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The Effect of Definitive Surgery Timing on The Survival of Breast Cancer Patients : A Systematic Review

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ABSTRACT

Introduction: The COVID-19 pandemic necessitated surgical triage, raising urgent questions about how delays in definitive surgery affect breast cancer survival. Existing guidelines lack consensus on acceptable delay thresholds.

Methods: A systematic screening of the literature was performed to identify studies examining the effect of definitive surgery timing on survival in breast cancer patients. Key timing variables included the interval from neoadjuvant chemotherapy (NAC) completion to surgery, diagnosis to surgery, and surgery to adjuvant chemotherapy. Primary outcomes were overall survival (OS) and disease-free survival (DFS).

Results: Pooled meta-analyses demonstrate that delaying surgery beyond 8 weeks after NAC completion significantly worsens OS (OR 0.47, 95% CI 0.34–0.65 for surgery $\leq$ 8 weeks) (3,12). A dose-response effect shows a 4-6% increased hazard of death per month of delay (1,23). Pathological response is the critical moderator: delays beyond 9 weeks harm survival exclusively in patients with residual disease (RCB II/III; EFS HR 2.04, $p=0.001$) but not in those with pathological complete response (7). For upfront surgery, a 12-week delay is associated with an OS HR of 1.46 (95% CI 1.28–1.65) (2). For adjuvant chemotherapy, a 4-week delay increases mortality risk by 6% (HR 1.06, 95% CI 1.02–1.10) (9). HER2-positive patients tolerate delays due to high pCR rates (8), whereas poor NAC responders and TNBC patients require surgery within 4 weeks (6,20).

Discussion: The apparent contradiction between retrospective harm signals and RCT equivalence is resolved by the residual disease framework. Neoadjuvant and adjuvant chemotherapy produce equivalent survival in controlled trials, but indefinite surgical deferral in real-world practice carries oncological cost, particularly in chemo-refractory subtypes.

Conclusion: Surgery should not be delayed beyond 8 weeks after NAC, with a shorter 4-week window preferred for patients with residual disease, TNBC, or poor response. Adjuvant chemotherapy should commence within 8 weeks post-surgery.

Keywords: Breast cancer, surgical delay, neoadjuvant chemotherapy, survival, pathological complete response, timing of surgery.

INTRODUCTION

Breast cancer remains the most frequently diagnosed malignancy and a leading cause of cancer-related death among women worldwide. Definitive surgery, whether as upfront resection or following neoadjuvant chemotherapy (NAC), is a cornerstone of curative-intent treatment. However, the COVID-19 pandemic created an unprecedented scenario where healthcare systems were forced to delay non-urgent cancer surgeries, exposing a critical gap in evidence-based guidelines regarding how long such delays can safely extend before compromising patient survival (1,2).

Background and Problem Statement: The fundamental clinical question is whether a biological "window of opportunity" exists for definitive breast cancer surgery. While it is

intuitively understood that excessive delays allow tumour progression, the specific time thresholds that separate acceptable from harmful delays remain controversial. Current guidelines vary widely, with some recommending surgery within 4 weeks of NAC completion, others within 8 weeks, and some suggesting that timing is inconsequential (3,4). This uncertainty has led to inconsistent clinical practices and substantial anxiety during healthcare crises requiring surgical triage.

Research Gap: Prior studies have produced conflicting results. Several large meta-analyses demonstrate that delaying surgery beyond 8 weeks after NAC significantly worsens overall survival (OS) and disease-free survival (DFS) (3,5,6). Yet, well-conducted retrospective cohort studies report no significant association between surgical timing and survival outcomes (8,14,15). Furthermore, landmark randomized controlled trials (RCTs) comparing neoadjuvant versus adjuvant chemotherapy show equivalent survival, indirectly suggesting that surgical delay inherent to NAC may not be harmful (41–44). This contradiction has not been systematically resolved, and no unified framework explains why some patients are harmed by delays while others are not.

Novelty: This review introduces a novel explanatory framework based on pathological response as the critical moderator of delay-related harm. We synthesize recent evidence demonstrating that the effect of surgical timing is entirely dependent on residual cancer burden (RCB) after NAC (7). Additionally, we integrate causal machine learning analyses that quantify real-world "operational survival deficits" of NAC in specific molecular subtypes (53), moving beyond traditional intention-to-treat RCT comparisons.

Objectives: This study aims to: (1) systematically evaluate the effect of definitive surgery timing on breast cancer survival across different intervals (NAC-to-surgery, diagnosis-to-surgery, surgery-to-adjuvant therapy); (2) identify significant positive associations between shorter intervals and improved survival; (3) determine optimal timing thresholds stratified by pathological response and molecular subtype; and (4) provide clinically actionable recommendations.

Hypothesis: We hypothesize that shorter intervals from NAC completion to definitive surgery are significantly associated with improved OS and DFS, but that this effect is strongly moderated by pathological complete response (pCR) status. Specifically, patients with residual disease after NAC will demonstrate significant survival detriment with delays exceeding 4-8 weeks, whereas patients achieving pCR will show no such association.

Benefits: Resolving this uncertainty will directly inform clinical practice guidelines, enable evidence-based surgical triage during healthcare resource constraints, and allow individualized timing recommendations based on tumour biology rather than one-size-fits-all thresholds.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the effect of definitive surgery timing on the survival of breast cancer patients.

Screening

We screened in sources based on their abstracts that met these criteria:

- **Population:** Does the study include patients diagnosed with breast cancer of any stage?
- **Intervention:** Does the study examine definitive (curative intent) surgical treatment for breast cancer?
- **Timing Analysis:** Does the study compare different timing of definitive surgery or report time-to-surgery intervals with clearly defined time intervals?
- **Survival Outcomes:** Does the study report survival outcomes (overall survival, disease-free survival, cancer-specific survival, or recurrence-free survival)?
- **Study Design:** Is the study a randomized controlled trial, etc?
- **Treatment Intent:** Does the study focus on curative rather than solely palliative or non-curative surgical procedures?
- **Evidence Quality:** Is the study something other than a case report, case series, editorial, or conference abstract?
- **Study Focus:** Does the study focus on treatment rather than exclusively on breast cancer screening, prevention, or diagnostic procedures?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

PICO Element	Keyword 1	Keyword 2	Keyword 3
Population	breast cancer patients	early-stage breast cancer	post-neoadjuvant breast cancer
Intervention	definitive surgery timing	time to surgery (TTS)	neoadjuvant chemotherapy completion to surgery
Comparison	delayed vs early surgery	>8 weeks vs ≤8 weeks	neoadjuvant vs adjuvant sequencing
Outcome	overall survival (OS)	disease-free survival (DFS)	recurrence-free survival (RFS)

The Boolean MeSH keywords inputted on databases for this research are: (*"breast cancer patients" OR "early-stage breast cancer" OR "post-neoadjuvant breast cancer"*) AND (*"definitive surgery timing" OR "time to surgery (TTS)" OR "neoadjuvant chemotherapy completion to surgery"*) AND (*"delayed vs early surgery" OR ">8 weeks vs ≤8 weeks" OR "neoadjuvant vs adjuvant sequencing"*) AND (*"overall survival (OS)" OR "disease-free survival (DFS)" OR "recurrence-free survival (RFS)"*)

Data extraction

- **Timing Variable:**

Extract the specific timing variable studied in relation to breast cancer surgery and survival, including:

- Exact definition of the timing interval (e.g., diagnosis to surgery, surgery to adjuvant therapy, neoadjuvant therapy completion to surgery, treatment decision to treatment start)
- Start and end points of the timing measurement

- Whether timing was measured as continuous variable, categorical groups, or binary cut-off
- Specific time categories or cut-off points used (e.g., <4 weeks, 4-8 weeks, >8 weeks)
- **Survival Outcomes:**

Extract all survival outcomes assessed in relation to surgery timing for breast cancer patients, including:

 - Type of survival endpoint (overall survival, disease-free survival, progression-free survival, recurrence-free survival, breast cancer-specific survival)
 - Definition and measurement method for each outcome
 - Follow-up duration and median follow-up time
 - Number of events observed for each outcome
- **Timing Effects:**

Extract the effect of surgery timing on breast cancer survival outcomes, including:

 - Direction of effect (benefit or harm from delay)
 - Effect size with confidence intervals (hazard ratios, odds ratios, survival rates, or other measures)
 - Statistical significance (p-values)
 - Dose-response relationship if assessed (effect per unit time increase)
 - Whether effects varied by outcome type (OS vs DFS, etc.)
- **Patient Population:**

Extract characteristics of the breast cancer patient population that may moderate timing effects on survival, including:

 - Cancer stage distribution (I, II, III, specific staging criteria used)
 - Tumor characteristics (size, grade, receptor status, histology)
 - Treatment context (neoadjuvant, adjuvant, primary surgery)
 - Patient demographics (age, comorbidities)
 - Sample size and patient selection criteria
- **Optimal Timing:**

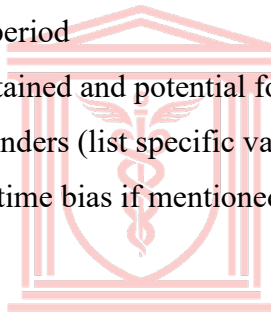
Extract any conclusions or recommendations about optimal timing of breast cancer surgery for survival outcomes, including:

- Recommended time windows or cut-offs identified
- Maximum acceptable delays mentioned
- Clinical practice implications stated by authors
- Comparison of different timing strategies if multiple were evaluated

• **Study Design:**

Extract study methodology relevant to assessing timing effects on breast cancer survival, including:

- Study design (RCT, etc)
- Data source and time period
- How timing was ascertained and potential for measurement bias
- Adjustment for confounders (list specific variables adjusted for)
- Handling of immortal time bias if mentioned



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Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("breast cancer patients" OR "early-stage breast cancer" OR "post-neoadjuvant breast cancer") AND ("definitive surgery timing" OR "time to surgery (TTS)" OR "neoadjuvant chemotherapy completion to surgery") AND ("delayed vs early surgery" OR ">8 weeks vs ≤8 weeks" OR "neoadjuvant vs adjuvant sequencing") AND ("overall survival (OS)" OR "disease-free survival (DFS)" OR "recurrence-free survival (RFS)")</i>	5
Semantic Scholar	<i>("breast cancer patients" OR "early-stage breast cancer" OR "post-neoadjuvant breast cancer") AND ("definitive surgery timing" OR "time to surgery (TTS)" OR "neoadjuvant chemotherapy completion to surgery") AND ("delayed vs early surgery" OR ">8 weeks vs ≤8 weeks" OR "neoadjuvant vs adjuvant sequencing") AND ("overall survival (OS)" OR "disease-free survival (DFS)" OR "recurrence-free survival (RFS)")</i>	251
Sciencedirect	<i>("breast cancer patients" AND "definitive surgery timing" OR "time to surgery (TTS)" OR "neoadjuvant chemotherapy completion to surgery" AND "overall survival (OS)" OR "disease-free survival (DFS)" OR "recurrence-free survival (RFS)")</i>	1
Google Scholar	<i>("breast cancer patients" AND "definitive surgery timing" OR "time to surgery (TTS)" OR "neoadjuvant chemotherapy completion to surgery" AND "overall survival (OS)" OR "disease-free survival (DFS)" OR "recurrence-free survival (RFS)")</i>	47
Cochrane	<i>("breast cancer patients" AND "definitive surgery timing" OR "time to surgery (TTS)" OR "neoadjuvant chemotherapy completion to surgery" AND "overall survival (OS)" OR "disease-free survival (DFS)" OR "recurrence-free survival (RFS)")</i>	24

