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Original Research Article

Correlation and Clinical Utility of Cytological and Histological Grading in Breast Cancer: A Comprehensive Analysis

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Abstract:

Background: The correlation between cytological and histological grading in breast cancer is crucial for accurate diagnosis and treatment planning. This study aims to evaluate the agreement between these grading systems across various clinical and pathological parameters.

Methods: A retrospective cohort of 195 patients diagnosed with infiltrating ductal carcinoma underwent fine-needle aspiration cytology (FNAC) and subsequent surgical biopsy. Cytological specimens were graded using the modified Bloom-Richardson system, assessing nuclear pleomorphism, tubule formation, and mitotic count. Histological grading utilized the Nottingham Histologic Score, evaluating the same parameters. Statistical analyses included Pearson correlation and Cohen's Kappa coefficient to measure agreement.

Results: Strong correlations were found between cytological and histological grading across all grades of differentiation. For well-differentiated tumors (Grade 1), cytology demonstrated a sensitivity of 90.5% (CI 77.4% - 97.3%) and specificity of 93.8% (CI 88.6% - 97.1%). Moderate to high sensitivity and specificity were observed for moderately differentiated (Grade 2) and poorly differentiated (Grade 3) tumors. The overall concordance between cytological and histological grades was supported by Pearson correlation coefficients ranging from 0.78 to 0.85 and Cohen's Kappa coefficients from 0.67 to 0.76 across different subgroups, including tumor size, menopausal status, hormone receptor status (ER and PR), HER2 status, and lymph node involvement.

Conclusion: In conclusion, our study underscores the clinical relevance of cytological grading as a reliable adjunct to histological evaluation in breast cancer management. The strong correlations observed across diverse patient profiles support its role in optimizing diagnostic workflows and treatment strategies, ultimately contributing to improved outcomes and patient care in breast cancer management.

Keywords: Breast cancer, cytological grading, histological grading, fine-needle aspiration cytology, modified Bloom-Richardson system, Nottingham Histologic Score.

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Introduction

Breast cancer stands as one of the most prevalent and concerning malignancies worldwide, with increasing incidence rates across diverse populations. The grading of breast cancer serves as a critical determinant for prognosis and treatment decisions, providing essential insights into tumor aggressiveness and patient outcomes. Historically, histological grading has been the cornerstone of assessing breast cancer, involving the evaluation of architectural patterns, nuclear pleomorphism, and mitotic activity [1,2].

Despite its established role, histological grading necessitates invasive biopsy procedures, which can be associated with patient discomfort and healthcare costs. In contrast, cytological grading, primarily conducted through fine-needle aspiration cytology (FNAC), offers a non-invasive and rapid diagnostic alternative. FNAC allows for the collection of cellular material directly from breast lesions, facilitating timely evaluation and decision-making in clinical settings [3,4]. However, the adoption of FNAC in routine clinical practice has been tempered by concerns over its accuracy and reliability compared to histological assessment. Studies examining the concordance between cytological and histological grading have reported varying degrees of correlation, often influenced by factors such as sampling variability and observer subjectivity [5,6,7]. Despite these challenges, FNAC remains a valuable tool for initial diagnosis and triaging of breast lesions, potentially obviating

the need for more invasive procedures in select cases [8].

Recent meta-analyses have highlighted the diagnostic performance of FNAC, revealing sensitivity rates ranging from 70% to 90% and specificity rates ranging from 60% to 80% in differentiating between benign and malignant breast lesions [9]. These findings underscore the evolving role of cytological grading in breast cancer management, emphasizing the need for comprehensive studies to elucidate its clinical utility and optimize diagnostic algorithms.

This study aimed to assess the correlation between cytological and histological grading in a cohort of breast cancer patients, leveraging a comprehensive dataset of FNAC and subsequent histopathological examinations. By addressing existing gaps in knowledge and evaluating predictive values, this research seeks to enhance the integration of FNAC into routine clinical practice, thereby improving diagnostic accuracy, patient care outcomes, and resource allocation.

Materials and Methods

Study Design and Patient Selection: This retrospective cohort study enrolled patients diagnosed with breast cancer (infiltrating duct carcinoma) between April 2021 and April 2024 at tertiary care centre, India. Inclusion criteria encompassed patients with available cytological grading through fine-needle aspiration cytology (FNAC) and subsequent histological grading from surgical biopsy. Exclusion criteria included incomplete records or insufficient follow-up data. Institutional Review Board (IRB) approval was obtained.

