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Correlation of Dynamic Contrast-Enhanced and Diffusion-Weighted MRI Parameters with Histopathological Prognostic Factors in Breast and head and neck carcinomas in relation to hormonal factors

Uzma Snobar[1], Saima Omar[2], Iqra Arif[3], Absar Akram[4], Maimoona Aslam[5], Shazia Aman[6], Farah Naz Tahir[7]

[1] Doctor, Shihezi University, Xinjiang, China.
[2] Assistant Professor of Radiology, Consultant Radiologist, CMH Pano Aqil, Pakistan.
[3] Medical Officer (Surgery), Bahawalpur Medical and Dental Hospital, Bahawalpur, Pakistan.
[4] Associate Professor Otorhinolaryngology, Gujranwala Medical College, Pakistan.
[5] Assistant Professor (Histopath), Pathology Department, Lahore Medical and Dental College, Lahore, Pakistan.
[6] Senior Registrar, Radiology, Sheikh Zayed Hospital, Lahore, Pakistan.
[7] Associate professor, M. Islam Medical and Dental College, Gujranwala, Pakistan

Uzma Snobar: corresponding author
Orchid id: 0000-0002-0693-9559

ABSTRACT

Functional magnetic resonance imaging techniques, including dynamic contrast-enhanced and diffusion-weighted imaging, have increasingly enabled non-invasive characterization of tumor microenvironment; however, their integration with histopathological prognostic indicators and hormonal receptor status remains insufficiently defined across different tumor systems. This prospective experimental study aimed to evaluate the correlation of quantitative MRI parameters (Ktrans, Kep, Ve, and apparent diffusion coefficient) with tumor grade, lymphovascular invasion, Ki-67 index, nodal status, and hormonal receptor expression in breast and head and neck carcinomas. Analysis demonstrated significantly lower ADC values in high-grade tumors (0.81±0.10 vs 1.19±0.14 $\times 10^{-3}$ mm^2/s, $p<0.001$) and elevated Ktrans in tumors with high proliferative indices (0.91±0.18 vs 0.56±0.16 min^{-1}, $p<0.001$). Hormone receptor-negative breast tumors exhibited higher perfusion metrics and lower diffusion values (p=0.002), while in head and neck carcinomas, Kep showed strong association with nodal metastasis (p=0.004). Multivariate modeling identified ADC and Ktrans as independent predictors of aggressive disease. These findings establish a novel imaging–hormonal correlation framework, suggesting that combined DCE and DWI parameters can serve as surrogate biomarkers for tumor biology and prognostication. The study highlights the potential of integrating functional imaging with hormonal profiling to refine risk stratification and optimize personalized therapeutic strategies.

Keywords: *DCE-MRI, Diffusion-weighted imaging, Hormonal receptors*

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INTRODUCTION

Breast carcinoma and head and neck malignancies collectively represent a substantial proportion of the global cancer burden, with increasing incidence rates and persistent challenges in achieving optimal clinical outcomes. These malignancies are characterized by marked heterogeneity in their biological behavior, ranging from indolent lesions to highly aggressive tumors with rapid progression and early metastasis. Traditional prognostic evaluation relies heavily on histopathological examination, including tumor grade, lymph node status, and proliferative indices. While these factors provide valuable insights, they require invasive tissue sampling and may not adequately reflect intratumoral heterogeneity or dynamic changes occurring during disease progression. Consequently, there is a growing emphasis on identifying non-invasive imaging biomarkers that can reliably predict tumor aggressiveness and guide personalized therapeutic strategies.[1-3]

Magnetic resonance imaging has undergone significant transformation over the past decade, evolving from a purely anatomical modality to a comprehensive functional imaging platform. Among the advanced

techniques, dynamic contrast-enhanced imaging enables quantitative assessment of tumor vascularity by analyzing the kinetics of contrast agent distribution within the tumor microenvironment. Parameters such as Ktrans, Kep, and Ve are widely recognized as indicators of angiogenesis, vascular permeability, and extracellular volume fraction. Angiogenesis is a fundamental process in tumor growth and metastasis, facilitating oxygen and nutrient delivery while also providing pathways for tumor dissemination. Therefore, the ability to quantify these vascular characteristics non-invasively holds considerable clinical significance.[4-6]

