Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial

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Summary

Background Patients with isolated locoregional recurrences (ILRR) of breast cancer have a high risk of distant metastasis and death from breast cancer. We aimed to establish whether adjuvant chemotherapy improves the outcome of such patients.

Methods The CALOR trial was a pragmatic, open-label, randomised trial that accrued patients with histologically proven and completely excised ILRR after unilateral breast cancer who had undergone a mastectomy or lumpectomy with clear surgical margins. Eligible patients were enrolled from hospitals worldwide and were centrally randomised (1:1) to chemotherapy (type selected by the investigator; multidrug for at least four courses recommended) or no chemotherapy, using permuted blocks, and stratified by previous chemotherapy, oestrogen-receptor and progesterone-receptor status, and location of ILRR. Patients with oestrogen-receptor-positive ILRR received adjuvant endocrine therapy, radiation therapy was mandated for patients with microscopically involved surgical margins, and anti-*HER2* therapy was optional. The primary endpoint was disease-free survival. All analyses were by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00074152.

Findings From Aug 22, 2003, to Jan 31, 2010, 85 patients were randomly assigned to receive chemotherapy and 77 were assigned to no chemotherapy. At a median follow-up of 4·9 years (IQR 3·6–6 ·0), 24 (28%) patients had disease-free survival events in the chemotherapy group compared with 34 (44%) in the no chemotherapy group. 5-year disease-free survival was 69% (95% CI 56–79) with chemotherapy versus 57% (44–67) without chemotherapy (hazard ratio 0·59 [95% CI 0·35–0·99]; p=0·046). Adjuvant chemotherapy was significantly more effective for women with oestrogen-receptor-negative ILRR ($p_{interaction}$=0·046), but analyses of disease-free survival according to the oestrogen-receptor status of the primary tumour were not statistically significant ($p_{interaction}$=0·43). Of the 81 patients who received chemotherapy, 12 (15%) had serious adverse events. The most common adverse events were neutropenia, febrile neutropenia, and intestinal infection.

Interpretation Adjuvant chemotherapy should be recommended for patients with completely resected ILRR of breast cancer, especially if the recurrence is oestrogen-receptor negative.

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Introduction

Local or regional recurrence of breast cancer after mastectomy or lumpectomy heralds a poor prognosis, and accompanies or precedes metastasis in a high proportion of patients. Patients with isolated locoregional recurrences (ILRR)—ie, those without evidence of distant metastasis—harbour a substantial risk of developing subsequent distant metastasis, with 5-year survival probabilities ranging between 45% and 80% after locoregional recurrence,[1–10] as reviewed by Wapnir and colleagues.[11]

In a retrospective review of ten National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials involving 6468 patients who had undergone a lumpectomy, 5-year distant-disease-free survival after an ipsilateral breast tumour recurrence was 67% for women with node-negative primary breast cancers and 51% for women with node-positive primary breast cancers.[9,10] Other locoregional recurrences, such as nodal and chest wall recurrences, resulted in a distant-disease-free survival of 29% and 19% for node-negative and node-positive cancers, respectively. The corresponding 5-year overall survival after ipsilateral breast tumour recurrence was 77% in patients with node-negative disease and 60% in patients with node-positive disease, and 35% and 24%, respectively, after other locoregional recurrences. These analyses show the powerful negative prognostic importance of ILRR events and the need for treatments beyond surgical removal of the ILRR.

Adjuvant chemotherapy and endocrine therapies reduce the risk of relapse and death in patients with

primary breast cancer.[12,13] However, few data are available to inform the recommendation of systemic treatment for locoregional recurrence. The Swiss Group for Clinical Cancer Research randomised trial[14] showed an increase in disease-free survival with the use of tamoxifen after locoregional recurrence in hormone-responsive patients who had undergone a mastectomy.

The International Breast Cancer Study Group (IBCSG) initiated the Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial in collaboration with the Breast International Group (BIG) and NSABP (IBCSG 27-02, BIG 1-02, NSABP B-37), to establish whether chemotherapy improves the outcome of patients with ILRR.

