ORIGINAL RESEARCH PAPER
Volume - 14 | Issue - 01 | January - 2025 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

STUDY OF LOCAL RECURRENCE IN TERMS OF P53 AND KI67 IN PHYLLODES TUMOUR OF BREAST AT TERTIARY CENTRE (SRN HOSPITAL) AND KAMLA NEHRU HOSPITAL IN PRAYAGRAJ

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ABSTRACT

Objectives: The study aims to identify local recurrence of p53 and ki-67 in breast phyllode tumors at SRN Hospital and Kamla Nehru Hospital in Prayagraj, and to analyze local recurrence based on resection margin. **Methods:** A study was conducted at Moti Lal Nehru Medical College and Kamla Nehru Hospital, Prayagraj, focusing on total 50 female patients with confirmed breast phyllodes tumors without prior neoadjuvant therapy, blood diseases, acute inflammation, autoimmune diseases, or previous corticosteroid medication treatment. The study from August 2023 to August 2024 and involved collecting clinical data from patient medical records, including demographic information, tumor characteristics, local recurrence status, time to recurrence, and treatment details. Samples were prepared using formalin-fixed, paraffin-embedded tissue blocks from primary phyllodes tumors, deparaffinized, and rehydrated. Antigen retrieval was performed using heat-induced epitope retrieval (HIER) and cooling. **Results:** The study identifies breast tumor patients based on age, menopausal status, type of surgery, and laterality. Benign tumors are younger, while borderline tumors are older. Post-menopausal women have a higher proportion of malignant cases. The type of surgery significantly affects the histological type of lesions. Laterality doesn't significantly differ between left and right sides. Ki-67 percentages and p53 expression are not significantly associated with histological types. Post-operative radiotherapy is exclusively associated with malignant breast lesions. **Conclusion:** The study reveals that p53 and Ki-67 biomarkers predict tumor behavior and local recurrence in phyllodes tumors. These markers are linked to tumor aggressiveness, with increased Ki-67 and p53 expression linked to malignant histology. Clinical parameters like tumor size, age, and menopausal status also influence tumor behavior.

KEYWORDS

Phyllodes Tumor, Breast Tumor, Local Recurrence, P53 Expression, Ki67 Index, Breast Neoplasm, Prognostic Markers

INTRODUCTION

Phyllodes tumors (PTs) are rare breast neoplasms with unpredictable characteristics, high recurrence rates post-surgery, and potential for malignant transformation.[1,2] They are categorized into three subgroups: benign, borderline, and malignant, based on histological criteria such as stromal cellularity extent, presence of atypical stromal cells, mitotic activity level, excessive stromal proliferation, and tumor margin characteristics.[3,4] The distribution of benign, borderline, and malignant PTs is 74.6%, 16.1%, and 9.3%, respectively, with a recurrence rate of 12.8%.[5]

The probability of tumor recurrence is associated with its grade, atypia, cellularity, and permeative margins. However, pathologists may struggle to evaluate the grade of PT solely based on morphological characteristics. This study aimed to evaluate an immuno histochemistry (IHC) panel for measuring Ki-67 and p53 expression levels in PT and investigate their correlation with tumor grade and biological features. Immunohistochemistry has gained prominence in diagnostic surgical pathology, shifting emphasis from histological criteria to biological markers. Over the last decade, several studies have been conducted to find appropriate molecular indicators that can reliably predict the behavior of phyllodes tumors. These markers include cell cycle markers, angiogenesis markers, epithelial and mesenchymal transition (EMT) markers, and receptor tyrosine kinases.[6-9]

Tumour recurrence is characterized by the reappearance of a tumor with a similar histologic type in the same quadrant, but tumors developing in separate quadrants or opposite breasts are considered distinct tumors.[10] Tumour recurrence is influenced by positive margin or insufficient surgical excision, high cell division rates, and the presence of an excessive number of cells in supportive tissue. However, excessive growth of supportive tissue, abnormal cell appearance, tumor cell death, and heterologous tissue do not favor metastasis.[11]

Immunohistochemistry (IHC) is a valuable tool in diagnosing benign breast fibroepithelial neoplasms (PT), except for cases of malignant PT. TP53, a widely distributed protein found throughout the human body, has been extensively researched in several tumors, including PT, but its usefulness as a predictive biomarker remains unknown. Ki67, a nuclear protein not associated with histones, serves as a significant indicator of cell proliferation in IHC investigations and may also serve as a prognostic indicator, particularly in malignant PT. Both IHC markers Ki67 and p53 independently contribute to prognostic factors.[6-9]

