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## Efficacy of Full Dose and Sandwich Neoadjuvant Chemotherapy in Breast Cancer: A Literature Review

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### Abstract

**Introduction.** Breast cancer is the leading cause of death in productive-age women, and that needs to be addressed with systemic medication. There has been a big-scale success using adjuvant chemotherapy; however, the optimal method of chemotherapy administration has yet to be determined. Two methods have been introduced today: full dose and sandwich methods. In full dose, we administer chemotherapy before surgical intervention, whereas in the sandwich method, we administer chemotherapy before and after surgical intervention. In this literature review, we aim to observe the effectiveness of chemotherapy administration through both full-dose and sandwich methods.

**Method.** In the initial phase, 51 articles were enrolled. We excluded duplicate studies, studies that did not meet the inclusion/exclusion criteria, and studies with different outcome measures, resulting in two articles. The effectiveness of each method is based on three main outcome measures: pathological complete response (pCR), overall survival (OS), and disease-free survival (DFS).

**Results.** The pCR of the full dose method was higher (17.7%) when compared to the sandwich method (8.6%),  $p = 0.012$ . Overall survival in the full dose method is better, as observed from the hazard ratio (HR); the HR of the full dose method is 1.37, while the sandwich method is only 1.08. Regarding DFS, there is no significant effect difference between the two methods,  $p = 0.237$ .

**Conclusion.** Neoadjuvant administration with the full-dose method shows higher overall survival, whereas the sandwich method exhibits comparable disease-free survival.

**Keywords:** neoadjuvant chemotherapy, full dose method, sandwich method, overall survival, disease-free survival, pathological complete response

### Introduction

Breast cancer is the leading cause of death for women in their reproductive age. Around two million women worldwide are plagued with the disease.<sup>1</sup> Its survival rate varies from country to country: countries like India, Iran, Indonesia, Malaysia, and some African countries have a lower survival rate compared to China, Korea, and Cuba due to different healthcare systems, genetics, and education levels. Breast cancer survival rates vary among countries due to factors such as the efficacy of the healthcare system, access to treatment, and human development levels. Higher Human Development Index (HDI) countries tend to have better survival rates, with disparities linked to a country's developmental position and efficiency of healthcare services. In the Eastern Mediterranean region, survival rates differ significantly, with about half of patients not surviving beyond ten years, in contrast with more developed countries. European countries exhibit varying survival rates, with higher GDP per capita countries showing higher survival rates due to better access to treatments and healthcare services. Additionally, differences in cancer survival between Europe and the US in the late 1990s were mainly attributed to lower survival rates in Eastern Europe, possibly due to constrained healthcare quality. Based on the literature, the survival rate for breast cancer in Indonesia is 51%.<sup>2,3</sup> This may be caused by several factors, including the implementation of early detection methods, education, and different tendencies of the tumor's location.<sup>3</sup>

Surgery is a mainstay in the treatment of breast cancer. However, being a systemic disease, it requires additional treatment that addresses its systemic nature; in the case of breast cancer, it can be addressed through chemotherapy. Chemotherapy has risen in popularity for treating and preventing metastatic lesions in patients with breast cancer. Evidence from large-scale studies has shown that adjuvant therapy with chemotherapy has a role in improving the prognosis of breast cancer

patients.<sup>4,5</sup> Even so, the order in which it is administered relative to surgery that optimizes outcome is still inconclusive.<sup>5</sup> There are currently two alternative methods of chemotherapy administration: the sandwich method, where chemotherapy is given before and after surgery, and the full-dose method, where chemotherapy is given in its entirety one dose before surgery. The full-dose method and sandwich chemotherapy are prominent due to their potential to overcome drug resistance and improve therapeutic responses in cancer treatment. High-dose chemotherapy, including full weight-based dosing, aims to increase drug dosage to combat resistance.<sup>6,7</sup>

Both techniques have their advantages and disadvantages. The sandwich method has the potential to reduce the length of therapy and improve patients' quality of life. However, the recurrence rate in patients receiving the sandwich method is higher than that of those who received standard therapy. The full-dose method, on the other hand, allows the tumor resection process to be more straightforward. However, it delays surgery as the chemotherapy is supposed to be given in 6 cycles or more.<sup>6</sup> This review aims to investigate the evidence in the literature regarding the efficacy of neoadjuvant chemotherapy given using the sandwich method and the full-dose method on patients with breast cancer.

