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Comparative analysis of radiation therapy outcomes in breast cancer patients with and without prior chemotherapy

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► ***Original article***

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ABSTRACT

Background: Chemotherapy is often prescribed for breast cancer treatment; however, how it affects disease-free survival, quality of life, and recurrence rates remains inadequately defined. This study aims at investigating relationships between chemotherapy and disease-free survival, quality of life, and recurrence percentages among breast cancer patients. ***Materials and Methods:*** This was a retrospective chart review of 350 breast cancer patients who underwent surgery between 2015 and 2022 at a university medical center. The participants received treatment such that the target group consisted of those receiving chemotherapy (n=105) and those not receiving chemotherapy (n=245). Comparison of demographic data such as tumor characteristics and treatment details between the two study groups will be carried out. Cox proportional hazards models as well as multivariate analysis of variance (MANOVA) and logistic regression will be used to evaluate disease-free survival, quality of life, and recurrence. Follow up assessment was done at 12 months. ***Results:*** Chemotherapy patients were significantly less likely to experience disease recurrence than those not exposed to Chemotherapy (HR=0.65, p=0.02) or local recurrence (OR=0.42, p=0.01). Patients who had chemotherapy again had lower physical and social functioning scores compared with those who were not given chemotherapy (p=0.04 and p=0.02, respectively). Chemotherapy was associated with an increased 12 -month survival probability (92.5% vs 85.1%, p=0.03). ***Conclusion:*** Chemotherapy has an association with improved disease-free survival and decreased local recurrence in breast cancer patients, but it also adversely affects life quality, particularly specific aspects such as physical and social functions. These results emphasize that balance between benefit of treatment and quality of life should be carefully considered in treatment of breast cancer and that further investigations must occur for optimizing chemotherapy usage.

INTRODUCTION

Breast cancer remains the most frequently diagnosed type of cancer among women and the second leading cause of female cancer death worldwide [1]. In general, diagnosis is made by physical examination, mammography, and biopsy; treatment options include surgery, chemotherapy, radiation therapy, hormone therapy, and immunotherapy [2]. However, the effectiveness of any of these modalities largely depends on the tumor type and stage, its genetic mutations, and biomarkers [3]. Recent research has drawn attention to the assessment of the spectrum of symptoms experienced by breast cancer patients across different stages of treatment and the varying impacts of elements such as obesity and sociodemographic characteristics on the health of survivors [4].

Chemotherapy has evoked considerable interest, especially in the neoadjuvant setting (i.e., given prior to surgery), in the management of breast cancer [5]. Multiple studies have shown neoadjuvant chemotherapy to shrink tumors and render them more amenable to breast-conserving surgery with a higher rate of pathological complete response (pCR) [6]. The rationale behind this is that the systemic effects of chemotherapy are probably not changed by pre- or postoperative administration [7]. Studies have shown that neoadjuvant chemotherapy could reduce the mastectomy rates and overall survival [8]. Moreover, new findings show that neoadjuvant chemotherapy has fewer adverse side effects compared with adjuvant chemotherapy [9]. Nonetheless, clinical applicability differs as it becomes contingent on tumor size, involvement of lymph nodes, or patient's age, factors influencing surgical decisions [10].

Some studies indicate that preoperative chemotherapy is equivalent to postoperative chemotherapy for survival and disease progression [11]. However, the role of the preoperative radiation therapy is much debated. Some studies have indicated that patients responding well to chemotherapy would not receive advantage from the

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addition of radiation therapy after mastectectomy; conversely, others have shown that postoperative radiation can benefit patients with complete pathological response to chemotherapy [12]. In the case of triple-negative breast cancer, chemotherapy is shown to increase pCR in some regimens over others [13, 14].

Chemotherapy has become the keystone in the treatment of locally advanced or inoperable breast cancer with a view to achieving downstaging and facilitating surgical resection [15]. In operable breast cancer, it may aid in preserving the breast and achieving improved clinical outcomes [16]. Data points toward chemotherapy successfully reducing mastectomy rates without downgrading local disease control, and its side effects usually seem to be milder than those associated with post-operative chemotherapy [17]. Chemotherapy has also been efficacious in early-stage breast cancer, achieving survival rates comparable to those found with post-operative chemotherapy [18]. Despite these merits, chemotherapy still hesitates to find universal acceptance in daily clinical practice, with much more work needed to define its place in breast cancer management [19].