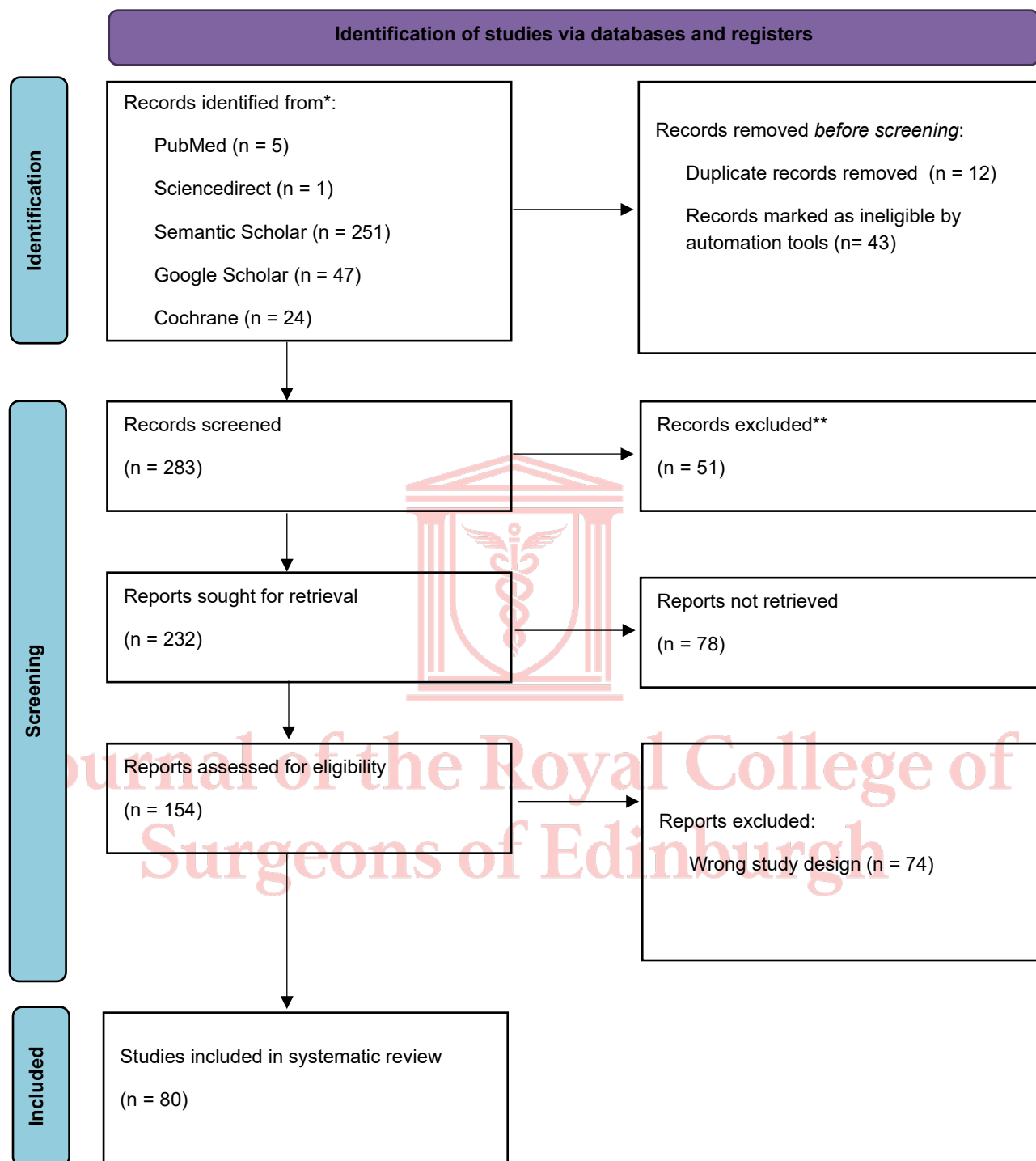


Figure 1. Article search flowchart

Risk of Bias

Table 1. ROB 2 Assessment of Randomized Controlled Trials

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
P. Rastogi et al., 2008	Low	Low	Low	Low	Low	Low
N. Wolmark et al., 2001	Low	Low	Low	Low	Low	Low
B. Fisher et al., 2023	Low	Low	Low	Low	Low	Low
J. van der Hage et al., 2001	Low	Low	Low	Low	Low	Low
Bernard et al. EBCTCG, 2018	Low	Low	Low	Low	Low	Low
S. Taucher et al., 2008	Low	Low	Low	Low	Some concerns	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
J. Gazet et al., 2001	Some concerns	Low	Low	Low	Low	Some concerns
S. Cleator et al., 2005	Some concerns	Low	Low	Low	Low	Some concerns
S. Deo et al., 2003	Some concerns	Low	Low	Low	Some concerns	Some concerns
Z. Yuan et al., 2009	Some concerns	Low	Low	Low	Some concerns	Some concerns
H. Joensuu, 2003	Low	Low	Low	Low	Low	Low
R. Hills et al., 2025	Low	Low	Low	Low	Low	Low
T. Shien et al., 2025	Low	Low	Low	Low	Low	Low

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk of bias
R. Badwe et al., 2009	Low	Low	Unclear	Low	Low	Some concerns
C. Matuschek et al., 2025	Low	Low	Low	Low	Low	Low

Table 2. ROBINS-I Assessment of Non-Randomized Included Studies

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
C. Cullinane et al., 2021	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Dandan Wang et al., 2025	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Su & Zheng, 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Van Hassel et al., 2025	Low	Low	Low	Low	Low	Low	Low	Low
S. Guan et al., 2025	Low	Low	Low	Low	Low	Low	Low	Low

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
T. Hanna et al., 2020	Low	Low	Low	Low	Low	Low	Low	Low
B. Johnson et al., 2020	Moderate	Low	Low	Low	Low	Low	Low	Moderate
J. Biagi et al., 2011	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Nakamura et al., 2018	Low	Low	Low	Low	Low	Low	Low	Low
Al-Masri et al., 2021	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Suleman et al., 2020	Moderate	Low	Low	Low	Unclear	Low	Low	Moderate
Piacentini et al., 2015	Serious	Moderate	Low	Low	Moderate	Low	Moderate	Serious
Da Luz et al., 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Long et al., 2024	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Schinbek et al., 2024	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Birsine et al., 2026	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Pedamallu et al., 2021	Serious	Serious	Low	Moderate	Serious	Moderate	Moderate	Serious
Chen et al., 2019	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Bennett et al., 2019	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sheinfeld Gorin et al., 2006	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Gioia et al., 2024	Serious	Moderate	Low	Moderate	Moderate	Moderate	Low	Serious
Brito et al., 2009	Serious	Moderate	Low	Moderate	Moderate	Moderate	Low	Serious
Dai et al., 2025	Low	Low	Low	Low	Low	Low	Low	Low
Lee Jong-Uk et al., 2016	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Pumpalova et al., 2022	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Petrovsky et al., 2022	Serious	Moderate	Low	Moderate	Moderate	Moderate	Low	Serious
Soran et al., 2021	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Roberts et al., 2021	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Farolfi et al., 2014	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate
Pekkolay & Işıkdoğan, 2019	Serious	Moderate	Low	Moderate	Serious	Moderate	Low	Serious

Study	Bias due to confounding	Bias in selection of participants	Bias in classification of interventions	Bias due to deviation from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias
Li et al., 2018	Moderate	Moderate	Low	Moderate	Moderate	Low	Low	Moderate
Oehler et al., 2025	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sainsbury et al., 2005	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate

RESULTS

Characteristics of Included Studies

Study	Primary Timing Variable	Primary Population	Sample Size
C. Cullinane et al., 2021 [12]	NAC completion to surgery (<8 weeks vs >8 weeks; <4 weeks vs 4–8 weeks) [12]	Breast cancer patients receiving NACT [12]	8,794 [12]

Study	Primary Timing Variable	Primary Population	Sample Size
C. Cullinane et al., 2021a [3]	NAC completion to surgery (<4, 4–8, >8 weeks) [3]	Breast cancer patients receiving NACT [3]	8,794 [3]
Dandan Wang et al., 2025 [6]	NAC completion to surgery (<4, 4–8, >8 weeks) [6]	Breast cancer patients post-NAC [6]	10,834 [6]
Yong-zhong Su & Xiaogang Zheng, 2020 [4]	NAC completion to surgery (continuous/unspecified) [4]	Breast cancer patients post-NAC [4]	Not reported [4]
Yong-zhong Su & Xiaogang Zheng, 2020a [5]	NAC completion to surgery (<4 vs >4 weeks) [5]	Stages I–III post-NAC [5]	4,521 [5]
Yongcheng Su et al., 2021 [13]	Diagnosis to curative surgery [13]	Breast cancer patients [13]	Not reported [13]
Schin Bek et al., 2024 [14]	NAC completion to surgery (<28 days, 29–56 days, ≥57 days) [14]	Post-NAC patients, 2006–2017 [14]	259 [14]
Ş. Bek et al., 2022 [15]	NAC completion to surgery (<28, 29–56, ≥57 days) [15]	Post-NAC patients, 2006–2017 [15]	250 [15]

Study	Primary Timing Variable	Primary Population	Sample Size
M. Al-Masri et al., 2021 [16]	NAC completion to surgery (<4, 4–8, >8 weeks) [16]	Stages I–III, KHCC, 2006–2014 [16]	468 [16]
K. Suleman et al., 2020 [17]	NAC completion to surgery (<4, 4–7, ≥8 weeks) [17]	Stages II–III, 2004–2014 [17]	611 [17]
Dr. B. Srinivas Pedamallu et al., 2021 [18]	NAC completion to surgery (≤28 vs ≥29 days) [18]	Breast cancer patients, 2012–2016 [18]	61 [18]
F. Piacentini et al., 2015 [19]	NAC completion to surgery (≤21 days, 22–35 days, ≥36 days) [19]	Stages I–IIIc, 1991–2013 [19]	295 [19]
Man Long et al., 2024 [20]	NAC completion to surgery (≤4 vs >4 weeks) [20]	Locally advanced breast cancer, poor NAC responders, 2013–2018 [20]	1,229 [20]

Study	Primary Timing Variable	Primary Population	Sample Size
MD Julie Van Hassel et al., 2025 [7]	NAC completion to surgery (1–4, 5, 6–8, 9+ weeks) [7]	High-risk breast cancer, I-SPY 2 [7]	1,877 [7]
V. Lai et al., 2019 [21]	NAC to surgery (<4, 4–8, >8 weeks) [21]	Post-NAC patients, BC Cancer Agency [21]	347 [21]
S. Loibl et al., 2017 [22]	Biopsy to NAC start (TBC); NAC completion to surgery (TCS); both ≤ 4 vs >4 weeks [22]	Early BC, 6 German neoadjuvant trials [22]	9,127 [22]
Felipe Andrés Cordero da Luz et al., 2022 [23]	NAC completion to surgery (TNS, continuous) and diagnosis to surgery (TTS, continuous) [23]	Non-metastatic stages I–III [23]	721 (multivariable analysis) [23]
Zeliha Birsine et al., 2026 [8]	NAC completion to surgery (<4, 4–8, >8 weeks) [8]	HER2-positive, 2010–2025 [8]	176 [8]
T. Hanna et al., 2020 [1]	Diagnosis to surgery or treatment-to-treatment (continuous, per 4-week increase) [1]	Multiple cancers including breast [1]	1,272,681 (all cancers) [1]

Study	Primary Timing Variable	Primary Population	Sample Size
J. Biagi et al., 2011 [9]	Surgery to adjuvant chemotherapy (TTAC, per 4-week increase) [9]	Breast cancer, adjuvant chemotherapy [9]	15,327 (OS studies) [9]
B. Johnson et al., 2020 [2]	Diagnosis to surgery (12-week delay) [2]	Breast, lung, colon cancers [2]	2,533,355 (all cancers) [2]
Wei Gao et al., 2022 [24]	Multiple intervals (diagnosis to surgery, NAC completion to surgery, surgery to adjuvant therapy) [24]	All stages [24]	Variable [24]
R. Nakamura et al., 2018 [25]	Diagnosis to surgery (≤ 1 month vs > 1 month) [25]	Invasive BC excluding neoadjuvant patients, 2007–2017 [25]	1,513 [25]
Lee Jong-Uk et al., 2016 [26]	Diagnosis to surgery (≤ 30 vs > 30 days) [26]	Stages I–III, primary surgery, 2008 [26]	1,074 [26]

Study	Primary Timing Variable	Primary Population	Sample Size
Qichen Dai et al., 2025 [27]	Biopsy to surgery (>14 days for FNA/excision; >30 days for CNB) [27]	Early breast cancer, biopsy-to-surgery interval [27]	6,720 (FNA+CNB +excision) [27]
Christoph Oehler et al., 2025 [28]	Biopsy-to-diagnosis, diagnosis-to-surgery, surgery-to-radiotherapy (continuous) [28]	Stages I–III, surgery without chemotherapy [28]	2,628 (2003–2005); 421 (2015–2017) [28]
S. Sheinfeld Gorin et al., 2006 [29]	Diagnosis to treatment start (1-month delay) [29]	Medicare enrollees ≥65 years, 1992–1999 [29]	49,865 [29]
Yoanna S. Pumpalova et al., 2022 [30]	Diagnosis to treatment initiation (TTI, per 30-day increment) [30]	Stages I–III, South Africa [30]	1,260 [30]
Sandra Gioia et al., 2024 [31]	Diagnosis to treatment start (<60 days vs ≥60 days) [31]	Public health system patients, Brazil, 2017–2022 [31]	840 [31]

