International Journal of Medicine
pISSN 1468-3814 | eISSN 2667-7008
https://theinternationalmedicine.com/

Original Researcher Article *DOI: 10.61336/im/26-08-166*

Histomorphological Changes in Axillary Lymph Nodes Following Neoadjuvant Chemotherapy in Breast Carcinoma: Association with Pathological Nodal Response.

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Received: 27-05-2026
Revised: 15-07-2026
Accepted: 17-08-2026
Published: 24-08-2026

Abstract

Background: Axillary lymph nodes exposed to neoadjuvant chemotherapy may show a spectrum of stromal, inflammatory and tumour-related alterations. Correct recognition of these changes is relevant when distinguishing residual metastasis from treatment-associated regression. ***Objective:*** To describe the histomorphological changes in axillary lymph nodes after neoadjuvant chemotherapy for invasive breast carcinoma and examine their association with post-treatment nodal status. ***Methods:*** This prospective observational study included 43 consecutive women with invasive breast carcinoma treated with neoadjuvant chemotherapy followed by breast and axillary surgery between February 2025 and February 2026 at a tertiary care hospital. Gross nodal characteristics, residual tumour and twelve predefined histomorphological features were recorded. Cases were grouped as ypN0 or ypN-positive (ypN+), and associations were assessed at a significance threshold of $p<0.05$. ***Results:*** The mean age was 51.4±11.2 years. Twenty-two patients (51.2%) were ypN0 and 21 (48.8%) had residual nodal tumour. Fibrosis was the most frequent nodal alteration (72.1%), followed by chronic inflammation (60.5%), hyalinization (55.8%) and hemosiderin-laden macrophages (51.2%). Fibrosis was more frequent in ypN0 than ypN+ cases (86.4% versus 57.1%; $p=0.032$), as was hyalinization (72.7% versus 38.1%; $p=0.021$). HER2-enriched and triple-negative tumours showed the highest descriptive ypN0 proportions, 66.7% and 64.3%, respectively. Among patients with Miller-Payne grade 4-5 breast response, 71.4% were ypN0. ***Conclusion:*** Fibrosis and hyalinization were significantly associated with post-treatment node-negative status. Careful appraisal of therapy-related nodal morphology may strengthen pathological interpretation of the treated axilla, although ypN staging remains dependent on identification of residual tumour and appropriate pretreatment nodal documentation.

Keywords: Axillary Lymph Node, Breast Carcinoma, Histomorphology, Neoadjuvant Chemotherapy, Nodal Response, ypN0.

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and continues to contribute substantially to cancer mortality.[1] For patients with locally advanced or biologically aggressive disease, neoadjuvant systemic therapy is now integrated into multidisciplinary care. It can reduce tumour burden, facilitate breast conservation, downstage the axilla and provide an in vivo measure of treatment sensitivity that may influence subsequent systemic management.[2]

Pathological response after neoadjuvant therapy carries prognostic information, but its interpretation depends on how response is defined. Large pooled analyses have shown that eradication of invasive tumour from both the breast and regional lymph nodes has a stronger association with favourable long-term outcomes than breast response alone.[3] Response is also heterogeneous across tumour biology. High-grade, HER2-positive and triple-negative cancers generally achieve pathological complete response more often than luminal tumours, although the prognostic meaning of response differs among subtypes.[4,5] The treated surgical specimen presents a distinct diagnostic challenge.

Chemotherapy may leave no viable tumour yet produce fibrosis, hyalinization, foamy macrophages, hemosiderin deposition, necrosis, chronic inflammation or lymphoid depletion within previously involved lymph nodes. Conversely, small residual deposits can be obscured by a regressed or fibrotic nodal background. Earlier pathology guidance therefore emphasised systematic examination of post-neoadjuvant breast and axillary specimens.[6] More recent international recommendations have reinforced mapping, adequate sampling and explicit documentation of treatment effect and residual disease because variation in processing and reporting can alter response classification.[7,8]

Despite the clinical importance of post-treatment nodal status, axillary histomorphology has received less attention than primary breast tumour response, particularly in modest-sized prospective series from routine pathology practice. The present study was undertaken to characterise the gross and microscopic changes in axillary lymph nodes after neoadjuvant chemotherapy and to examine whether individual histomorphological features were associated with post-treatment node-negative status.

MATERIALS AND METHODS

Study Design and Setting

A prospective observational study was conducted in the Department of Pathology of a tertiary care hospital from February 2025 to February 2026.

Study Population

All consecutive patients with invasive breast carcinoma who received neoadjuvant chemotherapy followed by axillary surgery during the study period were eligible. Patients with previous chemotherapy or radiotherapy, metastatic disease at presentation, or incomplete clinical or pathological records were excluded. The final study cohort comprised 43 patients.

