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Original Research Article

Role of Diffusion Weighted Imaging and 1h MR Spectroscopy in Prognostication of Breast Cancer

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Abstract:

Background: This study evaluated the diagnostic and prognostic roles of magnetic resonance spectroscopy (MR Spectroscopy) and diffusion-weighted imaging (DWI) in breast cancer.

Methods: Quantitative DWI and MR Spectroscopy were employed for lesion characterization. ADC values were calculated, and MR Spectroscopy assessed choline concentrations. Kinetic curve analysis and cross-tabulation with histopathological diagnosis were performed for validation. Statistical analysis included Cohen's Kappa and ROC curve analysis.

Results: A cohort of 77 women with 88 breast lesions underwent MR Spectroscopy and DWI, comprising 65 malignant and 23 benign cases. The mean age for malignancy was 48.1 years and for benign lesions was 36.2 years. The study included 77 women with 88 breast lesions, encompassing invasive ductal carcinoma, inflammatory intra-ductal carcinoma, and benign lesions such as fibroadenoma and idiopathic granulomatous mastitis. The study found a significant difference in mean ADC values between malignant (0.9526 x 10^-3 mm^2/s) and benign (1.48 x 10^-3 mm^2/s) breast lesions. The ADC cut-off of 1.1 x 10^-3 mm^2/s demonstrated 92.3% sensitivity and 73.9% specificity. No significant associations were observed between ADC values and ER/HER2 statuses, but a significant association was found with positive PR expression (p=0.04). MR Spectroscopy showed a mean total choline concentration of 0.186 ppm for malignancy and 0.104 ppm for benignity.

Conclusion: Quantitative DWI and MR Spectroscopy offer valuable insights into breast lesion characterization, with ADC values and choline concentrations serving as key discriminators between malignant and benign lesions. The study emphasizes the potential clinical utility of these imaging techniques for accurate diagnosis and prognostication in breast cancer.

Keywords: Breast cancer, Diffusion-weighted imaging, MR Spectroscopy, Diagnostic accuracy, Prognostication.

Introduction

Breast cancer stands as a formidable global health challenge, affecting millions of women worldwide and necessitating continuous advancements in diagnostic and prognostic tools. The ability to accurately predict disease progression and patient outcomes is pivotal for tailoring effective treatment strategies and improving overall survival rates.[1,2] While conventional imaging modalities such as mammography and ultrasound have long been cornerstones in breast cancer diagnosis, their limitations in providing comprehensive insights into tumor biology underscore the need for more sophisticated approaches.[2,3]

This research paper delves into the evolving landscape of breast cancer prognostication, focusing specifically on the emerging roles of Diffusion-Weighted Imaging (DWI) and Proton Magnetic Resonance Spectroscopy (1H MRS). These advanced MRI techniques offer unique perspectives into the cellular and molecular characteristics of breast tumors, providing valuable information that extends beyond the capabilities of traditional imaging methods.

Breast cancer is a heterogeneous disease with diverse clinical behaviors, necessitating a nuanced understanding of individual tumor characteristics for effective management.[4,5] Prognostication, the ability to foresee the likely course of the disease, plays a pivotal role in guiding treatment decisions, optimizing therapeutic interventions, and ultimately

improving patient outcomes. [5,6] While histopathological assessment remains central to prognostication, the integration of advanced imaging techniques offers a non-invasive means to obtain real-time information about the tumor microenvironment, aiding in a more comprehensive and dynamic assessment.[6,7]

Diffusion-Weighted Imaging (DWI) has emerged as a powerful tool in oncologic imaging, leveraging the inherent mobility of water molecules to provide insights into tissue microstructure and cellularity. In the context of breast cancer, DWI has shown promise in characterizing lesions, differentiating between benign and malignant tumors, and predicting responses to therapy. The quantification of the apparent diffusion coefficient (ADC) has become a valuable metric, reflecting the degree of water diffusion within tissues and offering a surrogate marker for tumor aggressiveness. [8,9]

Complementing DWI, Proton Magnetic Resonance Spectroscopy (1H MRS) focuses on the metabolic alterations within tissues, providing a unique window into the molecular landscape of breast tumors. [10,11] The identification and quantification of specific metabolites, such as choline, lactate, and lipids, offer insights into cellular proliferation, energy metabolism, and membrane turnover. By elucidating these metabolic signatures, 1H MRS contributes to a more holistic understanding of tumor biology and has the potential to refine prognostic assessments.

