb B2 (−). A) The mean curve measurement of mass enhancement, non-mass enhancement, and parenchymal enhancement in the contralateral breast on dynamic contrast-enhanced breast MRI using ROI. (B) Displays type 3 enhancement pattern in the time–intensity curve while the non-mass enhancement and the parenchymal enhancement of the contralateral breast are seen as type 2.

metastatic carcinoma in the axillary nodes) was documented in the pathology reports.

### Statistical Analysis

All data were analyzed using SPSS v15.0 (SPSS Inc.; Chicago, IL, USA). Descriptive statistics were used to summarize patient demographics, tumor characteristics, and MRI findings. The association between MRI findings (e.g., kinetic curve type, internal enhancement pattern, and background enhancement) and receptor status or molecular subtype was evaluated using the Pearson chi-square test. Similar chi-square analyses were used to assess the relationships between receptor status and other categorical variables, such as lymph node positivity and background enhancement patterns. Differences were considered statistically significant at a $P$-value < .05.

## RESULTS

### Patient and Tumor Characteristics

This study included 154 female patients with invasive breast carcinoma (mean age: 51.4 years; range: 24-80). Histopathological analysis identified invasive ductal carcinoma in 96.7% (149/154) and invasive lobular carcinoma (ILC) in 3.3% (5/154) of cases. The MRI BI-RADS categorization classified 63.1% (97/154) of the lesions as BI-RADS 4 (suspicious), 30.5% (49/154) as BI-RADS 5 (highly suggestive of malignancy), and 5.2% (8/154) as BI-RADS 6 (biopsy-proven).

