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Original Article

Role of Neoadjuvant Chemotherapy in Breast Cancer Patients: Systematic Review and Meta-analysis

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Abstract

Background: The present systematic review and meta-analysis critically assessed the impact of neoadjuvant chemotherapy (NACT) in comparison to ACT in breast cancer patients in terms of oncological and functional outcomes. **Methods:** Randomized controlled trials comparing NACT with ACT in breast cancer patients were identified through Medline and Cochrane Register of Controlled Trials on January 21, 2016. Cochrane risk of bias assessment tool was used to assess the risk of bias. Meta-analysis was performed using fixed-effects or random-effects method depending on heterogeneity (I^2). Grading of the evidences was also done. Subgroup meta-analysis on the basis of total preoperative chemotherapy or sandwich chemotherapy was also performed. **Results:** The present meta-analysis shows increased breast-conserving surgery (BCS) rate (n = 9, risk ratio [95% confidence interval (CI)] = 1.19 [1.03–1.37]) with NACT. Further, NACT was found equally effective regarding overall survival (n = 15, hazard ratio [HR] [95% CI] = 0.98 [0.89–1.08]), disease-free survival (DFS) (n = 14, HR [95% CI] = 1.01 [0.86–1.18]), and distant metastasis (n = 13, HR [95% CI] = 0.97 [0.82–1.16]). Although locoregional recurrence (LRR) rate was noted to be significantly higher in NACT group (n = 15, HR [95% CI] = 1.23 [1.06–1.43]), its significance disappeared (n = 13, HR [95% CI] = 1.17 [0.98–1.40]) by excluding the trials where surgery was not provided for patients with complete tumor response. After excluding such trials, preoperative NACT was associated with increased BCS with similar LRR in ACT group. **Discussion:** NACT has no major impact on breast cancer survival. However, it is associated with increased BCS rates. NACT downgrades tumor size facilitating more BCSs without increasing LRR. The evidences were graded for all outcomes as high except DFS and BCS as moderate.

Keywords: *Breast cancer, meta-analysis, neoadjuvant chemotherapy, sandwich chemotherapy, systematic review*

Introduction

Neoadjuvant chemotherapy (NACT) has become standard of care, especially for locally advanced breast cancer (LABC) patients since its introduction in the 1980s, and it is being increasingly used even in early breast cancer patients. The proposed advantages of NACT include making inoperable breast cancers into operable one, downstaging the tumor size, and increasing breast-conserving surgery (BCS) rates and *in vivo* testing of chemosensitivity. During the past four decades, majority of the studies dealt with NACT in breast cancer using different patient selection criteria, multiple chemotherapy regimens, and variable end points; for example, overall survival (OS), disease-free survival (DFS), relapse-free survival (RFS), locoregional recurrences (LRR), and distant metastasis (DM).

A number of randomized controlled trials (RCTs) have reported a beneficial effect of NACT regarding OS, DFS, and BCS.[1-5] However, some other RCTs have reported contradictory findings.[6,7] In view of such mixed reporting and implications of large-scale use of NACT at global level, there is a need to critically analyze the benefits of NACT among breast cancer patients.

Two systematic reviews and meta-analysis were published in literature pertaining to this topic.[8,9] The last systematic review and meta-analysis were performed >10 years ago, which concluded that the OS and DFS are similar in both the groups of NACT and ACT.[9] NACT increased breast conservation rate but with increased LRR. This review

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could not consider DM as one of the end points; however, it is more aggressive and clinically more important. Furthermore, in the last review, RFS was merged into DFS though there is a basic difference in the definition between the two. In the past decade, with increasing use of NACT, newer regimens of chemotherapy also emerged, and these may result in more RCTs and updated publication of the existing RCTs with increased follow-up. Hence, there is a need to review critically the current available evidence on the effectiveness of NACT in comparison to ACT among breast cancer patients.

In view of the above fact, the present systematic review aims to assess the effectiveness of NACT versus ACT in terms of oncological and functional outcomes. Having considered the RCTs till January 2016, the present review obviously provides the current evidence on the topic.

Objective

The objective of the study was to assess the effectiveness of NACT in comparison to ACT on the basis of OS, DFS, RFS, LRR, local recurrence (LR), regional recurrence (RR), DM, and BCS in female breast cancer patients by systematic review and meta-analysis of RCTs.

Methods/Design

The present systematic review manuscript is designed as per the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[10-12] This study has been registered with PROSPERO and the registration Number is CRD42015023339.[13]

Eligibility criteria

All studies assessing the efficacy of NACT in comparison to ACT in the management of breast cancer, published in English language, were considered. There was no restriction regarding the regimens used in the chemotherapy. The population, intervention, comparator, outcome, and time considered in the present systematic review is given below:

- Population All female breast cancer patients
- Intervention NACT
- Comparator ACT
- Outcome OS, DFS, RFS, LRR, LR, RR, DM, and BCS
- Time Assessed on and up to January 21, 2016

Outcomes

The outcomes of the present study were OS, DFS, RFS, time to LRR, time to DM, and BCS. OS is defined as time from randomization to death from any cause. DFS is defined as time to disease relapse or death. However, RFS is time to relapse and censored at death. LR and RR are defined as time to only local recurrence and only regional recurrence, respectively. LRR is presented as time to recurrence to local and/or regional area. DM is the time to metastasis to other parts of the bodies such as brain and lung. The type of surgery, i.e., whether it was BCS or mastectomy, was also considered as an outcome.

Information source

A comprehensive search of PubMed and Cochrane databases with a predefined sensitive search strategy including the search terms such as "Breast Neoplasms," Breast Cancer; neoadjuvant, preoperative, upfront, primary, induction; adjuvant and postoperative was performed on January 21, 2016. The WHO's Clinical Trial Registry, reference list of eligible articles, and related systematic reviews were also searched. Relevant abstracts of major conferences, i.e., ASCO Annual Meeting Abstracts (2005–2015), San Antonio Breast Cancer Symposium 1988, and St. Gallen 6th International Conference on Adjuvant Therapy of Primary Breast Cancer, were also searched. The search strategy was developed as per the Cochrane checklist of developing search strategy.[14]

Search limits

At the stage of searching, online databases were not restricted on the basis of language or publication time period.

Search terms

The study objective is furcated on the basis of PICOD criteria. For each of the section except outcome (e.g., (i) breast cancer, (ii) NACT, (iii) ACT, and (iv) RCTs), search terms were identified as the synonyms of these words. Synonyms of specific section were joined by "OR" operator; however, different sections were joined by "AND" operator. The detailed search strategies for PubMed as well as Cochrane Register of Controlled Trials are given in Appendix S1 – electronic search strategy.

