



Original Research Article

Diagnostic Accuracy of Ki-67 in Predicting Response to Neoadjuvant Chemotherapy in Breast Cancer

Article History

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Abstract

Background: Ki-67 is a marker of cellular proliferation that may help predict response to neoadjuvant chemotherapy in breast cancer. Identifying patients who are more likely to achieve complete pathological response may assist in treatment planning, particularly in locally advanced breast cancer. **Objective:** To determine the diagnostic accuracy of Ki-67 in predicting complete pathological response to neoadjuvant chemotherapy in locally advanced breast cancer, taking postoperative histopathology as the gold standard. **Study Design:** cross-sectional study. **Place and Duration of Study:** Department of Surgery, Unit I, Chandka Medical College, Larkana, from July 2025 to October 2025. **Methodology:** A total of 168 female patients with locally advanced breast cancer were enrolled using a non-probability consecutive sampling technique. All patients received six cycles of anthracycline-based neoadjuvant chemotherapy at 21-day intervals, followed by surgery. Postoperative histopathological response was assessed using the Miller-Payne grading system, with Grade V considered complete pathological response. **Results:** The mean age was 44.18 ± 9.76 years and mean duration of symptoms was 7.32 ± 3.14 months. HR+/HER2- was the most common subtype in 63 (37.5%) patients. The mean Ki-67 level was $39.64 \pm 17.82\%$, and 81 (48.2%) patients had Ki-67 >35%. Complete pathological response was achieved in 82 (48.8%) patients. Ki-67 >35% correctly identified 57 true-positive and 62 true-negative cases, with 24 false-positive and 25 false-negative results. Sensitivity was 69.5%, specificity 72.1%, positive predictive value 70.4%, negative predictive value 71.3%, and overall diagnostic accuracy 70.8%. **Conclusion:** Ki-67 >35% demonstrated moderate diagnostic accuracy for predicting complete pathological response after neoadjuvant chemotherapy in locally advanced breast cancer. Ki-67 may be a useful pretreatment biomarker when interpreted together with molecular subtype and other clinicopathological features.

Keywords: Breast cancer, Ki-67, neoadjuvant chemotherapy, complete pathological response, diagnostic accuracy, Miller-Payne grading.

INTRODUCTION

Breast cancer is the most frequent type of cancer diagnosed in women and is an important cause of cancer-related morbidity and mortality worldwide. It is a moderately prevalent disease worldwide, with about 2.3 million (MM) new cases diagnosed each year [1,2]. The risk of breast cancer has been linked to a number of factors such as old age, genetic

susceptibility, obesity, reproductive factors, parity, and hormonal medication [3]. Treatment is dependent on the stage and biology of the tumour, and may involve breast conserving surgery, mastectomy, systemic chemotherapy, endocrine therapy, targeted therapy or palliative treatment if the disease is advanced [4]. Breast cancer is a heterogeneous disease, and there are additional

categories of breast cancer based on the expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2 (HER2). These molecular properties are significant when choosing systemic treatment and for predicting treatment response [5]. In patients with locally advanced or initially unresectable breast cancer, systemic treatment given prior to definitive surgery is known as neoadjuvant chemotherapy (NAC) [6]. The primary goals of NAC are: to shrink tumors, to downstage disease, to make surgery more likely to be a successful option, and (in selected patients) to allow breast-conserving surgery. But the reaction to NAC is not the same for everyone and only a certain percentage of patients get a complete pathological response [7]. Complete pathological response after NAC is an important measure of treatment effectiveness and may also be used to give useful prognostic information. Thus, knowing which patients are likely to respond to NAC prior to the end of chemotherapy treatment could assist the clinician in choosing patients who are most likely to benefit from NAC. The Ki-67 protein is a nuclear protein encoded by the gene MKI67, and is expressed in the actively cycling cells of the cell cycle, including the G1, S, G2 and M phases [8]. It is commonly used as a marker of tumor-cell proliferation and has been studied as a predictive and prognostic marker in breast cancer [9]. The complete pathological response rates after NAC have been reported as variable in the previous studies. In one study, complete response of the primary tumor was reported in 48.9% of the patients [10]. Another study reported a sensitivity of 69.7% and a specificity of 71.6% for Ki-67 for predicting complete pathological response at a cut-off point of 35% [11]. A previous study with a higher cut-off (Ki-67 > 28%) showed a sensitivity of 65.7% and specificity of 100% [12]. The results indicate that Ki-67 could potentially be useful to predict the disease but might not be equally effective across populations and tumor types. Even with these results, the local data on the accuracy of Ki-67 is still scarce [13].