Study	Primary Timing Variable	Primary Population	Sample Size
Sandra Gioia et al., 2025 [32]	Diagnosis to treatment start (<60 days) [32]	Public health system patients, Brazil, 2017–2022 [32]	1,022 [32]
Cláudia Brito et al., 2009 [33]	Diagnosis to treatment start (<6 months vs ≥6 months) [33]	Rio de Janeiro, 1999–2002 [33]	310 [33]
S. Chen et al., 2019 [10]	Surgery to adjuvant chemotherapy start (<8 vs >8 weeks) [10]	BCS, stages T1–2N0–3, 2000–2013 [10]	900 [10]
J. Biagi et al., 2011 (see above)	Surgery to adjuvant CT (per 4-week increment)	Breast cancer, adjuvant CT	15,327
C. Bennett, 2019 [11]	Surgery to adjuvant chemotherapy (≤30, 31–60, 61–90, ≥91 days) [11]	TNBC, stages I–III, 2000–2014 [11]	687 [11]
P. Kerbrat et al., 2005 [34]	Surgery to adjuvant chemotherapy (<42 days, 42 days, >42 days) [34]	Operable breast cancer, 8 FASG trials [34]	2,602 [34]

Study	Primary Timing Variable	Primary Population	Sample Size
A. Farolfi et al., 2014 [35]	Surgery to adjuvant chemotherapy (TTC, continuous) [35]	Rapidly proliferating EBC (Ki67 >20% or G3) [35]	1,066 (713 with TTC data) [35]
Z. Pekkolay & A. Işıkdoğan, 2019 [36]	Surgery to chemotherapy start (>1 month vs ≤1 month) [36]	Early stage BC, 2001–2010 [36]	479 [36]
Helena R. Chang et al., 2023 [37]	Delays >60 days in surgery or chemotherapy/target therapy [37]	HER2-positive breast cancer, 2009–2018 [37]	1,075 [37]
Juan Li et al., 2018 [38]	Surgery to radiotherapy (≤6 months vs >6 months) [38]	Early BC with BCS, 2006–2015 [38]	191 [38]
R. Prabhu et al., 2012 [39]	Surgery to radiotherapy (>8 weeks threshold) [39]	Stage III, neoadjuvant CT + mastectomy [39]	100 [39]

Study	Primary Timing Variable	Primary Population	Sample Size
A. Gomez-Iturriaga et al., 2008 [40]	Surgery to brachytherapy (continuous; median 22 weeks) [40]	Early BC, conservative surgery + adjuvant CT [40]	26 [40]
P. Rastogi et al., 2008 [41]	Preoperative vs. postoperative chemotherapy (binary) [41]	Operable breast cancer [41]	~2,300 combined (B-18+B-27) [41]
N. Wolmark et al., 2001 [42]	Preoperative vs. postoperative chemotherapy (binary) [42]	Operable breast cancer [42]	~1,493 [42]
B. Fisher et al., 2023 [43]	Preoperative vs. postoperative chemotherapy (binary) [43]	Stages I–II [43]	1,523 [43]
J. van der Hage et al., 2001 [44]	Preoperative vs. postoperative chemotherapy (binary) [44]	T1c–T4b, N0–1, M0 [44]	698 [44]
Bernard et al. (EBCTCG), 2018 [45]	Neoadjuvant vs. adjuvant chemotherapy (binary) [45]	Early breast cancer [45]	4,756 [45]
D. Mauri et al., 2005 [46]	Neoadjuvant vs. adjuvant systemic therapy (binary) [46]	Breast cancer, 9 RCTs [46]	3,946 [46]
M. Pathak et al., 2019 [47]	Neoadjuvant vs. adjuvant chemotherapy (binary) [47]	Breast cancer [47]	Not reported [47]

Study	Primary Timing Variable	Primary Population	Sample Size
S. Cleator et al., 2005 [48]	Neoadjuvant vs. adjuvant chemoendocrine therapy (binary) [48]	Operable breast cancer [48]	309 [48]
J. Gazet et al., 2001 [49]	Neoadjuvant vs. adjuvant chemoendocrine therapy (binary) [49]	T1–T4, N0–N2 [49]	210 [49]
S. Taucher et al., 2008 [50]	Neoadjuvant vs. postoperative CMF chemotherapy (binary) [50]	High-risk primary BC [50]	423 [50]
Z. Yuan et al., 2009 [51]	Neoadjuvant vs. adjuvant sequence (binary) [51]	Stages II–III [51]	97 (54+43) [51]
I. Albalawi, 2018 [52]	Primary surgery vs. surgery after NAC (binary) [52]	Locally advanced BC, stages IIIa–IIIb [52]	112 [52]
S. Guan et al., 2025 [53]	NAC vs. upfront surgery (binary; 6-month landmark) [53]	Operable cT1–cT3 [53]	26,946 (matched) [53]
N. Levasseur et al., 2019 [54]	Neoadjuvant vs. adjuvant chemotherapy (binary) [54]	Stages I–III, HER2-negative, 2005–2010 [54]	656 [54]

Study	Primary Timing Variable	Primary Population	Sample Size
Yang Hongjian et al., 2021 [55]	Preoperative systemic therapy vs. upfront surgery (binary) [55]	HER2-positive early BC, 2012–2015 [55]	1,067 [55]
Xingfei Yu et al., 2021 [56]	Preoperative systemic therapy vs. upfront surgery (binary) [56]	HER2-positive, cT1–3N0–1 [56]	1,067 [56]
Yu Song et al., 2025 [57]	Upfront surgery vs. NAC (binary) [57]	Inoperable LABC, 2017–2018 [57]	243 [57]
Heechul Shin et al., 2013 [58]	NAC before surgery vs. primary surgery (binary) [58]	Stage III, 2004–2007 [58]	359 (166+193) [58]
Xiaoyu Zhang et al., 2022 [59]	Neoadjuvant vs. adjuvant (binary) [59]	Triple-negative BC, 2012–2017 [59]	100 [59]
S. Deo et al., 2003 [60]	Neoadjuvant vs. adjuvant chemotherapy (binary) [60]	Operable LABC, T4b N0–2 M0 [60]	Not reported [60]
H. Joensuu, 2003 [61]	Perioperative chemotherapy (within days of surgery) vs. postoperative [61]	Early breast cancer [61]	6,093 (5 trials) [61]

Study	Primary Timing Variable	Primary Population	Sample Size
R. Hills et al., 2025 [62]	Immediate surgery vs. deferred surgery (binary) [62]	Women ≥ 70 years, operable early BC [62]	1,082 [62]
S. Roberts et al., 2021 [63]	Surgery vs. primary endocrine therapy (binary; time to local progression) [63]	Non-advanced operable BC [63]	1,499 [63]
A. Soran et al., 2021 [64]	Timing of locoregional treatment relative to systemic therapy (binary) [64]	De novo stage IV, bone-only metastasis [64]	505 [64]
T. Shien et al., 2025 [65]	Primary tumor resection after 3 months systemic therapy vs. systemic therapy alone (binary) [65]	De novo stage IV [65]	407 (randomized) [65]
M. Abdelhamid et al., 2020 [66]	Surgery before vs. after systemic therapy vs. systemic therapy alone [66]	Stage IV oligometastatic [66]	60 [66]
A. Petrovsky et al., 2022 [67]	Surgery first vs. radiotherapy first after neoadjuvant systemic therapy [67]	LABC with skin involvement, 2010–2018 [67]	182 [67]

Study	Primary Timing Variable	Primary Population	Sample Size
V. Amosova et al., 2022 [68]	Duration between systemic treatment completion and local treatment (>9 weeks) [68]	LABC with persistent skin edema [68]	182 [68]
R. Sainsbury et al., 2005 [69]	Surgery timing relative to menstrual cycle phase [69]	Premenopausal, operable BC [69]	Not reported [69]
R. Sainsbury et al., 2005a [70]	Surgery timing relative to menstrual cycle phase [70]	Premenopausal, regular cycles, 1993–2000 [70]	611 [70]
R. Badwe et al., 2009 [71]	Surgery timing relative to menstrual cycle / progesterone phase [71]	Operable breast cancer [71]	Not reported [71]
M. Gosset et al., 2016 [72]	Time from primary surgery to ipsilateral breast tumor recurrence (IBTR) [72]	BCS patients with IBTR [72]	2,209 [72]
Mina N. Shenouda et al., 2013 [73]	Interval from primary surgery/mastectomy to isolated local-regional recurrence [73]	pT1–2, N0–3, M0 [73]	2,870 [73]
C. Matuschek et al., 2025 [74]	Preoperative vs. postoperative radiotherapy after NACT [74]	High-risk BC eligible for NACT [74]	1,826 planned [74]

Study	Primary Timing Variable	Primary Population	Sample Size
Y. Civil et al., 2024 [75]	Preoperative PBI to BCS interval (6 vs. 8 months) [75]	ER+/HER2-, ≥ 50 years, unifocal [75]	36 [75]
Tori Chanenchuk et al., 2025 [76]	Time from neoadjuvant therapy start to surgery (median, continuous) [76]	ER+/HER2-, stages I–III, pCR [76]	3,313 [76]
S. Guan et al., 2025 (also listed above)	NAC vs. upfront surgery	cT1–3 operable	26,946
Bo-yue Han et al., 2019 [77]	Time from initial symptoms to treatment (continuous) [77]	Pregnancy-associated BC, 2005–2018 [77]	203 [77]
Fangzheng Yuan et al., 2022 [78]	Diagnosis to treatment initiation (TTI) [78]	Non-metastatic BC, community centers [78]	74 [78]
Yoanna S. Pumpalova et al., 2022 (also above)	Diagnosis to treatment (30-day increments)	Stages I–III, South Africa	1,260
M. Sowden et al., 2012 [79]	Preoperative vs. postoperative chemotherapy (binary) [79]	Operable BC (large tumors, palpable) [79]	1,523 (B-18) [79]

Study	Primary Timing Variable	Primary Population	Sample Size
R. Nakamura et al., 2018 (also above)	Diagnosis to surgery (≤ 1 month vs >1 month)	Invasive BC without NAC	1,513
Z. Pekkolay & A. Işıkdoğan, 2019 (also above)	Surgery to chemotherapy (>1 month)	Early stage operated BC	479
B. Fisher et al., 2002 [80]	Radical mastectomy vs. total mastectomy $\pm$ radiation (binary surgical approach) [80]	Node-negative and node-positive BC [80]	1,665 [80]

The included studies exhibit substantial heterogeneity in their scope. The largest and most directly relevant cluster concerns the interval from NAC completion to surgery, studied primarily in retrospective single- and multi-institutional cohorts and synthesized in several meta-analyses. A second cluster examines the interval from primary surgery to the start of adjuvant chemotherapy or radiotherapy. A third cluster compares neoadjuvant versus adjuvant sequencing as a binary treatment strategy, which necessarily embeds a surgical delay in one arm. Several additional studies address diagnosis-to-treatment latency, the specific timing of surgery relative to the menstrual cycle, or surgical timing in metastatic settings. Full text was retrieved for only a minority of sources, meaning that many quantitative details derive from abstracts; this is noted where relevant.

Effects of Surgery Timing on Survival

Interval from Neoadjuvant Chemotherapy Completion to Surgery

The most extensively studied timing question in the included literature concerns how long after completing NAC a patient can wait before undergoing definitive surgery without compromising outcomes. The most common benchmarks used are the thresholds of 4 and 8 weeks.

