Improving breast cancer outcome by preoperative systemic therapy and image-guided surgery

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Part I

Preoperative systemic therapy

Part IA

Preoperative therapy and personalized treatment

Chapter 2

Neoadjuvant chemotherapy for operable breast cancer: a Cochrane systematic review

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ABSTRACT

Introduction

Neoadjuvant chemotherapy for early breast cancer can avoid mastectomy by shrinkage of tumor volume. Additional potential advantages are early introduction of systemic therapy, determination of chemosensitivity and early availability of prognostic information. However, concerns exist about local control after downsized surgery and the delay of local treatment in patients with tumors resistant to chemotherapy. This review assesses the effectiveness of neoadjuvant chemotherapy on clinical outcome.

Methods

All randomized trials comparing neoadjuvant and adjuvant chemotherapy for early breast cancer were assessed for eligibility and quality, and data were extracted by two independent reviewers. Hazard ratios (HR) were derived for time-to-event outcomes directly or indirectly using the methods described by Parmar *et al*. Relative risks were derived for dichotomous outcomes. Meta-analyses were performed using fixed effect model.

Results

Fourteen studies randomizing 5,500 women were eligible for analysis. Median follow-up ranged from 18 to 124 months. Eight studies described a satisfactory method of randomization. Overall survival was equivalent in both groups. In the neoadjuvant group, the mastectomy rate was lower (relative risk = 0.71, 95% CI = 0.67 to 0.75, $P < .0001$) without hampering local control (HR = 1.12, 95% CI = 0.92 to 1.37, $P = .25$). Neoadjuvant chemotherapy was associated fewer adverse effects. Pathological complete response is associated with better survival than residual disease (HR = 0.48, 95% CI = 0.33 to 0.69, $P < .0001$).

Conclusion

Neoadjuvant chemotherapy is an established treatment option for early breast cancer in order to down stage surgical requirement, to evaluate chemosensitivity and to facilitate translational research.

INTRODUCTION

Neoadjuvant, or preoperative, chemotherapy is the administration of chemotherapy before surgical treatment. Its use in breast cancer was introduced in the early 1980s in patients with locally advanced disease in order to convert inoperable into operable tumors.[1] Soon after achieving positive results in the locally advanced setting, randomized controlled trials were conducted to evaluate the technique for earlier, operable stages. A major benefit of neoadjuvant chemotherapy is its potential to increase breast conservation, which is associated with less morbidity and improved body image compared with complete breast removal.[2] However, there is concern about local control after down staging of the tumor and the delay to surgery in patients with tumors resistant to chemotherapy.

In their recently published meta-analysis on neoadjuvant and adjuvant chemotherapy, Mauri and colleagues[3] reported equivalent overall and disease-free survival rates, but an increased loco regional recurrence risk in the neoadjuvant group, particularly when surgery was withheld. However, this analysis excluded studies for which no peer-reviewed journal publication was available.[4] In addition, relative risks (RRs) for time-to-event data were used, whereas the hazard ratio (HR) would be a more appropriate statistic when individual patient data are not available.[5, 6] Furthermore, the change of local treatment in the neoadjuvant group was not assessed in a quantitative way and adverse effects were not analyzed. Finally, since the appearance of this publication, several studies have reported long-term follow-up results.

In the present report, the available evidence from randomized controlled trials is reviewed systematically to assess the effectiveness of neoadjuvant chemotherapy, compared with adjuvant chemotherapy, on treatment-related outcomes in women with operable breast cancer. The association between breast conservation surgery and loco regional recurrence is analyzed in detail. A substantial version of this review has appeared in the Cochrane Library.

MATERIAL AND METHODS

Search, selection and data collection

The Specialised Register maintained by the Editorial Base of the Cochrane Breast Cancer Group (CBCG) was searched using the codes 'early', 'locally advanced' and 'chemo'. The register includes both published and unpublished (including ongoing) trials and applies no language restrictions. Details of the search strategy are described in the Group's module in The Cochrane Library. Properly randomized controlled trials were selected that compared neoadjuvant with adjuvant chemotherapy in women with operable breast cancer (T1–3 N0–2 M0; American Joint Committee on Cancer stages

I–IIIA). Two independent reviewers assessed eligibility and quality, and extracted data from the included trials. Disagreements were resolved by consensus. Data were entered into Review Manager 4.2.7 and analyzed using Review Manager 1.0.2 (Cochrane Collaboration, Oxford, UK).

Data analysis

Time-to-event outcomes were overall survival and time to loco regional recurrence as first event, for which the HR is the most appropriate statistic.[5, 6] When possible, the HR and associated variances were extracted directly from the trial publication. If not reported, they were obtained indirectly using the methods described by Parmar *et al.*[7] and the Excel® (Microsoft, Redmond, Washington, USA) spreadsheet developed by Matthew Sydes (Cancer Division) in collaboration with the Meta-analysis Group of the Medical Research Council Clinical Trials Unit, London. To allow for immature follow-up, the numbers at risk were adjusted based on estimated minimum and maximum follow-up times. A pooled HR was obtained from the derived observed minus expected number of events and the variance for each trial using the fixed-effect model.[8] The pooled HR represents the overall risk of an event associated with neoadjuvant *versus* adjuvant chemotherapy.

