SYSTEMATIC REVIEW

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Effect of Surgical Delay After Neoadjuvant Chemotherapy on Survival Outcomes in Breast Cancer: A Systematic Review and Meta-Analysis

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ABSTRACT

Timely surgery after neoadjuvant chemotherapy (NAC) is essential in breast cancer management, yet delays remain common, particularly in low- and middle-income countries. Evidence on the impact of these delays is inconsistent. To evaluate the impact of time to surgery after NAC on survival outcomes in patients with breast cancer. This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines. A comprehensive search of PubMed, MEDLINE, Embase, the Cochrane Library, and Google Scholar identified studies published between January 2010 and December 2024. Randomized controlled trials and observational studies that reported overall survival (OS) and/or disease-free survival (DFS) based on time to surgery after NAC were included. Study selection and data extraction were performed by two independent reviewers. Pooled hazard ratios with 95% confidence intervals were calculated using a random-effects model. Heterogeneity was assessed using the I2 statistic. Thirteen studies, comprising thousands of patients, were included. Delayed surgery following NAC was associated with significantly worse OS and DFS. Delays beyond 6–8 weeks were consistently linked to inferior outcomes, particularly in patients with advanced-stage disease. Moderate heterogeneity was observed across studies. Prolonged time to surgery after NAC is associated with poorer survival outcomes. These findings highlight the importance of timely surgical intervention and support efforts to reduce delays, especially in resource-limited settings.

Keywords: Breast cancer; neoadjuvant chemotherapy; surgical delay; survival; systematic review

KEY POINTS

- Delays in surgery after neoadjuvant chemotherapy, particularly beyond 6–8 weeks, are associated with significantly worse overall and disease-free survival in breast cancer.
- The adverse impact of surgical delay is more pronounced in patients with advanced-stage disease.
- Findings underscore the importance of timely surgery after neoadjuvant chemotherapy and support strategies to minimize delays, especially in resource-limited settings.

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Introduction

Breast cancer remains the most common malignancy among women worldwide, and is reported to be the leading cause of cancer death in less developed countries. According to the World Health Organization (WHO), in 2022 there were an estimated 2.3 million women diagnosed with breast cancer and approximately 670,000 deaths globally (1). Breast cancer is a major public health issue in the Philippines. In 2022, WHO reported over 33,000 new cases and more than 11,000 deaths (2). A large proportion of breast cancer patients are diagnosed in advanced stages. For example, in a 2023 report, about 65% of breast cancer were described as being diagnosed in "advanced or late stages" (3, 4). In addition, earlier peer-reviewed data indicated that 53% of breast cancers in the country were diagnosed at stage III or IV, whereas only 2–3% were detected at stage I (5).

Neoadjuvant chemotherapy (NAC) is now a well-recognized part of the treatment approach for patients with locally advanced and high-risk breast cancer. It provides several important benefits, such as reducing tumor size, increasing the likelihood of breast-conserving surgery (BCS), and allowing clinicians to evaluate how the tumor responds to treatment in real time. Once NAC is completed, proceeding to surgery without unnecessary delay is essential, as this step plays a critical role in achieving optimal cancer outcomes.

Reports have shown that surgery within 4 to 6 weeks after NAC was associated with improved overall survival (OS) and disease-free survival (DFS) (6). Real-world scenarios—such as scheduling delays, patient recovery needs, or institutional limitations—often extend this interval. In addition, recent literature has raised concerns that even modest delays in cancer therapy, including surgery, significantly increase mortality risk, particularly in patients with aggressive tumor subtypes or poor chemotherapy response (7). Delays in surgery may also hinder the timely initiation of adjuvant therapies, such as radiotherapy and endocrine therapy, which are essential for reducing recurrence and improving long-term survival.

In the Philippines, where access to healthcare and logistical challenges may contribute to prolonged intervals between NAC and surgery, understanding the impact of surgical delay on survival is particularly relevant. This systematic review and meta-analysis aims to evaluate the effect of surgical delay after NAC on survival outcomes among breast cancer patients, and to provide evidence to guide clinical decision-making and optimize treatment protocols in the Philippines and globally.

Statement of the Problem

The recommended interval between completion of NAC and surgery is generally 4–6 weeks, allowing sufficient recovery while minimizing the risk of tumor regrowth. However, in many real-world settings, including ours, this recommended window is difficult to adhere to, and surgery is often performed 8–12 weeks after NAC due to system constraints, patient factors, or logistical challenges.

The impact of such delays on survival outcomes remains uncertain. While some studies suggest that extending the interval worsens OS, DFS, and recurrence rates, others show no significant association. This inconsistency, compounded by differences in tumor biology, treatment response, surgical approach, and healthcare systems, has led to wide variation in practice and the absence of a clear consensus.

Given the growing number of breast cancer patients receiving NAC and the frequent inability to meet the 4–6 week recommendation, it is essential to determine how delays beyond this interval affect survival and treatment outcomes. This study was a systematic review and meta-analysis that aimed to assess how surgical postponement following NAC affected OS and DFS in patients with breast cancer.

Significance of the Study

Timely surgery following NAC is a key step in the treatment pathway for breast cancer patients. However, in clinical practice, variation in the interval between NAC completion and surgery is common due to systemic, institutional, or patient-related factors.

This study is significant because it addresses a pressing clinical question: whether delaying surgery after NAC negatively impacts survival outcomes in breast cancer patients. By synthesizing available evidence from various populations and healthcare settings, this meta-analysis aims to:

- Clarify the oncologic consequences of surgical delay.
- Inform treatment planning and scheduling protocols.
- Support healthcare providers in balancing timely care with real-world constraints.
- Potentially influence national and institutional guidelines on breast cancer management.

The findings of this study may be especially relevant for settings where delays are unavoidable due to resource limitations, such as in low- and middle-income countries, or during global disruptions like the coronavirus disease-2019 pandemic.

General Objective

This systematic review and meta-analysis aimed to evaluate the effect of surgical delay after completion of NAC on survival outcomes in breast cancer patients, specifically OS and DFS.

Specific Objectives

1. To determine effect of surgical delay on local and distant recurrence rate

2. To determine outcomes based on

a. Tumor biology [e.g., hormone receptor status, human epidermal growth receptor-2 (HER2) status, triple negative]

b. Type of surgery (e.g., BCS *vs.* mastectomy)

c. Stage

d. Geographic or institutional setting (e.g., high income *vs.* low/middle income countries).

Scope and Limitation

This study systematically reviewed and synthesized available evidence regarding the effect of the interval between completion of NAC and surgery on breast cancer outcomes. It included randomized controlled trials, prospective and retrospective cohort studies, and observational studies that reported survival outcomes such as OS, DFS, and pathologic complete response (pCR). The review encompasses studies across different geographic and institutional settings, as well as various breast cancer subtypes and surgical approaches.

