VOLUME 31 · NUMBER 32 · NOVEMBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Breast-Conserving Treatment With or Without Radiotherapy in Ductal Carcinoma In Situ: 15-Year Recurrence Rates and Outcome After a Recurrence, From the EORTC 10853 Randomized Phase III Trial

Mila Donker, Saskia Litière, Gustavo Werutsky, Jean-Pierre Julien, Ian S. Fentiman, Roberto Agresti, Philippe Rouanet, Christine Tunon de Lara, Harry Bartelink, Nicole Duez, Emiel J.T. Rutgers, and Nina Bijker

Mila Donker, Harry Bartelink, and Emiel J.T. Rutgers, The Netherlands Cancer Institute; Nina Bijker, Academic Medical Center, Amsterdam, the Netherlands; Saskia Litière, Gustavo Werutsky, and Nicole Duez, European Organisation for Research and Treatment of Cancer (EORTC), Brussels, Belgium; Jean-Pierre Julien, Centre Henri-Becquerel, Rouen; Philippe Rouanet, Centre Régional de Lutte Contre le Cancer, Val d'Aurelle, Montpellier; Christine Tunon de Lara, Bergonie Institute, Bordeaux, France; Ian S. Fentiman, Guy's Hospital, London, United Kingdom; and Roberto Agresti, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico, Istituto Nazionale dei Tumori, Milan, Italy.

Published online ahead of print at www.jco.org on September 16, 2013.

Supported by a donation from the Kankerbestrijding/KWF from the Netherlands through the EORTC Charitable Trust.

The content of this article is the sole responsibility of the authors and does not necessarily reflect the official views of the Kankerbestrijding/KWF.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Nina Bijker, MD, PhD, Academic Medical Center, Department of Radiotherapy, PO box 227700, 1100DE Amsterdam, the Netherlands; e-mail: n.bijker@amc.uva.nl.

0732-183X/13/3132w-4054w/$20.00

DOI: 10.1200/JCO.2013.49.5077

ABSTRACT

Purpose
Adjuvant radiotherapy (RT) after a local excision (LE) for ductal carcinoma in situ (DCIS) aims at reduction of the incidence of a local recurrence (LR). We analyzed the long-term risk on developing LR and its impact on survival after local treatment for DCIS.

Patients and Methods
Between 1986 and 1996, 1,010 women with complete LE of DCIS less than 5 cm were randomly assigned to no further treatment (LE group, n = 503) or RT (LE+RT group, n = 507). The median follow-up time was 15.8 years.

Results
Radiotherapy reduced the risk of any LR by 48% (hazard ratio [HR], 0.52; 95% CI, 0.40 to 0.68; $P < .001$). The 15-year LR-free rate was 69% in the LE group, which was increased to 82% in the LE+RT group. The 15-year invasive LR-free rate was 84% in the LE group and 90% in the LE+RT group (HR, 0.61; 95% CI, 0.42 to 0.87). The differences in LR in both arms did not lead to differences in breast cancer–specific survival (BCSS; HR, 1.07; 95% CI, 0.60 to 1.91) or overall survival (OS; HR, 1.02; 95% CI, 0.71 to 1.44). Patients with invasive LR had a significantly worse BCSS (HR, 17.66; 95% CI, 8.86 to 35.18) and OS (HR, 5.17; 95% CI, 3.09 to 8.66) compared with those who did not experience recurrence. A lower overall salvage mastectomy rate after LR was observed in the LE+RT group than in the LE group (13% *v* 19%, respectively).

Conclusion
At 15 years, almost one in three nonirradiated women developed an LR after LE for DCIS. RT reduced this risk by a factor of 2. Although women who developed an invasive recurrence had worse survival, the long-term prognosis was good and independent of the given treatment.

J Clin Oncol 31:4054-4059. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Mammographic screening has substantially increased the incidence of ductal carcinoma in situ (DCIS) in the last few decades. A systematic review showed that the DCIS incidence in the United States increased from 5.8 per 100,000 in 1975 to 32.5 per 100,000 in 2004.[1] DCIS currently makes up 20% to 30% of mammographically detected breast cancers. After the introduction of radiotherapy (RT) after breast-conserving surgery for operable invasive breast cancer, several trials were initiated in the 1980s to investigate the addition of RT after a local excision (LE) of DCIS. Each of these trials unanimously showed that RT reduced the risk of both DCIS and invasive local recurrences (LR).[2-4]

Although RT has been proven to halve the risk of LR, this reduction has not translated into a survival benefit, as previously shown in the results of this trial from the European Organisation for Research and Treatment of Cancer (EORTC).[5,6] Survival after DCIS is good, with breast cancer–specific survival (BCSS) rates of approximately 95% at 10 years as demonstrated in a recent meta-analysis of randomized trials of RT in DCIS.[5-7] Therefore, the question arises of whether RT should be a standard part of the conservative treatment. Long-term follow-up of large clinical trials could help answer this question. In this report, we examined the effect of RT on the long-term outcomes of LR and survival in women treated with breast conservation for DCIS.

