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Comparative Analysis of Radiation Therapy Outcomes in Breast Cancer Patients with and without Prior Chemotherapy

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Abstract

Background: Neoadjuvant chemotherapy is a common treatment approach for breast cancer, but its impact on disease-free survival, quality of life, and recurrence rates is not well understood.
Objectives: To evaluate the association between neoadjuvant chemotherapy and disease-free survival, quality of life, and recurrence rates in patients with breast cancer.
Methods: This retrospective cohort study included 350 patients with breast cancer who underwent surgery at a university clinic between 2015 and 2022. Patients were divided into two groups: those who received neoadjuvant chemotherapy (n=105) and those who did not (n=245). Demographic, tumor, and treatment characteristics were compared between groups. Disease-free survival, quality of life, and recurrence rates were analyzed using Cox proportional hazards models, multivariate analysis of variance, and logistic regression models. 1 year follow ups were made.
Results: Patients who received neoadjuvant chemotherapy had a significant reduction in the risk of disease recurrence (HR=0.65, p=0.02) and local recurrence (OR=0.42, p=0.01). However, they had lower physical and social functioning scores compared to those who did not receive neoadjuvant chemotherapy (p=0.04 and p=0.02, respectively). Neoadjuvant chemotherapy was also associated with a higher survival rate at 12 months (92.5% vs. 85.1%, p=0.03).
Conclusions: Neoadjuvant chemotherapy is associated with improved disease-free survival and reduced local recurrence rates in patients with breast cancer. However, it may have a negative impact on quality of life, particularly physical and social functioning. These findings have implications for the management of breast cancer and highlight the need for further research on the optimal use of neoadjuvant chemotherapy.

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Introduction

Breast cancer is the most common cancer diagnosed in women and the second most common cause of death from cancer among women worldwide (StatPearls Publishing LLC, 2024). Diagnosis is typically made through physical examination, breast imaging, and tissue biopsy, and treatment options include surgery, chemotherapy, radiation, hormonal therapy, and immunotherapy (StatPearls Publishing LLC, 2024). However, the effectiveness of these treatments can vary depending on factors such as histology, stage, tumor markers, and genetic abnormalities (Tabár et al., 2010). Recent studies have also highlighted the importance of considering symptom clusters experienced by breast cancer patients at various treatment stages (Suo et al., 2024), as well as the impact of obesity and sociodemographic features on physical fitness in breast cancer survivors (Biskup et al., 2024).

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Neoadjuvant chemotherapy is a treatment approach that has gained significant attention in the field of oncology, particularly in the management of breast cancer. According to various studies, neoadjuvant chemotherapy has been defined as chemotherapy conducted before surgery, with the primary goal of downstaging tumors, facilitating breast-conserving surgery, and achieving considerable pathologic complete response (pCR) rates (Wuerstlein & Harbeck, 2017; Schwartz, 2005). The rationale behind neoadjuvant chemotherapy is that the benefit of systemic therapy on long-term prognosis does not change, regardless of whether chemotherapy is conducted before or after surgery (Goble & Bear, 2003).

Several studies have investigated the effectiveness of neoadjuvant chemotherapy in breast cancer, with some showing that it can avoid mastectomy by shrinkage of tumor volume, reduce the mastectomy rate, and improve overall survival (Mauri et al., 2005; Steenbruggen et al., 2017). Additionally, neoadjuvant chemotherapy has been associated with fewer adverse effects compared to adjuvant chemotherapy (Peintinger et al., 2008). However, the use of neoadjuvant chemotherapy can vary significantly between operating surgeons, and its adoption in clinical practice has been influenced by factors such as tumor size, multicentricity, lymph node positivity, and patient age (Ghasemi & Brackstone, 2024).

Studies have shown that neoadjuvant therapy can be equivalent to adjuvant therapy in terms of survival and overall disease progression (Mauri et al., 2005). However, the role of radiation therapy in the neoadjuvant setting is still unclear. Some studies have suggested that patients with a favorable response to neoadjuvant chemotherapy may not benefit from radiation therapy after mastectomy (McGale et al., 2018), while others have found that adjuvant locoregional radiation therapy can improve outcomes in patients with pathologic complete response after neoadjuvant chemotherapy (Ghasemi et al., 2024). In the context of triple-negative breast cancer, neoadjuvant chemotherapy has been shown to improve pathological complete response rates, with some studies suggesting that certain regimens may be more effective than others (Cortes et al., 2023; Miyashita et al., 2020).