Methods

Study design and patients

The CALOR trial was a pragmatic, multicentre randomised trial that enrolled patients from hospitals in the USA and Canada through NSABP, and from Europe, Australia, South Africa, and South America through BIG. Eligible patients were women of any age with histologically proven and completely excised first ILRR after unilateral breast cancer who had undergone a mastectomy or lumpectomy with clear surgical margins. Mastectomy for the ILRR was recommended for patients with previous breast-conserving surgery. Eligible patients also had to be medically suitable to receive chemotherapy for 3–6 months and have an available measurement of hormone receptor status. Exclusion criteria were no metastatic disease and previous malignancy other than the original breast cancer (except in situ of the uterine cervix and non-melanoma skin cancer).

Participating institutions' ethics committees or institutional review boards approved the trial according to local laws and regulations. All patients gave written informed consent, and the trial was done in compliance with the Helsinki Declaration. The data and safety monitoring committee reviewed accrual and safety data twice a year throughout the trial. Data were obtained at the participating centres and transmitted to the IBCSG data management centre in Amherst, NY, USA, via the DataFax or iDataFax system.

Randomisation and masking

Patients were randomly allocated (1:1) to either chemotherapy or no chemotherapy. Randomisation was done with permuted blocks generated by a congruence algorithm and was stratified by previous chemotherapy (yes *vs* no), whether the ILRR was oestrogen-receptor or progesterone-receptor positive according to institutional guidelines (yes *vs* no), and location of ILRR (breast *vs* mastectomy scar or chest wall *vs* regional lymph nodes). The IBCSG randomisation system used dynamic balancing of treatment assignment within each participating centre to achieve balance among institutions. After confirming eligibility, participating centre staff accessed the central randomisation system via the internet and entered required information including stratification factors. The randomisation system assigned a patient identification number, treatment group, and date of randomisation via the computer screen with a follow-up email. The IBCSG data management centre developed and maintains the randomisation system. Masking was not done in this trial. Patients, participating centre staff, trial management staff, and statistical centre staff who analysed the data were aware of the assigned treatment.

Procedures

Radiotherapy was recommended for all patients, but was required for those with microscopically involved surgical margins, using at least 50 Gy (lowered to 40 Gy in 2005) with conventional fractionation. After 2006, the administration of radiotherapy before randomisation was allowed. Endocrine therapy was recommended for all patients with oestrogen-receptor-positive or progesterone-receptor-positive recurrent tumours. *HER2* testing was not required, but in 2004 the study was amended to allow the use of trastuzumab, and, in 2008, other *HER2*-targeted therapies.

In patients randomly assigned to receive chemotherapy, choice of chemotherapy, dose adjustments, and supportive therapies were left to the discretion of the investigators. The protocol recommended at least two cytotoxic drugs for 3–6 months. Chemotherapy was to start within 4 weeks of randomisation and within 16 weeks of resection of locoregional recurrence.

At study entry, standard staging examinations were done (radiograph or CT scan of the chest, ultrasound or CT scan of the abdomen and pelvis, and bone scintigraphy if alkaline phosphatase concentrations were more than two times the normal level or if medically indicated). Follow-up clinical examinations were required every 3 months during the first 2 years, every 6 months during years 3–5, and yearly thereafter. Mammography was required every year, but other laboratory or imaging studies were left to the discretion of the treating physicians.

Adverse events were not recorded for this trial because only one treatment group received chemotherapy, and because the regimens were regarded as standard and the toxicities are well known. Only serious adverse events were recorded for regulatory purposes.

Outcomes

The primary endpoint was disease-free survival, defined as the time from randomisation to invasive local, regional, or distant recurrence (including invasive in-breast tumour recurrence), appearance of a second primary tumour, or death from any cause. Secondary endpoints were overall survival (defined as the time from randomisation to death from any cause), sites of first recurrence after randomisation, incidence of second

