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DETECTION OF NODAL METASTASIS IN BREAST CANCER PATIENTS: ROLE OF APPARENT DIFFUSION COEFFICIENT RATIO BETWEEN AXILLARY LYMPH NODE AND PRIMARY TUMOR

Original Research

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ABSTRACT

Background: Breast cancer is the leading type of cancer affecting women across the world thus there is a need to have accurate and efficient diagnostic and staging tools. The present investigation aimed to evaluate the diagnostic performance of the ADC ratio of the axillary Lymph nodes and primary breast tumors for nodal metastasis prediction in breast cancer.

Objective: The objective of the study was to evaluate the diagnostic accuracy of the ADC ratio in detecting nodal metastasis in breast cancer patients using MRI.

Methods: This case-control study was performed in the radiology department of Combined Military Hospital, Rawalpindi Pakistan. The study involved 66 women who were above 18 years of age with primary breast cancer, planned for surgical treatment, and who had preoperative. MRI exams and ADC measurements of breast cancer patients were analyzed by three senior radiologists to evaluate the ability of the ADC ratio in nodal metastasis detection. The data analysis for this study was conducted in Statistical Package for Social Sciences (SPSS) version 26.

Results: The Mean ADC and ADC ratios both were significantly lower in Metastatic axillary Lymph Nodes as compared to Benign lymph nodules. The result of the analysis indicated that there are differences that are statistically significant ($P<0.05$). Moreover sensitivity, specificity, PPV and NPV at the cut of the value of 1.04 were 89. 87%, 83. 11%, 80. 76%, and 79. 90%, respectively.

Conclusions: The study findings indicate that the ADC ratio is a reliable and accurate biomarker for identifying metastatic axillary lymph nodes in breast cancer patients, providing a non-invasive diagnostic alternative with high sensitivity and specificity.

Keywords: Apparent Diffusion Coefficient, Axillary Lymph Node, Breast Cancer Diagnosis, Diagnostic Imaging, MRI, Nodal Metastasis, Non-Invasive Diagnosis, Oncology, Radiology, Sensitivity and Specificity, Tumor Staging, Women’s Health.

INTRODUCTION

Breast cancer is the most common malignancy in women worldwide, as reported by the American Cancer Society (ACS). Consequently, it is imperative to employ precise and effective diagnostic and staging methods (1). The primary cause of elevated mortality rates in breast cancer patients is Axillary Lymph Node (ALN) metastases (2), which significantly impact prognosis. Research has shown that ALNs are the initial site of metastasis outside of the breast in up to 50% of early-stage breast cancer patients (3,4). Axillary lymph node metastases are one of the most significant indicators of breast cancer prognosis, with studies consistently demonstrating that patients with ALN involvement have a 40-50% lower survival rate compared to those without nodal involvement (5). Consequently, it is crucial to identify axillary metastases in newly diagnosed breast cancer to stage the disease and to devise additional treatment (5-8). There is still a significant amount of work to be done to enhance the diagnosis of malignant and benign nodes without the necessity of conducting a biopsy (9,10).

The sentinel lymph node biopsy (SLNB) (11), which is currently routinely performed and is considered the gold standard for evaluating nodal metastasis during conventional surgery, is frequently followed by axillary dissection. Nevertheless, dissection may reveal that up to 70% of individuals who do not exhibit signs of cancer spreading to other parts of the body may not have cancerous axillary nodes, indicating a significant number of patients undergo an invasive procedure without therapeutic benefit. Additionally, this procedure may result in complications such as seroma, infection, lymphedema, or arm pain (12,13,14). These potential adverse effects highlight the need for non-invasive diagnostic alternatives.