The association between pathological complete response and overall survival was analyzed in the neoadjuvant treatment arm. Pathological complete response was defined as complete disappearance of invasive carcinoma on histological examination after chemotherapy. The survival rate of patients with a complete response was compared with that of patients with residual disease using the univariate meta-analysis technique described above.

For loco regional treatment, data were used from studies in which the treatment protocol allowed the derivation of differences in breast conservation rate, preferably after follow-up, between research and control arms to calculate RRs. Mastectomy was scored as an event. Patients with no information available on loco regional treatment were excluded from the analyses. In the neoadjuvant group, the change in originally planned local treatment strategy was analyzed and the local recurrence rate in patients with down staged breast conservation *versus* preplanned breast conservation was compared. For adverse effects, the number of World Health Organization grade III and IV events of postoperative complications, cardiotoxicity, chemotherapy-related infectious complications (leucopenia, neutropenia or infection), nausea and vomiting, and alopecia were extracted. For these outcomes, a pooled RR was obtained using the fixed-effect (Mantel–Haenszel) model. For clinical interpretation, the pooled RR was converted to risk difference and numbers needed to treat (NNT).

The I^2 statistic was used to test for heterogeneity across studies.[9] An I^2 value greater than 50% was considered to represent substantial heterogeneity. Subgroup analyses were conducted for treatment arm (neoadjuvant, 'sandwich') and loco

regional treatment (breast-conserving surgery, mastectomy, exclusive radiotherapy). χ^2 tests for interaction were applied to these subgroup analyses.[10] Publication bias was tested by using funnel plots; an inverted symmetrical funnel plot assumes the absence of publication bias.[11]

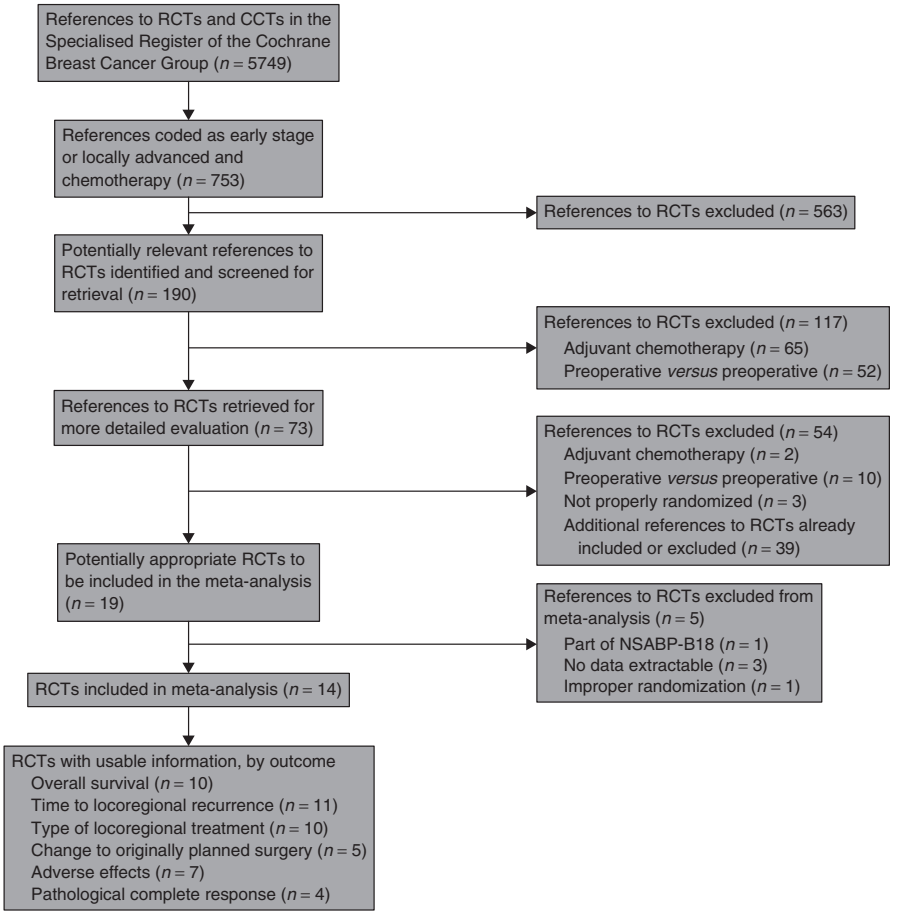

Figure 1. Flow chart of papers assessed for analysis. Search strategy applied 4 August 2005. RCT, randomized controlled trial; CCT, controlled clinical trial; NSABP, National Surgical Adjuvant Breast and Bowel Project.

