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Study of response of axillary lymph nodal metastases toneoadjuvant chemotherapy in carcinoma breast

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***Abstract*---**Background and aim of the study: Our study aims to evaluate pathological response in axillary lymph nodes with neoadjuvant chemotherapy. Absence of invasive disease in breast and axilla after completion of neoadjuvant chemotherapy on histological examination was taken as pathological complete response (pCR). Absence of invasive disease in axilla after completion of chemotherapy on histological examination was taken as pathological complete response in axilla. Materials and Methods: A prospective observational study was conducted on breast cancer patients who were treated at MNJ Institute of Oncology and Regional Cancer Centre for a period of 22 months. A total of 55 with operable breast cancer and cytologically proven axillary lymph node metastases and subsequently received neoadjuvant chemotherapy were considered for this study. All these patients were registered in our hospital and were followed prospectively. Of them, 2 patients defaulted chemotherapy, 3 patients did not visit hospital after completion of chemotherapy and 1patient died due to reason other than carcinoma breast and all these patients were excluded from the study. Results:In this study, we had pathological complete response in breast and axilla in 24.5% of the study population. ER negativity and PR negativity being statistically significant predictive factors and her2neu also being a predictive factor though it did not appear to be statistically significant. In our study, ER negative patients showing 40% pCR in axilla compared to

8.3% pCR in axilla in ER positive patients. PR status also had similar type of response in axilla. These results were statistically significant (p=0.016 and p=0.010 respectively). We saw a non- significant raise in the rates of pCR in axilla in her2neu positive breast cancer patients compared to her2neu negative breast cancer patients.Only 1 patient with her2neu positive breast cancer received trastuzumab due to financial constraints. Probably this could be the reason for only a nonsignificant increase in pCR rates. The present study showed pathological complete response in axilla was seen in 5.8% of HR+/her2neu-, 40% of HR-/her2neu+, 40% of TNBC and 14.3% of HR+/her2neu+ breast cancer patients. However, our study did not find a significant difference in pCR rates in axilla when different molecular subtypes were compared (p=0.078). This non significance could be due to smaller sample size. Conclusion: Age, menopausal status, clinical tumor size, clinical nodal status did not significantly effect the pathological response in axilla. But, reduction in tumour size has a significant correlation with pathological complete response in axilla.

***Keywords*---**pathological response, axillary lymph nodes, neoadjuvant chemotherapy.

Introduction

Breast cancer is the most common malignancy diagnosed in females and it is the most common leading cause of cancer related deaths in females. In both sexes combined, it is the second most common m1alignancy diagnosed second to lung cancer. As per GLOBOCAN 2018 estimates, 2,088,849 new breast cancer cases would be diagnosed per annum which accounts to about 11.6% of cancers from all sites. About 626,679 deaths were estimated from breast cancer and this constitutes about 6.6% of all cancer related deaths[1].

Neoadjuvant chemotherapy has been increasingly used in treatment of operable breast cancer to reduce mortality from breast cancer with reduced toxicity, to improve surgical options and to acquire early information on response and biology of the disease[2]. Predicting chances of response to systemic therapy is an important challenge. So, patients who have less chances of pathological complete response(pCR) might be spared unnecessary toxicity if low chance of clinically useful response is predictable prior to administration of systemic chemotherapy[3]. Various molecular subtypes respond to chemotherapy in different manner, with luminal A subtypes having the least favorable responses compared with luminal B, triple-negative, or HER2- overexpressing tumors. Thresholds for using NACT have decreased to facilitate breast conservation, especially in HER2/neu receptor positive cancers with high predicted partial, or indeed complete, pathologic response[4].

Pathological complete response to neoadjuvant chemotherapy is the best predictor of overall survival. It stands as an important surrogate marker for long term outcomes such as overall survival and disease-free survival[5]. Neoadjuvant

chemotherapy converts approximately 40-50% of node positive disease to node negative disease[6]–[8].

Aims & objectives of the study

AIMS: To evaluate the response of axillary lymph nodal metastases to neoadjuvant chemotherapy in carcinoma breast
OBJECTIVE: To evaluate pathological response of axillary lymph nodal metastases after neoadjuvant chemotherapy in patients with carcinoma of breast.

Materials & Methods

A prospective observational study was conducted on breast cancer patients who were treated at MNJ Institute of Oncology and Regional Cancer Centre for a period of 22 months (from the time of ethical approval).