Data Collection: Clinical and pathological data were systematically extracted from electronic health records. Variables of interest included patient demographics (age, sex, menopause status), clinical characteristics (tumor size, lymph node involvement), and pathological features (histological subtype, grade). Fine-needle aspiration cytology (FNAC) was performed using a 22-gauge needle under ultrasound guidance. Multiple passes were made into the breast mass to obtain representative cellular material. Smears were immediately prepared and fixed with ethanol. These smears were then stained using the Papanicolaou (Pap) staining method.

The cytological specimens were evaluated for nuclear pleomorphism, tubule formation, and mitotic count using the modified Bloom-Richardson grading system by experienced cytotechnologists and pathologists. The grading system assigns scores based on the following criteria: nuclear pleomorphism (scored 1-3), tubule formation (scored 1-3), and mitotic count (scored 1-3 The total score, derived from these individual scores, categorizes the tumor into three grades: a total score of 3 to 5 corresponds to Grade 1, indicating well-differentiated tumor cells with lower proliferative activity; a score of 6 to 7 corresponds to Grade 2, indicating moderately differentiated tumor cells; and a score of 8 to 9 corresponds to Grade 3, indicating poorly differentiated tumor cells with higher proliferative activity and aggressive behavior [10].

Surgical biopsy specimens were obtained subsequent to confirmation of malignancy by fine-needle aspiration cytology (FNAC). Following preparation and staining with Hematoxylin and Eosin (H&E), histological sections were evaluated by pathologists. The assessment utilized the Nottingham Histologic Score, also recognized as the Elston-Ellis modification of the Bloom-Richardson grading system.

This scoring system evaluates three distinct parameters: nuclear pleomorphism, assessing the degree of variation in nuclear size and shape on a scale from 1 to 3; tubule formation, which measures the extent of glandular structure formation similarly scored from 1 to 3; and mitotic count, quantifying the number of mitotic figures observed per high-power field, also scored from 1 to 3. Each parameter is individually scored, and the cumulative sum of these scores determines the overall histological grade of the tumor. A total score ranging from 3 to 5 designates low-grade tumors characterized by well-differentiated cells, while scores of 6 to 7 indicate intermediate-grade tumors, and scores of 8 to 9 signify high-grade tumors featuring poorly differentiated cells and heightened proliferative activity [11].

Statistical Analysis: Statistical analysis was conducted using SPSS version 21.0, with categorical variables presented as frequencies and percentages, and continuous variables as means ± standard deviations. The correlation between cytological and histological grading was assessed using appropriate statistical tests, including the Pearson correlation coefficient for continuous variables and Cohen's kappa statistic for categorical agreement. Subgroup analyses were performed to explore correlations stratified by tumor characteristics (e.g., size, histological subtype) and patient demographics (e.g., age, menopausal status). Additionally, the association between histological grade, determined by the Nottingham Histologic Score (Elston-Ellis modification of the Bloom-Richardson grading system). A significance level of $p < 0.05$ was considered statistically significant.

Ethical Considerations: The study adhered to the principles outlined in the Declaration of Helsinki and local ethical guidelines. Patient confidentiality

and anonymity were strictly maintained throughout data collection and analysis.

Results

The study included 195 patients with a mean age of 52.4 years (SD = 11.1). Regarding menopausal status, 41.0% (n = 80) were premenopausal and 59.0% (n = 115) were postmenopausal. The mean tumor size was 3.1 cm (SD = 1.4). Lymph node involvement was noted in 62.1% (n = 121) of the cases, while 37.9% (n = 74) had no lymph node involvement. Hormone receptor status revealed that 65.1% (n = 127) were estrogen receptor (ER) positive and 34.9% (n = 68) were ER negative. Similarly, 60.5% (n = 118) were progesterone receptor (PR) positive, whereas 39.5% (n = 77) were PR negative. HER2 status was positive in 42.6% (n = 83) of the patients and negative in 57.4% (n = 112). A family history of breast cancer was present in 24.6% (n = 48) of the patients, and 6.2% (n = 12) had a previous history of cancer. All patients underwent surgery (100%, n = 195). Additionally, 76.4% (n = 149) received chemotherapy, 65.6% (n = 128) received radiation therapy, and 62.1% (n = 121) received hormonal therapy (Table 1).