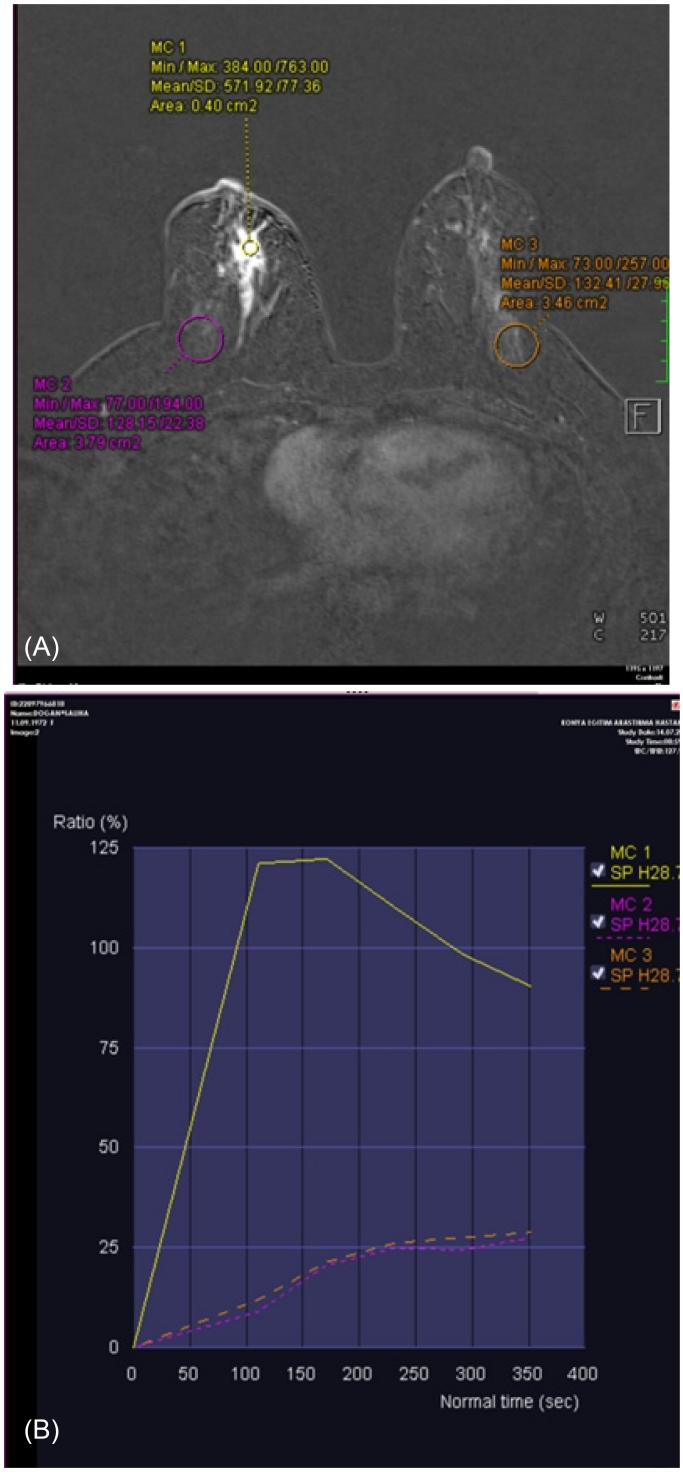


**Figure 3** On breast MRI, a 45-year-old female, a mass measuring 15 × 15 mm with linear shape and partly spiculated margins was located in the right breast retroareolar region and was diagnosed as invasive ductal carcinoma according to the biopsy results. (A) The mean curve measurement of mass enhancement, non-mass enhancement, and parenchymal enhancement in the contralateral breast on DCE Breast MRI using ROI. (B) Time–intensity curve displays type 3 mass enhancement pattern, non-mass enhancement, and parenchymal enhancement in the contralateral breast display type 1 pattern.

Tumors were predominantly left-sided (51.9%, 79/154), with bilateral involvement in 1.9% of cases (3/154).

**Imaging Features**

Morphologically, 56.6% (87/154) of the tumors exhibited irregular shapes (stellate or spiculated), while 43.4% (67/154) were round, oval, or lobulated. Margins were poorly defined or spiculated in 90.9% (140/154) of the lesions. Internal enhancement patterns on DCE-MRI included heterogeneous (40%, 62/154), rim (29%, 45/154), and homogeneous (31%, 47/154) patterns, with rim enhancement frequently observed in high-grade tumors showing central necrosis. Tumor size ranged from 3 mm to 60 mm (mean: 25 mm; median: 20 mm), and multifocal/multicentric disease was present in 54.6% (83/154) of patients.

**Molecular Subtype Distribution**

Immunohistochemical profiling revealed ER positivity in 39.4% (61/154) of patients, PR positivity in 43.5% (67/154), and HER2 overexpression in 36.4% (56/154). Molecular subtyping categorized tumors as Luminal A (17.4%, 27/154), Luminal B (36.8%, 57/154), or triple-negative (44.5%, 70/154).

**Enhancement Kinetics and Statistical Correlations**

Contrast enhancement kinetics were classified as type 1 (persistent, 37.7%, 58/154), type 2 (plateau, 36.4%, 56/154), or type 3 (washout, 26.0%, 40/154). Chi-square analysis demonstrated a significant association between Luminal A tumors and type 3 kinetics ($\chi^2 = 4.02$, $P < .05$) (Table 1). Luminal B tumors were correlated with moderate-to-marked BPE (BPE: Type 1 [$\chi^2 = 5.07$] and Type 2 [$\chi^2 = 5.53$], $P < .05$) (Table 2) and contralateral breast enhancement (Table 3). No significant relationships were observed between the molecular subtypes, enhancement patterns, or lymph node metastasis ($P > .05$) (Table 4).

## DISCUSSION

This study identified distinct DCE-MRI kinetic and enhancement profiles associated with breast cancer molecular subtypes. Luminal A tumors showed a significant propensity for *Type 3* "washout" kinetics, indicating rapid contrast uptake followed by fast washout. This was an unexpected finding, as classical literature often links Luminal A lesions to more gradual or persistent enhancement pattern.[11] The observation that Luminal A cancers can exhibit aggressive washout curves underscores the heterogeneity of tumor angiogenesis—vascular permeability and perfusion are not determined by receptor status alone, but by the tumor's overall biology. In contrast, Luminal B tumors (were associated in the authors' cohort with moderate-to-marked BPE) and conspicuous contralateral breast enhancement. Luminal B cancers generally have higher proliferation indices (e.g., elevated Ki-67) and often HER2 overexpression, contributing to a more aggressive phenotype. This aggressive biology may manifest on MRI as increased perfusion

**Table 1.** Contrast Enhancement Pattern vs. Tumor Markers/Subtypes

| Tumor Marker/ Subtype | Tip 1 $\chi^2$ | *P* | Tip 2 $\chi^2$ | *P* | Tip 3 $\chi^2$ | *P* |
|---|---|---|---|---|---|---|
| ER | 0.00 | >.05 | 0.74 | >.05 | 0.54 | >.05 |
| PR | 03.09 | >.05 | 0.25 | >.05 | 1.51 | >.05 |
| HER2 | 0.20 | >.05 | 1.29 | >.05 | 1.68 | >.05 |
| Triple negative | 0.03 | >.05 | 0.28 | >.05 | 0.17 | >.05 |
| Luminal A | 1.50 | >.05 | 1.13 | >.05 | 04.02 | <.05* |
| Luminal B | 0.00 | >.05 | 0.18 | >.05 | 0.10 | >.05 |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

