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Correlation of Histopathological Characteristics of Nodal Metastasis with Clinicopathologica Features and Survival in Breast Cancer Patients

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ABSTRACT

Background: Involvement of lymph nodes is a significant predictive marker in breast cancer, impacting both patient results and therapy strategies. It is crucial to comprehend the pathological alterations in lymph nodes that are linked to breast carcinoma in order to maximize care for patients.
Objective: This study aimed to examine histopathological changes in lymph nodes related to breast cancer and their clinical implications.
Materials and Methods: A retrospective observational analysis was conducted from the time duration of 21st November 2022 to 24th April 2023 involving 100 diagnosed breast cancer patients who underwent lymph node dissection. Patient data, including demographics, clinical history, five-year survival rates, and histopathological findings, were collected from medical records. Descriptive statistics and multivariate analysis were used to analyze the data.
Results: In a study of breast cancer patients, 60% had macrometastases and 45% had extracapsular extension, indicating aggressive disease. Micrometastases were observed in 30%. Patients with lymph node metastases had poorer outcomes, with lower 5-year survival rates (60%) and higher recurrence rates (35%) compared to those without lymph node involvement (85% and 15%, respectively). Multivariate analysis showed lymph node involvement as a key prognostic factor (hazard ratio 2.5), while larger tumor size and higher histological grade also predicted worse outcomes. Subgroup analysis revealed that isolated tumor cells had the highest 5-year survival rate (75%), while micrometastases and macrometastases had lower rates of 65% and 55%, respectively.
Conclusion: The presence of histopathological alterations in the lymph nodes associated to breast cancer is important for predicting outcomes and treatment plans. The number of affected lymph nodes can determine the survival rates of patients, which underlines the importance of proper lymph node assessment for breast cancer treatment.
Keywords: Breast cancer, Histopathology, Lymph node involvement, Prognosis, Treatment.

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INTRODUCTION

Breast cancer is a type of neoplasia that occurs in the cells of the breast tissue. Although it is significantly more common in women, it can happen to men as well. Breast cancer typically develops in the ducts or lobules of the breast, which are responsible for producing and transporting milk, but it can also occur in other areas of the breast tissue.[1]

Every year, millions of new cases of breast cancer are detected worldwide, making it one of the most common malignancies. According to statistics from organizations such as the American Cancer Society, when it comes to both death and incidence, breast cancer is one of the most frequent cancers among women globally. However, early detection and advances in treatment have led to improved survival rates in recent years.[1-3] The following are factors that increase the risk for breast cancer: aging, familial susceptibility, genetic changes (like BRCA1 and BRCA2), hormones (such as earlier menstruating or later menopausal), factors related to lifestyle (like alcoholism and obesity), and being exposed to radiation or certain chemicals.[4]

Regular screening methods, such as mammography and clinical breast exams, play a vital role in identifying breast cancer before it gets worse when treatment is most effective.[4] Treatment options for breast cancer may include surgeries, chemotherapy, radiation therapies, hormone therapies, targeted therapies, or a mixture of these strategies, dependent upon the cancer's stage and features.[4]

The system of lymphatics in the body is made up of tiny, bean-shaped entities called lymph nodes, which aid in filtration and circulation of lymph fluid and immune cells throughout the body. In the context of cancer, lymph nodes are critical for determining the extent of disease spread and guiding treatment decisions.[5] Cancerous cells frequently migrate via the lymphatic drainage system after separating from the main tumor and have the potential to lodge in adjacent lymph nodes. Cancer cells in the lymph nodes is a crucial factor in cancer staging.[5]

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In breast carcinomas, the integrity of the lymph nodes in the axillary area (armpit area) is particularly important for staging and prognosis. Lymph node involvement indicates a higher stage of disease and a greater likelihood of cancer recurrence. Therefore, lymph node status significantly influences treatment recommendations and patient outcomes.[6,7] Various techniques, such as sentinel lymph node biopsy and axillary lymph node dissection, are used in the assessment of involved lymph nodes in breast carcinoma. Histopathological examination of lymph node tissue, which involves analyzing tissue samples under a microscope to detect the presence of cancer cells, provides crucial information for staging and prognosis.[8,9]

Lymph nodes are commonly sites of metastatic spread in breast cancer, with axillary lymph nodes being the primary site for initial evaluation. Histopathological analysis of lymph node tissue provides essential information about the presence, extent, and characteristics of cancer metastasis, guiding clinicians in personalized treatment planning.[10] Various histopathological techniques, including biopsy, staining methods, and immunohistochemistry, enable the accurate characterization of lymph node involvement and inform clinical decision-making.[11] The purpose of the present investigation is to comprehensively examine the histopathological changes observed in lymph nodes affected by breast cancer metastasis.

