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Influence of surgical timing post-neoadjuvant chemotherapy on survival outcomes in breast cancer patients: A comprehensive systematic review and meta-analysis

Dandan Wang [1], Xiaowei Sun [1], Wen Sun [1], Ruoxi Wang, Hong Pan [*], Wenbin Zhou [**]

Department of Breast Centre, Department of General Surgery, The First Affiliated Hospital with Nanjing Medical University, 300 Guangzhou Road, 210029, Nanjing, China

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ABSTRACT

Background: Increasing evidence supports the use of neoadjuvant chemotherapy (NAC) prior to surgery for breast cancer. However, the optimal timing between NAC and surgery had yet to be fully elucidated. This meta-analysis aims to assess how the optimal interval time (OTT) between NAC and surgery affects outcomes in breast cancer, providing additional evidence for clinical practice and future research.

Methods: PubMed, Web of Science and Cochrane Library databases in English were systematically searched for this systematic review. All included studies investigated the variations in surgical timing following NAC and their effects on breast cancer outcomes. The endpoints included the rate of pathological complete response (pCR), overall survival (OS), recurrence free survival (RFS), and disease-free survival (DFS). This study has been registered with PROSPERQ.

Results: Eleven eligible studies were identified, encompassing a total of 10,834 cases, all of which received surgery post-NAC. All studies were retrospective in nature. Ultimately, compared to intervals within 4 weeks, patients who underwent surgery>8weeks post-NAC demonstrated a statistically significant worse OS (HR = 1.21, 95 % *CI*: 1.06–1.40, $p = 0.333$ for heterogeneity). No significant difference of OS was observed between patients with OTT of 4–8 weeks vs < 4 weeks. Notably, patients with an OTT of 4–8 weeks (HR = 1.18, 95 % *CI*: 1.10–1.26, $I^2 = 0.0$ %, p = 0.931 for heterogeneity) and>8weeks (HR = 1.21, 95 % *CI*: 1.13–1.29, $I^2 = 36.2$ %, $p = 0.195$ for heterogeneity) exhibited decreasing RFS, compared with those with OTTs of<4 weeks. DFS and pCR rates were similar in>8weeks vs < 4 weeks and 4–8weeks vs < 4 weeks.

Conclusion: Our systematic review and meta-analysis indicate that the optimal interval following NAC for breast cancer patients might be within four weeks, as delays exceeding eight weeks could be associated with poorer clinical outcomes. However, additional research is necessary to validate these preliminary findings.

1. Introduction

In 2023, the global landscape of breast cancer is marked by a staggering 310,720 new cases, accompanied by 42,250 fatalities. This malignancy continues to be the most prevalent form of cancer and the second most frequent cause of cancer-related mortality among women across the globe [1]. At present, neoadjuvant chemotherapy (NAC) has emerged as a pivotal strategy in the treatment for breast cancer to improve patient survival. NAC has the potential to transform inoperable, locally advanced breast cancer into operable conditions, reduce tumor size for breast and axillary conservation, and offer insights into drug responsiveness. Previous research has confirmed that patients who receive NAC and achieve a pathologic complete response (pCR) have better overall survival (OS), particularly those with triple-negative and human epidermal growth factor receptor-2 (HER-2) positive breast cancer [2]. However, there is an ongoing debate regarding the optimal time to interval (OTT) between the conclusion of NAC and surgical intervention for breast cancer patients. Kausar Suleman et al. reported that patients who received surgery within 4–7 weeks post-NAC experienced improved OS and disease-free survival (DFS) compared to those

* Corresponding author.
** Corresponding author.
E-mail addresses: pamghong@163.com (H. Pan), zhouwenbin@njmu.edu.cn (W. Zhou).
[1] Contributing equally to this article.

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underwent surgery after more than 8 weeks [3]. Conversely, Mahmoud Al-Masri et al. observed no significant impact on survival for breast cancer patients who underwent surgery within the first 8 weeks following NAC [4].

In light of these conflicting findings, a systematic review and meta-analysis is conducted to determine the most advantageous timing for surgery following NAC. The aim is to establish an evidence-based medical consensus that can inform and guide clinical practices in the treatment of breast cancer.

