

CORRELATION BETWEEN HISTOPATHOLOGICAL, RADIOLOGICAL (BIRADS), AND IMMUNOHISTOCHEMICAL FINDINGS IN NEOPLASTIC BREAST LESIONS

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ABSTRACT

Aim: The aim of the present study was to find a correlation between histopathological, radiological findings, and immunohistochemical findings in neoplastic breast lesions.

Methods: This study was a prospective study conducted at the Department of Pathology, Government Medical College and Rajindra Hospital Patiala, Punjab. A total of 70 cases of neoplastic breast lesions over a period of 2 years, which had BIRADS score reports, received in the pathology department as trucut biopsies, lumpectomy, and mastectomy specimens were examined histopathologically and immunohistochemistry (ER, PR, HER-2/neu) was done.

Results: In the present study, the age ranges from 14 to 80 years. Out of 70 patients with breast lumps, the highest percentage (42.9%) was seen in females aged 21 to 40 years (30 out of 70). Mean+ S.D age was 37.06 + 17.04. The median age was 35 years. The most common BIRADS category was category 3 with 30 out of 70 cases (42.9%) followed by category 4 with 21 out of 70 cases (30%). 10 cases (14.3%) were seen in category 5. In 70 breast lump cases studied, a broad spectrum of histopathological neoplastic breast lesions like benign, borderline, and malignant were identified. In benign breast lesions, the most common was a fibroadenoma, which was present in 48.6% of the cases. Among malignant breast lesions, the most common was an invasive ductal carcinoma which was present in 30% of the cases. 4 cases with borderline histopathology were also identified. A comparison of all the parameters showed a high diagnostic accuracy of 87.14%, a sensitivity of 89.66%, and a specificity of 85.37% in BIRADS and histopathology. Immunohistochemistry revealed 77.14% ER/PR positive and HER2 negative cases, 17.14% HER2/neu positive, 5.7% triple-negative, and 5.7% triple-positive tumors.

Conclusion: The present study concludes that, there is a statistical correlation between radiological (BIRADS), histopathological diagnosis, and immunohistochemistry findings in neoplastic breast lesions. All these techniques have high sensitivity, specificity, and accuracy in making the final diagnosis.

Keywords: BI-RADS, breast cancer, correlation

INTRODUCTION

Breast disease in women encompasses a spectrum of benign and malignant disorders. Among 42% of patients with breast symptoms, a palpable breast mass is a basis for a visit to a primary

care physician, and it accounts for more than half of breast complaints in women presenting to breast centres.^{1,2} The majority of breast lumps are benign.³ Benign breast lesions outnumber malignant breast lesions. Breast tissue specimens comprised 81.6% benign breast lesions and 18.3% malignant breast lesions.⁴ Breast carcinoma is the most frequent cancer in women around the world. It is the fifth leading cause of cancer death worldwide, but the second leading cause of death in developed countries.⁵

A breast lump is the most common presentation associated with benign or malignant breast lesions. Mammogram and ultrasound are the two noninvasive, affordable, widely available radiological interventions that aid in the diagnosis and play a key role in early detection, treatment and favorable prognosis, resulting in improved survival rates in breast cancer patients.⁶ Breast lesions are classified as benign, pre-malignant, and invasive.⁷ Benign lesions might appear symptomatically or as an incidental finding on imaging or histological examinations.⁸

Technical advancements in ultrasonography equipment have considerably boosted the value of the US in breast imaging.⁹ With the increasing use of the US in regular breast imaging, the American College of Radiology created the first version of the Breast Imaging Reporting and Data System (BI-RADS) US lexicon in 2003 in order to standardize breast lesion characterization with the US, similar to mammography.¹⁰ The second version of the BI-RADS US lexicon was published in the fifth edition of the BI-RADS atlas in 2013.¹¹

Immunohistochemistry (IHC) is utilized in all tissues to characterize intracellular proteins or diverse cell surfaces. The most helpful element of IHC is that it is a powerful and affordable instrument for light microscopy. Pathologists' morphologic observations are validated by the use of IHC.¹²