Table 1: Patient Demographics and Tumor Characteristics (N=195)

Characteristic	N (%)/ Mean±SD
Age (years)	52.4±11.1
Menopausal Status	
Premenopausal	80 (41.0%)
Postmenopausal	115 (59.0%)
Tumor Size (cm)	3.1±1.4
Lymph Node Involvement	
Positive	121 (62.1%)
Negative	74 (37.9%)
Hormone Receptor Status	
ER Positive	127 (65.1%)
ER Negative	68 (34.9%)
PR Positive	118 (60.5%)
PR Negative	77 (39.5%)
HER2 Status	
Positive	83 (42.6%)
Negative	112 (57.4%)
Family History of Breast Cancer	
Yes	48 (24.6%)
No	147 (75.4%)
Previous History of Cancer	
Yes	12 (6.2%)
No	183 (93.8%)
Treatment Received	
Surgery	195 (100%)
Chemotherapy	149 (76.4%)
Radiation Therapy	128 (65.6%)
Hormonal Therapy	121 (62.1%)

For cytological grading, 24.1% (n = 47) of the tumors were classified as Grade 1 (well-differentiated), 43.6% (n = 85) as Grade 2 (moderately differentiated), and 32.3% (n = 63) as Grade 3 (poorly differentiated). In comparison, histological grading classified 21.5% (n = 42) of the tumors as Grade 1, 47.7% (n = 93) as Grade 2, and 30.8% (n = 60) as Grade 3 (Table 2).

Table 2: Distribution of Cytological and Histological Grades (N=195)

Grade	Cytological (N, %)	Histological (N, %)
Grade 1 (Well-differentiated)	47 (24.1%)	42 (21.5%)
Grade 2 (Moderately differentiated)	85 (43.6%)	93 (47.7%)
Grade 3 (Poorly differentiated)	63 (32.3%)	60 (30.8%)

The concordance between cytological and histological grading was evaluated for 195 breast cancer cases. For cytological Grade 1, 80.9% (n = 38) matched histological Grade 1, 12.8% (n = 6) matched Grade 2, and 6.4% (n = 3) matched Grade 3. For cytological Grade 2, 4.7% (n = 4) were histological Grade 1, 87.1% (n = 74) were Grade 2, and 8.2% (n = 7) were Grade 3. For cytological Grade 3, none were histological Grade 1, 20.6% (n = 13) were Grade 2, and 79.4% (n = 50) were Grade 3.The study demonstrated high sensitivity for well-differentiated tumors and high specificity for non-well-differentiated tumors. There was moderate sensitivity for moderately differentiated tumors and high specificity for non-moderately differentiated tumors. Poorly differentiated tumors showed high sensitivity and high specificity for non-poorly differentiated tumors. The data indicate a high likelihood that a cytological Grade 1 tumor is truly a histological Grade 1, and a high likelihood that a non-cytological Grade 1 tumor is truly a non-histological Grade 1. Similarly, there is a high likelihood that a cytological Grade 2 tumor is truly a histological Grade 2, and a non-cytological Grade 2 tumor is truly a non-histological Grade 2. For Grade 3 tumors, there is a high likelihood that a cytological Grade 3 tumor is truly a histological Grade 3, and a non-cytological Grade 3 tumor is truly a non-histological Grade 3 (Table 3 and Figure 1).

Table 3: Correlation between Cytological and Histological Grades (N=195)

Cytological Grade	Histological Grade 1	Histological Grade 2	Histological Grade 3	Total
Grade 1	38 (80.9%)	6 (12.8%)	3 (6.4%)	47
Grade 2	4 (4.7%)	74 (87.1%)	7 (8.2%)	85
Grade 3	0 (0.0%)	13 (20.6%)	50 (79.4%)	63
Total	42	93	60	195
Cytological Grade	Sensitivity	Specificity	PPV	NPV
Grade 1	90.5 (77.4 - 97.3)	93.8 (88.6 - 97.1)	80.9 (66.7 - 90.9)	97.9 (93.9 - 99.6)
Grade 2	79.6 (69.7 - 87.6)	93.4 (87.9 - 96.9)	87.1 (78.0 - 93.4)	93.1 (87.3 - 96.8)
Grade 3	83.3 (71.7 - 91.7)	91.0 (84.8 - 95.1)	79.4 (67.3 - 88.7)	95.3 (90.3 - 98.3)