Study selection

Initial screening

The studies retrieved from different online databases were combined after removing duplicates on the basis of title and year. Search records were screened on the basis of title and abstract against predefined inclusion criteria. The reason for rejection of the article was also documented for each of the study. The screening of studies was very sensitive and broadly captured any relevant trial on the topic. A random sample of search records was also cross-checked by other reviewer. Further, the study was qualified for full-text review if the rejection reason was not sufficient. The doubts were resolved by discussion among the entire review team. After the full-text review, articles qualifying the predefined inclusion criteria were included in the systematic review. In case of multiple publications of the same study, the latest publication was considered. However, information was extracted from previous publications if not reported in latest publication. All the studies reporting any of the outcomes were included in the meta-analysis.

Data extraction

Data extraction form was designed as per Cochrane guidelines, and the data were extracted from each of the eligible full-text article or conference proceedings. For one article, information was extracted from the previous review.[9,15,16] All the extracted information was further cross-checked by another reviewer. The following information was extracted from the eligible full-text studies:

- Publication details: Year, language, country, authors, and journals
- Inclusion criteria
- Baseline factors: Age, menopause status, cancer stage, hormone status (ER, PR HER2), and tumor grade
- Comparator, i.e., NACT versus ACT; or NACT + ACT versus ACT
- Size of study population: Overall, NACT arm, ACT arm
- Follow-up time
- Treatment: Regimen and doses; radiotherapy, hormone therapy
- Outcome variables: OS, DFS, RFS, DM, LRR, and BCS.

Risk of bias in individual study

The risk-of-bias assessment of RCTs was done using the Cochrane Collaboration's tool for assessing the risk of bias.[14] It was performed under the key domains namely random sequence generation and allocation concealment for selection bias; incomplete outcome data (attrition bias); selective reporting of outcome (reporting bias); and other biases including publication bias. All the risk biases were assessed at study level.

Summary Measures

Hazard ratios were synthesized for all of the outcomes except BCS, for which relative risk was used. The summary statistics, i.e., log of hazard ratio and its variance for survival outcomes, were extracted using the method suggested by Parmar *et al*.[17]

Data synthesis and analysis

Data for all eligible studies were extracted in Excel spreadsheet, Microsoft Office 2007 (Washington, USA). Statistical heterogeneity was assessed using I^2 statistic.[18,19] The fixed-effects method and random-effects methods of meta-analysis were used depending on the extent of heterogeneity. All analyses were performed using Stata, version 14 (Stata Corp., Texas, USA). For systematic review and risk-of-bias assessment, Review Manager 5.3, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014, was used.

Risk of bias across studies

Evidence of publication bias was examined graphically by funnel plots and also tested by Egger's test.[20]

Additional analysis

As most of the trials have included participants of early as well as LABC, stage-wise meta-analysis (as committed during PROSPERO registration) was not feasible. Subgroup analyses on the basis of type of intervention, i.e., total NACT versus ACT or sandwich NACT (NACT + ACT) versus ACT, were also performed for all of the outcomes. Sensitivity analyses excluding the trials where surgery was omitted for the patients having complete response were also performed for all the outcomes.

Results

Study selection

A total of 58 records from 29 individual studies were screened on the basis of title and abstract out of 1239 searched records. The systematic review resulted into 19 RCTs involving 5944 breast cancer patients randomized to NACT arm (n_1 = 2969) and ACT arm (n_2 = 2975), fulfilling all eligibility criteria and measuring at least one of the considered outcomes.[3,5,16,21-36] As one study reported only toxicity, only 18 RCTs were eligible for meta-analysis.[35] These details are presented using the PRISMA flowchart giving reason for exclusion of each full-text reviewed article in Figure 1.[10]

Study characteristics

The study level sample size of the eligible 18 studies varies from 45 to 1523.[2,16] Out of these 18 RCTs, only four trials were multicentric trials.[2,21,22,30] Further, only three RCTs were from developing world.[6,22,31]

On the basis of timing of intervention, two types of studies were identified. The first group of studies compared total NACT with ACT and another set of RCTs compared sandwich NACT (i.e., NACT along with ACT) to ACT alone.[21-34] Further, there were three trials where surgery was not performed if patient had complete response.[5,25,28] The population, intervention, regimen, comparator, and

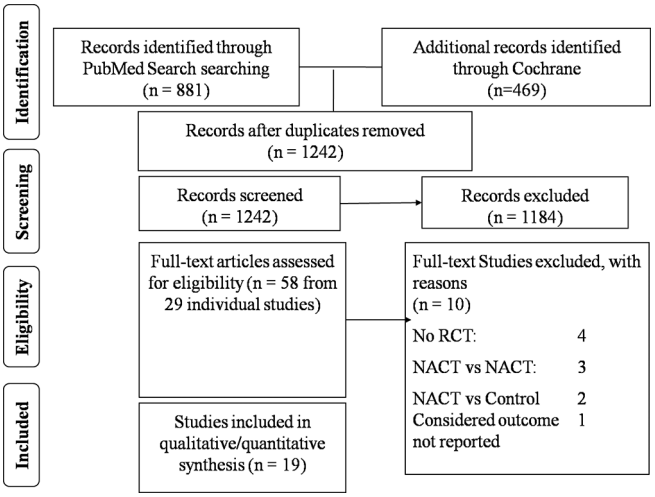

Figure 1: PRISMA 2009 flowchart

Table 1: Table of study characteristics as per population, intervention, comparator, and outcome criteria

