TYPE Systematic Review
PUBLISHED 23 November 2023
DOI 10.3389/fonc.2023.1288744

Curative effect of immediate reconstruction after neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis

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Background: The safety of mastectomy (MT) with immediate reconstruction (IR) in breast cancer patients who have completed neoadjuvant chemotherapy (NAC) is not apparent. This meta-analysis aims to systematically evaluate the differences in surgical complications and postoperative survival rates between MT with IR (MT+IR) and MT alone in post-NAC breast cancer patients.

Methods: The PubMed, Embase, Cochrane Library, WanFang Data, and CNKI databases were systematically searched, and cohort studies of post-NAC breast cancer patients with MT+IR or MT surgery were collected from databases inception to May 25, 2023. Two researchers independently executed literature screening, data extraction, and bias risk assessment, and meta-analysis was performed using Revman 5.3 software.

Results: A total of 12 studies involving 7378 cases who have accepted NAC were collected for this study. The results showed that compared with the MT group, the relative risk of surgical complications in the MT+IR group was increased by 44%, with no statistical significant [RR=1.44, 95% CI (0.99, 2.09), P=0.06]. While among study subgroups with a median follow-up of less than one year, more surgical complications occurred in the MT+IR group by 23% [RR=1.23, 95% CI (1.00, 1.52), P=0.05]. There was no significant differences in overall survival, disease-free survival, local relapse-free survival, and distant metastasis-free survival between the two groups.

Conclusions: Compared with the MT, MT+IR does not affect the postoperative survival rate in post-NAC breast cancer patients, accompanied by a mild increase in short-term surgical complications, but no significant difference in long-term complications.

Systematic review registration: https://www.crd.york.ac.uk/prospero, identifier CRD42023421150.

KEYWORDS

breast cancer, immediate reconstruction, mastectomy, neoadjuvant chemotherapy, meta-analysis

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RECEIVED 04 September 2023
ACCEPTED 08 November 2023
PUBLISHED 23 November 2023

CITATION
Li G, Ji H, Li J, Xiao L and Chen Z (2023) Curative effect of immediate reconstruction after neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis. *Front. Oncol.* 13:1288744. doi: 10.3389/fonc.2023.1288744

1 Introduction

Breast cancer (BC) is the most popular carcinoma among females worldwide (1). Most of these patients need a mastectomy (MT). Whereas patients who experienced MT, which often requires the removal of the entire breast, may experience long-term negative impacts on their physical and mental health, and their treatment compliance may be reduced (2, 3). MT with immediate reconstruction (MT+IR) has been shown to significantly improve a patient's quality of life by recent researches (4–6). Therefore, MT+IR has become a popular alternative to maintain the breast's appearance and improve patients' quality of life (7).

Neoadjuvant chemotherapy (NAC) is a critical element of systematic breast cancer treatment and is associated with improved survival compared to adjuvant chemotherapy in some breast cancer patients (8, 9). In early breast cancer, NAC can make breast-conserving surgery (BCS) more feasible than the same chemotherapy given after surgery (10, 11). The increasing use of NAC has led to a rapid worldwide increase in the rate of BCS over the past few decades (12–15). However, there is a certain proportion of patients still not suitable for BCS (12, 13, 16, 17). Some patients eligible for BCS post-NAC still chose MT and MT plus reconstructive surgery (18–21). In such cases, MT+IR presents an attractive alternative to BCS as it can help avoid psychosocial morbidity and suboptimal cosmetic outcomes (5, 22). In recent years, the proportion of reconstruction has increased yearly, accompanied by the incidence of complications decreasing (23–25). Due to the lack of high-quality evidence, the safety of IR in post-NAC is still controversial. In Japan, there is a considerable disparity in doctors' opinion of the safety of IR, with nearly one-quarter of doctors believing that IR could adversely impact patient prognosis (26).