As the field progresses, the synergistic application of DWI and 1H MRS emerges as a promising avenue for refining breast cancer prognostication.[9,10,11] This study explores the current state of knowledge regarding the individual and combined roles of these advanced imaging techniques, examining their contributions to predicting treatment response, differentiating tumor subtypes, and ultimately informing personalized therapeutic strategies.

This research paper aims to assess the alignment between Diffusion Weighted Imaging (DWI) and Proton (1H) MR Spectroscopy with histopathology in breast cancer, exploring their potential as reliable prognostication tools. The study's general objective is to evaluate the role of these advanced imaging techniques in characterizing breast lesions, contributing to a more comprehensive understanding of the disease. Specific objectives involve studying the association between apparent diffusion coefficient (ADC) and conventional histopathological prognostic factors, as well as determining the correlation between total choline-containing compounds obtained through MR Spectroscopy and established histopathological parameters. Through these objectives, the study seeks to elucidate the clinical utility of DWI and 1H MRS in enhancing breast cancer prognostication.

Methodology:

Study Population: This prospective observational study was conducted at the Department of Radiodiagnosis in collaboration with the Department of General Surgery and Department of Pathology at Jagannath Gupta Institute of Medical Sciences and Hospital, Kolkata. Institutional Ethical Committee approval was obtained. The study included 77 women with 88 suspicious breast lesions who underwent MR Mammogram between January 2021 and July 2022.

Inclusion Criteria:

Female patients with suspicious breast lesions identified through clinical/physical examination, ultrasonography, or mammography were included.

Exclusion Criteria:

- Lesions less than 1cm in size with contrast enhancement.
- Patients undergoing neo-adjuvant or radiation therapy.
- Previous interventional or surgical procedures within the three months preceding the examination.
- Male patients with breast lumps.
- Patients lacking histopathological confirmation of the breast lesion.
- Postmenopausal women on hormone replacement therapy.
- General contra-indications to MRI, including allergy to contrast, implanted cardiac pacemaker, aneurysm clips, cochlear devices, or claustrophobia.
- Unwillingness to participate in the study.

All patients provided written informed consent, underwent history-taking, and general and local examinations. MR imaging, including dynamic contrast-enhanced and DWI sequences, was performed during the second week of the menstrual cycle for premenopausal women.

MRI Acquisition and Post-processing: Bilateral breast MRI utilized a 1.5 T MR with a dedicated 16-channel bilateral breast coil. The imaging protocol included axial T2 and STIR sequences, DWI at b values of 0 and 800 s/mm², and an axial VIBRANT multiphase 3D T1-weighted dynamic gradient-echo sequence. Dynamic contrast-enhanced MRI comprised pre-contrast and 7 post-contrast series, with automated subtracted images obtained for each phase.

Proton MR spectroscopy was performed using a single-voxel water- and fat-suppressed technique.

MRI Interpretation: T2 and STIR images were analyzed for lesion presence, location, and size.

Dynamic curves were assessed based on initial and late-phase enhancement, classified according to the ACR BI-RADS MRI lexicon. MRI BI-RADS classification involved both morphology and kinetic curve assessment.

Diffusion-Weighted Imaging and MR Spectroscopy Analysis: ADC maps were generated from DWI, and ADC values were calculated using ROI analysis. MR spectroscopy utilized a volume of interest encompassing the enhancing part of the lesion. Total choline values were determined using freeware named iNMR.

