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ORIGINAL REPORT

Efficacy of Chemotherapy for ER-Negative and ER-Positive Isolated Locoregional Recurrence of Breast Cancer: Final Analysis of the CALOR Trial

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A B S T R A C T

Purpose

Isolated locoregional recurrence (ILRR) predicts a high risk of developing breast cancer distant metastases and death. The Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial investigated the effectiveness of chemotherapy (CT) after local therapy for ILRR. A report at 5 years of median follow-up showed significant benefit of CT for estrogen receptor (ER)–negative ILRR, but additional follow-up was required in ER-positive ILRR.

Patients and Methods

CALOR was an open-label, randomized trial for patients with completely excised ILRR after unilateral breast cancer. Eligible patients were randomly assigned to receive CT or no CT and stratified by prior CT, hormone receptor status, and location of ILRR. Patients with hormone receptor–positive ILRR received adjuvant endocrine therapy. Radiation therapy was mandated for patients with microscopically involved margins, and anti–human epidermal growth factor receptor 2 therapy was optional. End points were disease-free survival (DFS), overall survival, and breast cancer-free interval.

Results

From August 2003 to January 2010, 162 patients were enrolled: 58 with ER-negative and 104 with ER-positive ILRR. At 9 years of median follow-up, 27 DFS events were observed in the ER-negative group and 40 in the ER-positive group. The hazard ratios (HR) of a DFS event were 0.29 (95% CI, 0.13 to 0.67; 10-year DFS, 70% v 34%, CT v no CT, respectively) in patients with ER-negative ILRR and 1.07 (95% CI, 0.57 to 2.00; 10-year DFS, 50% v 59%, respectively) in patients with ER-positive ILRR ($P_{interaction}$ = .013). HRs were 0.29 (95% CI, 0.13 to 0.67) and 0.94 (95% CI, 0.47 to 1.85), respectively, for breast cancer-free interval ($P_{interaction}$ = .034) and 0.48 (95% CI, 0.19 to 1.20) and 0.70 (95% CI, 0.32 to 1.55), respectively, for overall survival ($P_{interaction}$ = .53). Results for the three end points were consistent in multivariable analyses adjusting for location of ILRR, prior CT, and interval from primary surgery.

Conclusion

The final analysis of CALOR confirms that CT benefits patients with resected ER-negative ILRR and does not support the use of CT for ER-positive ILRR.

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INTRODUCTION

The increased use of adjuvant radiation and systemic therapies and the improved efficacy of such therapies in the past two decades have resulted in a lower incidence of locoregional recurrence of breast cancer.[1-5] However, after an isolated locoregional recurrence (ILRR) event of breast cancer, the risk of distant metastases and death is high.[6-9] The Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial was designed as a prospective randomized study to determine the effectiveness of adjuvant chemotherapy (CT) after surgical excision of ILRR. Previously, we reported the results at a median follow-up of 5 years, which showed significant benefit of CT for estrogen

receptor (ER)–negative ILRR, whereas for patients with ER-positive ILRR, the benefit of CT was uncertain.[10]

In a separate analysis, we found that a subset of patients developed a second ILRR during the first 5 years. These events occurred within a short interval of the first ILRR (median, 1.6 years), were uniquely progesterone-receptor (PR) negative, and were strong indicators of subsequent risk of distant recurrence and death.[11] This report presents results at 9 years of median follow-up, focusing on the ER-status cohorts, with the aim of further clarifying the effect of CT in patients with ER-negative and ER-positive ILRR.

PATIENTS AND METHODS

Patients and Procedures

Briefly, CALOR is a pragmatic, open-label, randomized, multicenter and multinational trial for patients with completely excised ILRR after unilateral breast cancer.[10] Eligible patients were randomly assigned to CT (selected by the investigator; multidrug for at least 3 months recommended) or no CT and stratified by prior CT, hormone receptor (ER, PR) status of ILRR, and location of ILRR. Patients with ER- and/or PR-positive ILRR were to receive adjuvant endocrine therapy and, if recurrence occurred while receiving endocrine therapy, a regimen change (eg, substitution of a selective ER modulator with an aromatase inhibitor) was recommended. Radiation therapy was mandated for patients with microscopically involved margins and recommended for all patients who had not received radiotherapy as part of their primary treatment. Human epidermal growth factor receptor 2 (HER2)–directed therapy was optional. Follow-up clinical examinations were required every 3 months during the first 2 years, every 6 months during years 3 to 5, and yearly thereafter. Annual mammography was required, but other laboratory or imaging studies were left to the discretion of the treating physicians. 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 conducted in compliance with the Helsinki Declaration. Patient data were anonymized.