Study	Information source	Accrual	Accrual period	Population	Intervention	Outcomes
Gianni *et al*., 2009[21]	Full text: Published	902	1996-2002	Operable breast Cancer of stage T2-T3, N0-N1, M0	NACT Arm: 4× AT + 4× CMF → (BCS+RT or mast) + TAM for HR + ACT Arm: BCS + RT or Mast. → 4× AT + 4 × CMF	OS, RFS, LRR, DM, BCS
Taucher *et al*., 2008[22]	Full text: Published	429	1991-1999	Primary breast cancer patients staged T1-3, N0 or N1 and M0	NACT Arm: 3× CMF→ BCS/Mast ± RT→3×CMF for LN-and 3× EC for LN + ACT Arm: BCS/mast ±RT→3× CMF→3× CMF for LN- and 3× EC for LN +	OS, RFS, LRR, DM, BCS, Toxicity
Deo, *et al*., 2003[6]	Full text: Published	101	1997-2001	Operable breast locally advanced breast carcinoma stage T4b N0-2 M0	NACT Arm: 3× FEC→ Mast→ 3FEC ACT Arm: Mast→ 6× FEC	OS, RFS, DM, LRR, all mastectomy
Gazet *et al*., 2001[23]	Full text: Published	210	1990-1993	Nonmetastatic breast cancer patients	NACT Arm: Goserelin to ER+ and premenopausal//lentaron to ER+and Postmenopausal/4× MMM→BCS/ mast→ (responders ER+: as previous, responders ER- 4× MMM)/(nonresponder ER+: 8× MMM and ER-: 8× FEC) ACT Arm: BCS/Mast→ Goserelin to ER + and premenopausal/lentaron to ER+and Postmenopausal/8× MMM	OS, RFS, DM, LRR, BCS
UK Trial, 2005[24]	Full text: Published	309	1990-1995	Nonmetastatic breast cancer patients of ≤70 years	NACT Arm: 4× (3M or 2M) → BCS+RT/ Mast→4 ×(3M or 2M) ACT Arm: BCS + RT/Mast→8 ×(3M or 2M)	OS, RFS, DM, LRR, BCS
S6 Trial, 1995[25]	Full text: Published	414	1986-1990	Nonmetastatic operable breast tumors of diameter 3 cm-7 cm and with no prior cancer with N0, N1b	NACT Arm: 4×CAF→(Mast/BCS)/RT for CR patients ACT Arm: (Mast/BCS)/RT for CR patients→4×CAF	OS, RFS, DM, LRR, BCS, Toxicity
Semiglazov *et al*., 1994[26]	Full text: Published	271	1985-1990	Breast cancer patients stage IIb-IIIa diagnosed age 55 years and younger	NACT Arm: 1or 2×TMF→RT→MRM→ 4 or 5×TMF ACT Arm: RT→ MRM→ 6 × TMF	OS, RFS, DM, LRR, BCS, Toxicity
Takatsuka *et al*., 1994[27]	Full text: Published	73	1986-1992	Locally advanced breast cancer patients aged ≤70 years	NACT Arm: Epirubicine→RM→Epirubicine→TAM ACT Arm: RM→Epirubicine→TAM	OS, RFS, DM, LRR, Toxicity
S5, 1991[28]	Full text: Published	196	1983-1986	Tb3, N0-1b M0 breast cancer patients <65 years of age	NACT Arm: 2×CAF→ RT±Surgery→4 × CAF for responders and 4×AMVT to nonresponders ACT Arm: RT ±Surgery→6×CAF	OS, RFS, LRR, BCS
Danforth *et al*., 2003[29]	Full text: Published	53	1990-1998	Histological confirmed stage II (T1N1, T2 N0-1) breast cancer	NACT Arm: FLAC/G-CSF→ BCS+RT or MRM→Tamoxifen ACT Arm: BCS or MRM→FLAC/ G-CSF→RT→Tamoxifen	OS, RFS, DM, LRR, BCS, Toxicity
B18, 2008[2,3,36]	Full text: Published	1523	1991-1993	Breast cancer patients with operable, palpable breast cancer (T1-3, N0-1, M0)	NACT Arm: 4× AC →BCS+RT or MRM ACT Arm: 4× AC →BCS+RT or MRM	OS, RFS, DM, LRR, BCS, Toxicity

Contd...

Table 1: Contd...

Study	Information source	Accrual	Accrual period	Population	Intervention	Outcomes
EORTC, 2009[30]	Full text: Published	698	1991-1999	Primary early breast cancer patients (T1c, T2-3, T4b, N0-1 M0)	NACT Arm: 4× FEC → BCS with RT/ MRM ACT Arm: BCS with RT/MRM→4×FEC	OS, RFS, RFS, LRR-, BCS, Toxicity
Bordeaux, 1999[5]	Full text: Published	272	1985-1989	Women with breast tumor larger than 3 cm, T2 >3 cm or T3 N0-1 M0 breast tumors	NACT Group: 3× EVM→3× MTV→ BCS + RT/MRM/RT only for CR ACT Group: MRM →3 × EVM → 3× MTV	OS, RFS, LRR, DM, BCS, Toxicity
Chen *et al*., 2003[31]	Published in Chinese language	85	1990-1996-	Stage III women breast cancer of 30-60 years of age	Arm A: CAF → surgery → radiotherapy Arm B: Surgery → CAF → radiotherapy Arm C: Surgery → radiotherapy → CAF	OS, LRR and DM
Enomoto *et al*., 1998[16]	Conference proceeding and earlier review	45	1995-1997	Histological confirmed stage II with tumor size ≥4 cm and stage III breast cancer	NACT Arm: 2× EC→Mastectomy → 3× EC→ Tamoxifen ACT Arm: Mastectomy→5 × EC→ Tamoxifen	OS, RFS, LRR
Ragaz, 1997[32]	Conference proceeding	204	Not mentioned	Premenopausal breast cancer patients	NACT Arm: 1×CMF→Surgery→9×CMF ACT Arm: Surgery→ 9× CMF	
Ostapenko *et al*., 1998[34]	Conference proceeding	100	1994-1997	Stage II (T2N0-1) breast cancer patients, aged 28-50 years	NACT Arm: 2 × CMF → BCS + RT → Chemo-hormone therapy ACT Arm: BCS + RT → Chemo-hormone therapy	RFS, LRR, DM
Stauffer *et al*., 1993[33]	Conference proceeding	98	Not mentioned	Histological confirmed stage II breast cancer patients whose ages ranged from 25-67 years	NACT Group: 4× (Doxorubicine + cytoxan) → Surgery ACT Group: Surgery → 4 × (Doxorubicine + cytoxan)	DFS
Forouhi *et al*., 1995[35]	Full text: Published	79	Not mentioned	Nonmetastatic operable breast cancer larger than 4 cm in maximum diameter	NACT Arm: ER-: 4×CAP→MRM → 2 × CAP, ER+: Tamoxifen or Goserelin→ MRM ACT Arm: MRM → 6× CAP for ER- and Tamoxifen or Goserelin for ER +	Toxicity

NACT – Neoadjuvant Chemotherapy; ACT – Adjuvant Chemotherapy; OS – Overall Survival; DFS – Disease free survival; RFS – Relapse free survival; LRR – Loco-regional recurrence; LR – Local recurrence; RR – Regional recurrence; DM – Distant metastasis; BCS – Breast Conserving Surgery; LN – Lymph node; MRM – Modified radical mastectomy; RM – Radical mastectomy; Mast-Mastectomy; RT – Radiotherapy; TAM-Tamoxifen; AT – Adriamycin, Taxane; CMF – Cyclophosphamide, Methotrexate, 5-Flurourocil; EC – Epirubicine and cyclophosphamide, FEC – Fluorouracil, epirubicine and cyclophosphamide; MMM/3M – Mitoxantrone, methotrexate and mitomycin; 2M – Mitoxantrone and methotrexate; CAF – Cyclophosphamide, adriamycin, fluorouracil; FLAC – 5-Fulurourocil, Leucovorin calcium, doxorubicin, cyclophosphamide; AC – Adriamycin and cyclophosphamide; TMF – Thiotepa, Methotrexate, 5flurourocil; AMTV – Adriamycin, Methotrexate, thiotepa, Vindesine; EVM – Epirubicine, vincristine, methotrexate; MTV – Mitomycin, thiotepa, vindesine; CAP – Cyclophosphamide, adriamycin and prednisolone; → – followed by

outcome characteristics of all included RCTs are given in Table 1.