Histopathological examination, though confirmatory, is by itself invasive and comes with the same risks and complications. Therefore, the imaging techniques that can diagnose nodal metastasis without biopsy are useful. MRI is increasingly utilized in the diagnosis of nodal metastasis, and Apparent diffusion coefficient (ADC) and non-contrast enhanced DWI are particularly promising in this regard (15). ADC between the primary breast malignancy and the ALNs is considered as a possible marker for the diagnosis of metastasis ALNs. The ADC ratio may be beneficial in increasing the accuracy of measurements, improving the detection of nodal metastases and thus reducing the morbidity related to it (16). This approach could lead to great advancements in breast cancer staging and treatment, an invasive, safer, and more friendly for patients. Therefore, the present research aimed to evaluate the ADC ratio between ALNs and primary tumors for the diagnosis of nodal metastasis in patients with breast cancer.

METHODS

A Case-control study was carried out in the Radiology department of Combined Military Hospital, Rawalpindi. The study was carried out in a period of 1.5 years from Jan 2023 to June 2024. The study sample consisted of adult women who had histopathological confirmed primary breast cancer and were scheduled for surgical therapy. The eligibility criteria consisted of histopathological confirmed breast cancer. A preoperative MRI with diffusion-weighted imaging (DWI), and signed informed consent to participate in the study. We excluded patients who had previously undergone therapy for breast cancer or who had experienced a recurrence of breast cancer. Patients having contraindications for MRI, such as pacemakers or acute claustrophobia were excluded. We also excluded patients from the final analysis, who did not have comprehensive imaging and/or histological reports. The sample size for this unmatched case-control study was determined using the following parameters: using the control group and case group with 1:1, 95% confidence level, and the power of 80%, with 0% exposure among control and 24.5% exposure among breast cancer cases as reported by the incidence of sentinel lymph node metastasis in a local study (17). About the sample size, a Continuity Correction was made to the Kelsey's, Fleiss', and Fleiss' sample sizes whereby they were forecasted to be 56, 52, and 66, respectively. Calculated at the most conservative level of power and confidence, the required sample size amounted to 66 participants: 33 cases and 33 controls.

We employed a purposive sampling technique to recruit patients for this study. Patients referred to the OPD and Radiology department were selected for inclusion. Participants were enrolled from the oncology and surgery wards of our hospital, as well as from affiliated clinics and other referral hospitals. Potential participants were informed of the study objectives and procedures that would be followed before they agreed to participate in the study. Informed consent was obtained. To ensure the privacy of the data collected, measures of data security were upheld throughout the research process. The cases were defined as patients with histopathological evidence of cancer post-biopsy and the controls were those who did not have the evidence. These patients were diagnosed using MRI scans prior to surgery, and formal histopathological examination of the lymph nodes. The controls were breast cancer patients with non-metastatic axillary lymph nodes confirmed with histopathological examination. As in the cases, these patients had also had preoperative MRI of the breast and axilla, surgical removal of the axillary nodes, and histopathological assessment of the nodes for metastasis.

All patients underwent magnetic resonance imaging (MRI) using a 3 Tesla (3T) MRI scanner (Siemens Healthcare, Erlangen, Germany) equipped with a dedicated breast coil, ensuring high-resolution imaging in the prone position. The imaging protocol included several sequences. First, T2-weighted rapid spin-echo sequences were acquired for anatomical visualization of the breast tissue and axillary lymph nodes, which were essential for identifying the morphology and structural characteristics of both the tumor and lymph nodes. Next, conventional T1-weighted spin-echo sequences were obtained pre-contrast to provide baseline anatomical assessment and tissue differentiation. Diffusion-weighted imaging (DWI) was then performed using echo-planar imaging (EPI) sequences with multiple b-values (0, 500, and 1000 s/mm²) to assess the diffusion properties of the breast lesions and axillary lymph nodes. Apparent diffusion coefficient (ADC) maps were generated, and the ADC values of both the primary tumor and the largest visible axillary lymph node were calculated. The ADC ratio between the lymph node and the tumor (ADCLN/ADCT) was computed to evaluate its diagnostic potential for nodal metastasis. Finally, dynamic contrast-enhanced MRI (DCE-MRI) was performed using a fat-suppressed T1-weighted fast gradient-echo sequence following the intravenous administration of a gadolinium-based contrast agent (0.1 mmol/kg body weight) with a saline flush. Dynamic images were captured at multiple time points to assess the enhancement patterns in both the primary tumor and axillary lymph nodes, which facilitated the identification of potential metastatic involvement.