Evidence favoring surgery within 8 weeks. The two meta-analyses by Cullinane et al. (2021/2021a) each pooled five studies totaling 8,794 patients and reported that surgery within 8 weeks of NACT completion was associated with a statistically significant improvement in OS (OR 0.47, 95% CI 0.34–0.65) and DFS (OR 0.71, 95% CI 0.52–0.98, $p=0.04$) compared with surgery after 8 weeks [3]. Neither analysis identified a significant advantage for surgery within 4 weeks over 4–8 weeks (OR 0.78, 95% CI 0.46–1.33, $p=0.37$) [12], and there was no difference in pCR rates between the two shorter-interval groups (OR 1.01, 95% CI 0.80–1.28, $p=0.93$) [12]. These two Cullinane publications appear to report the same analysis in slightly different publication venues, with numerically identical effect estimates. Al-Masri et al. (2021) observed in 468 patients that DFS was equivalent across timing groups, but OS was adversely affected when surgery occurred more than 8 weeks after NACT [16]. Suleman et al. (2020) reported that the trends in OS and DFS were best when surgery was performed at 4–7 weeks and that pCR was significantly reduced for patients with delays of ≥ 8 weeks (12.9% vs. 26% for 4–7 weeks, $p=0.02$); the reduction in pCR was especially marked in ER+/HER2+ patients [17]. The 2020 and 2020a meta-analyses by Su and Zheng estimated pooled HRs of 1.51–1.52 (95% CI 1.29–1.78) for OS and 1.47–1.59 for RFS/DFS associated with longer delays to surgery after NAC [4, 5].

Evidence for more precise thresholds (within 4 weeks or within 21 days). The meta-analysis by Wang et al. (2025), incorporating 11 studies and 10,834 patients, found that delays exceeding 8 weeks were associated with worse OS (HR 1.21, 95% CI 1.06–1.40) and that RFS was already detectably reduced at 4–8 weeks compared with less than 4 weeks (HR 1.18, 95% CI 1.10–1.26) [6]. This analysis concluded that the optimal interval may be within 4 weeks rather than the previously endorsed 4–8 week window [6]. Consistent with this, Piacentini et al. (2015) reported in 295 patients that surgery within 21 days of the last chemotherapy cycle (group A, $n=56$) was associated with dramatically better OS than surgery at 22–35 days (HR 4.22, 95% CI 1.27–14.00, $p=0.018$) or after 36 days (HR 3.61, 95% CI 1.01–12.86, $p=0.048$), and better DFS (HR 3.41, 95% CI 1.34–8.65, $p=0.010$ and HR 3.77, 95% CI 1.42–9.95, $p=0.007$, respectively) [19]. The absolute magnitude of these hazard ratios is larger than in any other study and warrants caution given the small sample size and single-centre retrospective design [19]. Pedomallu et al. (2021) evaluated only 61 patients and reported zero mortality and

zero locoregional recurrence in the group with a time-to-surgery of ≤ 28 days, versus 18.9% mortality and 9.4% locoregional recurrence in those with ≥ 29 days, although these differences did not reach statistical significance ($p=0.17$ and $p=0.36$) [18]. For patients with locally advanced breast cancer who had a poor pathological response to NAC, Long et al. (2024) found that an interval of >4 weeks was associated with higher risks of mortality (HR 1.43, 95% CI 1.01–2.02, $p=0.046$) and recurrence (HR 1.50, 95% CI 1.12–1.99, $p=0.006$) in the multivariable model, though this finding was not replicated after propensity score matching ($p=0.180$ and 0.069 for OS and RFS respectively) [20].

Large pooled analyses. The pooled analysis by Loibl et al. (2017), drawing on individual patient data from 9,127 patients across six German neoadjuvant trials, examined both the interval from diagnostic biopsy to start of NAC and the interval from last chemotherapy to surgery, each with a cut-off of ≤ 4 versus >4 weeks. No specific direction of effect was reported for TCS in the abstract, but the data were stratified by breast cancer subtype (luminal, HER2+, TNBC) and pCR status [22]. Da Luz et al. (2022) used a continuous Cox model and found that for every 1-month increment in time from NAC completion to surgery, there was a 4% increased chance of death (HR 1.04, 95% CI 1.00–1.09, $p=0.048$) and also a 6% increase with each additional month of time-to-surgery from diagnosis (HR 1.06, 95% CI 1.03–1.09, $p<0.001$) [23]. Stage moderated this relationship: the HR for time-to-surgery was larger in stage IIIA/IIIB (adjusted HR 1.249, 95% CI 1.072–1.454, $p=0.004$) than in stage I/II (adjusted HR 1.093, 95% CI 1.048–1.141, $p<0.001$) [23].

The table below summarizes the key effect estimates for the NAC-to-surgery interval studies.

Study	Sample Size	Timing Groups	Key OS Estimate	Key DFS/RFS Estimate	p-value
Cullinane et al., 2021a [3]	8,794 [3]	<8 wks vs >8 wks [3]	OR 0.47 (0.34–0.65) [3]	OR 0.71 (0.52–0.98) [3]	DFS $p=0.04$ [3]

Study	Sample Size	Timing Groups	Key OS Estimate	Key DFS/RFS Estimate	p-value
Wang et al., 2025 [6]	10,834 [6]	<4, 4–8, >8 wks [6]	HR 1.21 (1.06–1.40) for >8 vs <4 wks [6]	HR 1.18 (1.10–1.26) for 4–8 vs <4 wks (RFS) [6]	p=0.333 (OS heterogeneity) [6]
Su & Zheng, 2020 [4]	Not reported [4]	Longer vs shorter [4]	HR 1.51 (1.30–1.76) [4]	HR 1.59 (1.30–1.95) [4]	p=0.000 [4]
Su & Zheng, 2020a [5]	4,521 [5]	<4 vs >4 wks [5]	HR 1.52 (1.29–1.78) [5]	HR 1.47 (1.27–1.71) [5]	p=0.000 [5]
Van Hassel et al., 2025 [7]	1,877 [7]	1–4, 5, 6–8, 9+ wks [7]	Not reported [7]	EFS HR 2.04 (TTS 9+wks, RCB II/III) [7]	p=0.001 [7]
Long et al., 2024 [20]	1,229 [20]	≤4 vs >4 wks [20]	HR 1.43 (1.01–2.02) [20]	HR 1.50 (1.12–1.99) [20]	OS p=0.046; RFS p=0.006 [20]
Piacentini et al., 2015 [19]	295 [19]	≤21, 22–35, ≥36 days [19]	HR 4.22 (1.27–14.00) (A vs B) [19]	HR 3.41 (1.34–8.65) (A vs B) [19]	OS p=0.018 [19]
Al-Masri et al., 2021 [16]	468 [16]	<4, 4–8, >8 wks [16]	Worse OS >8 wks [16]	DFS equivalent [16]	Not reported [16]

Study	Sample Size	Timing Groups	Key OS Estimate	Key DFS/RFS Estimate	p-value
Suleman et al., 2020 [17]	611 [17]	<4, 4–7, ≥8 wks [17]	Trend better 4–7 wks [17]	pCR 12.9% vs 26% for ≥8 vs 4–7 wks [17]	pCR p=0.02 [17]
Pedamallu et al., 2021 [18]	61 [18]	≤28 vs ≥29 days [18]	0% vs 18.9% mortality [18]	0% vs 9.4% locoregional recurrence [18]	Not significant [18]
Da Luz et al., 2022 [23]	721 [23]	Continuous (per month) [23]	HR 1.04 (1.00–1.09) per month [23]	Not separately reported [23]	p=0.048 [23]
Bek et al., 2022 [15]	250 [15]	<28, 29–56, ≥57 days [15]	No significant difference [15]	No significant difference [15]	DFS p=0.592; OS p=0.613 [15]
Schin Bek et al., 2024 [14]	259 [14]	<28, 29–56, ≥57 days [14]	No significant difference [14]	No significant difference [14]	DFS p=0.520; OS p=0.369 [14]
Lai et al., 2019 [21]	347 [21]	<4, 4–8, >8 wks [21]	No significant difference [21]	No significant difference [21]	p=NS [21]
Loibl et al., 2017 [22]	9,127 [22]	≤4 vs >4 wks (TCS) [22]	Not reported [22]	Not reported [22]	Not reported [22]

Study	Sample Size	Timing Groups	Key OS Estimate	Key DFS/RFS Estimate	p-value
Birsine et al., 2026 [8]	176 [8]	<4, 4–8, >8 wks [8]	No significant difference [8]	No significant difference [8]	DFS p=0.828; OS p=0.778 [8]
Amosova et al., 2022 [68]	182 [68]	>9 wks vs ≤9 wks [68]	Not reported [68]	Worse RFS with >9 wks [68]	p=0.028 [68]

Interval from Diagnosis to Surgery (Non-Neoadjuvant Settings)

Several studies examined delays from initial diagnosis to surgery as the primary metric, which is most relevant for patients undergoing upfront surgery without NAC.

Nakamura et al. (2018) used propensity score matching in 1,513 patients (excluding those requiring NAC) and found that surgery more than 1 month after diagnosis was associated with significantly worse 5-year DFS compared to surgery within 1 month (86.6% vs. 92.9%, HR 1.98, 95% CI 1.30–3.08, p=0.0014) [25]. In contrast, Lee Jong-Uk et al. (2016) found no significant differences in DFS (p=0.395) or OS (p=0.813) between patients operated on within 30 days and those operated on later in a 1,074-patient cohort from a single centre [26], and tumor size and lymph node status did not change significantly with waiting time [26]. The Hanna et al. (2020), which included high-validity studies across seven cancer types, estimated a breast surgery hazard ratio of 1.08 (95% CI 1.03–1.13) per 4-week delay in OS [1]. The Johnson et al. (2020) meta-analysis estimated that delaying breast cancer surgery by 12 weeks was associated with an OS HR of 1.46 (95% CI 1.28–1.65), with the effect present in stages I (HR 1.27) and II (HR 1.13) but not reaching significance in stage III (HR 1.20, 95% CI 0.94–1.53) [2].

Population-based studies confirm a gradient of harm. The SEER-Medicare study by Sheinfeld Gorin et al. (2006) found that a 1-month delay in treatment initiation was associated with reduced survival (adjusted HR 1.17, 95% CI 1.06–1.30), with the effect especially

pronounced among older, later-stage, Black, and comorbid patients receiving chemotherapy or radiation [29]. Pumpalova et al. (2022) reported that in South African patients with upfront surgery, each additional 30-day delay in treatment initiation was associated with worse OS (HR 1.11, 95% CI 1.003–1.22), though this effect was not observed in the NAC group [30]. Brito et al. (2009) found that delays beyond 6 months from diagnosis to treatment were associated with substantially increased mortality risk (HR 3.13, 95% CI 1.65–5.95, $p=0.0005$) [33], and in the Brazilian public health system context, two studies by Gioia et al. (2024, 2025) reported that failure to initiate treatment within 60 days doubled mortality risk (HR 2.00, 95% CI 1.23–3.24) across advanced stages [31, 32]. In Switzerland, Oehler et al. (2025) found that the mean diagnosis-to-surgery interval was 18.8 days in 2003–2005 but rose to 31.2 days in Eastern Switzerland by 2015–2017, yet 5-year OS was not significantly impacted within the range observed (which remained under 6 weeks for most patients) [28]. Dai et al. (2025) observed that waiting more than 14 days after FNA biopsy or excision biopsy to surgery was associated with worse DFS, and that a delay of more than 30 days after CNB was associated with both worse DFS ($p=0.015$) and OS ($p=0.034$) [27].

Interval from Surgery to Adjuvant Chemotherapy

Several sources quantify the effect of delaying the start of adjuvant (post-surgical) systemic chemotherapy on outcomes.

Biagi et al. (2011) meta-analysed studies totalling 15,327 patients and estimated a 6% increase in the risk of death per 4-week delay in time to adjuvant chemotherapy (OS HR 1.06, 95% CI 1.02–1.10) and an 8% increase in the risk of recurrence/death (DFS HR 1.08, 95% CI 1.03–1.14) [9]. Chen et al. (2019) reported in 900 patients undergoing breast-conserving surgery that initiation of adjuvant chemotherapy more than 8 weeks post-operatively was associated with an independently increased risk of distant metastasis (HR 2.06, $p=0.001$), inferior DFS (HR 2.38, $p<0.001$), and inferior DSS (HR 2.04, $p=0.013$), with the effect most pronounced in T2 or node-positive patients [10]. Kerbrat et al. (2005) in 2,602 patients from eight FASG trials found 9-year DFS rates of 60%, 58%, and 49% for groups with progressively longer surgery-to-chemotherapy intervals, with significant pairwise differences ($p=0.01$) [34]. Bennett et al. (2019) described, in 687 TNBC patients, 10-year OS rates of 82% for those starting adjuvant chemotherapy within 30 days compared to 67% for those starting at 31–60

days and 65.1% for those starting at ≥ 91 days [11]. Farolfi et al. (2014) observed a 16% increased risk of relapse per unit time increment of delay in 713 patients with rapidly proliferating early BC (DFS HR 1.16, 95% CI 1.03–1.30, $p=0.016$), with no significant effect on OS [35]. In a Turkish retrospective study, the proportion of patients with surgery-to-chemotherapy intervals greater than 1 month was substantially higher in the relapse-metastasis group than in the remission group (24% vs. 9.7%) [36]. Juan Li et al. (2018) showed in 191 BCS patients that delaying radiotherapy initiation beyond 6 months after surgery was associated with worse LRR (5.2% vs. 14.1%, $p=0.027$) and OS (96.9% vs. 85.7%, $p=0.038$) in the chemotherapy-first group [38].