RESULTS

Description of studies

On 4 August 2005, the Specialised Register of the CBCG contained 5,749 references of which 753 were identified during the search (Figure 1). After detailed evaluation of 73 references, 14 were included in this review (Table 1). In total, 5,500 women were randomized to either neoadjuvant or adjuvant chemotherapy. Median follow-

up ranged from 24 to 124 months. In eight studies, patients in the neoadjuvant arm received part of the chemotherapy courses after local treatment.[12, 15, 17, 19-21, 23, 24] In seven studies, tamoxifen was administered to eligible patients and started after surgery.[14, 16, 19, 20, 22, 23, 25] In one study, tamoxifen was administered before surgery.[23] Four studies gave both groups the same local treatment.[15, 19, 20, 24] Three studies administered preoperative radiotherapy.[17, 18, 24] Eight studies described a satisfactory method of randomization.[13, 14, 16, 19, 22-24] Six studies reported a satisfactory method of concealment of allocation.[15, 16, 21-23, 25] The randomization method was not reported in the remaining studies. Overall, 98.2% of the patients included in time-to-event outcomes were analyzed by intention to treat. For loco regional treatment, data on 5,292 (97.0%) of the 5,453 women randomized were available for analysis. For adverse effects, data on 3,382 (96.9%) of the 3,490 patients randomized were available for analysis.

Table 1. Characteristics of the included studies

Study	Inclusion period	N	Stage	Type of chemotherapy*	Median follow-up (months)	Survival (%)		Local recurrence (%)		Mastectomy (%)	
						Neo	Adj	Neo	Adj	Neo	Adj
ABCSG[12]	1991-1999	423	II-IIIA	CMF (3 of 6)[a]	n.a.	n.a.	n.a.	n.a.	n.a.	33	41
Bordeaux[13]	1985-1989	272	II-IIIA	EVM/MTV (6 of 6)	124	62	59	23	9	55[b]	100
ECTO[14]	1996-2002	902[c]	II-IIIA	AT + CMF (4 of 4)	50	87	90	3	4	35	66
Edinburgh[15]	n.a.	79	II-IIIA	CAP (4 of 6)[d]	n.a.	n.a.	n.a.	n.a.	n.a.	100	100
EORTC[16]	1991-1999	698	I-IIIA	FEC (4 of 4)	120	65	66	14	13	63	77
Institut Curie[17]	1983-1986	196	II-IIIA	FAC (2 of 6)	54	n.a.	n.a.	18	20	23	36
Institut Curie[18]	1986-1990	414	II-IIIA	FAC (2 of 6)	105	65	60	27[e]	19[e]	37[f]	35[f]
Japan[19]	1995-1997	50	II-III	FEC (2 of 5)	24	84	80	10	8	100	100
Lithuania[20]	1994-1997	100	II	CMF (2 of n.a.)	42	n.a.	n.a.	2	6	0	0
London[21]	1990-1993	210	I-IIIA	MMM (4 of 8)[d]	> 60	78	87	20	16	11	8
NSABP[22]	1988-1993	1523	I-IIIA	AC (4 of 4)	114[g]	69	70	15	13	32	40
Royal Marsden[23]	1990-1995	309	I-IIIA	MM(M) (4 of 4)	112	70	63	9	6	11	22
St Petersburg[24]	1985-1990	271	IIb-IIIa	TMF (1-2 of 6)	53	86	78	n.a.	n.a.	100	100
USA[25]	1990-1998	53	II	FLAC + G(M)-CSF (5 of 5)	108	87	72	12	7	58	59

* Values in parentheses are number of courses given before operation as a proportion of total number of courses. a Lymph node-positive patients received three courses of epirubicin, cyclophosphamide after surgery. b After 10 year median follow-up initial rate was 37%. c Three-arm study; second postoperative arm included 453 patients. d Patients with estrogen-positive tumors received endocrine therapy. e After 5-year median follow-up. f After 5-year median follow-up. Initial rate was 18%. g Mean.

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ECTO, European Cooperative Trial in Operable Breast Cancer; EORTC, European Organization for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project. CMF, cyclophosphamide, methotrexate, fluorouracil; EVM/MTV, epirubicin, vincristine, methotrexate/mitomycin C, thiotepa, vindesine; AT, doxorubicin, paclitaxel; CAP, cyclophosphamide, doxorubicin, prednisolone; FEC, fluorouracil, epirubicin, cyclophosphamide; FAC, fluorouracil, doxorubicin, cyclophosphamide; MMM, mitozantrone, mitomycin C, methotrexate; AC, doxorubicin, cyclophosphamide; TMF, thiotepa, methotrexate, fluorouracil; FLAC, fluorouracil, leucovorin, doxorubicin, cyclophosphamide; GM-CSF, granulocyte–macrophage colony-stimulating factor; n.a., not available.

Meta-analyses

Overall survival

Ten studies reported overall survival data on 4,620 randomized women and 1,139 estimated deaths. There was no survival difference between neoadjuvant and adjuvant chemotherapy (HR = 0.98, 95% CI = 0.87 to 1.09; Figure 2). The associated funnel plot shows a symmetrical distribution (Figure 3). Of note, no study demonstrated a significant effect in favor of neoadjuvant or adjuvant chemotherapy.

