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Original Article

Assessing The Potential Value of KI-67 in Predicting the Therapeutic Response to Neoadjuvant Chemotherapy in Breast Cancer Patients in Indian Population and to Determine the Best Ki-67 Cutoff Value that Increases the Prediction Accuracy in Making Treatment Decisions

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Abstract

Objective: To assess the potential value of Ki-67 in predicting the therapeutic response to neoadjuvant chemotherapy in breast cancer patients in the Indian population and to determine the best Ki-67 cutoff value that increases the prediction accuracy in making treatment decisions.

Materials and Methods: This is a prospective observational study where breast cancer patients who underwent MRM/BCS surgery after neoadjuvant chemotherapy at SSKM and IPGMER Hospital between January 2024 and September 2024 in 50 patients. The clinical and pathologic characteristics of all patients were obtained from the hospital medical records. The clinical and pathological response to chemotherapy was determined.

Result: As a result of the analysis from this study, clinical and pathological responses to NST were significantly improved when Ki-67 levels were high >17% ($P = 0.05$). Furthermore, a better rate of pathological complete response (pCR) was significantly associated with tumor size <5 cm ($P = 0.02$), and vascular invasion when positive ($P = 0.023$).

Conclusion: Clinical and pathological responses to NST were significantly improved when Ki-67 levels were high >17. Furthermore, a better rate of pCR was significantly associated with tumor size <5 cm, and vascular invasion when positive. Our analysis showed that a Ki-67 cutoff >17% predicted a better pCR rate.

Key words: Breast cancer, Ki-67, Neoadjuvant chemotherapy, Tumor size

INTRODUCTION

A number of clinical trials have been undertaken to determine the predictive factors for clinical and pathologic responses to neoadjuvant chemotherapy (NACT) because prediction of chemotherapy outcomes helps doctors decide on the need for NACT. Since most chemotherapy drugs are associated with severe adverse effects, it is important to avoid unnecessary systemic chemotherapy that delays the administration of other treatments.

It is reasonable to presume that tumors with a higher level of cell proliferation might respond better to chemotherapy than tumors with lower proliferation. Ki-67 is widely known as a proliferative marker, and numerous studies have shown

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a positive correlation between Ki-67 expression and the proliferative cell fraction in tumors.[1,2]

In many cases, NACT decreases tumor size, which enables patients who were initially inoperable to undergo mastectomy and breast-conserving surgery in patients who required mastectomy.[3] The outcome of NACT can be determined in a relatively short time, which makes this approach useful for deciding which drugs or regimens are effective for specific pathologic conditions. Moreover, this is a useful modality for investigating the efficacy of specific biological markers as predictive and prognostic factors.

NACT does not provide a survival advantage compared to post-operative adjuvant therapy.[4] However, patients who achieve a pathologic complete response (pCR) have significantly improved disease-free survival and overall survival compared to those with residual cancer.[5]

Several studies have underscored the utility of Ki-67 in this context: wajid *et al*.[6] demonstrated that changes in Ki-67 expression after NACT are predictive of pCR in breast cancer patients. Fasching *et al*.[7] highlighted that a significant decrease in Ki-67 post-NACT is associated with improved clinical outcomes. Tanei *et al*.[8] reviewed the role of Ki-67 as a prognostic marker and found that its dynamic changes during NACT offer insights into tumor sensitivity to treatment and potential for disease relapse.

Therefore, many clinicians have examined the relationship between KI67 expression and chemotherapy response in patients with breast cancer, and breast cancer with a high Ki-67 expression level has repeatedly been shown to respond better to chemotherapy.[9,10]

However, there is no clear standard value for classifying Ki-67 expression as high or low, therefore, each study has used a different standard for the classification of Ki-67 levels. There is no study showing such a relationship of Ki-67 as a marker of response to NACT in the Indian population.

METHODOLOGY

Type of study – Prospective observational study where breast cancer patients who underwent MRM/BCS surgery after NACT at SSKM and IPGMER Hospital between January 2024 and September 2024.