2. Methods

2.1. Literature search strategy

The review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [5]. The work has been reported in line with Assessing the methodological quality of systematic reviews (AMSTAR) [6]. A systematic literature search was conducted in English from inception until September 20, 2024, by two authors independently. Researchers were identified through searches of PubMed, Web of Science and Cochrane Library databases. The search strategies employed were as follows: ((neo-adjuvant chemotherapy) OR (neo-adjuvant chemotherapy)) AND ((surgery) OR (surgical)) AND ((breast cancer) OR (breast tumor) OR (breast carcinoma)) AND ((timing) OR (time interval) OR (time-interval)).

2.2. Inclusion and exclusion criteria

All identified articles were screened based on their titles and abstracts. The inclusion criteria were as follows [1]: retrospective or prospective studies [2]; studies that investigated the difference in time to surgery after NAC and its impact on clinical outcomes (e.g., pCR; OS, recurrence free survival (RFS), and DFS) [3]; stage I-III breast cancer [4]; all data of included studies calculated hazard ration (HR) with 95 % confidence interval (*CI*).

The exclusion criteria were as follows [1]: duplicated studies or data [2]; lacking relevant information [3]; published data that could not be accurately extracted or calculated [4]; articles not published in English [5]; case reports, review articles, or editorials.

2.3. Data extraction

We registered this study with The Preferred Reporting Items For Systematic Review and Meta-Analysis Protocols (PRISMA-P) under the identifier [7]. Data extraction was conducted independently by two authors. Any disagreements between them will be resolved through discussing with a third author. Data was recorded into a excel sheet and two authors verified its accuracy.

The following information was gathered from each study: first author's name, year of publication, country, follow-up period, study design, sample size, time to surgery after NAC, outcomes (including pCR, OS, RFS, DFS). Time to surgery means that the days from completion of NAC to the date who received surgery. pCR is defined as complete eradication of invasive cancer in the breast and axillary lymph nodes [8].

2.4. Literature quality assessment

Newcastle-Ottawa Scale(NOS) Quality Assessment Form [9] was used to evaluate the quality of studies, which was performed by two authors. If they have different opinions, the results will be discussed and agreed upon.

The NOS scale assesses the risk of bias by assessing the quality of cohort studies in three aspects: selection, comparability and outcome. The total score is 9 stars, of which 7–9 stars is high quality, 4–6 stars is middle quality and less than 4 stars is low quality.

2.5. Statistical analysis

Statistical analysis was performed using Stata software (version 16.0, STATA Corp., College Station, Texas, USA). It was conducted using Mantel-Haenszel model to estimate the survival outcomes (OS, DFS, and RFS), and these were expressed as HR with 95 % *CI*, and pCR was expressed as odds ratio (OR) with 95 % *CI*. I^2 tests were assessed heterogeneity. I^2>50.0 % is considered substantial heterogeneity and a random-effect model. Potential publication bias was evaluated with a funnel plot and the Egger's test. If only the total number of diagnoses was provided (e.g. pCR), it was included for analysis to maximise data-inclusion and investigated further through the meta-regression. $P < 0.05$ is confirmed statistical significance.

3. Results

3.1. Study selection and characteristics

At beginning, 1497 potentially relevant studies were identified, after excluding 76 duplicates of which 1421 were excluded after scanning titles and abstracts out of relevance. Then, a total of 27 studies were left for further assessment, of which 11 studies were included finally and all were retrospective cohort studies [3,4,10–18]. All search selection was shown in Fig. 1.

The characteristics of all included studies were shown in Table 1, including first author's name, publication year, country, follow-up period, study design, sample size, time to surgery, number of patients, NAC regimen, American Joint Committee on Cancer (AJCC) stage and clinical outcomes.

3.2. Study characteristics literature quality assessment

The 11 studies, published between 2015 and 2024, contained a total of 10,834 patients, and all of them received surgery after NAC from 1991 to 2019. These included studies had own OTT groups. The number of patients was 88 with OTT<2weeks, 14 with OTT 2–4 weeks, 4415 with OTT<4 weeks, 851 with OTT 4–6 weeks, 385 with OTT>8 weeks, 310 with OTT>6 weeks, 117 with OTT<3weeks and 91 with OTT>5 weeks.

