Survival benefit of neoadjuvant chemotherapy for resectable breast cancer
A meta-analysis

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Abstract
Background: Neoadjuvant chemotherapy (NAC) increases breast conservation rates in patients with resectable breast cancer at the associated cost of higher locoregional recurrence rates; however, the magnitude of the survival benefits of NAC for these patients remains undefined. Therefore, we aimed to clarify the survival benefit of NAC versus postoperative chemotherapy by conducting an updated meta-analysis of randomized clinical trials (RCTs).

Methods: The authors searched the Cochrane Library, PubMed, Embase, Web of Science, Chinese biomedical literature database, and Chinese Scientific Journals full-text database from their inception to December 2016. The authors identified relevant RCTs that compared NAC with postoperative chemotherapy in the treatment of operable breast cancer. The main endpoints were overall survival (OS) and recurrence-free survival (RFS).

Results: A total of 21 citations representing 16 unique studies were eligible. There were 787 deaths among 2794 patients assigned to NAC groups and 816 deaths among 2799 patients assigned to adjuvant chemotherapy groups. A meta-analysis of data indicated that there was no significant benefit in terms of OS (hazard ratio [HR] = 1.03, 95% confidence interval [CI]: 0.94–1.13, P = .51) and RFS (HR = 1.01, 95% CI: 0.93–1.10, P = .80) between the NAC and postoperative chemotherapy groups. The pooled HR estimate for OS was not influenced by NAC cycles, the total number of chemotherapy cycles, administration of tamoxifen, administration of adjuvant chemotherapy, or type of NAC regimen. Subgroup analysis showed that the pooled HR estimate for RFS was influenced by anthracycline-containing regimens. Patients with a pathological complete response had superior survival outcomes compared with patients who had residual disease.

Conclusion: The survival benefits for patients with operable breast cancer who received either NAC or adjuvant chemotherapy based on anthracycline regimens were comparable.

Abbreviations: BCS = breast conserving surgery, CI = confidence interval, ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2, HR = hazard ratio, MRI = magnetic resonance imaging, NAC = neoadjuvant chemotherapy, OS = overall survival, pCR = pathological complete response, RCTs = randomized clinical trials, RFS = recurrence-free survival.

Keywords: breast cancer, meta-analysis, neoadjuvant chemotherapy, surgery

1. Introduction

Breast cancer is the most common cause of cancer-related death among women worldwide and the most frequently diagnosed type of cancer in women.[1] Neoadjuvant chemotherapy (NAC) is defined as chemotherapy administered before locoregional treatment, such as surgery and/or irradiation. It is well established that NAC plays an important role in downstaging tumors, eliminating micrometastases, and relieving tumor-related symptoms in patients with locally advanced breast cancer.[2] Currently, NAC is widely used in the management of breast cancer. NAC increases the rate of breast conserving surgery (BCS) if the breast cancer cell is sensitive to chemotherapy.[3] By contrast, there is a potential risk for tumor progression in patients with tumors resistant to chemotherapy. A meta-analysis in 2007 indicated that NAC increases the rate of BCS, yet at an associated higher risk of locoregional recurrences.[4] Recent studies have shown that a higher risk of local recurrences may eventually result in a decrease in the overall survival (OS) benefit.[5,6] NAC was initially only used for patients with locally advanced disease; however, at present, more patients present with early-stage breast cancer than in the past decades, and NAC has become common for operable breast cancer.[7] The 9-year follow-up results of the ABCSG-07 trial showed that NAC results in shorter recurrence-free survival (RFS),
but not shorter OS, than does postoperative chemotherapy.\[^8\] By contrast, the NSABP Protocol B-18 study showed equivalent OS and RFS rates for women who received NAC and those who underwent postoperative chemotherapy over 16 years of follow-up.\[^7\] Furthermore, several studies have reported more recent long-term follow-up survival results. Given these circumstances, it is necessary to perform an updated meta-analysis to clarify the survival benefit of NAC versus postoperative chemotherapy in the treatment of operable breast cancer.