Inclusion criteria:

- Locally advanced breast cancer patients who received neoadjuvantchemotherapy.
- Women aged more than 18years.

Exclusion criteria:

- Recurrent breastcancer.
- Patients with distantmetastases.

*Sample size:*Fifty-five breast cancer patients who received neoadjuvant chemotherapy were considered and forty-nine patients who subsequently underwent surgery were included in the study.
Methods: Breast cancer patients who had cytologically proven ipsilateral axillary lymph node metastases and then received neoadjuvant chemotherapy were included in the study. After receiving neoadjuvant chemotherapy, clinical and radiological response was assessed and planned for surgery as indicated. Histopathology was reviewed and pathological response of axillary lymph nodes was evaluated.
Statistical analysis: Data was collected and analyzed by ExelStat and SPSS software using appropriate statistical tests.

Results

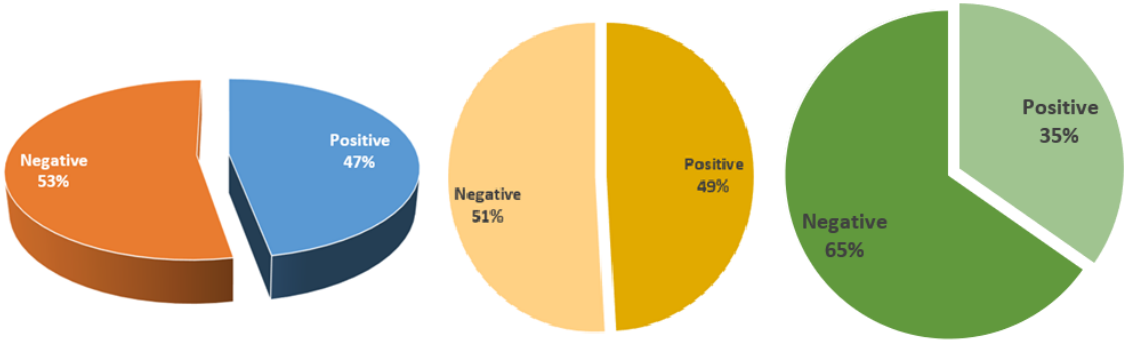
Table 1: Baseline characteristics of the patients of the study population

Total number(n=49)		
Age	Mean	46.78 yr(SD=+/-10.68)
	Range	27 yr-75 yr
	<30 yr	2
	31-40 yr	16
	41-50 yr	16

	51-60 yr	9
	61-70 yr	5
	>70 yr	1
Menopausal status	Premenopausal	21
	Postmenopausal	28

Among 49 patients included in the study, all patients underwent modified radical mastectomy. The age and menopausal status of the study population is depicted in Table 1.

Figure 1: ER, PR and her2neu status of the study population



The ER Negative is 53% and positive is 47%, PR negative is 54% and positive is 49% and negative 65% and positive 35% of her2neu receptor status of the study population are depicted in the above figure respectively. All patients received neoadjuvant chemotherapy and all patients underwent modified radical mastectomy.

Table 2: Tumour characteristics of the study population after NACT

Tumour Characteristics after NACT		Number
ycT	T0	14
	T1	8
	T2	12
	T3	4
	T4	11
ycN	N0	34
	N1	14
	N2	0
	N3	1
cCR	ycT0N0	14

All patients had infiltrating ductal cell carcinoma on histopathological examination. Majority of the patients had grade 2 (47/49) and one patient each

had grade 1 and grade 3 carcinoma.Clinical complete response was defined asabsence of tumorin breast and axillaon clinical and radiological examination. One patient had ipsilateral supraclavicular lymph node metastasesbefore chemotherapyandshehadnoresponsewithchemotherapy.Shedidnothavemetastases elsewhere. Modified radical mastectomy including level 3 and supraclavicular lymph node clearance was done in thispatient.