International Breast Cancer Study Group (IBCSG) and National Surgical Adjuvant Breast and Bowel Project/NRG Oncology 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 performed jointly.

Outcomes

The primary end point was disease-free survival (DFS), defined as time from randomization to invasive local, regional, or distant recurrence, including invasive in-breast tumor recurrence, appearance of a second primary tumor, or death from any cause. In the absence of an event, DFS was censored at the date of the last follow-up visit. Overall survival (OS) and breast cancer–free interval (BCFI)[12] were secondary end points. BCFI was defined as time from randomization to first invasive breast tumor recurrence, with second primary tumors ignored and death from causes other than breast cancer recurrence censored at the time of death. OS was defined as the time from randomization to death from any cause.

Statistical Analysis

The present analysis is the final update of the results of the CALOR trial within subgroups defined by the ER status of the ILRR. The subgroup analysis according to ER status was clinically motivated and prospectively specified in the protocol. Because the previously published results at 5 years

Table 1. Patient Characteristics and Treatment Modalities According to ER Status of the ILRR Cohorts

Characteristic	ER Negative		ER Positive	
	Chemotherapy (n = 29)	No Chemotherapy (n = 29)	Chemotherapy (n = 56)	No Chemotherapy (n = 48)
Prior chemotherapy				
Yes	17 (59)	21 (72)	32 (57)	31 (65)
No	12 (41)	8 (28)	24 (43)	17 (35)
Location of ILRR				
Breast	20 (69)	22 (76)	27 (48)	20 (42)
Mastectomy scar or chest wall	6 (21)	5 (17)	22 (39)	20 (42)
Regional lymph nodes	3 (10)	2 (7)	7 (13)	8 (16)
Primary surgery				
Mastectomy	7 (24)	7 (24)	26 (46)	24 (50)
Breast conserving	22 (76)	22 (76)	30 (54)	25 (50)
Time since primary cancer to surgery for ILRR				
Median No. of years (range)	3.7 (0.3-21.8)	3.4 (0.4-22.0)	6.1 (0.6-31.6)	8.2 (0.7-20.6)
≥ 2 years	23 (79)	22 (75)	49 (88)	43 (90)
Menopausal status at ILRR				
Premenopausal	7 (24)	6 (21)	13 (23)	8 (17)
Postmenopausal	22 (76)	23 (79)	43 (77)	40 (83)
Median age at ILRR, years (range)	55 (40-80)	56 (31-82)	56 (37-70)	56 (33-80)
ER of primary tumor				
Negative	21 (72)	20 (69)	6 (11)	0 (0)
Positive	7 (24)	8 (28)	42 (75)	39 (81)
Unknown	1 (3)	1 (3)	8 (14)	9 (19)
Treatment of ILRR				
Radiation therapy	7 (24)	8 (28)	24 (43)	21 (44)
Endocrine therapy for ER-positive ILRR			53 (92)	50 (98)
Chemotherapy				
Monotherapy	9 (31)		16 (29)	
Polytherapy	18 (62)		37 (66)	