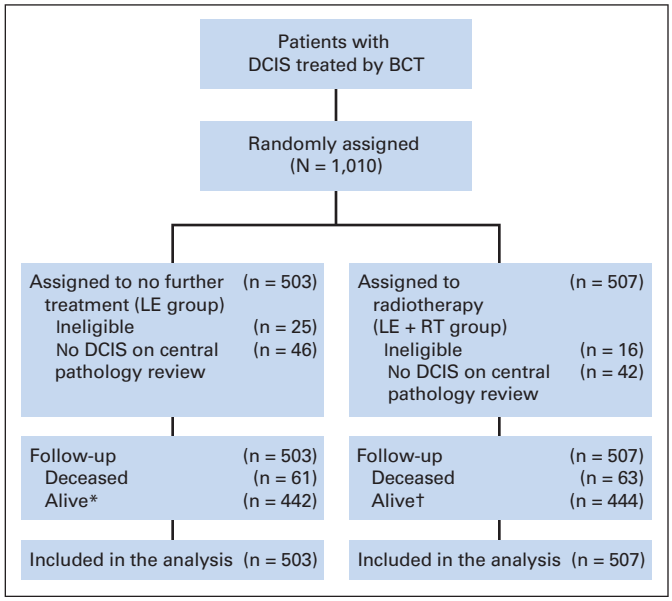

Fig 1. CONSORT diagram for the 15-year follow-up analysis of the European Organisation for Research and Treatment of Cancer 10853 trial. (*) Based off the follow-up received after the cutoff date used for the previous analysis (August 8, 2005), 134 of 442 patients were lost to follow-up. (†) Based off the follow-up received after the cutoff date used for the previous analysis (August 8, 2005), 124 of 444 patients were lost to follow-up. Reasons for ineligibility were as follows: age greater than 70 years (n = 11), lesion greater than 5 cm (n = 11), previous malignancy (n = 8), tumor margins not free at the time of random assignment (n = 7), presence of invasion at the time of random assignment (n = 4), Paget's disease of the nipple (n = 2), and randomly assigned after mastectomy (n = 1). Note that three patients had more then one reason for ineligibility. BCT, breast-conserving therapy; DCIS, ductal carcinoma in situ; LE, local excision; RT, radiotherapy.

PATIENTS AND METHODS

Patients

In the EORTC 10853 trial, patients with DCIS treated with breast-conserving surgery, called here LE, were randomly assigned to adjuvant RT (LE+RT group) or no further treatment (LE group) in a 1:1 ratio. Stratification was done by institution. Details of this study have been published previously.[5,6] Briefly, patients age less than 70 years with unilateral lesions up to 5 cm in diameter and without evidence of invasion or Paget's disease who underwent LE were considered eligible. The prescribed irradiation dose was 50 Gy in 25 fractions over a period of 5 weeks with tangential fields that included the whole breast. Although no boost was advised, 5% of the patients randomly assigned to RT received a boost. The use of tamoxifen was not specified in the protocol. The investigations were approved by the local institutional committee for medical ethics in each of the participating centers, and informed consent was obtained from all patients.

Forty-one patients were randomly assigned who did not meet the criteria for inclusion (Fig 1). Furthermore, the trial included a central pathology review available on 863 patients that focused on the diagnosis and classification of the lesion. In this review, invasion was defined as a focus with the common feature of invasive carcinoma of at least 1 mm outside the periductal stromal cuff. DCIS was confirmed in 775 of the 863 patients. Pathology reports of these 775 patients have been reviewed for margin assessment.[8] For this review, the margin status was considered free if it was reported as free ($>$ 1 mm) or if a re-excision was performed and no residual DCIS was found. The margin status was classified as not free when margins were reported to be close ($<$ 1 mm) or involved or status was not specified. Patients with margins that were close/involved/NS composed 21% of the 775 patients with confirmed DCIS (Table 1).