**Table 2.** Background Parenchymal Enhancement vs Tumor Markers/Subtypes

| Tumor Marker/Subtype | Tip 1 $\chi^2$ | *P* | Tip 2 $\chi^2$ | *P* |
|---|---|---|---|---|
| ER | 0.16 | >.05 | 0.23 | >.05 |
| PR | 0.41 | >.05 | 0.13 | >.05 |
| HER2 | 02.09 | >.05 | 2.45 | >.05 |
| Triple negative | 1.23 | >.05 | 0.67 | >.05 |
| Luminal A | 1.52 | >.05 | 1.29 | >.05 |
| Luminal B | 05.07 | <.05* | 5.53 | <.05* |

BPE, background parenchymal enhancement; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

in surrounding normal tissue, explaining the elevated BPE the authors observed. Prior studies have indeed suggested that more aggressive, higher-grade tumors can induce greater vascularization in adjacent parenchyma.[12]The authors' finding aligns with this concept although the specific association of high BPE with Luminal B subtype is a novel contribution of this study.

The observed association between Luminal A tumors and type 3 (washout) enhancement kinetics in this study presents an intriguing finding that warrants careful interpretation within the context of contemporary literature. Traditionally, washout kinetics have been associated with more aggressive tumor subtypes, particularly triple-negative breast cancer and HER2-enriched tumors.[6] However, recent investigations have revealed increasing complexity in the relationship between enhancement patterns and molecular biology. Blaschke and Abe[13] demonstrated that HER2-positive lesions exhibit significantly greater rapid early contrast uptake compared to luminal subtypes, with 93.8% of HER2+ tumors showing >100% early uptake vs. 77.3% in Luminal A/B tumors ($P < .01$). This apparent discrepancy with the authors' findings may reflect the heterogeneous nature of Luminal A tumors and the influence of various factors including tumor grade, proliferation index, and vascular architecture that can override the typical enhancement patterns associated with hormone receptor status.

The significant correlation between Luminal B tumors and moderate-to-marked BPE observed in this study aligns remarkably well with recent literature and provides important insights into the biological underpinnings of this molecular subtype. Wu et al.[14] established the foundational role of BPE in molecular subtype differentiation through their landmark external validation study, demonstrating that both tumor and BPE characteristics contribute significantly to subtype discrimination with area under the curve (AUC) values ranging from 0.66 to 0.79 across different molecular subtypes. The association between Luminal B tumors and increased BPE likely reflects the more aggressive biological profile of this subtype, characterized by higher proliferation indices (Ki-67) and potential HER2 expression, which may contribute to increased angiogenesis and vascular permeability not only within the tumor but also in the surrounding normal breast tissue.[8] This systemic effect is further supported by the authors' observation of increased contralateral breast enhancement in Luminal B tumors, suggesting a hormonal or growth factor-mediated influence that extends beyond the immediate tumor microenvironment.

**Table 3.** Contralateral Breast Enhancement vs. Tumor Markers/Subtypes

| Tumor Marker/Subtype | Tip 1 $\chi^2$ | *P* | Tip 2 $\chi^2$ | *P* |
|---|---|---|---|---|
| ER | 0.16 | >.05 | 0.23 | >.05 |
| PR | 0.07 | >.05 | 0.13 | >.05 |
| HER2 | 02.09 | >.05 | 2.45 | >.05 |
| Triple negative | 0.62 | >.05 | 0.67 | >.05 |
| Luminal A | 1.52 | >.05 | 1.29 | >.05 |
| Luminal B | 05.07 | <.05* | 5.53 | <.05* |

ER, estrogen Receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

**Table 4.** Lymph Node Involvement vs. Tumor Markers/Subtypes

| Tumor Marker/Subtype | Lymph Node Involvement (LN+) $\chi^2$ | *P* |
|---|---|---|
| ER | 0.00 | >.05 |
| PR | 1.11 | >.05 |
| HER2 | 0.05 | >.05 |
| Triple negative | 0.09 | >.05 |
| Luminal A | 0.02 | >.05 |
| Luminal B | 0.02 | >.05 |

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LN+, positive lymph node involvement; PR, progesterone receptor.