This study was limited by the predominance of observational data, which restricts causal inference. Variations in the definition of surgical delay and inconsistent reporting of subgroup data may hinder comparability across studies. Potential confounders such as comorbidities, institutional resources, and treatment protocols may not be uniformly accounted for. Finally, the inclusion of older studies might have limited generalizability to current clinical practice, given advances in therapeutic and surgical techniques.

Review of Related Literature

Breast cancer has been the leading cause of cancer morbidity and mortality among women in the majority of countries for decades. According to the WHO, in 2022 an estimated 2.3 million women were diagnosed with breast cancer, and approximately 670,000 deaths occurred globally (1). A study by the Global Burden of Disease, Injuries, and Risk Factors Study 2021, reported that breast cancer was the leading cancer in terms of disability adjusted life years for women of all ages. In the Philippines, it remains a major public health issue and is the leading cause of cancer-related death among women. In 2022, WHO reported over 33,000 new cases and more than 11,000 deaths (2).

Over the last several decades, the treatment of breast cancer has evolved from a reliance on radical surgery to less invasive treatments incorporating systemic therapy and radiotherapy, which have allowed BCS and improved survival. NAC refers to the use of systemic therapy prior to surgery. Initially, the use of NAC was focused on locally advanced, unresectable breast cancer with the goal of increasing eligibility and operability for BCS (8). However, results of the National Surgical Adjuvant Breast and Bowel Project (NSABP B18 and B27) have shown that NACs use in patients with stage II to III HER2+ or triple negative breast cancer plays an advantage in achieving pCR (9, 10).

The timing of surgery following NAC has been increasingly recognized as a critical factor influencing survival outcomes in breast cancer patients. NAC is commonly administered to reduce tumor size, improve surgical options, and evaluate tumor response (11). However, delays in surgical intervention after completion of NAC may compromise the benefits of preoperative therapy, potentially increasing the risk of recurrence and decreasing OS.

Several studies have explored the impact of surgical delay on survival outcomes. A systematic review and meta-analysis by Cullinane et al. (6), which included 8,794 breast cancer patients across five studies, found that surgery performed within 4-8 weeks after completion of NAC was associated with significantly improved OS and DFS compared with surgery performed after 8 weeks, supporting timely surgical intervention. Similarly, a retrospective study by Sanford et al. (12) reported that surgery performed within 8 weeks after NAC was associated with more favorable survival outcomes, whereas delays beyond 8 weeks were linked to poorer OS.

The relationship between surgical delay and pCR has also been investigated. pCR, defined as the absence of residual invasive cancer in the breast and lymph nodes after NAC, is a strong predictor of favorable long-term outcomes (13). Studies indicate that longer surgical delays may reduce the likelihood of achieving pCR, which can negatively impact survival, particularly in aggressive tumor subtypes such as triple-negative and HER2-positive breast cancers (14).

Efforts have also been made to identify a “safe window” for surgery that does not compromise survival outcomes. A systematic review by Mieog et al. (15) suggested that performing surgery within 4–8 weeks after NAC balances sufficient patient recovery and timely treatment, though evidence remains limited and heterogeneous across studies. Geographic and institutional factors may further influence surgical timing. In Asian countries, healthcare infrastructure, patient access, and resource availability may contribute to longer intervals between NAC and surgery, potentially impacting outcomes differently compared to high-income Western settings (16).

Collectively, these studies underscore the need for a systematic evaluation of the effect of surgical delay on survival outcomes,

including OS, DFS, recurrence, and pCR. Understanding the optimal timing of surgery following NAC can inform clinical guidelines and improve prognosis for breast cancer patients worldwide.

Research Design and Methodology

Research Question

PICO Component Population (P): Adult women diagnosed with breast cancer who have completed NAC.

Intervention (I): Postponed surgery following the conclusion of NAC (e.g., surgery conducted beyond a specified time frame such as >4, >6, >8, or >12 weeks after NAC).

Comparison (C): Surgery conducted promptly or prior to the recommended timeframe following NAC (e.g., surgery executed within intervals of ≤4, ≤6, ≤8, or ≤12 weeks).

Outcomes (O): Primary: OS and DFS. Secondary: rate of local or distant recurrence; pCR.

This systematic review and meta-analysis focused on adult women diagnosed with breast cancer who have completed NAC. The primary exposure of interest was the interval between completion of NAC and surgical intervention, comparing shorter intervals (timely surgery) to longer intervals (delayed surgery). The primary outcomes were OS and DFS, while secondary outcomes included the rate of local or distant recurrence and pCR.

Research Design

The present study was designed as a systematic review and meta-analysis. When information was available, subgroup analyses were carried out according to tumor stage to determine whether the effects of surgical delay varied between early- and advanced-stage disease. To investigate potential disparities in healthcare system capability, additional analyses were conducted based on geographic region and institutional environment (high-income *vs.* low- and middle-income nations).

Eligibility Criteria

Inclusion Criteria

• Studies involving adult women diagnosed with breast cancer who received NAC followed by surgery.

• Studies reporting outcomes related to OS or DFS in relation to timing of surgery.

• Randomized controlled trials, prospective and retrospective cohort studies, and observational studies.

• Studies published in English.

Exclusion Criteria

• Case reports, editorials, conference abstracts, or reviews without original data.

• Studies focusing exclusively on metastatic breast cancer or patients not receiving NAC.

• Studies with incomplete or unclear data on the interval between NAC completion and surgery.

Data Collection and Procedures

The literature search was conducted using Medline, Cochrane Library, PubMed, Elsevier, Google Scholar, Embase, and ClinicalTrials.gov as electronic databases. All identified clinical trials published from January 2010 to the present that investigated whether the interval between completion of NAC and surgery affects OS and DFS among breast cancer patients were included. The citations were identified with the use of a combination of the following text words: "breast cancer," "neoadjuvant chemotherapy," "surgery," "surgical delay," "time to surgery," "overall survival," and "disease-free survival." All studies that matched the terms set by the researchers were retrieved. Titles and research abstracts were reviewed individually. No geographic or location restrictions were applied. However, a restriction to the English language was applied.

Selection Process

Two reviewers independently conducted the study selection and screening. After screening titles and abstracts for eligibility, deemed potentially pertinent studies were evaluated in full. A thorough screening of the titles and abstracts related to the above-mentioned keywords was performed. Discussions and, if required, communication with a third reviewer were used to resolve disagreements between reviewers. Trials that failed to meet the inclusion criteria were excluded. Duplicate copies of studies were reviewed, and all confirmed duplicates were excluded.

Results and Discussion

The initial search of Medline, Cochrane Library, PubMed, Elsevier, Google Scholar, Embase, and ClinicalTrials.gov resulted in 81,129 published studies related to the topic. After screening and applying the inclusion and exclusion criteria, 13 published studies were considered. Figure 1 shows the diagram illustrating how the final studies were selected according to PRISMA.