Statistical Analysis

The primary end point was time to LR, measured from the date of random assignment to the date of DCIS or invasive LR in the ipsilateral breast. The secondary end points included time to regional recurrence, contralateral breast cancer (CLBC), distant metastasis, BCSS, and overall survival (OS). Regional recurrence was defined as a recurrence in the ipsilateral internal mammary chain, supraclavicular, infraclavicular, or axillary lymph nodes. CLBC included both DCIS and invasive cancer. BCSS was defined as freedom from breast cancer–caused mortality.

All analyses are based on the intent-to-treat principle. Analysis restricted to the subset of 775 patients with confirmed DCIS showed similar results (data not shown). The time-to-event curves were calculated using the Kaplan-Meier method and compared between the treatment arms using a two-sided log-rank test with 5% significance level.[9] An estimate of the size of the treatment effect is represented by the hazard ratio (HR) and its 95% CI. A Cox proportional hazards regression model was fitted for the multivariable analysis of time to LR.[10]

To identify periods with high risk of local relapse (including DCIS and invasive recurrence separately), the yearly hazard rates during different consecutive time windows were estimated. To study BCSS and OS after LR (DCIS or invasive), a landmark analysis at 5 years after random assignment was performed. This type of analysis was chosen to prevent lead-time bias induced by the known fact that some patients might not live long enough to be able to develop a recurrence.[11] OS and BCSS were investigated starting from the landmark depending on the type of recurrence, using Kaplan-Meier curves and log-rank tests.

RESULTS

Patient and Disease Characteristics

One thousand ten women were randomly assigned between March 1986 and July 1996, of whom 503 patients were assigned to the LE group and 507 patients were assigned to the LE+RT group (Fig 1). Twenty-six patients (5%) randomly assigned to RT received a boost. Patient, lesion, and treatment characteristics per treatment group are listed in Table 1. The present analysis was performed with a median follow-up time for all patients of 15.8 years. The median follow-up time of patients who did not experience recurrence was 15.7 years.

Effect of RT on LR

A total of 234 patients (23%) developed LR; 110 of these recurrences (48%) were DCIS and 121 (52%) were invasive. Two patients with a DCIS recurrence as first failure had a subsequent second invasive LR; one patient developed LR without further information on the histology. LR occurred in 149 patients (30%) in the LE group compared with 85 patients (17%) in the LE+RT group. Of these patients, 75 (50%) in the LE group and 48 (56%) in the LE+RT group had an invasive recurrence. Treatment with adjuvant RT after LE approximately halved the risk of LR (HR, 0.52; 95% CI, 0.40 to 0.68; $P < .001$). The 15-year LR-free rates were 69% in the LE group and 82% in the LE+RT group (Fig 2). RT reduced the risk of pure DCIS LR (HR, 0.49; 95% CI, 0.33 to 0.73; $P = .003$) and invasive LR (HR, 0.61; 95% CI, 0.42 to 0.87; $P = .007$). The 15-year DCIS LR-free rate was 84% in the LE group compared with 92% in the LE+RT group; the 15-year invasive LR-free rates were 84% and 90% in the LE and LE+RT groups, respectively.

The risk of LR was highest during the first 5 years after random assignment with hazard rates of 4.0% per year in the LE group and 2.0% per year in the LE+RT group (Data Supplement). The risk then

Table 1. Patient, Lesion, and Treatment Characteristics per Treatment Group

Characteristic	LE		LE+RT		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
All patients	503		507		1,010	
Age at random assignment, years						
> 40	465	92.4	480	94.7	945	93.6
≤ 40	38	7.6	27	5.3	65	6.4
Method of detection						
Clinical symptoms	145	28.8	130	25.6	275	27.2
Mammographic lesion only	350	69.6	373	73.6	723	71.6
Mean diameter of the lesion on mammography, mm	20		20		20	
Boost received*	—	—	26	5	—	—
Pathology-reviewed patients	427		436		863	
Pathologic diagnosis						
Benign/LCIS	22	5.2	26	6.0	48	5.6
DCIS	381	89.2	394	90.4	775	89.8
Suspicion of invasion	24	5.6	16	3.7	40	4.6
DCIS-confirmed patients	381		394		775	
Histologic type						
Well	147	38.6	137	34.8	284	36.6
Intermediate	100	26.2	99	25.1	199	25.7
Poor	134	35.2	158	40.1	292	37.7
Architecture						
Clinging/micropapillary	105	27.6	99	25.1	204	26.3
Cribriform	140	36.7	129	32.7	269	34.7
Solid/comedo	135	35.4	164	41.6	299	38.6
Missing	1	0.3	2	0.5	3	0.4
Margins						
Close/involved/NS	82	21.5	81	20.6	163	21.0
Free	280	73.5	298	75.6	578	74.6
Missing	19	5.0	15	3.8	34	4.4

