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A PROSPECTIVE OBSERVATIONAL STUDY ON PATHOLOGICAL COMPLETE RESPONSE IN HER2-POSITIVE BREAST CANCER

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ABSTRACT

Background: Pathological complete response (pCR) is recognized as a key prognostic factor in breast cancer, particularly in HER2-positive subtypes. Achieving pCR following neoadjuvant chemotherapy (NACT) correlates with improved long-term outcomes, including overall survival (OS) and disease-free survival (DFS). **Objectives:** This study aims to assess the prognostic significance of pCR in HER2-positive breast cancer and to evaluate the rates of pCR, defined as the absence of invasive cancer in the breast and axillary lymph nodes after completion of NACT and surgical intervention. **Methods:** A prospective observational study was conducted at the Department of Medical Oncology, Bharath Hospitals and Institute of Oncology, Mysuru, spanning a duration of six months. After obtaining informed consent, data from 70 HER2-positive breast cancer patients were collected and analyzed using immunohistochemistry (IHC) reports, pathological grading, breast cancer staging systems, BI-RADS categories, and histopathology findings. **Results:** Among the 70 patients diagnosed with HER2-positive breast cancer, targeted therapy regimens were administered as follows: 38.57% received the TCH protocol (docetaxel, carboplatin, trastuzumab), while 25.71% were treated with TCHP (TCH combined with Pertuzumab). Neoadjuvant chemotherapy regimens included AC + Paclitaxel in 15.71% of patients, Paclitaxel monotherapy in 12.85%, and the AC regimen alone in 7.14%. The overall pathological complete response (pCR) rate observed was 37.14%. **Conclusion:** Achieving pCR is strongly associated with improved long-term outcomes, notably enhanced OS and event-free survival (EFS) in HER2-positive breast cancer. The integration of advanced targeted therapies has significantly improved treatment efficacy and prognosis in this aggressive breast cancer subtype.

KEYWORDS: Breast Cancer, HER2-positive, Post NACT, pCR, Targeted Therapy.

1. INTRODUCTION

Breast cancer arises from the epithelial cells lining the ducts or lobules of the breast tissue, as defined by the World Health Organization (WHO). It is the most frequently diagnosed cancer among women globally, accounting for approximately 25% of all female cancer cases.[1] The incidence of breast cancer is projected to rise substantially in South-East Asia, with an anticipated increase of 61.7% by 2040. In India, breast cancer constitutes 28.2% of all female cancers, with an estimated 216,108 new cases reported in 2022. Since 1990, the age-standardized incidence rate of female breast cancer has increased by 39.1% across all Indian states, highlighting a growing public health concern.[3]

Clinically, breast cancer often presents as a palpable lump in the breast or axillary region. Awareness through regular breast self-examinations (BSEs) enhances early detection by helping individuals recognize changes in breast texture, size, skin condition, and other symptoms. Common clinical manifestations include breast swelling or masses, axillary lymphadenopathy, nipple discharge

(clear or bloody), nipple pain or retraction, skin alterations such as scaling or pitting, persistent tenderness, and atypical breast discomfort.[12]

Breast cancer encompasses a wide spectrum of pathological subtypes, broadly classified into non-invasive and invasive categories. Non-invasive lesions, including ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS), remain confined within the ductal or lobular structures without invading adjacent tissues, with DCIS being the most prevalent. Invasive breast cancers breach the basement membrane, infiltrating surrounding fatty and connective tissues. The predominant invasive histology's are invasive ductal carcinoma (IDC), representing.

approximately 80% of cases, and invasive lobular carcinoma (ILC), accounting for 10–15%. Additionally, special invasive subtypes such as triple-negative and inflammatory breast cancers, although less common, are often associated with more aggressive clinical behavior. Rare variants include Paget's disease of the nipple and phyllodes tumors, which originate from the nipple–areola complex and breast stromal tissue, respectively.[2]

Breast cancer is a heterogeneous disease characterized by distinct molecular subtypes defined primarily by immunohistochemical expression of hormone receptors. These subtypes include estrogen receptor-positive (ER+), progesterone receptor-positive (PR+), human epidermal growth factor receptor 2-positive (HER2+), and triple-negative breast cancer (TNBC), which lacks expression of ER, PR, and HER2.[4] HER2 amplification or overexpression, occurring in approximately 15% of invasive breast cancers, drives oncogenic signaling pathways that promote tumor cell proliferation, survival, and invasion.[5]