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: ER, estrogen receptor; ILRR, isolated locoregional recurrence.
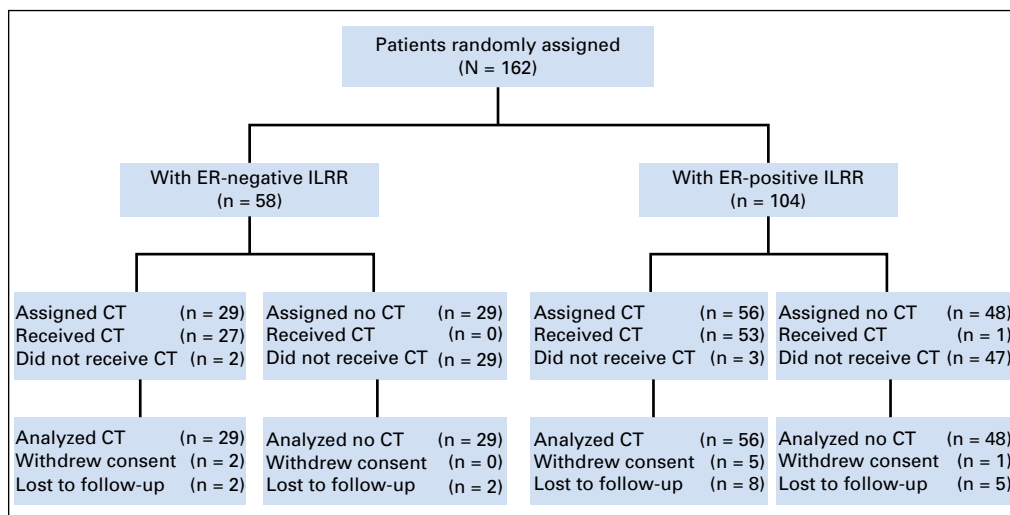
Fig 1. CONSORT diagram of Chemotherapy as Adjuvant for LOcally Recurrent breast cancer (CALOR) trial update according to estrogen receptor (ER) status of the ILRR. CT, chemotherapy; ILRR, isolated locoregional recurrence; LFU, lost to follow-up; no CT, no chemotherapy.

of median follow-up indicated a significant interaction between CT effect and ER status of the ILRR,[10] the focus of this update is to provide separate analyses within ER status cohorts.

We calculated Kaplan-Meier estimates[13] of end points at 10 years, with SEs by Greenwood formula. Cox regression models were used to estimate HRs (95% CI) for treatment effects within cohorts, to adjust for the following covariables: location of ILRR, prior chemotherapy, interval from primary surgery, and ER status of ILRR, and to estimate HRs (95% CIs) for treatment effects across covariable subgroups by including treatment-by-covariable interaction in the model; the two-sided P values for treatment-by-covariable interaction was reported along with the HR (95% CI) in forest plots.[14]

The sample size and protocol modifications have been described elsewhere. Briefly, the original statistical design was modified because of lower-than-planned accrual, and CALOR closed on Jan 31, 2010, with 162 patients enrolled.[10] All patients randomly assigned are included in this intention-to-treat analysis. The database lock was September 2016.

RESULTS

The study cohort consisted of 162 women enrolled from August 2003 to January 2010 (Fig 1). The patient and treatment characteristics according to ER status are listed in Table 1. The median time to recurrence from primary cancer to ILRR was 3.6 years for the ER-negative cohort compared with 6.8 years for the ER-positive cohort; 94% of patients with ER-positive ILRR received prior endocrine therapy, and only a small proportion of patients (9%) with ER-positive primary cancers were receiving such treatment at the time of the ILRR diagnosis.

At 9 years of median follow-up, CT improved DFS substantially in patients with ER-negative ILRR (Fig 2A): 10-year DFS was 70% (SE, 9%) in patients with and 34% (SE, 9%) in patients without CT (hazard ratio [HR] 0.29; 95% CI, 0.13 to 0.67). In contrast, CT had no benefit in patients with ER-positive ILRR: 10-year DFS was 50% (SE, 9%) in patients with and 59% (SE, 8%) in patients without CT (HR, 1.07; 95% CI, 0.57 to 2.00; Fig 2D). Similarly, BCFI was prolonged by CT in patients with ER-negative ILRR (breast cancer free at 10 years, 70% v 34%; HR,0.29; 95% CI, 0.13 to 0.67), but not in patients with ER-positive ILRR (58% v 62%; HR, 0.94; 95% CI, 0.47 to 1.85; Figs 2B and 2E). OS at 10 years in patients with ER-negative ILRR was 73% with CT versus 53% without CT (HR, 0.48; 95% CI, 0.19 to 1.20); among patients with ER-positive ILRR, 10-year OS was 76% versus 66%,

