

# Comparative Study between Results of Neo Adjuvant Chemotherapy and Upfront Surgery in Breast Cancer in Aswan Oncology Center: Cohort Study

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**Background:** Breast cancer affects millions of people globally each year, making it a major health concern. The management of breast cancer has undergone a significant transformation with the introduction of neoadjuvant chemotherapy (NACT).

**Aim and objectives:** Neoadjuvant chemotherapy and upfront surgery for breast cancer were compared in terms of clinicopathological characteristics, surgical techniques, and outcome metrics with the goal of comparing the outcomes in term of local recurrence rates and metastasis in 2 groups.

**Subjects and methods:** This is a comparative research, which included (40) women who had been diagnosed with breast cancer and were split into two groups: In group A: 20 patients underwent upfront surgery, Group B: 20 patients received neo adjuvant chemotherapy over a year.

**Result:** The two study groups differed statistically significantly in terms of local recurrence and metastatic work up.

**Conclusion:** Neoadjuvant chemotherapy significantly increases the risk of metastasis compared to upfront surgery while having a marginally positive effect on pathological complete response (PCR) in patients with breast cancer. We discovered that upfront surgery is preferable in the treatment of early breast cancer, but neoadjuvant chemotherapy is preferable in the treatment of late breast cancer.

**Key word:** Breast Cancer, Neoadjuvant Chemotherapy, Surgery, Outcome.

## Introduction

The standard of care surgical technique for patients with early breast cancer (EBC) is breast conserving surgery (BCS). Patients with locally advanced breast cancer (LABC) and large operable breast cancer (LOBC) are typically not seen to be excellent candidates for BCS. But in these patients, neoadjuvant chemotherapy (NACT) can downstage the tumours, allowing certain LOBC and LABC patients to undergo BCS. Due to numerous potential benefits over adjuvant chemotherapy, NACT is frequently used in EBC as well. These benefits include down-staging the tumour to reduce the amount of breast tissue that must be removed, assessing the tumor's response to chemotherapy in-situ, and possibly avoiding micro-metastases.<sup>1</sup>

Numerous large, excellent prospective randomised controlled trials (RCTs) with extensive follow-up have firmly confirmed the viability of primary BCS in EBC. To our knowledge, no randomised trials have compared the results of post-NACT and main BCS, hence the safety of post-NACT BCS is not as well established as that of upfront BCS. Nevertheless, the results of post-NACT BCS are frequently compared to those of initial BCS with adjuvant chemotherapy. This opinion is mostly supported by rather shoddy retrospective data, notably for LOBC and LABC. Numerous studies, including a few RCTs, have

compared the results of post-NACT BCS with post-NACT modified radical mastectomy (MRM), showing that BCS results in a slightly greater locoregional recurrence but no adverse effect on overall survival. A significant majority of instances of early-stage breast cancer (EBC) are found through population-based screening programmes. Since a substantial percentage of breast cancer patients in poor nations like India have LOBC and LABC, NACT is a frequently used technique anytime a patient is eager to save her breast.<sup>2</sup>

Neoadjuvant chemotherapy, or NACT, was first developed in the 1970s<sup>1</sup> with the goal of regressing locally advanced (Inoperable) illness and making it operable. NACT is currently routinely utilised, especially for big tumours, and was later expanded to operable (Early) breast cancer for the purpose of allowing breast-conserving surgery. Furthermore, compared to chemotherapy administered just after surgery, NACT may have a slightly higher likelihood of curing micrometastatic illness.<sup>3</sup>

NACT may lessen the surgically-induced stimulatory impact on occult disease<sup>5</sup> and lessen the release of tumour cells. NACT may also offer helpful in-vivo data on the chemosensitivity of the local (And, by extension, disseminated) tumour to various chemotherapy regimens, assisting in the selection of following medications. NACT, on the other hand,

may raise the chance of metastatic spread by postponing surgery, especially for cancers that are resistant to treatment.<sup>3</sup>