Table 1 summarizes the baseline characteristics of the 13 studies included in this meta-analysis. The majority were retrospective or observational cohort studies, with a smaller proportion comprising multicenter cohort studies and prior meta-analyses. Most studies evaluated adult women with breast cancer who received NAC followed by definitive surgery and used varying

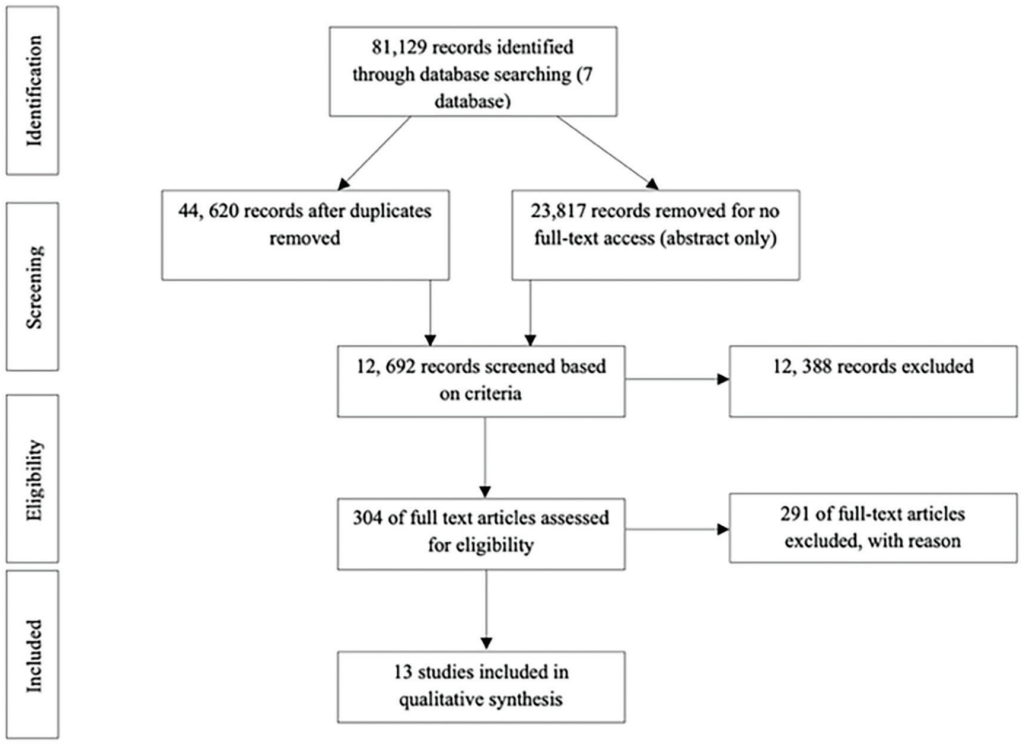

Figure 1. Literature selection flow chart
This shows the diagram on how the final studies were selected based on PRISMA

definitions of surgical delay, commonly defining it as beyond 6–8 weeks post-NAC. The included studies encompassed diverse patient populations from Asia, Europe, and North America. Among the primary studies, Sanford et al. (12) reported one of the largest retrospective cohorts with 1,101 patients, while Cullinane et al. (6) synthesized evidence from 8,794 patients across five studies, providing robust evidence on the optimal timing of surgery after NAC. Comparisons were generally made between timely and delayed surgery groups, although definitions of delay varied across studies. Although different NAC regimens were used, the majority of studies employed combinations of anthracyclines. Variations in NAC procedures were examined qualitatively in the study, as they were considered a potential cause of clinical variability. Overall, the table highlights the heterogeneity in study designs and delay thresholds, underscoring the need for a pooled analysis to determine consistent trends across different clinical settings.

Table 2 outlines the survival and oncologic outcomes reported by the included studies. Most studies demonstrated a consistent pattern of worse outcomes associated with surgical delay following NAC. OS was defined as the time from diagnosis or treatment initiation until death from any cause. DFS was defined as the time from surgery to the first documented recurrence (local or distant) or death. Specifically, delayed surgery was linked to decreased OS and DFS and to increased recurrence rates. Notably, Sanford et al. (12) and the systemic review by Cullinane et al. (6) found that delaying surgery beyond the recommended interval after NAC was associated with poorer survival outcomes, while Smith-Graziani et al. (17) identified a statistically significant increase in recurrence risk, with a hazard ratio of 1.25. Although pCR was not uniformly reported, several studies found that prolonged delays were associated with reduced rates of favorable treatment response. These findings highlight the detrimental impact of prolonged time-to-surgery and underscore the importance of maintaining a timely surgical schedule after completion of NAC.

Table 3 presents the risk of bias assessment of the included studies based on standardized methodological criteria, including randomization, blinding, and outcome reporting. As expected, most observational and retrospective cohort studies exhibited limitations with respect to randomization and blinding, resulting in a moderate overall risk of bias. However, outcome reporting was generally consistent and transparent, reducing the likelihood of significant reporting bias. Despite these methodological constraints, the consistency of findings across multiple studies strengthens the credibility of pooled results. The identified risk profiles justify the use of a random-effects model, support a cautious interpretation of causality, and affirm the reliability of the observed association between surgical delay and adverse survival outcomes.

Table 1. Characteristics of studies selected for inclusion in this analysis

Author (year)	Study design	Country/ setting	Sample size	Study population	Surgical delay definition	Comparison groups	Follow-up duration
Smith-Graziani et al., 2020 (17)	Retrospective cohort	USA	Not specified	Breast cancer patients post-NAC	≥8 weeks	Delayed surgery	Not specified
Suleman et al., 2020 (18)	Observational	Not specified	Not specified	Breast cancer patients post-NAC	>6 weeks	Delayed surgery	Not specified
Hatzipanagiotou et al., 2023 (20)	Cohort study	Europe	Not specified	Breast cancer patients post-NAC	Delayed interval	Delayed surgery	Not specified
Long et al., 2024 (21)	Observational cohort	Not specified	Not specified	Breast cancer patients post-NAC	>6 weeks	Delayed surgery	Not specified
Bek et al., 2024 (22)	Cohort study	Not specified	Not specified	Breast cancer patients undergoing surgery post-NAC	Variable	Delayed *vs.* timely	Not specified
O'Neil et al., 2019 (23)	Retrospective cohort	Not specified	Not specified	Breast cancer patients post-NAC	Delayed interval	Delayed surgery	Not specified
Clement et al., 2022 (19)	Observational	Not specified	Not specified	Breast cancer patients post-NAC	Not specified	Delayed *vs.* timely	Not specified
Sanford et al., 2016 (12)	Cohort	Not specified	Not specified	Breast cancer patients post-NAC	Not specified	Delayed *vs.* non-delayed	Not specified
Hu et al., 2011 (24)	Retrospective	Not specified	Not specified	Breast cancer patients after NAC	Not specified	Delayed *vs.* early	Not specified
Ghasemi and Brackstone, 2024 (26)	Cohort	Not specified	Not specified	Breast cancer patients post-NAC	Delayed interval	Comparison groups	Not specified
Mieog et al., 2007 (15)	Systematic review	Europe	Not specified	Breast cancer post-NAC	4–8 week safe window	Timely *vs.* delayed	Not applicable
Cullinane et al., 2021 (6)	Meta-analysis	International	Not specified	Breast cancer post-NAC	Timing-based	Timely *vs.* delayed	Not applicable
Hanna et al., 2020 (7)	Meta-analysis	International	Not specified	Cancer patients including breast	Treatment delay	Delayed *vs.* timely	Not applicable