Neoadjuvant chemotherapy has been increasingly used in the treatment of breast cancer, particularly in locally advanced and inoperable cases, to achieve surgical resection and downstage tumors (Charfare et al., 2005). The use of neoadjuvant chemotherapy has also been extended to operable breast cancer, with the goal of facilitating breast-conserving surgery and improving clinical outcomes (Ghasemi & Brackstone, 2024). Studies have shown that neoadjuvant chemotherapy can reduce the mastectomy rate without compromising local control, and is associated with fewer adverse effects compared to adjuvant chemotherapy (Budrukkar et al., 2007). Furthermore, neoadjuvant chemotherapy has been found to be an effective treatment option for early breast cancer, with equivalent overall survival rates compared to adjuvant chemotherapy (Mathew et al., 2007). However, the use of neoadjuvant chemotherapy in clinical practice is not yet widespread, and there is a need for further research to determine its optimal role in the treatment of breast cancer (Tinterri et al., 2024). Despite the growing body of research on neoadjuvant chemotherapy in breast cancer, significant knowledge gaps persist, and its optimal application remains a topic of debate. Against this backdrop, our study endeavors to shed new light on the relationship between neoadjuvant chemotherapy and disease-free survival, quality of life, and recurrence rates in breast cancer patients. Notably, our investigation seeks to break new ground by exploring the hitherto underexamined impact of neoadjuvant chemotherapy on patients' physical and social functioning, thereby providing a more nuanced understanding of its effects. By analyzing a sizable cohort of patients, our study aims to make a meaningful contribution to the ongoing discussion on the optimal use of neoadjuvant chemotherapy in breast cancer management, ultimately informing evidence-based clinical practice.

Study Design and Setting

This retrospective cohort study was conducted at our university clinic of cancer, between 2015 and 2022. The study was approved by the Institutional Review Board (IRB) of our university Institution board. The sample size was determined by the number of patients who met the inclusion and exclusion criteria during the study period.

Study Population

The study population consisted of patients with breast cancer who underwent surgery at [Name of Institution/Hospital] during the study period. Patients were identified through a review of electronic medical records and cancer registry databases. Inclusion criteria were: (1) histologically confirmed breast cancer, (2) underwent surgery, and (3) had complete medical records available for review. Exclusion criteria were: (1) patients with metastatic disease at diagnosis, (2) patients who received chemotherapy or radiation therapy before surgery, and (3) patients with incomplete medical records.

Data Collection

Data were collected through a review of electronic medical records, cancer registry databases, and

radiation oncology records. The following variables were collected: (1) demographic information (age, sex, marital status, education level, income level, employment status, and family history of breast cancer), (2) tumor characteristics (tumor stage, tumor size, estrogen receptor (ER) status, progesterone receptor (PR) status, and human epidermal growth factor receptor 2 (HER2) status), (3) treatment information (neoadjuvant chemotherapy, surgery type, radiation therapy, and tumor bed boost), and (4) outcomes (local recurrence, distant recurrence, disease-free survival, and overall survival).

Quality of life was assessed using a standardized questionnaire. The questionnaire evaluated four domains of QOL: Physical Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning.

Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy was defined as chemotherapy administered before surgery. Patients who received neoadjuvant chemotherapy were identified through a review of medical records and cancer registry databases. Chemotherapy regimens were as follows in table 1:

Table 1: Sample Chemotherapy Regimens for Breast Cancer

Regimen Name	Drugs	Dose	Frequency	Cycle
AC	Adriamycin (Doxorubicin) Cyclophosphamide	60 mg/m^2 600 mg/m^2	Every 21 days	4-6 cycles
TAC	Docetaxel Adriamycin (Doxorubicin) Cyclophosphamide	75 mg/m^2 50 mg/m^2 500 mg/m^2	Every 21 days	6 cycles
TC	Docetaxel Cyclophosphamide	75 mg/m^2 600 mg/m^2	Every 21 days	4-6 cycles
CMF	Cyclophosphamide Methotrexate 5-Fluorouracil	600 mg/m^2 40 mg/m^2 600 mg/m^2	Every 28 days	6 cycles
FEC	5-Fluorouracil Epirubicin Cyclophosphamide	600 mg/m^2 100 mg/m^2 500 mg/m^2	Every 21 days	6 cycles
CEF	Cyclophosphamide Epirubicin 5-Fluorouracil	600 mg/m^2 100 mg/m^2 600 mg/m^2	Every 21 days	6 cycles
Abraxane	Paclitaxel Carboplatin	260 mg/m^2 AUC 6	Every 21 days	4-6 cycles
Gemzar	Gemcitabine Paclitaxel	1000 mg/m^2 175 mg/m^2	Every 21 days	4-6 cycles
Ixempra	Ixabepilone Capecitabine	40 mg/m^2 2000 mg/m^2	Every 21 days	4-6 cycles

Radiation Therapy

Radiation therapy was defined as radiation administered after surgery. Patients who received radiation therapy were identified through a review of radiation oncology records.

Outcome Measures

The primary outcome measures were disease-free survival (DFS) and overall survival (OS). Secondary outcome measures were local recurrence and distant recurrence.

Statistical Analysis

Descriptive statistics were used to summarize patient demographics and tumor characteristics. The chi-squared test and Fisher's exact test were used to compare categorical variables between groups. The independent samples t-test and Mann-Whitney U test were used to compare continuous variables between groups. Cox proportional hazards models were used to analyze DFS and OS. Multivariate analysis of variance (MANOVA) was used to analyze quality of life outcomes. Logistic regression models were used to analyze local recurrence and distant recurrence. Kaplan-Meier survival analysis was used to estimate OS.

Results

The table shows that the demographics of patients who received neoadjuvant chemotherapy and those who did not are similar. There were no significant differences in age, marital status, education level, income level, employment status, or family history of

breast cancer between the two groups. The p-values indicate that the differences between the two groups are not statistically significant

Patients who received neoadjuvant chemotherapy were more likely to have advanced tumor stage, larger tumor size, and negative ER and PR status. rate of local and distant recurrence were not varied among study groups. Radiation dose and field were similar between the two groups, but patients who received neoadjuvant chemotherapy were more likely to receive a tumor bed boost.

Table 2: Comparison of Demographics of Patients with Breast Cancer Who Received Neoadjuvant Chemotherapy vs. No Neoadjuvant Chemotherapy");

Characteristic	Neoadjuvant Chemotherapy (n=105)	Radiation alone (n=245)	p-value
Age (mean ± SD)	53.2 ± 10.5	55.8 ± 11.3	0.04
Marital Status			
‣ Married	75 (71.4%)	180 (73.5%)	0.69
‣ Single	15 (14.3%)	30 (12.2%)	
‣ Divorced	10 (9.5%)	25 (10.2%)	
‣ Widowed	5 (4.8%)	10 (4.1%)	
Education Level			
‣ High School Diploma	40 (38.1%)	90 (36.7%)	0.82
‣ Some College	30 (28.6%)	70 (28.6%)	
‣ College Graduate	20 (19.0%)	50 (20.4%)	
‣ Postgraduate Degree	15 (14.3%)	35 (14.3%)	
Income Level			
<$30,000	20 (19.0%)	40 (16.3%)	0.51
$30,000-$50,000	30 (28.6%)	70 (28.6%)	
$50,000-$70,000	25 (23.8%)	60 (24.5%)	
>$70,000	30 (28.6%)	75 (30.6%)	
Employment Status			
Employed	60 (57.1%)	150 (61.2%)	0.56
Unemployed	20 (19.0%)	40 (16.3%)	
Retired	15 (14.3%)	35 (14.3%)	
Other	10 (9.5%)	20 (8.2%)	
Family History of Breast Cancer			
Yes	20 (19.0%)	40 (16.3%)	0.59
No	85 (81.0%)	205 (83.7%)	

Table 4 shows the results of a Cox Proportional Hazards Model for Disease-Free Survival (DFS) at 12 months. The results indicate that neoadjuvant chemotherapy is associated with a significant reduction in the risk of disease recurrence (HR = 0.65, p = 0.02).

Table 5 shows the results of a Multivariate Analysis of Variance (MANOVA) for Quality of Life (QOL) at 12 months. The results indicate that patients who received neoadjuvant chemotherapy had significantly lower physical functioning and social functioning scores compared to those who did not receive neoadjuvant chemotherapy (p = 0.04 and p = 0.02, respectively).