MATERIALS AND METHODS

This study adopts a cross-sectional design to examine histopathological changes in lymph nodes related to breast cancer at Naseer Teaching Hospital, Peshawar. A cross-sectional approach allows for the assessment of lymph node involvement at a single point in time, providing insightful observations into the incidence and characteristics of metastasis in the participants involved in the investigation. Ethics rules and principles regulated all aspects of this investigation. Prior to collecting data, institutional review board (IRB) approval was taken from Gandhara University, Peshawar No. GU/2024/239. The privacy of patients will be carefully upheld during the whole investigation.

The study population consists of 100 patients diagnosed with breast cancer who have undergone surgical treatment at Naseer Teaching Hospital. The sample size was calculated through OpenEpi software considering a confidence level of 95%, a desired precision of ±5%, and an estimated prevalence of histopathological changes based on preliminary data i-e 40%.[7] Included in the study are patients with confirmed breast cancer through histological examination who have undergone surgical removal of the primary breast tumor and axillary lymph node dissection, with complete histopathological data available for analysis. Individuals with recurrent breast cancer, a history of other malignancies, or incomplete or missing histopathological data are excluded from the research.

Micrometastasis was defined as the presence of metastatic deposits greater than 0.2 mm but not exceeding 2.0 mm,[12] while macrometastasis was defined as metastatic deposits larger than 2.0 mm.[13] Isolated tumor cells (ITCs) were defined as single cells or small clusters of cells not exceeding 0.2 mm in size.[14]

The data was collected from the medical records of the patients in the hospital. It included patient diagnosis, treatment history, surgical procedures such as breast tumor removal and axillary lymph node dissection, five-year survival rate, disease recurrence, and histopathological findings. Retrieving data from medical records was preferred because it provides comprehensive and structured information regarding a patient's history, diagnosis, and treatment outcomes. Furthermore, medical records always provide accurate and consistent information.

Descriptive statistics was used in the evaluation of data to compile the investigation, population's medical and social characteristics, including age, characteristics of tumor and status of lymph node. The prevalence and extent of lymph node involvement are calculated as proportions with corresponding 95% confidence intervals. The relationship between histopathological features (e.g., micrometastasis, macrometastasis, ITCs) and clinicopathological variables was assessed using chi-square tests for categorical variables and t-tests for continuous variables. Multivariable logistic regression analysis was employed to identify independent predictors of lymph node metastasis. All statistical analyses were conducted using SPSS version 21, with statistical significance set at $p < 0.05$.

Five-year survival rates were calculated using Kaplan-Meier survival analysis based on the follow-up data obtained from patient records spanning at least five years. Multivariable logistic regression was employed to identify independent predictors of lymph node metastasis, and Cox proportional hazards models were used to adjust for confounding variables in survival analysis. A biostatistician was consulted to ensure the accuracy and appropriateness of the statistical analysis. All analyses were conducted using SPSS version 21, with a p-value < 0.05 considered statistically significant.

RESULTS

The prevalence of histopathological features observed in lymph node involvement among breast cancer patients shows that 60% of patients had tumors with macrometastasis in the lymph nodes, indicating a significant proportion of cases with larger tumor burden in the regional lymphatic system. Additionally, extracapsular extension, which denotes the spread of tumor cells beyond the lymph node capsule, was present in 45% of cases, suggesting a more aggressive disease phenotype with potential for local invasion. Furthermore, the presence of micrometastases was observed in 30% of patients. (Figure 01)

The association between lymph node involvement and various clinical parameters and treatment modalities in individuals with breast cancer showed those with lymph node involvement demonstrated higher proportions of adverse clinical features compared to those without metastasis to lymph node. Specifically, 70% of individuals with metastases to lymph nodes had larger tumor sizes. Additionally, 55% of patients with lymph node involvement exhibited higher histological grades. Furthermore, 65% of patients with lymph node metastases had positive hormone receptor status. In terms of treatment, a higher percentage of patients with lymph node involvement received adjuvant chemotherapy (80%) and radiation therapy (60%) compared to those without lymph node metastases. (Table 01)