Clinical and Tumour Variables

Age, menopausal status, presenting complaint, pretreatment clinical T and N categories, overall clinical stage, histological type and grade, immunohistochemistry-based molecular subtype, Ki-67 proliferation index, chemotherapy regimen and number of cycles were recorded. Receipt of anti-HER2 targeted therapy was recorded separately; because it was documented in only two patients, no treatment-specific response analysis was undertaken. Surgical variables included the type of breast operation, the axillary procedure and the number of lymph nodes retrieved.

Axillary Specimen Assessment

Axillary specimens were evaluated grossly for nodal size, consistency and cut-surface appearance. Microscopic assessment documented residual metastatic tumour and the presence or absence of fibrosis, hyalinization, necrosis, foam cell infiltration, hemosiderin-laden macrophages, chronic inflammation, granulomatous reaction, sinus histiocytosis, lymphoid depletion, germinal centre hyperplasia, vascular proliferation and calcification. Extracapsular extension and therapy-related cytological change were recorded among nodes containing residual tumour.

Outcome Definitions

The principal nodal outcome was post-treatment pathological nodal status, classified as ypN0 when no residual nodal metastasis was identified and ypN+ when residual tumour was present. Because pretreatment nodal metastasis was not pathologically documented in every patient, ypN0 was interpreted as post-treatment node-negative status and was not automatically equated with axillary pathological complete response. Residual tumour size was retained in the study-defined strata of <2 mm, 2-20 mm and >20 mm. Response in the breast was graded using the Miller-Payne system, in which grade 1 represents no meaningful reduction in cellularity and grade 5 denotes absence of viable invasive tumour.

Statistical Analysis

Continuous variables were summarised as mean±standard deviation, while categorical variables were expressed as frequency and percentage. Associations between individual histomorphological features and ypN status were examined using categorical tests, with $p<0.05$ considered statistically significant. Given the modest subgroup sizes, molecular subtype, histological grade, Ki-67 category and breast-response comparisons were treated as exploratory and reported descriptively.

Ethical Considerations

Written informed consent was obtained from all participants before enrolment. Participant confidentiality was maintained throughout the study, and the research was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Clinical and Tumour Profile

All 43 participants were women. Their mean age was 51.4±11.2 years; 14 patients (32.6%) were aged 41-50 years, which was the largest age stratum. Twenty-five patients (58.1%) were postmenopausal. A breast lump was the presenting complaint in 37 (86.0%) cases. Before neoadjuvant chemotherapy, 19 patients (44.2%) had cT2 disease and 20 (46.5%) had cN1 disease. Clinically node-positive disease (cN1-cN3) was recorded in 38 of 43 patients (88.4%). Stage IIB was the most frequent pretreatment clinical stage (32.6%), followed by stage IIIA (27.9%) (Table 1).

Invasive ductal carcinoma of no special type accounted for 35 cases (81.4%). Grade II tumours were most common (48.8%), while 16 (37.2%) were grade III. Triple-negative carcinoma was the largest molecular group (32.6%), followed by luminal A (27.9%), HER2-enriched (20.9%) and luminal B (18.6%). A Ki-67 index of at least 20% was present in 28 patients (65.1%) (Table 1).

Table 1. Baseline clinical and tumour characteristics of the study cohort (n=43)

Variable	Category	n (%)
Age, years	≤40	9 (20.9)
	41-50	14 (32.6)
	51-60	12 (27.9)
	>60	8 (18.6)
	Mean±SD	51.4±11.2
Menopausal status	Premenopausal	18 (41.9)
	Postmenopausal	25 (58.1)
Clinical presentation	Breast lump	37 (86.0)
	Nipple discharge	3 (7.0)
	Skin changes	2 (4.7)
	Other	1 (2.3)
Clinical T category	cT1	4 (9.3)
	cT2	19 (44.2)
	cT3	13 (30.2)
	cT4	7 (16.3)
Clinical N category	cN0	5 (11.6)
	cN1	20 (46.5)
	cN2	13 (30.2)
	cN3	5 (11.6)
Clinical stage	IIA	6 (14.0)
	IIB	14 (32.6)
	IIIA	12 (27.9)
	IIIB	7 (16.3)
	IIIC	4 (9.3)
Histological type	Invasive ductal carcinoma, NST	35 (81.4)
	Invasive lobular carcinoma	5 (11.6)
	Mixed ductal-lobular carcinoma	2 (4.7)
	Other	1 (2.3)
Histological grade	Grade I	6 (14.0)
	Grade II	21 (48.8)
	Grade III	16 (37.2)
Molecular subtype	Luminal A	12 (27.9)
	Luminal B	8 (18.6)
	HER2-enriched	9 (20.9)
	Triple-negative	14 (32.6)
Ki-67 proliferation index	<20%	15 (34.9)
	≥20%	28 (65.1)
	Mean±SD	28.6±14.3

NST: no special type; SD: standard deviation; HER2: human epidermal growth factor receptor 2

Treatment, surgery and gross nodal findings

The most frequently used neoadjuvant regimen was anthracycline based (37.2%), followed by sequential anthracycline and taxane therapy (32.6%). Twenty-five patients (58.1%) received five to six cycles, and the mean number of cycles was 5.2±1.4. Modified radical mastectomy was performed in 24 patients (55.8%), while 19 (44.2%) underwent breast-conserving surgery. Axillary lymph node dissection was undertaken in 32 patients (74.4%) and sentinel lymph node biopsy in 11 (25.6%). The mean nodal yield was 13.8±5.2; most specimens contained 10-15 nodes (46.5%) (Table 2).