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See **Online** for appendix

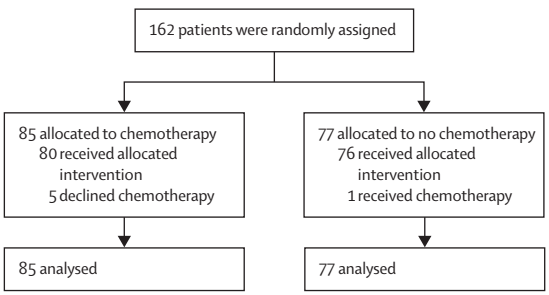

Figure 1: **Trial profile**

	Chemotherapy (n=85)	No chemotherapy (n=77)
Primary surgery		
Mastectomy	33 (39%)	31 (40%)
Breast-conserving surgery	52 (61%)	46 (60%)
Previous chemotherapy*		
Yes	49 (58%)	52 (68%)
No	36 (42%)	25 (32%)
Time from primary surgery to ILRR surgery		
Median (IQR), years	5·0 (2·9–9·5)	6·2 (2·9–11·3)
≥2 years	72 (85%)	65 (84%)
Menopausal status at ILRR		
Premenopausal	20 (24%)	14 (18%)
Postmenopausal	65 (76%)	63 (82%)
Age at ILRR, years	56 (48–61)	56 (50–64)
Location of ILRR		
Breast	47 (55%)	42 (55%)
Mastectomy scar or chest wall	28 (33%)	25 (32%)
Regional lymph nodes	10 (12%)	10 (13%)
Oestrogen-receptor status of the ILRR		
Negative	29 (34%)	29 (38%)
Positive	56 (66%)	48 (62%)
Progesterone-receptor status of the ILRR		
Negative	39 (46%)	40 (52%)
Positive	44 (52%)	35 (45%)
Unknown	2 (2%)	2 (3%)
Oestrogen-receptor status of primary tumour		
Negative	27 (32%)	20 (26%)
Positive	49 (58%)	47 (61%)
Unknown	9 (11%)	10 (13%)
Treatment for ILRR		
Radiation therapy	31 (36%)	29 (38%)
HER2-directed therapies	6 (7%)	4 (5%)
Oestrogen-receptor-positive or progesterone-receptor-positive ILRR	58 (68%)	52 (68%)
Any endocrine therapy in receptor-positive patients†	53 (91%)	50 (96%)
LHRH agonist or oophorectomy	4 (7%)	10 (19%)
Fulvestrant	0	1 (2%)
Tamoxifen	15 (26%)	15 (29%)
Aromatase inhibitors	47 (81%)	41 (79%)
None	5 (9%)‡	2 (4%)§

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	Chemotherapy (n=85)	No chemotherapy (n=77)
Study treatment received		
No chemotherapy	5 (7%)	76 (99%)
Chemotherapy	80 (94%)	1 (1%)
Monochemotherapy	25 (29%)	0
Docetaxel or paclitaxel	16 (19%)	0
Capecitabine	9 (11%)	0
Polychemotherapy	55 (65%)	0
Cyclophosphomide, methotrexate, fluorouracil	2 (2%)	0
Gemcitabine plus navelbine	1 (1%)	0
Anthracycline-based	38 (45%)	0
Taxane-based	13 (15%)	1 (1%)
Anthracycline plus taxane-based	1 (1%)	0

Data are number (%) or median (IQR). ILRR=isolated locoregional recurrence. LHRH=luteinising-hormone-releasing hormone. *See appendix for information about the types of adjuvant chemotherapy given for the trial ILRR and as previous chemotherapy. †Patient might have received more than one endocrine therapy. ‡Five patients did not receive endocrine therapy (two withdrew from the study, one relapsed before starting endocrine therapy, and two had oestrogen-receptor-negative disease). §Two patients did not receive endocrine therapy (one died before starting endocrine therapy and one had progesterone-receptor-positive/oestrogen-receptor-negative disease).

Table 1: **Characteristics and treatment of patients according to randomly assigned treatment**

(non-breast) malignancies, and causes of deaths without relapse of breast cancer.

Statistical analysis

The 5-year disease-free survival for the group receiving no chemotherapy was originally assumed to be 50%; 347 events were needed to detect an improvement in 5-year disease-free survival from 50% to 60% (hazard ratio [HR] 0·74) with 80% power using a two-sided 0·05 level log-rank test and a sample size of 977 patients. Due to a lower than anticipated rate of accrual and to the availability of more active adjuvant agents, in particular taxanes, the third protocol amendment (done in 2008) decreased the anticipated HR to 0·60, corresponding to an increase in 5-year disease-free survival from 50% to 66%, thereby decreasing the planned sample size to 265 (124 disease-free survival events), allowing for 5% of patients to be non-assessable. No results from CALOR were available when this amendment was activated.