Although a lot of research has been done on chemotherapy in breast cancer, there are still unknowns in its optimal use and in its overall role in treatment [20]. The present study will contribute to the ongoing controversy by examining the association between chemotherapy and endpoints such as disease-free survival, quality of life, and breast cancer recurrence rates [21]. The study will probably pay special attention to assessing the relatively unexplored area of chemotherapy impact on physical and social functioning that will strengthen the understanding of chemotherapy effects [22]. With a large cohort of patients, findings from this study may help generate valuable information for evidence-based practice in breast cancer management [23].

MATERIALS AND METHODS

It was a retrospective chart review cohort study which was conducted in the cancer clinic of the university from 2015 to 2022 and received approval from the university's governing IRB. The sample size depended upon the number of patients who met the inclusion and exclusion criteria during the study period.

Study population

The study cohort included breast cancer patients that had undergone surgery across the study period at this medical center. Patient identification was done by reviewing electronic health records and cancer registry databases. Inclusion criteria included: (1) histologically confirmed diagnosis of breast cancer, (2) completed surgery, and (3) comprehensive medical records available. Patients were excluded if they met any of the following: (1) metastatic disease at diagnosis, (2) chemotherapy or radiotherapy before surgery, and (3) incomplete medical records.

Data collection

Data collection was made possible by reviewing the electronic health records and cancer registry databases and radiation oncology records. The following variables were collected: (1) demographic (age, gender, 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, type of surgery, radiation therapy, and tumor bed boost), and (4) clinical outcomes (local recurrence, distant recurrence, disease-free survival, and overall survival).

Assessment of quality of life (QOL)

Assessment of quality of life made use of a standardized questionnaire measuring four domains: Physical Functioning, Emotional Functioning, Cognitive Functioning, and Social Functioning. The tool thus allowed for objective assessment of the patients' well-being over the study period.

Neoadjuvant chemotherapy

Neoadjuvant chemotherapy means the chemotherapy which is given before surgery. Patients are identified who received this treatment after a review of their medical records as well as cancer registry information. The specifics of which chemotherapy regimens are employed are indicated in table 1.

Radiation therapy

Radiation therapy has been defined as radiation delivered following surgery. This treatment is usually in a fractionated dose of 1.8-2.0 Gy per fraction, with 5 fractions per week. Patients received a total prescription dose of 45-60 Gy over 5-6 weeks, with some patients receiving an additional boost of 10-16 Gy in 5-8 fractions. Radiation therapy was given by tangential fields and supraclavicular fields as required to the adequate coverage of the target area while reducing the amount of irradiated surrounding normal tissues. Treatment plans devised a homogeneous dose within the planning target volume, with no more than 5% dose variation.

Radiation therapy patients were defined through an investigation of patients' records for radiation oncology. Each of the patients were internalized utilizing a linear accelerator, which was specifically

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the Precise Trilogy (Shanghai Huanxing Medical Equipment Co., Ltd, China). The radiation field had been defined using the Xinga CT Simulator (Beijing Wandong Medical Equipment Co., Ltd, China), followed by treatment delivery by the aid of the SmartArc technique. Treatment plans were made using the HiArt Planning System (Tianjin Kehui Medical Technology Co., Ltd, China) and validated by the MapCheck 2 quality assurance device (Sichuan Chuanxi Medical Equipment Co., Ltd, China). Positioning of patients was done using the Qfix kVue immobilization system (Shenzhen Qfix Medical Equipment Co., Ltd, China) and imaging was done using the uCT2 cone beam computed tomography scanner (Shanghai United Imaging Healthcare Co., Ltd, China) combined with the iohexol contrast agent (Beijing Beilu Pharmaceutical Co., Ltd, China).

Table 1. Sample chemotherapy regimens for breast cancer.