On gross examination, lymph nodes measuring 5-10 mm constituted the largest category (44.2%). Firm consistency was observed in 21 cases (48.8%), and 10 (23.3%) showed a hard or fibrotic consistency. The cut surface was homogeneous in 41.9%, heterogeneous in 37.2% and necrotic or cystic in 20.9% (Table 2).

Table 2. Neoadjuvant treatment, surgical procedures and gross axillary nodal findings (n=43)

Variable	Category	n (%)
Chemotherapy regimen	Anthracycline based (AC/EC)	16 (37.2)
	Taxane based	8 (18.6)
	Sequential anthracycline + taxane	14 (32.6)
	Anthracycline + taxane + platinum	3 (7.0)
	Anti-HER2 targeted therapy with chemotherapy	2 (4.7)
Number of cycles	3-4	12 (27.9)
	5-6	25 (58.1)
	>6	6 (14.0)
	Mean±SD	5.2±1.4
Breast surgery	Breast-conserving surgery	19 (44.2)
	Modified radical mastectomy	24 (55.8)
Axillary surgery	Sentinel lymph node biopsy	11 (25.6)
	Axillary lymph node dissection	32 (74.4)
Total lymph nodes retrieved	<10	9 (20.9)
	10-15	20 (46.5)
	>15	14 (32.6)
	Mean±SD	13.8±5.2
Lymph node size	<5 mm	8 (18.6)
	5-10 mm	19 (44.2)
	11-20 mm	11 (25.6)
	>20 mm	5 (11.6)
Nodal consistency	Soft	12 (27.9)
	Firm	21 (48.8)
	Hard/fibrotic	10 (23.3)
Cut surface	Homogeneous	18 (41.9)
	Heterogeneous	16 (37.2)
	Necrotic/cystic	9 (20.9)

AC: doxorubicin and cyclophosphamide; EC: epirubicin and cyclophosphamide; HER2: human epidermal growth factor receptor 2

Histomorphological changes in axillary lymph nodes

Fibrosis was the most prevalent microscopic alteration, present in 31 cases (72.1%). Chronic inflammation was identified in 26 (60.5%), hyalinization in 24 (55.8%), and hemosiderin-laden macrophages in 22 (51.2%). Sinus histiocytosis and foam cell infiltration were recorded in 44.2% and 41.9%, respectively. Granulomatous reaction and calcification were uncommon, occurring in 9.3% and 7.0% of cases (Table 3 and Figure 1).

Table 3. Frequency of histomorphological changes in axillary lymph nodes (n=43)

Histomorphological feature	Present, n (%)	Absent, n (%)
Fibrosis	31 (72.1)	12 (27.9)
Hyalinization	24 (55.8)	19 (44.2)
Necrosis	14 (32.6)	29 (67.4)
Foam cell infiltration	18 (41.9)	25 (58.1)
Hemosiderin-laden macrophages	22 (51.2)	21 (48.8)
Chronic inflammation	26 (60.5)	17 (39.5)
Granulomatous reaction	4 (9.3)	39 (90.7)
Sinus histiocytosis	19 (44.2)	24 (55.8)
Lymphoid depletion	16 (37.2)	27 (62.8)
Germinal centre hyperplasia	11 (25.6)	32 (74.4)
Vascular proliferation	8 (18.6)	35 (81.4)
Calcification	3 (7.0)	40 (93.0)

