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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 random assignment to 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 Parmer et al's method by means of the following formula: $\ln(HR) = (O - E)/V$,[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 $\log(HR)$.[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
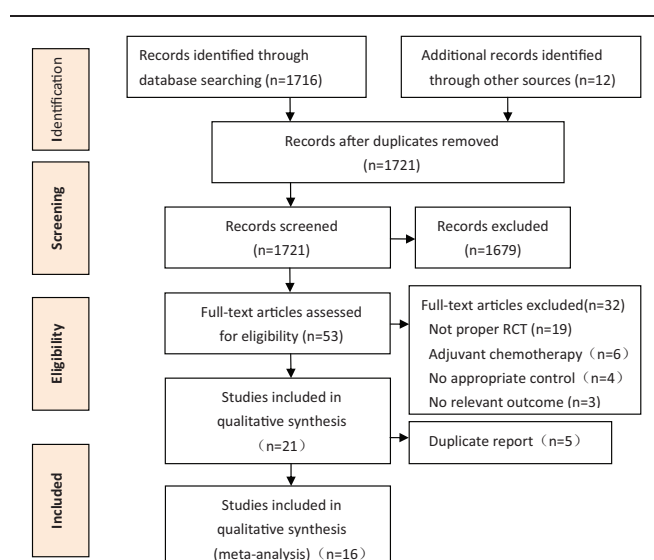

Figure 1. Preferred Reporting Items for Systematic Reviews statement of search results.

Table 1

The characteristics of included studies.

First author, year	Recruitment period	Study location	Stage	Sample size	Regimen	NAC schedule	Median follow-up
Scholl, 1991[2]	1983–1986	France	II–IIIa	196	FAC	2 cycles of 6	54 mo
Semiglazov, 1994[12]	1985–1990	Russian	IIb–IIIa	271	TMF	1–2 cycles of 6	53 mo
Forouhi, 1995[13]	Not available	UK	II–IIIa	79	CAP	4 cycles of 6	Not available
Enomoto, 1998[14]	1995–1997	Japan	II–III	50	FEC	2 cycles of 5	24 mo
Ostapenko, 1998[15]	1994–1997	Lithuania	II	100	CMF	2 cycles of 6	42 mo
Scholl, 1994[16]; Broet, 1999[17]	1986–1990	France	II–IIIa	390	FAC	2 cycles of 6	105 mo
Mauriac, 1991[18], 1999[19]	1985–1989	France	II–IIIa	272	EVM/MTV	6 cycles of 6	124 mo
Wolmark, 2001[20]; Rastogi, 2008[7]	1988–1993	USA	I–IIIa	1523	AC	4 cycles of 4	192 mo
Gazet, 2001[21]	1990–1993	UK	I–IIIa	210	MMM	4 cycles of 8	60 mo
van der Hage, 2001[22]; van Nes, 2009[23]	1991–1999	Belgium	I–IIIa	698	FEC	4 cycles of 4	120 mo
Danforth, 2003[24]	1990–1998	USA	II	53	FLAC	5 cycles of 5	108 mo
Deo, 2003[25]	1997–2001	India	T4bN0–2	101	FEC	3 cycles of 6	25 mo
Makris, 1998[26]; Cleator, 2005[27]	1990–1995	UK	I–IIIa	293	MM (M)	4 cycles of 4	112 mo
Taucher, 2008[8]	1991–1999	Austria	II–IIIa	423	CMF	3 cycles of 6	108 mo
Gianni, 2009[28]	1996–2002	Italy	II–IIIa	1355	AT/CMF	4 cycles of 4	76 mo
Liu, 2010[29]	1996–2006	China	III	522	FEC/TEC	4–6 cycles of 6	67.4 mo

AC = doxorubicin/ cyclophosphamide, AT = doxorubicin/paclitaxel, CAP = cyclophosphamide/doxorubicin/prednisolone, CMF = cyclophosphamide/methotrexate/fluorouracil, EVM/MTV = epirubicin/vincristine, methotrexate/thiotepa/vindesine, FAC = fluorouracil/doxorubicin/cyclophosphamide, FEC = fluorouracil/epirubicin/cyclophosphamide, FLAC = fluorouracil/leucovorin/doxorubicin/cyclophosphamide, MMM = mitozantrone/mitomycin C/methotrexate, NAC = neoadjuvant chemotherapy, TEC = docetaxel/epirubicin/cyclophosphamide, TMF = thiotepa/methotrexate/5-fluorouracil.

trials were conducted in France,[2,16,18] 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,[25] 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 2794 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 ($I^2 = 0\%$, $P = .89$). HRs for OS in individual trials are shown in Fig. 4. The associated funnel plot showed a symmetrical distribution (Fig. 5).