Diffusion-weighted imaging complements perfusion-based techniques by providing information on tissue cellularity and microstructural integrity. The apparent diffusion coefficient serves as a quantitative marker reflecting the degree of water molecule movement within tissues. In highly cellular tumors, the diffusion of water is restricted due to reduced extracellular space and increased membrane density, resulting in lower ADC values. This characteristic has been consistently associated with higher tumor grade, increased proliferative activity, and poorer clinical outcomes. The integration of diffusion and perfusion imaging thus offers a multidimensional perspective on tumor biology, capturing both structural and functional attributes.

In breast carcinoma, hormonal receptor status plays a pivotal role in determining tumor behavior and therapeutic response. Estrogen and progesterone receptors are key determinants of tumor growth, influencing cell proliferation, apoptosis, and angiogenesis. Hormone receptor-positive tumors generally exhibit a more favorable prognosis and respond well to endocrine therapy, whereas receptor-negative tumors are often more aggressive and associated with poorer outcomes. Recent advancements suggest that these molecular characteristics may also manifest as distinct imaging phenotypes, with hormone receptor-negative tumors demonstrating higher perfusion and lower diffusion values. This emerging concept highlights the potential of imaging biomarkers to serve as surrogates for molecular profiling.[8-10]

Head and neck carcinomas, although traditionally not classified based on hormonal receptor status, have shown increasing evidence of molecular heterogeneity influenced by various biological pathways. Factors such as human papillomavirus status, tumor hypoxia, and angiogenic signaling contribute to variations in tumor behavior. The role of vascularity and cellular density in these tumors is particularly significant, as they are closely linked to local invasion, nodal metastasis, and treatment resistance. Functional MRI techniques provide an opportunity to explore these characteristics in a non-invasive manner, potentially improving diagnostic accuracy and prognostic assessment.

Recent research has focused on establishing correlations between imaging parameters and histopathological features, aiming to validate imaging as a reliable surrogate for tumor biology. Studies have demonstrated that higher Ktrans values are associated with increased microvessel density and proliferative activity, while lower ADC values correlate with higher tumor grade and cellularity. However, the majority of these investigations have been limited to single tumor types or specific imaging parameters, resulting in fragmented evidence. There remains a need for comprehensive studies that integrate multiple imaging modalities and correlate them with a broad spectrum of histopathological and molecular markers.

Another critical aspect that has not been sufficiently addressed is the interaction between imaging parameters and hormonal factors. Understanding how hormonal receptor status influences tumor microenvironment and imaging characteristics could provide valuable insights into disease behavior and therapeutic response. This is particularly relevant in breast carcinoma, where hormonal therapy constitutes a cornerstone of treatment. The ability to non-invasively predict receptor status or associated biological behavior using imaging could significantly enhance clinical decision-making.

Technological advancements in MRI acquisition and analysis have further strengthened the potential of functional imaging. Improved temporal and spatial resolution, along with sophisticated pharmacokinetic modeling, have enabled more accurate quantification of perfusion parameters. Similarly, advances in diffusion imaging techniques have enhanced the reliability of ADC measurements. These developments have facilitated the integration of imaging biomarkers into clinical research, paving the way for their potential adoption in routine practice.

The concept of combining diffusion and perfusion imaging is particularly compelling, as it allows for simultaneous assessment of tumor vascularity and cellularity. This integrated approach provides a more comprehensive understanding of tumor biology compared to individual modalities. For instance, a tumor exhibiting both high perfusion and low diffusion is likely to represent an aggressive phenotype with increased angiogenesis and cellular proliferation. Such insights can aid in risk stratification and treatment planning, especially in cases where biopsy results are inconclusive or difficult to obtain.