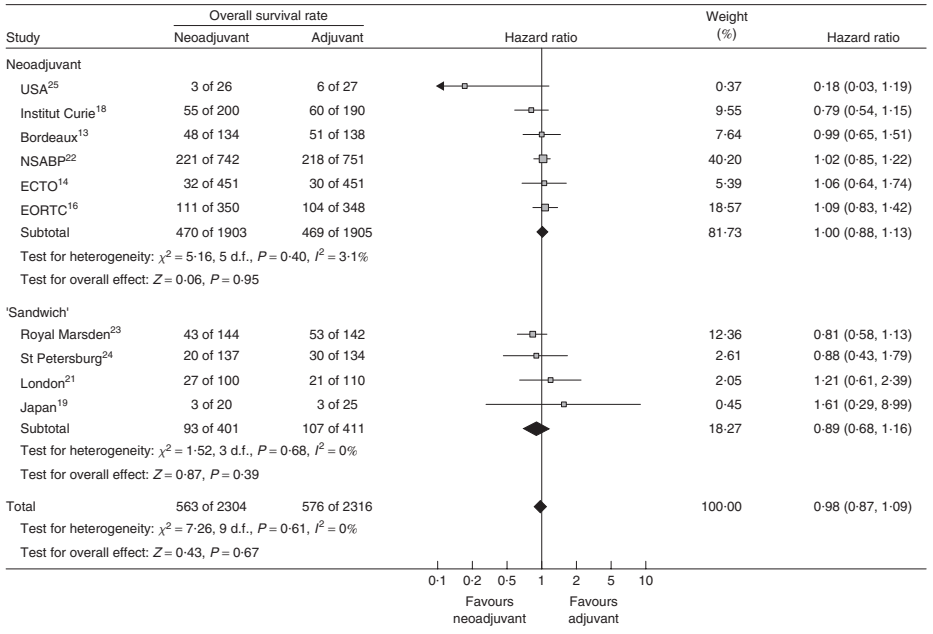

Figure 2. Overall survival of patients who had neoadjuvant or adjuvant chemotherapy stratified by treatment arm protocol (neoadjuvant or 'sandwich'). Hazard ratios are given with 95% CI. NSABP, National Surgical Adjuvant Breast and Bowel Project; ECTO, European Cooperative Trial in Operable Breast Cancer; EORTC, European Organization for Research and Treatment of Cancer.

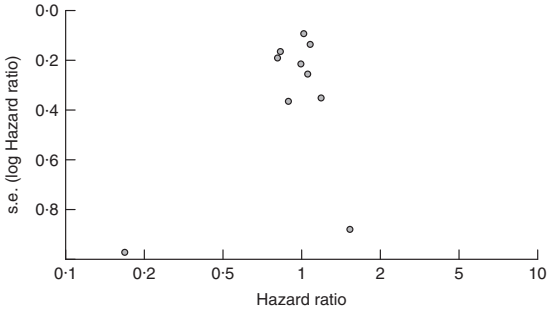

Figure 3. Funnel plot of the studies reporting on overall survival. The symmetrical distribution indicates a low risk of publication bias.

Loco regional recurrence

Eleven studies reported time to loco regional recurrence data on 5,041 randomized women and 570 estimated recurrences. There was a significant difference in favor of adjuvant chemotherapy (Figure 4). However, in three studies, more than one-third of patients received exclusive radiotherapy and no surgery after complete tumor regression.[13, 17, 18] The recurrence rates for these patients were reported separately in only one study.[13] In this study, after a 10-year follow-up, there was a loco regional recurrence rate of 30% when surgery was omitted after neoadjuvant chemotherapy. Therefore, it was decided to exclude these studies from the analysis of loco regional recurrence, because of inadequate loco regional treatment. After this exclusion, the remaining eight studies demonstrated no difference in loco regional recurrence rate between the neoadjuvant and adjuvant groups (HR = 1.12, 95% CI = 0.92 to 1.37, P = .25).

When patients were analyzed according to type of surgery, loco regional recurrence rates were not influenced by the timing of chemotherapy in those who had breast-conserving surgery or women who underwent mastectomy (Figure 5). Two studies reported a non-significant increase in loco regional recurrence in patients