According to the American Society of Clinical Oncology - College of American Pathologists (ASCO - CAP) guidelines, HER2 positivity is defined by either strong (3+) immunohistochemical staining in at least 10% of tumor cells or gene amplification confirmed by fluorescence in situ hybridization (FISH).[6] HER2-positive tumors are further subclassified into luminal HER2 (ER+, PR+, HER2+, with moderate proliferative index measured by Ki-67) and HER2-enriched (ER–, PR–, HER2+, with a high Ki-67 index), reflecting differences in tumor biology and proliferation rates.[7]

HER2 status is assessed primarily through two diagnostic modalities: immunohistochemistry (IHC), which evaluates HER2 protein expression on tumor cell membranes, and FISH, which detects HER2 gene amplification when IHC results are equivocal. Tumors scoring 0 or 1+ by IHC are considered HER2-negative; 2+ is equivocal and warrants FISH testing for confirmation; 3+ is indicative of HER2 positivity.[8]

Management of HER2-positive breast cancer routinely involves neoadjuvant chemotherapy (NACT) to reduce tumor burden prior to surgery and improve operability.[9] The TCH regimen comprising docetaxel, carboplatin, and trastuzumab is commonly employed, with docetaxel and carboplatin targeting cellular proliferation and trastuzumab specifically inhibiting HER2-mediated signaling. This regimen is typically administered every 21 days for six cycles, followed by one year of trastuzumab maintenance therapy, with vigilant monitoring for cardiotoxicity and hematologic adverse effects. Alternative regimens include AC (doxorubicin and cyclophosphamide) and paclitaxel-based therapies, often tailored based on patient-specific factors and tumor characteristics.[10]

Pathological complete response (pCR), defined as the absence of invasive and in-situ carcinoma in the breast and regional lymph nodes (ypT0 ypN0), is a validated surrogate marker of favorable long-term outcomes following neoadjuvant therapy. Regulatory agencies such as the FDA endorse pCR as a primary endpoint in clinical trials evaluating neoadjuvant treatments. Patients harboring aggressive tumor subtypes - including triple-negative, HER2-positive, hormone receptor-negative, and high-grade hormone receptor-positive/HER2-negative tumors - derive the greatest survival benefit from achieving pCR.[11]

This study focuses on evaluating the prognostic relevance of pCR in HER2-positive breast cancer and examining its occurrence following neoadjuvant chemotherapy and surgical management involving axillary lymph node dissection.

1. MATERIALS AND METHODS

1.1 Study Site

This prospective observational study was conducted at Bharath Hospitals & Institute of Oncology, located on Outer Ring Road, Hebbal, Mysuru. The center operates as a comprehensive cancer care facility under the aegis of Sada Sharada Tumor & Research Institute, Mysuru, Karnataka, India. The hospital has an approximate bed capacity of 100 and offers specialized services in medical oncology, radiation oncology, surgical oncology, and pediatric oncology.

1.2 Study Design

The study was designed as a prospective observational study.

1.3 Study Period

Data collection and patient follow-up were carried out over a six-month period from March 2024 to August 2024.

1.4 Department Selected for Study

The research was conducted in the Department of Medical Oncology, which houses a fully operational outpatient department (OPD). This day-care OPD features 30 beds and typically manages 75–100 patients

daily.

1.5 Ethical Approval
The study protocol received approval from the Institutional Ethics Committee of Bharath Hospitals & Institute of Oncology, Mysuru. Written informed consent was obtained from all participants prior to enrollment.

1.6 Study Criteria
1.6.1 Inclusion Criteria
- Female patients aged between 20 and 70 years
- Histopathologically confirmed HER2-positive breast cancer
- Patients undergoing neoadjuvant chemotherapy followed by surgical intervention
- Evaluation of pathological complete response (pCR) post-treatment

1.6.2 Exclusion Criteria
- Patients' non-adherent to prescribed treatment protocols
- Absence of immunohistochemistry (IHC) reports confirming HER2 status
- Lack of confirmatory Fluorescence In Situ Hybridization (FISH) testing for equivocal IHC results

1.7 Sample Size
Sample size was calculated using the single proportion formula: $N = Z^2 \times P \times Q / d^2$
Where:
N = required sample size
Z = 1.96 (standard normal deviate for 95% confidence interval)
P = estimated prevalence (10%)
Q = 1 − P
d = allowable margin of error (5%)
Based on this calculation, a total of 70 patients were enrolled in the study.