Reference Standard: Lesions categorized as MR BI-RADS 3, 4, or 5 underwent surgical excision or core needle biopsy under ultrasound. Histopathological reports provided the gold standard diagnosis, including tumor grade, estrogen receptor (ER), progesterone receptor (PR), and HER2 status.

Statistical Analysis: Data were summarized as mean and standard deviation. Student's t-test compared numerical variables between benign and malignant subgroups. Receiver Operating Characteristics (ROC) curve analysis identified cut-offs for ADC and total choline to predict malignancy. Correlation between mean ADCs/total choline and histological grade and biological factors was analyzed using MedCalc and Statistical software. Significance was set at $P < 0.05$.

Result

Demographic data for the study

77 women (between 18 and 85 years of age) with 88 breast lesions were included in the study, of which 65 were malignant and 23 were benign.

The mean age of women with malignant breast lesions was 48.1 years (age range 22-85 years; standard deviation 12.7) and for benign it was 36.2 years (age range 18-49 years; standard deviation 9.04), Figure 1.

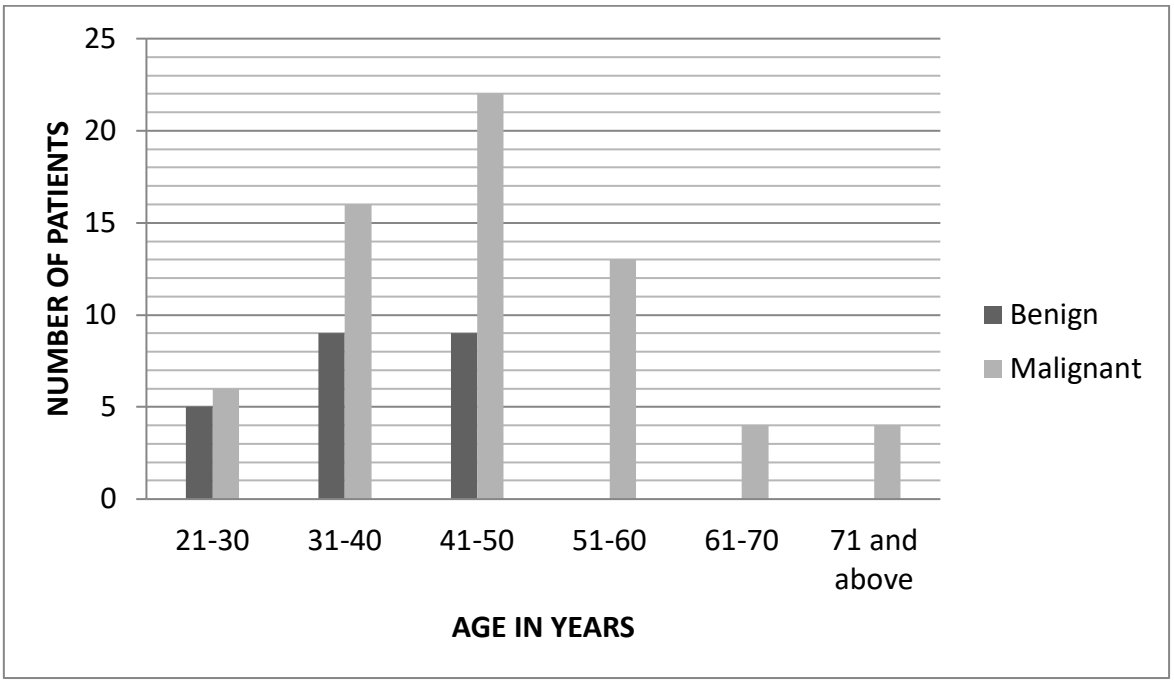