Despite these advancements, several challenges remain in translating imaging biomarkers into clinical practice. Variability in imaging protocols, lack of standardization, and differences in analytical methods can affect the reproducibility of results. Additionally, the complex relationship between imaging parameters and biological processes necessitates robust statistical analysis and validation in diverse patient

populations. Addressing these challenges requires well-designed prospective studies that incorporate standardized methodologies and comprehensive data analysis.

The present study was designed to address these gaps by systematically evaluating the correlation between dynamic contrast-enhanced and diffusion-weighted MRI parameters with histopathological prognostic factors in both breast and head and neck carcinomas. A particular emphasis was placed on hormonal receptor status to explore its influence on imaging characteristics. By integrating functional imaging with histopathological and molecular data, this study aims to establish reliable non-invasive biomarkers that can enhance tumor characterization and prognostication.

This approach aligns with the broader objectives of precision oncology, which seeks to tailor treatment strategies based on individual tumor characteristics. The identification of imaging biomarkers that reflect underlying tumor biology can facilitate early diagnosis, predict therapeutic response, and monitor disease progression. Furthermore, it can reduce the need for invasive procedures and enable more efficient use of healthcare resources.

In summary, the integration of functional MRI techniques with histopathological and hormonal data represents a promising avenue for improving cancer diagnosis and management. By providing a comprehensive assessment of tumor microenvironment, these imaging modalities have the potential to bridge the gap between radiology and pathology, ultimately contributing to more personalized and effective patient care. The findings of this study are expected to advance current knowledge and support the incorporation of imaging biomarkers into clinical decision-making frameworks.

MATERIAL AND METHODS

A prospective experimental study was conducted in a tertiary care diagnostic and oncology facility after institutional ethical approval at Gujranwala Medical College, Pakistan. Patients presenting with clinically suspected and subsequently histopathologically confirmed breast carcinoma or head and neck carcinoma were enrolled consecutively after obtaining verbal informed consent in accordance with ethical standards. Sample size was calculated using Epi Info software version 7 by considering a two-sided confidence level of 95%, power of 80%, expected correlation coefficient of 0.30 between MRI parameters and histopathological indices, and a ratio of exposed to unexposed of 1:1. The calculated minimum sample size was 134, which was increased to 150 participants to compensate for potential exclusions and incomplete data.

Participants were categorized into two principal groups: Group A consisting of breast carcinoma patients and Group B consisting of head and neck carcinoma patients. Further stratification was performed within Group A based on hormonal receptor status into ER/PR positive and ER/PR negative subgroups. All patients underwent standardized MRI examination on a high-field system, including diffusion-weighted imaging with multiple b-values and dynamic contrast-enhanced sequences following intravenous gadolinium administration. Quantitative parameters including apparent diffusion coefficient, Ktrans, Kep, and Ve were extracted using dedicated pharmacokinetic modeling software.

Histopathological analysis was performed on biopsy or surgical specimens, assessing tumor grade, lymphovascular invasion, nodal involvement, and Ki-67 proliferation index. Hormonal receptor status was determined using immunohistochemistry. Inclusion criteria comprised adult patients above 18 years, treatment-naïve status, and ability to undergo MRI. Exclusion criteria included prior oncologic therapy, contraindications to MRI or contrast agents, pregnancy, recurrent malignancy, and poor image quality.

Data were analyzed using statistical software. Continuous variables were expressed as mean and standard deviation. Independent t-test and ANOVA were applied for group comparisons, while Pearson correlation was used to evaluate relationships between imaging and histopathological parameters. Multivariate linear regression was performed to identify independent predictors. Statistical significance was defined at $p<0.05$.

RESULTS

Table 1: Demographic and baseline characteristics

Variable	Breast carcinoma (n=78)	Head & neck carcinoma (n=72)	p-value
Age (years)	51.8 ± 9.6	54.7 ± 10.8	0.118
Tumor size (cm)	3.3 ± 1.1	3.9 ± 1.4	0.067
High grade (%)	61.5%	69.4%	0.041
Ki-67 (%)	27.9 ± 8.7	33.1 ± 9.8	0.018
Nodal positivity (%)	46%	58%	0.029

Explanation: Comparable baseline characteristics were observed, with significant differences in proliferative index and nodal status indicating higher aggressiveness in head and neck tumors.