Approximately 75% of breast cancers are positive for ER and/or PR. The ER-positive tumors express ER, PR, ER-responsive genes, and other genes that encode luminal epithelial cell proteins they are referred to as the luminal group.^{13,14} The luminal-A subtype is the most common, accounting for 50%-60% of all breast cancers. These tumors typically have a low histological grade, with a good prognosis. Luminal-A subtype is ER-positive and/or PR-positive tumors with negative HER2 and a low Ki67 index.¹⁵ HER2-positive breast cancer accounts for 15-20% of all subtypes of breast cancer. HER2 positive is associated with more aggressive biological and clinical behavior. These tumors are extremely proliferative, with 75% having a high histological and nuclear grade and more than 40% having p53 mutations.¹⁶ ER positivity is found in about half of the HER2-positive breast tumors, but at lower levels. The immunohistochemical profile of ER-negative and HER2-positive does not correspond perfectly with the intrinsic subtype since only 70% of HER2 tumors by microarray have the protein overexpressed on immunohistochemistry.^{17,18}

The aim of the present study was to find a correlation between histopathological, radiological findings, and immunohistochemical findings in neoplastic breast lesions.

MATERIALS AND METHODS

This study was a prospective study conducted at the Department of Pathology, Government Medical College and Rajindra Hospital Patiala, Punjab. A total of 70 cases of neoplastic breast lesions over a period of 2 years, which had BIRADS score reports, received in the pathology department as trucut biopsies, lumpectomy, and mastectomy specimens were examined histopathologically and immunohistochemistry (ER, PR, HER-2/neu) was done.

INCLUSION CRITERIA

1. Patients who gave consent for the study were included in the study.
2. All histopathology specimens surgically resected, were neoplastic breast lesions with BIRADS report.

EXCLUSION CRITERIA

1. Patients not willing to give consent to participate in the study, were not included in the study.
2. Females who were already diagnosed with malignancy and on treatment.

METHODOLOGY

1. Details of the study protocol were explained to the subject.
2. Informed consent was taken from all the subjects.
3. History was taken from the patients.
4. Details of radiological findings (BIRADS) on sonomammography were collected.
5. Histopathological examination was done of samples received of neoplastic breast lesions in the Department of pathology at Govt. Medical College, Patiala who underwent surgery at Rajindra Hospital, Patiala. Breast carcinoma cases were histologically graded according to the Modified bloom Richardson Score (MBR).
6. Immunohistochemistry (ER, PR, and HER2 neu) was applied to neoplastic breast lesions.
7. Statistical analysis to find the correlation of histopathological, radiological, and immunohistochemical findings in neoplastic breast lesions.

RESULTS

Table 1: Patient details

AGE (IN YEARS)	NO. OF CASES	PERCENTAGE
0-20	15	21.3%
21- 40	30	42.9%
41- 60	16	22.9%
61 - 80	9	12.9%
BIRADS CATEGORY		
Category 2	8	11.4%
Category 3	30	42.9%

Category 4	21	30.0%
Category 5	10	14.3%
Category 6	1	1.4%

In the present study, the age ranges from 14 to 80 years. Out of 70 patients with breast lumps, the highest percentage (42.9%) was seen in females aged 21 to 40 years (30 out of 70). Mean \pm S.D age was 37.06 ± 17.04 . The median age is 35 years. The most common BIRADS category was category 3 with 30 out of 70 (42.9%) followed by category 4 with 21 out of 70 cases (30%). 10 cases (14.3%) were seen in category 5. There were seen eight cases in category 2 of BIRADS. Only one case was found in category 6. Of this, categories 2 and 3 were considered benign and categories 4 and 5 were considered suspicious of malignancy or malignant.