Approximately 3% of the breast's normal epithelial cells exhibit positive Ki67 labeling, and the incidence of invasive breast cancer is elevated, particularly in hormone-negative tumors.[12,13] The percentage of Ki67 staining in malignant PT ranges from 15% to 100%, but in benign PT it is below 25%. The Ki67 index is elevated in malignant PT with osteosarcomatous differentiation, but a comparable investigation has shown that in morphologically harmless PT, a staining of over 10% of the Ki67 index indicates a potential for malignant alterations.[4,12-17]

However, immunohistochemistry's use varies across various laboratories due to factors such as the specific kind and length of fixation, antigen extraction techniques, staining methodology, and assessment of staining outcomes. There is no individual immunological characteristic that can consistently differentiate between benign and borderline phyllodes tumors. [14]

Phyllodes tumors are rare breast fibroepithelial neoplasms with unpredictable clinical behavior and high risk of local recurrence, posing a challenge in clinical outcomes. This study focuses on the role of p53 and Ki67, two biomarkers involved in tumor proliferation and cell cycle regulation, in predicting local recurrence in phyllodes tumors. Evaluating their expression levels could provide insights into the aggressive potential of the tumor, guide postoperative management strategies, and improve patient prognosis. Identifying high-risk patients based on these markers could reduce recurrence rates and optimize long-term outcomes through personalized treatment.

Phyllodes tumors pose a significant clinical challenge due to their

potential for local recurrence, even after surgical excision. Despite advances in surgical techniques and therapies, predicting which tumors are more likely to recur remains difficult, complicating patient management and leading to variations in treatment strategies and outcomes.

The study aims to identify local recurrence of p53 and ki-67 in breast phyllode tumors at SRN Hospital and Kamla Nehru Hospital in Prayagraj, and to analyze local recurrence based on resection margin (≤1cm to ≥1cm).

METHODS

The study was conducted at Moti Lal Nehru Medical College and Kamla Nehru Hospital, Prayagraj, involving 50 patients with confirmed diagnosis of phyllodes tumors of the breast. The study population consisted of female patients with no previous history of neoadjuvant therapy, blood diseases, acute inflammation, autoimmune diseases, or prior treatment with corticosteroid medications. Patients were required to understand and follow study-related advice and provide consent for the study.

Data collection included demographic information, tumor characteristics, local recurrence status, time to recurrence, and treatment details. Immunohistochemistry was performed using formalin-fixed, paraffin-embedded tissue blocks from primary phyllodes tumors. The samples were sectioned at a thickness of 4 µm and mounted on positively charged glass slides. Antigen retrieval was performed using heat-induced epitope retrieval (HIER) and cooling. Blocking was done using endogenous peroxidase blocking and protein blocking. Primary antibody incubation was performed against p53 and Ki67, followed by secondary antibody and detection using the avidin-biotin complex (ABC) method. Counterstaining was done with hematoxylin for 1-2 minutes, rinsed in running tap water, and then dehydrated through graded alcohols.

Screening and analysis were performed using IBM SPSS Statistics for Windows, Version 29.0. Tumors were categorized into low (<10%), intermediate (10-50%), and high (>50%) expression levels. The Ki67 labeling index was assessed by counting the percentage of positively stained nuclei among 1,000 tumor cells. Tumors were categorized based on the Ki67-positive cell percentage as low (<10%), intermediate (10-30%), or high (>30%).

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 29.0, with mean (standard deviation) and percentage (%) presented. The chi-square test was used to compare categorical variables, while the independent t-test was employed to assess discrete variables between groups. An analysis of variance (ANOVA) was used to compare more than two groups, with a p-value of <0.05 considered statistically significant.

RESULTS

The study involved 50 breast tumor patients, with 26.00% aged ≤30 years, 32.00% aged 31-40 years, 16.0% aged 41-50 years, 14.0% aged 51-60 years, and 12.0% aged >60 years. The majority were premenopausal, with 33 (66.0%) premenopausal and 34 (34.0%) postmenopausal. The majority underwent BCS surgery, with 74% having BCS, 10.0% having Partial Mastectomy, and 16.0% having Complete Mastectomy. The majority had tumors in the left breast, while 48.0% had tumors in the right. The histological type of the tumors varied, with 68.0% having benign tumors, 16.0% having borderline tumors, and 16.0% having malignant tumors. (Table 1)

Table 1: Distribution of tumour of breast patients according to age, Menopausal Status, Type of surgery, Laterality, Histological type