Sample size – 50 patients

n (sample size)= $z\alpha^2(1-\text{Sensitivity}) \times \text{Sensitivity}/(P \times d^2)$ where P is Prevalence of the disease, d is precision here α = 5% hence $z\alpha$ (the value of the standard normal variate at 5% error) = 1.96

Sensitivity = 71%; prevalence is assumed at 40%. d = 20%. Using these values in the above formula, n comes as 50. Hence, a minimum of 50 patients will be included in the study.

Ethics clearance – Done by the Institute authority.

Patient criteria – Inclusion criteria – All patients who were pathologically diagnosed with invasive breast cancer.– Exclusion criteria – (1) Inflammatory breast cancer, (2) breast cancer with distant metastasis.

The clinical, pathologic, and histologic characteristics of all patients will be obtained from the hospital medical records.

The clinical response to chemotherapy will be determined by comparing the baseline tumor size to the tumor size after NACT using radiological imaging.

For the quantitative analysis of clinical response to chemotherapy – Response Evaluation Criteria in Solid Tumors guidelines are as follows:

- Clinical complete response (cCR), disappearance of all target lesions with a reduction in the short axis of any pathologic lymph nodes to <10 mm
- Clinical partial response (cPR), a decrease of at least 30% in the sum of the diameters of the target lesions, with reference to the sum of the baseline diameters
- Clinical progressive disease (cPD), an increase of at least 20% in the sum of the diameters of the target lesions, with reference to the smallest sum recorded in the study; and
- Clinical stable disease (cSD), the presence of lesions with neither sufficient shrinkage to qualify as cPR nor sufficient increase to qualify as cPD.

The residual tumor size and lymph node status will be evaluated to assess the pathologic response to NACT

- pCR
- Non-complete pathological response – if evidence of residual invasive carcinoma is present either by positive resection margin or by evidence of metastasis to axillary lymph nodes, or both.

Statistical Analysis

The data are tabulated in Microsoft Excel and analyzed with Statistical Package for Social Sciences V.24 software. The continuous variables are presented with mean and standard deviation. The categorical variables are presented with frequency and percentage. The Chi-square test is used for the statistical analysis. The optimal cutoff value for the Ki-67 percentage was assessed by receiver operating characteristic (ROC) curve analysis and the area under the curve. The cutoff value refers to the value corresponding to

maximum sensitivity and minimum specificity. The cutoff value for Ki-67 used in our series to define either high or low classification was 17%. The $P \leq 0.05$ is considered statistically significant.

RESULTS

In total of 57 patients were selected for the study. The patient characteristics showed that the mean age of the patients was 48.7 ± 8.47 years. Of the patients, 32% were pre-menopausal and 68% were postmenopausal. Regarding the tumor size, 56% had <5 cm and 44% had >5 cm. Nodal status was positive for 40% and negative for 30% of the patients [Table 1].

Regarding the cancer stage, 2% of the patients were in stage 1, 26% in stage 2A, 24% in stage 2B, 14% in stage 3A, and 34% in stage 3B. The majority of patients, 38%, underwent six cycles of chemotherapy, whereas 36% had eight cycles. Only 14%, 10%, and 2% of the patients received three, four, and five cycles, respectively [Table 1].

As for the NST regimens, 6% of patients received the AC regimen, 46% received AC+T, and 48% received the AC+T+TR regimen. In terms of surgical intervention, 26% of patients underwent BCS with ALND, 2% underwent BCS with SLNB, 62% MRM and 10% underwent MRM with reconstruction. Histologically, 96% of the tumors were ductal, and 4% were lobular [Table 1].

For nuclear grading, 4% of patients had grade 1 tumors, 84% had grade 2, and 12% had grade 3. Vascular invasion was present in 14% of cases and absent in 86%. Estrogen receptor (ER) positivity was observed in 40% of patients, whereas 60% were ER-negative. Progesterone receptor (PR) status showed the same distribution as ER, with 40% being positive and 60% negative. H2N was positive in 66% of patients and negative in 34% [Table 1].

When considering molecular subtypes, 20% of patients were classified as Luminal A, 30% as Luminal B, 20% as H2N enriched, and 30% had triple-negative breast cancer (TNBC). With the study cutoff value of Ki-67 >17%, 29 patients (58%) were considered to have a high level of Ki-67 as shown in Figure 1.