2. Methods

2.1. Search strategy and selection criteria

We searched the Cochrane Library, PubMed, Embase, Web of Science, Chinese biomedical literature database, and Chinese Scientific Journals full-text database from their inception to December 2016 to identify relevant randomized clinical trials (RCTs) that compare NAC with postoperative chemotherapy in the treatment of operable breast cancer. We used the following search terms: “breast cancer,” “breast carcinoma,” “neoadjuvant chemotherapy,” “primary chemotherapy,” and “preoperative chemotherapy.” We retrieved the bibliographies of eligible articles and previously published meta-analyses to identify additional relevant publications. Conference proceedings, including the American Society of Clinical Oncology and the European Society for Medical Oncology, were searched to identify any other trials. Literature searches were restricted to publications in English and Chinese. We included the study with the largest sample size and longest follow-up time when multiple articles of the same trial were published. Selection criteria for eligible trials were as follows: patients with operable breast cancer and no metastatic disease; RCTs that compared NAC followed by surgery with postoperative chemotherapy in the initial management of operable breast cancer; investigations of the survival benefits of NAC with any regimen; and RCTs published as a full-length article or an abstract. The present meta-analysis was based on previously published studies and no ethical approval or patient consent was required.

2.2. Data extraction

Two investigators independently assessed potentially relevant articles for eligibility; data were extracted by the same 2 investigators. Discrepancies were discussed until a consensus was reached. The following data were extracted from each eligible trial: first author’s name, year of publication, recruitment period, study location, stage, sample size, NAC regimen, NAC schedule, follow-up time, and study endpoints of OS and RFS in each arm. The primary outcome measure was OS; the secondary outcome measure was RFS. OS was defined as the time from randomization to death from any cause. RFS was measured from the time of breast cancer progression or relapse.

2.3. Assessment of the risk of bias of included studies

We assessed the risk of bias of included studies according to the following criteria: sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective outcome reporting, and other possible sources of bias.\[^9\]

2.4. Statistical methods

To assess the survival effects of NAC in operable breast cancer patients, hazard ratios (HRs) were used to compare trials. For meta-analyses of time-to-event outcomes such as OS and RFS, the most appropriate statistic is the HR. Where possible, the HRs and the 95% confidence intervals (CIs) were obtained directly from each published article. When the HRs were unavailable, we estimated the HR indirectly using Parmar et al’s method by means of the following formula: \( \text{ln}(HR) = (O - E)/V \),\[^10\] where \( O \) refers to the observed number of events in each arm, \( E \) is the log rank of the expected number of events in each arm, and \( V \) is the variance of \( \log(\text{HR}) \).\[^10\] The \( I^2 \) and \( P \) statistics were used to test statistical heterogeneity among included studies; an \( I^2 \) value above 50% was considered to represent large heterogeneity across studies.\[^11\]

We used a fixed-effect model to combine HRs for OS and RFS when there was no significant heterogeneity among included studies (\( I^2 < 50\% \)); alternatively, a random-effects model was used. A funnel plot was used to investigate the presence of publication bias in the present meta-analysis. All statistical tests were 2-sided, and the significance level was set at 5%. Data were analyzed using Revman version 5.3 software provided by the Cochrane Collaboration.

3. Results

3.1. The characteristics of included studies

A total of 21 citations representing 16 unique studies were eligible. Figure 1 presents the Preferred Reporting Items for Systematic Reviews statement of the search results. One trial compared NAC plus radiotherapy with neoadjuvant radiotherapy;\[^12\] the other trials were randomized comparisons of NAC versus surgery alone. Different combinations of NAC regimen, dosage, and cycle were tested in all the included studies; the main agents were fluorouracil, cyclophosphamide, and epirubicin compounds. Eligible patients received tamoxifen in 7 studies.\[^7,14,15,22,24,27,28\] All trials were open-label without blinding procedures. Two studies had been published only in abstract form,\[^14,15\] whereas the other studies were full-text publications. Five of the included studies extended their follow-up results,\[^7,17,19,21,27\] and the survival data included in the present meta-analysis are from the updated final publications. All included studies reported follow-up times except for 1 trial\[^13\]; median follow-up times ranged from 24 to 192 months. Three

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Figure 1. Preferred Reporting Items for Systematic Reviews statement of search results.
trials were conducted in France,[2,12,16,18] 3 in the UK,[13,21,26] 2 in the United States,[7,24] and 1 each in Russia,[12] Japan,[14] Lithuania,[15] Belgium,[22] India,[23] Austria,[8] Italy,[28] and China.[29] The characteristics of the included studies are described in Tables 1 and 2.

