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ORIGINAL REPORT

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

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ABSTRACT

Purpose
The European Organisation for Research and Treatment of Cancer conducted a randomized trial investigating the role of radiotherapy (RT) after local excision (LE) of ductal carcinoma-in-situ (DCIS) of the breast. We analyzed the efficacy of RT with 10 years follow-up on both the overall risk of local recurrence (LR) and related to clinical, histologic, and treatment factors.

Patients and Methods
After complete LE, women with DCIS were randomly assigned to no further treatment or RT (50 Gy). One thousand ten women with mostly (71%) mammographically detected DCIS were included. The median follow-up was 10.5 years.

Results
The 10-year LR-free rate was 74% in the group treated with LE alone compared with 85% in the women treated by LE plus RT (log-rank $P < .0001$; hazard ratio [HR] = 0.53). The risk of DCIS and invasive LR was reduced by 48% ($P = .0011$) and 42% ($P = .0065$) respectively. Both groups had similar low risks of metastases and death. At multivariate analysis, factors significantly associated with an increased LR risk were young age (≤ 40 years; HR = 1.89), symptomatic detection (HR = 1.55), intermediately or poorly differentiated DCIS (as opposed to well-differentiated DCIS; HR = 1.85 and HR = 1.61 respectively), cribriform or solid growth pattern (as opposed to clinging/micropapillary subtypes; HR = 2.39 and HR = 2.25 respectively), doubtful margins (HR = 1.84), and treatment by LE alone (HR = 1.82). The effect of RT was homogeneous across all assessed risk factors.

Conclusion
With long-term follow-up, RT after LE for DCIS continued to reduce the risk of LR, with a 47% reduction at 10 years. All patient subgroups benefited from RT.

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INTRODUCTION

Since the introduction of mammographic screening in the Western world, ductal carcinoma-in-situ (DCIS) has changed from being a rare disease to a lesion detected in up to 20% to 30% of breast cancers in screening programs.[1] Before the advent of screening, this preinvasive form of breast cancer was normally treated by mastectomy. After the proven success of radiotherapy (RT) in breast-conserving treatment (BCT) for invasive breast cancer,[2,3] in the mid and late 1980s, several randomized clinical trials in Europe and North America were initiated to evaluate optimal BCT for patients with DCIS. Three studies investigated the role of breast RT after local excision (LE) of the lesion.[4-6] In the European Organisation for Research and Treatment of Cancer (EORTC) 10853 study, more than 1,000 women were randomly allocated to RT to the whole breast or no further treatment after complete LE of DCIS. The early results, published in 2000,[6] indicated an overall reduction of the risk of local recurrence (LR)

as a result of RT. With this report, we analyzed the efficacy of RT with 10 years of follow-up on both the overall risk of LR and related to various clinical, histologic, and treatment factors.

PATIENTS AND METHODS

Women with DCIS of the breast were randomly assigned between RT and no further treatment after complete LE of the lesion. Extent of free margins was not specified other than that DCIS should not be present at microscopic examination of the margins. Patients with lesions up to 5 cm in diameter, without evidence of (micro)invasion or Paget's disease, were eligible for the study. The prescribed irradiation dose was 50 Gy in 25 fractions to the whole breast. No boost was advised (5% of the patients randomly assigned to RT received a boost). The use of tamoxifen was not recommended. The primary end points were both invasive and DCIS LR in the treated breast. Secondary end points included metastasis, death, and contralateral breast cancer (CLBC). Further information about study design, eligibility criteria, surgery and RT protocols, quality assurance, and follow-up procedures has been given previously.[6]

The data obtained from a general review, during which mammographic, surgical, histologic, and follow-up data were checked in the patients' medical files, served as a basis for the previous and current analyses. In the 16% for whom no detailed review data were available, the original data reported to the EORTC Data Center were used for the analyses.

All patients were required to have bilateral mammograms preoperatively and annually during follow-up. Although the protocol did not require postoperative mammograms, a specimen x-ray was made in 90% of the patients with nonpalpable DCIS.[7]

The trial included a central pathology review, available on 863 patients.[8] For the current analysis, we have used the data of the pathology review for analyses related to the risk of recurrence. At pathology review, invasive growth was found in 27 cases, and in 13 there was suspicion of invasion. In 48 cases, benign proliferative lesions or lobular carcinoma in situ were diagnosed at review. These cases have been included in all analyses of the effect of RT on the primary and secondary end points. Analysis restricted to confirmed DCIS cases yielded the same results (data not shown).

Because the extent of the lesion and the width of the tumor-free margin could not reliably be assessed by review of the histologic slides, the pathology reports were reviewed. The size of the DCIS was mentioned in the pathology report in only 193 cases (25%). The margin status was considered free if it was reported free (> 1 mm), or if a re-excision was performed and no residual DCIS was found. When margins were reported to be close (≤ 1 mm) or involved, and when the margin status was not specified, the margin status was classified under not free. A previous analysis had shown that at a median follow-up of 5.4 years, the first groups, as well as the last three groups, had similar recurrence rates.[8]

All analyses are based on the intent-to-treat principle with recurrence-free intervals defined as the time between the date of random assignment and the date of recurrence. The time-to-recurrence curves were calculated using the Kaplan-Meier technique[9] and compared using a two-sided log-rank test with 5% type I error.[10] An estimate of the size of the treatment effect was calculated based on the hazard ratio (HR) and its 95% two-sided CI. The HRs are presented with the level of the variable considered best as the baseline. A Cox proportional hazards regression model[11] was fitted for the multivariate analysis of LR, using variables with significant P values (< 0.05) in the univariate analysis.