Currently, there are no available RCT researches on the effect of MT+IR following NAC. Previous studies have primarily focused on comparing the outcomes of MT+IR after NAC and adjuvant therapy after MT+IR (27–29). However, these studies do not provide sufficient information for breast cancer patients who have completed NAC and are preparing for operation.

It is necessary to conduct a meta-analysis of the differences in surgical complications and postoperative survival between MT+IR and MT alone after NAC. We aimed to provide more reference data for breast cancer patients who are not candidates for BCS after NAC.

Abbreviations: BC, Breast cancer; MT, mastectomy; MT+IR, MT with immediate reconstruction; NAC, Neoadjuvant chemotherapy; BCS, breast-conserving surgery; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; OS, overall survival; DFS, disease-free survival; LRFS, local recurrence-free survival; DMFS, distant metastasis-free survival; NOS, Newcastle Ottawa Scale; RR, relative risk; HR, hazard ratio; DR, delayed reconstruction; SSM, skin-sparing mastectomy; NSM, nipple-sparing mastectomy; TNM, Tumor Node Metastasis.

2 Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards (30), and the protocol was registered in the PROSPERO database (CRD42023421150).

2.1 Literature search

Two independent researchers searched PubMed, Embase, the Cochrane Library, the Wanfang database, and the CNKI database for studies on breast cancer patients who underwent MT combined with or without IR surgery after NAC. The retrieval time limit was from the establishment of the database to May 25, 2023. The index words used were as follows: "Mammaplasty", "Breast Implantation" and "Neoadjuvant Therapy". An approach involving the combination of subject words and free words was adopted in the retrieval (Supplementary Table 1).

2.2 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) cohort studies or randomized control studies; (2) patients with breast cancer who underwent breast surgery after NAC; (3) comparison of the MT+IR with the MT; and (4) report of relevant outcomes, including overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS), distant metastasis-free survival (DMFS), and surgical complications.

Studies were excluded if they met the following criteria: (1) literature in languages other than Chinese and English; (2) no outcome indicators mentioned above; (3) repeat studies; (4) uncontrol studies; (5) study without valid data or data that could not be extracted; and (6) abstracts, lectures, conference abstracts, and incomplete data.

2.3 Risk of bias assessment

The included studies used the Newcastle Ottawa Scale (NOS) to assess the risk of bias (31). Two independent researchers conducted the cross-check. If the NOS score was ≥6, the study's quality was considered high.

2.4 Data extraction

Two independent researchers extracted the data, such as the general information, specific intervention measures, number of cases in the MT+IR and MT groups, total number, publication time, research time, first author, and number of complications. The comparison of survival data (OS, DFS, LRFS, and DMFS) between the two groups used the hazard ratio (HR). If the HR value and 95% CI were directly reported in the literature or the survival rates of the two groups at multiple time points were reported, the ln(HR) and

SE[ln(HR)] of the OS, DFS, LRFS, and DMFS between the two groups could be calculated by using the Excel attachment calculations spreadsheet provided by Tierney et al. (32) If the survival curves of OS, DFS, LRFS, and DMFS of the two groups were reported in the literature, the survival data were extracted using Engauge Digitizer version 4.1 software and then calculated using the Excel attachment calculations spreadsheet provided by Tierney et al. (32) We finally used the ln(HR) and SE[ln(HR)] from each study for meta-analysis.

2.5 Statistical analysis

Data were analyzed by RevMan5.3 software. The relative risk (RR) was used as the effective index for count data, and HR was used as the effective index for survival data. The heterogeneity between the results of the studies was assessed using χ2 inspection analysis, with the inspection level set at α=0.10, combined with I2 to determine the heterogeneity size. The fixed effect model was used when the homogeneity of the results was not significant (I^2<50%, P≥0.05). The random effect model was used when the heterogeneity test showed that the heterogeneity of the results was statistically significant (I^2≥50%, P<0.05), and the source of heterogeneity was further analyzed. Sensitivity analysis was used to evaluate the stability of the results using the one-by-one exclusion method.