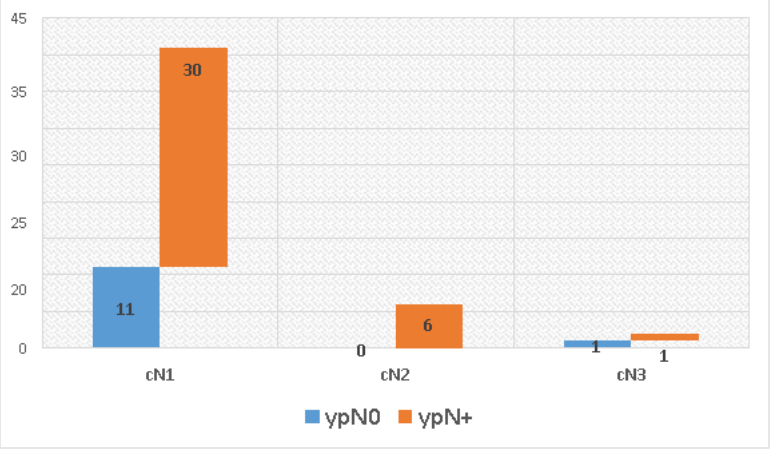
Results of histopathological examination

Pathological complete response was defined as absence of invasive disease in complete resected breast specimen and all sampled regional lymph nodes on pathological examination aftercompletion of neoadjuvant systemic therapy. The pCR rate in our study population was 24.5%. All patients with no residual disease in axilla did not have any residual disease in breast too.

Relationship of age with pathological complete response in axilla

The relationship of age group with pathological complete response in axilla was evaluated and tabulated. The relationship between age group and pathological complete response in axilla was not statistically significant (p=0.329). Therelationshipbetweenmenopausalstatusandpathologicalcompleteresponseinaxill ahasbeen tabulatedMenopausal status was not a significant predictive factor for pathological complete response in axilla (p=0.443). The relationship between baseline tumor stage and pathological complete response in axilla has been tabulated among 27 patients who had cT3 tumors, 6 (22.2%) had pathological complete response in axilla where as 6out of 21 patients (28.6%) withcT4 tumorshadpathologicalcompleteresponseinaxilla. The relationship was not statistically significant(p=0.589).

Figure 2: Relationship between nodal stage and pathological complete response in axilla



Of 41 patients with baseline cN1 disease prior to neoadjuvant chemotherapy, 11 patients (26.8%) had complete absence of invasivediseaseinaxilla after completion

of chemotherapy. Noneofthe patients with cN2 disease had complete pathological response in axilla. Of the two patients with cN3 disease, one patient had complete response on histopathological examination of regional lymph nodes. This relation was not statisticallysignificant(P=0.250).

Table 3: Relationship between ER status and pathological complete response in axilla

	ypN0	ypN+	
ER positive	2	21	23
ER negative	10	16	26
	12	37	49

Two patients (8.3%) with ER positivity had complete pathological response in axilla among 23 ER positive carcinoma breast patients.Instead,40%ofERnegativepatients(10/26)hadcomplete response in axilla on pathological evaluation and this difference was statistically significant(p=0.016).

Table 4: Relationship between PR status and pathological complete response in axilla

	ypN0	ypN+	
PR positive	2	22	24
PR negative	10	15	25
	12	37	49

On evaluation of relationship between PR status and pathological response in axilla, only 8.3%of patients with PR positivity had complete response whereas 40% of PR negative patients had complete response. This result was similar to the relationship with ER positivity and pathological response and is statistically significant(p=0.010).

Table 5: Relationship of her2neu status with pathological complete response in axilla

	ypN0	ypN+	
Her2neu positive	5	12	17
Her2neu negative	7	25	32
	12	37	49

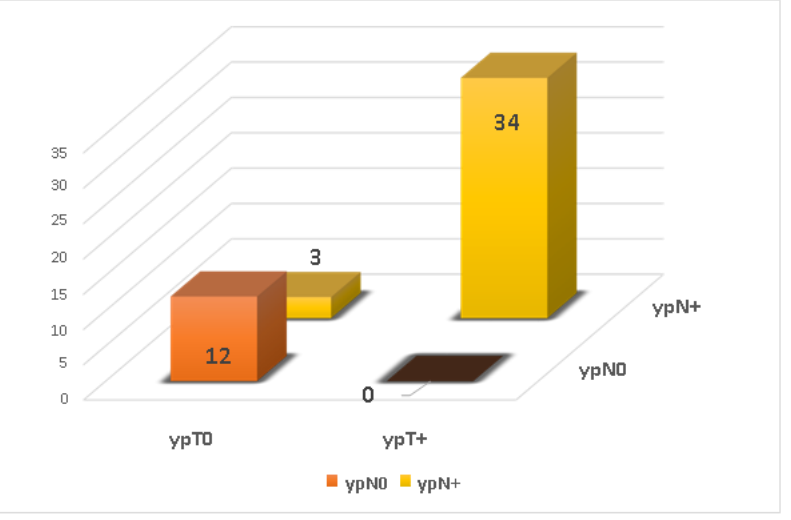
Her2neu positivity has been correlated with pathological response in axilla and 29.4% of her2neu positive patients had complete response in axilla on pathological evaluation whereas 21.8 % of her2 neunegative patients had complete pathological response inaxilla. Her2neuisnotstatistically significantly related to pathological response in axilla (p=0.559).