Based on NOS assessment, eight studies was 7–9 stars (showing high

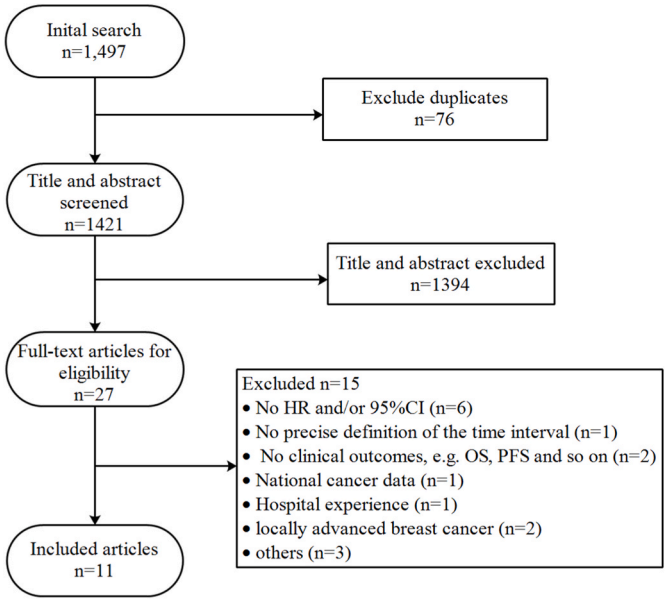

Fig. 1. PRISMA flow diagram illustrating the study selection process.

Table 1
Characteristics of included studies in this systematic review.

First author (Ref)	Year	Country	Follow-up period	Study design	Sample size	Time to surgery	Number	NAC Regimen	AJCC Stage	Clinical outcomes
An, Doyeon	2022	Korea	2012–2019	cohort	266	>8week 2–4weeks 4–8weeks 0–2week	20 14 444 88	unknown	I,II,III	OS
Mahmoud Al-Masri	2021	Jordan	2006–2014	retrospective analysis	468	<4weeks 4–8weeks >8weeks	142 284 42	unknown	I,II,III	OS, DFS, pCR
Thomas L. Sutton	2020	USA	2011–2017	cohort	463	≤4weeks 4–6weeks >6weeks	220 175 68	ACT/Targeted therapy/ TCy/other	I,II,III	DFS, RFS, pCR
Kausar Suleman	2019	Egypt	2004–2014	retrospective analysis	611	<4weeks 4–7weeks >8weeks	94 424 93	Anthracyclines/ Anthracyclines + trastuzumab/	II/III/ Unstageable	OS, DFS, pCR
Valerie Lai	2020	Canada	2012–2018	retrospective analysis	343	<4weeks 4–8weeks >8weeks	78 233 32	unknown	I/II/III	OS, DFS, pCR
Cletus Arciero	2019	USA	1998–2010	retrospective analysis	353	≤4weeks 4–6weeks 6–8weeks >8weeks	98 152 55 44	unknown	I/II/III	OS, DFS
C. Omarini	2016	Italy	1991–2015	retrospective analysis	319	>3week ≤3weeks	258 61	Anthracyclines/Taxane/ Anthracyclines + Taxane/ others	I/II/III	OS, RFS, pCR
Rachel A.	2015	USA	1995–2007	retrospective analysis	1101	0–4weeks 4–6weeks >6weeks 0–8weeks >8weeks	335 524 242 1031 70	unknown	I/II/III	OS, RFS
Sibylle Loib	2017	Germany	unknown	cohort	6420	≤4weeks >4weeks	3448 2972	anthracycline-taxane based	unknown	OS, DFS, pCR
Katherine Garcia,	2024	Ecuador	2009–2011	retrospective analysis	195	<8weeks >8weeks	111 84	unknown	II/III	OS, pCR
Piacentini, F.	2015	Italy	1991–2013	retrospective analysis	295	<3weeks 3–5weeks >5weeks	56 148 91	anthracycline-taxane based	I/II/III	OS, DFS