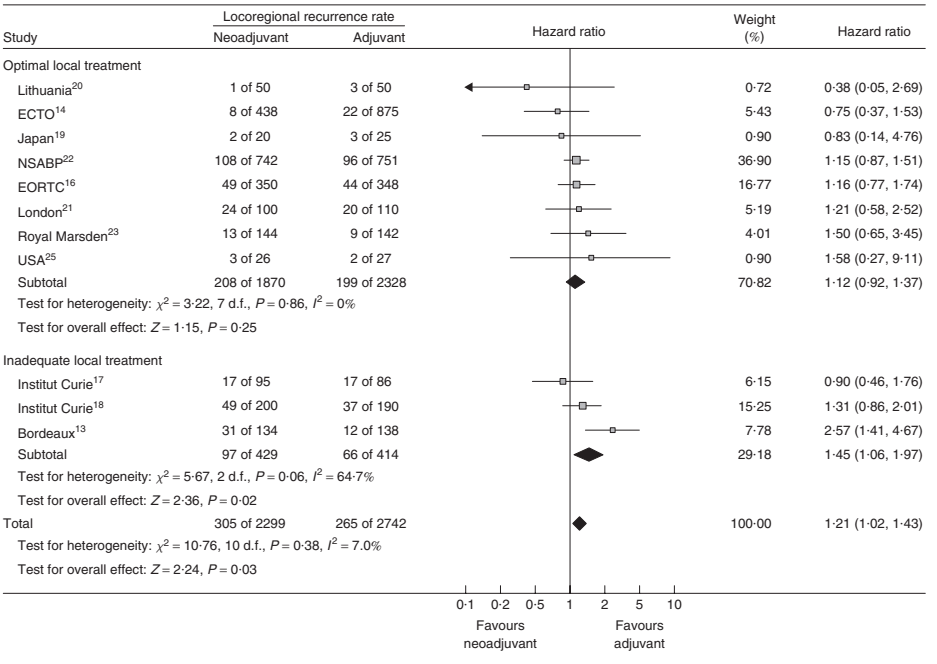

Figure 4. Time to loco regional recurrence in patients who had neoadjuvant or adjuvant chemotherapy. Hazard ratios are given with 95 per cent confidence intervals. The pooled result excluding three studies that omitted surgery in a vast proportion of patients showed a non-significant increase in the neoadjuvant group. This recurrence rate was lower than that in the three excluded trials (χ^2 for difference = 1.66, 1 d.f., P = .20). ECTO, European Cooperative Trial in Operable Breast Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project; EORTC, European Organization for Research and Treatment of Cancer.

who could be treated by breast-conserving surgery because of down staging of the tumor compared with patients for whom the initial plan before the administration of neoadjuvant chemotherapy was breast-conserving surgery (Figure 6).

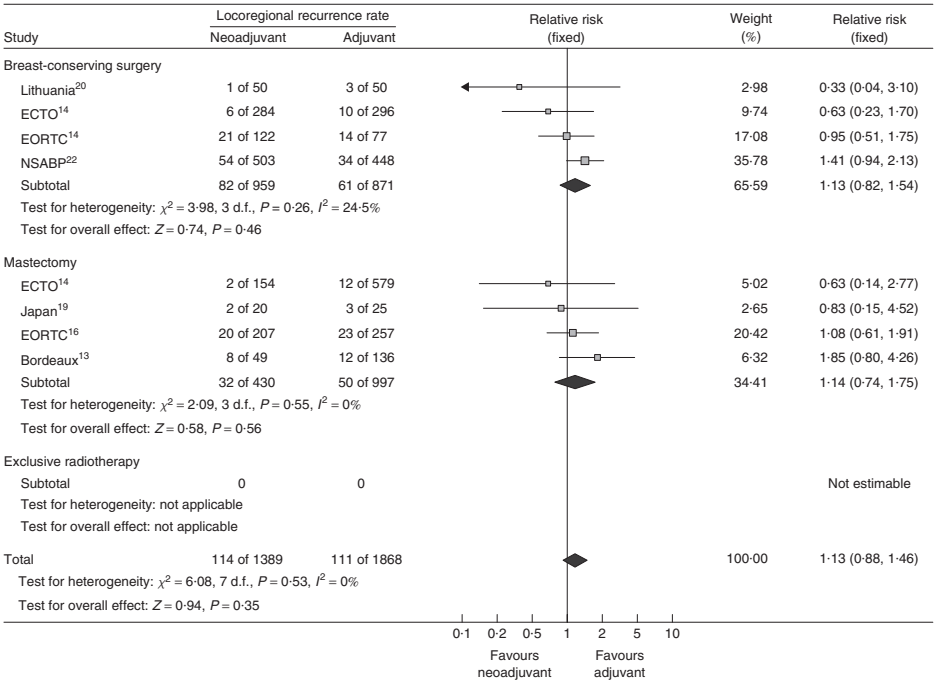

Figure 5. Loco regional recurrence rates in patients who had neoadjuvant or adjuvant chemotherapy stratified by type of surgery. Relative risks are given with 95% CI. There was no difference between breast-conserving surgery and mastectomy (χ^2 = 0.01, 1 d.f., P = .92). ECTO, European Cooperative Trial in Operable Breast Cancer; EORTC, European Organization for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project.

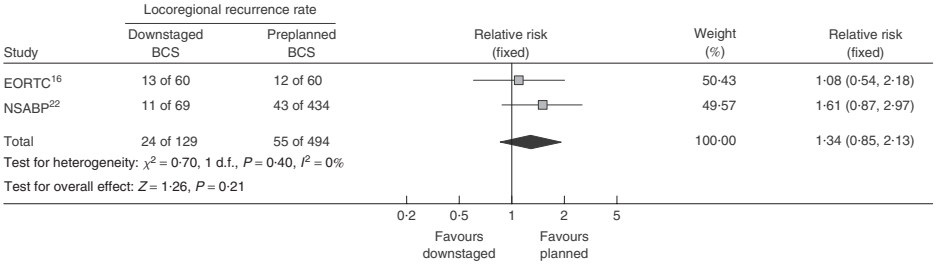

Figure 6. Loco regional recurrence rates in the neoadjuvant group after down staged versus preplanned breast-conserving surgery (BCS). Relative risks are given with 95% CI. The recurrence rate was non-significantly higher in the down staged group, represented by a risk difference of 7.5% (95% CI = 1.7 to 13.2); risk in adjuvant group was 11.1%. EORTC, European Organization for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Loco regional treatment