Regimen Name	Drugs	Dose mg/m²	Frequency	Cycle Length
AC	Adriamycin (Doxorubicin)	60	Every 21 days	4-6 cycles
	Cyclophosphamide	600		
TAC	Docetaxel	75	Every 21 days	6 cycles
	Adriamycin (Doxorubicin)	50		
	Cyclophosphamide	500		
TC	Docetaxel	75	Every 21 days	4-6 cycles
	Cyclophosphamide	600		
CMF	Cyclophosphamide	600	Every 28 days	6 cycles
	Methotrexate	40		
	5-Fluorouracil	600		
FEC	5-Fluorouracil	600	Every 21 days	6 cycles
	Epirubicin	100		
	Cyclophosphamide	500		
CEF	Cyclophosphamide	600	Every 21 days	6 cycles
	Epirubicin	100		
	5-Fluorouracil	600		
Abraxane	Paclitaxel	260	Every 21 days	4-6 cycles
	Carboplatin	AUC 6		
Gemzar	Gemcitabine	1000	Every 21 days	4-6 cycles
	Paclitaxel	175		
Ixempra	Ixabepilone	40	Every 21 days	4-6 cycles
	Capecitabine	2000		

Outcome measures

Primary outcome measures were disease-free survival (DFS) and overall survival (OS). Other measured outcomes included local recurrence and distant recurrence.

Statistical analysis

Descriptive statistics were used to summarize participant demographics and tumor characteristics. Between-group categorical variables were assessed using the chi-square test and Fisher exact test compared. Independent Samples t-test and Mann-Whitney U test were used for continuous variables. Cox Proportional hazard models were used for analyzing DFS and OS. Quality of life outcomes were analyzed using multivariate analysis of variance (MANOVA) designs, while local and distant recurrence scenarios were analyzed using logistic regression models. Kaplan-Meier survival analysis was used to estimate OS.

RESULTS

As shown in table 2, the comparison focuses on two populations, namely, referring to surgery; patients pre-treated with neoadjuvant chemotherapy (105), and those receiving radiation therapy alone (245). The study showed that the chemotherapy group consisted of younger patients by a mean difference of 2.6 years (mean 53.2 years vs. mean 55.8 years; p=0.04). In extension to that, for tumor staging, the chemotherapy group exhibited more advanced stages, with 51(48.6%) patients being classified into stage III in comparison to 32(13.1%) in the radiation-only cohort. In contrast, 123 (50.2%) of the radiation-only group had stage I tumors while only 11 (10.5%) in the chemotherapy group had stage I tumors (p<0.001). Chemotherapy patients tended to have tumors of larger average size than those of radiation-alone patients; mean 3.5 cm versus 2.4 cm (p<0.001).

Moreover, the chemotherapy group included more patients with negative estrogen receptor (ER) and progesterone receptor (PR) status- having 41 (39%) negative to ER and 54 (51.4%) negative to PR- compared with those from the radiation-only group, who had 61 (24.9%) and 102 (41.6%), respectively (p=0.02 for ER and p=0.07 for PR). Higher percentages of positive HER2 status were recorded in the patients undergoing chemotherapy as compared to the radiation-only group, that is, 23(21.9%)-vs-15 (6.1%) respectively (p<0.001).

In any case, considering the mean dose of radiation received, it is slightly higher in the chemotherapy group with 50.9 Gy to the radiation-only group that received 48.2 Gy (p=0.01). The patients receiving chemotherapy are more likely to have received tumor bed boost treatment; 42 (40%) received this treatment as compared with 53 (21.6%) in the radiation-only group (p=0.002). However at first outset, the two groups behaved the same with respect to all indices of local and distant recurrence. The one-year local recurrence rate was 3.6% in the chemotherapy group and 4.5% in the radiation-only group (p=0.45). The one-year distant recurrence rate was 10.1% in the chemotherapy group and 9.4% in the radiation-only group (p=0.12).

As presented in table 3, the findings of a Cox Proportional Hazards Model of Disease-Free Survival

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(DFS) at 12 months show neoadjuvant chemotherapy to be associated with a significantly lower hazard of disease recurrence: HR 0.65 (95% CI: 0.45-0.94, p=0.02), meaning that patients who received neoadjuvant chemotherapy had a lower risk of disease recurrence compared to patients who did not receive neoadjuvant chemotherapy by 35%. By contrast, age was not proved to be a significant predictor of DFS, with HR 1.03(95% CI: 0.99-1.07, p=0.17), which means that for each additional year of being alive, there was a 3% increase in the risk of disease recurrence, although not statistically significant. Tumor size, on the other hand, was shown to be an independent predictor of DFS with HR 1.15 (95% CI: 1.04-1.26, p=0.005), which indicates that every additional centimeter of tumor size increased the risk of disease recurrence by 15%. Status of ER and PR were not significant predictors of DFS with HRs 0.78(95% CI: 0.54-1.13, p=0.19) and 0.92(95% CI: 0.63-1.35, p=0.67).