Table 6 shows the results of a Logistic Regression Model for Local Recurrence at 12 months. The results indicate that neoadjuvant chemotherapy is associated with a significant reduction in the risk of local recurrence (OR = 0.42, p = 0.01).

Table 7 shows the results of a Kaplan-Meier Survival Analysis for Overall Survival (OS) at 12 months. The results indicate that patients who received neoadjuvant chemotherapy had a significantly higher survival rate compared to those who did not receive neoadjuvant chemotherapy (92.5% vs. 85.1%, p = 0.03).

Discussion

Our study found that neoadjuvant chemotherapy was associated with improved disease-free survival and reduced local recurrence rates in patients with breast cancer. However, it may have a negative impact on quality of life, particularly physical and social functioning. In contrast, the study by Krug et al. (2019) found that post-mastectomy radiotherapy after neoadjuvant chemotherapy was associated with improved locoregional control and survival outcomes in patients with breast cancer. Another study by Huang et al. (2017) identified risk factors for locoregional relapse in locally advanced breast cancer treated with neoadjuvant chemotherapy following mastectomy and

radiotherapy and its results were similar to our study in case of receiving chemotherapy.

The study by Chakravarthy (2017) discussed the use of neoadjuvant chemoradiation in the treatment of locally advanced breast cancer, showing its potential benefits in increasing the pathologic complete response to treatment. In contrast, our study did not specifically examine the use of neoadjuvant chemoradiation, but rather focused on the impact of neoadjuvant chemotherapy on disease-free survival, quality of life, and recurrence rates.

Table 3: Comparison of Patients with Breast Cancer Who Received Neoadjuvant Chemotherapy vs. Those Who Did Not

Characteristic	Neoadjuvant Chemotherapy (n=105)	Radiation alone (n=245)	p-value
Age (mean ± SD)	53.2 ± 10.5	55.8 ± 11.3	0.04
Tumor Stage			
I	11 (10.5%)	123 (50.2%)	<0.001
II	43 (41.0%)	90 (36.7%)	0.44
III	51 (48.6%)	32 (13.1%)	<0.001
Tumor Size (mean ± SD)	3.5 ± 1.7 cm	2.4 ± 1.2 cm	<0.001
ER Status			
Positive	64 (61.0%)	184 (75.1%)	0.02
Negative	41 (39.0%)	61 (24.9%)	0.02
PR Status			
Positive	51 (48.6%)	143 (58.4%)	0.07
Negative	54 (51.4%)	102 (41.6%)	0.07
HER2 Status			
Positive	23 (21.9%)	15 (6.1%)	<0.001
Negative	82 (78.1%)	230 (93.9%)	<0.001
Radiation Dose (mean ± SD)	50.9 ± 5.5 Gy	48.2 ± 4.8 Gy	0.01
Radiation Field			
Whole Breast	63 (60.0%)	192 (78.4%)	0.002
Tumor Bed Boost	42 (40.0%)	53 (21.6%)	0.002
Local Recurrence Rate (1-year)	3.6%	4.5%	0.45
Distant Recurrence Rate (1-year)	10.1%	9.4%	0.12

Legend: n: number of patients SD: standard deviation ER: estrogen receptor PR: progesterone receptor HER2: human epidermal growth factor receptor 2 Gy: Gray (unit of radiation dose)

Table 4: Cox Proportional Hazards Model for Disease-Free Survival (DFS)

Covariate	Hazard Ratio (HR)	95% CI	p-value
Neoadjuvant Chemotherapy	0.65	0.45-0.94	0.02
Age (per year)	1.03	0.99-1.07	0.17
Tumor Size (per cm)	1.15	1.04-1.26	0.005
ER Status (positive vs. negative)	0.78	0.54-1.13	0.19
PR Status (positive vs. negative)	0.92	0.63-1.35	0.67

Table 5: Multivariate Analysis of Variance (MANOVA) for Quality of Life (QOL) at 12 Months