1.8 Data Collection Sources
- **Outpatient Department (OPD) Records:** Patient demographics, clinical presentations, diagnoses, and treatment plans were obtained during OPD consultations.
- **Hospital Medical Records**: Comprehensive clinical data including medical history, laboratory results, imaging studies, treatment outcomes, and prior interventions were extracted from hospital files, electronic health records & documented follow-up visits.

1.9 Experimental Design
Step 1: Preparation of Informed Consent Form (ICF)
An ICF was developed in English and Kannada to ensure clear communication and comprehension. The form was reviewed and approved by the institutional ethics committee. Patients were thoroughly informed about the study objectives and procedures in their native language, and consent was secured via signature or thumb impression.

Step 2: Preparation of Data Collection Form
A structured data collection instrument was designed to capture demographic information (name, age, gender, weight, address), clinical parameters (diagnosis, cancer staging, pathological and immunohistochemical findings, fluorescence in situ hybridization results, TNM classification, BI- RADS category, tumor grading, cytology, mammography), and therapeutic details (neoadjuvant chemotherapy regimens, pre- and post-operative treatments, concomitant medications).

Step 3: Patient Enrollment
Eligible patients were enrolled following informed consent, with documentation translated into the participant's preferred language. Enrollment was conducted during routine OPD visits.

Step 4: Data Collection
Patients were interviewed in their regional languages to obtain relevant clinical and demographic data. Laboratory and pathology reports, including IHC results, were systematically documented. Tumor grading, breast cancer staging, and BI-RADS categories were recorded based on diagnostic findings.

Step 5: Statistical Analysis
Data were analyzed using SPSS version 20. Descriptive statistics including means, percentages, tables, and graphical representations summarized the findings. Inferential statistics such as the chi- square test were applied to evaluate associations, with significance set at $p < 0.05$.

Step 6: Interpretation
Pathological complete response in HER2-positive breast cancer was defined and interpreted in accordance with ASCO-CAP guidelines. Assessment incorporated immunohistochemistry, tumor grading, pathological staging, and BI-RADS classification. pCR was confirmed histologically by the absence of residual carcinoma (ypT0N0) in surgical specimens.

1.10 Methodology for pCR Assessment
The evaluation of pCR involved integration of clinical data, pathological examination, and treatment response criteria. This comprehensive approach ensured accurate determination of the absence of invasive and in situ tumor cells post-neoadjuvant therapy and surgery.

HER2‑positive breast cancer
According to the American Society of Clinical Oncology–College of American Pathologists (ASCO–CAP) guidelines, HER2‑positive breast cancer is defined as tumors showing 3+ immunohistochemical (IHC) staining in at least 10% of tumor cells or demonstrating HER2 gene amplification by fluorescence in situ hybridization (FISH). In patients with HER2‑positive breast cancer, neoadjuvant therapy is administered prior

to surgery to reduce tumor burden, facilitate breast-conserving surgery, and enable an early assessment of treatment response.

The following neoadjuvant chemotherapy regimens were used in our patients

AC regimen: AC is a standard chemotherapy regimen for breast cancer, comprising Adriamycin/doxorubicin and cyclophosphamide. The regimen consists of doxorubicin 60 mg/m² intravenously on day 1 and cyclophosphamide 600 mg/m² intravenously on day 1, repeated every 21 days for a total of 4 cycles.

Weekly paclitaxel: Paclitaxel was administered at a dose of 175 mg/m² as 3-hour intravenous infusion every 3 weeks.

TCH regimen (docetaxel + carboplatin + trastuzumab): This regimen included docetaxel (Taxotere) 75 mg/m² intravenously on day 1, carboplatin at an area under the curve (AUC) of 6 intravenously on day 1, and trastuzumab (Herceptin) 4 mg/kg as an intravenous loading dose followed by 2 mg/kg weekly. Chemotherapy was repeated every 21 days for a total of 6 cycles. After completion of chemotherapy, trastuzumab was continued at 6 mg/kg intravenously every 3 weeks for a total duration of 1 year.