NOTE. Because treatment with tamoxifen was not advised, information about the administration was not collected.
Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; LE, local excision; NS, not specified; RT, radiotherapy.
*Median dose of the boost was 10 Gy.

decreased to 2.0% and 1.2% in the LE and LE+RT groups, respectively, in the next 5 years and to 1.3% and 0.6%, respectively, from 10 years onward. When hazard rates were analyzed for DCIS LR only, a similar trend was observed. Likewise, the highest risk of an invasive LR was also observed during the first 5 years after random assignment. However, this difference in risk between the two treatment groups disappears after 5 years. As was also observed previously,[5,6] RT was effective (HR, 0.51) in reducing any LR, independent of age, detection method, histologic type, architecture, and margin status.

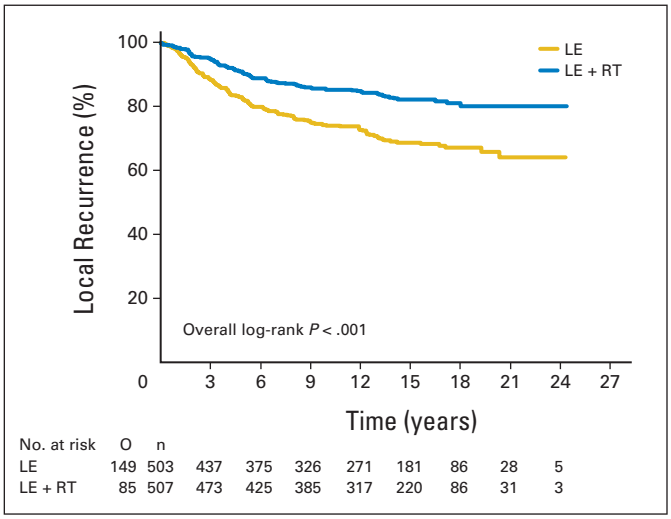

Fig 2. Time to local recurrence by treatment arm. LE, local excision; n, number of patients; O, observed; RT, radiotherapy.

Risk Factors Associated With LR

In a multivariable analysis, the following independent high-risk factors for LR were identified: young age (< 40 years), DCIS detected by clinical examination (as opposed to mammography detection), a solid or cribriform growth pattern (as opposed to clinging/micropapillary subtypes), and margins that were not free (Table 2). Treatment with RT was related to both DCIS and invasive recurrences, whereas involved or close margin status was an independent factor only for invasive recurrence. However, the small number of events may have prevented detection of other independent risk factors for DCIS or invasive recurrences separately.

To identify a subgroup that would only marginally benefit from RT and could thus be spared the additional burden of RT, the absolute and relative risks of invasive LRs were analyzed in both treatment arms (Data Supplement). RT was found to reduce the risk of an invasive LR in all subgroups. The subgroup with the lowest risk of an invasive LR was the clinging/micropapillary DCIS group. In this group, RT still lowered the risk of an invasive LR from 12.4% to 5.1%.

Table 2. Multivariable Analyses of Risk Factors Related to All Local Recurrences and to DCIS and Invasive Recurrences Separately

Parameter	Local Recurrence			DCIS Local Recurrence			Invasive Local Recurrence		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Age, years									
> 40	1		.009	1		.131	1		.173
≤ 40	1.94	1.18 to 3.17		1.74	0.85 to 3.57		1.60	0.81 to 3.16	
Method of detection									
Radiography finding only	1		.014	1		.169	1		.068
Clinical symptoms	1.48	1.08 to 2.04		1.38	0.87 to 2.19		1.49	0.97 to 2.29	
Histologic type									
Well	1		.113	1		.120	1		.896
Intermediate	1.55	1.03 to 2.36		1.93	1.03 to 3.60		1.40	0.65 to 1.99	
Poor	1.40	0.84 to 2.34		1.64	0.78 to 3.47		1.11	0.55 to 2.26	
Architecture									
Clinging/micropapillary	1		.008	1		.095	1		.103
Cribriform	2.03	1.28 to 3.21		1.95	0.96 to 3.99		1.89	1.05 to 3.39	
Solid/comedo	2.06	1.18 to 3.62		2.42	1.06 to 5.51		1.51	0.70 to 3.25	
Margins									
Free	1		.001	1		.261	1		.001
Close/involved/NS	1.69	1.23 to 2.31		1.31	0.82 to 2.08		2.01	1.32 to 3.06	
Treatment									
LE	1		< .001			.002			.014
LE+RT	0.51	0.38 to 0.69		0.50	0.33 to 0.78		0.60	0.40 to 0.90	

Abbreviations: DCIS, ductal carcinoma in situ; LE, local excision; NS, not specified; RT, radiotherapy.