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 regimens (yes vs. no), and administration of taxane-containing regimens (yes vs. no) were performed. There was no statistically significant difference between the pooled HR estimates in these

Table 2

The characteristics of included studies continued.

First author, year	Median age NAC	Median age AC	ER negative NAC	ER negative AC	ER positive NAC	ER positive AC	PR negative NAC	PR negative AC	PR positive NAC	PR positive AC	Premenopausal NAC	Premenopausal AC	Adjuvant radiation NAC	Adjuvant radiation AC
Scholl, 1991[2]	50	50	NA	NA	NA	NA	NA	NA	NA	NA	61	59	Yes	Yes
Semiglazov, 1994[12]	49.7	51.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	No
Forouhi, 1995[13]	51	51	20	20	20	19	NA	NA	NA	NA	NA	NA	NA	NA
Enomoto, 1998[14]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	No	No
Ostapenko, 1998[15]	28–50	28–50	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	No	No
Broet, 1999[17]	45	45	NA	NA	NA	NA	NA	NA	NA	NA	200	190	Yes	Yes
Mauriac, 1999[19]	52.2	51.8	NA	NA	NA	NA	NA	NA	NA	NA	51	50	Yes	No
Rastogi, 2008[7]	49.7	48.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes	Yes
Gazet, 2001[21]	46	44	NA	NA	NA	NA	NA	NA	NA	NA	39	38	Yes	Yes
van der Hage, 2001[22]	NA	NA	59	83	138	157	NA	NA	NA	NA	NA	NA	Yes	Yes
Danforth, 2003[24]	49	43	9	11	16	16	9	9	16	18	13	19	Yes	Yes
Deo, 2003[25]	50	48	NA	NA	NA	NA	NA	NA	NA	NA	20	25	Yes	Yes
Makris, 1998[26]; Cleator, 2005[27]	56	55	NA	NA	NA	NA	NA	NA	NA	NA	44	48	Yes	Yes
Taucher, 2008[8]	50.3	51.5	181	164	19	17	158	154	36	25	100	97	No	No
Gianni, 2009[28]	50	50	31	31	68	68	31	31	68	68	NA	NA	Yes	Yes
Liu, 2010[29]	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	201	191	Yes	No

AC = adjuvant chemotherapy, ER = estrogen receptor, NA = not available, NAC = neoadjuvant chemotherapy, PR = progesterone receptor.
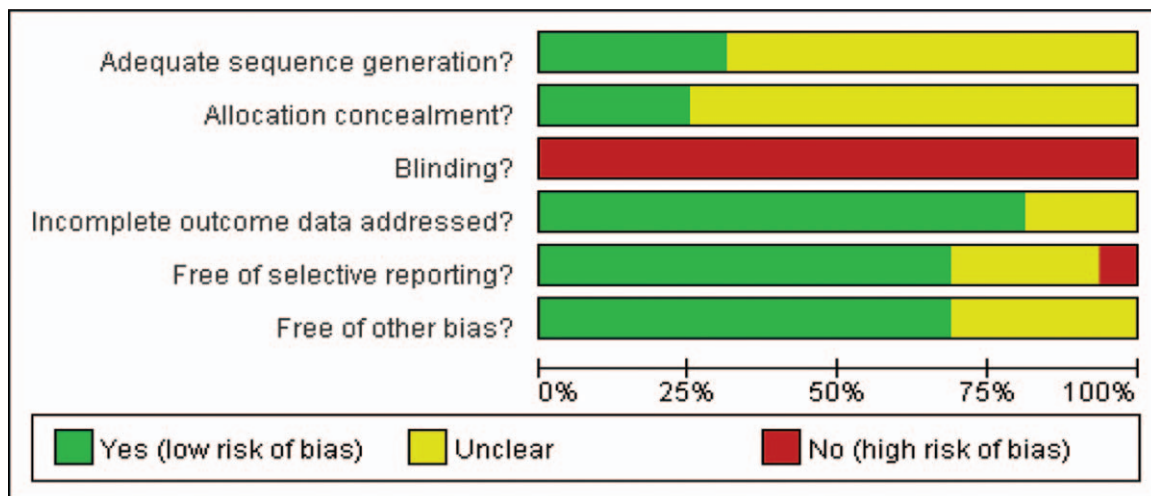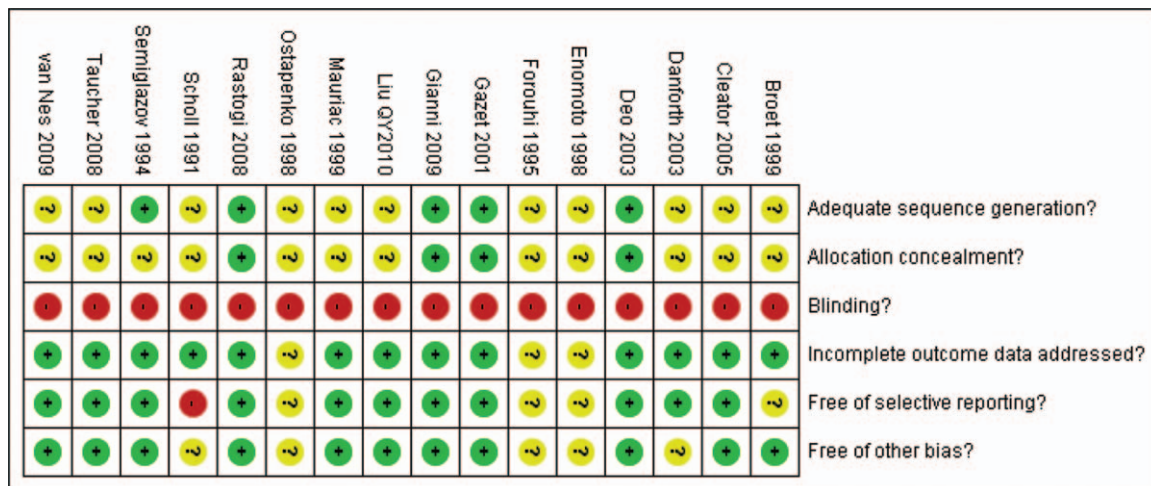
Figure 2. Risk of bias graph.