Risk of bias within studies

Due to limited information in conference article, it was not possible to judge risk of bias in various domains. All the RCTs had proper randomization except one where 87 participants were randomized, however analyzed 92.[33] This RCT measured only DFS. Except one RCT, the random allocation was concealed or not reported.[6] Due to noncompliance, incomplete outcome data were reported only for one trial.[28] Another trial also had analyzed less than the randomized number of patients, but excluded patients who had similar characteristics. Selective reporting bias, although difficult to measure due to nonpublication of protocol of the trials, was subjectively measured on the basis of reporting of general outcomes. Baseline parameters were generally balanced between the two arms. Sensitivity analysis was performed

Table 2: Efficacy of neoadjuvant chemotherapy in comparison to adjuvant chemotherapy

Outcome	Number of studies	Egger's test (*P*)	I^2 Statistic (%)	Hazard ratio/risk ratio (95% CI)
OS				
Overall	15	0.420	0.0	0.98 (0.89-1.08)
Preoperative NACT	07	0.159	1.2	0.98 (0.89-1.10)
Sandwich NACT	08	0.832	0.0	0.98 (0.80-1.20)
DFS				
Overall	06	0.930	26.3	0.99 (0.83-1.19)
Preoperative NACT	04	0.535	44.9	0.96 (0.77-1.19)
Sandwich NACT	02	-	0.0	1.34 (0.75-2.40)
RFS				
Overall	11	0.369	49.6	1.02 (0.85-1.22)
Preoperative NACT	04	0.381	10.0	1.03 (0.90-1.19)
Sandwich NACT	07	0.060	63.6	0.87 (0.58-1.31)
DFS/RFS				
Overall	14	0.127	47.2	1.01 (0.86-1.18)
Preoperative NACT	07	0.547	26.1	1.04 (0.90-1.19)
Sandwich NACT	07	0.060	63.6	0.87 (0.58-1.31)
RR				
Overall	04	0.557	0.0	0.82 (0.53-1.28)
Preoperative NACT	03	0.753	0.0	0.83 (0.52-1.32)
Sandwich NACT	01	-	-	0.74 (0.16-3.46)
LR				
Overall	10	0.836	0.1	1.33 (1.11-1.56)
Preoperative NACT	05	0.537	36.1	1.34 (1.06-1.75)
Sandwich NACT	05	0.927	0.0	1.23 (0.87-1.76)
LRR				
Overall	15	0.479	0.0	1.23 (1.06-1.43)
Preoperative NACT	07	0.716	18.9	1.28 (1.03-1.58)
Sandwich NACT	08	0.088	0.0	1.16 (0.85-1.59)
DM				
Overall	13	0.434	43.5	0.97 (0.82-1.16)
Preoperative NACT	07	0.247	52.6	0.91 (0.74-1.12)
Sandwich NACT	06	0.456	27.6	1.12 (0.81-1.53)
BCS*				
Overall	09	0.138	90.1	1.19 (1.03-1.37)
Preoperative NACT	05	0.203	92.8	1.37 (1.07-1.76)
Sandwich NACT	04	0.143	11.4	1.01 (0.94-1.08)

*For breast-conserving surgery, risk ratio is used as effect size. Publication bias was considered substantial if Egger's test $P<0.05$. Effect size was synthesized by random-effects method if I^2 statistic >25%. NACT – Neoadjuvant chemotherapy; OS – Overall survival; DFS – Disease-free survival; RFS – Relapse-free survival; LRR – Locoregional recurrence; LR – Local recurrence; RR – Regional recurrence; DM – Distant metastasis; BCS – Breast-conserving surgery

excluding the trials having any bias but did not change the synthesized effect for any of the outcomes. Hence, the risk of bias was considered adequate for the outcomes. Summary risk of bias is presented in Figure 2. However, the risk of bias for individual study is given in Figure S1.

Publication bias

None of the synthesized outcomes showed evidence of publication bias [Table 2].

Results of Individual Study

Outcome-wise individual study effect sizes are reported in the forest plots [Appendix S2].

Meta-analysis

The distribution of a number of studies measuring a particular outcome along with associated heterogeneity is presented in Table 2. In view of the study-wise reporting of outcomes, sample size was highest for OS (n = 15) and LRR (n = 15) and lowest for regional recurrence (RR) (n = 4). Three outcomes including OS, LRR, RR, and local recurrence (LR) showed no heterogeneity (I^2 = 0%) in their effect size. Further, another two outcomes (RFS and DM) showed the moderate extent of heterogeneity (i.e., I^2 = 47.2% and 43.5%, respectively). Interestingly, the highest heterogeneity was found in case of BCS (I^2 = 90%). It was due to the fact that one RCT

has considered taxanes as regimen and another trial had flexible protocol of changing planned mastectomy to BCS. After removing these two trials, heterogeneity completely disappeared.