METHODOLOGY

This cross-sectional study was conducted at the Department of Surgery, Unit I, Chandka Medical College, Larkana, from July 2025 to October 2025. A total of 168 female patients with locally advanced breast cancer were enrolled using a non-probability consecutive sampling technique. The sample size was calculated using the CPSP-recommended calculator for sensitivity and specificity, taking Ki-67 sensitivity as 69.7%, specificity as 71.6%, prevalence of complete pathological response as 48.9%, 95% confidence interval, and 10% desired precision. Female patients aged 18–60 years with locally advanced breast cancer were included. Patients with recurrent or bilateral breast cancer, those opting for

neoadjuvant chemotherapy before breast-conservation surgery, patients with chronic kidney disease with eGFR <60 mL/min, congestive cardiac failure, and pregnant females were excluded.

Data Collection

After approval from CPSP and the institutional ethical review committee, eligible patients were enrolled after obtaining written informed consent. Demographic and clinical information including age, residence, and duration of symptoms was recorded. Tru-cut biopsy reports were reviewed to document Ki-67 levels and breast cancer subtype. Ki-67 >35% was considered predictive of complete pathological response. All patients received six cycles of anthracycline-based neoadjuvant chemotherapy at 21-day intervals, followed by modified radical mastectomy or wide local excision. Resected specimens were sent for postoperative histopathological examination, and response was assessed using the Miller–Payne grading system. Grade V was considered complete pathological response. Findings were recorded on a predefined data collection proforma.

Statistical Analysis

Data were analyzed using SPSS version 26.0. Normality of continuous variables was assessed using the Shapiro–Wilk test. Age and Ki-67 levels were presented as mean±SD or median with interquartile range, as appropriate, while categorical variables including residence, cancer subtype, and complete pathological response were presented as frequencies and percentages. A 2×2 contingency table was constructed to calculate sensitivity, specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy of Ki-67, taking postoperative histopathology as the gold standard. Confounding variables including age and cancer subtype were controlled through stratification, and diagnostic accuracy measures were recalculated after stratification.

RESULTS

Among 168 patients, the mean age was 44.18±9.76 years and the mean duration of symptoms was 7.32±3.14 months. Most patients were from rural areas, 96 (57.1%), while 72 (42.9%) were urban residents. HR+/HER2– was the most common subtype in 63 (37.5%), followed by HR+/HER2+ in 39 (23.2%), triple-negative breast cancer in 38 (22.6%), and HR–/HER2+ in 28 (16.7%). The mean Ki-67 level was 39.64±17.82%, with Ki-67 >35% observed in 81 (48.2%) patients and ≤35% in 87 (51.8%) (Table 1).

Table 1. Baseline Demographic and Tumor Characteristics of Patients

Variable	Result
Total patients	168
Age, years, Mean±SD	44.18±9.76

Duration of symptoms, months, Mean±SD	7.32±3.14
Rural residence, n (%)	96 (57.1)
Urban residence, n (%)	72 (42.9)
HR+/HER2-, n (%)	63 (37.5)
HR+/HER2+, n (%)	39 (23.2)
HR-/HER2+, n (%)	28 (16.7)
Triple-negative breast cancer, n (%)	38 (22.6)
Ki-67 level, %, Mean±SD	39.64±17.82
Ki-67 >35%, n (%)	81 (48.2)
Ki-67 ≤35%, n (%)	87 (51.8)

Following neoadjuvant chemotherapy, 15 (8.9%) patients had Miller–Payne Grade I response, 23 (13.7%) Grade II, 28 (16.7%) Grade III, 20 (11.9%) Grade IV, and 82 (48.8%) Grade V response. Overall, complete pathological response was achieved in 82 (48.8%) patients, while 86 (51.2%) did not achieve complete pathological response. (Table 2).