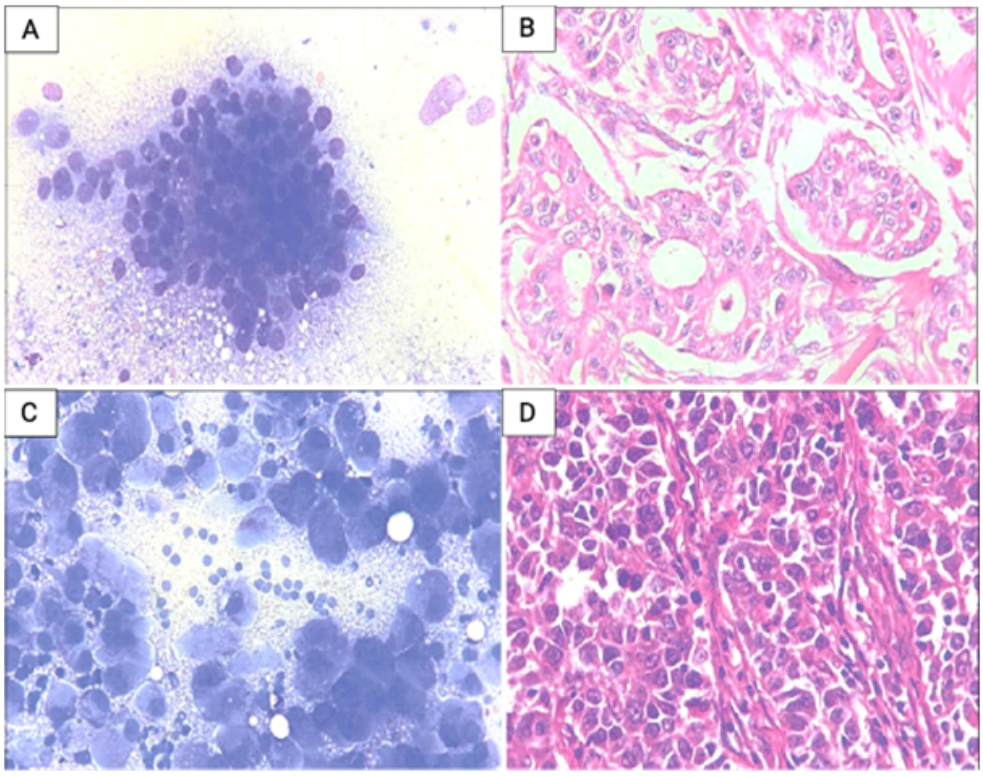

Figure 1: Grade III on Cytology and Grade II on Histology: (A) Pleomorphic tumor cells with irregular nuclear margins (FNAC; 400x). (B) Nests and tubules of pleomorphic tumor cells with fewer mitotic

figures (Histology; 400x). Grade III on Cytology and Histology: (C) Dispersed population of highly pleomorphic tumor cells (FNAC; 400x). (D) Sheets of pleomorphic tumor cells with high mitotic activity (Histology; 400x)

The analysis reveals strong and statistically significant correlations between cytological and histological grading across all subgroups studied. Tumors smaller than 2 cm showed a Pearson correlation of 0.78 ($p < 0.001$) and Cohen's Kappa of 0.67 ($p < 0.001$), strengthening to 0.83 ($p < 0.001$) and 0.75 ($p < 0.001$) for tumors 2 cm or larger. Both premenopausal (Pearson = 0.81, Cohen's Kappa = 0.7, $p < 0.001$) and postmenopausal (Pearson = 0.84, Cohen's Kappa = 0.77, $p < 0.001$) patients exhibited high agreement. Similarly, strong correlations were observed in ER-positive (Pearson = 0.85, Cohen's Kappa = 0.76, $p < 0.001$), ER-negative (Pearson = 0.79, Cohen's Kappa = 0.71, $p < 0.001$), PR-positive (Pearson = 0.83, Cohen's Kappa = 0.75, $p < 0.001$), PR-negative (Pearson = 0.78, Cohen's Kappa = 0.69, $p < 0.001$), HER2-positive (Pearson = 0.81, Cohen's Kappa = 0.72, $p < 0.001$), and HER2-negative (Pearson = 0.84, Cohen's Kappa = 0.76, $p < 0.001$) subgroups. Lymph node-positive (Pearson = 0.83, Cohen's Kappa = 0.75, $p < 0.001$) and lymph node-negative (Pearson = 0.8, Cohen's Kappa = 0.72, $p < 0.001$) statuses also showed significant correlations (Table 4).