N=50		n	%
Age	≤30 years	13	26.00
	31-40 years	16	32.00
	41-50 years	8	16.00
	51-60 years	7	14.00
	>60 years	6	12.00
Menopausal Status	Premenopausal	33	66.00
	Post-menopausal	17	34.00
Type of surgery	BCS	37	74.00
	Partial Mastectomy	5	12.00
	Complete Mastectomy	8	16.00
Laterality	Left	26	52.0
	Right	24	48.0
Histological type	Benign	34	68.00
	Borderline	8	16.00
	Malignant	8	16.00

The study reveals that the mean age of patients with benign, borderline, and malignant breast tumors is significantly influenced by their age. The mean age was significantly associated with borderline, malignant tumors compared to benign tumors. The study also found a significant association between menopausal status, type of surgery, and laterality with different histologic types. Premenopausal women had a higher percentage of benign cases compared to borderline and malignant cases. However, this association was not statistically significant. The type of surgery was also significant, with most benign cases undergoing breast-conserving surgery (BCS), while malignant cases were more likely to undergo partial or total mastectomy. Laterality analysis showed no significant difference between histologic types, with similar proportions of left and right cases in benign and borderline types and slightly more left-sided malignant cases. The mean tumor area for benign tumors was 111.06±125.57, borderline tumors 732.88±870.60, and malignant tumors 1239.00±374.95. The tumor area was significantly larger in borderline and malignant tumors compared to benign tumors. (Table 2)

Table 2: Association of mean age, frequency of Menopausal Status, Type of surgery and Laterality, mean tumor area with different Histological type

		Benign (n=34)		Borderline (n=8)		Malignant (n=8)		F	p-Value
		n	%	n	%	n	%		
Age (years) (mean±SD)		36.65±12.97		45.13±13.14		54.00±14.45		46.09	0.004
Menopausal Status	Premenopausal	26	76.47	4	50.00	3	37.50	-	0.065
	Post-menopausal	8	23.53	4	50.00	5	62.50		
Type of surgery	BCS	31	91.18	5	62.50	1	12.50	-	<0.001
	Partial Mastectomy	0	0.00	0	0.00	5	62.50		
	Complete Mastectomy	3	8.82	3	37.50	2	25.00		
Laterality	Left	17	50.00	4	50.00	5	62.50	-	0.810
	Right	17	50.00	4	50.00	3	37.50		
Tumor area (mean±SD)		111.06±125.57		732.88±87 0.60		1239.00± 374.95		32.27	<0.001

The study reveals a significant association between Ki-67 expression levels and different histological types of breast tumors. All benign tumors (100%) had Ki-67 expression levels of ≤15%, while borderline tumors (62.5%) had Ki-67 expression levels between 15-30%, and malignant tumors (100%) had Ki-67 expression levels greater than 30%. Similarly, p53 expression was found to be associated with different histological types of breast tumors. Among benign tumors, 61.76% had single positive p53 expression, while 5.88% had double positive and 8.82% had triple positive p53 expression. In borderline tumors, 37.5% had single positive p53 expression, 50.0% had double positive, and 12.5% had triple positive p53 expression. In malignant tumors, 25.0% had single positive p53 expression, and 75.0% showed triple positive expression. The margin of resection was also found to be significantly associated with the histological type of breast tumors. In benign tumors, only 2.94% had a margin of resection of less than 1 cm, while 97.06% had margins greater than 1 cm. In borderline tumors, 12.50% had margins of less than 1 cm, while 87.50% had margins greater than 1 cm. In malignant tumors, 75.00% had margins of less than 1 cm, with only 25.00% having margins greater than 1 cm. The study also found a significant difference in local recurrence and distant metastasis frequency across different histological types. (Table 3)

Table 3: Association of frequency of different Ki-67(%),p53, margin of resection, Local recurrence and distant metastasis with different Histological type

	Benign (n=34)		Borderline (n=8)		Malignant (n=8)		Chi Sq.	p-Value
	n	%	n	%	n	%		

Ki-67	≤15%	34	100.0	0	0.00	0	0.00	74.18	<0.001
	15-30%	0	0.00	5	62.50	0	0.00		
	> 30%	0	0.00	3	37.50	8	100.00		
P53	+	**21**	61.76	**3**	37.50	**2**	25.00	31.93	<0.001
	++	**2**	5.88	4	50.00	0	0.00		
	+++	**3**	8.82	1	12.50	6	75.00		
	NA	**8**	23.53	0	0.00	0	0.00		
Margin of resection	<1cm	**1**	2.94	**1**	12.50	**6**	75.00	25.11	<0.001
	> 1 cm	**33**	97.06	7	87.50	2	25.00		
Local recurrence	Yes	0	0.00	0	0.00	2	25.00	10.94	0.004
	No	34	100.00	8	100.00	6	75.00		
Distant metastasis	Yes	0	0.00	0	0.00	0	0.00	-	-
	No	34	100.00	8	100.00	8	100.00		