### Method

A literature review was conducted to identify evidence regarding the efficacy of the sandwich and full-dose methods in administering chemotherapy to improve patient outcomes. Systematic literature searches were done using PubMed, ScienceDirect, Scopus, and ProQuest electronic databases. The keywords and boolean operators that were used were the following: ("breast cancer") AND ("neoadjuvant" OR "neo-adjuvant" OR "neoadjuvant" OR "preoperative") AND ("chemotherapy" OR "chemotherapies") AND ("mortality" OR "overall

survival" OR "relapse-free survival" OR "clinical improvement" OR "pathologic complete response" OR "partial response" OR "disease-free survival") AND ("sandwich" OR "sequential chemotherapy" OR "full-dose"). No limits were imposed on the search.

The search results underwent further screening based on the inclusion and exclusion criteria. Duplicates were removed. Interventional studies that investigated neoadjuvant with the sandwich or full-dose method on breast cancer patients that reported overall survival disease-free survival, recurrence, and pathologic complete response (pCR) were included. The excluded studies were conducted on non-humans, had a descriptive design, and were published as a correspondence letter, editorial, commentary, case report, or case series.

## Results

The systematic search yielded 51 studies: 10 from PubMed, five from ScienceDirect, 16 from Scopus, and 20 from ProQuest. Upon removal of duplicates, 32 articles were included (Figure 1). The 32 articles were then further screened, excluding 30 studies after title, abstract, and full-text screening, resulting in two articles being included for qualitative synthesis. Three studies were excluded because two used a different sandwich method for adjuvant chemotherapy and radiotherapy. One study was excluded because the disease being treated was not breast cancer but colon rectal cancer.

The consideration for administering chemotherapy either in a sandwich or full-dose sequence aims to enhance the quality of life for breast cancer patients by reducing treatment duration and increasing survival rates. Studies indicate that the sandwich technique may lower pathological complete response rates than full-dose chemotherapy.

cancer subjects. Nowadays, the administration of chemotherapy remains controversial. A study conducted by Abbas et al.<sup>8</sup> found that chemotherapy administered using the sandwich method showed lower mortality rates, although it shows a lower efficacy. No difference was found in locoregional or distant recurrence-free survival. While the National Comprehensive Cancer Network suggests post-chemotherapy radiotherapy, evidence remains limited. Institutional protocol shifts reflected evolving radiation therapy practices, favoring chemotherapy completion prior to radiotherapy. Two-dimensional post-mastectomy and three-dimensional planning for breast conservation demonstrated dosimetric improvements and reduced skin toxicity. On the other hand, a study showed that the full-dose technique showed a lower 5-year recurrence rate yet has a higher toxicity. The study observed 282 deaths, 228 from breast cancer. Five-year survival rates were 95.5% (stage I), 85.1% (stage II), and 62.1% (stage III). Patients from the SUS had higher stage diagnoses (42% stage III), associated with shorter survival in univariate analysis (HR = 2.22). Tumor size, grade, node count, and age impacted survival.<sup>9,10</sup>

The systematic review by Pathak, et al<sup>6</sup> did a subanalysis comparing neoadjuvant chemotherapy administered using a full-dose method and the sandwich method. In the same study, a subanalysis was conducted to compare adjuvant and neoadjuvant chemotherapy.<sup>7</sup> In this study, it was reported that there was an increase in breast-conserving therapy in patients given neoadjuvant chemotherapy (n = 9; RR [CI 95%] = 1.19 [1.3-1.37]). These patients also had an overall survival as well as a disease-free survival rate that shows the similar efficacy of adjuvant chemotherapy given in full-dose or using the sandwich method. Even so, the incidence of locoregional recurrence was significantly higher in the neoadjuvant chemotherapy group. (n = 15, HR [CI 95%] = 1.23 [1.06-1.43]). Based on the analysis, the results obtained by the sandwich group did not change significantly after a sensitivity analysis was done. It was worth noting also that the full-dose subgroup showed an overall survival that is significantly higher than the sandwich method subgroup in a sensitivity analysis (HR 1.37 (1.07-1.76) vs 1.01 (0.94-1.08); I<sup>2</sup> = 90.1 p <0.001). The results support the administration of chemotherapy in full doses.

The low recurrence of subjects receiving full-dose chemotherapy is reflected in the study undertaken by Krishnan et al.<sup>11</sup>, taking into consideration that the pCR of full-dose administration is significantly higher than that of the sandwich method. Even so, the relationship between pCR and recurrence is still put into question, as the reduction in mass size due to chemotherapy often causes the mass to be so small that it becomes hard to operate on.<sup>12</sup> The most influential factors on survival seem to be tumor size (T), invasion of lymph nodes (N), metastasis (M), presence of hormone receptors, and overexpression of HER2.40.