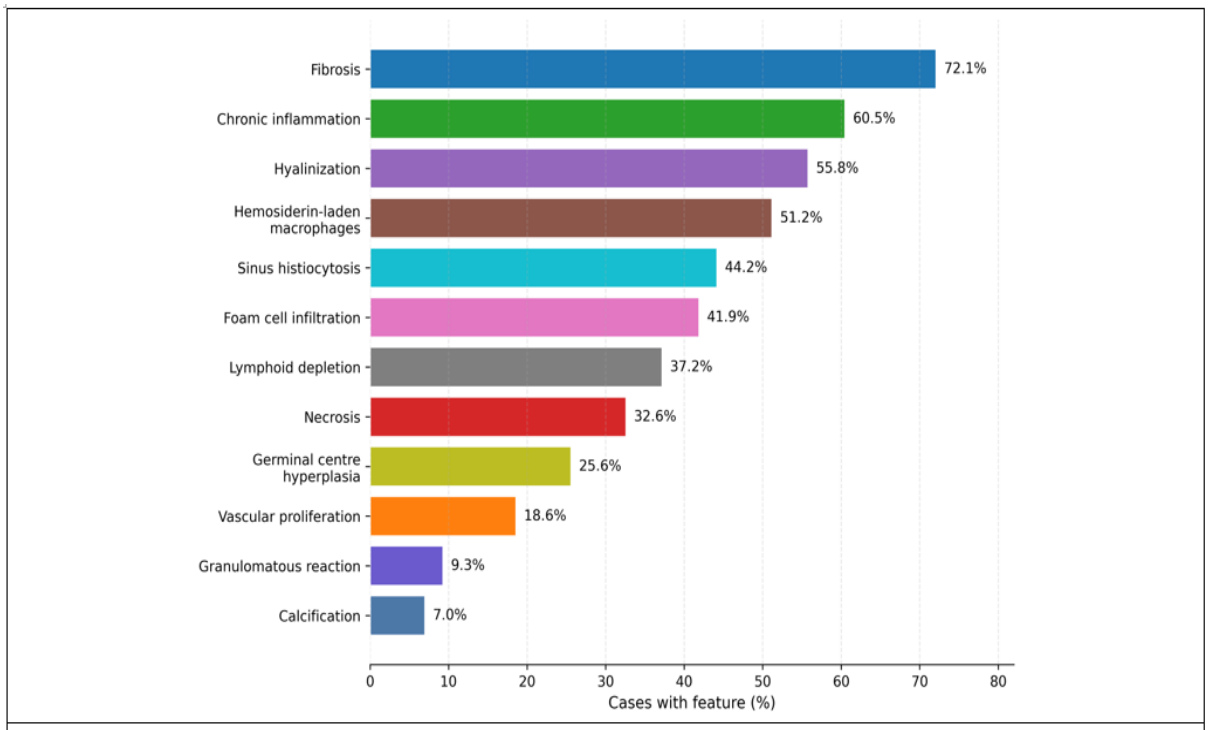

Figure 1. Prevalence of histomorphological changes in axillary lymph nodes after neoadjuvant chemotherapy

Horizontal bars represent the percentage of cases in which each feature was present

Residual nodal tumour and pathological nodal response

No residual nodal tumour was identified in 22 patients (51.2%), who were therefore classified as ypN0; the remaining 21 patients (48.8%) were ypN+ (Figure 2). Among the 21 ypN+ cases, residual deposits measured <2 mm in six, 2-20 mm in five and >20 mm in ten. Extracapsular extension was identified in seven of 21 ypN+ cases (33.3%). Therapy-related change in residual tumour cells was present in 18 of 21 (85.7%) and absent in three (14.3%) (Table 4).

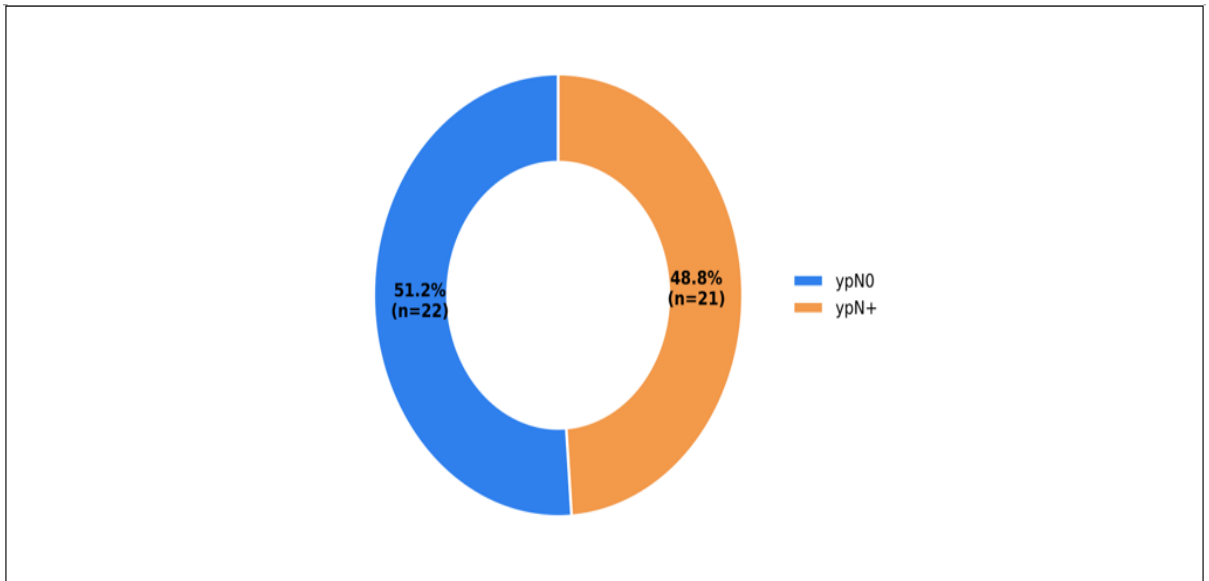

Figure 2. Post-treatment pathological nodal status in the study cohort

The donut chart shows the proportion of patients classified as ypN0 and ypN-positive (ypN+); counts are displayed within segments