Table 2. 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)

The results of a MANOVA for Quality of Life (QOL) at 12 months is presented in table 4. Subjects who received neoadjuvant chemotherapy and subjects who did not were significantly different with respect to both physical functioning and social functioning. Patients on neoadjuvant chemotherapy reported worse physical functioning, with a mean score of 80.2 ± 12.5, versus 85.1 ± 10.9 for patients off neoadjuvant chemotherapy (p=0.04). Similarly, for social functioning, patients undergoing neoadjuvant chemotherapy had a score of 75.1 ± 14.1 versus 80.5 ± 12.3 for patients off neoadjuvant chemotherapy (p=0.02). In contrast, emotional functioning scores were not significantly different between the two groups: 70.5 ± 15.2 for neoadjuvant chemotherapy and 75.3 ± 13.5 for no neoadjuvant chemotherapy (p=0.07) and cognitive functioning scores of 85.6 ± 11.1 for neoadjuvant chemotherapy and 88.2 ± 9.5 for no neoadjuvant chemotherapy (p=0.16).

Table 3. 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

Legend: ER: estrogen receptor, PR: progesterone receptor.

Table 4. MANOVA for 1-year QOL.

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

As per table 5, the Logistic Regression Model for Local Recurrence at 12 months. It demonstrated that neoadjuvant therapy is associated with a highly reduced risk of regional reemergence, having an odds ratio (OR) for 0.42 (95 percent confidence interval: 0.22-0.82, p=0.01). This means that those undergoing chemotherapy had 58% lesser chances of regional reemergence in comparison to those who did not undergo chemotherapy. Cancer stage was found to influence local recurrence as well, having an OR of 2.15 (95% CI 1.23-3.76, p=0.01) for stage II tumors as compared to stage I tumors, i.e. showed 115% higher risk of local recurrence among stage II tumors. Human epidermal growth factor receptor 2 (HER2) status thus found not being significant in prediction of local recurrence; OR: 1.63 (95 % CI: 0.93-2.85, p=0.08), although there was a trend for increasing local recurrence risk in patients with positive HER2 status.

Table 5. 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

Legend: HER2: human epidermal growth factor receptor 2.

Figure 1 shows the results of a Kaplan-Meier Survival Analysis for Overall Survival (OS) at 12 months. It revealed a significant difference in survival frequencies between those who underwent chemotherapy and those who abstained. Those who underwent chemotherapy had a better survival frequency, with 92.5% surviving at 12 months (95%

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CI: 85.6-96.5%), compared to 85.1% (95% CI: 78.2-90.3%) for those who refrained from chemotherapy (p=0.03). This implies that patients underwent chemotherapy had an absolute improvement of 7.4% in survival frequency at 12 months as opposed to patients who did not undergo chemotherapy.

There's a major difference in survival frequencies between subjects in treatment and those abstaining. Those undergoing treatment had a better survival frequency of 92.5% (95% CI: 85.6-96.5%) at 12 months compared to an 85.1% survival rate at 12 months (95% CI: 78.2-90.3%) for those who did not receive treatment (p=0.03). This means that participants receiving treatment experienced an absolute difference in survival frequency at 12 months relative to those who did not receive treatment of 7.4%.

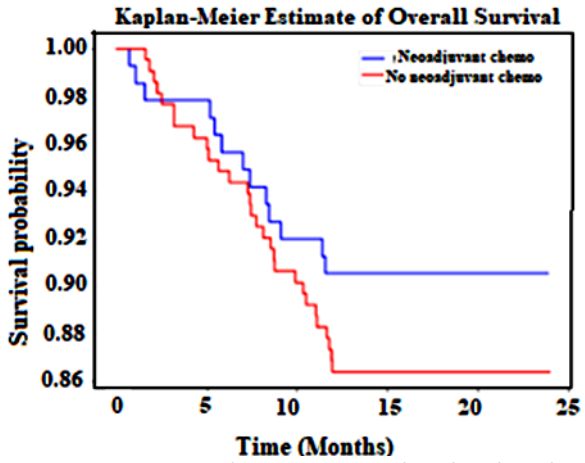

Figure 1. One year Kaplan-Meier Survival Analysis based on the chemotherapy status.