Table 2. Sites of First Failure (DFS events) After Randomization According to Treatment Group Within ER Status of the ILRR Cohorts

Site	ER Negative, No. (%)			ER Positive, No. (%)		
	CT	No CT	Total	CT	No CT	Total
Total patients	29	29	58	56	48	104
DFS events	8 (28)	19 (66)	27 (47)	22 (39)	18 (38)	40 (38)
Sites of first failure after primary ILRR						
Local	1 (3)	4 (14)	5 (9)	3 (5)	3 (6)	6 (6)
Regional	2 (7)	2 (7)	4 (7)	0	1 (2)	1 (1)
Distant	5 (17)	12 (41)	17 (29)	13 (23)	11 (23)	24 (23)
Soft tissue	0	1 (3)	1 (2)	0	1 (2)	1 (1)
Bone	1 (3)	1 (3)	2 (3)	8 (14)	4 (8)	12 (12)
Viscera	4 (14)	10 (34)	14 (24)	5 (9)	6 (13)	11 (11)
Contralateral breast	0	1 (3)	1 (2)	1 (1)	1 (2)	2 (2)
Second (nonbreast) malignancy	0	0	0	3 (5)	1 (2)	4 (4)
Death without prior cancer event	0	0	0	2 (4)	0	2 (2)
Death cause unknown	0	0	0	0	2 (4)	2 (2)

Abbreviations: CT, chemotherapy; DFS, disease-free survival; ER, estrogen receptor; ILRR, isolated locoregional recurrence.

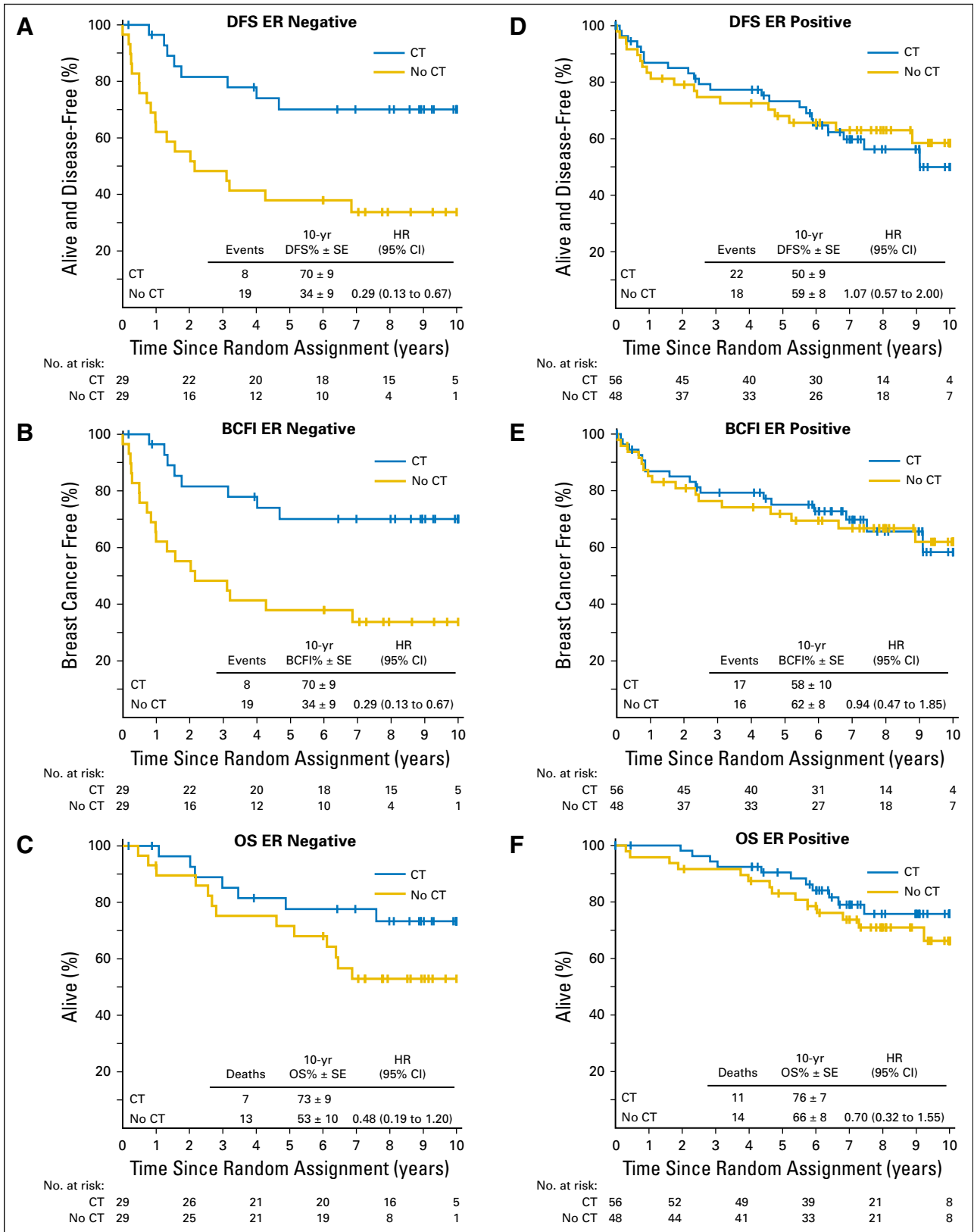© 2018 by American Society of Clinical Oncology **3**