NACT was found to have similar effect in comparison to ACT for OS (hazard ratio [HR] (95% confidence interval [CI]) = 0.98 (0.89–1.08), DFS (n = 14, HR = 1.01 [0.86–1.18]), and DM (n = 13, HR = 0.97 [0.82–1.16]), whether it was given in total preoperative or sandwich setting. Further, sensitivity analysis excluding one study[3] not having proper randomization did not change pooled effect estimate of DFS because this trial contributed merely 2% of weight. However, LRR was higher in NACT group (n = 14, HR = 1.23 [1.06–1.44]). However, significance disappeared in the sensitivity analysis by excluding trials, in which surgery was withheld for the patients having a complete clinical response (n = 11, HR = 1.17 [0.98–1.40]).[5,25] Some of the RCTs also compared LR (n = 10; HR [95% CI] = 1.31 [1.11–1.56]) and RR (n = 4; HR [95% CI] = 0.82 [0.53–1.28]). Out of the total 5333 randomized women in 13 RCTs, 2815 women had BCS (1588 in NACT group and 1227 in ACT group). Three RCTs having mastectomy to all randomized patients and one trial planning mastectomy to all the patients of ACT arm cannot be included in the meta-analysis. Overall, NACT is found to be associated with increased BCS rates (n = 9, RR = 1.19 [1.03–1.37]). Two major trials highly supported breast conservation.[21,30] Out of these two, one trial administered taxane-based chemotherapy.[21] Another trials had protocol to change earlier planned MRM to BCS, depending on the response.[30] Even after excluding these two studies in sensitivity meta-analysis, NACT was found to be associated with increased BCS rate (I^2 = 0%, n = 7, RR = 1.05 [0.99–1.11], especially in total NACT group (n = 3, RR = 1.11 [1.04–1.17]) but not in sandwich NACT group (n = 4, RR = 1.01 [0.94–1.08]).

Grading of Evidence

All the included studies were assessed for risk bias except few small studies; the studies' quality was high [Table 3]. Further, as reported in sensitivity analysis, these small studies did not alter the pooled effect size. Hence, the risk of bias was taken as not serious. Heterogeneity was low to moderate for all of the outcomes except BCS (I^2 = 90.1%). Indirectness and imprecision were assessed as not serious. Overall, the quality of evidence for all of the outcomes was high except DFS and BCS. In a sensitivity analysis for BCS after excluding two trials, heterogeneity index came down to 0% and graded the evidence as high quality.[21,30]

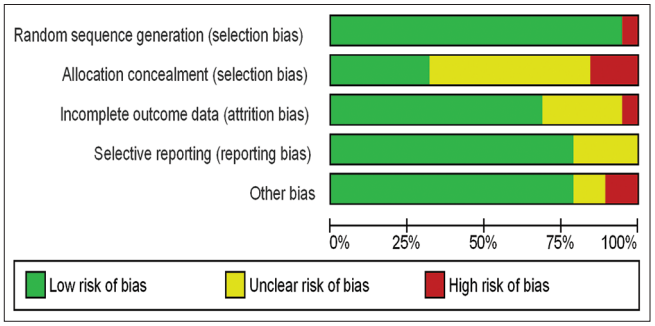

Figure 2: Risk of bias across studies

Table 3: Summary of findings according to GRADE

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)
	Risk with adjuvant chemotherapy	Risk with neoadjuvant chemotherapy			
OS	298 per 1000	293 per 1000 (270-317)	HR 0.98 (0.89-1.08)	5584 (15 RCTs)	⊕⊕⊕⊕high
RFS	373 per 1000	373 per 1000 (331-424)	HR 1.00 (0.86-1.18)	5185 (14 RCTs)	⊕⊕⊕◯moderate[a]
LRR	114 per 1000	138 per 1000 (119-158)	HR 1.23 (1.05-1.43)	5247 (15 RCTs)	⊕⊕⊕⊕high
LRR (sensitivity analysis)	105 per 1000	122 per 1000 (103-114)	HR 1.17 (0.98-1.40)	4451 (11 RCTs)	⊕⊕⊕⊕high
DM	275 per 1000	268 per 1000 (232-312)	HR 0.97 (0.82-1.16)	5066 (13 RCTs)	⊕⊕⊕⊕high
BCS	533 per 1000	634 per 1000 (549-730)	RR 1.19 (1.03-1.37)	4618 (9 RCTs)	⊕⊕⊕◯moderate[b]
LR	98 per 1000	126 per 1000 (108-148)	HR 1.31 (1.11-1.56)	4908 (10 RCTs)	⊕⊕⊕⊕high
Regional recurrence	42 per 1000	35 per 1000 (23-54)	HR 0.82 (0.53-1.28)	2009 (4 RCTs)	⊕⊕⊕⊕ high

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI), GRADE working group grades of evidence, High certainty: We are very confident that the true effect lies close to that of the estimate of the effect, Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different, Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect, Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect, [a]One study by Satuffer *et al*. randomized 87 participants but analyzed 92 participants, but even after excluding this study, there is no effect on pooled estimate, [b]Heterogeneity index I^2 is 90.1%. OS – Overall survival; RFS – Recurrence-free survival; LRR – Locoregional recurrence; DM: Distant metastasis; BCS – Breast-conserving surgery; LR – Local recurrence; CI – Confidence interval; HR – Hazard ratio; RR – Risk ratio;⊕ – One plus point out of 4; ◯ – Zero point out of four

Discussion

In the last four decades, various RCTs had assessed the effectiveness of NACT in the treatment of breast cancer. RCTs have compared the effectiveness among different patient-related characteristics, varying chemotherapy regimens, and variable end points. Among these, a number of RCTs have reported NACT to be beneficial in terms of oncological outcomes as well as functional outcomes.[1-5] However, some other RCTs have reported contradictory findings.[6,7] In view of such mixed reporting, there was a need to critically apprise and analyze the benefits of NACT in breast cancer.

A systematic review by Mauri *et al*., 2005, compared neoadjuvant systemic therapy (chemotherapy and hormone therapy) instead of NACT alone with adjuvant systemic therapy.[8] However, another systematic review by Mieog *et al*., 2007, assessed the role of NACT on clinical outcomes in women with operable breast cancer.[9] The above-mentioned review reported equivalent survival benefits of NACT in comparison to ACT with fewer adverse effects. In addition, it also reported that NACT increased BCS but at the associated cost of increased LRR. The present study is an extension of this only systematic review.[9] The previous review totally relied on Cochrane Register of Controlled Trials up to August 4, 2005. However, the present review could consider additional search database, for example, PubMed up to January 21, 2016. Hence, the present systematic review is able to include more number of studies as well as data on longer follow-up. In addition to the 14 studies considered in earlier review, five more studies could be identified and included in the present review. Further, data on longer follow-up for four studies included in the present review could be available through their updated publications after previous review was published. As a result, minimum and maximum median follow-ups of previous review were upgraded from 24 and 124 months to 25 and 192 months, respectively. Accordingly, the present study is able to achieve the reported importance of extended follow-up (15–20 years) in breast cancer trials.[37] In addition to the outcomes analyzed in previous review (OS, DFS, LRR, and BCS), the present review could also analyze few more outcomes such as LR, RR, and DM. Further, this review could analyze the couple of the outcomes considered even in previous review using longer follow-up. In addition, subgroup analyses on the basis of preoperative and sandwich chemotherapy for each of the considered outcomes were also performed. The present review has some additional gains over previous review as well. Unlike previous review which used only fixed-effects method, the present review considered fixed-effects as well as random-effects methods appropriately depending on heterogeneity level, with a belief that appropriate analytical method needs to be preferred regardless of the change in the results in comparison to inappropriate statistical method.