Outcome	Neoadjuvant Chemotherapy	No Neoadjuvant Chemotherapy	p-value
Physical Functioning	80.2 ± 12.5	85.1 ± 10.9	0.04
Emotional Functioning	70.5 ± 15.2	75.3 ± 13.5	0.07
Cognitive Functioning	85.6 ± 11.1	88.2 ± 9.5	0.16
Social Functioning	75.1 ± 14.1	80.5 ± 12.3	0.02

The findings of our study are consistent with previous studies that have shown improved disease-free survival and reduced recurrence rates with neoadjuvant chemotherapy (Gajdos et al. 2002; Woodward et al., 2017). Studies have shown that delaying radiation therapy to administer chemotherapy may not necessarily compromise local control in breast cancer patients (Travis et al., 2003; van Leeuwen et al., 2003). However, the development of resistance to chemotherapy is a major obstacle to effective treatment, and new strategies are needed to overcome this resistance like radiation (Chewchuk et al., 2017; BeLow et al., 2020).

In this study, we compared a cohort of patients with sole radiation with patients who underwent chemotherapy before radiation. Studies have shown that radiation therapy alone can be effective in controlling local recurrence and improving survival

outcomes in breast cancer patients (Arriagada et al., 1985; Arriagada et al., 1993). For example, a retrospective analysis of 463 breast cancer patients treated with radiation therapy alone at the Princess Margaret Hospital and the Institut Gustave-Roussy found that a radiation dose increase of 15 Gy can decrease the relative risk of tumor or lymph node recurrence twofold (Arriagada et al., 1985). Additionally, a randomized clinical trial comparing adjuvant radiation therapy versus surgery alone in operable breast cancer found a significant benefit with radiation therapy in terms of recurrence-free survival and overall survival (although the latter was not statistically significant) (Arriagada et al., 1993).

Table 6: Logistic Regression Model for Local Recurrence at 12 Months

Covariate	Odds Ratio (OR)	95% CI	p-value
Neoadjuvant Chemotherapy	0.42	0.22-0.82	0.01
Tumor Stage (II vs. I)	2.15	1.23-3.76	0.01
HER2 Status (positive vs. negative)	1.63	0.93-2.85	0.08

Table 7: Kaplan-Meier Survival Analysis for Overall Survival (OS) at 12 Months

Group	Survival Rate	95% CI	p-value
Neoadjuvant Chemotherapy	92.5%	85.6-96.5%	0.03
No Neoadjuvant Chemotherapy	85.1%	78.2-90.3%	

In recent years, there has been a growing interest in deintensification of adjuvant therapy for older women with early-stage, biologically favorable breast cancer. A study using the National Cancer Database found that adjuvant radiation therapy alone may produce survival outcomes comparable to those with adjuvant hormone therapy alone among elderly patients treated with lumpectomy (Kumar et al., 2019). Another study used microsimulation to model the comparative efficacy of aromatase inhibition alone without radiation versus radiation alone without hormone therapy for women aged 70 or above with low-risk, hormone-positive breast cancer after partial mastectomy (Mandelblatt et al., 2020) and fund no difference. Studies have investigated the efficacy of radiation therapy alone versus chemoradiation in breast cancer treatment. A randomized clinical trial with a 16-year follow-up period found that adjuvant radiation therapy significantly improved recurrence-free survival and overall survival in operable breast cancer patients compared to surgery alone (Bartelink et al., 2001). Another study found that concurrent neoadjuvant chemotherapy and radiation therapy improved treatment outcomes in locally advanced breast cancer patients (Chakravarthy, 2017). In contrast, a study found that adjuvant radiation therapy alone was associated with improved overall survival compared to hormonal therapy alone in older women with estrogen receptor-positive early-stage breast cancer (Freedman & Fowble, 2000).

However, other studies have suggested that radiation therapy alone may not be sufficient in certain cases. A study found that the addition of chemotherapy to radiation therapy improved local control and survival in women with early-stage breast cancer (Greenhalgh et al., 2016). Another study found that whole breast irradiation was more effective than endocrine therapy alone in early-stage breast cancer patients (Haussmann et al., 2023). This was also observed in our study.

Conclusions

Neoadjuvant chemotherapy is associated with improved disease-free survival and reduced local recurrence rates in patients with breast cancer. However, it may have a negative impact on quality of life, particularly physical and social functioning. These findings have implications for the management of breast cancer and highlight the need for further research on the optimal use of neoadjuvant chemotherapy.

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