Fig 2. Disease-free survival (DFS), breast cancer–free interval (BCFI), and overall survival (OS) for patients with (A-C) estrogen-receptor (ER)-negative and (D-F) ER-positive isolated locoregional recurrence (ILRR). Interaction tests comparing the effect of chemotherapy (CT) for patients with ER-negative ILRR versus ER-positive ILRR are $P_{interaction}$ = .013 for DFS (A v D); $P_{interaction}$ = .034 for BCFI (B v E); and $P_{interaction}$ = .53 for OS (C v F). No CT, not assigned to chemotherapy; HR, hazard ratio.

Table 3. Multivariable Model of Disease-Free Survival

Variable	Hazard Ratio (95% CI)	P
Location of ILRR		
Breast	(reference group)	
Mastectomy scar or chest wall	0.78 (0.43 to 1.43)	.43
Lymph nodes	1.01 (0.47 to 2.16)	.98
Prior chemotherapy (yes/no)	0.86 (0.52 to 1.43)	.56
Interval from primary surgery (per year)	0.92 (0.87 to 0.97)	.0036
Interaction of treatment by ER of ILRR		.024
ER negative	0.26 (0.11 to .60)	
ER positive	0.87 (0.46 to 1.64)	

Abbreviations: ER, estrogen receptor; ILRR, isolated locoregional recurrence.

respectively (HR, 0.70; 95% CI, 0.32 to 1.55; Figs 2C and 2F). Interaction tests comparing CT effect for ER-positive ILRR versus ER-negative ILRR are $P_{interaction}$ = .013 for DFS (Fig 2A v 2D); $P_{interaction}$ = .034 for BCFI (Fig 2B v 2E); and $P_{interaction}$ = .53 for OS (Fig 2C v Fig 2F). The overall DFS, BCFI, and OS results, not separated by ER status of the ILRR, are presented in the Data Supplement.

Overall, there were 67 DFS events, as listed in Table 2. The site of first recurrence after randomization and therefore after the primary ILRR recurrence was local and regional for 16 patients, six in the CT arm and 10 in the no-CT arm. Distant disease was the first site of recurrence for 41 patients, 18 patients in the CT arm and 23 patients in the no-CT arm. In the ER-positive cohort, visceral and bone metastasis rates were similar overall and between treatment groups. In the ER-negative cohort, bone metastases as site of first recurrence after ILRR were rare (two of 58 patients, one in each treatment group), whereas visceral metastases were more common and differed according to treatment group (four of 29 [14%] in the CT arm; 10 of 29 [34%] no CT arm). All 10 nonbreast cancer DFS events occurred in the ER-positive cohort; thus, DFS and BCFI outcomes were the same in the ER-negative cohort (Table 2; Figs 2A and 2B).