Targeted therapies consisted of Pertuzumab - 840 mg as an intravenous infusion followed by 420 mg every 3 weeks, and trastuzumab 8 mg/kg as an initial intravenous infusion followed by 6 mg/kg every 3 weeks. Patients diagnosed with HER2-positive breast cancer received these agents either as monotherapy or in combination, which demonstrated promising efficacy in achieving pathological complete response (pCR).

Pathological complete response is defined as the absence of residual invasive and in situ carcinoma on hematoxylin and eosin staining of the entire resected breast specimen and all sampled regional lymph nodes after completion of neoadjuvant systemic therapy (corresponding to ypT0 ypN0 in the current American Joint Committee on Cancer [AJCC] staging system). Following neoadjuvant chemotherapy, a high pCR rate was observed, which is associated with improved overall survival and disease-free survival. Post-modified radical mastectomy (MRM) pathology reports were reviewed to assess pCR in patients with HER2-positive breast cancer.

2. RESULTS

A total of 70 patients from the Department of Medical Oncology who met the predefined eligibility criteria were included in the analysis.

2.1 HER2-positive breast cancer

The age distribution of the study population with HER2-positive breast cancer is summarized in Table 1.

Table 1: Age group distribution of the study population with HER2-positive breast cancer.

Age (in years)	No. of Patients	Percentage
Pre-Menopausal (30-45)	13	18.57
Menopause (46-55)	24	34.28
Post-Menopausal (56-85)	33	47.14

2.1.1 Age

The mean age of the patients was 56 years. The majority belonged to the 56–85 years age group (n=33; 47.14%), followed by the 46–55 years group (n=24; 34.28%) and the 30–45 years group (n=13; 18.57%). The age distribution is depicted in Figure 1.

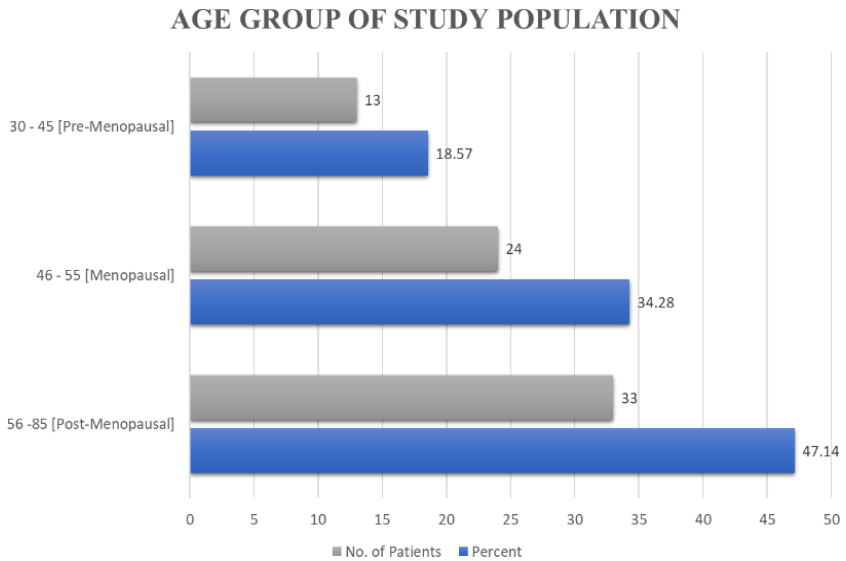

Figure 1: Age group distribution of the study population with HER2-positive breast cancer.

2.1.2 Diagnosis

Table 2: Diagnosis distribution in patients with HER2-positive breast cancer.

Diagnosis	No. of Patients	Percentage
Carcinoma Left Breast	38	54.29
Carcinoma Right Breast	32	45.71

On analysis of the study population, a total of 70 patients were diagnosed with HER2-positive breast cancer. Of these, carcinoma of the left breast was observed in 38 patients (54.29%) and carcinoma of the right breast in 32 patients (45.71%). The distribution of HER2-positive breast cancer by side is illustrated in Figure 2.

