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IMPACT OF TIMING OF SURGERY AFTER NEOADJUVANT CHEMOTHERAPY ON OPERATIVE OUTCOMES IN BREAST CANCER PATIENTS

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Abstract

Background: *Neoadjuvant chemotherapy (NAC) is widely employed in the management of breast cancer to reduce tumor burden, improve surgical outcomes, and allow for breast-conserving procedures. However, the optimal interval between the completion of NAC and definitive surgery—referred to as time to surgery (TTS)—remains a subject of ongoing debate. Concerns primarily revolve around whether early or delayed surgery post-NAC influences the rates of postoperative wound complications and operative mortality.* ***Objective:*** *To evaluate the impact of timing of surgery after NAC on postoperative wound infections and operative mortality in patients undergoing surgery for breast cancer.* ***Methods:*** *This randomized controlled trial was conducted at the Department of General Surgery, Nishtar Medical University/Hospital, Multan, over a period of six months from May 2024 to October 2024. A total of 60 female patients aged 30–65 years, diagnosed with grade I or II breast cancer and having completed a standardized NAC regimen, were enrolled. Patients were randomly allocated into two groups: Group A (Early Surgery): Underwent definitive surgery within 3 to 6 weeks of completing NAC. Group B (Delayed Surgery): Underwent surgery more than 6 weeks after completing NAC. Postoperative outcomes, including wound infections and operative mortality, were assessed and recorded during a 30-day postoperative follow-up period. The occurrence of wound infection was diagnosed clinically based on signs of erythema, warmth, purulent discharge, and delayed wound healing. Operative mortality was defined as death occurring within 30 days of surgery. Comparative analysis between the groups was performed using the chi-square test, with a p-value ≤ 0.05 considered statistically significant.* ***Results:*** *A total of 60 patients were enrolled, with 30 in the Early Surgery group and 30 in the Delayed Surgery group. There were no significant differences in baseline characteristics such as age, BMI, and blood loss between the groups. Postoperative outcomes showed similar wound infection rates (30.0% vs. 20.0%, p=0.37). However, operative mortality was significantly higher in the Delayed Surgery group (16.7%) compared to the Early Surgery group (0%), with a p-value of 0.02, suggesting that early surgery may reduce the risk of mortality.*

Conclusion: *Early surgery within 3–6 weeks after neoadjuvant chemotherapy (NAC) in breast cancer patients significantly reduces operative mortality compared to delayed surgery. Timely tumor resection before disease progression improves survival outcomes, despite no significant difference in wound infection rates. This supports the benefit of early surgery for better overall patient outcomes.*

INTRODUCTION

Neoadjuvant chemotherapy (NAC) is an integral component of the multidisciplinary management of breast cancer, particularly for patients with triple-negative breast cancer (TNBC), human epidermal growth factor receptor 2 (HER2)-positive tumors, clinically node-positive disease, and locally advanced breast cancer.[1–2] Despite its widespread application, the optimal time interval between completion of NAC and definitive surgery remains an area of ongoing investigation.

Considerable attention has been given to the timing of surgery following neoadjuvant treatment in other malignancies, such as esophageal, gastric, rectal, and ovarian cancers, where timing has been shown to influence oncologic and perioperative outcomes.[3–4] However, in breast cancer, the evidence remains limited and inconclusive regarding the ideal timing for surgery post-NAC. Emerging literature suggests that delays in surgery following NAC may adversely affect disease-free and overall survival outcomes.[5–6] Notably, Sutton et al. reported a higher incidence of wound infections in patients undergoing early surgery (29.9%) compared to those who had delayed surgery (21.4%) after NAC.[7] In contrast, Pedamallu et al. observed a higher operative mortality rate in patients undergoing delayed surgery (18.9%) compared to no mortality in the early surgery cohort.[8] These contradictory findings underscore the need for further research to establish evidence-based guidelines.

The objective of the present study is to evaluate the impact of the timing of surgery following NAC on postoperative outcomes in patients with breast cancer. This research is particularly relevant given the current lack of specific recommendations by the European Society for Medical Oncology regarding the optimal surgical interval following NAC. The findings of this study aim to bridge the existing knowledge gap, clarify the implications of surgical timing, and contribute to the formulation of evidence-based clinical guidelines for the management of breast cancer.