In ten studies, the protocol allowed derivation of differences in type of loco regional treatment after neoadjuvant chemotherapy. These studies contained 5,292 women of whom 2,395 underwent mastectomy (Figure 7). There was a statistically significant decrease in mastectomy rate in favor of neoadjuvant chemotherapy (RR = 0.71, 95% CI = 0.67 to 0.75, $P < .001$), representing a risk difference of 16.6% (95% CI = 15.1 to 18.1; NNT = 6). Two studies accounted for the substantial heterogeneity ($I^2 = 83.2\%$) in the forest plot. One study had an intensive chemotherapy regimen and achieved high response rates, allowing more conservative treatment.[14] In the other, all patients in the adjuvant chemotherapy arm underwent mastectomy as only those with tumors unsuitable for conservative treatment were included.[13] The remaining eight studies ($I^2 = 25.8\%$) showed a pooled RR of 0.82 (95% CI = 0.76 to 0.89, $P < .001$), representing a risk difference of 8.0% (95% CI = 6.3 to 9.7; NNT = 13).

Five studies reported the change in the originally planned local treatment after neoadjuvant chemotherapy (Table 2). Of the 1,549 assessable women, 397 (25.6%, 95% CI = 23.5 to 27.8) had their surgical treatment down staged; in 66 women (4.3%, 95% CI = 3.3 to 5.3) tumor progression necessitated more radical surgery than originally planned.

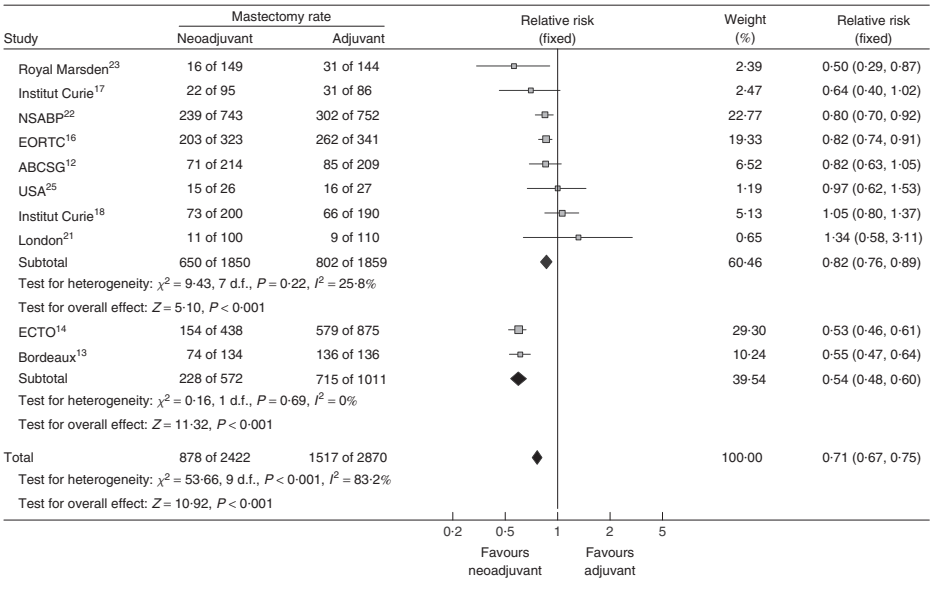

Figure 7. Mastectomy rate in the neoadjuvant and adjuvant chemotherapy groups. Two studies accounted for the substantial heterogeneity (χ^2 for difference = 44.07, 1 d.f., $P < .001$). Neoadjuvant chemotherapy reduced the absolute mastectomy rate by 16.6% (95% CI = 15.1 to 18.1); risk in adjuvant group was 52.9%. NSABP, National Surgical Adjuvant Breast and Bowel Project; EORTC, European Organization for Research and Treatment of Cancer; ABCSG, Austrian Breast and Colorectal Cancer Study Group; ECTO, European Cooperative Trial in Operable Breast Cancer.

Table 2. Change of local treatment after neoadjuvant chemotherapy

Study	BCS → BCS	Mast → Mast	Mast → BCS	Mast → RT	BCS → RT	BCS → Mast	Total
Bordeaux[13]	—	49	40	44	0	0	133
EORTC[16]	60	190	60	0	0	14	324
Institut Curie[18]	—	36	62	102	0	0	200
NSABP[22]	435	187	69	0	0	52	743
Royal Marsden[23]	113	16	19	0	1	0	149
Total	608	478	250	146	1	66	1549

Surgical requirement was down staged in 397 women (25.6% (95% CI = 23.5 to 27.8)). BCS, breast-conserving surgery; Mast, modified radical mastectomy; RT, radiotherapy; EORTC, European Organization for Research and Treatment of Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Pathological complete response

Four studies reported overall survival data in association with a pathological complete response in a total of 1,290 assessable women; there were 381 estimated deaths.[16, 22-24] In these studies the pathological complete response rate ranged from 4.0 to 29.2%. Patients with a pathological complete response had improved overall survival (HR = 0.48, 95% CI = 0.33 to 0.69, $P < .001$).