Table 2: Distribution of neoplastic breast lesions according to histopathological diagnosis

BROAD HISTOPATHOLOGICAL CATEGORIES		No. of Cases	Percentage
BENIGN	Fibroadenoma	34	48.6%
	Phyllodes tumor	2	2.9%
	Benign proliferative breast disease	2	2.9%
	Intraductal papilloma	1	1.4%
	Micro glandular adenosis	1	1.4%
	Tubular adenoma	1	1.4%
BORDERLINE	Ductal Carcinoma In Situ	2	2.9%
	Papilloma with focal DCIS features	1	1.4%
	Borderline phyllodes tumor	1	1.4%
MALIGNANT	Invasive Ductal Carcinoma	21	30.0%
	Invasive Lobular Carcinoma	2	2.9%
	Medullary Carcinoma	1	1.4%
	Mucinous carcinoma	1	1.4%

	Total	70	100.0%
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In 70 breast lump cases studied, a broad spectrum of histopathological neoplastic breast lesions like benign, borderline, and malignant were identified. In benign breast lesions, the most common was a fibroadenoma, which was present in 48.6% of the cases. Among malignant breast lesions, the most common was an invasive ductal carcinoma which was present in 30% of the cases. 4 cases with borderline histopathology were also identified.

Table 3: Age-wise distribution of neoplastic breast lesions

AGE (IN YEARS)	BENIGN	BORDERLINE	MALIGNANT	TOTAL
0-20	15	0	0	15
21- 40	24	1	5	30
41- 60	2	1	13	16
61 - 80	0	2	7	9
Total	41	4	25	70
Fisher Exact Value	46.846			
P value	<0.001			
Significance	HS			

Most of the benign breast lesions were seen in 21 to 40 years (24 out of 70 cases) and malignant lesions were common in 41 to 60 years (13 out of 70 cases).

Table 4: Association between histopathological categories and BIRADS categories

HISTOPATHOLOGICAL EXAMINATION		BIRADS CATEGORY						TOTAL	
		2	3	4a	4b	4c	5		6
B Z	Fibroadenoma	7	23	4	0	0	0	0	34
	Phyllodes tumor	0	1	1	0	0	0	0	2
	Benign Proliferative Breast Disease	0	2	0	0	0	0	0	2

	Intraductal papilloma	0	1	0	0	0	0	0	1
	Micro glandular adenosis	1	0	0	0	0	0	0	1
	Tubular adenoma	0	0	1	0	0	0	0	1
BORDERLINE	Ductal Carcinoma In Situ	0	0	2	0	0	0	0	2
	Papilloma with focal DCIS features	0	0	0	0	1	0	0	1
	Borderline phyllodes tumor	0	0	1	0	0	0	0	1
MALIGNANT	Invasive Ductal Carcinoma	0	3	1	3	5	8	1	21
	Invasive Lobular Carcinoma	0	0	0	0		2	0	2
	Medullary Carcinoma	0	0	0	0	1	0	0	1
	Mucinous carcinoma	0	0	1	0	0	0	0	1
	Total	8	30	11	3	7	10	1	70
	Fisher Exact Value	133.651							
	P value	<0.001							
	Significance	HS							

Out of 34 cases of fibroadenoma, 23 cases were seen in BIRADS category 3 followed by 7 cases in category 2. However, 4 cases of fibroadenoma were in category 4a. Phyllodes tumor and tubular adenoma both presented with category 4a. Most of the borderline cases had features of BIRADS category 4a. Category 4c was seen in papilloma with focal DCIS features. Invasive ductal carcinoma was the most common malignant tumor in the present study, which presented a wide range of BI-RADS categories from category 3 to category 6. However, the most common category was category 5 (8 cases). Two cases of invasive lobular carcinoma were seen in BIRADS category 5. There was a statistically significant association between BIRADS categories and the histopathological findings (p-value was < 0.001), showing that the histopathological findings were dependent on the BIRADS categories.

Table 5: Comparison of BIRADS with histopathology with sensitivity and specificity parameters

BIRADS CATEGORY	HISTOPATHOLOGICAL EXAMINATION			TOTAL
	Benign	Borderline	Malignant	
Benign (category 2, 3)	35	0	3	38
Malignant/ suspicious of malignancy (category 4,5,6)	6	4	22	32
TOTAL	41	4	25	70
SENSITIVITY	89.66%			
SPECIFICITY	85.37%			
NPV	81.25%			
PPV	92.11%			
ACCURACY	87.14%			

The above table showed the Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of BIRADS categories against histopathology results. The statistical comparison of all the parameters showed a high diagnostic accuracy of 87.14%, a sensitivity of 89.66%, and a specificity of 85.37% in BIRADS and histopathology.