In November, 2009, the independent data and safety monitoring committee recommended the trial close due to low accrual, and CALOR closed on Jan 31, 2010, with 162 patients enrolled. In April, 2010, the statistical analysis plan was amended to specify that the first analysis should occur after a median follow-up of 4 years and a minimum follow-up of 2·5 years. The previously planned interim analysis was eliminated and replaced by this single time-driven analysis with statistical significance based on a

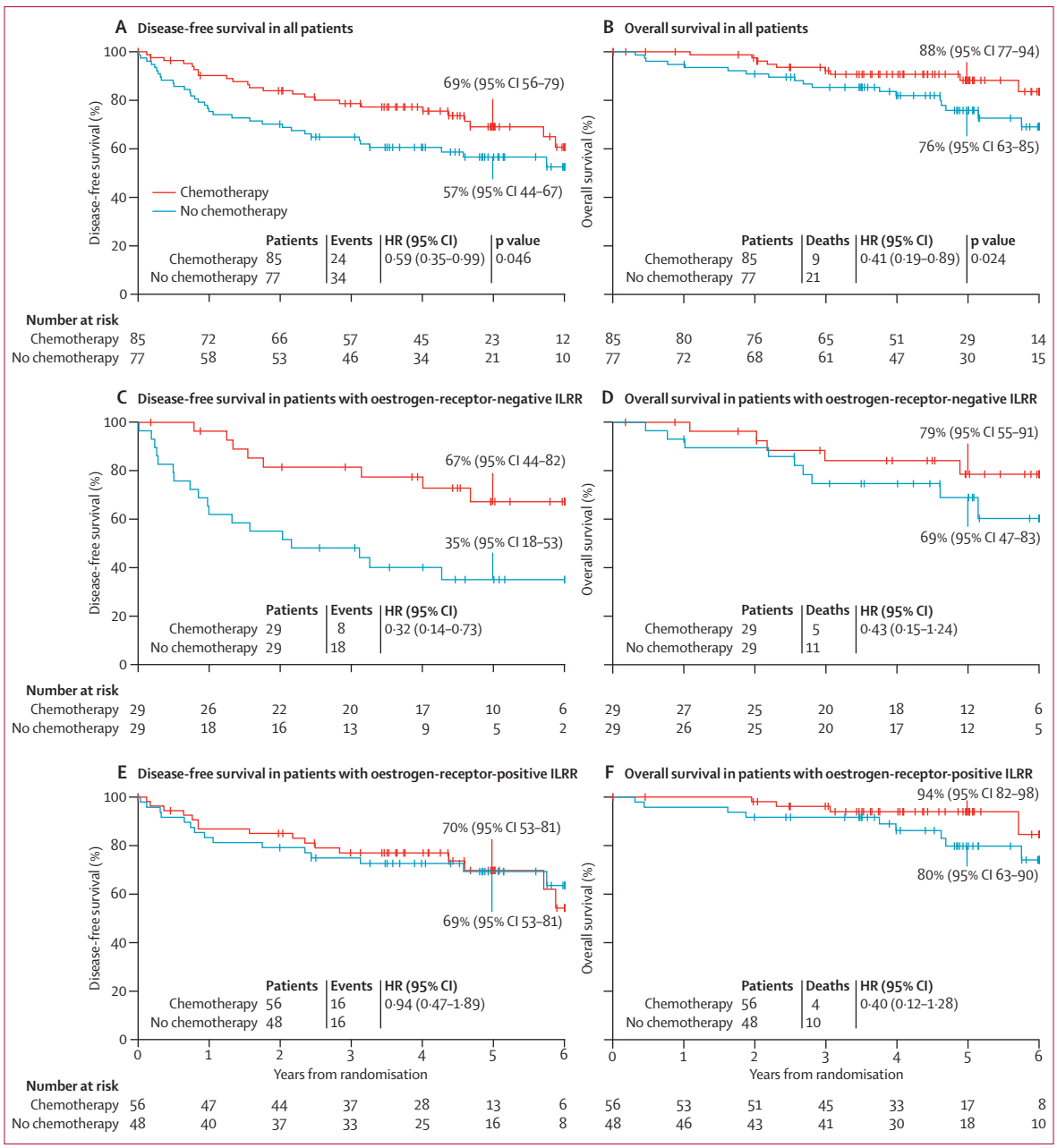

***Figure 2*: Kaplan-Meier curves of disease-free survival and overall survival according to assigned treatment group**
Disease-free survival (A) and overall survival (B) in all patients; patients with oestrogen-receptor-negative ILRR (C and D); and patients with oestrogen-receptor-positive ILRR (E and F). 5-year disease-free survival or 5-year overall survival are presented, as applicable, on each graph. HR=hazard ratio. ILRR=isolated locoregional recurrence.

two-sided p value of 0·05 or less. No results from CALOR, except for the lower than planned enrolment, were available at the time that this revised analysis plan was adopted.