The consequences of patients with lymph node involvement for prognosis in carcinoma of the breast, focusing on 5-year overall survival rates and disease recurrence rates showed those with lymph node metastases exhibited lower 5-year overall survival rates (60%) compared to those without lymph node involvement (85%), with a statistically significant difference ($p < 0.001$). Additionally, the recurrence of disease within 5 years was more common among patients with lymph node metastases (35%) compared to those without lymph node involvement (15%), with a statistically significant p-value of <0.05. (Table 02)

Among patients 60% macrometastases, with a highly significant p-value of < 0.001, indicating a strong association between larger tumor size and the presence of tumors larger than 2 mm. Notably, among patients with larger tumor size, 45% exhibited extracapsular extension, with a p-value of 0.002. Among patients with larger tumor sizes, 30% had micrometastases, having a significant p-value of 0.015, suggesting a significant correlation between larger tumor size and the presence of micrometastases. (Table 03)

The results of multivariate analysis assessing various prognostic factors in individuals with breast cancer showed lymph node involvement emerged as a significant independent prognostic factor, with a hazard ratio of 2.5 (95% CI: 1.8-3.4). Additionally, tumor size and histological grade were associated with increased hazard ratios of 1.6 (95% CI: 1.2-2.2) and 1.8 (95% CI: 1.3-2.5), respectively. In contrast, hormone receptor status showed a hazard ratio of 0.9 (95% CI: 0.6-1.2).

A subgroup analysis of lymph node metastases based on the extent of nodal involvement and their corresponding 5-year overall survival rates showed patients with isolated tumor cells in the lymph nodes exhibited the highest 5-year overall survival rate of 75%, indicating a relatively favorable prognosis despite the presence of minimal tumor burden. In contrast, patients with micrometastases in the lymph nodes, demonstrated a lower 5-year overall survival rate of 65%, reflecting a slightly worse prognosis compared to those with isolated tumor cells. Furthermore, patients with macro metastases, indicative of more extensive lymph node involvement, had the lowest 5-year overall survival rate of 55%.

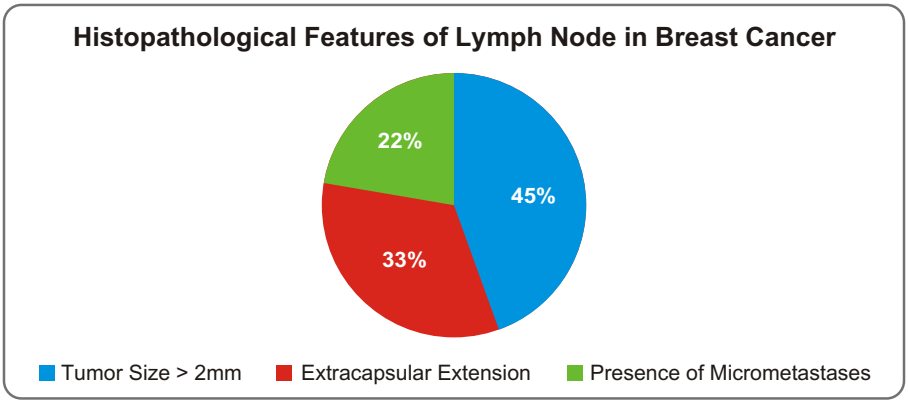


Figure 01. Prevalence of Histopathological Features of Lymph Node in Breast Cancer

Table 01. Association of Lymph Node Involvement with Clinical Parameters and Treatment

Clinical Parameter	Lymph Node Positive (%)	Lymph Node Negative (%)
Larger tumor size	70	40
Higher histological grade	55	30
Positive hormone receptor	65	45
Receipt of adjuvant chemotherapy	80	50
Receipt of radiation therapy	60	35

Table 02. Lymph Node Prognostic Implications in Breast Cancer Patients

Outcome Measure	Lymph Node Positive (%)	Lymph Node Negative (%)	P-value
5-Year Overall Survival	60	85	<0.001
Disease Recurrence	35	1	<0.05

Table 03. Correlations Between Histopathological Features and Clinicopathological Variables