3 Results

3.1 Literature screening

Initially, we identified a total of 2040 articles from various databases, including 132 articles from the CNKI database, 425 articles from the Wanfang database, 411 articles from the PubMed database, 13 articles from the Cochrane Library, and 1059 articles from the Embase database. After screening and reviewing the title, abstract and full text, we included 12 cohort studies involving 7378 patients (33–44). The literature screening process is shown in Figure 1.

3.2 Study characteristics and risk of bias

The 12 included studies comprised 2019 patients with MT+IR and 5359 patients with MT. Bias risk assessment showed that the NOS scores of all 12 studies were ≥6, and the studies were regarded as high-quality research (Table 1).

3.3 Surgical complications

3.3.1 Meta-analysis results

A total of five studies reported surgical complications between the two groups (34–37, 39), including 989 patients in the MT+IR group and 3150 patients in the MT group. Meta-analysis using the random effect model showed no significant difference in the incidence of complications between the two groups [RR=1.44, 95% CI (0.99, 2.09), P=0.06] (Figure 2A).

3.3.2 Subgroup analysis of surgical complications

According to different median follow-up times, subgroup analysis was conducted on surgical complications. Among study subgroups with a median follow-up of less than one year, more surgical complications occurred in the MT+IR group [RR=1.23, 95% CI (1.00, 1.52), P=0.05]. However, in the study subgroup with a longer median follow-up, there was no significant difference in the incidence of surgical complications between the two groups [RR=1.98, 95% CI (0.80, 4.94), P=0.14] (Figure 3).

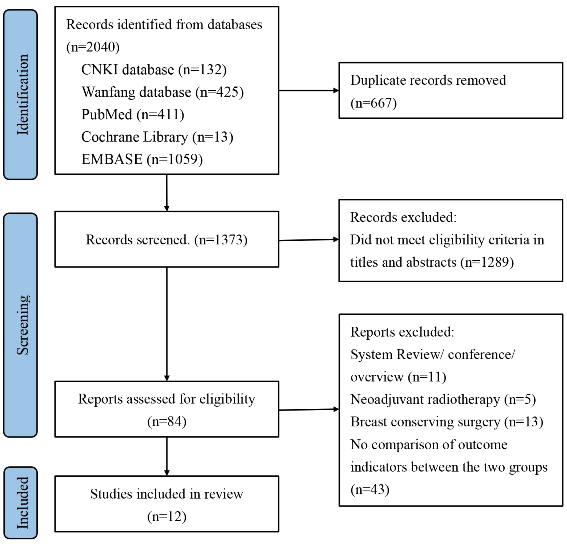

FIGURE 1
Preferred Reporting Items for Systematic Review and Meta-Analysis of Diagnostic Test Accuracy Studies (PRISMA) flow diagram for study selection.

TABLE 1 Basic characteristics of the included studies.

First author, year	Study type	Study time	Country	MT +IR/ MT(n)	Match the propensity scores	Operation program of MT+IR group	Outcomes	Median follow-up	NOS score
Gouy 2005 (33)	R	1985-1995	France	48/181	no	MT	LRFS/DMFS	10 years	6
Golshan 2011 (34)	P	2004-2008	USA	13/24	no	MT	Complication	1 year	7
Prabhu 2012 (35)	R	1997-2010	USA	40/60	no	SSM	Complication	31.6 months/30 months	8
Kansal 2013 (36)	P	2007-2010	USA	62/57	yes	MT	Complication	1 year	7
Abt 2014 (37)	R	2005-2011	USA	820/2876	no	MT	Complication	30 days	6
Aurilio 2014 (38)	R	1995-2006	Italy, Europe	59/74	no	MT	OS/DFS	8.2 years	9
Gerber 2014 (39)	R	2007-2010	Germany, Switzerl	54/142	no	MT	Complication	12 weeks	6
Ryu 2017 (40)	R	2008-2015	Korea	31/85	yes	NSM/SSM	OS/DFS/ DMFS/LRFS	29.2 months/38.8 months	9
Vieira 2019 (41)	R	2005-2011	Brazil	48/96	yes	NSM/SSM	OS/DFS/LRFS	75.9 months/67 months	8
Wu 2020 (42)	R	2010-2016	Korea	323/323	yes	NSM/SSM	OS/DFS/ DMFS/LRFS	67 months/ 68 months	9
Park 2021 (43)	R	2008-2014	Korea	345/1354	no	MT	OS	30.1 months	8
Wu 2022 (44)	R	2010-2016	Korea	209/209	yes	NSM	OS/DFS/ DMFS/LRFS	70 months/ 74months	9