Other Events and Survival

There was no significant difference in the incidence of CLBC (7% in LE group *v* 10% in LE+RT group; HR, 1.36; 95% CI, 0.89 to 2.10; $P = .157$). Regional recurrences occurred in 28 patients (19 in the LE group and nine in the LE+RT group; HR, 0.46; 95% CI, 0.21 to 1.02; $P = .051$). In only two patients (one in each treatment group), recurrence consisted of an isolated regional recurrence without prior or concurrent LR. Distant metastases were observed in 33 patients in the LE group and 33 patients in the LE+RT group (HR, 0.99; 95% CI, 0.61 to 1.61; $P = .982$). Distant metastasis without prior or concurrent invasive LR occurred in 12 patients in the LE group and 20 patients in the LE+RT group. Overall, there were 124 deaths, including 46 breast cancer–related deaths (22 in the LE group and 24 in the LE+RT group), 29 second primary tumor–related deaths (10 *v* 19, respectively), 15 deaths as a result of cardiovascular disease (10 *v* five, respectively), and 34 deaths as a result of other/unknown causes (19 *v* 15, respectively). None of the differences in cause of death were significant between both treatment arms. There was no statistically significant difference between the LE group and LE+RT group for BCSS (15-year BCSS: 95% *v* 96%, respectively; HR, 1.07; 95% CI, 0.60 to 1.91; $P = .814$) and OS (15-year OS: 90% *v* 88%, respectively; HR, 1.02; 95% CI, 0.71 to 1.44; $P = .931$). In the group of patients who died because of breast cancer, no prior or concurrent invasive recurrence was observed in 16 of the 22 patients in the LE group and 11 of the 24 patients in the LE+RT group.

Treatment After LR

After LR, the majority of the patients (97% in both treatment groups) underwent surgery of the breast (breast-conserving surgery with or without adjuvant RT or a mastectomy). In the LE group, fewer patients who developed LR were treated with a salvage mastectomy compared with patients in the LE+RT group (94 [63%] of 149 patients *v* 64 [75%] of 85 patients). However, women initially treated with LE had an ultimately higher risk of a mastectomy; 19% of women (94 of 503 women) in the LE group had mastectomy at 15 years compared with 13% of women (64 of 507 women) treated with LE+RT (HR, 0.66; 95% CI, 0.48 to 0.90; Fig 3).

Prognosis After LR

No difference was observed in women who developed DCIS recurrence compared with women who remained free of recurrence in BCSS (HR, 0.65; 95% CI, 0.16 to 2.71) and OS (HR, 1.19; 95% CI, 0.59 to 2.37). On the contrary, the hazard of dying after an invasive LR was

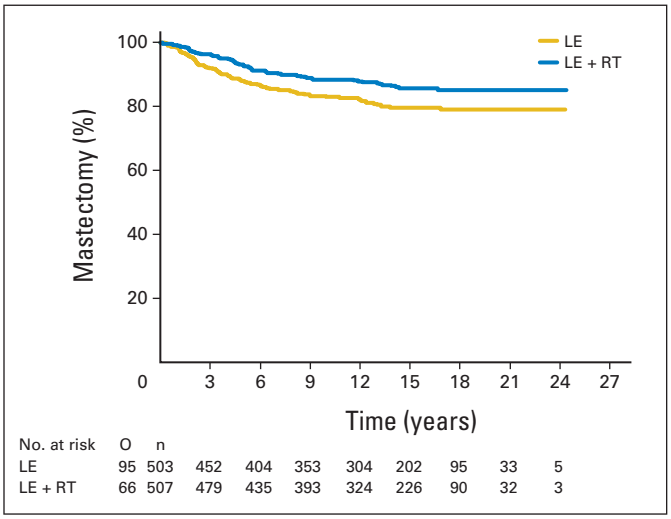

Fig 3. Time to mastectomy for all randomly assigned patients. LE, local excision; n, number of patients; O, observed; RT, radiotherapy.