3.2. Risk of bias in included studies

The risk of bias is summarized in Figs. 2 and 3. Inter-reviewer agreement for risk of bias assessment was excellent (κ = 0.91).

3.3. Results of the meta-analysis

3.3.1. Overall survival. OS data were available for a subset of 12 of the 16 trials with a total of 5593 patients. There were 787 deaths among 2799 patients assigned to NAC groups and 816 deaths among 2799 patients assigned to adjuvant chemotherapy groups. Meta-analysis indicated that there was no survival benefit between the NAC arm and the adjuvant chemotherapy arm in patients with operable breast cancer (HR = 1.03, 95% CI: 0.94–1.13, P = .51). This 0.03 relative increase in the risk of death was equivalent to an absolute detriment of 0.8% at 10 years decreasing the 10-year OS from 64% to 63.2%. There was no statistical heterogeneity among included studies (I² = 0%).

Subgroup analyses of OS according to NAC cycles (≥3 vs. <3), total number of chemotherapy cycles (≥6 vs. <6), administration of tamoxifen (yes vs. no), administration of adjuvant chemotherapy (yes vs. no), administration of anthracycline-containing (yes vs. no), and administration of taxane-containing (yes vs. no) were performed. There was no statistically significant difference between the pooled HR estimates in these.
Figure 2. Risk of bias graph.

Figure 3. Risk of bias summary.

| Study or Subgroup | Neoadjuvant Events | Adjuvant Events | Total Events | O-E | Variance | Weight | Hazard Ratio | Hazard Ratio |
|-------------------|---------------------|-----------------|-------------|-----|----------|--------|--------------|--------------|
| Broet 1999        | 55                  | 200             | 255         | -4.49 | 47.62    | 10.0%  | 0.91 [0.69, 1.21] |              |
| Cheover 2005      | 43                  | 144             | 187         | -7.26 | 34.46    | 7.5%   | 0.67 [0.58, 1.13] |              |
| Deco 2003         | 12                  | 49              | 61          | 3.67  | 19.67    | 4.3%   | 1.20 [0.77, 1.87] |              |
| Enomoto 1998      | 3                   | 20              | 23          | 0.62  | 1.30     | 0.3%   | 1.61 [0.29, 8.66] |              |
| Gazet 2001        | 27                  | 100             | 127         | 1.57  | 8.26     | 1.8%   | 1.21 [0.61, 2.39] |              |
| Gianni 2008       | 32                  | 451             | 483         | 2.79  | 29.24    | 6.3%   | 1.10 [0.77, 1.58] |              |
| Liu DQ 2010       | 43                  | 264             | 307         | 4.26  | 24.87    | 5.4%   | 1.19 [0.60, 1.76] |              |
| Maurici 1999      | 48                  | 134             | 182         | -0.22 | 21.74    | 4.7%   | 0.99 [0.65, 1.51] |              |
| Rastogi 2008      | 310                 | 742             | 1052        | 1.67  | 168.66   | 36.1%  | 1.01 [0.67, 1.68] |              |
| Semiglazov 1994   | 48                  | 137             | 185         | -0.21 | 21.64    | 4.7%   | 0.99 [0.65, 1.51] |              |
| Taucher 2008      | 55                  | 203             | 258         | 0.67  | 31.25    | 6.8%   | 1.25 [0.48, 3.37] |              |
| van Nes 2009      | 111                 | 350             | 461         | 4.78  | 55.55    | 12.0%  | 1.09 [0.64, 1.84] |              |
| Total (95% CI)    | 2794                | 2799            | 5593        | 100.0%| 1.03 [0.94, 1.13] |              |

Total events: 787
Heterogeneity Chi² = 5.75, df = 11 (P = 0.89); I² = 0%
Test for overall effect Z = 0.65 (P = 0.51)

Figure 4. Forest plot of HRs comparing OS for patients NAC compared with surgery. HR = hazard ratio, NAC = neoadjuvant chemotherapy, OS = overall survival.
Patients who achieve pCR compared with no pCR
Administration taxane-containing NAC regimens or not
Administration anthracycline-containing NAC regimens or not
Administration adjuvant chemotherapy or not
Administration tamoxifen or not

≥NAC
Total number of chemotherapy cycles

48% to 47.6%. There was moderate statistical heterogeneity
detriment of 0.4% at 10 years decreasing the 10-year RFS from
relative increase in the risk of death was equivalent to an absolute
for RFS for the trials that compared NAC followed by surgery
Subgroup Cases

Results of subgroup analysis.