Table 4. Residual tumour characteristics and post-treatment nodal status

Parameter	Category	n/N (%)
Post-treatment nodal status	ypN0	22/43 (51.2)
	ypN+	21/43 (48.8)
Residual tumour size among ypN+	<2 mm	6/21 (28.6)
	2-20 mm	5/21 (23.8)
	>20 mm	10/21 (47.6)
Extracapsular extension among ypN+	Present	7/21 (33.3)
	Absent	14/21 (66.7)
Therapy-related change in residual tumour cells	Present	18/21 (85.7)
	Absent	3/21 (14.3)
Residual-tumour measurements are shown in the prespecified study strata. ypN+: residual nodal tumour present after neoadjuvant chemotherapy		

Association of nodal histomorphology with ypN status

Fibrosis was present in 19 of 22 ypN0 cases (86.4%) compared with 12 of 21 ypN+ cases (57.1%), a statistically significant difference (p=0.032). Hyalinization showed a similar pattern, occurring in 72.7% of ypN0 and 38.1% of ypN+ cases (p=0.021). None of the remaining evaluated features reached the prespecified significance threshold, although foam cell infiltration, hemosiderin-laden macrophages and chronic inflammation were numerically more frequent in the ypN0 group (Table 5 and Figure 3).

Table 5. Association between selected histomorphological features and post-treatment nodal status

Feature present	ypN0 (n=22)	ypN+ (n=21)	p-value
Fibrosis	19 (86.4)	12 (57.1)	0.032*
Hyalinization	16 (72.7)	8 (38.1)	0.021*
Necrosis	8 (36.4)	6 (28.6)	0.584
Foam cell infiltration	12 (54.5)	6 (28.6)	0.085
Hemosiderin-laden macrophages	14 (63.6)	8 (38.1)	0.094
Chronic inflammation	16 (72.7)	10 (47.6)	0.091
Sinus histiocytosis	12 (54.5)	7 (33.3)	0.162
Lymphoid depletion	10 (45.5)	6 (28.6)	0.249
Germinal centre hyperplasia	7 (31.8)	4 (19.0)	0.334
*Statistically significant at p<0.05. Percentages are calculated within each nodal-status group			

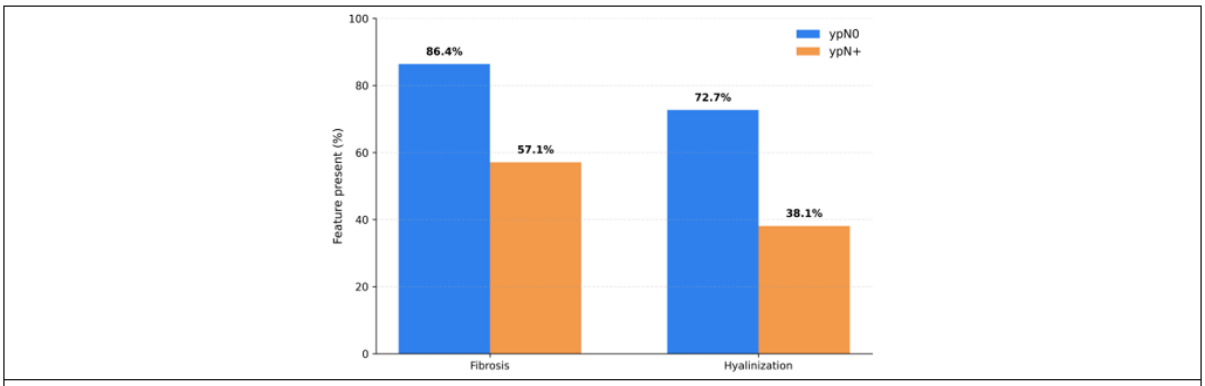

Figure 3. Fibrosis and hyalinization according to post-treatment nodal status

Grouped bars show within-group percentages. Fibrosis: p=0.032; hyalinization: p=0.021

Tumour biology and breast response in relation to ypN status

The ypN0 proportion was 66.7% in HER2-enriched tumours and 64.3% in triple-negative tumours, compared with 37.5% in luminal B and 33.3% in luminal A tumours (Table 6 and Figure 4). Grade III tumours had a higher descriptive ypN0 proportion than grade II and grade I tumours, 62.5%, 47.6% and 33.3%, respectively. Likewise, ypN0 occurred in 60.7% of tumours with Ki-67≥20% and 33.3% of those with Ki-67<20%. These patterns were considered exploratory.

Miller-Payne grade 5 breast response was observed in 11 patients (25.6%), while grades 4 and 3 were recorded in 10 (23.3%) and 11 (25.6%), respectively. When grades 4-5 were grouped as good or complete breast response, 15 of 21

patients (71.4%) were ypN0. In contrast, only three of 11 patients (27.3%) with grade 1-2 response were ypN0 (Table 6 and Figure 5).