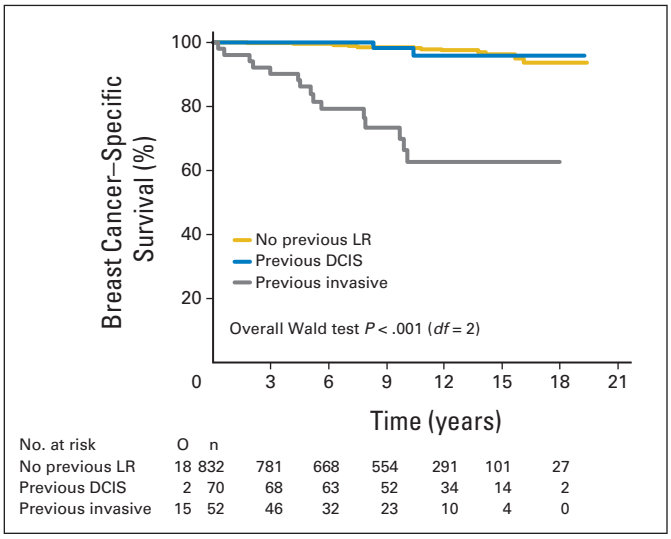

Fig 4. Breast cancer–specific survival after a local recurrence (LR) 5 years after random assignment. DCIS, ductal carcinoma in situ; n, number of patients; O, observed.

five times higher compared with patients without an LR (HR, 5.17; 95% CI, 3.09 to 8.66). The hazard of BCSS was 17 times higher after an invasive LR (HR, 17.66; 95% CI, 8.86 to 35.18; Fig 4).

DISCUSSION

This randomized trial demonstrates that adjuvant RT after LE for DCIS reduces the LR rate and this effect is maintained in the long term. After a median follow-up time of 15.8 years, the magnitude of this reduction (HR, 0.52) is comparable with the analysis performed at 10.5 years (HR, 0.53) and slightly larger compared with the analysis performed after 4.25 years (HR, 0.62).[5,6] Approximately half of the LRs were invasive, and there was a comparable effect of RT in reducing the incidence of a DCIS recurrence (15-year LR rates reduced from 16% to 8%; HR, 0.49) compared with an invasive recurrence (15-year LR rates reduced from 16% to 10%; HR, 0.61).

A few other trials evaluated the effect of RT after LE for DCIS on the risk of LR. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 trial[2] (N = 813) and the SweDCIS trial[3] (N = 1,067), women with localized DCIS were randomly assigned to LE or LE+RT. In these two trials, with a median follow-up of 17.3 and 8.4 years, respectively, RT reduced the risk of LR by 52% (95% CI, 33% to 69%) to 60% (95% CI, 30% to 54%). In the United Kingdom/Australia and New Zealand (ANZ) DCIS trial, 1,030 patients were randomly assigned in a 2 × 2 factorial trial to RT, tamoxifen, or both.[4] With a median follow-up time of 12.7 years, the reduction was 59% (95% CI, 30% to 56%) when RT was given after LE for DCIS. There was no effect from tamoxifen on the incidence of invasive LRs (HR, 0.95; 95% CI, 0.66 to 1.38).

A meta-analysis of all four randomized trials (including the EORTC 10853 trial) revealed a risk reduction in LR after RT of 0.46 (SE, 0.05; $P < .001$).[7] In all trials, there was a comparable magnitude of reduction in the incidence of invasive and noninvasive recurrences. RT reduced LRs irrespective of the age at diagnosis; the use of tamoxifen; the method of detection; tumor size, grade, and architecture; presence of comedonecrosis; focality; and margin status. Our analysis of risk factors is in line with results reported in the available literature.[2,4,12] Local treatment including adjuvant RT was the strongest predictive factor for both DCIS and invasive LRs.

With the available data from this trial, it was not possible to identify subgroups of patients with an a priori low risk of an invasive LR. Moreover, RT reduced the incidence of an invasive LR in all subgroups.

There are a few limitations to this trial. First, this trial was too small to find an effect on OS. Second, the effect of tamoxifen was not investigated. Although no significant reduction in LRs with tamoxifen was found in the United Kingdom/ANZ trial,[4] in the NSABP B-24 trial with a median follow-up of 13.6 years, tamoxifen after LE+RT for DCIS reduced the incidence of an LR by 32% ($P = .25$).[13] Third, in 10% of the patients with central pathology review available, DCIS was not confirmed. However, analysis restricted to only patients with confirmed DCIS showed similar results. Although negative margins were a requirement to enter the trial, 21% of patients with confirmed DCIS had close, involved, or not specified margins.