Table 6: Relationship between molecular subtypes and pathological complete responseinaxilla

	ypN0	ypN+	
HR+/her2neu -	1	16	17
HR-/her2neu+	4	6	10
TNBC	6	9	15
HR+/her2neu+	1	6	7
	12	37	49

Pathological complete response in axilla was seen in 5.8% of HR+/her2neu-, 40% of HR-/her2neu+, 40% of TNBC and 14.3% of HR+/her2neu+ breast cancer patients. The relationship between individual molecular subtype based on histochemical markers and pathological response in axilla does not appear to be significant (p=0.078).

Figure 3: Relationship between pathological complete response in breast versus axilla



80% of tumors with complete pathological response in breast had pCR in axilla also. Whereas, none of the patients with Pcr inaxillahad residual disease in breast.Thisrelationofpathological primary tumor response with pathological nodal response is statisticallysignificant(p<0.001).

Discussion

Pathological complete response was evaluated as surrogate marker for overall survival and disease free survival and many observational studies concluded that pCR is the most important determinant for overall and disease free survival. ButpooledanalysisdonebyCortazaretal.,statedthatthough pCR has shown improved survival, it cannot be validated as a surrogate endpoint for overall and disease freesurvival.[5]

Manyclinicaltrialswereperformedtodetermineclinicopathologicalfactorswhichpredictclinical and pathological response to neoadjuvant chemotherapy. This analysis of predictive factors is important to avoid unnecessary systemic therapy which has significant toxicity profile and especially delays other treatmentoptions[9]. Age, menopausal status, clinical tumor stage and clinical nodal stage did not appear to have significant predictive value for pathological response in axilla. These results were similar to the previous studies [10]. But few studies show that younger women have lower rates ofpathological complete response compared toolder women. Thisisduetothefactofheterogeneityofincidence of molecular subtype of breast cancer in different age groups. Hormone receptor positive breast cancer incidence is more in older population compared to younger population[11].

Menopausal status has no significant effect on pathological response of tumour. Though clinical baseline tumour size and nodalstatushavenosignificanteffectoncompletepathological response inaxilla, pathological response of primary tumour size to neoadjuvant chemotherapy ispositively related with complete pathological responseinaxilla. These results have also been consistent with previous major studies [8][11].In our study, we had pathological complete response in breast and axilla in 24.5% of the study population.ThiswassimilartothemetaanalysisdonebyLauraM.Springetal.[11]in2020 which included 52 studies which included a total of 27,895 evaluable patients. The overall pCR rate in this metaanalysis was 21.1%(range: 10.1-74.2%), with the highest rates of pCR seen in HER2+ tumors at 36.4% (range: 17.5-74.2%) and TN tumors at 32.6% (range: 20.3-62.2%), with HR+/HER2- tumorsthelowestat9.3%(range:5.5-31.3%). Themedianfollow-uptimeamongall studies was 48 months (range 21.3 – 107) for EFS and 49.9 months (range 31.2 – 118) for OS. Overall, patients who had pCR, ascomparedtoabsenceofpCR, had significantly better EFS (HR 0.31,95%PI:0.24-0.39,n=26,378). Similarly, patients who had pCR, ascomparedtoabsenceof pCR, had significantly better overall survival (HR 0.22, 95% PI: 0.15-0.30, n =23,329).

Neoadjuvant chemotherapy can convert clinically positive nodes to pathological node negative status in about 40-75% cases [12]–[15]. pCR in our study is similar to the study by Vila et al.[8] topredictnomogramsforpathologicalresponseinaxilla.InthestudybyVilaetal.,theodds ratio ofnodalconversionwas significantlyimprovedfortumorswithER-status(OR3.5,95%CI4.4– 5.1),PR-status(OR4.3,95%CI3.0–6.2),orher2neustatus(OR4.7,95%CI3.1–7.3).Theodds of conversion to pathologic node-negative status decreased as the amount of ER percentage stainingincreased(OR0.98perunit,95%CI0.975–0.984).
Theresultsofourstudycorrelatewith this study with ER negativity and PR negativity being statistically significant predictive factors and her2neu also being a predictive factor though it did not appear to be statisticallysignificant.