Figure 1: Demographic data for the study

Distribution of the study Lesion: Invasive ductal carcinoma (n= 48) ,invasive ductal carcinoma with ductal carcinoma in situ(n= 3),inflammatory intraductal carcinoma(n= 8),invasive lobular carcinoma (n=1), pure mucinous carcinoma (n= 1), mixed mucinous carcinoma (n=1), malignant phylloides (n=1) and invasive Metaplastic carcinoma (n=2) while the benign lesions included fibroadenoma (n= 4), idiopathic granulomatous mastitis (n= 5), benign phylloides (n= 1), fibrocystic disease of breast (n= 4), fibroadenolipoma (n=2), benign proliferative lesion (n=1),ductal adenoma (n=2), tubular adenoma (n=1), hyalinised fibroadenoma (n=1), fibroadenosis with epitheliosis (n=1) and intraductal papilloma(n= 1), Figure 2.

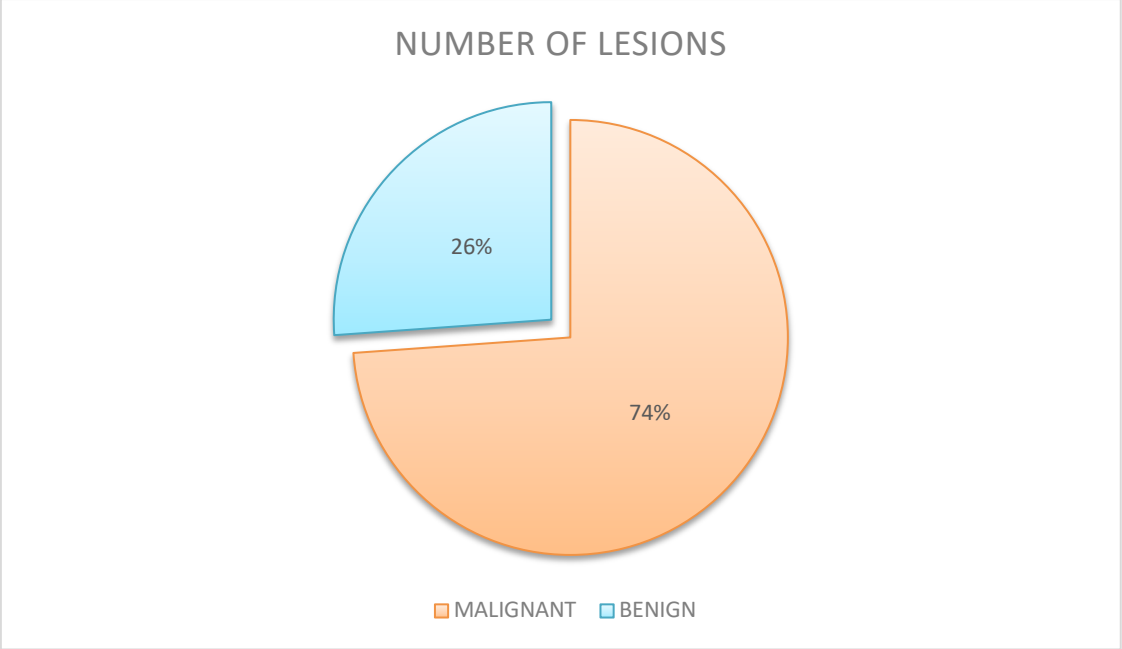

Figure 2: Distribution of lesions among the population

Table 1: Cross-tabulation of diagnosis by ADC cut-off vis-a-vis the gold standard histopathological diagnosis with extent of agreement depicted as Cohen's Kappa

	Status ADC		
Histopathological diagnosis	**Benign**	**Malignant**	
Benign	17	6	23 (26.1%)
Malignant	12	53	65 (73.9%)
	29(33.0%)	59(67.0%)	88
Kappa	0.511		
95% CI	0.317 to 0.706		