NACT and the same chemotherapy administered postoperatively have been contrasted in several randomised studies. However, these studies are difficult to interpret since tumour shrinking following NACT frequently caused differences in the frequency of breast-conserving surgery between groups. High incidences of local recurrence with NACT in these studies have been linked to failure to administer final local treatment in several trials where some good responders to NACT did not undergo surgery. Comparisons of the effectiveness of NACT with that of adjuvant chemotherapy are complicated by any such variations in the scope of surgery. Another difficulty is that analyses based on postsurgical features would be significantly influenced by down staging, necessitating the inclusion of prerandomization data in studies examining the

impact of tumour characteristics on outcome.<sup>3</sup>

### Aim of work

We compared the clinicopathological characteristics, surgical techniques, and outcome parameters of neoadjuvant chemotherapy and upfront surgery in breast cancer in this retrospective analysis of data from a retrospectively maintained database with the goal of comparing the outcome in terms of ipsilateral local recurrence rates and metastasis in 2 groups.

### Patients and methods

#### Technical design

**Study design:** This study is a Retrospective Comparative study.

**Setting:** This study was carried at Aswan oncology center.

**Time of the study:** from March 2019 till September 2020

Topic	Period
Preparatory phase	One month
Design of examination sheet	Two months
Review of literature	One months
Collection, organization, entering of data and statistical analysis	6 month

### Target population:

The research consisted of 40 individuals in total. The participants in our study were split into two groups: Neoadjuvant chemotherapy patients made up Group I. Group (II): Patients undergoing elective surgery.

**Inclusion criteria:** 18 to 70 years old. Early-stage primary breast cancer (T2, T3, N0-1, and M0). Lobular carcinoma and invasive duct carcinoma.

**Exclusion criteria:** patients who are older than 70. a metastatic tumour. Slowly expanding tumour breast cancer on both sides. Any type of breast cancer out of lobular carcinoma and invasive duct carcinoma.

**Sample size:** The research consisted of 40 individuals in total.

**Sampling technique:** This study used a method called systematic random sampling.

### Methods

**History:** Thorough history-taking When collecting a history, factors such age, place of residence, job, family history, parity, gravidity, prior abortion, results of prior pregnancies, and the existence of comorbid conditions like hypertension were assessed. Clinical evaluations include general evaluations and regional evaluations, including breast examinations.

Regular laboratory tests, mammogram and breast ultrasound. Bone scan and ct with contrast of the chest, pelvis, and abdomen (Metastatic work up).

**Preoperative markings:** The patient was site-marked prior to going into surgery. First, we asked the patients to stand up so that we could evaluate their breast meridians on both sides. After then, the inframammary fold (IMF) was identified. We designated the new nipple position at a point parallel to the plane of the IMF by using meridian marks and the IMF's position in reference to the nipple areolar complex (NAC). We then drew a triangle with 8 to 10 cm on either side of the NAC starting from the new place of the nipple. We chose 8 to 10 cm in length since it gives us greater freedom to arrange the superior mastectomy flaps. The breast base was narrowed as necessary by adjusting the base of the triangle joining these two limbs.

The medial and lateral IMF markers were connected by a softly curved line that was drawn next. Before finishing, we reevaluated to make sure the new nipple position was within the boundaries of the bilateral breast meridians.

Received uniform multidisciplinary care in accordance with institute procedures, which comprised a mammogram as a preoperative diagnostic tool and a core needle biopsy. Before being sent to our facility, nine of the research participants had an incisional or

excisional biopsy performed elsewhere.

All patients who were scheduled to receive NACT had a core-needle biopsy for the examination of histology and biomarkers (ER, PR, and HER2neu). The majority of patients who had NACT with the goal of receiving BCS afterwards underwent tumour mapping using surgical clips or percutaneous wire markers put at tumour margins, as previously mentioned. By spotting the radio-opaque markers in complete responders, a post-NACT mammography was utilized to ascertain the response to NACT and the initial location of the tumour. All patients underwent BCS, either in the form of a wide local excision (WLE) or a segmental or partial mastectomy, with or without oncoplastic reconstruction, and intraoperative margin assessment with frozen section histology of margins, followed by traditional paraffin section histopathology of the entire surgical specimen. Any invasive or in-situ infiltrating margins were removed again. Due to many infiltrated margins and severe DCIS, seven patients required conversion to mastectomy and were therefore excluded from this research group.