R, Retrospective cohort study; P, Prospective cohort study; MT, mastectomy; IR, immediate reconstruction; NSM, nipple-sparing mastectomy; SSM, skin sparing mastectomy; OS, overall survival; DFS, disease free survival; LRFS, local recurrence free survival; DMFS, distant metastasis free survival; NOS, Newcastle–Ottawa scale.

Subgroup analysis of surgical complications in the MT+IR and IR groups was performed according to whether the propensity score matched. There were no significant differences in surgical complications, regardless of propensity score matching (Supplementary Figure 1).

3.4 Survival

3.4.1 OS

Six studies compared postoperative OS between the two groups (38, 40–44), including 982 MT+IR patients and 2028 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the OS between the two groups [HR=0.91, 95% CI (0.72, 1.16), P=0.45] (Figure 4A).

3.4.2 DFS

Five studies compared postoperative DFS between the two groups (38, 40–42, 44), including 670 MT+IR patients and 787 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the DFS between the two groups [HR=1.06, 95% CI (0.87, 1.29), P=0.54] (Figure 4B).

3.4.3 LRFS

Five studies compared postoperative LRFS between the two groups (33, 40–42, 44), including 659 MT+IR patients and 894 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the LRFS between the two groups [HR=1.02, 95% CI (0.62, 1.65), P=0.95] (Figure 4C).

3.4.4 DMFS

Four studies compared postoperative DMFS between the two groups (33, 40, 42, 44), including 611 MT+IR patients and 798 MT patients. Meta-analysis using a fixed effect model showed no significant difference in the DMFS between the two groups [HR=0.97, 95% CI (0.76, 1.22), P=0.77] (Figure 4D).

3.4.5 Subgroup analysis of survival

Subgroup analysis of OS, DFS, LRFS, and DMFS in the MT+IR and IR groups was performed according to whether the propensity score matched. Among each subgroup, there were no significant differences in OS, DFS, LRFS, and DMFS between the two groups (Supplementary Figures 2-5).

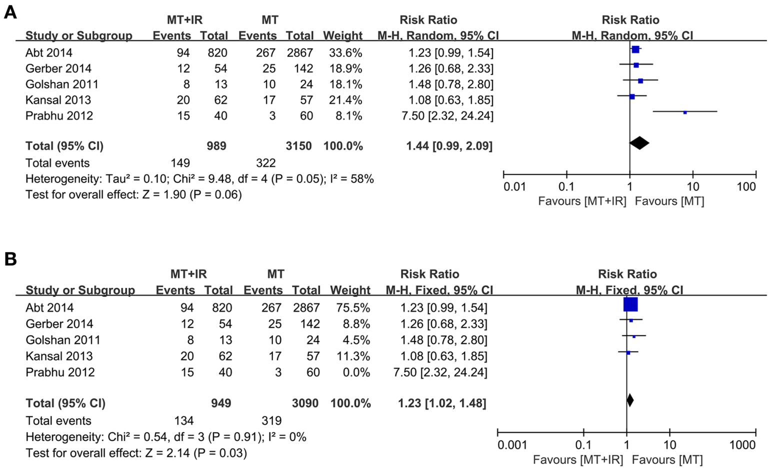

FIGURE 2
Forest plot of surgical complication in two groups. **(A)** All of five studies was included. **(B)** The study of Prabhu et al. was excluded. MT, Mastectomy; IR, Immediate reconstruction.