Table 3

| Subgroup                          | OS                     | Heterogeneity | RFS                     | Heterogeneity |
|-----------------------------------|------------------------|---------------|-------------------------|---------------|
| NAC ≥ 3 cycles versus NAC < 3 cycles |                        |               |                         |               |
| ≥3                                | 4369                   | 1.02 (0.91–1.14) | 0.80 4173 0.97 (0.88–1.07) | 0.58          |
| <3                                | 1204                   | 1.05 (0.88–1.26) | 0.63 1204 1.14 (0.97–1.35) | 0.04          |
| Total number of chemotherapy cycles ≥6 or <6 |                 |               |                         |               |
| ≥6                                | 2169                   | 1.07 (0.92–1.24) | 0.82 2008 1.12 (0.97–1.29) | 0.11          |
| <6                                | 3424                   | 1.01 (0.90–1.13) | 0.65 3369 0.96 (0.87–1.06) | 0.34          |
| Administration tamoxifen or not   |                        |               |                         |               |
| Yes                               | 3424                   | 1.01 (0.90–1.13) | 0.65 3424 0.96 (0.87–1.06) | 5.38          |
| No                                | 2169                   | 1.07 (0.92–1.24) | 0.82 1953 1.12 (0.97–1.30) | 45.10         |
| Administration adjuvant chemotherapy or not | |           |                         |               |
| Yes                               | 1414                   | 1.06 (0.90–1.26) | 0.74 1204 1.14 (0.97–1.35) | 0.04          |
| No                                | 3481                   | 1.00 (0.89–1.13) | 0.64 4173 0.97 (0.88–1.07) | 0.58          |
| Administration anthracycline-containing NAC regimens or not | | | | |
| Yes                               | 2726                   | 1.02 (0.91–1.15) | 0.80 2681 0.93 (0.84–1.03) | 0.47          |
| No                                | 2867                   | 1.05 (0.90–1.22) | 0.67 2696 1.20 (1.04–1.38) | 0.44          |
| Administration taxane-containing NAC regimens or not | | | | |
| Yes                               | 1430                   | 1.14 (0.87–1.49) | 0.78 1424 1.15 (0.93–1.44) | 0.58          |
| No                                | 4163                   | 1.02 (0.92–1.12) | 0.83 3953 0.99 (0.91–1.09) | 0.07          |
| Patients who achieve pCR compared with no pCR | |           |                         |               |
| Yes                               | 557                    | 0.43 (0.29–0.58) | 0.904 659 0.45 (0.34–0.56) | 0.535         |
| No                                | 2987                   |                | 3336                     |               |

Bold values represent significant differences between groups.
CI = confidence interval, HR = hazard ratio, NAC = neoadjuvant chemotherapy, OS = overall survival, pCR = pathological complete response, RFS = recurrence-free survival.
16 studies assessed the effectiveness of NAC on clinical outcomes. These data were sufficient to provide reliable evidence regarding the application of NAC in the treatment of breast cancer. The present meta-analysis revealed several main findings. First, OS and RFS for patients with operable breast cancer who received either NAC or adjuvant chemotherapy were comparable. Second, anthracycline-containing regimens were superior to other regimens in terms of RFS; therefore, anthracycline-containing regimens should still be the first choice for NAC in patients with operable breast cancer. Third, OS reduction was not influenced by the number of NAC cycles, total number of chemotherapy cycles, administration of tamoxifen, administration of adjuvant chemotherapy, administration of anthracycline-containing regimens, and administration of taxane-containing regimens. Fourth, patients with a pCR achieved better OS and RFS than those with residual disease.