Although no formal anthropometry had been

recorded in the computerized data, the kind of BCS for each patient was designed to produce the optimum aesthetic effect for the volume of tissue removed. According to protocol, all patients underwent intraoperative whole-breast irradiation and tumour bed boost to the region indicated by radio-opaque metallic clips. Patients who tested positive for HER2Neu or hormone receptors got the appropriate hormone treatment or targeted therapy. Between patient groups receiving primary and post-NACT BCS, margin infiltration, IBTR, and IBTR-free survival outcomes were compared. Margin infiltration was defined as any margin(s) reported infiltrated at either frozen section histology or paraffin section histology. Patients were considered to have IBTR if they had a recurring breast tumour in the ipsilateral breast on follow-up clinical and/or mammographic examination and the cytopathology or histology verified the recurrence of a malignant lesion. In addition to overall survival Met work up, local (IBTR) recurrence free interval was computed from month of surgery to month of last follow-up or recurrence if it happened sooner than last follow-up. (Figs. 1, 2).

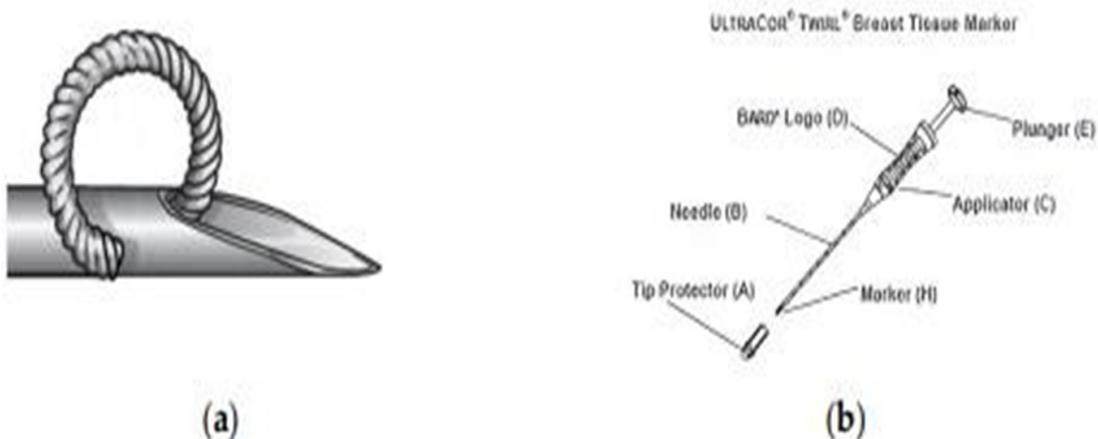


Fig 1: Ultracor Twirl clip (a) and applicator (b).

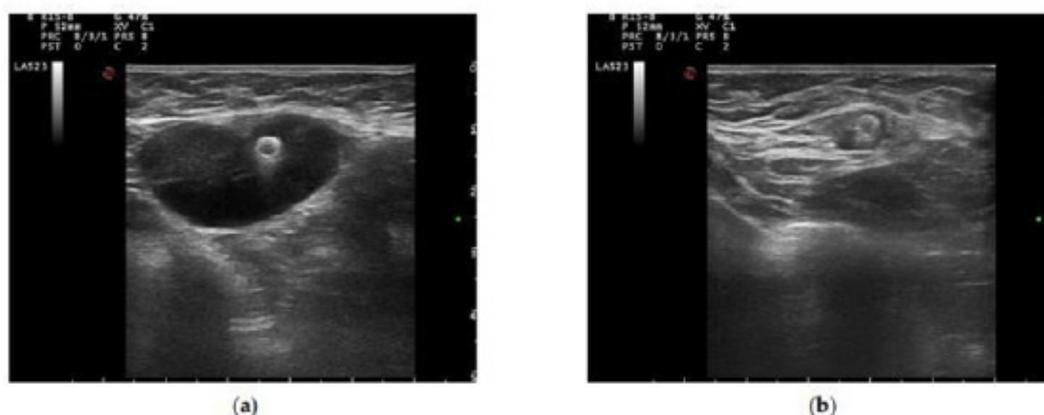


Fig 2: (a) Clip in breast lesion; (b) clip in a lymph node.