3.5 Sensitivity analysis

We conducted a sensitivity analysis by excluding one study at a time. When the survey of Prabhu et al. (35) was excluded, the statistical heterogeneity of the meta-analysis results decreased significantly (I^2 = 0%, P=0.91). The results significantly differed in the incidence of surgical complications between the MT+IR group and the MT group [RR=1.23, 95% CI (1.02, 1.48), P=0.03] (Figure 2B).

4 Discussion

Breast reconstruction has been widely accepted as a mean to enhance breast cancer patients' quality of life, mental well-being, and aesthetics degree post-surgery as evidenced by recent studies (45, 46). Our study provides valuable information that MT+IR in breast cancer patients after NAC may bring more short-term surgical complications than MT. The results of previous studies have been controversial on whether IR increases surgical complications. Mortenson et al. (47) and Lee et al. (48) both observed an increased incidence of wound complications when IR was combined with MT. The study of Hamahata et al. (49) yielded reports of a 10.0% postoperative complication rate in the IR group versus 6.1% in the non-IR group. A network meta-analysis of 51 studies revealed that the risk of overall complications and surgical site infection was more significant in the MT+IR group than in the MT group (50). Conversely, other studies found no significant difference in the incidence of complications between the two groups (51, 52).

A meta-analysis investigated the incidence of complications between MT+IR after NAC and adjuvant chemotherapy after MT +IR. There was no significant difference in the incidence of complications between the two groups (27). However, when the implant reconstruction subgroup was analyzed, there was some evidence suggesting that implant losses were more likely to occur in patients post-NAC compared to those in control groups (27). Another meta-analysis included 26 studies comparing surgical complications in breast cancer patients with or without NAC who

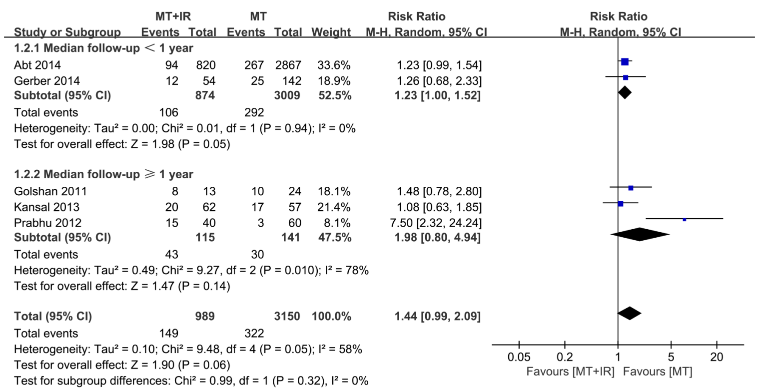

FIGURE 3
Subgroup analysis of different follow-up time on surgical complications.

