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Ki -67 proliferative index as a predictive tool for axillary pathological complete response in node-positive breast cancer

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Abstract

Background: *Upfront chemotherapy is considered the standard of care in the management of early breast cancer including node-positive disease.Ki-67 proliferation index is a biomarker that can be used to predict the histopathological response to therapeutic upfront chemotherapy in the breast primary tumor as well as predict the prognosis.*

Objective: *Our aim in this study, to address the predictive/prognostic value of Ki-67 proliferative index in downgrading the axilla in node-positive breast cancer.*

Material and Methods: *A group of 64 patients included, have been diagnosed with node-positive breast cancer and triaged for neoadjuvant chemotherapy before surgical intervention. The Ki-67 proliferative index has been measured before chemotherapy and the correlation between Ki-67 expression and achievement of pathological complete response has been explored.*

Results: *The patient's group with high Ki-67 and both breast and axillary p-CR is 08 patients (12.5%), and the group with high Ki-67 and only axillary p-CR is 07 patients (11%), which gives a sum of 15 patients (23.4%) who achieved p-CR.*

Conclusion:
The outcome of the current study shows that there was a marginally significant correlation between the p-CR (Complete Pathological Response) and higher rates of Ki-67 expression.

Keywords: *Breast cancer, Ki-67, Neoadjuvant chemotherapy, Axillary lymph nodes*

I. INTRODUCTION

The primary breast cancers usually metastasize to lymph nodes, lungs, bones, and brain, however, metastasis to the axillary lymph nodes is recognized as a loco-regional disease which amenable to curative treatment [1]. Since the discovery of Ki-67 in early the 1980s by Gerdes, Ki-67 has increasingly been used as a diagnostic, prognostic, and predictive tool in cancer management in addition to its role in cancer targeted therapy[2]. Some reports claimed that patients with a higher level of Ki-67 expression are more susceptible to disease recurrence and poor prognosis [3].

II. OBJECTIVES

In this study, we addressed the predictive/prognostic value of Ki-67 proliferative index in downgrading the axilla in node-positive breast cancer.

III. MATERIAL & METHODS

Sixty-four patients have been enrolled in this cohort (who were diagnosed by imaging-guided biopsy of breast tumors and lymph nodes, all had proven to have the node-positive disease), all have been recommended to have upfront chemotherapy before surgery. The prognostic and predictive value was assessed by evaluation of the degree of pathological response to upfront chemotherapy in both breast tumor as well as the axillary lymph nodes.

IV. RESULTS

All the patients were of the female gender, age ranges between 27 and 82 years. Tumour size ranges between 09 and 109 mm with the most frequent size of T2(60%), followed by T3(23%) where T1 only 15%, (see Fig.1). Most of the histology subtype was invasive carcinoma, NST in 58 patients (90%), followed by invasive lobular carcinoma in 3 patients (04.6%) (see Fig.2). The histological grade was G I in 3 patients (5%), G II in 31 patients (48%), and G III in 30 patients (47%) (see Fig.3). The immunohistochemistry analysis showed ER-positive in 42 patients (66%), Her-2/neu positive in 26 patients (40%), and triple-negative disease in 10 patients (15.6%)(see Table.1). Most of the cases (77%) had high Ki-67 expression, with a cut-off point of 20%.
Pathological complete response (p-CR) in both breast and axilla has been achieved in 13 patients (20.3%), and in axilla only in 07 patients (11%) (see Table 2 and Fig.4).
The patient's group with high Ki-67 and both breast and axillary p-CR is 08 patients (12.5%), and the group with high Ki-67 and only axillary p-CR is 07 patients (11%), which gives a sum of 15 patients (23.4%) who achieved p-CR (see Table 3).

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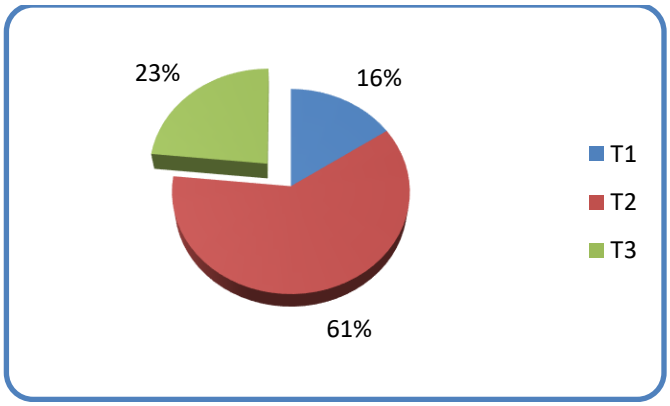

Figure 1. Tumour size distribution in 64 patients with early breast cancers.