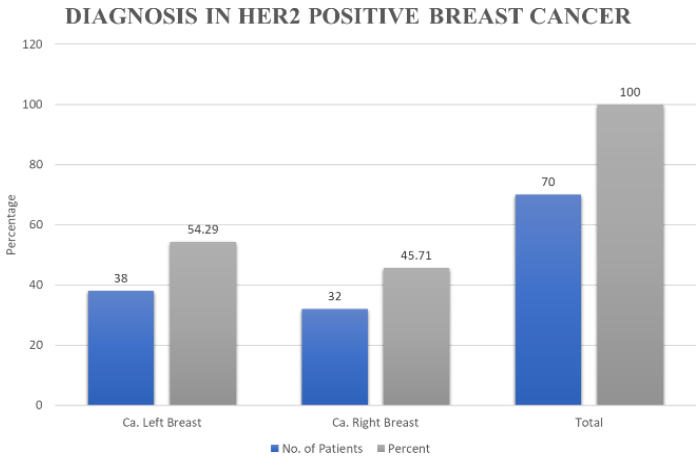

Figure 2: Diagnosis distribution in patients with HER2-positive breast cancer.

2.1.3 Histopathology

Table 3: Histopathology in patients with HER2-positive breast cancer.

Histopathology	No. of Patients	Percentage
Invasive Ductal Carcinoma	56	80.0
Infiltrating Ductal Carcinoma	14	20.0

On analysis of the histopathology in the study population of 70 patients who were diagnosed with HER2-positive breast cancer, Invasive ductal carcinoma was observed in 56 patients (80.0%), and infiltrating ductal carcinoma in 14 patients (20.0%).

2.1.4 Molecular Subtypes – IHC

Table 4: Molecular subtypes in patients with HER2-positive breast cancer.

	No. of Patients	Percentage
ER: +ve, PgR: -ve, HER2: +ve	16	22.81
ER: -ve, PgR: -ve, HER2: +ve	54	77.1

On analysis of the molecular subtypes in HER2-positive breast cancer, luminal A tumors (ER-positive, PR-negative, HER2-positive) were observed in 16 patients (22.81%), whereas tumors that were ER-negative, PR-negative, and HER2-positive were observed in 54 patients (77.1%).

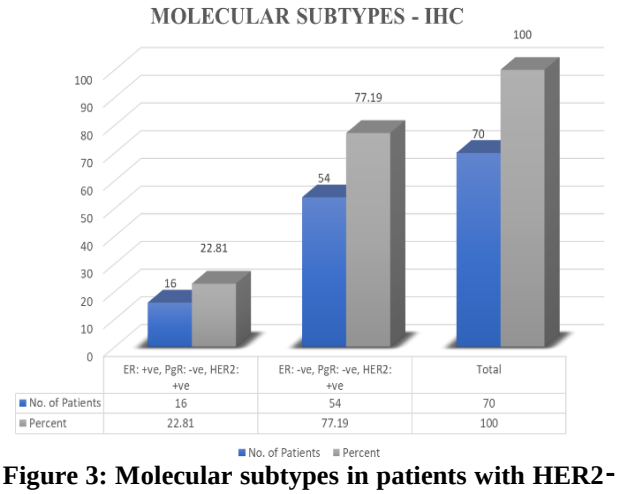

Figure 3: Molecular subtypes in patients with HER2-positive breast cancer.

2.1.5 Ki 67 – Proliferation Index

Table 5: Ki-67 proliferation index in patients with HER2-positive breast cancer.

Ki 67	No. of Patients	Percentage
<15%	42	60.0
>15%	28	40.0

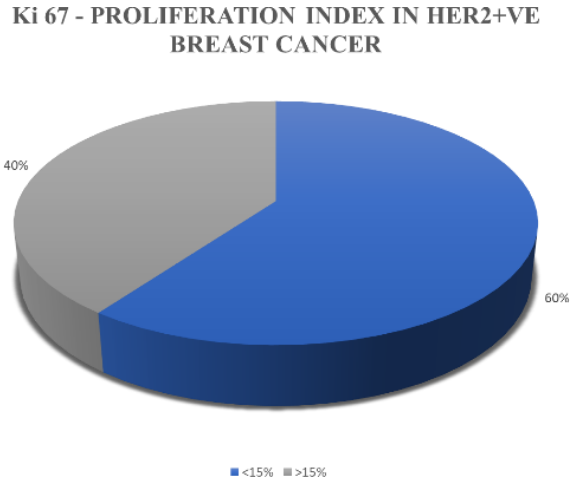

Figure 4: Ki 67- Proliferation Index in patients with HER2-positive breast cancer.