Objective

To determine the effect of timing of surgery on postoperative outcomes following NAC in breast cancer patients.

Methodology:

This randomized controlled trial was conducted at the Department of General Surgery, Nishtar Medical University/Hospital, Multan, over a duration of six months from May 2024 to October 2024 following the approval of the research synopsis. A total of 60 female patients diagnosed with grade I or II breast cancer who had completed a standardized course of neoadjuvant chemotherapy were enrolled in the study. The sampling technique employed was non-probability consecutive sampling. Patients were randomly assigned into two equal groups of 30 each. The sample size was calculated using the WHO sample size calculator, based on prior estimates indicating an operative mortality of 18.9% in the delayed surgery group compared to 0% in the early surgery group, with a power of 80% and a significance level of 5%.

Inclusion Criteria:

Female patients aged between 20 and 70 years were eligible for inclusion in the study. All participants were histologically diagnosed with Grade I or II breast cancer and had completed a full course of neoadjuvant chemotherapy (NAC). Additionally, only those patients who were scheduled to undergo definitive surgical management, either breast-conserving surgery or mastectomy, were included.

Exclusion Criteria:

Patients with a history of recurrent breast cancer were excluded. Additionally, those diagnosed with distant metastasis at the time of evaluation were excluded

Data Collection Procedure:
Following ethical approval, a total of 60 eligible female breast cancer patients who had completed neoadjuvant chemotherapy (NAC) were enrolled in the study after obtaining informed consent. Participants were randomly assigned into two groups using a draw method: Group A (Early Surgery), where surgery was performed within 3–6 weeks (≤28 days) post-NAC, and Group B (Delayed Surgery), where surgery took place after 6 weeks (≥29 days) post-NAC. All patients underwent either breast-conserving surgery or mastectomy under general anesthesia. Postoperatively, patients were monitored weekly for one month for any signs of wound infection, based on predefined clinical criteria, and operative mortality, defined as death occurring within 30 days due to surgical complications. Data were meticulously recorded using a structured proforma.

Data Analysis:
Data were analyzed using SPSS version 25. Continuous variables, including age, BMI, and blood loss, were summarized as mean ± standard deviation. Categorical variables, such as postoperative infections and mortality, were presented as frequencies and percentages. The chi-square test was used to compare infection and mortality rates between the two groups. Stratification was performed to control for potential confounders, including age and BMI. A p-value of ≤0.05 was considered statistically significant.

Results
A total of 60 patients were enrolled, with 30 in the Early Surgery group and 30 in the Delayed Surgery group. There were no significant differences in baseline characteristics such as age, BMI, and blood loss between the two groups. However, postoperative results showed that wound infection rates were similar (30.0% vs. 20.0%, p=0.37). Significantly, operative mortality was higher in the Delayed Surgery group (16.7%) compared to the Early Surgery group (0%) with a p-value of 0.02, indicating that early surgery may reduce the risk of mortality.

Table 1: Baseline Characteristics of Patients

Variable	Early Surgery (n=30)	Delayed Surgery (n=30)	p-value
Age (years)	49.2 ± 8.3	50.1 ± 7.9	0.61
BMI (kg/m²)	26.4 ± 3.1	27.1 ± 3.3	0.43
Blood loss (ml)	220 ± 40	230 ± 45	0.38

The baseline characteristics of the patients in the study are summarized in Table 1. The mean age of patients in the early surgery group was 49.2 ± 8.3 years, while the delayed surgery group had a mean age of 50.1 ± 7.9 years, with no significant difference between the two groups (p=0.61). Regarding body mass index (BMI), the early surgery group had a mean BMI of 26.4 ± 3.1 kg/m², while the delayed surgery group had a mean BMI of 27.1 ± 3.3 kg/m², with the difference not reaching statistical significance (p=0.43). Blood loss during surgery was similar between the two groups, with the early surgery group experiencing a mean blood loss of 220 ± 40 ml and the delayed surgery group having a mean blood loss of 230 ± 45 ml, with no significant difference between the groups (p=0.38).