Recent advances in radiomics and artificial intelligence have substantially enhanced the authors' understanding of the relationship between DCE-MRI features and molecular subtypes, providing both validation and expansion of traditional imaging-pathology correlations. Xu et al[15] recently demonstrated that combined intratumoral and peritumoral radiomics signatures based on DCE-MRI can distinguish between luminal and non-luminal breast cancer molecular subtypes with remarkable accuracy, achieving AUC values of 0.956 in training, 0.945 in internal validation, and 0.896 in external validation sets. This multicenter study of 305 patients represents a significant advancement over traditional qualitative assessment methods and provides strong evidence that peritumoral regions contain complementary biological information that enhances molecular subtype prediction. The superior performance of combined intratumoral and peritumoral analysis (AUC 0.896) compared to intratumoral analysis alone (AUC 0.883) supports the concept that tumor biology extends beyond the visible tumor boundaries, influencing the surrounding tissue architecture and vascular characteristics.

The concept of kinetic heterogeneity within breast tumors has emerged as a particularly promising avenue for molecular subtype prediction, as demonstrated by the innovative work of Feng et al[16] who developed a radiomics model based on intra-tumoral kinetic heterogeneity for predicting breast cancer molecular subtypes. Their approach of segmenting tumors into 3 subregions (persistent, washout, and plateau) based on voxel-level contrast enhancement patterns represents a paradigm shift from traditional whole-tumor analysis to region-specific characterization. The superior performance of their washout region model, achieving AUC values of 0.924 for luminal subtype, 0.876 for HER2, and 0.816 for HER2 status prediction, suggests that specific kinetic regions within tumors may harbor more discriminatory information than global tumor characteristics. This finding has particular relevance to this study's observation of washout kinetics in Luminal A tumors, as it suggests that even within traditionally "less aggressive" subtypes, there may be regions of rapid contrast washout that reflect underlying biological heterogeneity and potentially more aggressive tumor components.

The integration of multiparametric MRI approaches has further enhanced the discriminatory power of imaging-based molecular subtype prediction. He et al[17] conducted a comprehensive analysis of 194 breast cancer patients using T2-weighted imaging, diffusion-weighted imaging, and DCE-MRI, employing unsupervised clustering analysis to

identify distinct patient clusters with significant differences in molecular subtypes. Their findings revealed statistically significant differences in Luminal A subtype distribution ($P = .03$), ER status ($P = .01$), PR status ($P = .04$), mean tumor size ($P < .01$), lymph node metastasis ($P = .01$), and edema ($P < .01$) between the identified clusters. This multiparametric approach addresses the limitation of single-sequence analysis and provides a more comprehensive characterization of tumor biology, potentially explaining some of the apparent contradictions in single-parameter studies and supporting the need for integrated imaging biomarkers in clinical practice.

The evolution toward deep learning and artificial intelligence-based approaches has marked a significant milestone in the field of imaging-based molecular subtype prediction. Contemporary studies have demonstrated that deep neural networks can effectively combine DCE-MRI with other imaging modalities to achieve superior performance compared to traditional radiomics approaches.[18] The development of multi-institute deep learning models (MBCNN) for predicting molecular subtypes from DCE-MRI represents a crucial step toward clinical translation, as these models must demonstrate robustness across different imaging protocols, patient populations, and institutional practices. The combination of DCE-MRI with non-mass enhancement diffusion-weighted imaging via deep neural networks has shown particularly promising results, achieving significant improvements in breast cancer molecular subtype prediction compared to either imaging modality alone.[9] This multimodal integration addresses the inherent limitations of single-sequence analysis and provides a more comprehensive assessment of tumor characteristics, including both vascular and cellular properties.

The clinical implications of the authors' findings, when viewed in the context of the broader literature, extend beyond mere academic interest to potential practical applications in personalized breast cancer management. The ability to predict molecular subtypes non-invasively could significantly impact treatment planning, particularly in cases where tissue sampling is challenging or when assessing tumor heterogeneity across large lesions. However, several important limitations must be acknowledged. The authors' study's retrospective design and single-center nature limit the generalizability of findings, particularly given the demonstrated importance of external validation in imaging biomarker studies.[14] The relatively small number of patients in certain molecular subtype categories, particularly HER2-enriched tumors, may have limited the authors' ability to detect significant associations and contributed to the apparent discrepancies with some literature findings. Furthermore, the evolution of molecular subtyping criteria over time, including the recent recognition of HER2-low tumors as a distinct entity,[19] highlights the dynamic nature of breast cancer classification and the need for imaging biomarkers to adapt accordingly.