Adverse effects

Four studies reported infectious complications due to chemotherapy. The data set consisted of 327 events in 2,799 women. A significant decrease in the rate of such complications in the neoadjuvant chemotherapy group was demonstrated (RR = 0.69, 95% CI = 0.56 to 0.84, $P < .001$) with an absolute risk difference of 4.2% (95% CI = 2.3 to 5.6; NNT = 24; Figure 8). Cardiotoxicity events were less frequent in women receiving neoadjuvant chemotherapy (RR = 0.74, 95% CI = 0.53 to 1.04, $P = .08$).

DISCUSSION

This review demonstrates that neoadjuvant chemotherapy results in overall survival rates equivalent to those associated with adjuvant chemotherapy, while permitting more breast-conserving therapy. Neoadjuvant treatment is associated with a decrease in adverse events and does not adversely affect loco regional control of disease. The findings relating to time-to-event data are in concordance with those of the earlier meta-analysis of Mauri and colleagues.[3] However, more studies were available for analysis in the present review and Cochrane Collaboration methodology was used.[6]

The present study, however, has some limitations. First, the maximum median follow-up of the included studies is 10 years, which may be too short to identify differences in clinical outcome. The latest Early Breast Cancer Trialists' Collaborative Group report demonstrated the importance of extended follow-up (15–20 years) in

early-stage breast cancer trials.[26] Furthermore, this report estimated that for every four recurrences one breast cancer death can be avoided over the next 15 years. Another limitation is that seven of the 11 studies reporting on loco regional recurrence provided this outcome as a RR instead of a HR,[13, 14, 18-20, 22, 25] thereby adversely affecting the accuracy of the pooled analysis. Third, the effect of neoadjuvant chemotherapy on breast conservation may be overestimated by detection and performance bias; the unblinded physician assessing tumor response may be more prone to advising breast-conserving therapy. Moreover, as time passes and recurrences develop, subsequent salvage mastectomies will decrease the breast conservation rate. Most studies reported only the initial breast conservation rates. Despite these limitations, the included studies were properly randomized and study quality was generally adequate. In addition, the funnel plot showed a symmetrical distribution suggesting a low risk of publication bias.

Neoadjuvant chemotherapy increases the breast conservation rate. It is well known that breast-conserving surgery is associated with a higher loco regional recurrence rate than mastectomy, without, however, affecting long-term overall survival.[27] The limited and non-significant increase in loco regional recurrence rate in the neoadjuvant group can, therefore, be explained by the increased breast conservation rate and the fact that a substantial proportion of patients in three studies had no surgery after neoadjuvant chemotherapy. To date, direct evidence of local recurrence after down staged surgery following neoadjuvant chemotherapy is still lacking. In the present analysis, no clear risk difference between down staged and preplanned conservative surgery could be found. However, this indirect comparison is based on limited data without correction for confounding effects.

This review demonstrates that the increased local recurrence rate associated with neoadjuvant treatment is greatly reduced after excluding studies in which patients received exclusive radiotherapy after complete tumor regression. This finding emphasizes the importance of incorporating surgery in the loco regional treatment strategy after neoadjuvant chemotherapy. Otherwise stated, the clinical assessment of tumor response by conventional means is insufficiently sensitive safely to withhold surgery. Recently, the introduction of magnetic resonance imaging (MRI) in the monitoring of tumor response has been shown to be of benefit in the assessment of surgical strategy after down staging by neoadjuvant chemotherapy.[28] However, concern exists about the higher false-positive rate of MRI.[29]

The rate of chemotherapy-related infectious complications was significantly lower in the neoadjuvant group. However, no obvious explanation is available. The actual number of chemotherapy courses received was equal in both treatment arms. It is possible that the immune system of patients who underwent primary surgery was already depressed as a result of surgical stress, making them more vulnerable to the negative effects of chemotherapy. In the neoadjuvant group, on the other hand,

patients were able to recover from the chemotherapy before they had surgery. The rate of cardiotoxicity also appeared to be lower in the neoadjuvant group. Known factors influencing cardiotoxicity are anthracycline use, taxane use, increasing age, previous cardiac disease and radiotherapy. The present analysis is driven by the European Cooperative Trial in Operable Breast Cancer (ECTO) 2005 study.[14] Because this study added a taxane to the anthracycline chemotherapy regimen, the assessment of cardiotoxicity was an important endpoint. No imbalance in prognostic variables or difference in method of assessment was found between the treatment arms. An additional literature search did not provide a satisfactory explanation for the reduced risk and, as it does not reach statistical significance, it may be explained simply by chance.