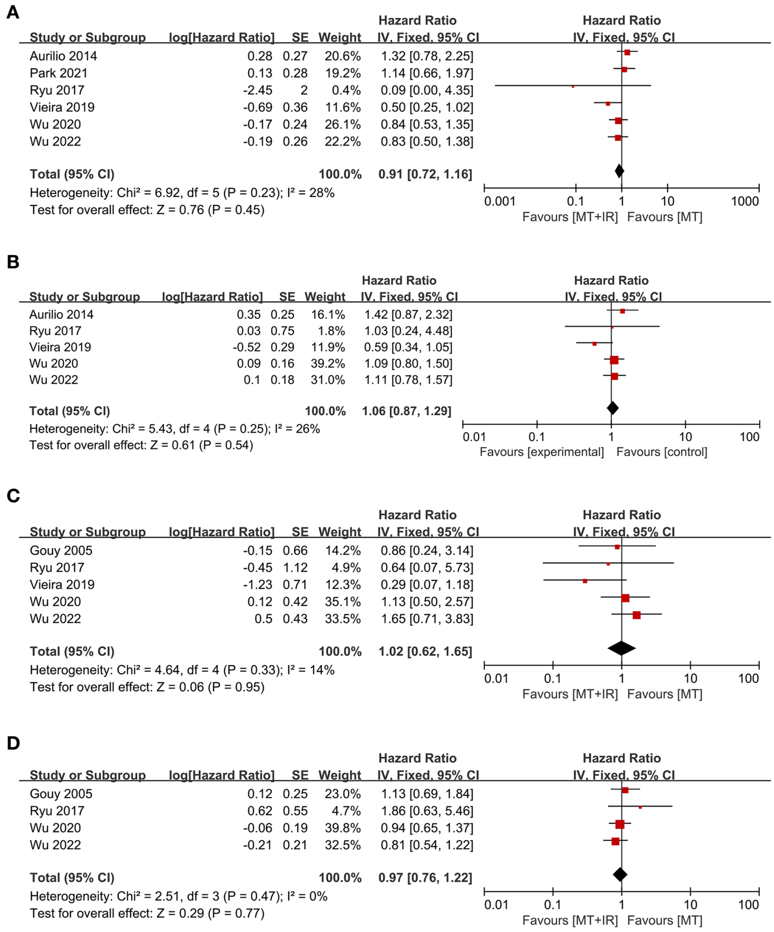

FIGURE 4
Forest plot of postoperative survival condition in two groups. **(A)** Overall survival; **(B)** Disease-free survival; **(C)** Local recurrence-free survival; **(D)** Distant metastasis-free survival. MT, Mastectomy; IR, Immediate reconstruction.

underwent any breast surgery (29). In that study, it was found that NAC did not increase the risk of certain complications, including seroma, wound complications, skin or nipple necrosis, flap ischemia or loss, and implant loss (29). However, these studies have limited reference significance for patients who have completed or underwent NAC when formulating the following surgery scheme. Matar et al. (53) showed that compared with MT+IR, delayed reconstruction (DR) after MT has a lower incidence of surgical complications, especially hematoma and postoperative infection. Although there is no significant correlation between the occurrence of surgical complications and the recurrence rate and mortality of breast cancer, DR may be a better alternative for patients afraid of complications (54). Among the five studies that investigated complications we included, only Abt et al. (37) studied wound and systemic complications containing Accordion Expanded grades 1 to 6 but did not report detailed numbers of occurrence of each complication (55, 56). The other four studies examined only wound complications that included complications of Accordion Expanded grades 1 to 4 (34–36, 39).

Without considering the influence of NAC, several previous meta-analyses proved that there was no significant difference in postoperative DFS, OS, and local recurrence rate between the MT +IR group and the MT group (57, 58). However, Shen et al. (50) conducted a Bayesian analysis and concluded that the OS of the MT +IR group was more advantageous than that of the MT group. Generally, there is a biased selection in the MT+IR group, for the patients may be younger or have higher schooling, some of them have a lower clinical stage and a better response to NAC (41, 59). Baseline characteristics of patients before NAC and the response to NAC can affect the prognosis of patients (60, 61). Based on this selective factor, some studies showed that the MT+IR group had higher OS and LRFS and a lower recurrence rate (62, 63). However, when propensity score matching was used, the survival rate between the two groups did not show significant differences in many studies. Lee et al. (64, 65) compared DMFS and breast cancer-specific survival rates between the two groups after propensity score matching, and the results showed no significant difference. Yi et al. (66) found no significant difference in the DFS between the two groups after adjusting for the clinical TNM staging. A study by Song et al. (67) showed that in patients with tumor sizes greater than 3 cm, the DFS of the MT group was higher than the MT+IR group, especially in HER2-positive and triple-negative patients. We performed subgroup analyses of propensity-matched studies that were matched for age, clinical stage, molecular type, and response to

NAC (40–42, 44). Similar to other studies, our study showed no significant difference between the two groups in OS, DFS, LRFS and DMFS, regardless of propensity score matching (Supplementary Figures 2-5).