Two schedules of NACT, i.e., total NACT and sandwich NACT, were analyzed as subgroup analyses regarding every considered outcome. Further, sensitivity analysis was performed for all the outcomes with and without consideration of the studies in which patients having complete response were not operated. For further clarity regarding the effectiveness of NACT under the present review, sensitivity analyses were carried out in each subgroup.

The present review reaffirms the finding reported under previous review that patients receiving NACT experienced higher LRR. However, this result disappeared under sensitivity analysis excluding those studies in which patients showing complete response were not operated. These results also remain true under preoperative subgroup analysis. Interestingly, results under sandwich subgroup remain unchanged under sensitivity analysis, which was already insignificant, supporting the views expressed under previous review; the patients receiving NACT experience higher breast-conserving rates. In addition, the preoperative subgroup showed significantly higher breast-conserving rates even in sensitivity analysis. Based on these results, it may be suggested that total preoperative NACT may be a preferred choice.

Keeping in view of varying considerations regarding each of the measured toxicities reported under the RCTs, strictly speaking, there was little scope to carry out the related meta-analysis toward synthesization of the related results. In spite of that, an exploratory analysis was carried out. The result in relation to leukopenia showed considerable significance of NACT as a protective option. It is worthwhile to mention here that such occasional findings are difficult to be explained. In summary, the analytical results on toxicity have no relevance in terms of comparing NACT with ACT.

Limitation

In case of survival outcomes, hazard ratio, if not reported, was estimated using the method suggested by Parmar *et al*.[17] The limitation associated with this method may lead to a biased pooled result. As blinding of physicians cannot be performed in these RCTs, the breast conservation rate may be overestimated as they may advise more breast conservation in NACT arm. Further, most of the RCTs have proper randomization including concealment, but the quality of systematic review obviously depends on the quality of included RCTs. The screening was duplicated by the same reviewer, and only a sample was checked by another reviewer. The screening and data extraction could not be performed by two reviewers independently and in duplicate.

Conclusion

The present review further confirmed that the use of NACT has similar survival as of ACT. However, NACT downgrades the tumor size, hence facilitating more BCSs without increasing LRR. As a result of the availability

of criterion regarding grading of the evidence generated, it was possible to generate grading for every considered outcome under the present review.[38] For every outcome, it emerged to be high grade except regarding two outcomes, DFS and BCS showing moderate grades. However, in sensitivity analysis, it was also graded high.

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Conflicts of interest

There are no conflicts of interest.

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Appendices

Database-wise Search Strategy

Medline Search Strategy

((("Breast Neoplasms"[Mesh]) OR (breast AND (cancer OR tumour OR tumor OR neoplas*)))

AND (neoadjuvant OR preoperat* OR upfront OR pre?operat* OR (neo)adjuvant OR (pre)operative OR (up)front OR primary OR induction)

AND (adjuvant OR postoperative OR post$operative OR (post)operative OR "chemotherapy, adjuvant"[MeSH Terms] OR adjuvant chemotherapy[Text Word])

AND ((Chemotherapy[MeSH Terms]) OR Chemotherapy))

AND ((((randomized controlled trial[pt]) OR (randomized controlled trials[mh]) OR (random allocation[mh]) OR (double-blind method[mh]) OR (single-blind method[mh]) OR singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw])) AND (mask*[tw] OR placebos[mh] OR placebo*[tw] OR random*[tw] OR (research design[mh:noexp]) OR (follow-up studies[mh]) OR (prospective studies[mh]) OR (cross-over studies[mh]) OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animal[mh] NOT human[mh]))

Search Strategy for Cochrane Register of Controlled Trials

Table S1: Search strategy regarding Cochrane Central Register of Controlled Trial

#1	MeSH descriptor: (Breast Neoplasms) explode all trees
#2	breast and (cancer* or tumor* or tumor* or neoplas*)
#3	#1 or #2
#4	neoadjuvant
#5	preoperat*
#6	upfront
#7	pre?operat*
#8	(neo) adjuvant
#9	(pre) operative
#10	(up) front
#11	primary
#12	{or #4-#11}
#13	postoperative
#14	adjuvant
#15	(post) operative
#16	{or #13-#15}
#17	chemotherapy
#18	MeSH descriptor: (drug therapy) explode all trees
#19	#17 or #18
#20	(#12 near #19) and (#16 near #19)
#21	#20 and #3 in trials

Search Strategy for WHO Clinical Trial Registry

Keyword:

Title Breast Cancer

Condition Breast Cancer

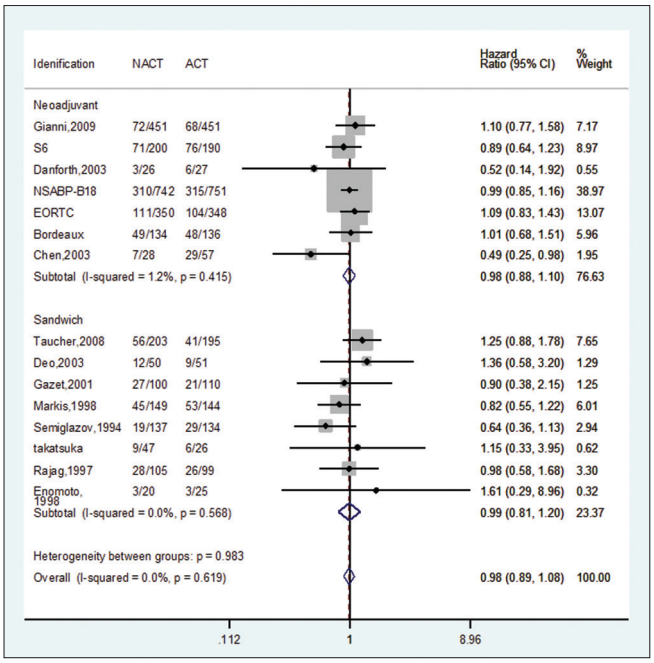
Intervention Neoadjuvant Chemotherapy

Article retrieved: 24

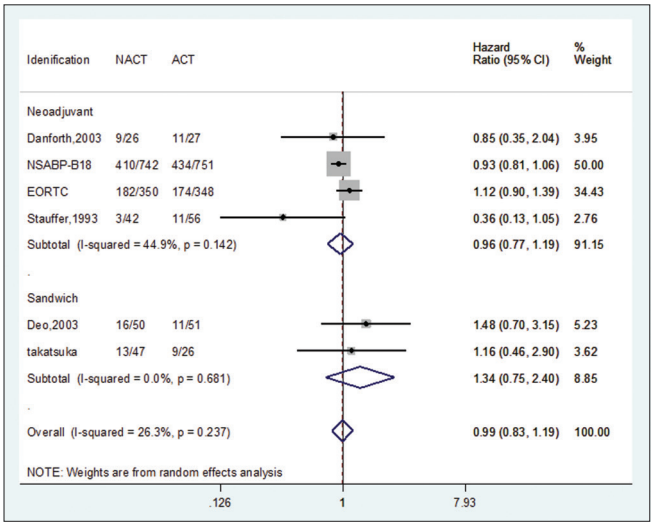
None of the registered trials compares NACT with ACT