Blinded to the histopathological findings, three consultant radiologists evaluated the MRIs of the breasts separately. The radiologists worked together to examine the DWI images and identify the lymph node that stood out the most as potentially problematic. They meticulously avoided the fatty hilum when they manually drew the Regions of interest (ROIs) for ADC measurement on the biggest and most noticeable ALN. The purpose of this research was to find out how well the ADC ratio detects nodal metastases in breast cancer patients by carefully examining these factors. All MRI reports and images were obtained and analyzed within three months of the MRI scans, ensuring timely and accurate data collection. The final assessment of each lymph node was decided by consensus between the three radiologists, ensuring that the evaluations were thorough and consistent. The study protocol was reviewed and approved by the research and ethical committee of the Combined Military Hospital. Informed consent was obtained prior to participant's recruitment and confidentiality was maintained throughout the study.

RESULTS

The results of the study demonstrated significant differences between metastatic and benign axillary lymph nodes (ALNs) in breast cancer patients. Demographic and clinical characteristics such as age, BMI, tumor size, menopausal status, family history, and PR status showed no statistically significant differences between groups. However, cancer staging revealed a significant difference in Stage I distribution, with 9.1% of metastatic ALN cases compared to 30.3% of benign ALN controls (p = 0.02), while no significant differences were found in Stages II and III. Analysis of the mean apparent diffusion coefficient (ADC) values and ADC ratios also indicated significant disparities; metastatic ALNs had lower ADC values (0.787 ± 0.145) compared to benign ALNs (1.152 ± 0.258, p = 0.03) and a lower ADC ratio (0.986 ± 0.17 vs. 1.475 ± 0.417, p = 0.04). The ROC curve analysis highlighted that the ADC ratio demonstrated better diagnostic efficacy (AUC = 0.884) than the ADC value alone (AUC = 0.844), with high sensitivity (89.87%) and specificity (83.11%) at the cut-off value of 1.04.

Table 1 Comparison of demographic and clinical characteristics between groups

Variables	Cases (Malignant ALN) N=33	Controls (Benign ALN) N=33	P value
Age (mean ± SD)	55.3 ± 10.4	52.8 ± 11.2	0.345
BMI (mean ± SD)	27.5 ± 4.8	26.7 ± 5.2	0.577
Tumor size (cm, mean ± SD)	3.4 ± 1.2	2.9 ± 1.1	0.126
Menopausal status n (%)			

Pre-menopausal	12 (36.4%)	15 (45.5%)	0.592
Post-menopausal	21 (63.6%)	18 (54.5%)	0.592
Family history n (%)			
Yes	8 (24.2%)	6 (18.2%)	0.554
No	25 (75.8%)	27 (81.8%)	
PR status n (%)			
Positive	18 (54.5%)	19 (57.6%)	0.823
Negative	15 (45.5%)	14 (42.4%)	

The study compared 33 cases with malignant axillary lymph nodes (ALN) to 33 controls with benign ALN, with an emphasis on a variety of sociodemographic and clinical characteristics. The mean age of cases was 55.3 years, while the mean age of controls was 52.8 years (p = 0.345). Additionally, the mean BMI of cases was 27.5, while it was 26.7 for controls (p = 0.577). The average tumor size for cases was 3.4 cm, while it was 2.9 cm for controls (p = 0.126). In contrast to the 45.5% and 54.5% of controls, 36.4% of cases were pre-menopausal and 63.6% were post-menopausal (p = 0.592). Family history was present in 24.2% of cases and 18.2% of controls (p = 0.554). PR-positive status was detected in 54.5% of cases and 57.6% of controls (p = 0.823).