One of the strongest predictors of death in advanced-stage breast cancer is whether one has a breast cancer subtype of ER+HER2- or ER+HER2+, as well as invasion of lymph nodes >5 years after diagnosis. Breast cancer patients with an ER- subtype tend to have higher mortality <5 years since diagnosis compared to those with an ER+ subtype. The ER- subtype is associated with higher progressivity and earlier death (<5 years), consistently showing a higher mortality rate and Ki67 expression. The findings underscore the necessity of molecular testing and the integration of molecular subtype with pTN status to accurately predict recurrence and death risks. It recommends implementing multi-marker molecular-based risk scores and evaluating clinically available tumor markers' impact on patient survival. The study, one of the largest population-based analyses to date, highlights the importance of high-quality registry data for evaluating the clinical impact of new multigene signatures, which is crucial as many countries adopt multigene molecular analysis for treatment decisions. Despite

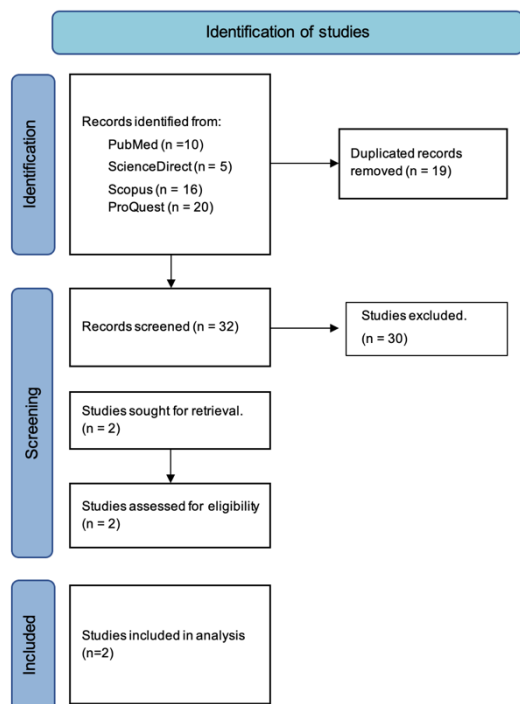


Figure 1. Literature search using PRISMA flow.

## Discussion

The consideration of administering chemotherapy in either a sandwich or full-dose method aims to improve the quality of life for patients by reducing treatment duration and increasing survival rates among breast

challenges like small sample sizes for specific tumor characteristics and lack of adjustment for socioeconomic status, the study provides valuable insights into the combined effect of various tumor characteristics on breast cancer death, aiding in better prognostic stratification and treatment decisions.<sup>13</sup>

In our literature review, only one study stated that the pCR of full-dose administration is higher than the sandwich technique, whereas two studies showed that there was no significant effect of full-dose administration and sandwich administration on overall survival and disease-free survival. The latter notion is supported by other studies stating that the full-dose method and the sandwich do not have a significant difference in survival rate outcome. We further corroborate these findings by additional studies indicating that both methods yield comparable survival outcomes. Consequently, the ideal chemotherapy dose for breast cancer treatment remains unclear and warrants further investigation. The divergent results highlight the complexity of determining the most effective chemotherapy regimen and underscore the need for additional research to elucidate the optimal dosing strategy for maximizing treatment efficacy and patient outcomes in breast cancer therapy.

The limitation of this review lies in the restricted pool of literature available for analysis, as only two articles have explored the research question. Despite thorough efforts to gather comprehensive data, the scope of available literature could have been broadened, potentially limiting our analysis's depth and breadth. This limitation could have implications for the generalizability and robustness of our findings, as our conclusions are based on the existing body of literature within the specified parameters. Future research endeavors may benefit from expanding the search criteria or exploring alternative sources to mitigate this limitation and provide a more comprehensive understanding of the subject matter. This limited dataset may affect the robustness and generalizability of the findings and suggests the need for further research to validate and expand upon the current conclusions.

## Conclusions

The administration of neoadjuvant using the full-dose method resulted in an HR of 1.37 (1.07-1.76) in a sensitivity analysis, whereas administration using the sandwich method is 1.01 (0.94-1.08);  $I^2 = 90.1$   $p = 0.000$ ). The administration of neoadjuvant in full-dose and sandwich methods has a similar disease-free survival (DFS) [ $I^2 = 26.3\%$ ,  $p = 0.237$ ; and HR = 0.99 (0.83-1.19)].

The pathological complete response that occurred in patients administered neoadjuvant in full dose is 17.7%, whereas in those administered neoadjuvant using the sandwich method is 8.6%.

## Disclosure

The authors declare no conflict of interest.

## Role of authors

Conceptualization IGN, Data curation SVP, Formal analysis SVP, Funding acquisition SVP, Investigation SVP, Methodology IGN, Project administration SVP, Resources SVP, Software IGN, Supervision IGN, Validation IGN, Visualization SVP, Writing original draft preparation SVP, Writing review and editing SVP.

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