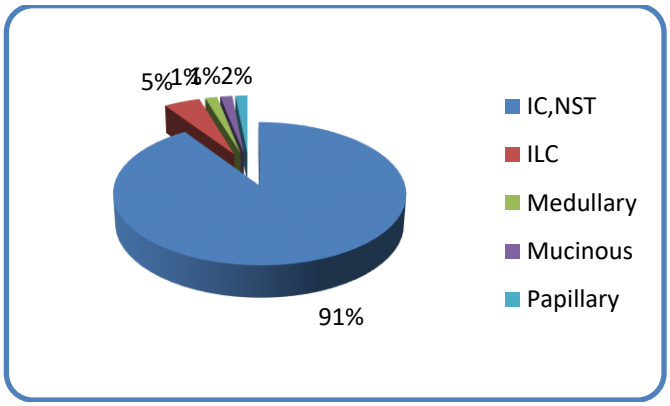

Fig.2: Histopathological subtypes in 64 patients with early breast cancers.IC, NST: Invasive carcinoma of no special type. ILC: Invasive lobular carcinoma

V. DISCUSSION

Worldwide, breast cancer is regarded as the most commonly detected female cancer and the second most common cancer overall. In the UK, breast cancer is the most common cancer UK, as it accounts for accounting for 15% of all newly diagnosed cancers. Breast cancer is a heterogeneous disease with several biological subtypes, the most common phenotype is invasive ductal carcinoma of no special type, followed by invasive lobular carcinoma and other less frequent types as mucinous and medullary carcinoma[4, 5]the image used in each figure is clear, Neo-adjuvant chemotherapy is one of the standard therapeutic modalities used in the management of invasive breast, it enables the clinician to reduce the initial tumor size and converts the inoperable tumor to a resectable one as well as improves the chance of performing breast conservation surgery rather than mastectomy.Ki-67 proliferative index is a nuclear antigen protein, expressed in all stages of the cell cycle, however not in the G0 (Resting phase).

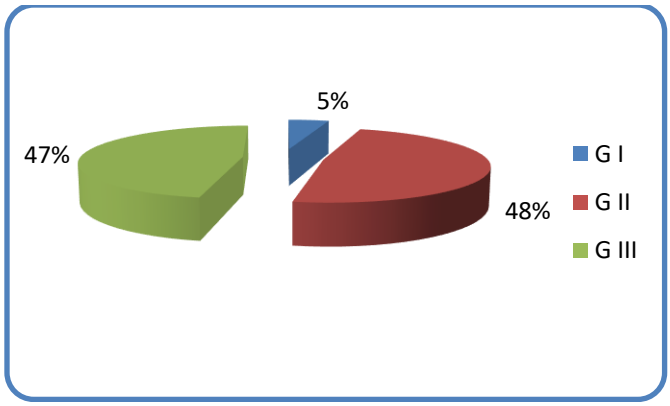

Figure 3: Histopathological grade in 64 patients with early breast cancer.

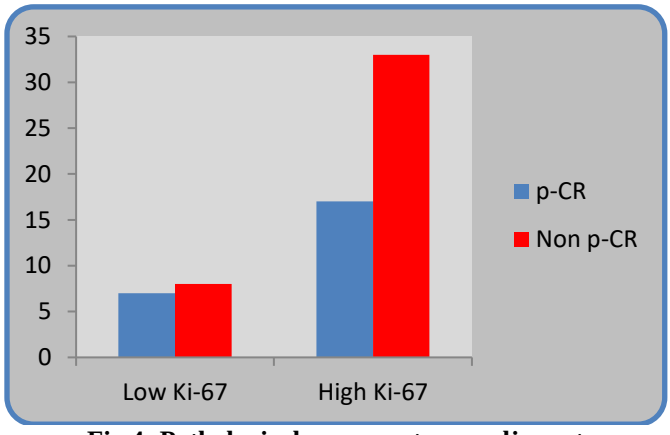

Fig.4: Pathological response to neoadjuvant chemotherapy in 64 patients with early breast cancers.
p-CR: Pathological complete response. Non-p-CR: Pathological incomplete response.

It has been reported for the first time by Gerdes et al in 1983, it was mentioned that Ki-67 was present in proliferating cells, but not detected in resting cells, a mouse monoclonal antibody directed against a nuclear antigen from a Hodgkin's lymphoma-descended cell line was used in this module [6-8].

Cancer proliferation assessment by the Ki-67 labeling index estimation has increasingly become an essential biomarker of early-stage breast cancer management [9]. An association has been found between Ki-67 expression and the common histopathological parameters, the strongest correlation was detected between the histological grading and Ki-67 expression. The previous reports concluded that the Ki-67 proliferative index has an independent prognostic value in terms of breast cancer patients' overall survival as well as tumor recurrence rate.