Operational design: All study participants were introduced to the researcher, who then requested their participation after briefly outlining the study's objectives. All participants got thorough information on the study's goal and anticipated advantages. The entire project was conducted with the utmost ethical attention.

### Administrative design

**Approvals:** All participants verbally and written consented after being fully informed, and information confidentiality was guaranteed. The manager of the Aswan oncology centre and the dean of the medical school at Ain Shams University both provided a formal written administrative approval letter. To secure their participation, the study's title and goals were communicated to them.

**Ethical committee:** Additionally, permission from the faculty of medicine's ethics committee and institutional review board clearance were acquired.

### Statistical analysis of the data

With the aid of the IBM SPSS software package version 20.0, data were fed into the computer and evaluated. IBM Corp., Armonk, New York Number and percentage were used to describe qualitative data. The normality of the distribution was examined using the Kolmogorov-Smirnov test. The range (Minimum and maximum), mean, standard deviation, median, and interquartile range were used to characterise quantitative data (IQR). The 5% threshold of significance was used to determine the results' significance.

**The used tests were:** Chi-square test: To contrast several groupings using categorical variables.

**Fisher's Exact or Monte Carlo correction:** When

more than 20% of the cells have an anticipated count that is less than 5, the chi-square should be corrected.

**Student t-test:** To compare two groups under study for quantitative variables with normally distributed distributions.

### Results

This study is a Comparative study that was conducted on 40 women diagnosed with breast cancer they were divided into two groups:

Group A: 20 upfront surgery patients

Group B: 20 Neo adjuvant chemotherapy patients

Patients were recruited from attendee of Aswan oncology center.

**(Table 1)** shows that there was no statistically significant difference between the two studied groups as regard history data.

**(Table 2)** shows that there was no statistically significant difference between the two studied groups as regard staging.

**(Table 3)** shows that there was no statistically significant difference between the two studied groups as regard staging.

**(Table 4)** shows that there was no statistically significant difference between the two studied groups as regard biomarkers.

Nb.ki67 was not available in our center at time of study.

**(Table 5)** shows that there was statistically significant difference between the two studied groups as regard Metastatises.

**Table 1: Comparison between the two studied groups according to history data**

History data	Group A(n = 20)		Group B(n = 20)		Test of Sig.	p
<b>Age (years)</b>						
Range.	30 – 63		32 – 55		t= 0.409	0.685
Mean ± SD.	43.9 ± 8.08		42.95 ± 6.53			
<b>Menopausal status</b>						
No	16	80.0	15	75.0	χ <sup>2</sup> = 0.143	0.705
Yes	4	20.0	5	25.0		
<b>Family history</b>						
No	17	85.0	18	90.0	χ <sup>2</sup> = 0.140	0.701
Yes	3	15.0	2	10.0		

t: Student t-test □2: Chi square test.

p: p value for comparing between the studied groups.

\*: Statistically significant at p ≤ 0.05.

**Table 2: Comparison between the two studied groups according to Staging**

Stage	Group A (n = 20)		Group B (n = 20)		$\chi^2$	p
	No.	%	No.	%		
T	2	15	75.0	10	3.692	0.158
	3	5	25.0	10		
	4	0	0.0	0		
N	0	7	35.0	8	4.468	0.107
	1	13	65.0	12		
	2	0	0.0	0		

$\chi^2$ : Chi square test.

p: p value for comparing between the studied groups.

\*: Statistically significant at  $p \leq 0.05$ .

**Table 3: Comparison between the two studied groups according to histology**

Histology	Group A (n = 20)		Group B (n = 20)		Testof Sig.	p
	No.	%	No.	%		
IDCA	19	95.0	17	85.0	$\chi^2 = 1.111$	0.302
lobular carcinoma	1	5.0	3	15.0		

IDCA: Infiltrative ductal carcinoma  $\chi^2$ : Chi square test.

p: p value for comparing between the studied groups.