There is no suitable report to provide a reference for the conclusion of the effect of IR on prognosis in post-NAC patients. Although no difference in prognosis was observed in our study, the accuracy is also limited by the bias caused by retrospective analysis. Liu et al. (28) demonstrated the same OS benefits for both NAC and non-NAC cases in patients with breast cancer receiving MT+IR. However, some studies suggest that MT+IR patients who received NAC had worse OS than MT+IR patients without NAC (68). It is necessary to consider the patient's response to NAC, as patients with pathologic complete response after NAC have a better prognosis than patients with limited or no response (41, 69, 70). Only a few studies have matched this factor, which could decrease the influence of different factors. After matching patients in the MT +IR and MT groups based on their responsiveness to NAC, Vieira et al. (41) found no statistically significant difference in DFS and LRFS between the two groups. However, the MT+IR group had a better OS and cancer-related survival, which they still attributed to selecting patients with a better response to NAC for IR. Ryu et al. (40) proved that OS, DFS, DMFS, and LRFS did not differ significantly between the two groups, whose matched variables included age, clinical stage before NAC, response to NAC, and pathologic stage after NAC. Two studies from Korea matched the response to NAC and also found no significant differences in OS, DFS, DMFS, and LRFS between the two groups, even in patients with locally advanced breast cancer (42, 44). In addition, some studies have shown that the best operation time after NAC is 4-8 weeks because it is related to increased OS and DFS and reduced complications (71, 72). However, due to the lack of relevant data, this study did not further analyze subgroups.

The heterogeneity test results comparing surgical complications between the two groups revealed significant heterogeneity among the studies. When the study of Prabhu et al. (35) was excluded, the heterogeneity decreased significantly, suggesting that this study may be one of the sources of heterogeneity. Further data analysis indicated that the patients had locally advanced breast cancer, and the surgical method in the MT+IR group was skin-sparing mastectomy (SSM). In contrast, other studies employed nipple-sparing mastectomy (NSM), SSM, and traditional MT as surgical methods in the MT+IR group. SSM/NSM retains a portion of the native breast structure, resulting in better breast appearance and quality of life for the patients. However, it may also bring about more surgical complication (73). Future research needs to analyze the specific surgical scheme after differentiation.

This study has the following limitations: (1) the investigation was conducted with a limited number of studies, which may present a risk of publication bias; (2) most of the included studies were retrospective studies, which may have selection bias and retrospective bias; (3) the long-term cosmetic effects of the two groups were not studied; (4) because the radiotherapy data in each study could not be extracted, our study did not consider radiotherapy, which may introduce bias; and (5) it is necessary to organize criteria related to complications of breast surgery as the number of patients submitted to IR is increasing, and the complications are decreasing yearly.

It is impossible to perform prospective randomized studies related to oncoplastic surgery because we can not randomize the type of breast surgery, and matched studies represent the best study form. It is necessary to take more studies matched by the response to NAC and other baseline characteristics with adequate follow-up to evaluate the long-term results of MT+IR after NAC. Further standardization of surgical complications and IR categories must be studied to obtain the most suitable and safe reconstruction method for breast cancer patients after NAC. The long-term cosmetic and symmetrization rates of IR in post-NAC patients need further evaluation.

5 Conclusion

Our meta-analysis demonstrated that compared with the MT, MT+IR does not affect the postoperative OS, DFS, LRFS, and DMFS in post-NAC breast cancer patients, accompanied by a mild increase in short-term surgical complications, but no significant difference in long-term complications.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Author contributions

GL: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Software, Validation, Visualization, Writing – original draft, Writing – review and editing, Funding acquisition, Resources. HJ: Writing – original draft, Writing – review and editing, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Software, Validation, Visualization. JL: Conceptualization, Writing – review and editing, Investigation, Supervision. LX: Writing – review and editing, Conceptualization, Investigation, Supervision. ZC: Writing – review and editing, Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Validation.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by the Natural Science Foundation of Xiamen City (No. 3502Z20227125).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1288744/full#supplementary-material

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