We used unstratified log-rank tests to compare the two groups,[15] and calculated Kaplan–Meier estimates.[16] We used Cox proportional hazards regression to adjust for the prespecified prognostic factors location of the ILRR, oestrogen-receptor status of the ILRR, interval from the surgery of the primary tumour to the surgery of the ILRR, and whether chemotherapy was administered for the primary tumour.[17] The subgroup analysis according to oestrogen-receptor status was clinically motivated and prospectively specified before analysis of any data from the current trial. We also tested the interaction between the randomised comparison and oestrogen-receptor status in a Cox proportional hazards model. We did Grambsch and Therneau tests for violations of proportionality for all final

	HR (95% CI)	p value
Oestrogen-receptor status of ILRR (positive *vs* negative)	0·77 (0·43–1·37)	0·37
Location of ILRR		
Breast	Reference group	NA
Mastectomy scar or chest wall	0·84 (0·45–1·58)	0·59
Lymph nodes	1·18 (0·53–2·64)	0·69
Previous chemotherapy (yes *vs* no)	0·99 (0·57–1·73)	0·97
Interval from primary surgery (in years, continuous)	0·90 (0·85–0·96)	0·0021
Treatment (chemotherapy *vs* no chemotherapy)	0·49 (0·29–0·84)	0·0098

HR=hazard ratio. NA=not applicable.

***Table 2*: Multivariable proportional hazards regression model of disease-free survival**

models,[18] and all yielded non-significant results. All analyses are by intention to treat, and all reported p values are two-sided. Data as of Oct 16, 2012, were used for the efficacy analyses. We used SAS version 9.2 for this analysis.

This study is registered with ClinicalTrials.gov, number NCT00074152.

Role of the funding source

IBCSG and NSABP were responsible for the design of the study. IBCSG coordinated the collection and management of the data, medical review, and data analysis. The reporting of the results was done jointly. Members of the trial steering committee (appendix) reviewed the manuscript and were responsible for the decision to submit for publication. SG and SJA had access to the raw data. The corresponding author (SA) had full access to all the data in the study and had final responsibility to submit for publication.

Results

From Aug 22, 2003, to Jan 31, 2010, the CALOR trial accrued 162 patients from 54 hospitals in Europe, South Africa, North and South America, and Australia. 85 patients were randomly assigned to receive chemotherapy and 77 to no chemotherapy (figure 1). Five patients did not receive assigned chemotherapy. One patient randomly assigned to no chemotherapy requested and received chemotherapy. All 162 randomly assigned patients are included in the intention-to-treat analysis. The patient and disease characteristics, and treatments received for ILRR, were well balanced across the two treatment groups (table 1).

The median age in both groups was 56 years (IQR 50–63) at study entry (table 1). Most patients in both treatment groups had their ILRR surgery at least 2 years after the diagnosis of their primary cancer (table 1). 64 (40%) of all randomly assigned patients had undergone a previous mastectomy, and 101 (62%) had received previous adjuvant chemotherapy (table 1).

Overall, 110 patients had hormone-receptor-positive ILRR (table 1). Most (103 [94%] of 110) patients with oestrogen or progesterone receptor-positive ILRR received adjuvant endocrine therapy. However, two patients with oestrogen and progesterone receptor-negative ILRR also received hormonal treatments. The proportion of patients with available data who received endocrine therapy did not differ significantly between treatment groups (53 [91%] of 58 in the chemotherapy group *vs* 50 [96%] of 52 in the no chemotherapy group; p=0·31). Of the 76 (89%) patients in the chemotherapy group and the 67 (87%) patients in the no chemotherapy group whose oestrogen-receptor status of their primary tumour was known, 13 (17%) versus eight (12%), respectively, had discordant oestrogen-receptor expression in the ILRR (six cases converted from negative to positive and 15 from positive to negative). Progesterone-receptor expression was discordant in 16 (22%) of 72 patients in the chemotherapy group and 19 (29%) of 65 patients in the no chemotherapy group with known progesterone-receptor expression data. *HER2*-directed therapies, trastuzumab and lapatinib, were planned in ten (6%) of all patients (table 1).

Chemotherapies were selected by the treating physicians on the basis of patient and disease characteristics and previous or ongoing therapies for the primary breast cancer, and were mostly combination regimens (mainly anthracycline-based; table 1).