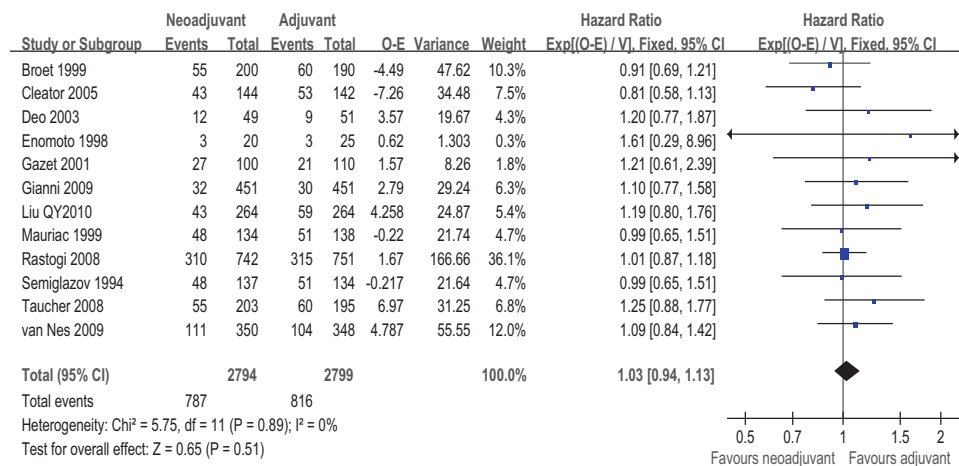**Figure 3.** Risk of bias summary.

Figure 4. Forest plot of HRs comparing OS for patients NAC compared with surgery. HR = hazard ratio, NAC = neoadjuvant chemotherapy, OS = overall survival.
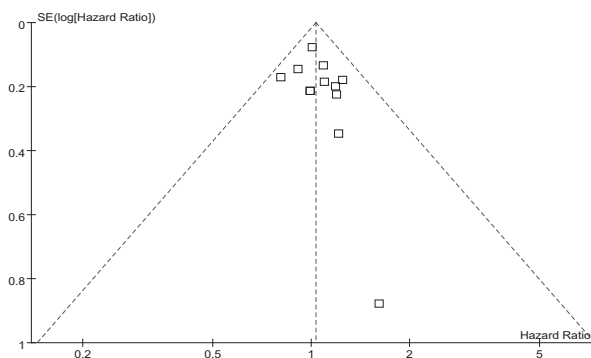
Figure 5. Funnel plot of the studies reporting on overall survival.

subgroups (Table 2). Furthermore, patients with a pathological complete response (pCR) had a superior OS compared with patients without pCR (HR=0.43, 95% CI: 0.29–0.58, P=.65); the results are shown in Table 3.