After NST, 18% of patients showed cCR, 56% had cPR, 14% had cPD, and 12% had Csd [Figure 2].

The complete absence of residual invasive carcinoma cells in the breast was confirmed by histological examination in 27 patients (54%); however, 23 (46%) patients had residual carcinoma cells in the breast or in the resected lymph nodes.

Table 1: Distribution of patient characteristics

Patient characteristics	Values
Age, years	
Mean±standard deviation	48.7±8.47
Menopausal status	
Pre-menopausal	16 (32%)
Post-menopausal	34 (68%)
Tumor size	
<5 cm	28 (56%)
>5 cm	22 (44%)
Nodal status	
Positive	20 (40%)
Negative	30 (60%)
Cancer stage	
1	1 (2%)
2A	13 (26%)
2B	12 (24%)
3A	7 (14%)
3B	17 (34%)
Number of cycles	
3	7 (14%)
4	5 (10%)
5	1 (2%)
6	19 (38%)
8	18 (36%)
NST regime	
AC	3 (6%)
AC+T	23 (46%)
AC+T + TR	24 (48%)
Type of surgery	
BCS+ALND	13 (26%)
BCS+SLNB	1 (2%)
MRM	31 (62%)
MRM+RECON	5 (10%)
Histological type	
Ductal	48 (96%)
Lobular	2 (4%)
Nuclear grade	
1	2 (4%)
2	42 (84%)
3	6 (12%)
Vascular invasion	
Present	7 (14%)
Absent	43 (86%)
Estrogen receptor	
Positive	20 (40%)
Negative	30 (60%)
Progesterone receptor	
Positive	20 (40%)
Negative	30 (60%)
H2N	
Positive	33 (66%)
Negative	17 (34%)
Molecular subtypes	
Luminal A	10 (20%)
Luminal B	15 (30%)
H2N enriched	10 (20%)
Triple-negative breast cancer	15 (30%)
Ki-67	
<17%	21 (42%)
>17%	29 (58%)
C response	
Clinical complete response	9 (18%)
Clinical partial response	28 (56%)
Clinical progressive disease	7 (14%)
Clinical stable disease	6 (12%)
P response	
Pathological complete response	27 (54%)
Non-pathological complete response	23 (46%)

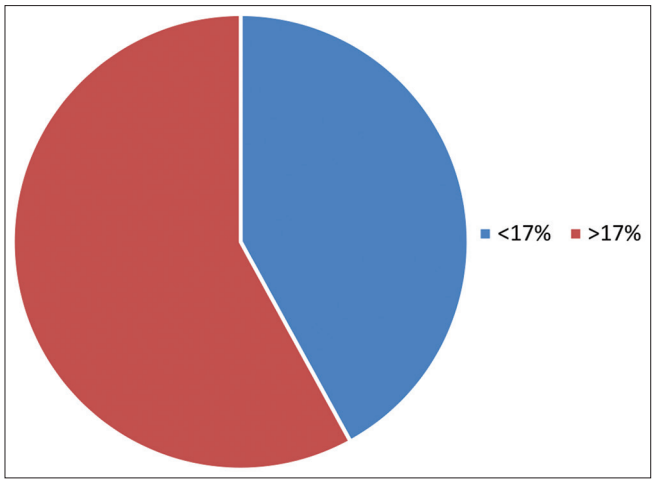

Figure 1: Ki-67% cutoff distribution

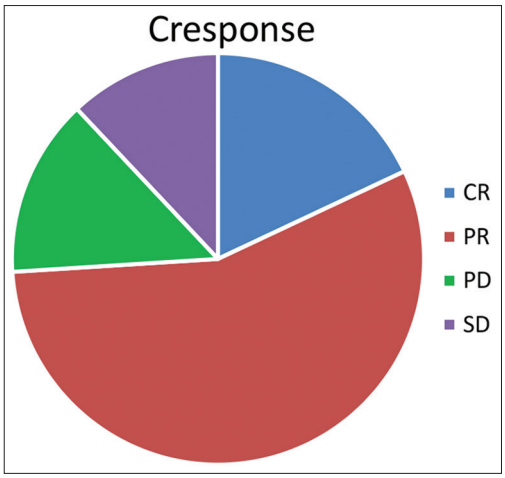

Figure 2: Distribution of clinical response in patients

Analysis of the Relationships Between the pCR Rate and Ki-67

As a result of the analysis from this study, clinical and pathological responses to NST were significantly improved when Ki-67 levels were high >17% ($P = 0.05$). Furthermore, a better rate of pCR was significantly associated with tumor size <5 cm ($P = 0.02$), and vascular invasion when positive ($P = 0.023$) [Table 2].