At a median follow-up of 4·9 years (IQR 3·6–6·0) (4·6 years [3·5–5·8] in the chemotherapy group and 5·0 years [4·0–6·0] in the no chemotherapy group) disease-free survival was significantly improved in the adjuvant chemotherapy group compared with the no chemotherapy group (figure 2A). 5-year disease-free survival was 69% (95% CI 56–79) in the chemotherapy group compared with 57% (44–67) in the no chemotherapy group (HR 0·59 [95% CI 0·35–0·99]; p=0·046).

Chemotherapy reduced both distant and second local failures. The sites of failure after resection of ILRR were second local or regional (six in the chemotherapy group *vs* nine in the no chemotherapy group); distant (15 *vs* 22), comprising soft tissue (none *vs* two), bone (eight *vs* five), and viscera (seven *vs* 15); contralateral breast (one *vs* one); second non-breast malignancy (one *vs* none); death without previous cancer event (one *vs* none); and death, cause unknown (none *vs* two). The reduction in the risk of a disease-free survival event between treatment groups remained statistically significant in a multivariable proportional hazards model that included factors for oestrogen-receptor status, location of ILRR, previous chemotherapy use, and interval from primary surgery (table 2).

Overall survival was also significantly longer in the chemotherapy group (figure 2B). 5-year overall survival was 88% (95% CI 77–94) in the chemotherapy group and 76% (63–85) in the no chemotherapy group (HR 0·41 [95% CI 0·19–0·89]; p=0·024).

In a prespecified analysis according to oestrogen-receptor status, patients assigned to chemotherapy for oestrogen-receptor-negative ILRR tumours had a greater chance of disease-free survival than did those assigned to

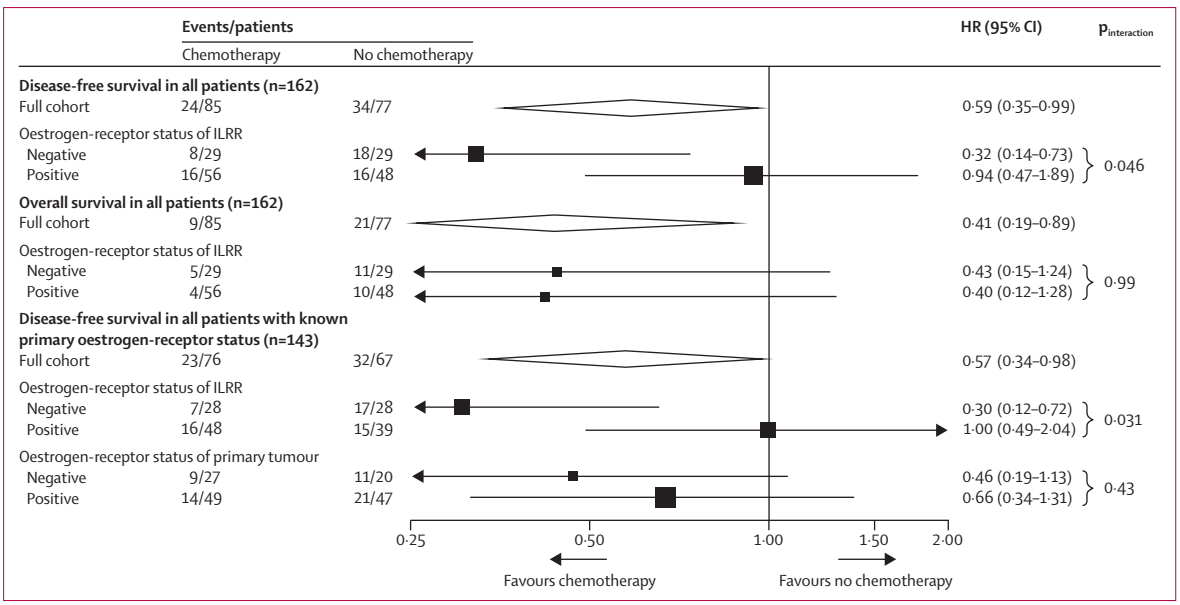

***Figure 3*: Subgroup analyses of disease-free survival and overall survival in full cohort and according to oestrogen-receptor status**
Disease-free survival and overall survival for all 162 patients together and according to the oestrogen-receptor status of the ILRR, and disease-free survival for 143 patients who had oestrogen-receptor status available for both primary tumour and ILRR (C). The size of the boxes is proportional to the number of events. The x-axis is on a log scale. HR=hazard ratio. ILRR=isolated locoregional recurrence.