3.3.2. Recurrence-free survival. Data on RFS were available for a subset of 11 of the 16 trials with a total of 5377 patients. Meta-analysis indicated that there was no significant difference in RFS between the 2 groups for patients with operable breast cancer (HR=1.01, 95% CI: 0.93–1.10, P=.80). This 0.01 relative increase in the risk of death was equivalent to an absolute detriment of 0.4% at 10 years decreasing the 10-year RFS from 48% to 47.6%. There was moderate statistical heterogeneity among included studies ($I^2=40\%$, P=.08). The pooled estimates for RFS for the trials that compared NAC followed by surgery with surgery alone are shown in Fig. 6. The associated funnel plot showed a symmetrical distribution (Fig. 7).

The subgroup analysis showed that RFS was decreased when the meta-analysis was restricted to studies of anthracycline-containing regimens (yes vs. no); a significant decrease in RFS was observed in the arms without anthracycline-containing regimens (HR=1.20, 95% CI: 1.04–1.38, P=.01; Table 2). This 0.20 relative increase in the risk of death was equivalent to an absolute detriment of 6.5% at 10 years decreasing the 10-year RFS from 48% to 41.5%. The subgroup analysis showed that RFS was not improved even when the meta-analysis was restricted to trials on NAC cycle (≥3 vs. <3), total number of chemotherapy cycles (≥6 vs. <6), the administration of tamoxifen (yes vs. no), the administration of adjuvant chemotherapy (yes vs. no), or the administration of taxane-containing regimens (yes vs. no) (Table 3). Patients with a pCR had better RFS than patients without pCR (HR=0.45, 95% CI: 0.34–0.56, P=.535); the results are shown in Table 3.

4. Discussion

NAC for the management of inoperable or locally advanced breast cancer only began in the 1970s.[25] During the past 20 years, numerous RCTs have studied the effect of NAC in the treatment of early-stage or operable breast cancer; however, whether these patients gain survival benefits and obtain improved prognoses remains controversial. The earlier meta-analysis indicated that NAC improved absolute breast conservation rates by 16.6% compared to postoperative chemotherapy, although at the associated cost of higher numbers of locoregional recurrences. Nevertheless, NAC was associated with fewer adverse effects.[4] However, it is still unclear whether higher locoregional recurrence rates would translate into a deterioration in survival. The objective of the present meta-analysis was to estimate the magnitude of OS and RFS benefits of NAC in patients with operable breast cancer based on time-to-event data. We identified

Table 3
Results of subgroup analysis.