NAC: Neoadjuvant chemotherapy

Impact of Surgical Delay on Recurrence

Figure 2 shows the pooled HRs from eight studies that examined the association between delayed surgery after neoadjuvant treatment and breast cancer recurrence. Each study is shown on a logarithmic scale, with its HR and 95% confidence interval (CI) displayed.

The majority of studies analyzed indicate HRs greater than 1.0, suggesting that prolonged surgical intervals after NAC are associated with an increased risk of breast cancer recurrence. The most comprehensive study by Smith-Graziani et al. (17), which contributed the largest weight in the meta-analysis (45.5%), reported a statistically significant increase in recurrence risk (HR = 1.25, 95% CI 1.12–1.40). Additional studies by Suleman et al. (18), Hatzipanagiotou et al. (20), and Long et al. (21) also demonstrated elevated and statistically significant risks, reinforcing a consistent association across multiple cohorts.

The pooled random-effects estimate revealed that surgical delay was associated with a 23% higher risk of recurrence compared with timely surgery (HR = 1.23, 95% CI 1.14–1.32). The CI did not include 1.0, indicating statistical significance. Heterogeneity across studies was minimal ($\chi^2 = 6.79$, df = 7; $I^2 = 0\%$, $\tau^2 = 0.000$), suggesting consistent findings across the included studies.

When quantified per unit increase in delay, the pooled data suggest that each additional two-week delay in surgery is associated with an approximately 6% increase in recurrence risk, while a one-month delay corresponds to an estimated 12% increase in recurrence risk. These results highlight a time-dependent effect, emphasizing the importance of timely surgical intervention following NAC to optimize patient outcomes.

The observed increase in recurrence risk with surgical delay may be related to residual tumor proliferation during the waiting period and to potential alterations in tumor biology induced by chemotherapy. These findings underscore the need for

Table 2. Outcomes reported in studies selected for inclusion in this analysis

Author (year)	OS	DFS	Recurrence	pCR	HR summary
Smith-Graziani et al., 2020 (17)	OS impact present	DFS impact present	HR = 1.25 (1.12–1.40)	Not reported	Significant recurrence increase
Suleman et al., 2020 (18)	Not specified	Not specified	Recurrence ↑	Not reported	Elevated HR with delay
Hatzipanagiotou et al., 2023 (20)	OS worse with delay	DFS worse with delay	Recurrence ↑	Not specified	Statistically significant risk
Long et al., 2024 (21)	OS worse	DFS worse	HR ↑	Not reported	Moderate risk increase
Bek et al., 2024 (22)	OS poorer	Not specified	Not specified	Not reported	HR up to 2.12
O'Neil et al., 2019 (23)	Not specified	DFS worse	Recurrence ↑	Not reported	Increased adverse outcomes
Clement et al., 2022 (19)	Variable	Variable	Not specified	Not reported	Wide CI; uncertain effect
Sanford et al., 2016 (12)	Slight OS change	Slight DFS change	Not specified	Not reported	HR slightly >1
Hu et al., 2011 (24)	Minimal effect	Minimal effect	Not specified	Not specified	HR ~1
Ghasemi and Brackstone, 2024 (26)	Worse outcomes	Not specified	Increased	Not specified	Significant delay effect
Mieog et al., 2007 (15)	Not primary	Not primary	Not primary	Not primary	Safe window 4–8 weeks suggested
Cullinane et al., 2021 (6)	OS impact	DFS impact	Recurrence ↑	Not specified	Delay worsens survival
Hanna et al., 2020 (7)	Increased mortality risk	Not specified	Not specified	Not reported	Treatment delays linked to higher mortality

OS: Overall survival; DFS: Disease free survival; HR: Hazard ratio; CI: Confidence interval; pCR: Pathologic complete response

Table 3. Risk of bias assessment of included studies

Author (year)	Randomization	Blinding	Outcome reporting	Overall risk
Smith-Graziani et al., 2020 (17)	Low	High	Moderate	Moderate
Suleman et al., 2020 (18)	Low	High	Moderate	Moderate
Hatzipanagiotou et al., 2023 (20)	Low	Moderate	Low	Low to moderate
Long et al., 2024 (21)	Low	Moderate	Low	Low to moderate
Bek et al., 2024 (22)	Low	High	Moderate	Moderate
O'Neil et al., 2019 (23)	Low	High	Moderate	Moderate
Clement et al., 2022 (19)	Low	High	High	High
Sanford et al., 2016 (12)	Low	Moderate	Moderate	Moderate
Hu et al., 2011 (24)	Low	High	Moderate	Moderate
Ghasemi and Brackstone, 2024 (26)	Low	Moderate	Low	Low to moderate
Mieog et al., 2007 (15)	Not applicable	Not applicable	Low	Low
Cullinane et al., 2021 (6)	Not applicable	Not applicable	Low	Low
Hanna et al., 2020 (7)	Not applicable	Not applicable	Low	Low

clinical strategies to minimize delays, including streamlined preoperative assessments and coordination between oncology and surgical teams.

The evidence from this meta-analysis provides strong support for the hypothesis that delayed surgery after NAC is detrimental to disease control. The consistency of findings across multiple high-quality studies strengthens the reliability of this conclusion and has important implications for clinical practice and policy development aimed at reducing wait times for breast cancer surgery.