Table 2 Distributions of primary breast cancer types among groups

Subtypes	Cases n = 33	Controls n = 33	P value
Invasive carcinoma	29 (87.9%)	30 (90.9%)	0.746
Invasive lobular carcinoma	2 (6.1%)	1 (3.0%)	0.558
Mixed invasive carcinoma	2 (6.1%)	1 (3.0%)	0.558

Metastatic ALN patients and benign ALN controls were compared concerning the distribution of primary breast cancer subtypes. Invasive carcinoma was present in 90.9% of the control group and absent in 87.9% of the patients (p = 0.746). With a p-value of 0.558, the frequency of invasive lobular carcinoma was 3.0% in controls and 6.1% in cases. With a p-value of 0.558, the frequency of mixed invasive carcinoma was 3.0% in controls and 6.1% in cases.

Table 3 Cancer stage distribution among our study sample

Stage	Cases (Metastatic ALN) n = 33	Controls (Benign ALN) n = 33	P value
Stage I	3 (9.1%)	10 (30.3%)	0.02*
Stage II	13 (39.4%)	12 (36.4%)	0.14
Stage III	15 (45.5%)	9 (27.3%)	0.90
Not staged	2 (6.1%)	2 (6.1%)	1.000

The cancer stages of patients with metastatic ALN and controls with benign ALN exhibited substantial differences. The categories of cases and controls exhibited a significant disparity during Stage I. In particular, 9.1% of cases and 30.3% of controls were identified. This discrepancy was statistically significant, with a p-value of 0.02. Throughout Stage II, no statistically significant disparity was observed between the two groups. The percentages of cases and controls were 39.4% and 36.4%, respectively (p = 0.14). There was no statistically significant difference (p = 0.90) in the percentage of cases (45.5%) and controls (27.3%) classified as Stage III. The p-value was 1.000, and the percentage of individuals who were not staged was 6.1% in both categories.

Table 4 Mean ADC and ADC ratios of the metastatic ALNs and Benign ALNs

Parameter	Metastatic ALN (n = 33)	Benign ALN (n = 33)	P value
Mean ADC (×10-3 mm2/s)	0.787 ± 0.145	1.152 ± 0.258	0.03*
ADC ratio (×10-3 mm2/s)	0.986 ± 0.17	1.475 ± 0.417	0.04*

When comparing the apparent diffusion coefficient (ADC) values of metastatic axillary lymph nodes compared to benign ALNs, there was a notable difference ($p = 0.03$), as shown in Table 4. A significant difference ($p = 0.04$) was shown by the ADC ratios of benign ALNs (1.475 ± 0.417) and metastatic ALNs (0.986 ± 0.17).

A sensitivity of 89.87%, specificity of 83.11%, PPV of 80.76%, and NPV of 79.90% were obtained at the cut-off value of 1.04. The utilization of ADC and ADC ratios may facilitate the differentiation between metastatic ALN and benign ALN in breast cancer patients, as demonstrated by the ROC curve analysis. The ADC ratio's diagnostic efficacy is somewhat superior to that of the ADC value, as evidenced by its higher AUC of 0.884 in comparison to the ADC value's AUC of 0.844. The ROC curve for ADC and ADC ratio is illustrated in Figure 1.