Table 1 presents a cross-tabulation of histopathological diagnoses against ADC cut-off values in a cohort of 88 breast lesions, with the extent of agreement quantified using Cohen's Kappa statistic. The table reveals that 23 lesions (26.1%) were histopathologically diagnosed as benign, out of which 17 were correctly identified as such based on ADC values, while 6 were misclassified as malignant. For the 65 malignant lesions (73.9%), 53 were accurately characterized as such by ADC cut-off values, while 12 were erroneously classified as benign. The overall agreement between ADC cut-off values and histopathological diagnosis is represented by a Kappa value of 0.511, with a 95% confidence interval from 0.317 to 0.706. This Kappa value suggests moderate to substantial agreement, indicating that ADC cut-off values demonstrate a noteworthy level of concordance with histopathological diagnoses in distinguishing between benign and malignant breast lesions in the studied cohort.

Table 2: Cross-tabulation of diagnosis by Kinetic curve analysis vis-a-vis the gold standard histopathological diagnosis with extent of agreement depicted as Cohen's Kappa

Observer A	**Status Kinetic Curve**			
Observer B	**Histopathological diagnosis**			
	Status Kinetic Curve			
Histopathological diagnosis	**Benign (Type1 curve)**	**Malignant (Type 3 curve)**	**Indeterminate (Type 2 curve)**	
Benign	7	6	10	23 (26.1%)
Malignant	0	54	11	65 (73.9%)
Indeterminate	0	0	0	0 (0.0%)
	7 (8.0%)	60 (68.2%)	21 (23.9%)	88
Kappa	0.355			
95% CI	0.219 to 0.491			

Table 2 presents a cross-tabulation of histopathological diagnoses against kinetic curve analysis, as assessed by two observers (Observer A and Observer B), in a cohort of 88 breast lesions.

The table categorizes lesions into three groups based on kinetic curve patterns: Benign (Type 1 curve), Malignant (Type 3 curve), and Indeterminate (Type 2 curve).

The results show that out of the 23 lesions histopathologically diagnosed as benign, 7 were correctly identified as having a benign kinetic curve (Type 1), 6 were misclassified as having a malignant kinetic curve (Type 3), and 10 were deemed indeterminate (Type 2). For the 65 histopathologically malignant lesions, 54 were accurately characterized as having a malignant kinetic curve (Type 3), while 11 were misclassified as having a benign kinetic curve (Type 1). No lesions were categorized as indeterminate by kinetic curve analysis.

The overall agreement, as measured by Cohen's Kappa, is 0.355 with a 95% confidence interval from 0.219 to 0.491. This Kappa value indicates fair to moderate agreement, suggesting that kinetic curve analysis demonstrates a reasonable level of concordance with histopathological diagnoses.

Table 3: Role of Advanced Imaging Techniques in Breast Cancer Diagnosis and Prognostication

Parameter	MR Spectroscopy (Choline Peak)	DWI	MR Spectroscopy (Total Choline)
Number of Lesions	58	46	28
Histological Distribution	38 Malignant / 20 Benign	Grade II (28) / Grade III (18)	ER-positive (11) / ER-negative (22) / HER-2neu (25)
Sensitivity	84.21% [CI 68.75% - 93.98%]	Not specified	Not specified
Specificity	40% [CI 19.12% - 63.95%]	Not specified	No significant difference between ER-positive and -negative
True Positive (Choline Peak)	32	Not specified	Not specified
False Positive (Choline Peak)	12	Not specified	Not specified
True Negative (No Choline Peak)	8	Not specified	Not specified
False Negative (No Choline Peak)	6	Not specified	Not specified
Total Choline Cut-off for Malignancy	> 0.1046 ppm	Not applicable	> 0.1046 ppm
ADC Values	Not specified	Grade II: (0.994 ± 0.256) / Grade III: (0.911 ± 0.089)	No significant difference between PR-positive and -negative
ADC and ER/PR Status	Higher in ER-positive (1.046 ± 0.302) vs. ER-negative (0.914 ± 0.124)	Higher in PR-positive (1.063 ± 0.314) vs. PR-negative (0.915 ± 0.127)	No significant difference between HER-2neu positive and negative
Her-2neu Status and Choline Concentration	Not specified	Not specified	No significant difference between grade II and III