2.1.6 Pathological Staging

The distribution of patients according to pathological staging after treatment, categorized by tumor (T) and node (N) stages, is summarized below.

1. **ypT0N0** (no residual tumor and no lymph node involvement) was the most frequent stage, observed in 37.14% of patients.
2. **pT1** was present in 30.0% (21 patients) and comprised small tumors (T1) with variable lymph node status (N0, N1, N1a, N3a), indicating early-stage cancer with limited to moderate nodal involvement.
3. **pT2** was observed in 12.8% (9 patients), with moderately larger tumors (T2) and lymph node stages ranging from N0 to N3a, reflecting more extensive local disease while remaining potentially curable.
4. **pT3** was found in 11.4% (8 patients), characterized by larger tumors (T3) and significant lymph node involvement (N1, N1a, N3a), indicating advanced local tumor burden with notable regional spread.
5. **pT4** occurred in 8.57% (6 patients); the frequency decreased progressively with increasing T stage.

Further details are presented in Figure 4.

Table 6: Pathological staging in patients with HER2-positive breast cancer.

Pathological Staging	No. of Patients	Percentage
YpT0N0	26	37.14
pT1 [N0, N1, N1a, N3a]	21	30.0
pT2[N0, N1, N1a, N2, N2a, N3, N3a]	9	12.8
pT3[N1, N1a, N3a]	8	11.4
pT4 [N0, N1, N1a, N2]	6	8.57

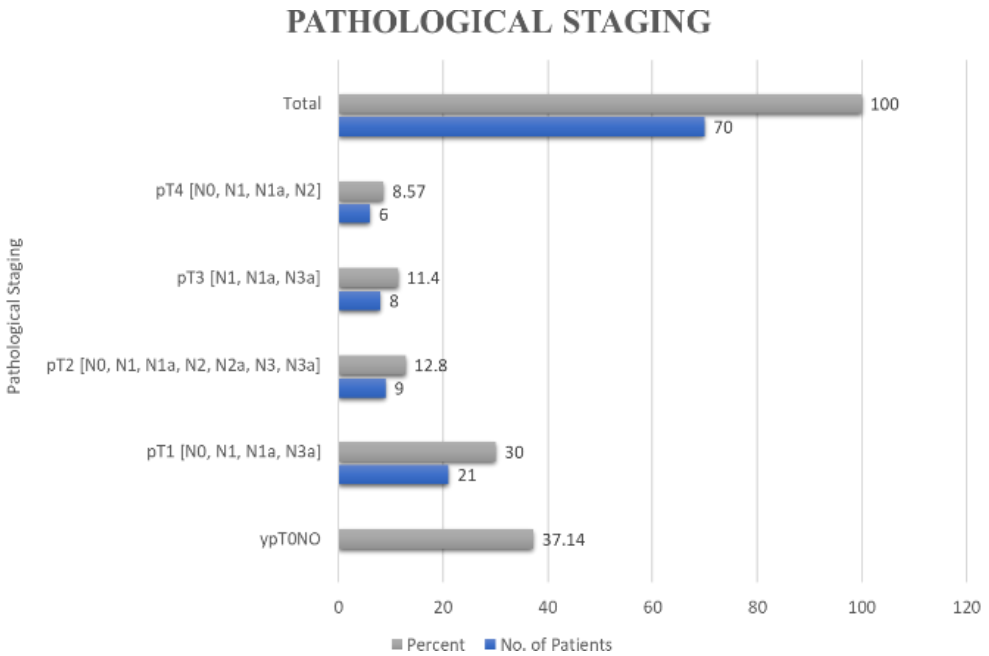

Figure 5: Pathological staging in patients with HER2-positive breast cancer.

3.1.6 Surgery

Table 7: Surgery in patients with HER2-positive breast cancer.

Surgery	No. of Patients	Percentage
Mastectomy + Axillary Dissection	28	40.0
Breast Conservative Surgery + Axillary dissection	42	60.0

Of the 70 patients, two types of surgical procedures were performed: mastectomy with axillary lymph node dissection in 28 patients (40%) and breast-conserving surgery with axillary lymph node dissection in 42 patients (60%). The distribution of surgical procedures is shown in Figure 6.