Table 6. Post-treatment nodal status according to molecular subtype, histological grade, Ki-67 and breast response

Variable	Category	ypN0, n/N (%)	ypN+, n/N (%)
Molecular subtype	Luminal A	4/12 (33.3)	8/12 (66.7)
	Luminal B	3/8 (37.5)	5/8 (62.5)
	HER2-enriched	6/9 (66.7)	3/9 (33.3)
	Triple-negative	9/14 (64.3)	5/14 (35.7)
Histological grade	Grade I	2/6 (33.3)	4/6 (66.7)
	Grade II	10/21 (47.6)	11/21 (52.4)
	Grade III	10/16 (62.5)	6/16 (37.5)
Ki-67 proliferation index	<20%	5/15 (33.3)	10/15 (66.7)
	≥20%	17/28 (60.7)	11/28 (39.3)
Breast response	MP grade 1-2	3/11 (27.3)	8/11 (72.7)
	MP grade 3	4/11 (36.4)	7/11 (63.6)
	MP grade 4-5	15/21 (71.4)	6/21 (28.6)
MP: Miller-Payne; HER2: human epidermal growth factor receptor 2. These comparisons are descriptive			

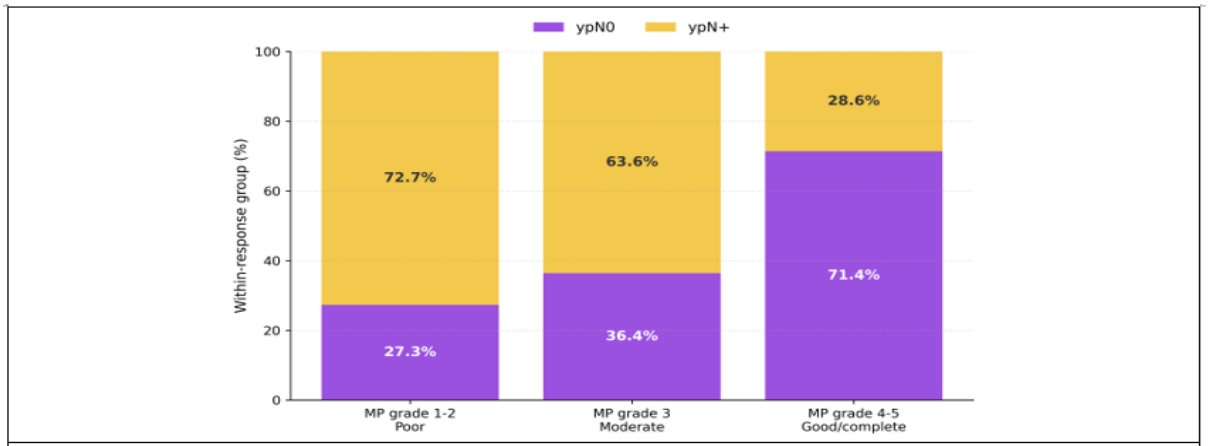

Figure 5. Post-treatment nodal status according to grouped Miller-Payne breast response

Each stacked bar represents 100% of the corresponding breast-response group

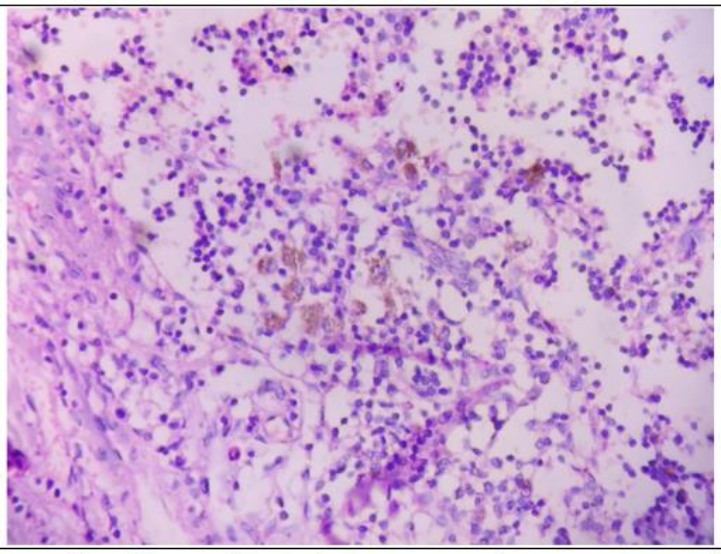

Figure 1 showing scattered hemosiderin laden macrophages as a secondary change after chemotherapy (10x view, H&E)