For the Luminal A subtype, 50% of the patients had Ki-67 levels below 17%, and 50% had Ki-67 levels above 17% [Figure 3]. For the Luminal B subtype, 26.7% of the patients had Ki-67 levels below 17%, whereas 73.3% had Ki-67 levels above 17%. For the HER2 enriched subtype, 70% of the patients had Ki-67 levels below 17%, while 30% had Ki-67 levels above 17%. For the TNBC subtype, 33.3% of the patients had Ki-67 levels below 17%, and 66.7% had Ki-67 levels above 17% [Table 3]. There was no significant association between Ki-67 levels and molecular subtypes ($P = 0.145$)

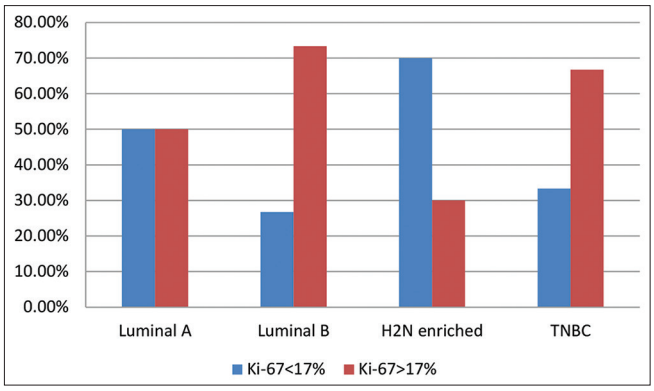

Figure 3: Relation of Ki-67 with different molecular subtypes

DISCUSSION

Ki-67 is considered to be of prognostic value as a proliferative marker. It is also considered to be a modulator and has been shown to be an appropriate endpoint for pre-operative studies involving hormonal therapies.[11-13] A decrease in Ki-67 pre-surgically serves as an appropriate surrogate marker for outcomes in patients who are administered antiestrogen therapy.[14]

There is not a universally defined cutoff value for categorizing Ki-67 expressions. The Ki-67 cut points are used in various ranges, from 5% to 34%.[2] In a study of prognostic factors in breast cancer, the researchers determined a cut-off value for Ki-67 at 12%.[10] This value was observed in patients without recurrence, providing a rationale for their categorization. In another related study, a cutoff value of 20% was adopted.[15] Our study population of 50 patients showed a pCR of 70.4% in patients with a Ki-67 value of more than 17% which was significant ($P = 0.05$).

High Ki-67 level is correlated with an increased probability of achieving pCR in breast cancer patients undergoing NAC.[16] This correlation can be explained by the fact that high Ki-67 represents rapidly dividing cells and that NAC typically targets dividing cells, resulting in enhanced elimination of tumor cells.[17]

Tumor size has been considered in numerous studies as a predictor of pCR. Consistent with our findings, Chen *et al*.[18] in their study, which included 1010 BC patients, concluded that tumor sizes <4 cm were more likely to attain pCR ($P = 0.039$). This finding parallels with the idea that small tumors might exhibit a more robust response to treatment.[19] Our study confirms similar results, with a pCR rate of 62.9% for tumors <5 cm versus 37.1% for tumors >5 cm ($P = 0.02$).