no chemotherapy (HR 0·32 [95% CI 0·14–0·73]; 5-year disease-free survival was 67% (95% CI 44–82) in the chemotherapy group *vs* 35% (18–53) in the no chemotherapy group; figure 2C). In patients with oestrogen-receptor-positive ILRR, the corresponding disease-free survival HR was 0·94 (95% CI 0·47–1·89), and 5-year disease-free survival was 70% (53–81) in the chemotherapy group versus 69% (53–81) in the no chemotherapy group (figure 2E). Kaplan-Meier curves of overall survival according to oestrogen-receptor status of ILRR also show that overall survival was improved in the chemotherapy group (figures 2D and 2F).

For disease-free survival, the interaction between treatment group and expression of oestrogen receptor was statistically significant ($p_{interaction}$=0·046), showing that the effect of chemotherapy in patients with oestrogen-receptor-negative ILRR was significantly different from that of the oestrogen-receptor-positive cohort (figure 3). However, for overall survival, the interaction between treatment group and expression of oestrogen receptor was not statistically significant ($p_{interaction}$=0·99; figure 3). Confidence intervals are very wide because of the small number of deaths in each of the subpopulations. We further analysed disease-free survival according to the oestrogen-receptor status of the ILRR tumour and that of the primary tumour for the 143 patients for whom data were available (figure 3; appendix). Consistent with the overall population, a significant interaction was seen with regard to the chemotherapy effect according to oestrogen-receptor status of the ILRR ($p_{interaction}$=0·031). By contrast, the difference in chemotherapy effect according to oestrogen-receptor status of the primary tumour was less striking, and the interaction was not statistically significant ($p_{interaction}$=0·43; figure 3).

Of the 81 patients who received chemotherapy, 12 (15%) reported serious adverse events (appendix). Adverse events seen were neutropenia, febrile neutropenia, intestinal infection, abdominal pain, respiratory and pulmonary infection, cardiac ischaemia, motor neuropathy, musculoskeletal pain, severe fatigue, and endometrial mucosa thickening. The frequency and type of serious adverse events were as anticipated for the therapies used.

Discussion

Results of the CALOR trial assessing whether adjuvant chemotherapy in patients with ILRR of breast cancer improves outcomes showed that chemotherapy significantly increased overall and disease-free survival in these patients, particularly those with an oestrogen-receptor-negative ILRR.

Recommendations for systemic therapy, particularly chemotherapy, after the occurrence of an ILRR of breast cancer have been the subject of considerable debate. Prospective trials by other cooperative groups investigating adjuvant cytotoxic chemotherapy in this population of patients have been unsuccessful and unreported (panel).[19] The CALOR trial was designed to guide the adjuvant therapy of women with ILRR, and the characteristics of the participants—eg, a wide range of intervals between primary surgery and ILRR and a predominance of oestrogen-receptor-positive recurrences—were typical for the population under investigation. CALOR was a pragmatic trial, in that participating physicians used their

***Panel:* Research in context**

Systematic review

We searched PubMed for reports published in English from January, 1980, to June, 2013, that contained the terms "breast neoplasms/*drug therapy" AND "neoplasm recurrence, local" AND "randomized controlled trials". This search identified 170 citations, which were manually restricted to clinical trials with more than 50 participants. No trial fulfilling these criteria was identified. One Cochrane review addressing the issue of adjuvant chemotherapy after resection of locoregional recurrence[19] summarised three older and smaller randomised trials, with inconclusive results.

Interpretation

As far as we are aware, our study is the first sufficiently powered randomised trial to investigate whether adjuvant chemotherapy reduces the risk of further relapse and death in patients with isolated locoregional recurrence of breast cancer. Our results show that adjuvant chemotherapy in addition to radiation and endocrine therapy prolonged disease-free and overall survival, particularly in patients with oestrogen-receptor-negative locoregional relapse. This result challenges the current practice of inconsistent use of chemotherapy and provides evidence in favour of offering adjuvant chemotherapy to women with isolated locoregional relapse of breast cancer.

professional judgments when selecting cytotoxic drugs, and thus focused more broadly on the study question: the value of systemic chemotherapy. Furthermore, in an attempt to embrace variance in international practice patterns, the sequence of radiation and chemotherapy was not mandated by the trial. The study design required the use of endocrine therapy for hormone-responsive cancers on the basis of the reported results of a Swiss trial[14] that showed that tamoxifen prolonged median disease-free survival from 2·7 to 6·5 years.[14] Even with this pragmatic design, enrolment to the trial was terminated before reaching the planned sample size because of the slow rate of accrual.