NAC: neoadjuvant chemotherapy; AJCC: American Joint Committee on Cancer; ACT: doxorubicin, carboplatin, paclitaxel; TCy: paclitaxel and cyclophosphamide; OS: overall survival; RFS: recurrence free survival; DFS: disease-free survival; pCR: pathologic complete response.

quality) and three studies was 6 stars (showing middle quality). Importantly, there was no low-quality research (Table 2). In addition, there was no evidence of publication bias in the shape of funnel plots, and indicated that the dots were nearly symmetrically distributed within the pseudo 95 % confidence limits (Supplementary Fig. 1). The Egger's test identified no evidence of publication bias ($p > 0.05$).

3.3. Pathologic complete response (pCR)

Data on pCR were published in five studies. The analysis revealed that there is no significant difference in pCR rates between patients who undergo surgery within 4 weeks after completing NAC and those who have surgery after more than 4 weeks (odds ratio (OR) = 0.96, 95 % *CI* 0.80–1.17, $I^2 = 0.0$ %, $p = 0.647$ for heterogeneity, Fig. 2). For the analysis of pCR rate, we included a total of 5 studies. Using meta-regression analysis, we found that the age (>50 years old),

Table 2
Newcastle-Ottawa scale for retrospective and cohort studies.

Study	Selection				Comparability	Outcome			Total
	Representativeness of the Exposed Cohort	Selection of the Non-Exposed Cohort	Ascertainment of Exposure	Demonstration That Outcome of Interest was Not Present at Start of Study	Comparability of Cohorts Based on the Design or Analysis	Assessment of Outcome	Was Follow-up Long Enough for Outcomes to Occur	Adequacy of Follow up of Cohorts	Scores
Doyeon2022	1	1	1	0	2	1	0	1	7
Mahmoud2021	1	1	1	0	1	1	1	1	7
Thomas2020	1	1	1	0	1	1	1	1	7
Kausar 2019	1	1	1	0	1	1	0	1	6
Valerie 2019	1	1	1	0	2	1	1	1	8
Cletus2019	1	1	1	0	1	1	0	1	6
Omarini2016	1	1	1	0	2	1	1	1	8
Rachel 2015	1	1	1	0	1	1	2	1	8
Sibylle 2017	1	1	1	0	1	1	0	1	6
Katherine 2024	1	1	1	0	2	1	1	1	8
Piacentini 2015	1	1	1	0	1	1	1	1	7

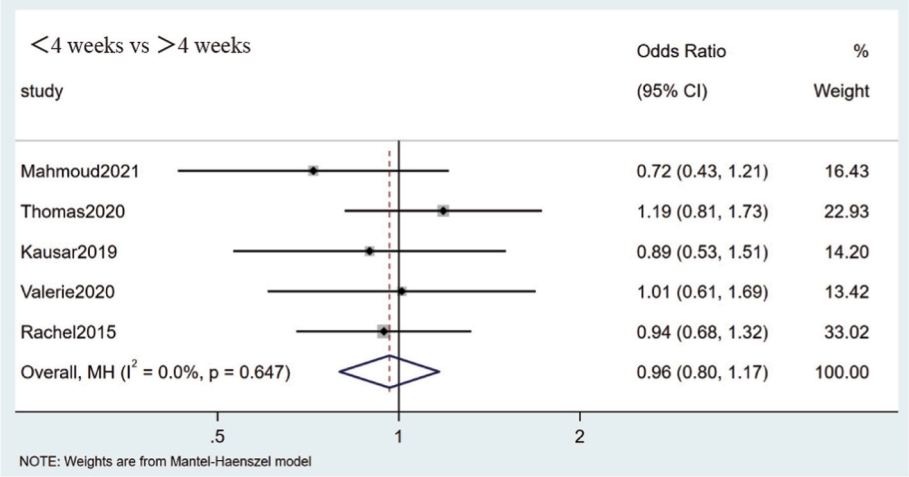

Fig. 2. Pathologic complete response (pCR) between<4 weeks vs > 4weeks.

pathological type, clinical stage, and molecular subtype (hormone receptor + rate, HER-2+ rate, triple negative breast cancer rate) of the included population in every studies were not found to be associated with the above conclusion (Supplementary Table 1).