Table 2: Postoperative Outcomes

Outcome	Early Surgery (n=30)	Delayed Surgery (n=30)	p-value
Wound infection	9 (30.0%)	6 (20.0%)	0.37
Operative mortality	0 (0.0%)	5 (16.7%)	0.02*

*Statistically significant

The postoperative outcomes of the two groups are presented in Table 2. Wound infection occurred in 9 patients (30.0%) in the early surgery group and 6 patients (20.0%) in the delayed surgery group, with no significant difference between the two groups (p=0.37). However, operative mortality was

significantly higher in the delayed surgery group, with 5 patients (16.7%) experiencing mortality compared to none in the early surgery group (p=0.02). This difference was statistically significant, indicating a potential impact of surgery timing on operative mortality.

Discussion

This study underscores the significant impact of surgical timing on operative mortality in breast cancer patients following neoadjuvant chemotherapy (NAC). Our findings indicate that early surgery is associated with a reduced risk of operative mortality compared to delayed surgery, a result that aligns with previous research. Pedamallu et al. (2020) reported similar findings, observing zero mortality in the early surgery group and a significantly higher mortality of 18.9% in the delayed surgery group. These results suggest that the timing of surgery after NAC could potentially influence patient survival, particularly in terms of operative outcomes (Pedamallu et al., 2020)[8].

The difference in mortality rates between the early and delayed surgery groups may be attributed to several factors, including progressive disease or the potential for a compromised immune response over time. Delayed surgery allows for more time for disease progression, which may increase the risk of complications during surgery[9]. In contrast, early surgery may offer the advantage of treating the tumor before the immune system has weakened or the cancer has had an opportunity to spread. This could explain why we observed zero operative mortality in the early surgery group. The delayed group, on the other hand, may experience worsened outcomes as a result of tumor regrowth or metastasis, which could complicate the surgical procedure and post-operative recovery[10].

The infection rate in our study, while not statistically significant, showed a trend towards a higher incidence in the early surgery group, with 30.0% of patients affected compared to 20.0% in the delayed surgery group. This observation is consistent with the findings of Sutton et al. (2019), who also noted higher infection rates in the early surgery cohort in their study. The biological rationale may be attributed to chemotherapy-induced immunosuppression and impaired wound healing potential persisting in the immediate post-chemotherapy period[9]. However, the infection rate difference did not reach statistical significance in our study (p=0.37), which suggests that the timing of surgery may not have a strong influence on the risk of infection, at least not in this cohort. Other factors, such as the type of surgical intervention, postoperative care, and patient comorbidities, may also play a role in determining the likelihood of infection, and further studies are needed to clarify these relationships[11].

Although our study observed a trend toward higher infection rates in the early surgery group, the most striking finding was the significantly higher operative mortality in the delayed surgery group. This suggests that early surgery may provide a mortality benefit, particularly in breast cancer patients who have undergone NAC. This finding is critical, as it emphasizes the importance of timely intervention in potentially improving survival outcomes for these patients[12].

Several limitations must be considered when interpreting our findings. The small sample size (n=30 per group) may have limited the statistical power to detect differences in infection rates and other postoperative outcomes[13]. Additionally, the relatively short follow-up period of the study means that long-term outcomes, such as recurrence rates and overall survival, were not assessed. Further research with larger sample sizes and extended follow-up periods would be necessary to determine whether early surgery confers long-term survival benefits. Furthermore, multicentric trials would help validate our findings across diverse patient populations and settings, providing more robust evidence to guide clinical decision-making.

Conclusion

Early surgery, performed within 3–6 weeks following neoadjuvant chemotherapy (NAC) in breast cancer patients, has been shown to significantly reduce operative mortality compared to delayed surgery. The early intervention allows for timely tumor resection before potential disease progression, which can worsen outcomes. While there was no statistically significant difference in wound infection rates between the early and delayed surgery groups, the lower mortality in the early surgery group highlights its potential benefit in improving patient survival. These findings emphasize the importance of a timely surgical approach post-NAC, suggesting that earlier

intervention may lead to better overall outcomes for breast cancer patients.

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