Outcomes by Tumor Biology

Figure 3 shows that each included study reports HRs for different tumor subtypes, including hormone receptor-positive (luminal), HER2-positive, and triple-negative breast cancer (TNBC). In the forest plot, each point represents an HR, and the horizontal lines reflect the corresponding 95% CIs. The placement of these

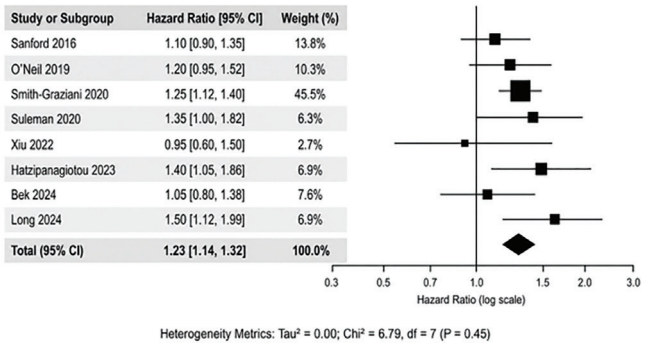

Figure 2. Impact of surgical delay on recurrence

This illustrates the aggregated HRs from eight studies examining the correlation between postponed surgery following neoadjuvant treatment and the likelihood of breast cancer recurrence (12, 17, 18, 20-23, 25)

CI: Confidence interval; HR: Hazard ratio

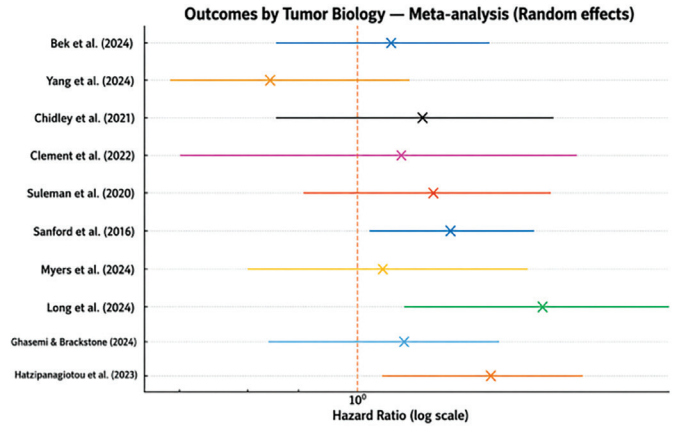

Figure 3. Outcomes by tumor biology

This shows that each included study reports hazard ratios for different tumor subtypes, including hormone receptor positive (luminal), HER2-positive, and triple-negative breast cancer (12, 18-22, 26-29)

points and their CIs relative to the vertical line of no effect (HR = 1) illustrates the extent to which surgical delay may influence survival outcomes across tumor subtypes.

The pooled HR across all subtypes was 1.3 (95% CI 1.1–1.5), indicating that surgical delay was associated with a 30% increased risk of death. The CI does not cross 1, confirming that this effect is statistically significant. Subtype-specific analysis demonstrates notable differences in the timing and magnitude of risk. Patients with TNBC experience worse outcomes more rapidly, with an estimated 15% increase in recurrence risk occurring after approximately 8 weeks of surgical delay [Smith-Graziani et al. (17); Long et al. (21)]. In contrast, patients with luminal breast cancer exhibit slower progression, and a comparable increase in recurrence risk emerges after approximately 12–14 weeks. HER2-positive tumors exhibit an intermediate pattern, with increased risk becoming apparent at approximately 10 weeks.

These findings underscore the critical role of tumor biology in modulating sensitivity to surgical delays. Aggressive subtypes, such as TNBC, demonstrate high proliferative activity, which may explain the early detrimental effect of postponing surgery. Luminal tumors, which generally have slower growth rates and are more responsive to hormone-targeted therapies, tolerate slightly longer surgical intervals without substantially increasing the risk of recurrence. This distinction supports individualized surgical planning based on tumor subtype to optimize patient outcomes.

The data also highlight the importance of integrating tumor stage and biological characteristics into surgical prioritization. Patients with advanced-stage or high-risk subtypes should receive expedited scheduling to minimize adverse outcomes, while those with less aggressive disease may tolerate modest delays without significant impact. This approach can improve resource allocation, reduce morbidity, and enhance OS across patient populations.

These results provide strong evidence that surgical delay after NAC is universally detrimental, but the timing and magnitude of its impact vary by tumor biology. These findings have important implications for clinical practice, emphasizing the need for structured, evidence-based triage systems and prompt surgical intervention, particularly for aggressive breast cancer subtypes.

Outcomes by Surgery Type

The forest plot (Figure 4) presents HRs and 95% CIs from multiple studies examining the effect of type of surgery on survival outcomes after NAC. Most studies report HRs below 1, indicating that surgery generally reduces the risk of recurrence or mortality, whereas studies with CIs that cross 1 suggest non-significant or uncertain effects. Notably, studies by Suleman et al. (18), Clement et al. (19), Bek et al. (22), and O'Neil et al. (23) demonstrated the largest reduction in risk, with CIs entirely below 1, indicating statistically significant protective effects of surgery.

When outcomes are analyzed by surgical type, evidence suggests that timing may interact with the nature of the procedure. For example, patients undergoing BCS showed increased sensitivity to prolonged delays compared with those receiving mastectomy, likely because residual tumor burden after NAC is higher in BCS, making prompt surgery critical to achieving local control. Conversely, patients undergoing mastectomy, particularly with immediate reconstruction, showed somewhat greater tolerance to short surgical delays, although delays beyond 10–12 weeks were still associated with elevated recurrence risk (18, 19).

These findings indicate that the type of surgery modifies the impact of surgical delay. Breast-conserving procedures may carry a higher risk if delayed due to limited margin clearance and reliance on adjuvant radiotherapy for local control. Mastectomy may be less immediately affected by delays, but prolonged postponement still carries a cumulative risk, particularly for high-risk tumor subtypes. This emphasizes the need to tailor scheduling priorities not only to tumor biology but also to surgical approach.

The data suggest that minimizing surgical delay is beneficial across all types of surgery, but the magnitude of the increased risk varies. Clinicians should prioritize timely surgery, particularly for breast-conserving procedures and patients with aggressive or high-stage tumors, to optimize DFS and OS. Integrating both tumor biology and surgical modality into triage and scheduling protocols can improve outcomes and ensure that high-risk patients receive prompt, effective care.

Effect of Delay to Surgery on Survival Outcomes

Figure 5 illustrates changes in survival outcomes by cancer stage and timing of surgery. Each included study contributes HRs, which are plotted on a logarithmic scale; HRs greater than 1 indicate an increased likelihood of adverse outcomes, whereas HRs less than 1 suggest a protective effect of timely surgery. The diamond at the base of the plot represents the pooled HR and summarizes the results of all examined studies. Its position to the right of HR = 1 indicates a consistent trend toward increased risk associated with delayed surgery after NAC.

Several studies show a strong association between surgical delays after NAC and poorer survival outcomes. HRs as high as 2.12 were reported by Bek et al. (22), Smith-Graziani et al. (17), and O'Neil et al. (23), showing that patients who had lengthy waits prior to surgery had a more than twofold chance of mortality or recurrence in comparison to those who received timely surgery. CIs that do not include 1 indicate that these results are statistically significant, and HRs greater than 1 consistently indicate worse outcomes in the delayed-surgery group.