The improvement of DFS by CT remained significant in a multivariable proportional hazards model that included factors for ER status of ILRR, location of ILRR, previous CT use, and interval from primary surgery. The interaction between ER status and CT effect was statistically significant, confirming the differential efficacy of CT depending on ER expression of the ILRR

(Table 3). The multivariable analysis of BCFI gave similar results, again with a statistically significant interaction between ER status and efficacy of CT (data not shown).

The interaction between ER expression and CT effect was strong and statistically significant if the ER status of the ILRR tissue was considered. In contrast, the ER status of the primary tumor tissue was less predictive of the efficacy of CT, and the interaction was not statistically significant (Fig 3).

DISCUSSION

The long-term follow-up results of the CALOR trial confirm the reported findings of the 5-year analysis[10]: the statistically significant benefit of CT for the cohort of patients with ER-negative ILRR was sustained. The extended follow-up now available strengthens conclusions for the ER-positive ILRR cohort: no benefit of CT was observed for these patients. Interactions between ER expression of the ILRR and the use of CT were significant for DFS and BCFI. These results were confirmed in multivariable analyses adjusting for location of ILRR, prior CT, and interval from primary surgery. This updated analysis demonstrates that patients with an ILRR should be managed according to the endocrine molecular profile of the recurrent cancer and not the primary cancer.

The CALOR trial investigated the role of pragmatically chosen CT, at the discretion of treating physicians. Seemingly, oncologists selected effective CT regimens for their patients on the basis of prior cytotoxic agent exposure and in consideration of experienced toxicities. Although not a trial question, endocrine therapy was mandated for patients with ER-positive ILRR. In fact, the protocol recommended a switch of therapy, for example, from a selective ER modulator to an aromatase inhibitor, especially for the few patients whose recurrence happened while receiving endocrine treatment. Because CT did not reduce the number of failures or any of the measured end points in patients with ER-positive ILRR, it is reasonable to conclude that endocrine therapy is the mainstay treatment of such patients.

The strengths of the CALOR trial included its prospective randomized design and the pragmatic assignment of individual CT by the participating oncologist. The median follow-up is now sufficiently long to capture the effects of adjuvant CT. The individualized choice of CT may seem to be a weakness, but the
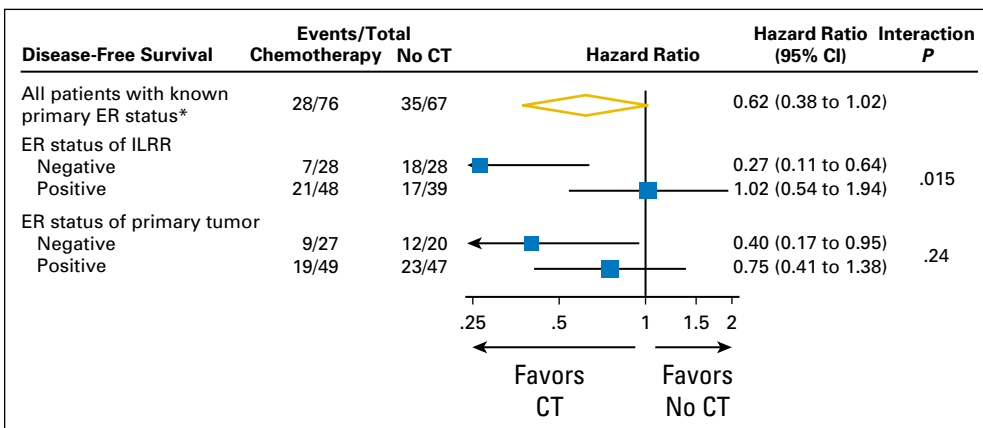

Fig 3. Subgroup analysis of disease-free survival according to estrogen-receptor (ER) status of isolated locoregional recurrence (ILRR) and ER status of primary breast cancer tissue among 143 patients with known primary ER status. The size of the boxes is proportional to the number of events. The x-axis is on a log scale. CT, assigned to chemotherapy; no CT, not assigned to chemotherapy. (*) 143 of the 162 randomly assigned patients.