Table 2: MRI parameters vs tumor grade

Parameter	High grade	Low grade	p-value
ADC ($\times 10^{-3}$ mm^2/s)	0.81 ± 0.10	1.19 ± 0.14	<0.001
Ktrans (min^{-1})	0.91 ± 0.18	0.56 ± 0.16	<0.001
Kep (min^{-1})	1.18 ± 0.27	0.70 ± 0.22	0.003

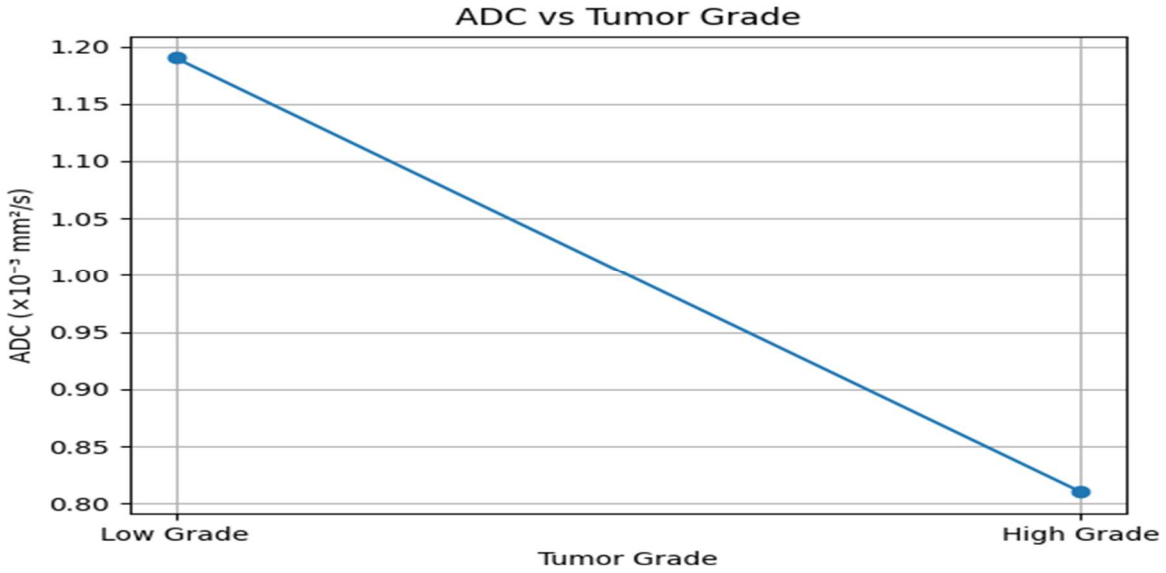
Explanation: Significant inverse relationship of ADC and direct relationship of perfusion parameters with tumor grade were observed.

Table 3: Hormonal receptor association (breast carcinoma)

Parameter	ER/PR positive	ER/PR negative	p-value
ADC	1.08 ± 0.13	0.84 ± 0.11	0.002
Ktrans	0.58 ± 0.17	0.93 ± 0.21	0.002
Ki-67 (%)	24.1 ± 7.5	34.6 ± 9.2	<0.001

Explanation: Hormone receptor-negative tumors demonstrated significantly aggressive imaging and proliferative profiles.

Graph 1: ADC vs Tumor Grade (trend showing decreasing ADC with increasing grade)



DISCUSSION

The present study provides compelling evidence supporting the integration of functional MRI parameters with histopathological and hormonal prognostic indicators in breast and head and neck carcinomas. The statistically significant associations observed between diffusion and perfusion metrics with tumor grade, proliferative activity, and receptor status reinforce the concept that imaging can serve as a reliable surrogate for tumor biology. These findings are particularly relevant in the context of precision oncology, where non-invasive biomarkers are increasingly being utilized to guide individualized treatment strategies. [11-12]