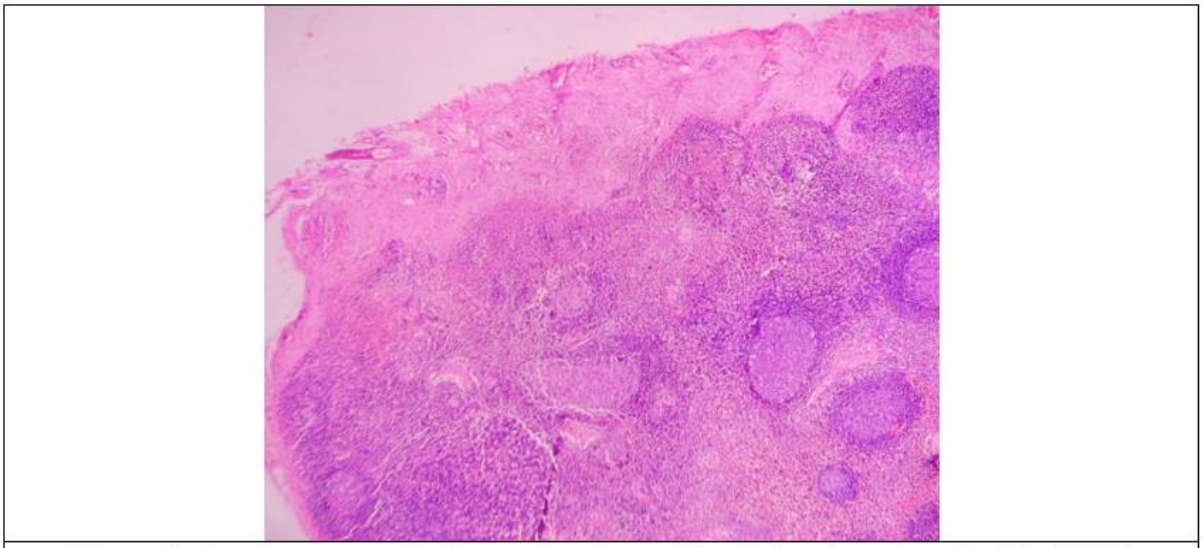

Figure 2 showing areas of subcapsular dense fibrosis in a lymph node. (4x, H&E)

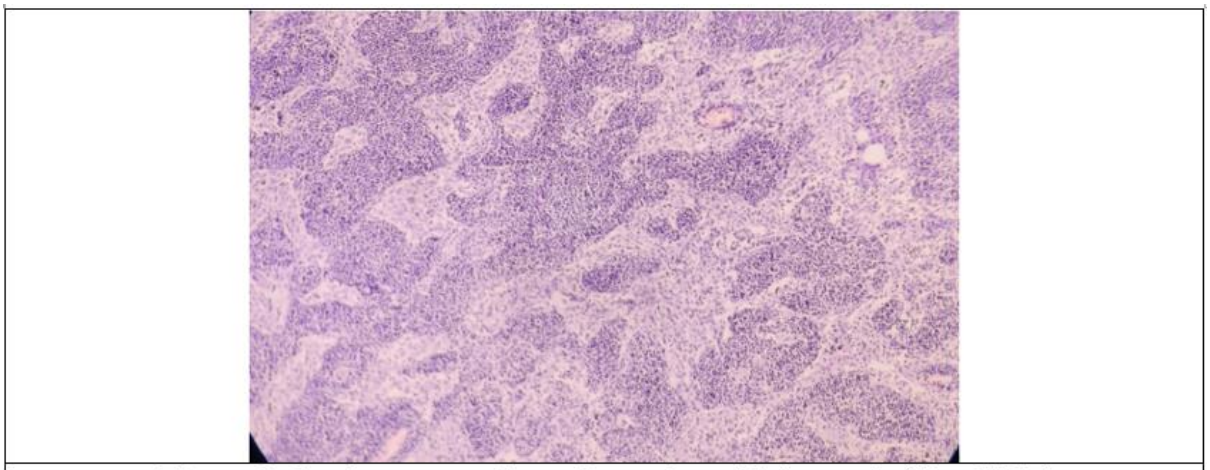

Figure 3 showing areas of prominent sinus histiocytosis (10x, H&E)

DISCUSSION

The present prospective series documents a broad spectrum of treatment-associated changes in axillary lymph nodes after neoadjuvant chemotherapy. Slightly more than half of the patients were ypN0 at surgery, while residual metastatic tumour persisted in 48.8%. Fibrosis was the dominant morphological finding, followed by chronic inflammation, hyalinization and hemosiderin-laden macrophages. Most notably, fibrosis and hyalinization were significantly more frequent in ypN0 nodes. These findings suggest that stromal remodelling is not merely an incidental post-treatment appearance; it may represent a morphological footprint of nodal regression. Still, regression morphology must be interpreted alongside the direct search for viable tumour, not as a substitute for pathological nodal staging.