Table 2. Pathological Response After Neoadjuvant Chemotherapy According to Miller–Payne Grade

Variable	Category	n (%)
Miller–Payne Grade	Grade I	15 (8.9)
	Grade II	23 (13.7)
	Grade III	28 (16.7)
	Grade IV	20 (11.9)
	Grade V	82 (48.8)
	Total	168 (100.0)
Pathological Response	Complete pathological response	82 (48.8)
	No complete pathological response	86 (51.2)
	Total	168 (100.0)

Using Ki-67 >35% to predict complete pathological response, 57 patients were true positives and 24 were false positives. Among patients with Ki-67 ≤35%, 25 were false negatives and 62 were true negatives. Thus, 82 patients had complete pathological response on histopathology, while 86 had no complete pathological response. (Table 3).

Table 3. Diagnostic Performance of Ki-67 >35% for Predicting Complete Pathological Response

Ki-67 Prediction	CPR Present	CPR Absent	Total
Ki-67 >35%	57 (TP)	24 (FP)	81
Ki-67 ≤35%	25 (FN)	62 (TN)	87
Total	82	86	168

Ki-67 >35% showed a sensitivity of 69.5% (95% CI: 58.9–78.4), specificity of 72.1% (95% CI: 61.8–80.5), positive predictive value of 70.4% (95% CI: 59.7–79.2), negative predictive value of 71.3% (95% CI: 61.0–79.7), and overall diagnostic accuracy of 70.8% (95% CI: 63.6–77.2). Stratified analysis showed diagnostic accuracy of 72.7%, 72.4%, and 68.6%

across the three age groups, while accuracy across tumor subtypes ranged from 65.8% in triple-negative disease to 74.4% in HR+/HER2+ tumors. (Table 4).

Table 4. Diagnostic Accuracy of Ki-67 for Predicting Complete Pathological Response

Diagnostic Measure	Value (%)	95% CI
Sensitivity	69.5	58.9–78.4
Specificity	72.1	61.8–80.5
Positive predictive value	70.4	59.7–79.2
Negative predictive value	71.3	61.0–79.7
Overall diagnostic accuracy	70.8	63.6–77.2

Stratified Diagnostic Accuracy

Variable	Category	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Age	18–30 years	70.0	75.0	70.0	75.0	72.7
	31–45 years	71.1	73.7	73.0	71.8	72.4
	46–60 years	67.6	69.4	67.6	69.4	68.6
Cancer subtype	HR+/HER2–	66.7	74.4	61.5	78.4	71.4
	HR+/HER2+	75.0	73.3	81.8	64.7	74.4
	HR–/HER2+	70.6	72.7	80.0	61.5	71.4
	Triple negative	64.7	66.7	61.1	70.0	65.8

DISCUSSION

This study aimed to assess the diagnostic performance of the Ki-67 marker in the prediction of the complete pathological response (CPR) to NAC in 168 patients with locally advanced breast cancer (LABC). The mean age of the patients was 44.18±9.76 years and the mean symptom duration was 7.32±3.14 months. The most common molecular subtype was HR+/HER2– (in 37.5% of the patients). In a previous study of patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, the median age was 48 years and the largest molecular group was luminal tumors (68%) [14]. These results suggest that the middle age group of women is often affected by locally advanced breast cancer and that patients with neoadjuvant treatment still have a substantial number of hormone receptor-positive cases. In the current study, 82 (48.8%) patients had complete pathological response while 86 (51.2%) patients had residual disease following neoadjuvant