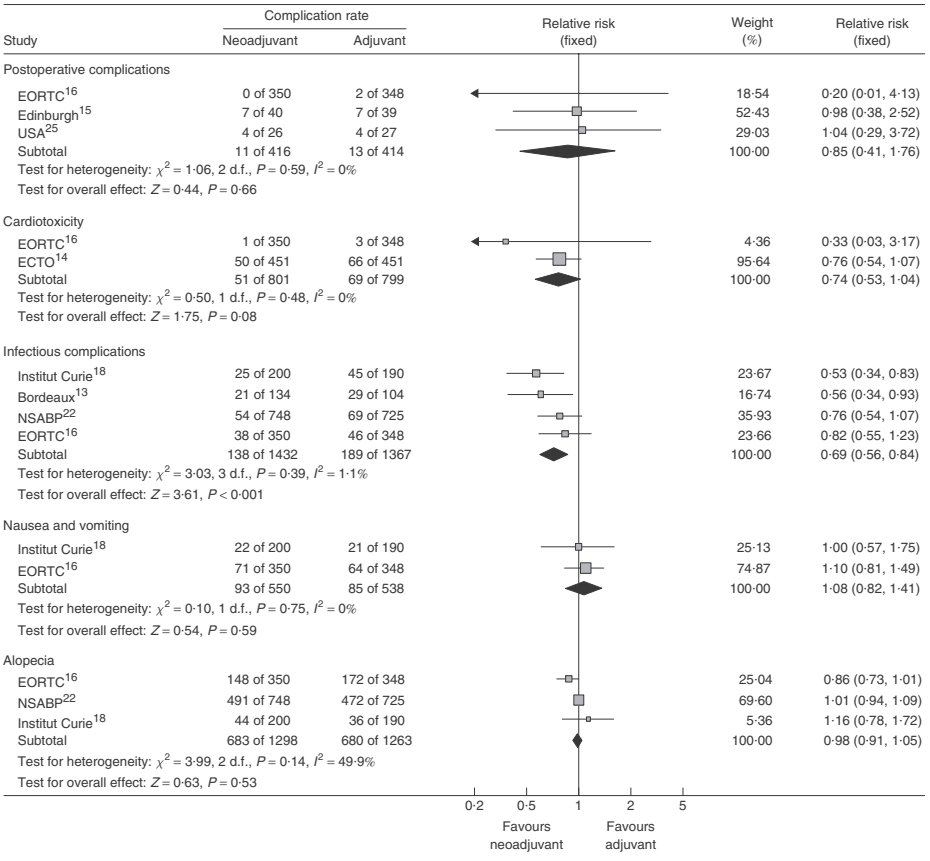

Figure 8. Adverse effects in the neoadjuvant and adjuvant chemotherapy groups. EORTC, European Organization for Research and Treatment of Cancer; ECTO, European Cooperative Trial in Operable Breast Cancer; NSABP, National Surgical Adjuvant Breast and Bowel Project.

Apart from higher breast conservation rates and fewer adverse effects, neoadjuvant chemotherapy facilitates monitoring of tumor response. By adjusting the

dose or switching to another drug in the case of treatment resistance, a patient may be saved the unnecessary burden of toxic side-effects.[30-32] This review suggests that neoadjuvant chemotherapy avoids a mastectomy in about 25% of patients. Conversely, a small percentage of patients (< 5%) originally suitable for breast conservation will require a mastectomy owing to disease progression while receiving neoadjuvant chemotherapy. This is an ethical concern. However, the included studies did not allow regimen change on tumor progression and it is reasonable to expect the percentage to be lower if switching to other cytotoxic drugs is permitted. Concerns might also be raised about the postoperative and thus 'blind' administration of chemotherapy to patients with tumors resistant to therapy. Such patients receive all chemotherapy courses while experiencing only the harmful side-effects, whereas resistance can be detected and adequately dealt with in the neoadjuvant setting. Although tumor response rate is an important predictor of survival, its role as a surrogate endpoint in clinical trials remains controversial.[33]

The introduction of neoadjuvant therapy has had a great impact on breast cancer research. The assessment of tumor behavior *in situ* during neoadjuvant therapy and the correlation of this behavior with clinical outcome is an excellent model with which to determine the predictive role of classical and molecular tumor characteristics. The ultimate goal of this translational research is the introduction of tailor-made treatment strategies based on individual risk profiles. Neoadjuvant therapy offers an excellent setting in which to determine the most efficient treatment approach for an individual patient.[34]

A suggested disadvantage of neoadjuvant chemotherapy is alteration of the lymphatic network, hampering the accuracy of sentinel lymph node biopsy.[35] However, a recently published meta-analysis has demonstrated equivalent accuracy of sentinel lymph node biopsy after neoadjuvant chemotherapy and primary surgery.[36] The apparent safety of this procedure after chemotherapy could decrease the need for axillary lymph node dissection, thereby reducing morbidity.[37] Whether this will affect prognosis, particularly in the situation of a clinically suspect axilla, remains unclear.

This systematic review demonstrates that neoadjuvant chemotherapy for early-stage breast cancer is safe. It induces tumor down staging and thereby an increase in breast conservation. Loco regional control of disease is not significantly influenced by neoadjuvant chemotherapy. Finally, it is an excellent tool with which to evaluate the tumor *in situ* and to facilitate translational research.

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