A molecular subtype is another factor that has been

Table 2: Association of *P* response with patient characteristics

Patient characteristics	*P*-response		*P*-value
	Pathological complete response (%)	Non-complete pathological response (%)	
Menopausal status			
Pre-menopausal	9 (33.3)	7 (30.4)	0.827
Post-menopausal	18 (66.7)	16 (69.6)	
Tumor size			
<5 cm	17 (62.9)	11 (47.8)	0.02
>5 cm	10 (37.1)	12 (52.2)	
Nodal status			
Positive	8 (29.6)	12 (52.2)	0.105
Negative	19 (70.4)	11 (47.8)	
Cancer stage			
1	1 (3.7)	0 (0.0)	0.092
2A	7 (25.9)	6 (26.1)	
2B	9 (33.3)	3 (13)	
3A	5 (18.5)	2 (8.7)	
3B	5 (18.5)	12 (52.2)	
Histological type			
Ductal	25 (92.6)	23 (100)	0.183
Lobular	2 (7.4)	0 (0.0)	
Nuclear grade			
1	0 (0)	2 (8.7)	0.279
2	24 (88.9)	18 (78.3)	
3	3 (11.1)	3 (13)	
Vascular invasion			
Present	1 (3.7)	6 (26.1)	0.023
Absent	26 (96.3)	17 (73.9)	
Estrogen receptor			
Positive	12 (44.4)	8 (34.8)	0.487
Negative	15 (55.6)	15 (65.2)	
Progesterone receptor			
Positive	13 (48.1)	7 (30.4)	0.203
Negative	14 (51.9)	16 (69.6)	
H2N			
Positive	19 (70.4)	14 (60.9)	0.480
Negative	8 (29.6)	9 (39.1)	
Molecular subtypes			
Luminal A	6 (22.2)	4 (17.4)	0.764
Luminal B	9 (33.3)	6 (26.1)	
H2N enriched	4 (14.8)	6 (26.1)	
Triple-negative breast cancer	8 (29.6)	7 (30.4)	
Ki-67			
<17%	8 (29.6)	13 (56.5)	0.05
>17%	19 (70.4)	10 (43.5)	

Table 3: Association of Ki-67 with molecular subtypes

Ki-67 (%)	Luminal A (%)	Luminal B (%)	H2N enriched (%)	Triple-negative breast cancer (%)	*P*-value
<17	5 (50)	4 (26.7)	7 (70)	5 (33.3)	0.145
>17	5 (50)	11 (73.3)	3 (30)	10 (66.7)	

correlated with pCR.[20] The improvement in pCR rates in these molecular subgroups may be due to the elevated levels of Ki-67 frequently observed in tumors with negative hormone receptors or exhibiting HER-2 overexpression.[21] Nonetheless, Petit *et al*.[21] concluded that the absence of hormone receptor expression (ER and PR) in the high Ki-67 group was a predictor of pCR ($P = 0.008$ and $P = 0.01$, respectively). However, HER-2 overexpression was not significantly associated with achieving pCR ($P = 0.99$). In our study, there was no significant association between Ki-67 levels and molecular subtypes ($P = 0.145$).

Another question is the impact of the chemotherapy regimen on achieving pCR in patients with high Ki-67. The meta-analysis of Chen *et al*.[18] demonstrated that Ki-67 was also a useful predictor of pCR in patients receiving chemotherapy regimens containing anthracyclines and/or taxanes ($n = 13$; OR: 2.90), anthracyclines plus taxanes

(n = 22; OR: 3.15), and anthracyclines (n = 5; OR: 4.67), compared to taxanes alone (n = 3; OR: 1.29).

Our study has some limitations. The small size of our sample contributed to the variability of certain results compared to other studies. Furthermore, there was no standard cutoff value for Ki-67. It was determined, in our study, using the ROC curve, which combines sensitivity and specificity. Further studies are necessary, involving larger patient groups with analyses of cutoff values, subtypes, and outcomes, which will reinforce the present findings.

CONCLUSION

Our results confirm the predictive role of Ki-67 in patients' response to chemotherapy in the neoadjuvant setting. The findings of the present study suggest that this marker could help select patients who may benefit from chemotherapy. Conclusion from this study, clinical and pathological responses to NST were significantly improved when Ki-67 levels were high >17% (P = 0.05). Furthermore, a better rate of pCR was significantly associated with tumor size <5 cm, and vascular invasion when positive. Our analysis showed that a Ki-67 cutoff >17% predicted a better pCR rate. Validation of this cutoff value in a larger population would be desirable.

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