chemotherapy. This result is similar to the previous study where full pathological response was seen in 48.9% of the patients after neoadjuvant chemotherapy [15]. Lower complete response rates of 16% to 34.7% have been reported in previous studies and so the pathological response can be quite variable depending on tumour stage, molecular subtype, chemotherapy regimen, HER2-targeted therapy and the definition of complete response [14,16]. The mean Ki-67 level in the present study was $39.64 \pm 17.82\%$, while 81 (48.2%) patients had Ki-67 >35%. With this cut-off, 57 patients were classified as true positives and 62 as true negatives, while 24 were false positives and 25 were false negatives. This corroborates the value of higher Ki-67 levels as a sign of higher sensitivity to chemotherapy. Previous studies among patients with locally advanced breast cancer also showed that there was a significant association between Ki-67 and complete pathological response ($p=0.00018$) with 63% achieving complete pathological response vs. 17% who had low Ki-67 [17].

In this study, the level of Ki-67 >35% had a sensitivity of 69.5% and specificity of 72.1% for prediction of complete pathological response. The positive predictive value was 70.4%, negative predictive value was 71.3% and overall diagnostic accuracy was 70.8%. This result is close to the previous study which defined the 35% as optimum cut-off for Ki-67 and obtained a sensitivity of 69.7% and specificity of 71.6% for prediction of complete pathological response [18]. In that study, Ki-67 >35% was also found to be an independent predictor of pathological complete response following neoadjuvant chemotherapy. The predictive value of Ki-67 has been also shown at other cut-off points. A previous study with a Ki-67 cutoff of 28% had a good predictive value for complete pathological response, achieving an AUC of 0.89 (95% CI, 0.75-0.96, $p<0.001$) [19]. The other previous study showed that a higher Ki-67 (>20%) was associated with increased complete pathological response rate compared to lower Ki-67 (<20%) (41.18% vs. 22.83%, $p=0.05$) [14]. Taken together, these observations have confirmed the correlation between high proliferation index and increased susceptibility to cytotoxic chemotherapy, but the most appropriate cut-off for Ki-67 varies between studies. The present stratified analysis revealed similar diagnostic accuracy in the different age groups, with an accuracy of 72.7% in the 18–30 age group, 72.4% in the 31–45 age group and 68.6% in the 46–60 age group. The same finding was observed by previous studies, which found that age was not significantly related with pathological complete response, but there was a trend toward higher overall response rates in younger patients compared to older patients (81.5% vs. 73.2%, $p=0.20$) [14]. This indicates that the predictive value of Ki-67 might not vary significantly with age in

adults. There was also some variation by molecular subtypes. The highest diagnostic accuracy was seen in HR+/HER2+ (74.4%), HR+/HER2– (71.4%), HR–/HER2+ (71.4%), and triple-negative (65.8%) tumors. The same has been shown by previous studies, which also revealed that the pathological complete response is linked to the HER2 status and molecular classification [20]. In the past, another study has reported a complete pathological response in 34.7 per cent of all cases, and 60 per cent of the pure HER2+ cases were complete responders [16]. The results point to the need for assessing Ki-67 in conjunction with hormone receptor and HER2 status and not as a standalone marker. There were a number of limitations in this study. It was a cross sectional study performed in one centre, with non-probability consecutive sampling, so the results may not be widely applicable and there could be selection bias. The sample size was quite small and Ki-67 was measured using a single cut-off value (Ki-67>35%), with different values reported in the literature. Long-term survival, recurrence or disease-free survival was also not assessed. Furthermore, the response to chemotherapy may have varied due to the biology of the tumors or due to molecular tumor types.

CONCLUSION

Ki-67 showed moderate diagnostic performance for predicting complete pathological response after neoadjuvant chemotherapy in locally advanced breast cancer. At a cut-off value of >35%, Ki-67 demonstrated a sensitivity of 69.5%, specificity of 72.1%, positive predictive value of 70.4%, negative predictive value of 71.3%, and overall diagnostic accuracy of 70.8%. These findings suggest that Ki-67 may be a useful pretreatment biomarker for identifying patients more likely to achieve complete pathological response, particularly when interpreted together with hormone receptor and HER2 status.

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