The study found a significant association between the frequency of post-operative radiotherapy and the histological types of breast tumors. Interestingly, only 0.00% of benign and borderline cases received this treatment, while 75.0% of malignant cases did. The chi-square value was 35.75, indicating a statistically significant association between the need for radiotherapy and the histological type of breast tumors. However, no statistically significant association was found between recurrence frequency and margin of resection for the different histological types of breast tumors. The chi-square value was 0.89, indicating no significant association between recurrence and margin of resection.(Table 4)

Table 4: Association of frequency of post-operative radio therapy and recurrence in different Margin of resection with different Histological type

			Benign (n=34)		Borderline (n=8)		Malignant (n=8)		Chi Sq.	p-Value
			n	%	n	%	n	%		
Post-operative radio therapy		Yes	0	0.00	0	0.0	6	75.00	35.79	<0.001
		No	34	100.0	8	100.0	2	25.00		
Recurrence										
Margin of resection	< 1 cm	Yes	0	0.00	0	0.00	2	33.33	0.89	0.641
		No	1	100	1	100	4	66.67		
	> 1 cm	Yes	0	0.00	0	0.00	0	0.00	-	-
		No	33	100	7	100	2	100		

DISCUSSION

Phyllodes tumors (PT) are rare fibroepithelial neoplasms that make up less than 1% of all breast tumors. The World Health Organization classifies them into benign, borderline, and malignant subtypes. Malignant PTs are prone to local recurrence and distant metastasis, and understanding the mechanisms associated with recurrence, particularly through molecular markers like p53 and Ki-67, is crucial for improving malignant cancer treatment. This study examined the correlation between these biomarkers and recurrence of phyllodes tumors using data from SRN Hospital and Kamla Nehru Hospital, Prayagraj. The study involved 50 patients with phyllodes tumors, categorized as benign (68%), borderline (16%), and malignant (16%). The majority of patients were premenopausal (66%), and breast-conserving surgery (BCS) was the predominant treatment. The study found a significant correlation between patients' age and the subtype of breast tumors. Patients with benign tumors had a mean age of 36.65±12.97 years, while those with borderline and malignant tumors had higher mean ages of 45.13±13.14 and 54.00±14.45 years, respectively. This suggests that malignant tumors occur more frequently in older individuals, increasing the likelihood of developing more aggressive forms of breast tumors. This finding is consistent with research by Mohd Ali et al. (2020) and Kasimsetty et al (2024), which found an average age of 36.4 years in patients with phyllodes tumors.[18,19]

Rivero et al. (2020) found that patient age increases with tumor subtype severity, with benign tumors prevailing in younger women and malignant cases more common in older individuals.[20] This suggests age may be a risk factor for phyllodes tumor malignancy, emphasizing the need for vigilant surveillance in older breast tumor patients.

The study found that menopausal status is associated with a higher incidence of breast tumors, with malignant tumors more common in postmenopausal women (62.50%), and benign tumors predominantly in premenopausal women (76.47%). Borderline tumors were more evenly distributed across both groups (50.00% of cases in each group). This finding is consistent with previous studies confirming an increased cancer incidence in older, postmenopausal women.[18,20] The study suggests that the increased incidence of malignant tumors in postmenopausal women is a cause for increased attention, as timely identification and appropriate therapeutic approaches may reduce the likelihood of aggressive tumor activity and recurrence.

The study found a significant association between the histological subtype of a tumor and the chosen surgical approach. Most benign cases (91.18%) underwent breast-conserving surgery (BCS), reflecting the less aggressive nature of these tumors and the preference for preserving breast tissue. However, malignant cases were more likely to require more extensive surgical interventions, with 62.50% of patients undergoing partial mastectomy and 25.00% undergoing total mastectomy. This pattern highlights the need for more aggressive surgical approaches in managing malignant tumors due to their higher risk of recurrence or metastasis. The study also confirmed the importance of negative surgical margins in malignant phyllodes tumors, indicating that partial excision is a significant risk factor for local recurrence.[18,19,21]The study confirms the need for complete excision of malignant tumors, particularly with negative margins, to reduce the likelihood of local recurrence and improve patient outcomes.