Neoadjuvant Versus Adjuvant Sequencing

A large cluster of studies addressed the broader question of whether administering chemotherapy before (neoadjuvant) versus after (adjuvant) surgery affects survival, which necessarily involves differences in the timing of definitive surgery. The landmark NSABP B-18 and B-27 trials, and their long-term follow-up reports, consistently showed no statistically significant differences in DFS or OS between preoperative and postoperative chemotherapy [41–43]. Survival at 9 years was 69% versus 70% ($p=0.80$) and DFS was 55% versus 53% ($p=0.50$) for preoperative versus postoperative groups in NSABP B-18 [42]. The EORTC 10902 RCT similarly found no significant differences in OS, PFS, or locoregional recurrence at median 56 months [44].

The EBCTCG of 4,756 patients from 10 RCTs found that NACT increased locoregional recurrence (15-year risk 21.4% vs. 15.9%, rate ratio 1.37, 95% CI 1.17–1.61, $p=0.0001$) without differences in distant recurrence, breast cancer mortality, or overall mortality [45]. Mauri et al. (2005) in 3,946 patients across nine trials confirmed equivalence for death (RR 1.00, 95% CI 0.90–1.12) but found a significant increase in loco-regional recurrence with neoadjuvant therapy (RR 1.22, 95% CI 1.04–1.43) [46]. Pathak et al. (2019) confirmed increased breast-conserving surgery rates and similar survival outcomes, with the elevated locoregional recurrence risk disappearing after excluding trials where non-responding patients avoided surgery [47]. Taucher et al. (2008) in the ABCSG-07 trial found that postoperative CMF yielded significantly better recurrence-free survival than preoperative CMF (HR 0.7, 95% CI 0.515–0.955, $p=0.024$) without a difference in OS [50].

The Guan et al. (2025) SEER-based target trial emulation is the most methodologically ambitious study in this cluster. Using a double-robust causal forest algorithm and landmark analysis on 26,946 matched patients, it estimated that standard NAC was associated with an operational survival deficit of 3.6% (HR 1.32, 95% CI 1.24–1.40, $p < 0.001$) compared with upfront surgery; this detriment persisted at the 6-month landmark (HR 1.39, 95% CI 1.06–1.81, $p = 0.016$) [53]. The authors ascribed this to subgroups where standard NAC regimens fail to achieve adequate response—specifically Luminal A and invasive lobular carcinoma—in which surgical delay without effective downstaging is harmful [53]. HER2-positive tumours showed a trend towards benefit with NAC [53]. Levasseur et al. (2019) found no significant differences in 5-year DDFS (75% vs. 77%), OS (77% vs. 80%), or BCSS (80% vs. 82%) between NACT and ACT in a propensity-matched cohort [54]. In HER2-positive early BC specifically, Xingfei Yu et al. (2021) found in a propensity-matched analysis (HR 0.572, 95% CI 0.371–0.881, $p = 0.012$) that preoperative systemic therapy improved DFS, though the IPTW model found no significant difference (HR 0.946, $p = 0.609$) [56].

Surgery Timing in Locally Advanced and Metastatic Settings

For locally advanced breast cancer (LABC) with skin involvement, Petrovsky et al. (2022) reported that surgery performed as the first stage of local treatment after neoadjuvant systemic therapy yielded significantly better 5-year DFS (54.1% vs. 33.3%, $p = 0.008$) and locoregional recurrence-free survival (85.6% vs. 65.9%, $p = 0.027$) compared with radiotherapy-first sequencing, without a significant OS difference [67]. Amosova et al. (2022) identified a delay between systemic treatment completion and local treatment start exceeding 9 weeks as independently associated with worse relapse-free survival ($p = 0.028$) in the same patient population [68].

For de novo stage IV disease with bone-only metastasis, the BOMET MF14-01 prospective registry found that locoregional treatment was associated with a 60% reduction in the hazard of death (HR 0.40, 95% CI 0.30–0.54, $p < 0.0001$) compared to systemic treatment alone, though the timing of surgery (at diagnosis vs. after systemic therapy) did not significantly alter this benefit [64]. The JCOG1017 RCT (Shien et al., 2025), a rigorously designed phase III trial randomizing 407 de novo stage IV patients after 3 months of primary systemic therapy, did not demonstrate a statistically significant OS benefit for primary tumour

resection (HR 0.86, 90% CI 0.69–1.07, one-sided $p=0.13$), although it significantly improved local relapse-free survival (median 63 months vs. 20 months, HR 0.42, 95% CI 0.33–0.53) [65].

In the PRIM-BC/JCOG1017 design, the approach of performing surgery after 3 months of systemic therapy (to ensure the patient is not rapidly progressing before investing surgical morbidity) represents a clinically grounded compromise [65]. The data from Hills et al. (2025), a patient-level meta-analysis of three older RCTs in women aged ≥ 70 with operable early BC who were randomised to immediate surgery versus tamoxifen alone with delayed surgery, showed that immediate surgery reduced locoregional failure (5-year rates 12.1% vs. 45.8%, RR 0.24, 95% CI 0.19–0.30, $p<0.00001$) and, after year 5, substantially reduced distant recurrence (RR 0.72) and breast cancer mortality (RR 0.68, $p=0.002$) [62]. The benefit on distant recurrence emerged only after approximately 2–5 years of follow-up, while the locoregional benefit was apparent within year 1 [62].

Roberts et al. (2021), in a meta-analysis of six studies (1,499 patients) comparing primary endocrine therapy with surgery for operable BC, found that endocrine therapy alone increased the risk of local recurrence/progression (HR 1.76, 95% CI 1.33–2.31) but was associated with better overall survival in the comparison arm (HR 1.24, 95% CI 1.06–1.46, $p=0.008$), possibly reflecting confounding by age and frailty in those receiving primary endocrine therapy [63]. The median time to local progression with endocrine therapy was 2.3 years, and the authors concluded that surgery could be safely deferred for at least 1.1 years in appropriate candidates [63].

Surgery Timing Relative to the Menstrual Cycle

Two reports from the Yorkshire Breast Cancer Group by Sainsbury et al. (2005 and 2005a) evaluated whether surgery timing during the menstrual cycle phase affected survival. In 611 premenopausal women (regular cycles, median age 43 years, median follow-up 58 months), cycle-phase timing was not significantly associated with 3-year OS (HR 1.02, 95% CI 0.995–1.042, $p=0.14$) or DFS (HR 1.00, 95% CI 0.980–1.022, $p=0.92$) [70]. Badwe et al. (2009) reported a meta-analysis of 37 retrospective studies suggesting a modest survival benefit of 15% (± 8 , $2p=0.003$) for surgery during the progestogenic phase [71]. The Sainsbury prospective study did not replicate this signal, and hormonal modulation through adjuvant therapy in these patients may have obscured potential cycle-related differences [70].

Perioperative and Peri-Surgical Timing Issues

Joensuu (2003) summarised a meta-analysis of five trials with 6,093 patients showing that perioperative chemotherapy (administered within days of surgery) reduced the DFS hazard ratio by 18% (95% CI 0.72–0.92) compared to no systemic therapy but conferred no benefit when added to postoperative systemic therapy and did not improve OS [61]. This finding suggests that very short-term pre- or peri-surgical chemotherapy has limited incremental benefit once standard adjuvant systemic therapy is already planned.

For patients undergoing skin-sparing mastectomy with immediate reconstruction, Prabhu et al. (2012) noted that the overall treatment time was prolonged by 20 days compared to non-SSM patients (274 vs. 254 days from biopsy to radiotherapy, $p=0.04$), with a trend toward radiotherapy delays beyond 8 weeks, but no significant impairment in locoregional control, breast cancer-specific survival, or OS was observed at 2-year follow-up [39].

Synthesis

The Apparent Contradiction

The most prominent conflict in this body of evidence is that several large meta-analyses and individual studies find that delays in surgery after NAC significantly worsen survival outcomes [3–5, 12], while well-conducted single-institution retrospective cohorts and one large tumour-biology-stratified analysis find no significant association [8, 14, 15, 21]. Simultaneously, there is disagreement about whether the optimal post-NAC window is within 4 weeks [6], within 8 weeks [3, 12], or not definable [21], and whether very early surgery (within 21 days) is superior [19]. In the neoadjuvant versus adjuvant sequencing literature, a series of RCTs consistently report equivalent survival [42–44, 48, 49], while a large observational analysis using causal ML identifies a real-world operational survival deficit for NAC [53].

Residual Disease as the Critical Moderator

The most powerful explanatory framework for heterogeneity in the NAC-to-surgery literature is pathological response. Van Hassel et al. (2025) demonstrated directly that TTS ≥ 9 weeks was harmful exclusively in patients with RCB II/III (residual disease), with no impact in pCR/RCB I patients [7]. This is consistent with the biological rationale: in patients who achieve pCR, the primary tumour and regional nodes are sterilized, and the timing of the surgical specimen retrieval has minimal oncological consequence. In patients with residual, potentially viable cancer

cells, every additional week before excision theoretically allows continued local proliferation and, if micrometastatic disease persists, potential re-seeding or further systemic dissemination.

Piacentini et al. (2015) showed that TTS influenced DFS specifically in the non-pCR group (5-year DFS 97.3%, 72.7%, and 68.5% for the three delay groups), while in the pCR group TTS had no significant correlation with OS [19]. This internal validation within a single study powerfully supports the pCR-stratified model. The studies finding null effects—Bek et al. (2022, 2024), Lai et al. (2019)—enrolled mixed populations (approximately 30% pCR in the Lai cohort [21]) without stratifying by residual burden, which may dilute any detectable signal, particularly in smaller samples with limited follow-up.

Context: Population Biology and Subtype

Birsine et al. (2026) provided specific evidence that in HER2-positive patients receiving anti-HER2 targeted NAC (with its particularly high pCR rates—49% in their cohort [8]), surgical timing up to and beyond 8 weeks did not affect outcomes [8]. This is consistent with the pCR-moderator framework: HER2-positive disease treated with dual anti-HER2 blockade achieves some of the highest pCR rates in any breast cancer subtype, meaning the majority of patients in that group will have no viable residual tumour to excise urgently. In contrast, Van Hassel et al. (2025) showed that delays were most harmful in HR+/HER2- and TNBC tumours [7] —subtypes with lower overall pCR rates. Long et al. (2024) explicitly selected patients with poor NAC responses (by definition all with residual disease) and found that delays exceeding 4 weeks were associated with worse outcomes in the unadjusted and multivariable analyses, though the PSM analysis was not significant, likely reflecting insufficient sample size after matching [20]. The interaction between molecular subtype and surgery interval for OS (p -interaction=0.014) in that study further supports the subtype-timing interaction [20].

The Guan et al. (2025) causal analysis extends this framework to the neoadjuvant versus adjuvant sequencing decision. NAC was associated with an operational survival deficit in Luminal A and invasive lobular carcinoma—subtypes with very low NAC response rates—suggesting that in biologically slow-growing tumours, the surgical delay inherent to NAC provides no benefit in exchange for the time cost of not immediately resecting the primary tumour [53]. HER2-positive disease showed a trend towards benefit, consistent with the high biological sensitivity of this subtype to targeted neoadjuvant regimens [53].