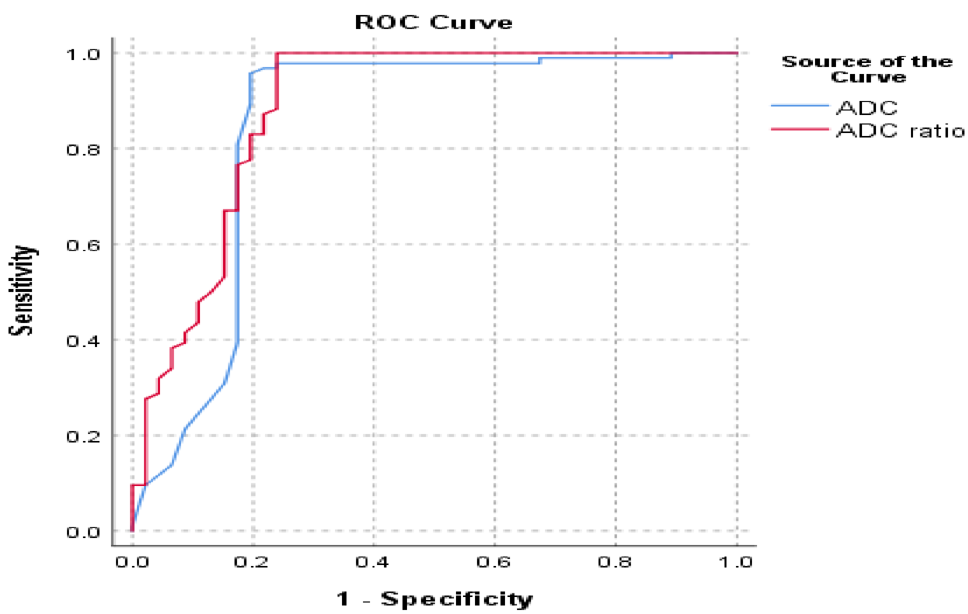

Figure 1 ROC curves for ADC and ADC ratio

DISCUSSIONS

The purpose of our research was to assess the effectiveness of the ADC ratio, namely between axillary lymph nodes and main tumors, in diagnosing nodal metastases in breast cancer. The findings of our study revealed substantial disparities between the two ratios. Specifically, the average ADC value of metastatic axillary lymph nodes (ALNs) was found to be lower compared to that of benign ALNs. Differentiating between benign and malignant breast lesions relies heavily on the ADC value. However, debate persists over the relevance and practicality of ALNs' DWI and ADC values. Studies back up the idea that breast cancer has a lower average apparent diffusion coefficient (ADC) than healthy breast tissue (18, 19, 20). Like tumour stage, metastatic axillary lymph nodes (ALNs) have apparent diffusion coefficient (ADC) values that are positively correlated with it. As previously reported in similar experiments (18, 21, 22), the average ADC of metastatic ALNs varied from "0.78 × 10−3 mm2/s to 1.5× 10−3 mm2/s". Past research has shown that the threshold values vary between 1 and 0.889 × 10−3 mm²/s. The specificity and sensitivity of these indices' censoring cut points varied from 70% to 94.7% and 75.8% to 94.8%, respectively. Percentages ranged from 1% to 93% in several studies (18,19,20,21,22). The average ADC of metastatic ALNs was found to be 0.787 × 10−3 mm2/s in our study, which agrees with the findings of other researches (22,23,24,25). The findings were consistent and expected, since the mean ADC of benign axillary lymph nodes (ALNs) was in line with values from 1.551 103 mm2/s to 1.043 103 mm2/s in prior research. "

To further assess its diagnostic efficacy, the ADC ratio was tested for sensitivity and specificity using a cut-off value of 1.04. The AUC for ADC was 0.884 according to the ROC analysis. It seems that the ADC ratio is more diagnostically significant in differentiating between benign and metastatic axillary lymph nodes (ALNs) since its Area Under the Curve (AUC) is bigger than that of the mean ADC. Cho et al. (18) and Lu et al. (19) have also found something similar. The diagnostic parameters, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), obtained in our investigation were consistent with the findings of earlier studies (18,19,20,21,22).

CONCLUSIONS

According to the results of the study, the ADC value of metastatic ALN was significantly lower than that of benign ALN in patients with breast cancer. The ADC ratio, which was established from the comparison of the axillary lymph nodes and breast lesions, was less in metastatic lymph nodes than in benign lymph nodes ($P < 0.05$). Thus, our findings indicate that the ADC ratio could be a reliable and accurate biomarker for the identification of metastatic axillary lymph nodes in breast cancer patients.

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