\*: Statistically significant at  $p \leq 0.05$ .

**Table 4: Comparison between the two studied groups according to biomarkers**

Biomarkers	Group A (n = 20)		Group B (n = 20)		$\chi^2$	p
	No.	%	No.	%		
Estrogen receptor	-ve	11	55.0	10	0.100	0.752
	+ve	9	45.0	10		
Progesterone receptor	-ve	10	50.0	13	0.921	0.337
	+ve	10	50.0	7		
Human epidermal growthfactor receptor 2	-ve	7	35.0	11	1.616	0.204
	+ve	13	65.0	9		

$\chi^2$ : Chi square test.

p: p value for comparing between the studied groups.

\*: Statistically significant at  $p \leq 0.05$ .

**Table 5: Comparison between the two studied groups according to Clinical response**

Biomarkers	GroupA (n = 20)		Group B(n = 20)		$\chi^2$	p
	No.	%	No.	%		
Local recurrence	No	18	90.0	18	0.0	1.0
	Yes	2	10.0	2		
Metastatic	No	19	95.0	14	4.329	0.037*
	Yes	1	5.0	6		

$\chi^2$ : Chi square test.

p: p value for comparing between the studied groups.

\*: Statistically significant at  $p \leq 0.05$ .

## Discussion

The most frequent malignancy in women is breast cancer (BC). In the United States, it is anticipated that 266,120 new cases of invasive BC would be detected in 2018. Despite being the most common cause of cancer-related deaths in women globally, BC is frequently discovered when it is still treatable. Because BC is physiologically diverse, several subtypes have varying prognosis. Five molecular subgroups with unique behaviours and clinical outcomes have been discovered by gene expression profiling: luminal A, luminal B, HER2 enriched, basal-like, and normal-like cancers. The triple negative phenotype, which is defined by the absence of the oestrogen receptor (ER), progesterone receptor (PR), and HER2/neu oncogene, is mostly represented by basal-like cancers.<sup>4</sup>

The most prevalent form of cancer in women is breast cancer, which is estimated to cause 42,170 deaths and 276,480 new cases in the USA in 2020. According to the World Health Organization's 2014 report, breast cancer accounted for 32% of newly diagnosed female cancer cases in Egypt and was the leading cause of death for female cancer patients. Nearly all Egyptian patients have locally advanced breast cancer (LABC).<sup>5</sup>

Our interdisciplinary teams for breast cancer are using neoadjuvant chemotherapy (NCT) more frequently (MDTs). NCT proven to be a great platform for researching various prognostic markers for long-term outcomes, including pathological complete response (pCR), in addition to its value in downstaging inoperable LABC and increasing rates of conservative breast surgery in the operable patients.<sup>6</sup>

In order to reduce the size of the tumour, enable conservative surgical removal, eradicate clinically silent metastatic foci, and provide prognostic information based on the tumor's pathologic response, neoadjuvant chemotherapy is being utilised more often for the treatment of breast cancer.<sup>7</sup>

The pathological response to neoadjuvant chemotherapy, which is demonstrated by complete or almost complete tumour eradication in the surgical specimen, is thought to be a powerful predictor of survival and an indication of a good overall prognosis.<sup>8</sup>

Patients with locally advanced, operable breast cancer frequently get neoadjuvant chemotherapy (NAC) to get rid of micrometastases before surgery. Additionally, NAC has the benefit of improving the likelihood of breast conservation with respectable local control and enabling doctors to assess tumour response to chemotherapy.<sup>9</sup>

The administration of NAC may also downstage the axilla prior to nodal assessment, making it ideal for many breast cancer patients with big initial tumours who prefer breast conservation. Additionally, it can be used to safely postpone surgery in some circumstances in order to treat a patient's systemic micrometastatic condition, such as by giving them time to improve their health before surgery or giving them the chance to do genetic testing.<sup>10</sup>

Time to treatment has also become crucial, as longer wait periods for surgery, chemotherapy, and radiation all result in minor but considerable survival disadvantages. Some believe that starting NAC more rapidly than going straight to surgery is the norm, however we were unable to uncover any support for this in the published medical literature.<sup>11</sup>

Neoadjuvant chemotherapy has not been shown to significantly improve survival compared to adjuvant treatment in prior trials. However, individuals with any receptor status are included in these investigations. The current study's objectives were to examine the variables that influence whether patients with breast cancer would receive neoadjuvant chemotherapy or upfront surgery and to ascertain if either treatment option offers a survival advantage.