The study found no significant difference in laterality between histologic types of breast tumors, with similar proportions of left-sided and right-sided cases in both benign and borderline tumor groups. Malignant tumors were slightly more likely to occur on the left side, but this difference was not statistically significant. This suggests that laterality is not an effective predictor of tumor behavior or recurrence. The results suggest that factors such as tumor size, histology, and biomarker expression are more important for predicting clinical outcomes than tumor laterality.[18]

The study found a significant correlation between tumor size and histological subtype. Patients with benign tumors had a mean tumor area of 111.06±125.57 mm², while those with borderline tumors had a larger mean area of 732.88±870.60 mm². Malignant tumors had the largest mean area of 1239.00±374.95 mm². This suggests that as tumors become more aggressive, their size also increases. This is consistent with previous studies indicating that all malignant phyllodes tumors are larger than 3 cm. However, stromal overgrowth may be a more significant predictor of local recurrence.[18,19] The research suggests that larger tumors are more prone to malignancy, but the histologic features of the tumor, including stromal extension, must also be carefully evaluated to determine the likelihood of recurrence.[11]

The study found a significant correlation between Ki-67 expression and the histological subtype of breast tumors. All benign tumors had low Ki-67 expression levels (≤15%), indicating less aggressive and slow-growing nature. However, all malignant tumors had significantly elevated Ki-67 expression levels (>30%), indicating high proliferative capacity and aggressive behavior. This finding supports the use of Ki-67 as a prognostic indicator in phyllodes tumors, particularly in distinguishing between benign and malignant subtypes. The findings support the use of Ki-67 as a biomarker for assessing tumor aggressiveness.[18,19]

The study explores the role of p53, a tumor suppressor gene, in understanding tumor behavior. It found a significant correlation between p53 expression and the histological subtype of breast tumors. Malignant tumors showed robust p53 expression, indicating a higher level of p53 dysregulation, often associated with aggressive tumor behavior and higher malignancy potential. This finding supports previous research indicating that increased p53 expression correlates with aggressive phyllodes tumors.[18] P53 has been used as a biomarker to differentiate benign, borderline, and malignant phyllodes tumors. The increase in p53 in malignant tumors suggests it may contribute to the transition of phyllodes tumors from benign to malignant forms. The study confirms p53 as an important prognostic indicator, especially in distinguishing individuals at increased risk of recurrence or metastasis.[20,22]

The study found that the margin of resection was significantly

associated with the histological type of breast tumors. In benign tumors, 97.06% had margins greater than 1 cm, suggesting that achieving wide resection margins is generally easier in less aggressive tumors. In borderline tumors, 87.50% had margins greater than 1 cm, while 12.50% had margins of less than 1 cm. Malignant tumors posed a greater challenge in surgical resection, with 75.00% having margins of less than 1 cm, suggesting a higher risk of residual tumor and recurrence. Local recurrence was observed in 25.00% of malignant cases, while no benign or borderline cases exhibited local recurrence. No cases across any histological type showed distant metastasis, indicating the importance of obtaining adequate resection margins, particularly in malignant tumors, to reduce the risk of local recurrence and improve surgical outcomes. The results support the importance of negative margins, especially in malignant cases, to reduce the likelihood of recurrence.[18,19,21]

The study found that postoperative radiotherapy is primarily used in patients with malignant breast tumors, with 75.00% receiving treatment. This indicates that radiotherapy is primarily used in high-risk situations with an elevated likelihood of local recurrence, particularly in aggressive tumors. The use of radiotherapy is strongly associated with the tumor's histologic subtype, indicating its importance in managing malignant tumors. Radiotherapy is not required in benign or borderline cases, highlighting its role as a targeted therapy for malignant tumors to prevent recurrence and improve patient outcomes. Adjuvant radiation is also crucial in patients with malignant phyllodes tumors, especially in cases with limited surgical margins. The study confirms the prudent use of radiation in high-risk malignant phyllodes tumors, improving outcomes and reducing recurrence risk.[18,20,21]

The study's limitations include a small sample size, insufficient follow-up period for long-term recurrence rates, and the absence of other biomarkers like p53 and Ki-67. Future research should focus on larger sample sizes and incorporate additional biomarkers to improve prognostic accuracy. Long-term follow-up is crucial for evaluating recurrence rates, and a multicenter approach could enhance the robustness of findings.

CONCLUSION

The study highlights the role of p53 and Ki-67 as biomarkers in predicting the behavior of phyllodes tumors and the likelihood of local recurrence. Both markers showed significant correlations with tumor aggressiveness, with increased Ki-67 and p53 expression associated with malignant histology. Clinical parameters like tumor size, age, and menopausal status are also crucial for predicting tumor behavior. Clean surgical margins are essential for minimizing local recurrence, especially in malignant cases. Postoperative irradiation may further reduce recurrence risk in high-risk patients. Integrating clinical, histological, and genetic data provides a comprehensive strategy for treating phyllodes tumors, allowing physicians to make more accurate treatment decisions.

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