3.4. Overall survival (OS)

OS data were reported across ten studies. When examining different OTT groups, no significant associations were observed between the 4–8 weeks interval and intervals less than 4 weeks (HR 1.14, 95 % *CI*: 0.98–1.33, $I^2 = 0.00$ %, $p = 0.997$ for heterogeneity, Fig. 3A). However, compared to patients with an OTT of less than 4 weeks, those who had surgery more than 8 weeks post-NAC exhibited poorer survival outcomes (HR 1.64, 95 % *CI*: 1.18–2.29, $I^2 = 26.0$ %, $p = 0.256$ for heterogeneity, Fig. 3B). Overall, patients who undergo surgery within 4 weeks after completing NAC had a better OS than less than 4 weeks (HR 1.21, 95 % *CI*: 1.06–1.40, $I^2 = 12.5$ %, $p = 0.333$ for heterogeneity, Fig. 3B). The consistent trend was observed across other studies not included in this analysis because of the inability to combine different OTT groups or absence of a cut-off value. The comprehensive analysis indicated that a prolonged time to surgery following NAC was associated with worse OS.

3.5. Disease free survival (DFS)

DFS was documented in five studies. The meta-analysis of these studies suggests no significant variation in DFS in the 4–8 week interval compared to intervals less than 4 weeks (HR = 1.13, 95 % *CI*: 0.77–1.66, $I^2 = 0.0$ %, $p = 0.401$ for heterogeneity, Fig. 4A) and in intervals greater than 8 weeks compared to less than 4 weeks (HR = 1.56, 95 % *CI*:

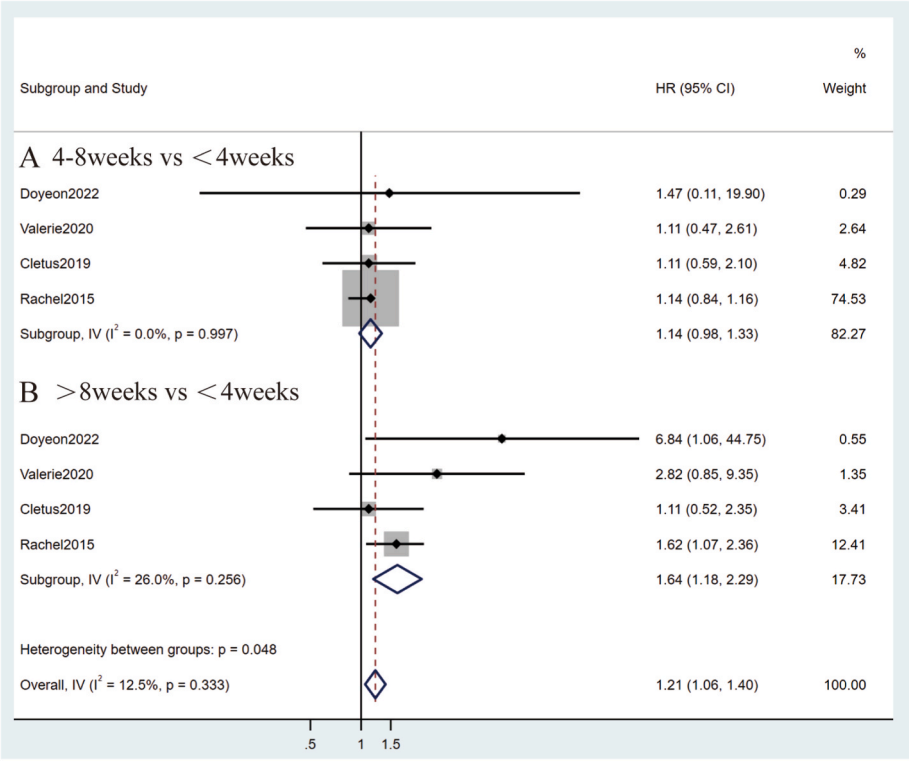

Fig. 3. Overall survival (OS). (A) 4–8weeks vs < 4 weeks. (A)>8weeks vs < 4 weeks.