Disease-Free Survival	Events/Total Chemotherapy	No CT	Hazard Ratio	Hazard Ratio (95% CI)	Interaction P
All patients with known primary ER status*	28/76	35/67		0.62 (0.38 to 1.02)	
ER status of ILRR					
Negative	7/28	18/28		0.27 (0.11 to 0.64)	.015
Positive	21/48	17/39		1.02 (0.54 to 1.94)	
ER status of primary tumor					
Negative	9/27	12/20		0.40 (0.17 to 0.95)	.24
Positive	19/49	23/47		0.75 (0.41 to 1.38)	

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robust benefit of CT in patients with ER-negative ILRR points to a generally beneficial effect of CT as chosen by the investigators. In addition, the availability of ER status for both ILRR and primary tumor enabled analyses showing that ILRR ER status was the better predictor of CT benefit. The main weakness of the trial was its small sample size due to the lower-than-anticipated accrual rate, which precludes definitive evaluation of several secondary questions. For example, given the limited number of ER-positive ILRR participants and the 12% lost to follow-up rate for this subgroup, a modest benefit of CT in patients with luminal recurrences could not be excluded. Furthermore, the benefit of CT in patients with luminal B-like (eg, ER-positive, PR-negative) recurrences could not be evaluated. Whereas the interval between primary breast cancer and ILRR is prognostic, the number of trial participants was insufficient to evaluate whether the time from primary adjuvant CT to ILRR was predictive of CT benefit after ILRR. In particular, because of small numbers and a median interval of 3.5 years between primary diagnosis and ER-negative ILRR, the question of whether CT effectiveness diminished for short intervals could not be addressed. The hypothesis of a more pronounced efficacy of CT in patients who experienced the ER-positive ILRR while receiving adjuvant endocrine therapy also could not be investigated because of the low number of patients with these characteristics. Similarly, although adjuvant taxanes became standard practice during the accrual period, the influence of their use before ILRR could not be evaluated. Furthermore, fewer than 5% of the participants received HER2-directed adjuvant therapy; thus, this trial cannot shed any light on the question of HER2-directed therapy for ILRR.

In conclusion, the CALOR trial indicates that at present, CT offers the best prospect of prolonged DFS in patients with ER-negative first ILRR, whereas adding CT to endocrine therapy seems to offer no benefit to patients with ER-positive ILRR.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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The Final Verdict: Chemotherapy Benefits Estrogen Receptor–Negative Isolated Local Recurrence

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In the article that accompanies this editorial, Wapnir et al[1] provide an important update on the final analysis of the Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer (CALOR) trial at 9 years of median follow-up. This trial provided practice-changing data on the management of isolated locoregional recurrence (ILRR) when results were initially published in 2014, demonstrating a benefit of chemotherapy in the estrogen receptor (ER)–negative but not the ER-positive patient population.[2] The current 9 years of follow-up data continue to show the interaction of ER status with the benefit of chemotherapy. The hazard ratio (HR) for the primary end point of disease-free survival (DFS) event was 0.29 (95% CI, 0.13 to 0.67) in the ER-negative ILRR and 1.07 (95% CI, 0.57 to 2.00) in the ER-positive ILRR cohorts. Comparably, at 4.9 years of median follow-up, the HRs were 0.32 (95% CI, 0.14 to 0.73) and 0.94 (95% CI, 0.0.47 to 1.89) in the ER-negative and ER-positive populations, respectively. These findings are important for the management of this unique patient population, for whom neither consensus nor randomized data existed before this trial. Since the CALOR data were first reported, it has become more common practice to treat ILRR with curative intent, because the trial demonstrated that the multimodality approach is associated with better outcomes and may translate into long-term DFS benefit. More specifically, in the ER-negative population, the results challenged the previously inconsistent data regarding the benefit of chemotherapy and provided evidence in favor of offering adjuvant systemic therapy and radiotherapy to women with completely resected ILRR.

Historically, patients with ILRR did poorly: the Early Breast Cancer Trialists Collaborative Group revealed that up to 25% of ILRRs were likely associated with breast cancer death.[3] Women with local recurrence had a considerably poorer prognosis with regard to breast cancer–specific death compared with those without local recurrence, particularly if the patient had a shorter time interval to local recurrence.[4] For example, the HR for breast cancer–specific death among patients with local recurrence 0.5 to 1 year after diagnosis of their primary tumor was 6.67 compared with women who did not experience local recurrence.[4]

The current update from the CALOR trial demonstrated a clear benefit in the ER-negative population of the addition of chemotherapy, which has been maintained since the initial analysis. We learned that multimodality treatment upfront with surgical resection, radiation, and chemotherapy leads to durable benefit in DFS that persists after almost a decade of follow-up.