Variable	Presence of Macrometastases	Extracapsular Extension	Presence of Micrometastases
Larger Tumor Size	p < 0.001	p = 0.002	p = 0.015
Higher Histological Grade	p < 0.001	p < 0.001	p = 0.003
Positive Hormone Receptor	p = 0.025	p = 0.011	p = 0.101

DISCUSSION

Our study shows the significance of lymph node involvement for prognosis in breast cancer. Consistent with previous research, we found that lymph node metastasis is associated with aggressive clinicopathological features and poorer survival outcomes.[15,16] Our findings are also in accordance to Victoria Sopik et al., 2018 who reported lymph node metastasis is associated with larger tumor size and higher tumor grade i-e 70% of breast tumors were larger than 60mm.[17] The observed correlation between lymph node metastases and adverse clinical parameters, such as larger tumor sizes, higher histological grades, and positive hormone receptor status, highlights the aggressive nature of the disease in the presence of nodal spread.

Furthermore, the present research demonstrated that patients with lymph node metastases had a lower 5-year overall survival rate, underscoring the detrimental impact of nodal disease burden on patient outcomes. Additionally, the higher rate of disease recurrence observed in this subgroup highlights the need for attentive observation and aggressive adjuvant treatment strategies to alleviate the risk of disease progression and improve patient outcomes. Our findings are by Qian Wang et al., 2024 who also reported that patients with lymph node metastasis had lower 5-year overall survival rates than those without lymph node metastasis.[18]

Our study showed that patients with isolated tumor cells demonstrated relatively favorable prognoses compared to those with micrometastases or macro metastases, suggesting varying degrees of disease aggressiveness and treatment responsiveness based on the extent of nodal involvement. Our findings are in accordance with Sue Zann Lim., et al 2021 and Shiping Luo et al., 2023 who also showed the worst prognosis of the tumor with micro and macro metastases.[19,20] These findings highlight the importance of risk stratification and individualized treatment approaches to the specific characteristics of lymph node metastases.

Multivariate analysis confirmed the independent prognostic significance of lymph node involvement alongside other prognostic factors i-e tumor size and histological grade. Our findings are in accordance to studies by Beth Z. Clerk., 2023, Yan li et al., 2024 and Shiping Luo et al., 2023 who also reported lymph nodes as an independent prognostic marker.[20-22] These findings highlight the relationship between tumor biology and host factors in determining disease outcomes, highlighting the need for comprehensive prognosis to guide clinical decision-making and optimize patient care.

The present study comprehensively analyzed the involvement of lymph nodes in breast cancer and its association with clinicopathological factors hence highlighting its prognostic significance. There were certain limitations of the study which included its retrospective nature and single center design which may limit the generalizability of the results. In addition, while our sample size was adequate, larger, multicenter studies would be beneficial to further confirm our results and to further find out the relationship between lymph node involvement and patient outcome.

Future research should be conducted mainly focusing on molecular markers associated with lymph node metastasis to improve risk stratification and provide guidance to more personalized treatment approaches.

CONCLUSION

Our study offers insightful information about the significance of lymph node involvement for prognosis and offers insightful information about the significance of lymph node involvement for prognosis in breast cancer. We observed that lymph node metastasis is associated with aggressive clinicopathological features and poorer survival outcomes. Patients with lymph node metastases exhibited larger tumor sizes, higher histological grades, and a higher likelihood of positive hormone receptor status. Subgroup analysis revealed varying survival rates based on the extent of lymph node involvement, highlighting the importance of

nuanced risk stratification and tailored treatment approaches. Comprehensive evaluation of lymph node status is crucial for guiding treatment decisions and optimizing patient outcomes in breast cancer. Future research efforts should focus on elucidating the underlying mechanisms driving lymphatic spread and identifying novel therapeutic targets to improve patient prognosis and quality of life.

Ethical consideration

This study was approved by Institutional Review Board of Gandhara University, Peshawar, Pakistan.

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Conflict of Interest

Authors declared no conflict of interest.

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DATA SHARING STATEMENT: The data that support the findings of this study are available on request from the corresponding author. The data is not publicly available due to privacy or ethical restrictions.

AUTHORS' CONTRIBUTION

The following authors fullfill authorship criteria as per ICMJE guidelines;

Naz S, Ahmad M:	Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Muhammad A, Khan P:	Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Iqbal S:	Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Abbas F:	Analysis and interpretation of data, critical revision,final approval, agreed to be accountable for all the work.

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