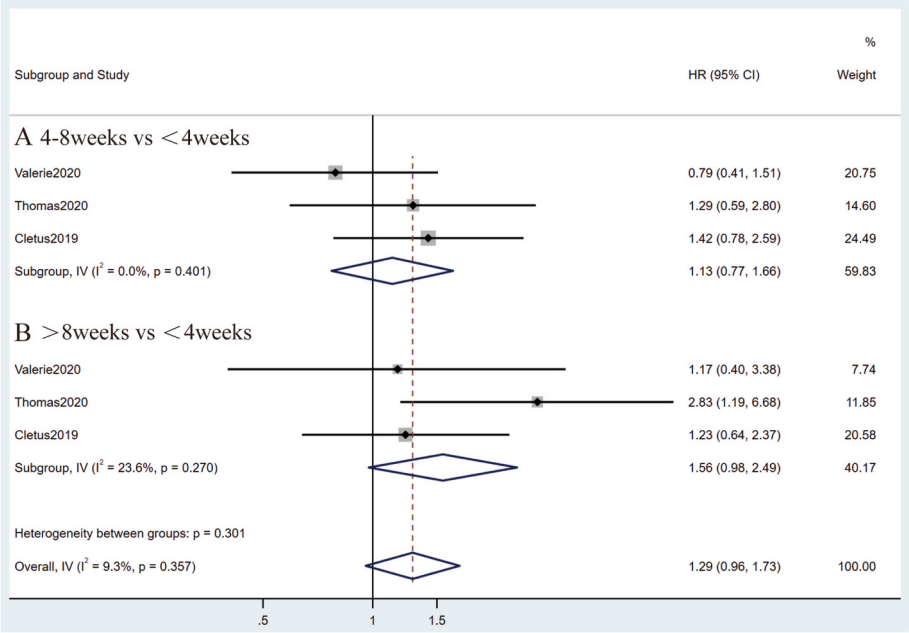

Fig. 4. Disease free survival (DFS). (A) 4–8weeks vs < 4 weeks. (A)>8weeks vs < 4 weeks.

0.98–2.49, $I^2 = 23.6$ %, $p = 0.357$ for heterogeneity, Fig. 4B).

3.6. Recurrence free survival (RFS)

Two studies compared RFS among patients who had surgery within 4–8 weeks versus less than 4 weeks and more than 8 weeks versus less than 4 weeks post-NAC. Patients who underwent surgery within 4 weeks post-NAC demonstrated significantly improved RFS compared to those who had surgery between 4 and 8 weeks (HR 1.18, 95 % *CI*: 1.10–1.26, $I^2 = 0.0$ %, $p = 0.931$ for heterogeneity, Fig. 5A). Similarly, RFS was higher for patients who had surgery within 4 weeks compared to those who had surgery more than 8 weeks post-NAC (HR 1.21, 95 % *CI*: 1.13–1.29, $I^2 = 36.2$ %, $p = 0.195$ for heterogeneity, Fig. 5B). Moreover, this beneficial effect was consistently observed across other studies that were not included in the analysis. The comprehensive analysis of the results indicated that patients reduced their OTT following NAC achieved the greatest benefit in terms of RFS.

4. Discussion

To date, the optimal interval time (OTT) between NAC and surgery for breast cancer has not been definitively established. This meta-analysis is organized to evaluated whether there is an influence of OTT on outcomes for breast cancer patients following NAC.

The findings from this meta-analysis suggest that patients with an OTT less than 4 weeks had improved OS, whereas those with an interval