In this investigation, we discovered that, with reference to historical data, there was no statistically significant difference between the two analysed groups.

In a research to compare the effectiveness of neoadjuvant vs adjuvant chemotherapy in Hispanic/Latino (H/L) women with locally recurrent or locally progressed triple-negative breast cancer, we discovered that age and postmenopausal status did not significantly differ between the two investigated groups.<sup>12</sup>

In a research to compare whether neoadjuvant or adjuvant chemotherapy improves outcomes for patients with different subtypes of breast cancer, we discovered that patient age and surgery type preferences did not change between the two groups.<sup>13</sup>

Shown that NAC patients were generally younger (51.9 11.6 vs. 54.9 11.1 years, P.0001). In comparison to individuals who underwent upfront surgery, they also had bigger tumours (cT3-cT4: 35.8% vs 4.9%, P.0001) and more nodal involvement (cN2-cN3: 14.4% vs 3.7%, P.0001).<sup>14</sup>

We discovered that, compared to patients receiving adjuvant chemotherapy, those receiving neoadjuvant chemotherapy were younger (P 0.05), had higher tumour diameters, and were at a more advanced clinical stage. Regarding patient race, tumour histology, or tumour grade, there was no difference between the groups (P > 0.05).<sup>15</sup>

We showed in this thesis that there was no statistically significant difference in staging between the two tested groups.

In a research to evaluate prognostic markers in patients with locally advanced breast cancer undergoing neoadjuvant and adjuvant chemotherapy, we discovered that there was no significant difference in tumour stage between the two study groups ( $p > 0.05$ ).<sup>16</sup>

In terms of tumour stage, we saw no significant differences between the groups.<sup>12</sup>

We discovered that NAC recipients had higher tumour diameters ( $P .001$ ) (T stage) and more axillary lymph nodes involved ( $P .003$ ) (N stage).<sup>13</sup>

In this investigation, we showed that there was no Histology-related statistically significant difference between the two groups.

We discovered that the groups' differences in main tumour, lateral tumour, or tumour histology were not very significant.<sup>12</sup>

We discovered that neither group differed from the other in terms of the tumor's histological type ( $p > 0.05$ ).<sup>13</sup>

According to a research comparing neoadjuvant and adjuvant treatment for breast cancer, neither group's tumour histology or tumour grade substantially differed from one another. Neoadjuvant chemotherapy was more likely to be linked to larger tumours (T2, T3, T4), nodal positive, and advanced stages (IIB, III) (All comparisons,  $P 0.0001$ ).<sup>17</sup>

In the study we conducted, we discovered that there was no statistically significant distinction between the two groups in terms of the biomarkers.

We discovered that the most prevalent tumour phenotype (55.98%) was hormone receptor positive and HER2 negative, with no appreciable molecular subtype difference between the two investigated groups.<sup>14</sup>

We discovered that 23 patients (44%), or 29 patients ( $n=55\%$ ), had negative HER-2 expression. where there was no discernible change in hormonal biomarkers between adjuvant or neoadjuvant therapy for locally advanced breast cancer.<sup>16</sup>

In terms of molecular marker status, we discovered no statistically significant difference between the two groups under study, with hormone receptor-positive and HER2-negative tumours accounting for the majority of cases (55.98%).<sup>14</sup>

Neoadjuvant chemotherapy was related with oestrogen receptor (ER)-negative tumours (21% ER negative versus 15% ER positive;  $p 0.001$ ), while upfront surgery and neoadjuvant chemotherapy did

not vary significantly from one another.<sup>18</sup>

This could be as a result of postoperative hormonal and target treatment neutralisation. Salem et al.<sup>19</sup> found that hormone receptor status was a major determinant in terms of distant relapse, which is different from what is stated above.