The absence of significant associations between molecular subtypes and lymph node metastasis in this study is consistent with multiple contemporary investigations and reflects the complex, multifactorial nature of metastatic spread in breast cancer.[20] This finding suggests that while DCE-MRI characteristics may effectively predict molecular subtypes, they may not be sufficient predictors of nodal involvement, which depends on additional factors including tumor size, histological grade, lymphovascular invasion, and proliferative rate. Recent large-scale multicenter studies have confirmed this limitation, with a comprehensive analysis of 1506 pre-treatment DCE-MRI cases demonstrating that imaging features alone are insufficient for reliable lymph node status prediction.[21] This limitation underscores the importance of integrating imaging biomarkers with clinical and pathological factors rather than relying on imaging characteristics in isolation.

Overall, this study highlights that DCE-MRI kinetic data and internal enhancement patterns can provide important insights into the molecular subtypes of breast cancer. It is worth noting that the distribution of molecular subtypes in this study differs from most population-based reports, where Luminal A is typically the most prevalent form of breast cancer. In the authors' series, Luminal A tumors accounted for only 17.4% of cases, while Luminal B and triple-negative subtypes were more frequent. Several factors may explain this discrepancy. First, as a tertiary oncology center, the authors' institution receives a disproportionate number of aggressive or diagnostically complex cases, potentially leading to selection bias. Second, the retrospective nature of this study limited the availability of proliferation index data (Ki-67), which is essential for accurately distinguishing between Luminal A and Luminal B subtypes. Consequently, some ER/PR-positive tumors with unknown or high proliferation rates may have been classified as Luminal B by default. Third, partial or low-level hormone receptor expression (e.g., ER or PR just above the 1% cutoff) may not correlate with classical Luminal A biology. These limitations likely contributed to the lower observed prevalence of Luminal A and should be considered when interpreting subtype-specific imaging patterns. However, the generalizability of these findings should be approached cautiously given the limited number of patients in certain subgroups (e.g., HER2-enriched) and the retrospective nature of the study. Differences in DCE-MRI protocols between centers, along with variability among readers, are further limitations that should be considered.

Future directions in this field are likely to focus on several key areas that address current limitations and expand clinical applicability. The standardization of DCE-MRI protocols across institutions represents a critical need, as variations in imaging parameters, contrast agents, and acquisition techniques can significantly impact radiomics feature extraction and model performance.[22] The development of federated learning approaches may enable the creation of robust, generalizable models while preserving patient privacy and institutional autonomy. Additionally, the integration of imaging biomarkers with genomic data through radiogenomics approaches holds promise for developing more comprehensive predictive models that capture both phenotypic and genotypic tumor characteristics.[23] The recent emergence of time-dependent diffusion MRI as an effective method for molecular subtype prediction[24] suggests that novel imaging techniques may provide complementary information to traditional DCE-MRI approaches, potentially improving overall predictive accuracy.

In conclusion, this study contributes to the evolving understanding of DCE-MRI characteristics in breast cancer molecular subtype prediction, while highlighting both the potential and limitations of current imaging-based approaches. The significant association between Luminal A tumors and washout kinetics, though seemingly contradictory to traditional expectations, may reflect the biological heterogeneity within molecular subtypes and the need for more sophisticated analytical approaches. The consistent association between Luminal B tumors and increased BPE across multiple studies suggests a robust biological relationship that may have clinical utility. As the field moves toward increasingly sophisticated artificial intelligence and radiomics approaches, the integration of multiple imaging parameters, external validation across diverse populations, and standardization of protocols will be essential for translating these research findings into clinically applicable tools. The ultimate goal remains the development of

comprehensive, non-invasive imaging biomarkers that can guide personalized treatment decisions and improve outcomes for breast cancer patients worldwide

**Data Availability Statement:** The data that support the findings of this study are available on request from the corresponding author.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Konya Necmettin Erbakan University (Approval No: 2214/5 Date: 20.01.2016).

**Informed Consent:** Given the retrospective design of the study, the requirement for informed consent was waived by the ethics committee.

**Peer-review:** Externally peer reviewed.

**Author Contributions:** Concept – A.F.T.; Design – A.F.T.; Supervision – S.Ö., İ.T.; Resources – A.F.T.; Materials – A.F.T.; Data Collection and/or Processing – A.F.T.; Analysis and/or Interpretation – A.F.T.; Literature Search – Y.C.K., V.T.; Writing Manuscript – A.F.T.; Critical Review –S.Ö., İ.T.; Other – İ.T.

**Declaration of Interests:** The authors have no conflict of interest to declare.

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