Finally, although the effect of RT is robust in reducing LR by half, it is possible that the overall risk of local relapses is decreasing in recent years because of a number of factors. Developments in preoperative assessment such as imaging, improvements in surgical management, and more standardized margin assessment are likely to reduce the overall incidence of LRs, as was also observed in invasive breast cancer.[14-16]

The majority of all LRs (83%) occurred in the first 10 years. For the onset of DCIS LRs, RT seemed to have a continuously protective effect, but for the onset of invasive LRs, this protective effect seemed to be restricted to the first 5 years after treatment. However, because the number of events was small and the CIs are wide, these outcomes should be interpreted with care. A meta-analysis of patients with invasive breast cancer revealed that the protective effect of RT was greatest in the first year (rate ratio, 0.31; 95% CI, 0.26 to 0.37) and diminished during the following years.[17]

In this trial, the reduction of 48% in the risk of developing LR in the LE+RT group did not translate to a survival benefit, which is in accordance with other large randomized trials.[7] Several reasons might explain this observation. Survival after breast-conserving therapy for DCIS is good, with BCSS rates of 95% after 15 years. The current trial was not powered to find a difference in the occurrence of distant metastases, BCSS, or OS. Moreover, the definitive treatment after an invasive LR (ie, surgery and systemic treatment) has an important impact on prognosis, which could lead to this difference in the invasive LR having no effect on survival. Furthermore, RT is known to have a carcinogenic effect. RT-induced malignancy rates are estimated to compose 3% to 8% of all second primaries in irradiated patients.[18] In this trial, there was a nonsignificant trend toward a higher incidence of CLBC and of patients who died as a result of second malignancies in the LE+RT group. In the NSABP B-17 and United Kingdom/ANZ DCIS trials, no significant difference was observed in the onset of second malignancies or death as a result of second malignancy; in the SweDCIS trial, this was not investigated.[2-4,19] In none of these trials was a significant increase observed in the incidence of CLBC. Finally, adjuvant RT might not prevent tumors that are destined to cause distant metastases from metastasizing because identical numbers of distant metastases were observed.

Mastectomy has been historically the standard local treatment when LR occurs after breast-conserving treatment that includes RT.

One of the arguments in favor of omitting RT after excision of the primary DCIS lesion is the hypothetical ability to perform salvage breast-conserving treatment including RT in case of LR. Indeed, in the LE+RT group, a higher percentage of patients who developed LR was treated with a salvage mastectomy compared with the LE group (75% *v* 63%, respectively), as was also observed in other studies.[20-22] Overall, however, the LE+RT group had a lower mastectomy rate compared with the LE group (13% *v* 19%, respectively).

A pure DCIS LR did not have a significant effect on survival compared with patients without LR. In contrary, being diagnosed with an invasive LR increased the mortality risk by a factor of five and the breast cancer–specific mortality by a factor of 17 compared with patients who did not experience LR. This effect is in accordance with the literature, although the prognosis seems to be worse in our trial.[2,23-26] In comparison, in the NSABP DCIS trials, the HR of OS in patients who developed an invasive LR was 1.75 and the HR for BCSS was 7.06.[2]

Adjuvant RT after LE reduced the incidence of both in situ and invasive LRs by a factor of two, resulting in an overall lower risk of mastectomy. Although reduction was seen in all subgroups, it did not affect OS. However, patients with invasive LR had a significantly worse survival compared with patients without LR, and thus, invasive LR should be prevented. On the basis of the results of this trial, a subgroup of patients in whom RT can be withheld could not be identified.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Mila Donker, Ian S. Fentiman, Harry Bartelink, Emiel J.T. Rutgers, Nina Bijker
Provision of study materials or patients: Jean-Pierre Julien
Collection and assembly of data: Mila Donker, Saskia Litière, Jean-Pierre Julien, Roberto Agresti, Philippe Rouanet, Christine Tunon de Lara, Nicole Duez, Emiel J.T. Rutgers, Nina Bijker
Data analysis and interpretation: Mila Donker, Saskia Litière, Gustavo Werutsky, Harry Bartelink, Emiel J.T. Rutgers, Nina Bijker
Manuscript writing: All authors
Final approval of manuscript: All authors