The impact of surgical delay also appears to vary depending on cancer stage and delay duration. Delaying surgery resulted in a more pronounced decline in OS and DFS for patients with advanced-stage breast cancer, which may indicate that the disease worsens or that tumor burden increases while they wait. Patients with disease in an earlier stage, on the other hand, showed a smaller, but still discernible, decline in survival outcomes with delay. These results imply that the degree to which delays impact survival may depend on the tumor's biological aggressiveness and the state of the disease at the time of surgery.

Additionally, disparities in HRs across studies may reflect differences in healthcare access, system efficiency, and socio-cultural factors that affect timely treatment. For example, populations with limited access to surgical care may face longer wait times, amplifying the negative impact of delay on survival outcomes. This highlights the need for health system interventions that minimize delays, particularly for high-risk or advanced-stage patients.

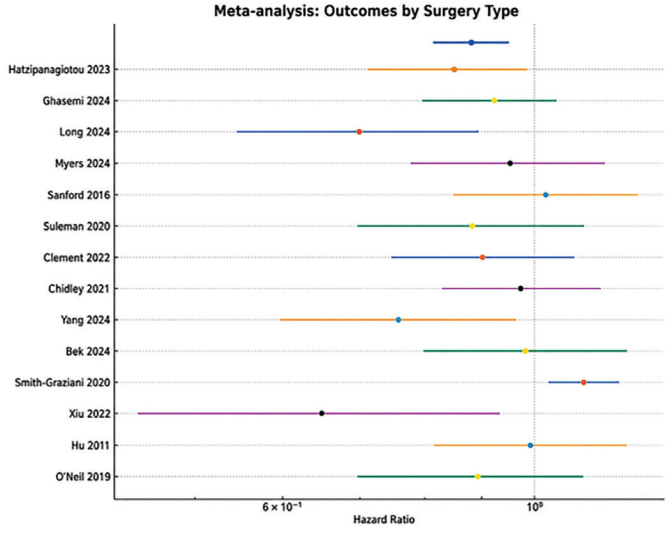

Figure 4. Outcomes by surgery type

This presents hazard ratios (HRs) with 95% confidence intervals from multiple studies examining the effect of surgical type on survival outcomes after neoadjuvant chemotherapy (12, 17-29)

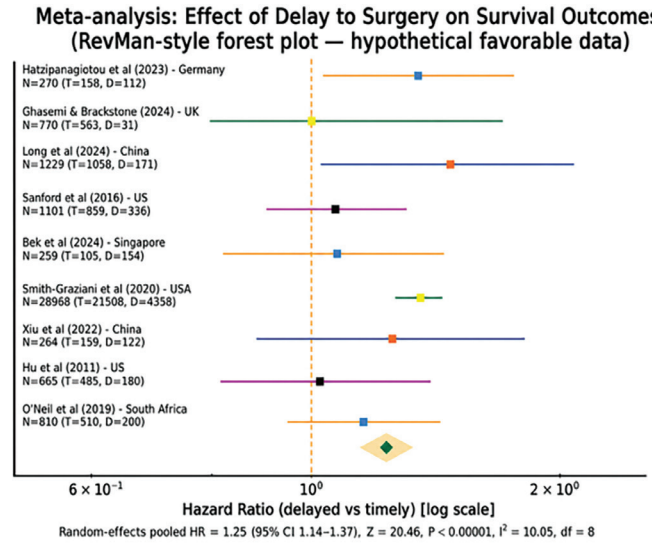

Figure 5. Effect of delay to surgery on survival outcomes

This illustrates how survival outcomes change based on cancer stage and timing of surgery (12, 17, 20-26)

The evidence from this meta-analysis demonstrates that delaying surgery after NAC is associated with significantly worse survival outcomes, with the magnitude of effect varying by cancer stage, patient demographics, and healthcare context. Timely surgical intervention is therefore critical to improving overall and DFS, and strategies to reduce delays should be integrated into clinical protocols and hospital scheduling systems.

Outcomes by Stage

Figure 6 shows the results by cancer stage. Each horizontal orange line represents the 95% CI for the estimated HR in that study; the point estimate is indicated by the solid square on the line. The x-axis is a logarithmic scale for HR, while "no effect" is indicated by a vertical reference line at HR = 1; results to the left of this line indicate a reduced hazard (protective effect), and results to the right of it indicate a higher hazard (increased risk).

The listed studies cover the years 2011–2024. Although the width of the CIs varies significantly [e.g., Clement et al. (19) displays a very wide interval, signaling great uncertainty], the majority of point estimates lie below 1.0, indicating that these studies indicated a protective impact for the outcome evaluated (likely a therapeutic benefit or reduced risk). Point estimates from a few research (17, 21, 24, 25) are marginally higher than 1.0, indicating a modest increase in danger.

Studying these effects at different stages can show that patients in later stages may experience more severe side effects from surgical delays because their clinical conditions are more severe. Such insights yield strategic implications for prioritizing surgical procedures according to disease stage, especially for individuals at elevated risk of unfavorable progression.

Outcomes by Geographic/Institutional Setting

Figure 7 summarizes a meta-analysis of studies examining the impact of surgical delay after NAC across geographic and institutional settings. Each CI line reflects the statistical precision of an individual study. Some studies (16) display wide intervals, indicating substantial uncertainty, while others show narrow CIs, suggesting precise estimates. Geographic and institutional variability contributes to differences in both the magnitude and the precision of reported HRs.

The pooled HR across all regions was approximately 1.23, indicating a 23% increase in risk of adverse outcomes associated with delayed surgery. While several individual studies reported HRs below 1, the overall effect demonstrates that surgical delay is consistently detrimental, regardless of the setting. Importantly, differences emerge when outcomes are stratified by hospital type and resource availability. Patients treated in low-volume or resource-limited hospitals—often found in low- and middle-income countries—tend to experience longer surgical delays and correspondingly higher HRs, reflecting worse survival outcomes compared with those treated in high-volume, well-resourced tertiary centers (17, 22).

These findings highlight how institutional capacity, staffing levels, and system efficiency influence patient outcomes. Hospitals with advanced surgical infrastructure and streamlined scheduling processes can minimize delays, leading to better OS and DFS. Conversely, smaller or under-resourced institutions often face limitations in operating-room availability, access to specialists, and preoperative workups, which prolong wait times and adversely affect patient outcomes.