This comprehensive comparison Table 3 synthesizes findings from studies utilizing MR Spectroscopy (MRS) with choline peak identification, Diffusion-Weighted Imaging (DWI), and MRS with total choline concentration assessment in breast cancer diagnosis and prognostication. The table highlights key parameters such as sensitivity, specificity, and cut-off values, emphasizing the distinctive strengths and characteristics of each imaging modality in the context of breast cancer assessment.

Receiver Operating Characteristics (ROC) curve analysis to see if there is any cut-off for the Total Choline for predicting malignancy

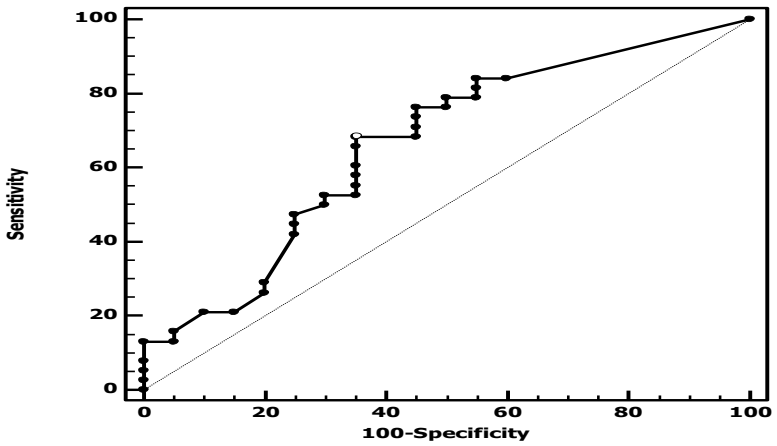

Figure 3: Graph shows receiver operating characteristic (ROC) curve for total choline.

Area under the curve, which represents the probability the lesion, will be classified accurately as benign or malignant according to the total choline value, is 0.663. ROC curve analysis is suggesting that Total Choline > 0.1046 ppm indicates the possibility of malignancy in the breast lesion with 68.4% (95% CI 51.3 - 82.5) sensitivity and 65.0% specificity (95% 40.8 - 84.6), Figure 3.

Discussion

In this study, we explored the utility of diffusion-weighted imaging (DWI) in distinguishing between benign and malignant breast lesions. DWI, a non-contrast, functional MRI sequence with a relatively short imaging time, has been recognized for its potential to enhance specificity of dynamic contrast-enhanced MRI (DCE-MRI). However, it is imperative to acknowledge the limitations associated with DWI, including susceptibility artifacts and image distortion, particularly challenging for characterizing small lesions [11,12,13].

Our investigation focused on the apparent diffusion coefficient (ADC) derived from DWI at a b-value of 800 s/mm². The mean ADC values exhibited a statistically significant difference between malignant and benign breast lesions. Malignant lesions demonstrated lower mean ADC values (0.9526 x 10^(-3) mm²/s) compared to benign lesions (1.48 x 10^(-3) mm²/s). This finding aligns with previous studies by Woodhams et al. (14), Abdulghaffar et al. [15], Park MJ et al. (16), Bansal R et al. [17], and Palle L et al. [18].

The established cutoff value for ADC, derived from receiver operating characteristic (ROC) analysis, was 1.1 x 10^(-3) mm²/s. The study demonstrated high sensitivity (92.3%) and specificity (73.9%) in distinguishing malignant from benign lesions. Notably, lower specificity was attributed to cases of idiopathic granulomatous mastitis, emphasizing the challenges in certain diagnostic scenarios. The study also observed elevated ADC values in pure and mixed mucinous carcinomas, potentially linked to their low cellularity compared to invasive ductal carcinoma (IDC), consistent with findings by Jin et al. [19] and Woodhams et al. [20].