Two reasons might explain the lower than anticipated accrual. First, advances in the local and systemic management of primary breast cancer have lowered the incidence of ILRR in the past 15 years, restricting the pool of eligible patients.[12,20] Second, despite no evidence from randomised trials, many oncologists believed that evidence from non-randomised series and randomised trials in other clinical settings was sufficient to decide whether or not to administer chemotherapy for ILRR.[21,22] CALOR did not obtain information about the *HER2* status of the primary cancer or ILRR; however, the intent to use *HER2*-directed therapies was recorded from 2004 onward, and we assume that these treatments are surrogate indicators of *HER2* overexpression. There is no indication of a differential distribution of *HER2*-directed therapies; therefore, the observed beneficial effect of chemotherapy is unlikely to be explained by differences in *HER2* status. The low number of patients that were given *HER2*-directed therapies makes it likely that investigators were reluctant to randomly assign patients with *HER2*-positive ILRR in a trial with a no chemotherapy group.

Participating co-investigators worldwide made reasonable choices of personalised chemotherapy regimens for their patients on the basis of previously received therapies and contemporary drug selections. This heterogeneity enhanced the weight of our findings—ie, the benefit of chemotherapy. Most patients who had previously received regimens similar to cyclophosphomide, methotrexate, and fluorouracil, or no previous adjuvant chemotherapies, received anthracycline-based regimens, whereas patients who had previously received adjuvant anthracyclines were given taxanes for their ILRR, and patients who previously received taxanes were preferentially given capecitabine. The individualised selection of chemotherapy by the investigators reduced the absolute risk of a disease-free survival event by 12% at 5 years after randomisation. This benefit in terms of disease-free survival should be weighed against the well known side-effects of chemotherapy.

Chemotherapy was particularly efficacious in patients with oestrogen-receptor-negative ILRR, reducing the relative risk of further relapses by about two-thirds. These findings, together with the reduction in relative risk of death, provide strong evidence that isolated breast cancer recurrences are a marker of concurrent occult systemic disease and that a second adjuvant course of chemotherapy should be recommended in this population of patients. A beneficial effect of chemotherapy in patients with oestrogen-receptor-positive ILRR cannot be excluded because the confidence intervals are wide and the 4·9 year median follow-up might be too short to detect a treatment effect. Thus, any benefit of chemotherapy added to endocrine therapy remains uncertain in the oestrogen-receptor-positive ILRR cohort. This uncertainty also applies to the choice of initial adjuvant therapy for some patients with oestrogen-receptor-positive breast cancer.

Evidence for the important role of metastatic lesion biopsy is increasing.[23–26] Our results strongly suggest that tailoring treatment according to the disease characteristics of the metastatic lesion, in this case ILRR, provides a better indication of the possible responsiveness to treatment than does relying on the characteristics of the primary tumour. In particular, the different outcomes based on receipt of chemotherapy according to oestrogen-receptor status were more striking when we examined cohorts according to oestrogen-receptor status in the ILRR than according to oestrogen-receptor status in the primary tumour.

By contrast with some randomised trials in oncology, the planned sample size for the CALOR trial did not have an overly optimistic estimate of treatment effect.[27] Although small studies might be at risk of false-positive results,[28] this limitation is unlikely to have occurred in the CALOR trial because the results recapitulate evidence about the effectiveness of adjuvant chemotherapies shown in patients with primary breast cancer.[12]

In summary, the CALOR trial is the first randomised study supporting the use of chemotherapy in patients

with ILRR, especially if the recurrence is oestrogen-receptor negative, although it does not exclude use of chemotherapy for patients with oestrogen-receptor-positive ILRR.

Contributors

SA, KNP, RDG, and ILW participated in the design. SA, SG, IL, AR, MM, JWRN, AHGP, MFR, JMBC, BT, EM, EPM, CEG Jr, KNP, RDG, PR, NW, and ILW participated in data collection. SA, SG, SJA, KNP, RDG, and ILW participated in data analysis. All authors participated in data interpretation, drafting, and finalising the report.

Conflicts of interest

We declare that we have no conflicts of interest.

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