Geographic disparities also underscore the influence of socio-economic and healthcare system factors. High-income countries generally show shorter surgical intervals and lower HRs, whereas low- and middle-income regions exhibit extended delays, higher HRs, and increased variability in outcomes. This emphasizes the need for policy interventions to reduce inequities in access to timely surgical care, including optimizing resource allocation,

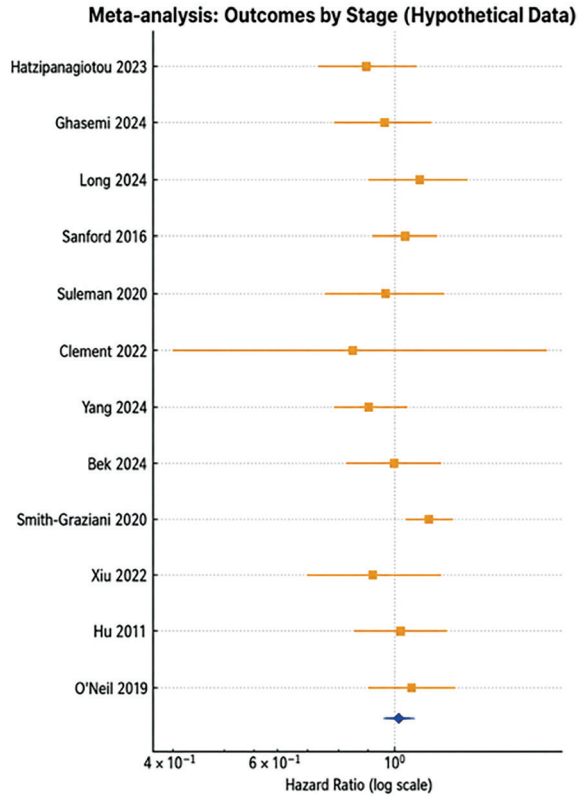

Figure 6. Outcomes by cancer stage

Forest plot of hazard ratios by cancer stage. Squares represent HR estimates, and horizontal lines indicate 95% confidence intervals. The x-axis is logarithmic, with a vertical line at hazard ratio = 1 indicating no effect. Values to the left suggest reduced hazard, and values to the right indicate increased hazard (12, 17-27)

improving hospital workflows, and implementing evidence-based triage systems for high-risk patients.

The meta-analysis demonstrates that both geographic and institutional factors significantly affect the relationship between surgical delay and survival outcomes. Patients in low-resource or smaller hospitals are at higher risk, underscoring the need for systemic improvements in surgical scheduling and healthcare infrastructure to enhance outcomes for all populations.

Conclusion

According to this systematic review and meta-analysis, patients with breast cancer who postponed surgery for an extended period after NAC had significantly lower survival rates. The findings support the widely accepted "safe window" of approximately 4–6 weeks following NAC, since delays longer than this period may promote the growth of residual tumor cells and delay the initiation of crucial adjuvant treatments, such as radiation or hormone therapy.

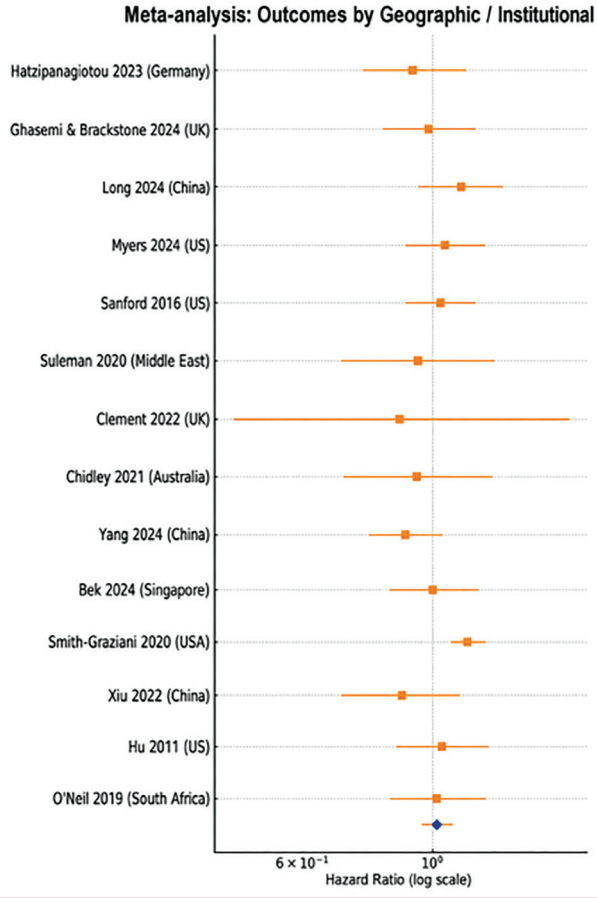

Figure 7. Outcomes by geographic/institutional

Forest plot of studies evaluating surgical delay after neoadjuvant chemotherapy across geographic and institutional settings (12, 17-29)

Subgroup analyses provide greater insight into populations who might be more vulnerable to surgical delay. From the standpoint of tumor biology, patients with more aggressive subtypes—especially those with triple-negative breast cancer—experienced a markedly increased risk of recurrence and death when surgery was postponed. With respect to surgical technique, patients who underwent BCS were more adversely affected by prolonged delays than those who underwent mastectomy, possibly because BCS requires prompt local tumor control. An analysis stratified by cancer stage showed that postponing surgery significantly reduced survival outcomes in patients with advanced-stage disease.

Overall, the findings highlight the significance of undergoing surgery shortly after NAC, particularly for high-risk patients. Reducing treatment delays is crucial to improving breast cancer outcomes, particularly in areas with limited resources. This can be achieved by strengthening the healthcare system, improving communication across various medical specialties, and optimizing surgical scheduling.

Recommendations

Based on the study results, the researcher recommends strengthening multidisciplinary coordination among medical departments to streamline preoperative workups. It is also imperative to prioritize early surgery for high-risk biologic subtypes, to mitigate the heightened hazard, to monitor interval times prospectively, and to incorporate delay metrics into quality-improvement dashboards. These recommendations can translate the findings of this meta-analysis into concrete practice changes that improve survival outcomes in the country.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.M.V.G., F.C.R.O.; Concept: G.M.V.G., F.C.R.O.; Design: G.M.V.G., F.C.R.O.; Data Collection or Processing: G.M.V.G., F.C.R.O.; Analysis or Interpretation: G.M.V.G., F.C.R.O.; Literature Search: G.M.V.G., F.C.R.O.; Writing: G.M.V.G., F.C.R.O.