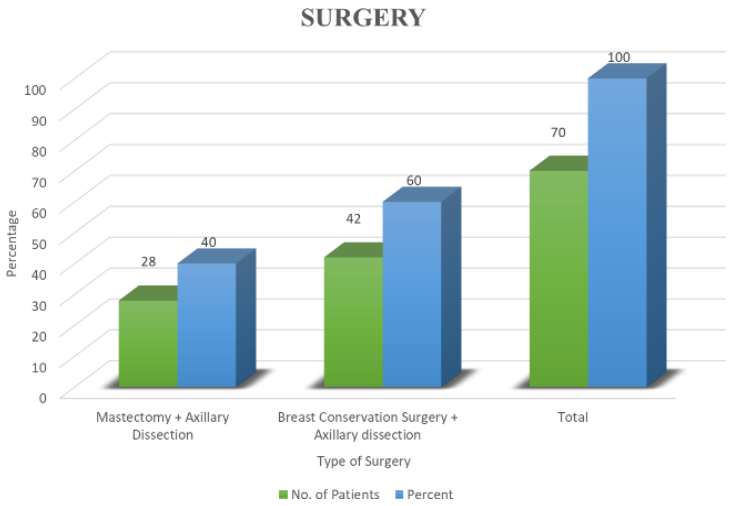

Figure 6: Surgery in patients with HER2-positive breast cancer.

3.1.6 Treatment Given In HER2+ve Breast Cancer

Table 8: Treatment given in patients with HER2-positive breast cancer.

Treatment	No. of Patients	Percentage
AC + PACLITAXEL	11	15.71
TCH	27	38.57
AC	5	7.14
PACLITAXEL	9	12.85
TCHP	18	25.71

On analysis of treatment in patients with HER2-positive breast cancer, the majority received targeted therapy-based regimens, most commonly TCH (docetaxel, carboplatin, and trastuzumab) in 27 patients (38.57%) and TCHP (TCH + Pertuzumab) in 18 patients (25.71%). Neoadjuvant chemotherapy without dual HER2-targeted blockade included AC plus paclitaxel in 11 patients (15.71%), paclitaxel alone in 9 patients (12.85%), and AC regimen in 5 patients (7.14%). Details of the treatment regimens administered are shown in Figure 7.

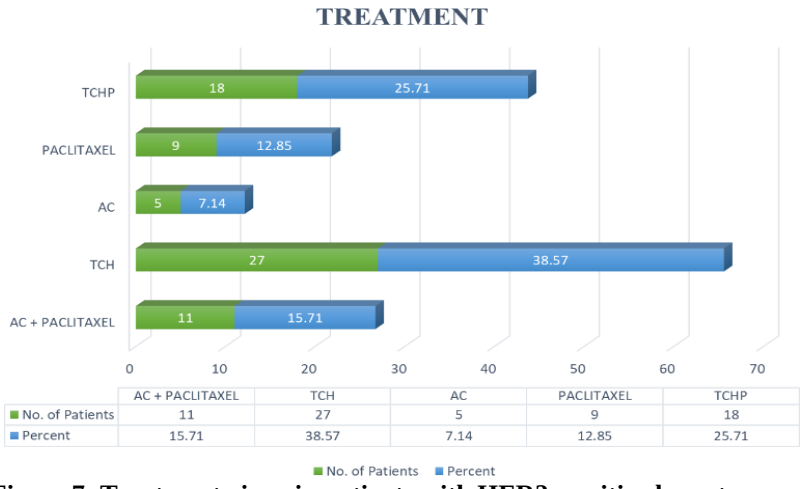

Figure 7: Treatment given in patients with HER2-positive breast cancer.

4. DISCUSSION

The present prospective observational study evaluated pathological complete response (pCR) and clinicopathological characteristics in 70 patients with HER2-positive breast cancer.

4.1 Pathological complete response (pCR)

In our study, the overall pCR rate was 37.14%, which falls within the range reported in previously published trials. Large clinical studies evaluating trastuzumab-based neoadjuvant therapy in HER2-positive breast cancer have reported pCR rates of approximately 30–50%.