To our knowledge, there is the potential risk for tumor progression or delay to surgery during the NAC period in patients with tumors resistant to the NAC regimen. Previous studies have demonstrated that tumor response rate may be an important predictor of survival benefit as a surrogate endpoint in trials of NAC for the treatment of breast cancer. A Cochrane Systematic Review also demonstrated that patients with pCR were associated with superior survival benefits compared with those who had residual disease at pathological examination (HR = 0.48; 95% CI: 0.33–0.69). Recently, the use of magnetic resonance imaging (MRI) to evaluate tumor response rates has shown benefits in predicting RFS after NAC in estrogen receptor (ER)-positive/human epidermal growth factor receptor 2 (HER2)-negative tumors; a radiological complete response at MRI after NAC is associated with a better prognosis. Moreover, it is worth emphasizing that pCR can only be confirmed with a histopathological examination, but not with radiological or clinical examinations. Who will gain the largest survival benefit from NAC for breast cancer remains unclear; therefore, the identification of molecular marker expression in patients with breast cancer would be useful in predicting the response rate to NAC and individualizing patient treatment. A number of studies have been dedicated to the identification of predictive factors for NAC. Several studies have indicated that molecular markers such as the Ki-67 antigen, tumor suppressor p53, epidermal growth factor receptor, Bcl-2, ER/progesterone receptor status, and nm23-H1 may predict the response to NAC.

### Figure 6.
Forest plot of HRs comparing RFS for patients NAC compared with surgery. HR = hazard ratio, NAC = neoadjuvant chemotherapy, RFS = recurrence-free survival.

### Figure 7.
Funnel plot of the studies reporting on recurrence-free survival.
incorporating paclitaxel into anthracycline-based NAC resulted in a significant improvement in RFS (HR = 0.73; 95% CI: 0.57–0.97) and distant RFS (HR = 0.70; 95% CI: 0.51–0.96). Furthermore, another meta-analysis demonstrated that the addition of taxane to an anthracycline-based regimen as adjuvant chemotherapy significantly improved both disease-free survival (HR = 0.83; 95% CI: 0.79–0.91) and OS (HR = 0.85; 95% CI: 0.79–0.87) for patients with high-risk early-stage breast cancer, irrespective of the type of taxane, ER expression, the number of axillary metastases, patient’s age, and menopausal status. A recent network meta-analysis identified the most effective adjuvant chemotherapy regimen for early-stage breast cancer in terms of OS by comparing regimens listed in the National Comprehensive Cancer Network guidelines, which showed that sequential anthracycline-cyclophosphamide and taxane is likely to be the most effective regimen regardless of hormone receptor status. Recently, a meta-analysis based on 5 RCTs indicated that NAC in combination with dual HER2-targeted therapy with lapatinib and trastuzumab significantly improved pCR rates in patients with HER2-positive breast cancer, regardless of the pCR definition or hormone receptor status. However, the administration of lapatinib is associated with a higher risk of adverse events, and thus adding anti-HER2 drugs to NAC is valuable. Therefore, future trials should identify the optimum NAC regimen and aim to minimize treatment toxicities and the effect of treatment on patients’ quality of life.

The pCR rate was only 2% for patients with lobular cancer, whereas it was 12% for patients with ductal cancer, confirming that breast cancer subtype may be a predictive factor for achieving pCR to NAC. Slavens et al. also suggested that sensitivity to NAC depends on breast cancer subtype; however, the predictive value of the histological breast cancer subtype was emphasized. It is well-known that breast cancer is a disease with clinical and biological heterogeneity; therefore, different molecular subgroups display distinct clinical behavior, which results in significant differences in survival outcomes. Our findings highlight the need to differentiate and analyze breast cancer subtypes separately in future trials. Thus, future trials should focus on the identification and selection of patients who will be most likely to benefit from specific treatment options.

Although recurrence rates of NAC and adjuvant chemotherapy are significantly different, they have comparable survival outcomes in terms of OS and RFS. Concerns may be raised as to why increases in locoregional recurrence rates did not translate to decreases in survival outcomes. It is possible that NAC increases the breast conservation rate compared with adjuvant chemotherapy. It is well known that BCS is associated with a lower locoregional recurrence rate than mastectomy, although evidence is increasingly demonstrating that BCS after systemic treatment can be equivalent to mastectomy in terms of long-term OS. Furthermore, adjuvant chemotherapy, radiotherapy, hormonal therapy, and molecular targeted therapy are important in the treatment of breast cancer. Multidisciplinary systemic treatment plays a crucial role in treating patients with breast cancer. In conclusion, the available evidence for operable breast cancer points to similar OS and RFS rates between NAC followed by surgery versus surgery followed by adjuvant chemotherapy.

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