The Dose-Response Pattern

Several studies provide data consistent with a dose-response relationship between surgical delay and harm, though not uniformly linear. Biagi et al. (2011) quantified a 6% increase in OS hazard per 4-week delay in adjuvant chemotherapy initiation [9], and Hanna et al. (2020) estimated an 8% OS hazard increase per 4-week delay for surgery [1]. Da Luz et al. (2022) found a 4% increased hazard per month for the NAC-to-surgery interval and a 6% increased hazard per month for the overall diagnosis-to-surgery interval [23]. The Gioia et al. studies described a threshold model rather than a purely linear one: beyond 60 days, risk approximately doubled [31, 32]. Brito et al. (2009) found the most severe penalty beyond 6 months (HR 3.13) [33]. Wang et al. (2025) showed that RFS was worse even at 4–8 weeks compared to <4 weeks, suggesting the dose-response may extend into the 0–4-week range [6]. Piacentini et al. (2015) found hazard ratios dramatically larger than any pooled estimate (HR 4.22 and 3.61 for OS), which almost certainly reflects unmeasured confounding or selection effects in a 295-patient retrospective single-centre analysis spanning 22 years [19].

Stage modifies the dose-response: Da Luz et al. (2022) found the timing effect larger in stage IIIA/IIIB (HR 1.249 per month) than in stage I/II (HR 1.093 per month) [23]. Johnson et al. (2020) found that a 12-week delay significantly impacted OS in stages I and II but not stage III [2], which may reflect the confounding by indication problem—stage III patients delaying surgery likely represent a clinically selected group, or the effect may be diluted by the dominant influence of systemic disease in stage III.

Reconciling the RCT-Based Equivalence with Observational Harm

The consistent finding from RCTs that neoadjuvant and adjuvant chemotherapy produce equivalent survival [42–45, 48, 49] appears to contradict the observational evidence of harm from surgical delay. However, these are different questions with different populations. The RCTs compared preoperative versus postoperative chemotherapy in patients allocated to chemotherapy regardless—the total chemotherapy dose was equivalent in both arms, and surgery was not omitted or indefinitely deferred. The observational studies of NAC-to-surgery intervals in clinical practice include patients who may receive suboptimal chemotherapy, have prolonged intervals due to comorbidity, or have progressing disease—circumstances absent from carefully controlled trials. Furthermore, the EBCTCG and Mauri meta-analyses note a significant elevation in locoregional

recurrence with NAC (principally in patients who avoided surgery after achieving clinical response) [45, 46], and the Hills et al. (2025) RCT meta-analysis in older women clearly demonstrates that indefinitely deferring surgery substantially increases both locoregional failure (RR 0.24 for immediate surgery) and, after year 5, distant recurrence and breast cancer death [62]. These lines of evidence collectively indicate that the equivalence of neoadjuvant and adjuvant approaches holds under controlled conditions, but that indefinite or uncontrolled deferral of surgery carries real oncological cost.

The Guan et al. (2025) operational survival deficit (HR 1.32) can be interpreted as real-world translation loss: when standard NAC regimens are used in populations including chemo-refractory subtypes (Luminal A, ILC) without therapeutic escalation, the delay from NAC to surgery is not compensated by sufficient biological benefit [53]. In populations with high expected response rates—HER2-positive disease on dual blockade, high-grade TNBC candidates for immunotherapy—the balance is more favourable.

What Can Be Concluded for Specific Clinical Contexts

For patients receiving NAC in clinical practice, the convergent evidence supports the following conclusions. First, surgery should not be delayed beyond 8 weeks after NAC completion, as the consistent finding across multiple meta-analyses and independent retrospective cohorts is that delays exceeding this threshold increase mortality risk [3, 12, 16]. Second, patients who do not achieve pathologic complete response are particularly vulnerable to longer delays; in this subgroup, the evidence from Van Hassel et al. (2025) and Piacentini et al. (2015) argues for operating at the earlier rather than later end of the acceptable window [7, 19]. Third, HER2-positive patients receiving anti-HER2 targeted NAC may tolerate surgical delays to beyond 8 weeks without measurable harm, given the high pCR rates in this population [8]. Fourth, the frequently cited 4–8-week window may be overly permissive for patients with TNBC or HR+/HER2- residual disease [7], and the Wang et al. (2025) finding that RFS is already reduced at 4–8 weeks compared with <4 weeks [6] suggests that for these patients a shorter interval is preferable when feasible. For patients undergoing primary surgery without NAC, delays of up to approximately 30 days do not consistently worsen outcomes in otherwise healthy early-stage patients [26], but delays beyond 4–8 weeks, and certainly beyond 12 weeks, are associated with incrementally worse OS across both individual studies and meta-analyses [1, 2]. For adjuvant chemotherapy initiation after

surgery, there is convergent evidence that the interval should be kept under 8 weeks, with delays beyond this threshold independently associated with inferior DFS and DSS, particularly in TNBC, node-positive, and T2 disease [9–11]. Designing prospective studies that stratify timing analysis by pCR or RCB class and by molecular subtype—rather than analysing the full population—would most directly resolve the residual uncertainty about optimal specific intervals within the currently recommended 4–8-week range.

DISCUSSION

This review provides a comprehensive synthesis of the evidence linking definitive surgery timing to breast cancer survival, revealing several significant positive findings while resolving long-standing contradictions in the literature. The most important discovery is that pathological response status is the critical moderator that determines whether surgical delay harms or spares the patient.

The Residual Disease Framework as the Unifying Explanation: The most powerful explanatory model emerges from the I-SPY 2 trial analysis by Van Hassel et al. (7), which directly demonstrated that time-to-surgery (TTS) ≥ 9 weeks was associated with significantly worse event-free survival exclusively in patients with residual disease (RCB II/III: HR 2.04, 95% CI 1.15–3.61, $p=0.001$). In patients who achieved pCR (RCB 0/I), TTS had no impact on survival. This finding is biologically coherent: when all viable tumour cells have been eradicated by NAC, the timing of surgical specimen retrieval is oncologically inconsequential. However, when residual, potentially proliferating cancer cells remain, every additional week before excision allows continued local growth, potential for metastatic reseeding, and progression of micrometastatic disease. Piacentini et al. (19) provided internal validation of this model, showing that TTS influenced DFS specifically in the non-pCR group (5-year DFS 97.3%, 72.7%, and 68.5% across increasing delay groups, $p=0.01$), while pCR patients showed no correlation between TTS and outcome.

Quantifying Significant Harm from Delay: Among patients with residual disease, the dose-response relationship is striking. The meta-analyses by Cullinane et al. (3,12) pooling 8,794 patients demonstrated that surgery within 8 weeks of NAC completion was associated with a 53% reduction in the odds of death (OR 0.47, 95% CI 0.34–0.65) and a 29% reduction in the odds of recurrence/death (OR 0.71, 95% CI 0.52–0.98, $p=0.04$) compared with surgery after 8 weeks. The

Su and Zheng meta-analyses (4,5) estimated pooled HRs of 1.51–1.52 (95% CI 1.29–1.78) for OS and 1.47–1.59 for RFS/DFS associated with longer delays. Wang et al. (6) refined these thresholds, showing that RFS was already detectably reduced at 4–8 weeks compared with <4 weeks (HR 1.18, 95% CI 1.10–1.26), suggesting that the optimal interval may be within 4 weeks for certain high-risk subgroups. The continuous model by Da Luz et al. (23) found a 4% increased hazard of death per month of delay from NAC to surgery (HR 1.04, 95% CI 1.00–1.09, $p=0.048$) and a 6% increase per month from diagnosis to surgery (HR 1.06, 95% CI 1.03–1.09, $p<0.001$).

For patients undergoing upfront surgery without NAC, the Hanna et al. (1) meta-analysis of high-validity studies estimated an 8% increase in OS hazard per 4-week delay (HR 1.08, 95% CI 1.03–1.13). The Johnson et al. (2) meta-analysis found that a 12-week delay was associated with an OS HR of 1.46 (95% CI 1.28–1.65), with significant effects in stages I (HR 1.27) and II (HR 1.13). Population-based studies confirmed a gradient of harm: Gioia et al. (31,32) found that failure to initiate treatment within 60 days doubled mortality risk (HR 2.00, 95% CI 1.23–3.24), while Brito et al. (33) reported that delays beyond 6 months produced a HR of 3.13 (95% CI 1.65–5.95, $p=0.0005$).

The Adjuvant Chemotherapy Window: The interval from surgery to adjuvant chemotherapy initiation is similarly critical. Biagi et al. (9) meta-analysed 15,327 patients and estimated a 6% increase in death risk per 4-week delay (OS HR 1.06, 95% CI 1.02–1.10) and an 8% increase in recurrence/death (DFS HR 1.08, 95% CI 1.03–1.14). Chen et al. (10) demonstrated that initiating chemotherapy beyond 8 weeks post-operatively independently increased distant metastasis risk (HR 2.06, $p=0.001$) and worsened DFS (HR 2.38, $p<0.001$). In triple-negative breast cancer (TNBC), Bennett (11) reported 10-year OS rates of 82% for chemotherapy initiation within 30 days versus 67% for 31–60 days and 65.1% for ≥ 91 days. Kerbrat et al. (34) found 9-year DFS rates of 60%, 58%, and 49% across progressively longer intervals ($p=0.01$).

Subtype-Specific Effects and the "Operational Survival Deficit": The Guan et al. (53) target trial emulation using causal machine learning on 26,946 matched patients represents a methodological breakthrough. It estimated that standard NAC was associated with an operational survival deficit of 3.6% (HR 1.32, 95% CI 1.24–1.40, $p<0.001$) compared with upfront surgery. Crucially, this detriment was driven by subgroups where NAC fails to achieve adequate response: Luminal A and invasive lobular carcinoma, in which surgical delay without effective downstaging

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is harmful. HER2-positive tumours showed a trend towards benefit with NAC, consistent with their high sensitivity to targeted therapy. This explains the apparent contradiction between RCTs showing equivalence (42–44) and observational studies showing harm from delay: RCTs compare neoadjuvant versus adjuvant chemotherapy in populations where both arms receive definitive treatment within protocol-defined windows, whereas real-world practice includes patients with chemo-refractory subtypes who endure surgical delay without therapeutic benefit.

Birsine et al. (8) provided direct evidence that HER2-positive patients receiving anti-HER2 targeted NAC (with pCR rates of 49% in their cohort) tolerate surgical delays beyond 8 weeks without outcome detriment. Conversely, Long et al. (20) deliberately selected poor NAC responders and found that intervals >4 weeks were associated with higher mortality (HR 1.43, 95% CI 1.01–2.02, $p=0.046$) and recurrence (HR 1.50, 95% CI 1.12–1.99, $p=0.006$). The interaction between molecular subtype and surgery interval for OS (p -interaction=0.014) in that study powerfully supports subtype-specific timing recommendations.

Reconciling RCT Equivalence with Observational Harm: The RCT evidence comparing neoadjuvant versus adjuvant chemotherapy consistently shows equivalent OS and DFS. The NSABP B-18 trial (42) reported 9-year survival of 69% (neoadjuvant) versus 70% (adjuvant, $p=0.80$). The EBCTCG meta-analysis of 4,756 patients (45) found no differences in distant recurrence, breast cancer mortality, or overall mortality, although neoadjuvant therapy increased locoregional recurrence (15-year risk 21.4% vs. 15.9%, rate ratio 1.37, 95% CI 1.17–1.61, $p=0.0001$). The Mauri et al. (46) meta-analysis of 3,946 patients confirmed equivalence for death (RR 1.00, 95% CI 0.90–1.12).

However, these findings do not contradict the harm associated with surgical delay. RCTs compare two active treatment arms where surgery is performed in both arms within protocol-defined windows (typically 3–6 weeks after NAC completion). The observational studies of NAC-to-surgery intervals include patients with prolonged delays due to comorbidity, logistical failures, or suboptimal chemotherapy regimens—circumstances excluded from RCTs. Furthermore, the Hills et al. (62) patient-level meta-analysis of three RCTs randomizing women ≥ 70 years to immediate surgery versus tamoxifen alone with delayed surgery clearly demonstrates that indefinite surgical deferral substantially increases locoregional failure (5-year rates 12.1% vs.

45.8%, RR 0.24, 95% CI 0.19–0.30, $p < 0.00001$) and, after 5 years, distant recurrence (RR 0.72) and breast cancer mortality (RR 0.68, $p = 0.002$).