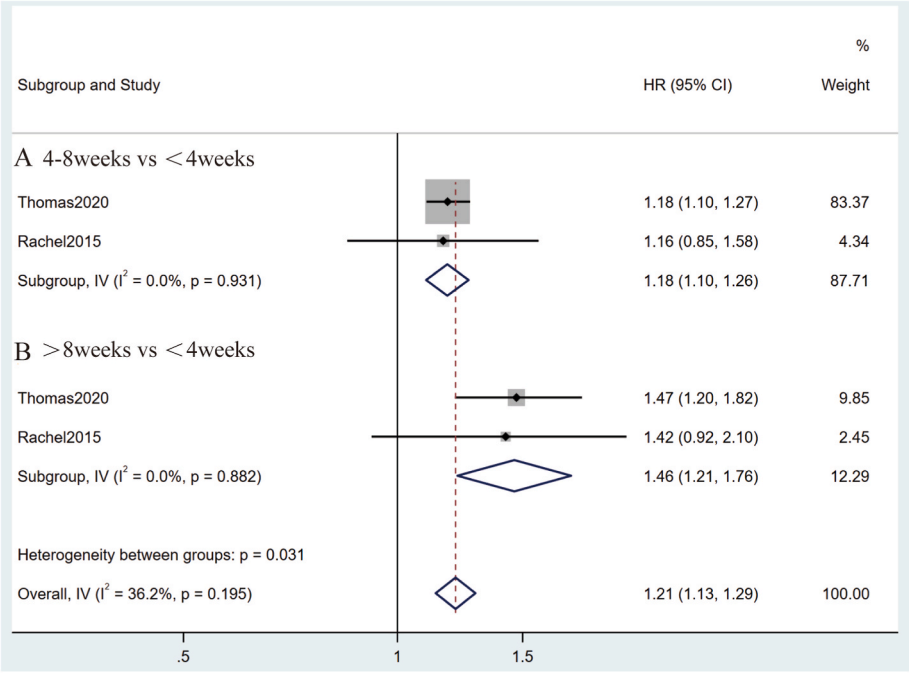

Fig. 5. Recurrence free survival (RFS). (A) 4–8weeks vs < 4 weeks. (A)>8weeks vs < 4 weeks.

greater than 8 weeks tend to have worse OS. Furthermore, when compared to patients with OTTs of 4–6 weeks and>8 weeks, patients with an OTT of less than 4 weeks achieve better RFS. This aligns with observations in gastric cancer, where shorter intervals have been linked to superior outcomes [19]. Angeliki et al. noted that performing surgery shortly after NAC in patients with high-grade serous ovarian carcinoma may correlate with a more favorable prognosis [20]. We believe that early initiation of surgery following NAC could potentially prevent the distant dissemination of residual tumor cells and decrease the tumor burden. As such, the time of surgery post-NAC merits careful consideration, with particular attention to the adverse effects of chemotherapy and the risk of residual tumor recurrence.

The delay of the optimal time between the initiation of NAC and breast surgery can be attributed to several detailed reasons [1]: Tumor Response Assessment: After NAC, oncologists may require time to conduct imaging studies (like MRI or CT scans) to assess the tumor's response to treatment. A longer interval allows for comprehensive evaluation before proceeding to surgery [2]. Patient Health Factors: Patients may have underlying health issues such as infections, poor nutritional status, or other medical conditions that need to be stabilized before surgery, which result in a longer wait [3]. Surgical Considerations: The surgical team may be operating under a backlog, or specific surgical techniques may require scheduling flexibility. Additionally, discussions regarding the type of surgery (lumpectomy vs. mastectomy) may take time [4]. Patient Decision-making and Preferences: Patients sometimes take time to make informed decisions regarding their surgical options, which can lead to a delayed surgery date [5]. Coordination of Care: Effective communication and coordination among various healthcare providers involved in the patient's care can sometimes lead to delays, especially if multiple specialists are consulted [6]. Adverse Events: Patients may experience adverse effects from NAC, such as hematologic toxicity (low blood counts), which may not allow for safe surgery until recovery [7]. Clinical Trials: If the patient is enrolled in a clinical trial, protocol stipulations concerning timing and additional treatments may extend the interval before surgery. By understanding these factors, healthcare providers can create tailored strategies to optimize timing for surgery while prioritizing patient safety and treatment efficacy. To ensure timely surgical treatment following NAC for breast cancer, it is essential to implement a multidisciplinary team (MDT) approach throughout the systemic therapy process. Effective coordination among various healthcare professionals is crucial. Specialist nurses play a pivotal role in monitoring patients for complications during chemotherapy, while oncologists address any related issues promptly, facilitating quicker recovery for patients during NAC. Additionally, increase capacity within home care, community care, and specialty care systems to ensure timely coordination of tests and appointments during chemotherapy. This will help accelerate decision-making processes and reduce waiting times for patients. Optimize processes when designing clinical trials for neoadjuvant chemotherapy. Moreover, it is essential to thoroughly consider the time intervals optimize processes when designing clinical trials for NAC.