In a research to assess the early results of breast surgery following neoadjuvant chemotherapy, we discovered that the mean disease-free survival (DFS) time was 29.8 6.1 months, with a median of 35 months, in the neoadjuvant chemotherapy (NACT) group. The mean in the group receiving adjuvant treatment was 31.2 3.8 months, with a median of 34 months ( $p$ -value = 0.4). In addition, he discovered that the mean tumour size before NACT was 20.1 7.5 mm (Range, 10-36) and 27.7 11.9 mm (Range, 11-60) ( $p$ -value=0.03).<sup>20</sup>

In the NACT group, 48/200 patients experienced distant metastases, compared to 60/190 individuals in the conventional group. The 5-year metastases-free rates ranged from 70 to 76 percent in the NACT group and from 60 to 68 percent in the conventional group, although these variations did not achieve statistical significance ( $P = 0.09$ ).<sup>21</sup>

3946 people were included in a meta-analysis of 9 randomised studies. Due to the greater proportion of breast-conserving surgery in the NACT cohort, he discovered that the probability of local recurrence was substantially higher in the NACT group compared to the ACT group ( $RR = 1.22$ ; 95% CI = 1.04–1.43;  $P = 0.018$ ).<sup>22</sup>

Although not statistically significant, we discovered that the ACT group had a lower risk of recurrence than the NACT group ( $HR=0.41$ , 95%CI=0.14-1.18,  $p=0.10$ ). Breast-conserving surgery, the difficulty of detecting tumours, and the disunity of the tumour regression model after NACT may all contribute to local recurrence after breast-conserving surgery.<sup>12</sup>

Patients with tumours greater than 3 cm were more likely to get breast preservation with neoadjuvant chemotherapy than with main surgery, according to our research.<sup>18</sup>

We discovered that there was no statistically significant difference between adjuvant therapy and neoadjuvant therapy in the survival analysis of patients, with a log rank value of 1.127 and  $p=0.288$ .<sup>16</sup>

Numerous prospective randomised studies have found no differences between individuals getting neoadjuvant chemotherapy (NAC) or adjuvant chemotherapy (AC) for the treatment of breast cancer in terms of overall survival (OS) or increased disease-free survival (DFS). Due to the strong clinical and pathologic responses frequently observed,

NAC is being administered increasingly frequently, particularly in instances of triple negative illness and human epidermal growth factor receptor 1 (HER2) positive disease. Pathologic complete response rates vary from 23.2% to 33.6% for triple negative illness and from 38.7% to 66.2% for HER2 positive, hormone-receptor negative disease.<sup>23</sup>

We hypothesised that NAC might increase the risk of perioperative complications, resulting in an extended hospital stay after surgery due to wound complications or other chemotherapy-related side effects, as a possible explanation for differences between the NAC group and those who had surgery first. However, our research revealed no distinction in hospital stay duration between AC and NAC. This is in line with other research that shown NAC does not raise the risk of short-term problems following mastectomy and implant-based reconstruction or autologous tissue reconstruction.<sup>24</sup>

Our study has a number of drawbacks, including a brief follow-up time, a small sample size, and its retrospective character, all of which may have an impact on our findings. Therefore, bigger, prospective studies should be used to confirm our findings. However, our findings demonstrate a significant association between clinicopathological variables and the clinical outcomes of breast cancer patients who received NAC.

In this study, we found that neoadjuvant chemotherapy significantly increase the risk of metastasis as compared to primary surgery and has a very significant effect on pathological complete response (PCR) in patients with breast cancer.

In this study, we showed that, while there was no statistically significant difference between the two investigated groups for local recurrence, there was a statistically significant difference between the two studied groups for metastasis.

## Conclusion

Neoadjuvant chemotherapy significantly increases the risk of metastasis compared to upfront surgery while having a marginally positive effect on pathological complete response (PCR) in patients with breast cancer. We discovered that early breast cancer responds best to upfront surgery, while late breast cancer responds best to neoadjuvant chemotherapy and make them candidate for BCS.

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