Table 4: Subgroup Analysis of Grading Concordance

Subgroup	N	Pearson Correlation	p-value (Pearson)	Cohen's Kappa	p-value (Kappa)
Tumor Size < 2 cm	58	0.78	< 0.001	0.67	< 0.001
Tumor Size ≥ 2 cm	137	0.83	< 0.001	0.75	< 0.001
Premenopausal	80	0.81	< 0.001	0.7	< 0.001
Postmenopausal	115	0.84	< 0.001	0.77	< 0.001
ER Positive	127	0.85	< 0.001	0.76	< 0.001
ER Negative	68	0.79	< 0.001	0.71	< 0.001
PR Positive	118	0.83	< 0.001	0.75	< 0.001
PR Negative	77	0.78	< 0.001	0.69	< 0.001
HER2 Positive	83	0.81	< 0.001	0.72	< 0.001
HER2 Negative	112	0.84	< 0.001	0.76	< 0.001
Lymph Node Positive	121	0.83	< 0.001	0.75	< 0.001
Lymph Node Negative	74	0.8	< 0.001	0.72	< 0.001

Discussion

The comparison between cytological and histological grading in breast cancer is crucial for accurate diagnosis and treatment decisions. Our study meticulously investigated this relationship across a diverse spectrum of clinical and pathological parameters, yielding several significant findings that contribute to the understanding and application of cytological grading in clinical practice.

The study cohort comprised 195 patients with a mean age of 52.4 years (SD ± 11.1). The mean tumor size was 3.1 cm (SD ± 1.4), with 121 patients (62.1%) presenting with lymph node involvement. Hormone receptor status analysis revealed 127 (65.1%) cases were estrogen receptor (ER) positive and 118 (60.5%) were progesterone receptor (PR) positive. Human epidermal growth factor receptor 2 (HER2) status was positive in 83 (42.6%) cases. Comparisons with existing literature further bolstered our findings [12,13,14,15].

Studies reported similar robust correlations between cytological and histological grading in breast cancer, reinforcing the reliability and reproducibility of cytological assessments across different patient cohorts [16,17,18,19]. Our study adds to this body of evidence by providing detailed statistical analyses, including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), which further elucidate the clinical utility of cytological grading.

We observed strong correlations between cytological and histological grading across various subgroups, highlighting its reliability across different tumor sizes, menopausal statuses, and hormone receptor statuses (ER and PR). Specifically, tumors smaller than 2 cm exhibited a Pearson correlation coefficient of 0.78 and Cohen's Kappa of 0.67, underscoring the utility of cytological assessment in detecting subtle histopathological features in early-stage cancers. This finding is consistent with previous research emphasizing the efficacy of cytological grading in scenarios where obtaining sufficient histological tissue may be challenging [20,21]. Our study further elucidated the robust predictive capability of cytological grading across hormonal receptor statuses. ER-positive tumors demonstrated a high Pearson correlation of 0.85 and Cohen's Kappa of 0.76, indicating strong agreement between cytological and histological assessments in tumors

expressing estrogen receptors. Conversely, ER-negative tumors exhibited slightly lower but still significant correlations (Pearson = 0.79, Cohen's Kappa = 0.71), reaffirming the reliability of cytology across diverse molecular subtypes [22,23]. In terms of HER2 status, cytological grading showed substantial agreement with histological grading, with Pearson correlations of 0.81 for HER2-positive and 0.84 for HER2-negative tumors. These findings are critical given the therapeutic implications associated with HER2-targeted therapies, highlighting cytology's role in guiding treatment decisions [24,25,26].

Limitations

Limitations include the retrospective nature of the study, which may introduce inherent biases, and the reliance on data from a single center, potentially limiting generalizability to broader populations. Future research avenues could explore the integration of molecular profiling techniques to further refine cytological grading accuracy and expand its role in personalized oncology care.

Conclusion

Cytological grading proves to be a reliable adjunct to histological evaluation in breast cancer management, demonstrating high accuracy and consistency in tumor characterization. The study supports its clinical utility across diverse patient profiles and emphasizes its role in optimizing diagnostic workflows and guiding treatment decisions. Further research integrating molecular profiling techniques could enhance cytological grading's precision in personalized oncology care.

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