Concerning hormonal receptor status, our study found no significant association between ADC values and estrogen receptor (ER) or human epidermal growth factor receptor 2 (HER2) statuses. However, a significant association was noted with positive expression of progesterone receptor (PR). The literature on the correlation between immunohistochemical markers and ADC values remains inconclusive, with varying results across different studies. Previous research by Soerjomataram et al. [21] and Bogner et al [22]. indicated associations between ER expression and ADC values, while Choi et al. [23] and Jeh et al. [24] reported conflicting results.

Regarding tumor cellularity, our study did not find a significant association between ADC values and histological grade, consistent with previous reports [24,25]. However, the study acknowledged recent findings by Cipolla et al. [25], indicating an association between low ADC values and high-grade invasive breast cancer.

Moving to in vivo proton magnetic resonance spectroscopy (1H-MRS), the study delved into its role in differentiating benign and malignant breast lesions. Quantitative MRS demonstrated superior specificity compared to qualitative MRS, while qualitative MRS exhibited higher sensitivity.

Benign lesions showing a choline peak in MRS included various types, such as tubular adenoma, ductal adenoma, fibrocystic disease, fibroadenolipoma, ductal papilloma, and idiopathic granulomatous mastitis. Notably, invasive ductal carcinoma and pure mucinous carcinoma did not exhibit a choline peak.

The study also evaluated the diagnostic performance of total choline (tCho) concentration levels measured by 1H-MRS, establishing a cutoff point (> 0.1046 ppm) for distinguishing benign from malignant lesions. The resulting sensitivity was 68.4%, and specificity was 65.0%. Comparing these findings with existing literature, our study reported a mean total choline concentration of 0.186 ± 0.15 ppm for malignancy at 3T, consistent with diverse ranges reported in prior studies [26-28].

Despite these valuable insights, the study has acknowledged limitations, including the exclusion of lesions smaller than 1 cm for DWI and potential partial volume effects in 1H-MRS due to the voxel size. Additionally, the absence of in-situ and grade 1 breast carcinomas reflects the current presentation trends in a tertiary care center in eastern India, highlighting the challenges posed by delayed diagnoses.

Overlapping ADC map values between benign and malignant lesions, unreliability for mucinous carcinoma and idiopathic granulomatous mastitis, and the study's limited sample size for the evaluation of DWI and MR Spectroscopy in prognostication further emphasize the need for larger cohorts to validate these findings.

Conclusion

In conclusion, our study underscores the effectiveness of quantitative diffusion-weighted imaging (DWI) as a valuable technique for characterizing breast lesions, providing a reliable apparent diffusion coefficient (ADC) cutoff for differentiating between benign and malignant lesions. However, limitations are acknowledged, particularly in the diagnosis of mucinous carcinoma and idiopathic granulomatous mastitis. Magnetic resonance spectroscopy of the breast emerges as a useful tool in distinguishing malignant from benign lesions, with choline concentration serving as a key discriminator. The study's findings reveal that neither the histologic grade of breast cancer nor the ADC value and mean total choline concentration exhibit significant associations. Moreover, no significant correlations were identified between ADC values and estrogen receptor (ER) or human epidermal growth factor receptor 2 (HER2) statuses. Notably, a significant association was observed between ADC values and positive expression of progesterone receptor (PR). Furthermore, no significant associations were found between mean total choline concentration and ER, PR, and HER2 statuses. These comprehensive insights highlight the multifaceted diagnostic potential of DWI and magnetic resonance spectroscopy in breast cancer characterization, emphasizing the nuanced interplay between imaging metrics and molecular markers in refining our understanding of breast lesions.

Ethical approval: The study was approved by the Institutional Ethics Committee

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