Kausar et al. reported that the trend of DFS was poorer in patients with ER+/HER-2+ tumors when surgery was delayed for 8 weeks or longer [3]. However, our analysis did not demonstrate significant improvements in DFS across different time intervals. We also refrain from conducting subgroup analyses based on molecular subtype due to a lack of available research. In the future, it is crucial to fully account for subgroups based on molecular subtypes, clinicopathological stages, histological grades, and distinct chemotherapy regimens when designing relevant clinical trials related to OTT following NAC. This comprehensive consideration will enable us to gain a deeper understanding of the outcomes of OTT across different patient populations.

Moreover, achieving a pCR is another treatment objective of NAC for breast cancer, as it has been shown to have a beneficial effect on OS [2,21]. In this study, we observe no significant association between pCR and OTT. As is well known, breast cancer can be classified into four molecular subtypes: hormone receptor (HR) positive/human epidermal growth factor receptor-2 (HER-2) negative luminal, HR positive/HER-2 positive, HR negative/HER-2 positive and triple negative breast cancer (TNBC). Recent studies had shown that target or immune therapies can improve pCR rates in breast cancer [21,22]. However, some included studies did not specify the regimen of target or immune therapies, which might cause bias in the reported pCR rates. These findings underscore the necessity for further research to determine the optimal timing for surgery following NAC in this patient population.

This meta-analysis does have some limitations. Firstly, all included studies are retrospective and do not encompass large sample cohorts. This limitation could potentially skew the results. Additionally, our analysis dose not extend to direct comparisons across various subgroups. We have not delved into the clinical characteristics such as tumor stage, molecular type, and grade in relation to the efficacy of breast cancer outcomes. The original research studies that we reviewed did not perform these types of analyses, possibly due to constraints in sample size, methodology, or the specific focus of those studies. Furthermore, several pooled analyses include only two or three studies, which are insufficient for conducting meta-regression analysis. This limitation restricts the ability to detect true effects and increases the potential for statistical errors, and we will seek further research to solidify conclusions. Lastly, our analysis is restricted to studies published in English, which could lead to publications bias. Indeed, conducting rigorous prospective clinical trials is a critical step towards enhancing the credibility and authenticity of research. Such trials offer compelling causal evidence and allow for more effective control over confounding factors. Moving forward, we are committed to implementing this approach in our clinicals.

In summary, our meta-analysis evaluates the relationship between the time to surgery following NAC and the clinical outcomes of breast cancer patients. The results imply that delays in the surgery for breast cancer who have undergone NAC may adversely affect outcome. This meta-analysis robustly suggests that it may be beneficial for breast cancer patients to undergo surgery within four weeks after completing NAC. Looking ahead, we advocate for the initiation of extensive cohort studies with large sample sizes.

CRediT authorship contribution statement

Dandan Wang: Data curation, Writing – original draft. **Xiaowei Sun:** Formal analysis, Software. **Wen Sun:** Conceptualization, Investigation, Methodology, Project administration, Resources. **Ruoxi Wang:** Data curation, Investigation, Methodology. **Hong Pan:** Conceptualization, Funding acquisition, Writing – review & editing. **Wenbin Zhou:** Conceptualization, Funding acquisition, Validation.

Declaration of generative AI in scientific writing

none.

Declaration of competing interest

none.

Acknowledgments

Authorship: Wenbin Zhou designed the study; Dan-dan Wang collected data and wrote the article; Xiaowen Sun and Wen Sun mainly performed analysis and interpretation of data. Ruoxi Wang reconfirmed the data. Hong Pan drafted the article or revising it critically for important intellectual content. Wenbin Zhou and Hong Pan finally approved the version to be submitted.

Assistance with the study: none.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2025.104454.

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