Molecularsubtypesinbreastcancerarethemostimportantpredictorsofpathologicalresponsefor neoadjuvant chemotherapy. Hormone receptor negative patients respond well to neoadjuvant chemotherapycomparedtohormonereceptorpositive patients.Thiswasconfirmedbymanylarge studies including both metanalysis by Houssamiet al.[4] and Spring et al.[11]. Themetanalysis bySpringetal.showsthattheoverallpCRratebasedonallpreviousmajorstudieswas21.1

% (range: 10.1-74.2%), with the highest rates seen in HER2+ tumors at 36.4% (range: 17.5-74.2%) and TNBC tumors at 32.6% (range: 20.3-62.2%); and the lowest rates seen with HR+/HER2- tumors 9.3% (range: 5.5-31.3%). Patients with pathological complete response has significantly improvedeventfreesurvivalaswellasoverallsurvivalparticularlyfortriplenegativeandher2neu positive breast cancer patients. Outcomes were similar with or without adjuvant chemotherapy in patients who obtained complete response. So, this highlights the potential for escalation or de- escalation strategies in the adjuvant setting based on response to neoadjuvant chemotherapy. Similarly,Houssamietal.[4] reported pCR rates of different molecular subtypesashormonereceptor positive (HR+/HER2–) 8.3%, HER2 positive/HR+ 18.7%, triple negative 31.1% and HER2 positive/HR– 38.9%.AlthoughtheoddsofpCRwerehighestfortheHER2positive/HR–subtype, being significantly higher in direct comparison with the triple negative subtype, the odds of pCR were very similar for the setwosubtypeswhentheminorityofstudiesthat included HER2-directed therapy with NAC were removed from the model. Our study also had very similar results as the study by Houssami etal.

In our study, ER negative patients showing 40% pCR in axilla compared to 8.3% pCR in axillain ER positive patients. PR status also had similar type of response in axilla. These results were statistically significant (p=0.016 and p=0.010 respectively). These results were similar to the results published by Kim et al.[10]. They evaluated pathological response in axilla following completion of neoadjuvant chemotherapy and various clinicopathological and imaging characteristics as independent predictive factors for pCR in axilla.

Studies showed that her2 neupositivityalsoisa positive predictive factor for pathological response following neoadjuvant chemotherapy[10]. Also inclusion of trastuzumab in neoadjuvant chemotherapy increases thechancesofpathologicalcompleteremissioninher2neupositivebreast cancer patients. Studies using HER2-directed therapy with NACT in all HER2 positive cases had an estimated pCR% of 46.4% studies using HER2-directed therapy with NACT in only some HER2 positive cases had an estimated pCR% of 27.4% whereas studies that did not use HER2- directed therapy with NACT had an estimated pCR% of 25.4%[4]. In our study, we saw a non- significant raise in the rates of pCR in axilla in her2neu positive breast cancer patients compared to her2 neunegative breast cancer patients. Inourstudy,only1patientwithher2neupositive breast cancer received trastuzumabduetofinancialconstraints. Probablythiscouldbethereasonforonly a nonsignificant increase in pCRrates. The present study showed pathological complete response in axilla was seen in 5.8% of HR+/her2neu-, 40% of HR-/her2neu+, 40% of TNBC and 14.3% of HR+/her2neu+ breast cancer patients. However, our study did not find a significant difference in pCR rates in axilla when different molecular subtypes were compared (p=0.078). This non significance could be due to smaller sample size.

Ourstudyshowedaverysignificantrelationshipbetweenpathologicalcompleterespons einbreast and pathological complete response in axilla. Eighty percent of patients with pCR in breast had pCR in axilla. Moreover, all patients with pathological complete response in axilla had pathological complete response in primary

tumour. This was similar to previous studies showing increased pathological complete response inaxillainpatientswithdecreased tumor sizeby>30%[10].

Conclusion

The overall pathological complete response in breast and axilla in breast cancer patients following neoadjuvant therapy was 24.5% in the present study. All patients who had complete response in axilla had complete response in primary too.Molecular subtypes are the most important predictors for pathological response in axilla with triple negative, hormonereceptornegativeandher2neu positive breast cancer shaving higher rates of pathological complete response inaxilla.Age,menopausalstatus,clinicaltumorsize,clinicalnodalstatusdidnotsignific antlyeffect the pathological response in axilla. But, reduction in tumour size has a significant correlation with pathological complete response in axilla.

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