Table 6: Immunohistochemistry pattern of ER, PR and Her2 neu status in histopathologically diagnosed cases

RECEPTOR STATUS	BENIGN	BORDERLINE	MALIGNANT	TOTAL
ER+/PR+/HER2neu-	41(100%)	3(75%)	10(40%)	54(77.14%)
ER-/PR-/HER2neu-	0(0%)	0(0%)	4(16%)	4(5.7%)
ER-/PR-/HER2neu+	0(0%)	0(0%)	8(32%)	8(11.4%)
ER+/PR+/HER2neu+	0(0%)	1(25%)	3(12%)	4(5.7%)
TOTAL CASES	41(100%)	4(100%)	25(100%)	70(100%)
Fisher Exact Value	30.885			
P value	<0.001			
Significance	HS			

Out of 70 total cases, all 41 benign cases were ER+/PR+/HER2-. In the borderline category, 3 cases (75%) were ER+/PR+/HER2- and 1 case was ER+/PR+/HER2+. In the malignant category, 10 cases (40%) were ER+/PR+/HER2- followed by 8 cases (32%), which were ER-/PR-/HER2+. 4 malignant cases were triple negative (ER-/PR-/HER2-). ER+/PR+/HER2- were the most common subtype seen among total cases (77.14%).

Table 7: Radiological characteristics and receptor status of neoplastic breast lesions

RECEPTER STATUS	BIRADS 2	BIRADS 3	BIRADS 4	BIRADS 5	BIRADS 6	FISHER EXACT VALUE	P VALUE	SIGNIFICANCE
Estrogen Receptor								
Positive	8	30	15	4	1	21.369	<0.001	HS
Negative	0	0	6	6	0			
Progesterone Receptor								
Positive	8	30	15	4	1	21.369	<0.001	HS
Negative	0	0	6	6	0			
Her2 neu Receptor								
Positive	0	1	6	4	1	14.567	0.002	HS
Negative	8	29	15	6	0			

Estrogen and progesterone receptors were positive for 30 cases in the benign category of BIRADS i.e., category 3 followed by category 4 with 15 cases, which is suspicious of malignancy. ER, PR positivity was less in categories 5 and 6. P-value was < 0.001, which was statistically significant. HER2 neu overexpression was seen in category 4 (6 cases) followed by category 5 (4 cases). p-value was 0.002, which was statistically significant. It was found that there was a strong correlation between BIRADS, histopathological diagnosis, and immunohistochemical findings in neoplastic breast lesions.

DISCUSSION

Female breast shows physiological and hormonal changes related to age, pregnancy, lactation, and menopause. Different breast lesions which are classified into inflammatory, benign, and malignant are seen in different age groups.¹⁹ Mammography is the most common method of detecting and diagnosing breast disease.²⁰ The breast lesions are classified by using BIRADS classification into various categories (categories 0 to 6).²¹ Radiological findings as per the BIRADS categories are a good tool to classify breast lesions ranging from inflammatory, and

benign to malignant.^{22,23} Histopathological examination reveals a spectrum of neoplastic breast lesions. Fibroadenoma, phyllodes tumor, and benign proliferative breast disease are examples of benign breast lesions, whereas invasive ductal carcinoma, invasive lobular carcinoma, medullary carcinoma, and papillary carcinoma are examples of malignant breast lesions.²⁴ Benign breast lesions are more common than malignant.²⁵ The immunohistochemical (IHC) classification of ER, PR, and HER-2/neu status in combination provides both therapeutic and prognostic information.²⁶ In addition to pathological grade and stage, breast cancers are frequently immunohistochemically evaluated for hormone receptor status (ER) and human epidermal growth factor receptor2 (HER2) expression.²⁷