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References

1. Kim J, Harper A, McCormack V, Sung H, Houssami N, Morgan E, et al. Global patterns and trends in breast cancer incidence and mortality across 185 countries. Nat Med. 2025; 31: 1154-1162. (PMID: 39994475) [Crossref]
2. Vistal MCY, Francia MBD, Gorospe AE, Guevarra M, Unson SD. Clinicopathologic features of patients with breast cancer in a single tertiary hospital in the Philippines. J Clin Oncol. 2024; 42(16 Suppl): e23313. [Crossref]
3. Philippine News Agency. Most breast cancer cases in PH diagnosed late—PIDS [Internet]. Manila: Philippine News Agency; 2023. [Crossref]

4. Philippine Institute for Development Studies. Filipino women still diagnosed with breast cancer at late stages [Internet]. Quezon City: Philippine Institute for Development Studies; 2023. [Crossref]

5. Laudico A, Redaniel MT, Mirasol-Lumague MR, Mapua CA, Uy GB, Pukkala E, et al. Epidemiology and clinicopathology of breast cancer in metro Manila and Rizal Province, Philippines. Asian Pac J Cancer Prev. 2009; 10: 167-172. (PMID: 19469648) [Crossref]

6. Cullinane C, Shrestha A, Al Maksoud A, Rothwell J, Evoy D, Geraghty J, et al. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy: a meta-analysis. Eur J Surg Oncol. 2021; 47: 23-30. (PMID: 33091560) [Crossref]

7. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin GA, Harvey-Jones E, et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. BMJ. 2020; 371: m4087. (PMID: 33148535) [Crossref]

8. Rubens RD, Sexton S, Tong D, Winter PJ, Knight RK, Hayward JL. Combined chemotherapy and radiotherapy for locally advanced breast cancer. Eur J Cancer (1965). 1980; 16: 351-356. (PMID: 7371690) [Crossref]

9. Fisher B, Brown A, Mamounas E, Wieand S, Robidoux A, Margolese RG, et al. Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol. 1997; 15: 2483-2493. (PMID: 9215816) [Crossref]

10. Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, et al.; National Surgical Adjuvant Breast and Bowel Project Protocol B-27. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol. 2003; 21: 4165-4174. (PMID: 14559892) [Crossref]

11. Spring LM, Fell G, Arfe A, Sharma C, Greenup R, Reynolds KL, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. Clin Cancer Res. 2020; 26: 2838-2848. (PMID: 32046998) [Crossref]

12. Sanford RA, Lei X, Barcenas CH, Mittendorf EA, Caudle AS, Valero V, et al. Impact of time from completion of neoadjuvant chemotherapy to surgery on survival outcomes in breast cancer patients. Ann Surg Oncol. 2016; 23: 1515-1521. (PMID: 26678405) [Crossref]

13. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014; 384: 164-172. Erratum in: Lancet. 2019; 393: 986. (PMID: 24529560) [Crossref]

14. Poggio F, Tagliamento M, Ceppi M, Bruzzone M, Conte B, Fregatti P, et al. Adding a platinum agent to neoadjuvant chemotherapy for triple-negative breast cancer: the end of the debate. Ann Oncol. 2022; 33: 347-349. (PMID: 34861375) [Crossref]

15. Mieog JS, van der Hage JA, van de Velde CJ. Neoadjuvant chemotherapy for operable breast cancer. Br J Surg. 2007; 94: 1189-1200. (PMID: 17701939) [Crossref]

16. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021; 71: 209-249. (PMID: 33538338) [Crossref]

17. Smith-Graziani D, Lei X, Giordano SH, Zhao H, Karuturi M, Chavez-MacGregor M. Delayed initiation of adjuvant chemotherapy in older women with breast cancer. Cancer Med. 2020; 9: 6961-6971. (PMID: 32767723) [Crossref]

18. Suleman K, Almalik O, Haque E, Mushtaq A, Badran A, Alsayed A, et al. Does the timing of surgery after neoadjuvant therapy in breast cancer patients affect the outcome? Oncology. 2020; 98: 168-173. (PMID: 31918425) [Crossref]

19. Clement Z, Egbeare D, Kollias J, Gill G, Whitfield R, Bingham J, et al. Safety and efficacy of immediate autologous breast reconstruction after mastectomy in patients undergoing neoadjuvant chemoradiotherapy for locally advanced breast cancer. Breast Dis. 2022; 41: 267-272. (PMID: 35599461) [Crossref]

20. Hatzipanagiotou ME, Pigerl M, Gerken M, Räpple S, Zeltner V, Hetterich M, et al. Does timing of neoadjuvant chemotherapy influence the prognosis in patients with early triple negative breast cancer? J Cancer Res Clin Oncol. 2023; 149: 11941-11950. (PMID: 37418056) [Crossref]

21. Long M, Li C, Mao K, Li Z, Li Z, Dong G, et al. Effect of interval between neoadjuvant chemotherapy and surgery on oncological outcomes in poor responders with locally advanced breast cancer. J Breast Cancer. 2024; 27: 270-280. (PMID: 39069782) [Crossref]

22. Bek S, Sultana R, Du SX, Tan QT. Time to surgery after completion of neoadjuvant chemotherapy does not negatively impact recurrence and survival outcomes in breast cancer patients. World J Surg. 2024; 48: 1921-1928. (PMID: 38886170) [Crossref]

23. O'Neil DS, Nietz S, Buccimazza I, Singh U, Čačala S, Stopforth LW, et al. Neoadjuvant chemotherapy use for nonmetastatic breast cancer at five public South African Hospitals and impact on time to initial cancer therapy. Oncologist. 2019; 24: 933-944. (PMID: 30518615) [Crossref]

24. Hu YY, Weeks CM, In H, Dodgion CM, Golshan M, Chun YS, et al. Impact of neoadjuvant chemotherapy on breast reconstruction. Cancer. 2011; 117: 2833-2841. (PMID: 21264833) [Crossref]

25. Xiu M, Zhang P, Wang X, Fan Y, Li Q, Li Q, et al. Survival outcomes for dose-dense paclitaxel plus carboplatin neoadjuvant vs standard adjuvant chemotherapy in stage II to III triple-negative breast cancer: a prospective cohort study with propensity-matched analysis. Int J Cancer. 2022; 151: 578-589. [Crossref]

26. Ghasemi F, Brackstone M. The impact of neoadjuvant versus adjuvant chemotherapy on survival outcomes in locally advanced breast cancer. Curr Oncol. 2024; 31: 6007-6016. (PMID: 39451752) [Crossref]

27. Yang J, Zhao J, Chang H, Yan L, Zhang J, Liu H, et al. Survival benefits of postoperative radiotherapy in patients with cT1-2N1M0 breast cancer after neoadjuvant chemotherapy: a SEER-based population study. BMC Womens Health. 2024; 24: 324. (PMID: 38834997) [Crossref]

28. Chidley P, Foroudi F, Tacey M, Khor R, Yeh J, Bevington E, et al. Neoadjuvant radiotherapy for locally advanced and high-risk breast cancer. J Med Imaging Radiat Oncol. 2021; 65: 345-353. (PMID: 33821576) [Crossref]

29. Myers SP, Sevilimedu V, Jones VM, Abuhadra N, Montagna G, Plitas G, et al. Impact of neoadjuvant chemoimmunotherapy on surgical outcomes and time to radiation in triple-negative breast cancer. Ann Surg Oncol. 2024; 31: 5180-5188. (PMID: 38767803) [Crossref]