Subgroup	Cases	OS HR (95% CI)	Heterogeneity I^2, %	P	Cases	RFS HR (95% CI)	Heterogeneity I^2, %	P
NAC ≥ 3 cycles versus NAC < 3 cycles								
≥3	4389	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)	60	.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)	42	.11
<6	3424	1.01 (0.90–1.13)	0	.65	3369	0.96 (0.87–1.06)	11	.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)	60	.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 (0.91–1.08)	46	.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 value represent significant difference was existed between two groups.
CI = confidence interval, HR = hazard ratio, NAC = neoadjuvant chemotherapy, OS = overall survival, pCR = pathological complete response, RFS = recurrence-free survival.
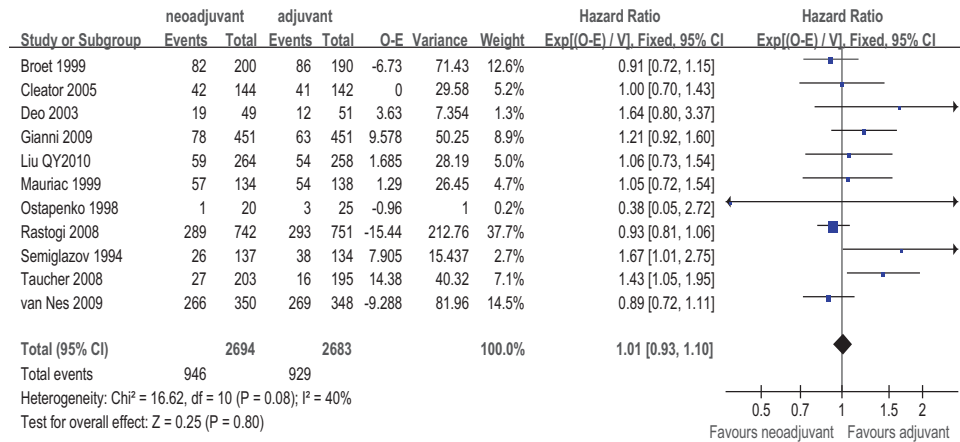
Study or Subgroup	neoadjuvant Events	Total	adjuvant Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Broet 1999	82	200	86	190	-6.73	71.43	12.6%	0.91 [0.72, 1.15]	
Cleator 2005	42	144	41	142	0	29.58	5.2%	1.00 [0.70, 1.43]	
Deo 2003	19	49	12	51	3.63	7.354	1.3%	1.64 [0.80, 3.37]	
Gianni 2009	78	451	63	451	9.578	50.25	8.9%	1.21 [0.92, 1.60]	
Liu QY2010	59	264	54	258	1.685	28.19	5.0%	1.06 [0.73, 1.54]	
Mauriac 1999	57	134	54	138	1.29	26.45	4.7%	1.05 [0.72, 1.54]	
Ostapenko 1998	1	20	3	25	-0.96	1	0.2%	0.38 [0.05, 2.72]	
Rastogi 2008	289	742	293	751	-15.44	212.76	37.7%	0.93 [0.81, 1.06]	
Semiglazov 1994	26	137	38	134	7.905	15.437	2.7%	1.67 [1.01, 2.75]	
Taucher 2008	27	203	16	195	14.38	40.32	7.1%	1.43 [1.05, 1.95]	
van Nes 2009	266	350	269	348	-9.288	81.96	14.5%	0.89 [0.72, 1.11]	
Total (95% CI)		**2694**		**2683**			**100.0%**	**1.01 [0.93, 1.10]**	
Total events	946		929						

Heterogeneity: Chi² = 16.62, df = 10 (P = 0.08); I² = 40%
Test for overall effect: Z = 0.25 (P = 0.80)

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

16 studies that 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 yielded 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.[4] 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.[28] 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).[30] 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.[31] 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 in patients with breast cancer.[32–34] Therefore, during the planning of an NAC treatment strategy, the choice of optimal treatment should be based not only on the disease stage but also on its biological characteristics that may predict cancer responsiveness to treatment. During the 2015 St. Gallen International Expert Consensus Conference on neoadjuvant therapy for early breast cancer, the panel strongly endorsed the use of NAC for stage II or III cancer and HER2-positive or triple-negative breast cancer as the preferred initial treatment approach. For HER2-positive cancers, the panel endorsed dual anti-HER2 neoadjuvant therapy with pertuzumab, or trastuzumab with chemotherapy. For triple-negative cancers, the panel recommended similar approaches to those that would be used in adjuvant therapy.[35] However, the design of the included studies was not based on molecular classification; therefore, it was not possible to carry out subgroup analysis according to cellular–molecular phenotype in the present meta-analysis.

Several studies have shown that different NAC regimens have distinct effects on the response rate of patients with breast cancer.[28] In the present meta-analysis, the NAC regimens were mostly fluorouracil, cyclophosphamide, and anthracycline regimens. The optimum NAC treatment regimen was not established, because included trials used different drugs, doses, and cycles of chemotherapy. Preliminary data from a trial have shown that
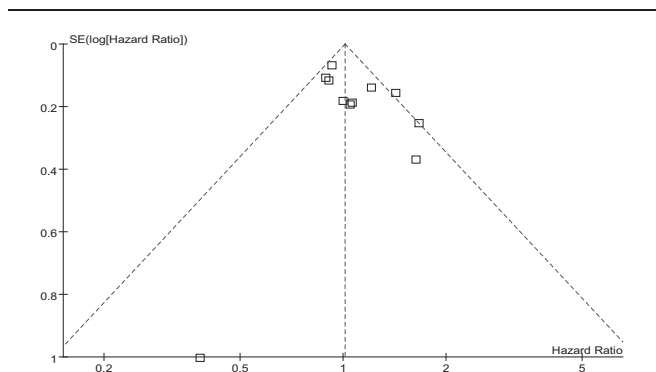

Figure 7. Funnel plot of the studies reporting on recurrence-free survival.

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).[28] 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.[36] 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.[37] 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.[38] However, the administration of lapatinib is associated with a higher risk of adverse events,[39] 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.[40] Straver et al[41] 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.[4] It is well known that BCS is associated with a higher 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.[42] 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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