REFERENCES

1. Virnig BA, Tuttle TM, Shamliyan T, et al: Ductal carcinoma in situ of the breast: A systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst 102:170-178, 2010

2. Wapnir IL, Dignam JJ, Fisher B, et al: Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS. J Natl Cancer Inst 103:478-488, 2011

3. Holmberg L, Garmo H, Granstrand B, et al: Absolute risk reductions for local recurrence after postoperative radiotherapy after sector resection for ductal carcinoma in situ of the breast. J Clin Oncol 26:1247-1252, 2008

4. Cuzick J, Sestak I, Pinder SE, et al: Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: Long-term results from the UK/ANZ DCIS trial. Lancet Oncol 12:21-29, 2011

5. Julien JP, Bijker N, Fentiman IS, et al: Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: First results of the EORTC randomised phase III trial 10853—EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet 355:528-533, 2000

6. Bijker N, Meijnen P, Peterse JL, et al: Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: Ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853—A study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol 24:3381-3387, 2006

7. Correa C, McGale P, Taylor C, et al: Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. J Natl Cancer Inst Monogr 2010:162-177, 2010

8. Bijker N, Peterse JL, Duchateau L, et al: Risk factors for recurrence and metastasis after breast-conserving therapy for ductal carcinoma-in-situ: Analysis of European Organization for Research and Treatment of Cancer Trial 10853. J Clin Oncol 19:2263-2271, 2001

9. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 50:163-170, 1966

10. Collett D: Modelling Survival Data in Medical Research (ed 2). New York, NY, Chapman and Hall, 2003

11. Anderson JR, Cain KC, Gelber RD: Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. J Clin Oncol 26:3913-3915, 2008

12. Solin LJ, Fourquet A, Vicini FA, et al: Long-term outcome after breast-conservation treatment with radiation for mammographically detected ductal carcinoma in situ of the breast. Cancer 103:1137-1146, 2005

13. Allred DC, Anderson SJ, Paik S, et al: Adjuvant tamoxifen reduces subsequent breast cancer in women with estrogen receptor-positive ductal carcinoma in situ: A study based on NSABP protocol B-24. J Clin Oncol 30:1268-1273, 2012

14. Chang MM, Huston T, Ascherman J, et al: Oncoplastic breast reduction: Maximizing aesthetics and surgical margins. Int J Surg Oncol 2012:907576, 2012

15. Millar EK, Leong AS: Significance and assessment of margin status in ductal carcinoma in situ of the breast. Adv Anat Pathol 8:338-344, 2001

16. Poortmans P, Aznar M, Bartelink H: Quality indicators for breast cancer: Revisiting historical evidence in the context of technology changes. Semin Radiat Oncol 22:29-39, 2012

17. Darby S, McGale P, Correa C, et al: Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: Meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707-1716, 2011

18. Berrington de Gonzalez A, Curtis RE, Gilbert E, et al: Second solid cancers after radiotherapy for breast cancer in SEER cancer registries. Br J Cancer 102:220-226, 2010

19. Emdin SO, Granstrand B, Ringberg A, et al: SweDCIS: Radiotherapy after sector resection for ductal carcinoma in situ of the breast—Results of a randomised trial in a population offered mammography screening. Acta Oncol 45:536-543, 2006

20. Solin LJ, Fourquet A, Vicini FA, et al: Salvage treatment for local or local-regional recurrence after initial breast conservation treatment with radiation for ductal carcinoma in situ. Eur J Cancer 41:1715-1723, 2005

21. Fisher B, Dignam J, Wolmark N, et al: Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 16:441-452, 1998

22. Cutuli B, Cohen-Solal-le Nir C, de Lafontan B, et al: Breast-conserving therapy for ductal carcinoma in situ of the breast: The French Cancer Centers' experience. Int J Radiat Oncol Biol Phys 53:868-879, 2002

23. Silverstein MJ, Lagios MD, Martino S, et al: Outcome after invasive local recurrence in patients with ductal carcinoma in situ of the breast. J Clin Oncol 16:1367-1373, 1998

24. Romero L, Klein L, Ye W, et al: Outcome after invasive recurrence in patients with ductal carcinoma in situ of the breast. Am J Surg 188:371-376, 2004

25. Lee LA, Silverstein MJ, Chung CT, et al: Breast cancer-specific mortality after invasive local recurrence in patients with ductal carcinoma-in-situ of the breast. Am J Surg 192:416-419, 2006

26. Voogd AC, van Oost FJ, Rutgers EJ, et al: Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer. Eur J Cancer 41:2637-2644, 2005