The present study revealed, the youngest patient was 14 years old and the oldest patient was 80 years old. Out of 70 patients with breast lumps, whose biopsies, lumpectomy, and mastectomy specimens were received, the highest percentage was seen in the age group of 21 to 40 years. The present study was in concordance with the study done by Dhariya et al²⁸ with a peak age distribution of 21 to 40 years. The most common BIRADS category was category 3 with 30 cases (42.9%) corresponding to likely benign lesions. Category 4 was the second most common category with 21 cases (30%) corresponding to suspicious of malignancy. Our findings were similar to studies done by Albahrani et al²⁹ and Dhariya et al.²⁸

Invasive carcinoma and in situ carcinoma cases had more frequent irregular shapes as compared to benign cases (40 out of 70 cases) which were mostly round to oval shaped. This was comparable with the study conducted by Rahbar et al³⁰ and Rani et al.³¹ Out of 34 cases of fibroadenoma, 23 cases were seen in BIRADS category 3 followed by 7 cases in category 2. However, 4 cases of fibroadenoma were in category 4a. Phyllodes tumor and tubular adenoma both presented with category 4a. Most of the borderline cases had features of BIRADS category 4a. Category 4c was seen in papilloma with focal DCIS features. Invasive ductal carcinoma was the most common malignant tumor in the present study, which presented a wide range of BIRADS categories from category 3 to category 6. However, the most common category was category 5 (8 cases). Two cases of invasive lobular carcinoma were seen in BIRADS category 5. The prospective study correlated with the study done by Anushree et al.³² Their study found 56.7% benign lesions, 4.9% borderline, and 38.27% malignant cases.

In the present study, it was noted that benign breast lesions were most common in 21 to 40 years of age whereas malignant lesions were more common in 41 to 60 years. The statistical analysis was done to find a correlation between the age of the patient and the pathological category of neoplastic breast lesions. It was similar to the observations made by a study done by Reddy et al.³³ The study conducted by them showed that benign lesions were most common in the 3rd and 4th decades. However, malignant lesions were common in the 5th decade.³³ In the present study, it was noted that out of 34 cases of fibroadenoma, 30 cases were in the likely benign category and 4 were in the suspicious of malignancy category. Borderline cases were mostly seen in category 4. Out of 21 cases of invasive ductal carcinoma, 18 cases were seen in the suspicious of malignancy/ malignant categories whereas, 3 cases were seen in the benign category. The findings were similar to studies done by Kutluer et al³⁴, Dhariya et al.²⁸

Out of 70 cases, histopathology was malignant for 3 cases, though it was placed in BIRADS category 2,3 (benign) radiologically. 6 cases that were malignant/suspicious of malignancy with categories 4,5,6 on BIRADS, were found to be benign on histopathological findings. The sensitivity of BIRADS in the diagnosis of carcinoma of the breast was 89.66 %, specificity was 85.37 %, positive Predictive value was 92.11 %, negative Predictive value was 81.25 %, and diagnostic accuracy was 87.14 %. The findings were in concordance with the studies done by Rani et al³¹ and Dhariya et al.²⁸ Immunohistochemistry revealed 77.14% ER/PR positive and HER2 negative cases, 17.14% HER2/neu positive, 5.7% Triple-negative, and 5.7% triple-positive tumors. This present study correlated to the observations made by Gupta et al.³⁵

In the present study, Estrogen and progesterone receptor were positive for 30 cases in the benign category of BIRADS I.e., category 3 followed by category 4 with 15 cases, which was suspicious of malignancy. ER, PR positivity was less in categories 5 and 6. The study found that there was a statistically significant association between the two (p-value < 0.001). This result was in discordance with the studies conducted by Kim et al³⁶ and Sohn et al.³⁷ This might be due to differences in sample size and various geographical factors.

HER 2 neu overexpression was seen in category 4 (6 cases) followed by category 5(4 cases). The study found that there was a statistically significant association between the two (p-value = 0.002). It was similar to the observations made by Sohn et al.³⁷

CONCLUSION

The present study concludes that, there is a statistical correlation between radiological (BIRADS), histopathological diagnosis, and immunohistochemistry findings in neoplastic breast lesions. All these techniques have high sensitivity, specificity, and accuracy in making the final diagnosis.

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