Appendix S2: Subgroup analysis on the basis of total preoperative chemotherapy and sandwich chemotherapy

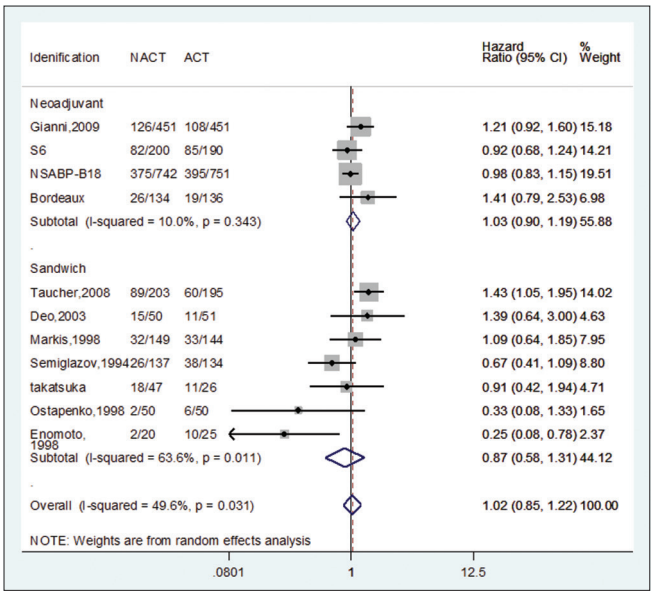
Overall Survival



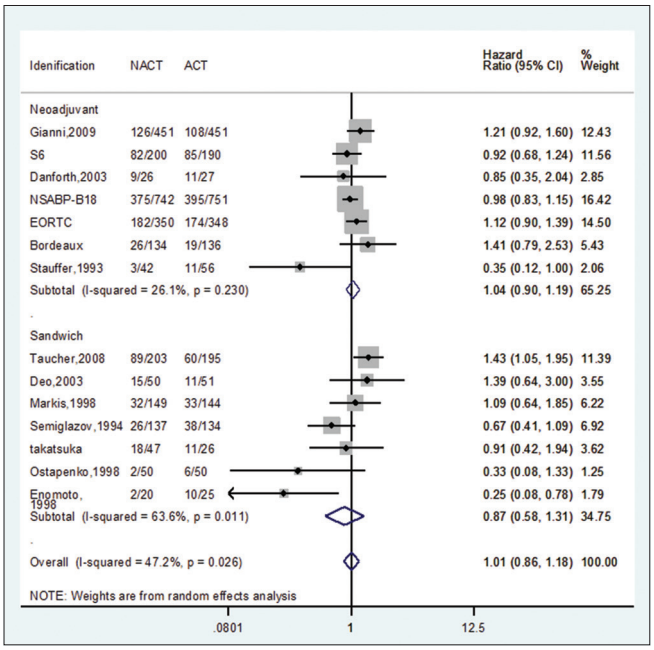
Disease-free survival



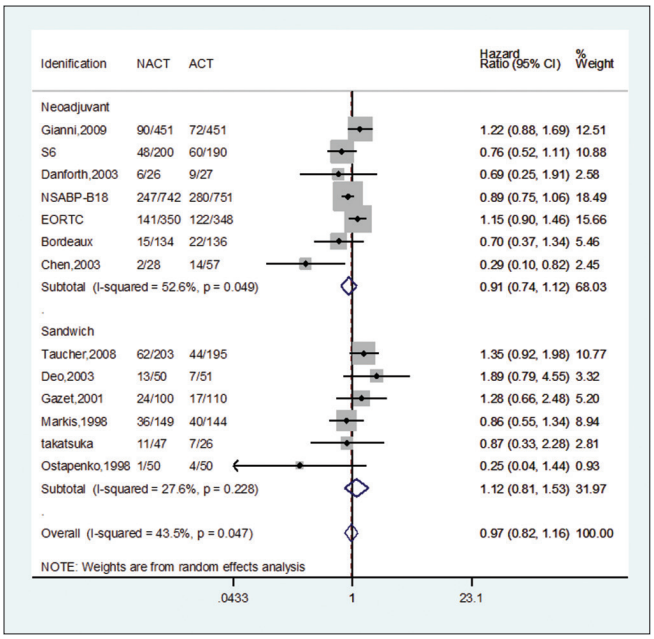
Relapse-free survival



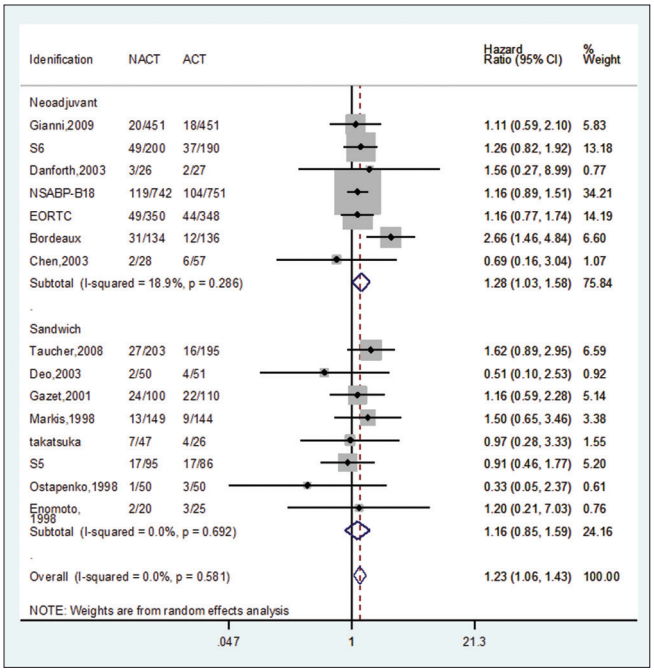
Disease-free survival or relapse-free survival