DISCUSSION

Our study found that neoadjuvant chemotherapy improved disease-free survival and local recurrence rates in patients with breast cancer. This treatment also appeared to have a negative impact on patients' quality of life, especially regarding physical and social functioning. On the contrary, Krug *et al.* [18] showed that post-mastectomy radiotherapy following neoadjuvant chemotherapy improved locoregional control and survival rates in women with breast cancer. Chakravarthy [19] discussed the possible advantages of chemoradiotherapy for the management of regionally advanced breast cancer with a possible increased rate of pathological complete response. Our study wasn't designed to directly assess the effect of chemoradiation but considered the impact of neoadjuvant chemotherapy on disease-free survival and, to a lesser degree, quality of life and recurrence rates.

Our results comply with previously published studies assessing the benefits of neoadjuvant chemotherapy for disease-free survival and for the reduction of recurrence rates [20, 21]. Other studies have shown that, in terms of local control, a delay in the provision of radiation therapy in favor of chemotherapy does not really matter [22, 23]. However, the issue of overcoming chemotherapy resistance remains a big one, with the need for other methods including radiation in attempting to circumvent it [24, 25].

In a comparison between patients getting sole radiotherapy and patients getting chemotherapy before radiation therapy, we came up with the conclusion that radiotherapy alone was effective for controlling local recurrence and improving survival in women with breast cancer [26, 27]. The researchers analyzed 463 breast cancer patients treated with radiotherapy only at these two centers: Princess Margaret Hospital and Institut Gustave-Roussy. They found that increasing radiation dose by 15 Gy significantly reduced the relative risk of tumor or lymph node recurrence [26]. In a randomized clinical trial comparing additional radiotherapy versus surgery alone in treatable breast cancer, additional radiotherapy clearly favored recurrence-free survival, although not statistically significant for overall survival [27].

Recently, there has been great interest in the minimization of additional treatment for older women with early-stage, biologically favorable breast cancer. One study with the National Cancer Database concluded that radiation therapy alone could yield survival outcomes equivalent to hormone therapy alone for older patients after breast-conserving surgery [28]. Another study using microsimulation analyzed the effectiveness of aromatase inhibition alone (no radiation) versus radiation alone (no hormone therapy) for women aged 70 and older with low-risk, hormone-positive breast cancer after partial mastectomy, finding no meaningful difference between the two strategies [29].

Research has also tapped into the effectiveness of radiation therapy alone relative to chemoradiation for breast cancer therapy. A clinical trial randomized and followed up for 16 years revealed, as compared to surgery alone, that adjuvant radiotherapy patients had improved recurrence-free survival and overall survival in operable breast cancer [30]. Huang *et al.* (2017) likewise identified factors associated with locoregional relapse in patients with locally advanced breast cancer treated with neoadjuvant chemotherapy, and their results correspond with our findings in chemotherapy patients [31]. In addition, combining neoadjuvant chemotherapy and radiation therapy improves the treatment outcome of patients with locally advanced breast cancer [19]. Evidence from this research has also proved that patients with advanced stages of the disease get improved outcome when chemotherapy is added before radiation therapy. Whole-breast irradiation was found to be more effective than endocrine therapy alone in patients with stage I and II breast cancer [31] and this

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observation was also found in our research.

CONCLUSION

Chemotherapy is associated with improved disease-free survival and reduced local recurrence rates with breast cancer. Nevertheless, it may adversely affect patients' quality of life, especially the physical and social domains. These consequences pose treatment implications for breast cancer and amplify the need for more studies regarding the ideal use of neoadjuvant chemotherapy.

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Conflicts of interests: None to be declared.

***Ethical consideration*:** this was a chart-review study of anonymized subjects that was approved by hospital research ethics sector; and while was endorsed by the IRB of university, it did not received any IRB code due to study design of chart-review.

***Author contribution*:** Y.Y. and X.C. formulated and structured the research, gathered and evaluated the information, and composed the document. Z.Z. assisted with the information evaluation and understanding of the outcomes. L.L. oversaw the research, offered essential feedback on the document, and granted final endorsement for submission. All contributors participated in the authoring and refining of the document and have perused and consented to the disseminated edition of the document.

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