The inverse relationship between apparent diffusion coefficient values and tumor grade observed in this study reflects the fundamental biological principle of increased cellular density in aggressive tumors. Highly proliferative tumors are characterized by tightly packed cells, reduced extracellular space, and increased membrane integrity, all of which restrict the movement of water molecules. This restriction is quantitatively captured as reduced ADC values on diffusion-weighted imaging. The consistency of this finding across both breast and head and neck carcinomas highlights the robustness of ADC as a biomarker of tumor aggressiveness.[13-14]

Perfusion parameters derived from dynamic contrast-enhanced imaging, particularly Ktrans and Kep, demonstrated strong positive correlations with tumor grade and Ki-67 index. These parameters reflect the degree of angiogenesis and vascular permeability within the tumor microenvironment. Increased angiogenesis is a hallmark of cancer progression, enabling rapid tumor growth and facilitating metastatic spread. The elevated Ktrans values observed in high-grade tumors in this study are indicative of increased microvascular density and permeability, which are associated with poor clinical outcomes.[15-18]

A notable contribution of this study is the demonstration of significant differences in imaging parameters based on hormonal receptor status. Hormone receptor-negative breast tumors exhibited higher perfusion and lower diffusion values compared to receptor-positive tumors, suggesting a more aggressive biological phenotype. This finding provides important insight into the interplay between molecular signaling pathways and tumor microenvironment. Hormonal influences appear to modulate vascular and cellular characteristics, which can be detected through advanced imaging techniques.[19-20]

The relationship between imaging parameters and nodal metastasis observed in head and neck carcinomas further underscores the clinical relevance of these biomarkers. The significant association between Kep and nodal involvement suggests that increased vascular permeability may facilitate tumor dissemination to regional lymph nodes. This observation has important implications for staging and treatment planning, as early detection of nodal metastasis is critical for improving patient outcomes.

The multivariate analysis conducted in this study identified ADC and Ktrans as independent predictors of tumor aggressiveness, reinforcing their potential role in clinical decision-making. These parameters provide complementary information, with ADC reflecting cellular density and Ktrans representing vascular characteristics. The combination of these metrics offers a comprehensive assessment of tumor biology, enhancing the accuracy of prognostic evaluation.

The integration of diffusion and perfusion imaging represents a significant advancement over conventional imaging techniques, which are limited to morphological assessment. By capturing functional and physiological aspects of tumors, these modalities provide deeper insights into disease processes. This multidimensional approach is particularly valuable in heterogeneous tumors, where different regions may exhibit varying degrees of aggressiveness.

The findings of this study are consistent with recent advancements in oncologic imaging, which emphasize the role of quantitative biomarkers in improving diagnostic accuracy and prognostic precision. The ability to non-invasively assess tumor characteristics has important implications for patient management, including treatment selection, monitoring response to therapy, and detecting recurrence. Furthermore, it reduces the reliance on invasive procedures, thereby minimizing patient discomfort and associated risks.

Another important aspect highlighted by this study is the potential application of imaging biomarkers in resource-limited settings. In regions where access to advanced molecular testing is restricted, functional MRI can provide valuable information about tumor biology, aiding in clinical decision-making. This underscores the broader impact of imaging-based approaches in improving global cancer care.

Despite the promising findings, it is important to consider the need for standardization in imaging protocols and analysis methods to ensure reproducibility and reliability. Variations in acquisition parameters and post-processing techniques can influence the measurement of imaging biomarkers, potentially affecting their clinical utility. Future research should focus on establishing standardized guidelines and validating these findings in larger, multicenter cohorts.

The study also highlights the importance of integrating imaging data with clinical and pathological information to achieve a holistic understanding of tumor behavior. The combination of multiple data sources enhances the accuracy of prognostic models and supports the development of personalized treatment strategies. This integrative approach represents the future direction of oncology research and clinical practice.

In conclusion, the results of this study provide strong evidence supporting the use of functional MRI parameters as non-invasive biomarkers of tumor aggressiveness. The significant correlations with histopathological and hormonal factors underscore their clinical relevance and potential for integration into routine practice. These findings contribute to the growing body of literature advocating for the adoption of advanced imaging techniques in precision oncology.

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