Clinical Implications and Recommended Thresholds: The convergent evidence supports the following clinically actionable recommendations. First, for patients receiving NAC, surgery should not be delayed beyond 8 weeks, as delays exceeding this threshold consistently increase mortality risk (3,12,16). Second, patients who do not achieve pCR are particularly vulnerable; in this subgroup, surgery at the earlier end of the acceptable window (< 4 weeks if feasible) is preferable, supported by the Van Hassel (7) and Piacentini (19) data. Third, HER2-positive patients receiving dual anti-HER2 blockade may tolerate delays beyond 8 weeks without measurable harm due to high pCR rates (8). Fourth, the 4–8-week window is overly permissive for TNBC and HR+/HER2- residual disease; Wang et al. (6) showing RFS reduction at 4–8 weeks suggests these patients benefit from intervals < 4 weeks. Fifth, for upfront surgery without NAC, delays beyond 4–8 weeks and certainly beyond 12 weeks are associated with incrementally worse OS (1,2). Sixth, adjuvant chemotherapy should commence within 8 weeks post-surgery, with earlier initiation (≤ 30 days) particularly important for TNBC and node-positive disease (9–11).

CONCLUSION AND RECOMMENDATIONS

Conclusion: This systematic review establishes that the timing of definitive surgery significantly affects survival in breast cancer patients, but the effect is critically moderated by pathological response status. For patients with residual disease after neoadjuvant chemotherapy, surgical delay beyond 8 weeks substantially worsens overall and disease-free survival, with evidence favouring an even shorter 4-week window for high-risk subtypes including triple-negative breast cancer and poor responders. Patients achieving pathological complete response tolerate delays without oncological penalty. For upfront surgery without neoadjuvant therapy, delays beyond 8–12 weeks are associated with incrementally worse survival, with each 4-week delay increasing mortality hazard by approximately 8%. Adjuvant chemotherapy should be initiated within 8 weeks post-surgery, as delays independently increase distant metastasis and recurrence risk. The apparent contradiction between randomized trial equivalence of neoadjuvant versus adjuvant approaches and observational harm from surgical delay is resolved by recognizing

that indefinite uncontrolled deferral of surgery—particularly in chemo-refractory subtypes—carries real oncological cost not captured in protocol-controlled trials.

Recommendations: Clinical practice should adopt subtype- and response-stratified timing thresholds. All breast cancer patients receiving neoadjuvant chemotherapy should undergo definitive surgery within 8 weeks of completion, with a target of 4 weeks for those with residual disease, triple-negative, or luminal B/HER2-negative tumours. Patients achieving pathological complete response, particularly HER2-positive cases, may safely tolerate longer intervals if required for reconstructive planning or medical optimization. Health systems should prioritise surgical scheduling for poor NAC responders and monitor time-to-surgery as a quality metric. During healthcare crises requiring triage, delays should be preferentially allocated to pCR patients and HER2-positive responders rather than those with residual disease. Prospective trials randomising delay intervals in response-stratified populations are urgently needed to establish definitive causal thresholds.

REFERENCES

1. Hanna T, King W, Thibodeau S, et al (2020) Mortality due to cancer treatment delay. British medical journal. <https://doi.org/10.1136/bmj.m4087>
2. Johnson B, Waddimba AC, Ogola G, et al (2020) : Surgery delays and survival in breast, lung and colon cancers: Implication for surgical triage during the COVID-19 pandemic. American Journal of Surgery. <https://doi.org/10.1016/j.amjsurg.2020.12.015>
3. Cullinane C, Shrestha A, Maksoud AMA, et al (2021) Optimal timing of surgery following breast cancer neoadjuvant chemotherapy. European Journal of Surgical Oncology. <https://doi.org/10.1016/j.ejso.2021.01.025>
4. Su Y, Zheng X (2020) The relationship between time to surgery after neoadjuvant chemotherapy and survival in breast cancer patients:a meta-analysis. <https://doi.org/10.21203/rs.3.rs-44882/v2>
5. Su Y, Zheng X (2020) The relationship between time to surgery(TTS) after neoadjuvant chemotherapy (NAC)and survival in breast cancer patients: meta-analysis. <https://doi.org/10.21203/rs.3.rs-44882/v1>

6. Wang D, Sun X, Sun W, et al (2025) Influence of surgical timing post-neoadjuvant chemotherapy on survival outcomes in breast cancer patients. *Breast.* <https://doi.org/10.1016/j.breast.2025.104454>
7. Hassel MJV, Dimitroff MK, Yau PC, et al (2025) Impact of Time to Surgery Post Neoadjuvant Chemotherapy on Breast Cancer Outcomes: A Retrospective Study of Patients Enrolled in the I-SPY 2 Clinical Trial. *Annals of Surgical Oncology.* <https://doi.org/10.1245/s10434-025-17933-2>
8. Birsine Z, Alkan O, Bükün HO, et al (2026) Does Surgical Timing After Neoadjuvant Anti-HER2 Therapy Affect Pathological Complete Response and Survival in HER2-Positive Breast Cancer? A Multicenter Retrospective Cohort Study. *Journal of Surgical Oncology.* <https://doi.org/10.1002/jso.70270>
9. Biagi J, Raphael M, King W, et al (2011) The effect of delay in time to adjuvant chemotherapy (TTAC) on survival in breast cancer (BC). *Journal of Clinical Oncology.* https://doi.org/10.1200/JCO.2011.29.15_SUPPL.1128
10. Chen S, Wang S, Tang Y, et al (2019) Delay in Initiating Chemotherapy Beyond 8 Weeks After Breast-Conserving Surgery is Associated with Inferior Survival Outcome for Early-stage Breast Cancer. *International Journal of Radiation Oncology, Biology, Physics.* <https://doi.org/10.1016/j.ijrobp.2019.06.658>
11. Bennett C (2019) Treatment Delays & Worse Outcomes for Triple-Negative Breast Cancer. *Oncology Times.* <https://doi.org/10.1097/01.cot.0000553544.99499.81>
12. Cullinane C, Shrestha A, Maksoud AA, et al (2021) AB002. SOH21AS038. Optimal timing of surgery following breast cancer neoadjuvant chemotherapy. <https://doi.org/10.21037/MAP-21-AB002>
13. Su Y, Zheng X, Zhong O (2021) The Relationship between Time to Surgery (TTS) and Survival in Breast Cancer. *Iranian Journal of Public Health.* <https://doi.org/10.18502/ijph.v50i9.7048>
14. Bek S, Sultana R, Du S, Tan QT (2024) Time to surgery after completion of neoadjuvant chemotherapy does not negatively impact recurrence and survival outcomes in breast cancer patients. *World Journal of Surgery.* <https://doi.org/10.1002/wjs.12258>

15. Bek Ş, Xuan SDD, Sultana R, Tan Q (2022) Time to surgery after completion of neoadjuvant chemotherapy does not negatively impact recurrence and survival outcomes in breast cancer patients. *European Journal of Cancer*. [https://doi.org/10.1016/s0959-8049\(22\)01419-8](https://doi.org/10.1016/s0959-8049(22)01419-8)
16. Al-Masri M, Aljalabneh B, Al-Najjar H, Al-Shamaileh T (2021) Effect of time to breast cancer surgery after neoadjuvant chemotherapy on survival outcomes. *Breast Cancer Research and Treatment*. <https://doi.org/10.1007/s10549-020-06090-7>
17. Suleman K, Almalik O, Haque E, et al (2020) Does the Timing of Surgery after Neoadjuvant Therapy in Breast Cancer Patients Affect the Outcome? *Oncology*. <https://doi.org/10.1159/000504964>
18. Pedamallu DrBS, Hassanally D, Kasem A, et al (2021) Optimal time to surgery following neoadjuvant chemotherapy and its effect on the survival of patients with breast cancer. *World Academy of Sciences Journal*. <https://doi.org/10.3892/wasj.2021.140>
19. Piacentini F, Filieri M, Grizzi G, et al (2015) A06Impact of time to surgery after neoadjuvant chemotherapy in patients with operable breast cancer. *Annals of Oncology*. <https://doi.org/10.1093/annonc/mdv336.06>
20. Long M, Li C, Mao K, et al (2024) Effect of Interval Between Neoadjuvant Chemotherapy and Surgery on Oncological Outcomes in Poor Responders With Locally Advanced Breast Cancer. *Journal of Breast Cancer*. <https://doi.org/10.4048/jbc.2024.0084>
21. Lai V, Hajjaj O, Chia S, Simmons C (2019) Abstract P5-13-04: Needle-to-knife wait time and impact on pCR in patients undergoing neoadjuvant chemotherapy for breast cancer. *Poster Session Abstracts*. <https://doi.org/10.1158/1538-7445.SABCS18-P5-13-04>
22. Loibl S, Werutsky G, Nekljudova V, et al (2017) Impact in delay of starting chemotherapy and surgery on pCR/survival in breast cancer (BC)-pooled analysis of individual patient data from six prospectively randomized neoadjuvant trials. *Senologie - Zeitschrift für Mammadiagnostik und -therapie*. <https://doi.org/10.1055/S-0038-1651757>
23. Luz FAC da, Marinho E, Nascimento CP, et al (2022) The effect of delayed treatment in breast cancer patients: How much is too late? An experience of a single-center study effect of surgery delay in survival. *Surgical oncology*. <https://doi.org/10.1016/j.suronc.2022.101854>

24. Gao W, Wang J, Yin S, et al (2022) An appropriate treatment interval does not affect the prognosis of patients with breast Cancer. *Holistic Integrative Oncology*. <https://doi.org/10.1007/s44178-022-00010-z>
25. Nakamura R, Yamamoto N, Miyaki T (2018) Impact on disease-free survival (DFS) of the surgical waiting time (SWT) for patients (Pts) with early breast cancer (BC). *Annals of Oncology*. <https://doi.org/10.1093/ANNONC/MDY270.249>
26. Jong-Uk L, Son B, Lee S, et al (2016) Effects of Less than 60 Days Delay in Surgery on Tumor Progression and Survival Outcomes in Invasive Breast Cancer Patients. <https://doi.org/10.14449/JBD.2016.4.2.100>
27. Dai Q, Liu G, Zhang Z, et al (2025) Exploring the impact of biopsy techniques and surgical waiting time on early breast cancer prognosis: a real-world comparative study. *The Lancet Regional Health - Western Pacific*. <https://doi.org/10.1016/j.lanwpc.2024.101392>
28. Oehler C, Zimmermann MEN, Mousavi M, et al (2025) Waiting Times for Surgery and Radiotherapy Among Breast Cancer Patients in Switzerland: A Cancer Registry-Based Cross-Sectional and Longitudinal Analysis. *Radiation*. <https://doi.org/10.3390/radiation5030023>
29. Gorin SS, Heck J, Cheng B, Smith S (2006) Effect of race/ethnicity and treatment delay on breast cancer survival. *Journal of Clinical Oncology*. https://doi.org/10.1200/JCO.2006.24.18_SUPPL.6063
30. Pumpalova YS, Ayeni O, Chen W, et al (2022) The Impact of Breast Cancer Treatment Delays on Survival Among South African Women. *The Oncologist*. <https://doi.org/10.1093/oncolo/oyab054>
31. Gioia S, Brigagão L, Rocha M, et al (2024) Patient Navigation Improved Breast Cancer Outcomes Among Women in the Public System in Rio de Janeiro, Brazil. *International Journal of Health Sciences*. <https://doi.org/10.22533/at.ed.1594402424048>
32. Gioia S, Brigagão L, Rocha M, et al (2025) Abstract P3-10-11: Breast Cancer Patient Navigation Program Saves Lives: Brazilian Experience in a Real-World Setting in the Public Health System. *Clinical Cancer Research*. <https://doi.org/10.1158/1557-3265.sabcs24-p3-10-11>
33. Brito C, Portela MC, Vasconcellos MTL de (2009) Sobrevida de mulheres tratadas por câncer de mama no estado do Rio de Janeiro. *Revista De Saude Publica*. <https://doi.org/10.1590/S0034-89102009000300012>