The NeoSphere trial reported a pCR rate of 45.8% with dual HER2 blockade using trastuzumab and Pertuzumab in combination with docetaxel (Gianni et al., 2012). Similarly, the NOAH trial demonstrated improved pCR rates (38%) with the addition of trastuzumab to chemotherapy compared with chemotherapy alone (Gianni et al., 2010).

Achieving pCR is considered a surrogate marker for improved long-term outcomes, particularly in HER2-positive breast cancer, where it is strongly associated with better disease-free survival and overall survival (von Minckwitz et al., 2012).

4.2 Age distribution

The majority of patients in this study belonged to the 56–85 years age group (47.14%), with a mean age of 56 years, indicating that HER2-positive breast cancer predominantly affects postmenopausal women. However, 18.57% of patients were aged 30–45 years, suggesting that early-onset disease remains clinically relevant.

This age distribution is consistent with epidemiological trends reported in developing countries, where breast cancer incidence increases with advancing age.

4.3 Histopathological characteristics

Invasive ductal carcinoma (IDC) was the most common histological subtype in our cohort (80%), followed by infiltrating ductal carcinoma (20%). This finding aligns with global data, in which IDC accounts for approximately 70–80% of breast cancers.

The predominance of IDC among HER2-positive tumors supports previously documented pathological patterns in this subtype.

4.4 Pathological staging after neoadjuvant therapy

Post-treatment pathological staging showed that ypT0N0 disease constituted 37.14% of patients, corresponding to the overall pCR rate. The ypT0N0 stage indicates complete eradication of invasive tumor in both the breast and axillary lymph nodes, reflecting an excellent response to neoadjuvant systemic therapy.

Higher pathological stages (pT1–pT4) were observed in the remaining patients, indicating partial or residual disease.

4.5 Treatment regimens and their impact

The TCH regimen (docetaxel, carboplatin, and trastuzumab) was the most frequently administered protocol (38.57%) in our study. Trastuzumab-based regimens have been shown to significantly improve response rates in HER2-positive breast cancer. The favorable pCR rate observed in this study may be attributed to the widespread use of HER2-targeted therapies, including dual blockade with Pertuzumab in selected patients.

4.6 Surgical outcomes

Breast-conserving surgery with axillary lymph node dissection was performed in 60% of patients, whereas 40% underwent mastectomy with axillary dissection. The higher proportion of breast-conserving procedures suggests effective tumor downstaging following neoadjuvant therapy, enabling organ-preserving surgery in a substantial subset of patients.

4.7 Proliferation index

A significant proportion of patients demonstrated a Ki-67 index greater than 15%, indicating high proliferative activity. HER2-positive tumors with elevated Ki-67 levels are generally more responsive to chemotherapy and targeted therapy, which may have contributed to the observed pCR rate in this cohort.

5. CONCLUSION

In this prospective observational study of 70 patients with HER2-positive breast cancer, the pathological complete response (pCR) rate was 37.14%, which is comparable to previously reported outcomes with neoadjuvant chemotherapy and HER2-targeted therapies. The findings underscore the effectiveness of HER2-directed treatment in achieving significant tumor downstaging and improving surgical outcomes. Pathological complete response remains an important prognostic indicator in HER2-positive breast cancer, although long-term survival outcomes require further follow-up in this cohort.

6. Limitations

This study has a few limitations. The main drawback is the relatively small sample size, which may limit the generalizability of the findings. Although pCR is generally associated with improved outcomes, not all patients who achieve pCR experience long-term survival, and there remains a risk of recurrence or relapse. In addition, limited biomarkers are available to predict which patients would achieve pCR following neoadjuvant chemotherapy. Finally, affordability and feasibility constraints of HER2-targeted therapies may affect real-world applicability, particularly in resource-

limited settings.

Future Directions

Novel agents such as Trastuzumab Deruxtecan and other emerging HER2-targeted therapies may be incorporated into neoadjuvant and post-neoadjuvant treatment regimens to further improve response rates and long-term outcomes in HER2-positive breast cancer. Future research should aim to integrate pCR with additional prognostic factors, including tumor biology, genomic signatures, and minimal residual disease detection, to develop more refined risk stratification and predictive models. Machine learning and artificial intelligence-based approaches hold promise for optimizing treatment selection and personalizing therapeutic strategies in this patient population.

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Competing Interests

The authors declare that no competing interests exist.

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