Uncertainty remains for the best approach to treat women with ER-positive ILRR. The original study was planned with a sample size of 977 patients; however, because of a lower-than-anticipated accrual rate, the sample size was decreased to 365. In November 2009, the independent Data and Safety Monitoring Committee recommended that the trial be closed because of low accrual. The study closed in January 2010 with a total of 162 patients, and a revised analysis plan was adopted.[2] This series of events highlights the understandable challenges for designing clinical trials in this unique population, because ILRR is not a common occurrence. Studies of large randomized trials have demonstrated that locoregional recurrences occur in approximately 5% to 15% of patients.[3] Although the sample size was adequate for the ER-negative population, it may not have been adequately powered to exclude a benefit in the subgroup of patients with ER-positive disease. In addition, 11.5% of patients in the ER-positive population were lost to follow-up. Therefore, one cannot draw the definitive conclusion that there is no potential benefit in the ER-positive subgroup, especially in the luminal B molecular subtype.

The authors provide interesting insight into the progesterone receptor (PR)–negative population in a separate analysis published in 2017, which found that a second ILRR represented one third of all recurrence events after the initial ILRR, and all were PR negative.[5] It is also important to highlight the distributions of DFS events for the patients who were ER-positive/PR-negative: 54% had a DFS event (second ILRR or distant recurrence), compared with patients with ER-positive/PR-positive disease, in whom only 21% had a DFS event.[5] One may postulate that it is the ER-positive/PR-negative population that may benefit from the addition of chemotherapy, although the data are insufficient to support this.

It is notable that the statistically significant difference in DFS ($P = .013$) did not translate into overall survival (OS) benefit ($P = .53$) on the basis of interaction tests comparing chemotherapy effect for ER-positive versus ER-negative status. At the 4.5-year follow-up, there was only a significant OS benefit reported for all patients according to the assigned treatment groups of chemotherapy versus nonchemotherapy cohort, with a P value of .02. For the prespecified analysis according to ER status, however, the CIs for OS were wide because of the small number of deaths in each of the subgroups. At 4.5 years of follow-up, the ER-negative chemotherapy group had five deaths versus 11 deaths in the ER-negative nonchemotherapy group.[2]

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At 9 years of follow-up, the ER-negative chemotherapy and non-chemotherapy groups each had only two additional deaths.

The authors mention that individualized choice of chemotherapy may be perceived as a weakness,[1] but one may consider this as the strength of the trial, because the results were independent of the chemotherapy selected. The decision to leave the choice of chemotherapy to the discretion of treating physicians makes this trial more applicable to real-life practice.

Breast cancer is a heterogeneous group of diseases, and in-depth analysis of the underlying biology that drives the proliferative and metastatic potential can assist in therapy decisions. The ER-positive subgroup for whom the benefit of chemotherapy is unclear in the locoregional recurrence setting remains to be elucidated. Recently, there have been major advances in genomic profiling of tumors in search of more reliable tools to prospectively identify patients who are more likely to benefit from chemotherapy.[6] Data are also emerging for comprehensive liquid biopsies using cell-free DNA and circulating tumor cells as prognostic tools.[7] Moreover, expanded genomic profiling can identify patients harboring circulating tumor cells with high proliferation status who have significantly reduced PFS and OS.[8] These efforts can bring focus to developing predictive gene signatures of response to chemotherapy, which goes beyond molecular subtype inferred from immunohistochemical studies. Perhaps chemotherapy for patients with luminal B molecular subtype breast cancer will be stratified by one of these tools in our armamentarium in the near future. However, for patients with ER-negative IRLL, the uncertainty regarding the role of chemotherapy has now been resolved, and chemotherapy should be offered as standard of care in addition to surgical resection and radiation for such patients.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The Final Verdict: Chemotherapy Benefits Estrogen Receptor–Negative Isolated Local Recurrence

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