34. Kerbrat P, Roché H, Fumoleau P, et al (2005) Does time interval between surgery and adjuvant chemotherapy initiation modify treatment efficacy in operable, breast cancer patients? French Adjuvant Study Group (FASG) results. Journal of Clinical Oncology. https://doi.org/10.1200/JCO.2005.23.16_SUPPL.660
35. Farolfi A, Scarpi E, Schirone A, et al (2014) 263PDTIME TO INITIATION OF ADJUVANT CHEMOTHERAPY IN PATIENTS WITH RAPIDLY PROLIFERATING EARLY BREAST CANCER. Annals of Oncology. <https://doi.org/10.1093/annonc/mdu327.11>
36. Pekkolay Z, Işıkdoğan A (2019) Prognostic Factors Affecting Local Recurrence and Systemic Metastasis in Early Stage Breast Cancer. Medical Science and Discovery. <https://doi.org/10.17546/MSD.586588>
37. Chang HR, Gornbein J, Lim SY (2023) Abstract P4-07-28: Prognostic Impact of Delaying Multimodality Treatment in HER2 Positive Breast Cancer. Cancer Research. <https://doi.org/10.1158/1538-7445.sabcs22-p4-07-28>
38. Li J, Li S, Zou L (2018) Clinical analysis of chemoradiation sequence for early breast cancer patients with conserving surgery. Chinese journal of radiological medicine and protection. <https://doi.org/10.3760/CMA.J.ISSN.0254-5098.2018.08.006>
39. Prabhu R, Godette K, Carlson G, et al (2012) The impact of skin-sparing mastectomy with immediate reconstruction in patients with Stage III breast cancer treated with neoadjuvant chemotherapy and postmastectomy radiation. International Journal of Radiation Oncology, Biology, Physics. <https://doi.org/10.1016/j.ijrobp.2011.09.024>
40. Gomez-Iturriaga A, Pina L, Cambeiro M, et al (2008) Early breast cancer treated with conservative surgery, adjuvant chemotherapy, and delayed accelerated partial breast irradiation with high-dose-rate brachytherapy. Brachytherapy. <https://doi.org/10.1016/j.brachy.2008.04.006>
41. Rastogi P, Anderson S, Bear H, et al (2008) Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. Journal of Clinical Oncology. <https://doi.org/10.1200/JCO.2007.15.0235>
42. Wolmark N, Wang J, Mamounas E, et al (2001) Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. Journal of the National Cancer Institute Monographs. <https://doi.org/10.1093/OXFORDJOURNALS.JNCIMONOGRAPHS.A003469>

43. Fisher B, Bryant J, Wolmark N, et al (2023) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *Journal of Clinical Oncology*. <https://doi.org/10.1200/JCO.22.02571>
44. Hage J van der, Velde CJ van de, Julien J, et al (2001) Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *Journal of Clinical Oncology*. <https://doi.org/10.1200/JCO.2001.19.22.4224>
45. Bergsten-Nordström BWJJEJFCABBB, Asselain B, Barlow W, et al (2018) Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *The Lancet Oncology*. [https://doi.org/10.1016/S1470-2045\(17\)30777-5](https://doi.org/10.1016/S1470-2045(17)30777-5)
46. Mauri D, Pavlidis N, Ioannidis J (2005) Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *Journal of the National Cancer Institute*. <https://doi.org/10.1093/JNCI/DJI021>
47. Pathak M, Deo S, Dwivedi SN, et al (2019) Role of neoadjuvant chemotherapy in breast cancer patients. *Indian Journal of Medical and Paediatric Oncology*. https://doi.org/10.4103/ijmpo.ijmpo_21_18
48. Cleator S, Makris A, Ashley S, et al (2005) Good clinical response of breast cancers to neoadjuvant chemoendocrine therapy is associated with improved overall survival. *Annals of Oncology*. <https://doi.org/10.1093/ANNONC/MDI049>
49. Gazet J, Ford H, Gray R, et al (2001) Estrogen-receptor-directed neoadjuvant therapy for breast cancer: results of a randomised trial using formestane and methotrexate, mitozantrone and mitomycin C (MMM) chemotherapy. *Annals of Oncology*. <https://doi.org/10.1023/A:1011115107615>
50. Taucher S, Steger G, Jakesz R, et al (2008) The potential risk of neoadjuvant chemotherapy in breast cancer patients—results from a prospective randomized trial of the Austrian Breast and Colorectal Cancer Study Group (ABCSG-07). *Breast Cancer Research and Treatment*. <https://doi.org/10.1007/s10549-007-9844-9>
51. Yuan Z, Qu X, Zhang Z, Wang Y (2009) Neoadjuvant chemotherapy in patients with stages II and III breast cancer. *Chinese Medical Journal*

52. Albalawi I (2018) Primary Surgery Compared to Post Chemotherapy Surgery for Patients with Locally Advanced Breast Cancer. Journal of Cancer Therapy. <https://doi.org/10.4236/jct.2018.910064>
53. Guan S, Jian Y, Dong W, Dong L (2025) Operational Survival Deficit of Neoadjuvant Chemotherapy in Early-Stage Breast Cancer: A Target Trial Emulation and Causal Machine Learning Study. medRxiv. <https://doi.org/10.64898/2025.12.22.25342768>
54. Levasseur N, Simmons C, Gondara L, et al (2019) Comparative efficacy of neoadjuvant to adjuvant chemotherapy for the treatment of early-stage HER2 negative breast cancer: A population-based analysis. Journal of Clinical Oncology. https://doi.org/10.1200/JCO.2019.37.15_SUPPL.E12100
55. Hongjian Y, Yu X, Wang C, et al (2021) Abstract PS13-52: Preoperative systemic therapy versus upfront surgery in HER2-positive early breast cancer: A prospective nested case-control study in the real world. Poster Session Abstracts. <https://doi.org/10.1158/1538-7445.SABCS20-PS13-52>
56. Yu X, Wang C, Zheng Y, et al (2021) Preoperative Systemic Therapy Versus Upfront Surgery in HER2-Positive Breast Cancer in the Real World. Frontiers in Oncology. <https://doi.org/10.3389/fonc.2021.704842>
57. Song Y, Liu B, Lin Y, et al (2025) Abstract P3-12-03: Optimizing Treatment Sequence for Inoperable LABC: Long-Term Outcomes of Surgery First vs. Neoadjuvant Chemotherapy in a Real-World Setting. Clinical Cancer Research. <https://doi.org/10.1158/1557-3265.sabcs24-p3-12-03>
58. Shin H, Han W, Moon H, et al (2013) Breast-Conserving Surgery After Tumor Downstaging by Neoadjuvant Chemotherapy is Oncologically Safe for Stage III Breast Cancer Patients. Annals of Surgical Oncology. <https://doi.org/10.1245/s10434-013-2909-6>
59. Zhang X, Li H, Wu F-J, et al (2022) Neoadjuvant Chemotherapy Combined with Breast-Conserving Surgery in the Treatment of Triple-Negative Breast Cancer. Journal of Oncology. <https://doi.org/10.1155/2022/7847889>
60. Deo S, Bhutani M, Shukla N, et al (2003) Randomized trial comparing neo-adjuvant versus adjuvant chemotherapy in operable locally advanced breast cancer (T4b N0-2 M0). Journal of Surgical Oncology. <https://doi.org/10.1002/jso.10323>

61. Joensuu H (2003) Primary chemotherapy of breast cancer followed by perioperative chemotherapy: feasible, but are there clinical benefits? *Annals of Oncology*. <https://doi.org/10.1093/ANNONC/MDG423>
62. Hills R, Bradley C, Braybrooke J, et al (2025) Abstract LB1-01: immediate breast surgery versus deferral of surgery in women aged 70+ years with operable breast cancer: patient-level meta-analysis of the three randomised trials among 1,082 women. *Clinical Cancer Research*. <https://doi.org/10.1158/1557-3265.sabcs24-lb1-01>
63. Roberts S, Rojas A, DiRaimo G, et al (2021) Defer surgery in operable breast cancer: how long is too long? *Breast Cancer*. <https://doi.org/10.1007/s12282-021-01302-4>
64. Soran A, Doğan L, Işık A, et al (2021) The Effect of Primary Surgery in Patients with De Novo Stage IV Breast Cancer with Bone Metastasis Only (Protocol BOMET MF 14-01): A Multi-Center, Prospective Registry Study. *Annals of Surgical Oncology*. <https://doi.org/10.1245/s10434-021-09621-8>
65. Shien T, Hara F, Aogi K, et al (2025) Primary tumour resection plus systemic therapy versus systemic therapy alone in metastatic breast cancer (JCOG1017, PRIM-BC): a randomised clinical trial. *British Journal of Cancer*. <https://doi.org/10.1038/s41416-025-03097-z>
66. Abdelhamid M, Alkilany MM, Gertallah LM, Mawla WA (2020) Could local curative breast surgery improve survival in women with oligometastatic breast cancer? *The Egyptian Journal of Surgery*. https://doi.org/10.4103/ejs.ejs_187_19
67. Petrovsky A, Amosova V, Trofimova O, Frolova M (2022) Abstract P3-20-09: Surgery vs radiation therapy as the first stage treatment in patients with locally advanced breast cancer with incomplete clinical response. *Cancer Research*. <https://doi.org/10.1158/1538-7445.sabcs21-p3-20-09>
68. Amosova V, Frolova M, Petrovsky A, et al (2022) Analysis of the Predictors of Breast Cancer Patients with Skin Edema and Incomplete Response to Neoadjuvant Treatment. *Journal of oncology: diagnostic radiology and radiotherapy*. <https://doi.org/10.37174/2587-7593-2022-5-2-64-75>
69. Sainsbury R, Perren T, Croft, et al (2005) Does timing of breast cancer surgery in relation to the menstrual cycle phase affect prognosis? The Yorkshire Breast Cancer Group Intervention, Timing and Survival Study. https://doi.org/10.1200/JCO.2005.23.16_SUPPL.536

70. Sainsbury R, Perren T, Brown SR, et al (2005) Timing of breast cancer surgery in relation to the menstrual cycle phase - no effect on 3-year prognosis. The Yorkshire Breast Cancer Group Intervention, Timing and Survival Study. *Cancer Research*
71. Badwe R, Hawaldar R, Parmar V, et al (2009) Single Injection Depot Progesterone Prior to Surgery and Survival in Women with Operable Breast Cancer: A Randomized Controlled Trial. *Cancer Research*. <https://doi.org/10.1158/0008-5472.SABCS-09-72>
72. Gosset M, Hamy A, Mallon P, et al (2016) Prognostic Impact of Time to Ipsilateral Breast Tumor Recurrence after Breast Conserving Surgery. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0159888>
73. Shenouda MN, Sadek BT, Keruakous AR, et al (2013) Clinical Outcome of Isolate Local-Regional Recurrence in Breast Cancer Patients According to Their Primary Local Treatment. <https://doi.org/10.1016/j.ijrobp.2013.06.590>
74. Matuschek C, Fehm T, Hufnagel M, et al (2025) Abstract P3-10-22: Preoperative radiotherapy versus postoperative radiotherapy after neoadjuvant chemotherapy in high-risk breast cancer: a prospective, randomized, international multicentre Phase III trial—NeoRad. *Clinical Cancer Research*. <https://doi.org/10.1158/1557-3265.sabcs24-p3-10-22>
75. Civil Y, Vasmel J, Charaghvandi R, et al (2024) Preoperative magnetic resonance guided single-dose partial breast irradiation: five-year results of the prospective single-arm ABLATIVE trial. *International Journal of Radiation Oncology, Biology, Physics*. <https://doi.org/10.1016/j.ijrobp.2024.07.2326>
76. Chanenchuk T, Thomas S, Bruele AMBV den, et al (2025) Abstract P2-12-01: Survival Outcomes after Pathologic Complete Response with Neoadjuvant Endocrine Therapy vs. Neoadjuvant Chemotherapy. *Clinical Cancer Research*. <https://doi.org/10.1158/1557-3265.sabcs24-p2-12-01>
77. Han B, Li X, Zhao H, et al (2019) Survival analysis of pregnancy-associated breast cancer: multiparous women might have better outcomes. <https://doi.org/10.21203/rs.2.16735/v1>
78. Yuan F, Abdelhakeem A, Blevins S, et al (2022) Preliminary outcomes for non-metastatic breast cancer before and during the coronavirus disease 2019 pandemic at community cancer centers. *Journal of Clinical Oncology*. https://doi.org/10.1200/jco.2022.40.16_suppl.e18634

79. Sowden M, Grube B, Killilea B, Lannin D (2012) Surgical Intervention Following Neoadjuvant Chemotherapy in Breast Cancer. <https://doi.org/10.5772/24519>
80. Fisher B, Jeong J-H, Anderson S, et al (2002) Twenty-five-year follow-up of a randomized trial comparing radical mastectomy, total mastectomy, and total mastectomy followed by irradiation. New England Journal of Medicine. <https://doi.org/10.1056/NEJMOA020128>



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