The Miller-Payne system was developed to grade reduction in primary breast tumour cellularity after chemotherapy and remains familiar in routine practice.[9] Sataloff and colleagues similarly emphasised separate evaluation of response in the breast and axillary nodes, acknowledging that the two compartments may not respond identically.[10] That distinction is visible in the current cohort. Good or complete breast response, represented by Miller-Payne grades 4-5, was accompanied by ypN0 in 71.4% of patients, whereas residual nodal disease remained in 28.6%. The result reinforces a practical point: an impressive breast response raises the probability of nodal clearance, but it cannot establish it.

Pathological response systems have evolved from descriptive grading toward quantitative assessment of residual disease. The Residual Cancer Burden framework integrates the dimensions and cellularity of the residual breast tumour with nodal burden, producing a continuous index that is strongly linked to outcome.[11] Although RCB could not be reconstructed in this series, the present findings support its underlying logic. The axilla contributes information that is distinct from the breast, and both residual tumour and evidence of regression should be documented systematically.

The observed frequency of fibrosis was higher than that reported in the Indian series by Chakrabarti et al., who described chemotherapy-associated morphological changes in breast and nodal specimens and found malignant cells in a subset of axillary nodes.[12] Direct numerical comparison is difficult because cohorts differ in stage distribution, treatment regimens, nodal sampling and definitions of individual histological changes. Agarwal et al. also demonstrated that post-neoadjuvant response varies when assessed using different grading systems, with complete response representing only one end of a broader continuum of partial and absent response.[13] The higher ypN0 proportion in the present cohort may partly reflect biological composition and treatment exposure, but another important issue is baseline nodal status: five patients were clinically cN0, and clinical nodal staging does not prove that every node-negative surgical specimen represents eradication of a previously documented metastasis.

The association of fibrosis and hyalinization with ypN0 is biologically plausible. Cytotoxic injury and tumour clearance can be followed by collagen deposition, stromal contraction and hyaline scarring. Histiocytic and inflammatory changes may accompany removal of cellular debris and altered blood products. Yet none of these features is specific in isolation. Fibrosis can occur in a node without known prior metastasis, and small residual deposits may remain within a markedly fibrotic node. Chung et al. showed that grading regression in metastatic axillary nodes can provide prognostic information beyond a simple positive-versus-negative classification.[14] Their work supports more explicit reporting of nodal treatment effect, particularly when pretreatment nodal involvement has been documented.

The molecular patterns in this cohort were consistent with the broader observation that HER2-enriched and triple-negative tumours are often more chemosensitive than luminal cancers. The ypN0 proportions were 66.7% and 64.3% in these two subgroups. Because the study was small and treatment exposure was heterogeneous, these values should be read as descriptive rather than definitive subtype estimates. The same caution applies to the higher ypN0 proportion among grade III tumours and tumours with Ki-67≥20%. High proliferative activity may increase susceptibility to cytotoxic chemotherapy, but patient-level multivariable modelling would require a larger cohort and internally consistent biomarker records.

Breast and axillary responses were directionally concordant. Morgan et al. reported that pathological response in the breast predicts axillary response among patients with biopsy-proven nodal disease, but the relationship is not absolute.[15] A nationwide Korean analysis likewise found a strong association between breast pathological complete response and axillary clearance, while showing that the residual nodal risk depends on initial clinical nodal burden.[16] In the present series, the predominance of ypN0 among Miller-Payne grade 4-5 tumours follows this pattern. Nevertheless, almost three in ten good or complete breast responders retained nodal tumour, which argues against assuming axillary response from breast morphology alone.

The study has practical relevance for pathology services in Indian tertiary hospitals, where post-neoadjuvant specimens are increasingly routine but preoperative nodal documentation, specimen mapping and access to comprehensive biomarker testing may vary. A structured nodal assessment that records residual tumour, the largest deposit, extracapsular extension and recognisable treatment effect can improve communication with the multidisciplinary team. It also makes the report more useful when adjuvant decisions depend on the presence of residual disease.

Several limitations merit attention. This was a single-centre study with 43 patients, restricting precision and subgroup analysis. Pretreatment nodal metastasis was not pathologically documented for every patient, so ypN0 should not be treated as synonymous with axillary pathological complete response across the entire cohort. Chemotherapy regimens were heterogeneous, and anti-HER2 targeted therapy was recorded in only two patients; this limited meaningful assessment of treatment-specific response in HER2-associated tumours. Interobserver reproducibility of histomorphological features was not assessed. The study also lacked survival follow-up, and the modest cohort did not support stable multivariable modelling.

CONCLUSION

Axillary lymph nodes after neoadjuvant chemotherapy displayed diverse regressive and reactive changes. Fibrosis was the most common alteration, and both fibrosis and hyalinization were significantly associated with ypN0 status. HER2-enriched and triple-negative tumours, high Ki-67 tumours and good or complete Miller-Payne breast responders showed higher descriptive proportions of node-negative disease. These patterns support systematic documentation of therapy-related nodal morphology, while confirming that the final assessment must remain anchored to residual tumour detection, ypN staging and reliable pretreatment nodal information.

Source of Funding
Nil.

Conflict of Interest
None declared.

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