Table 1: Immunohistochemical criteria of 64 confirmed invasive breast carcinomas., Ki-67 cutoff point is 20%.

Variable	*Cases number*	*Percentage*
ER+,PR+,Her2/neu-	22	34.3
Triple positive *	11	17.1
ER-,PR-,Her2/neu+	10	15.6
Triple negative**	10	15.6
ER+,PR-,Her2/neu+	5	07.81
ER+,PR-,Her2/neu-	4	06.2
ER-,PR+,Her2/neu-	2	03.1
High Ki-67 (>20%)	49	77.0
Low Ki-67 (≤20%)	15	23.0

*ER+/PR+/HER2+; **ER-/PR-/HER2

Table 2: Pathological response to neoadjuvant chemotherapy on the postoperative samples for 64 breast cancer patients.

Variable	*Percentage*
Breast and axilla p-CR	20.3
Breast and axilla non-p-CR	59.3
Breast only p-CR*	01.5
Axilla only p-CR	12.5
Breast only non-p-CR	06.25

*Breast showed residual 1mm DCIS only.

It is well-documented that stronger expression of the Ki-67 proliferative index is significantly associated with high relapse and poor survival rates [10-12], and a cut-off >25 % threshold of Ki-67 is associated with higher mortality compared with lower expression rates [13]. When upfront chemotherapy is indicated in breast cancers, including luminal-type breast cancers, the use of Ki-67 proliferative index as a biomarker becomes increasingly included in the pre-treatment assessment for this therapy choice [9].processing of papers for publication. If you need to refer to an Internet email address or URL in your paper, you must type out the address or URL fully in Regular font.

Recently the concept of restaging the axilla post upfront chemotherapy became the subject of many types of research and clinical trials. The current study enrolled 64 patients with confirmed node-positive breast cancer. All were treated with neoadjuvant chemotherapy before surgery which included breast surgery(mastectomy or breast conservation surgery) and axillary node clearance. We evaluated the correlation between Ki-67 proliferative index expression and the degree of pathological response to chemotherapy in the axilla. With a cut-off point of 20%, we have observed that Ki-67 was high in 77 % of patients and 50% of the cohort had Ki-67 expression in 70% or more of tumor cells.

Table 3: Correlation between Ki-67 expression and the pathological response to neoadjuvant chemotherapy on the postoperative samples for 64 breast cancer patients.

Variable	*Percentage*
High Ki-67, breast and axilla p-CR	12.5
High Ki-67, breast and axilla non-p-CR	46.8
High Ki-67, breast only p-CR	07.8
High Ki-67, axilla only p-CR	10.9
Low Ki-67, breast and axilla p-CR	09.3
Low Ki-67, breast and axilla non-p-CR	12.5
Low Ki-67, breast only p-CR	0
Low Ki-67, axilla only p-CR	0

Pathological complete response (p-CR) in both breast and axilla has been achieved in 13 patients (20.3%), and in axilla only in 07 patients (11%). The patient's number with high Ki-67 and both breasts and axillary p-CR is 08 (12.5%), and the group with high Ki-67 and only axillary p-CR is 07 patients (11%), which gives a sum of 15 patients (23.4%) who achieved p-CR. This indicates a marginally significant correlation between the p-CR (Pathological Complete Response) and higher rates of Ki-67 expression.

- The axillary lymph nodes status is recognized as the most important determinant of breast cancer overall survival, and node-negative disease patients have a favorable prognosis and survival [14]. A positive correlation between nodal status and the degree of Ki-67 expression has been found, as node-negative cancers are more likely to have a low Ki-67proliferation index level [15], in our study 77% of cases were associated with high expression of Ki-67. The ability to identify significant correlations between the breast a specific biomarker and the axillary pCR to neoadjuvant chemotherapy may help to identify a subgroup of breast cancer cases who might benefit from re-staging investigations/procedures and de-escalation of the radical axillary surgery, where the surgery could be limited or even omitted. The concept of restaging the axilla post upfront chemotherapy recently became increasingly the subject of different clinical trials, however performing re-staging sentinel lymph node biopsy post-neo-adjuvant chemotherapy is faced with some reluctance, this is due to the high FNR (False Negative Rate) up to 12.6% in (Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer trial) which also known as (ACOSOG)Z1071 trial [16], and even a higher FNR of 14.2% quoted in SENTINA (Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy trial)[17].

VI. CONCLUSIONS

The outcome of the current study shows the prognostic and predictive significance of high K-i67 expression in node-positive breast cancer before upfront chemotherapy. Based on the results of this paper, the level of the Ki-67 proliferative index can provide complementary information

aside from other biomarkers as molecular subtypes, receptor status which is helpful to predict the degree of the pathological response to chemotherapy.

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