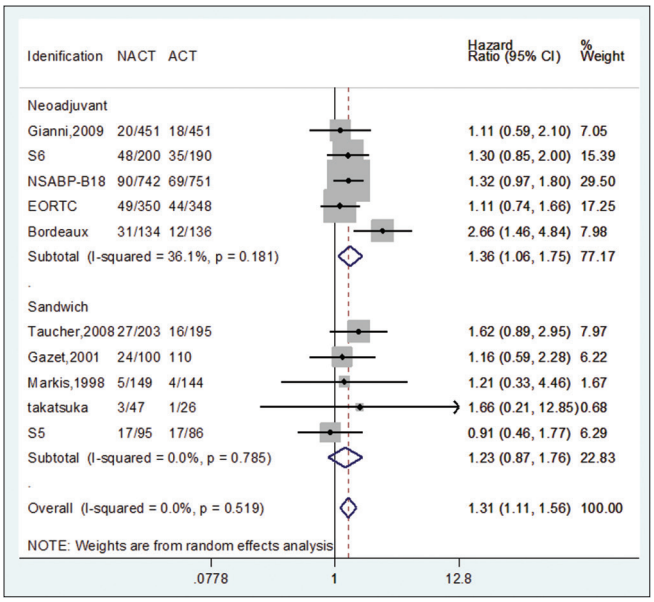
Distant metastasis



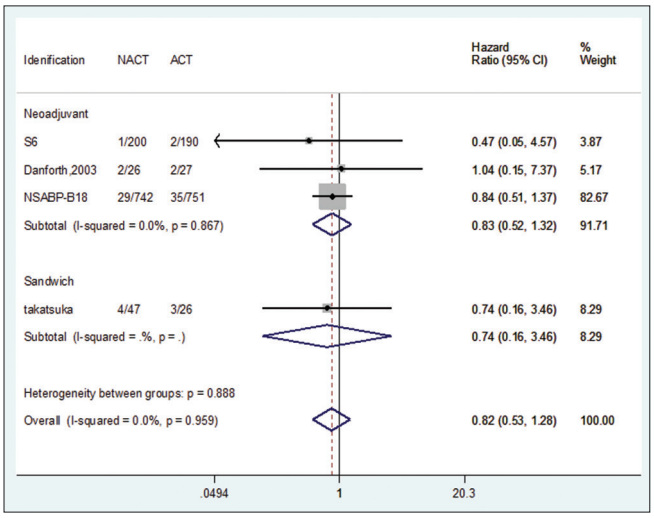
Locoregional recurrence



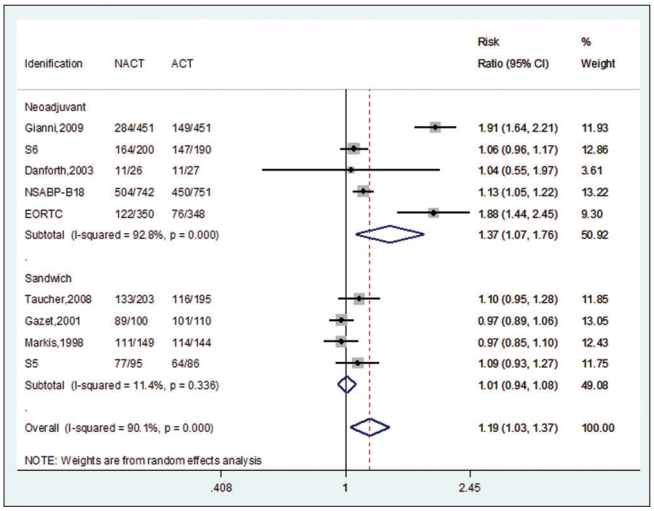
Local recurrence



Regional recurrence



Breast-conserving surgery



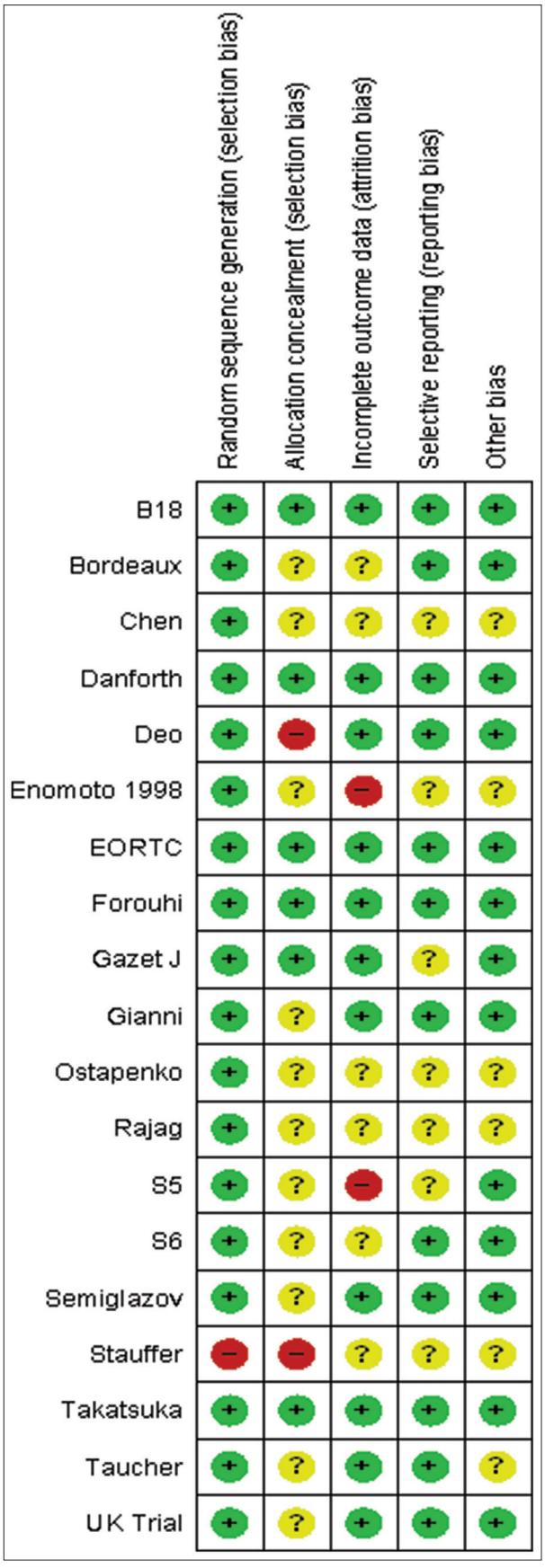


Figure S1: Risk-of-bias graph for all the included studies