RESULTS

Between March 1986 and July 1996, 1,010 women were randomly assigned to no further treatment (503 patients) or to RT (507 patients) after LE. The previous report demonstrated that patient, tumor, and treatment characteristics according to treatment group were well balanced between the arms.[6] The median age of the women was 53 years; 71% of them were mammographically detected. The present analysis was performed in August 2005, at a median duration of follow-up of 10.5 years.

LR-Free Interval

One hundred thirty-two patients developed LRs in the LE group and 75 in the LE + RT group. The risk of LR was reduced with 47% in the LE + RT group compared with that in the LE group (log-rank $P < .0001$), the 10-year LR-free rates were 85% and 74%, respectively (Table 1; Fig 1). One hundred three patients had LRs of DCIS, and 106 patients developed invasive LRs. Two patients with a DCIS LR subsequently developed an invasive LR. There was a similar reduction in the risk of DCIS and invasive LR. The 10-year DCIS LR-free rate was 93% in the LE + RT group versus 86% in the LE group ($P = .0011$); the 10-year invasive LR-free rates were 92% and 87%, respectively ($P = .0065$; Table 1; Fig 1).

A salvage mastectomy was performed in 144 (70%) of the 207 LRs, whereas 56 patients underwent BCT. Thirty patients, originating from the LE group, received adjuvant RT. In seven patients, treatment of LRs was not reported.

Other Events

Table 1 demonstrates no significant difference in the 10-year CLBC-free interval. The 10-year metastasis-free rate was the same in the two treatment arms (96%). In 25 patients, metastases originated from an invasive LR (15 in the LE group and 10 in the LE + RT group). Two patients (in the LE + RT group) developed metastases after a DCIS LR. In five patients, distant metastasis developed without a prior LR or CLBC, and in nine patients, metastatic disease was preceded by a CLBC. Two patients developed metastases simultaneously with a regional recurrence (without an LR).

Of the 59 deaths, 32 were breast cancer–related (15 in the LE group and 17 in the LE + RT group): 23 patients died as a result of metastatic disease after an LR, four patients from metastases as first event without prior LR, and another five patients after an invasive CLBC. Another malignancy was the cause of death in 13 patients, seven died as a result of cardiovascular disease, five because of various other causes, and for two patients the cause of death was unknown. The 10-year overall survival rate was 95% in both arms.

Risk Factors Associated With Recurrence

The analyses on risk factors were performed on 775 cases in which the diagnosis of DCIS was confirmed. Table 2 shows results of the univariate analysis. Women 40 years of age or younger were at high risk for developing an LR (34% at 10 years). In the LE group, 16 of 38 young women developed an LR (43% at 10 years). In the LE + RT group, seven of 27 women had an LR (23% at 10 years). Young women had a higher rate of symptomatically detected lesions (66%, compared with 25% of women older than 40), mostly because they were not in the screening age range. Twenty-seven percent (11 of 41) of the young patients had margins that were not free, compared with 22% (152 of 700) of the women older than 40 years of age. Of the younger patients, 37% had poorly differentiated lesions, compared with the 38% of patients older than 40 years of age.

Also at a high risk of LR were patients with not-free margins (32% LRs at 10 years). The LR rate after LE was 39%, and after LE + RT, 24% at 10 years. Low LR rates were observed in lesions with a clinging/micropapillary growth pattern; overall, 9% LRs at 10 years were found,

Table 1. Event-Free Estimates at 10 Years and Hazard Ratios According to Treatment

Event	No. of Patients*	10-Year Event-Free Estimate† (%)	Hazard Ratio‡	95% CI	Log-Rank *P*
Local recurrence			0.53	0.40 to 0.70	< .0001
LE	132	74			
LE + RT	75	85			
DCIS recurrence			0.52	0.34 to 0.77	.0011
LE	67	86			
LE + RT	36	93			
Invasive recurrence			0.58	0.39 to 0.86	.0065
LE	66	87			
LE + RT	40	92			
Regional recurrence			0.46	0.20 to 1.07	.064
LE	17	97			
LE + RT	8	99			
Distant metastasis			1.14	0.63 to 2.08	.66
LE	20	96			
LE + RT	23	96			
Death			1.18	0.70 to 1.96	.53
LE	27	95			
LE + RT	32	95			
Contralateral breast cancer			1.41	0.87 to 2.30	.16
LE	28	96			
LE + RT	39	92			
Contralateral DCIS			1.10	0.47 to 2.59	.82
LE	10	98			
LE + RT	11	98			
Contralateral invasive			1.48	0.83 to 2.65	.18
LE	19	97			
LE + RT	28	94			
Event-free survival			0.72	0.57 to 0.91	.0066
LE	160	70			
LE + RT	123	76			

Abbreviations: LE, local excision; RT, radiotherapy; DCIS, ductal carcinoma in situ.
*Overall totals 503 on LE and 507 on LE + RT.
†Kaplan-Meier estimate at 10 years.
‡Values < 1 indicate a better outcome for LE + RT.

with 13% in the LE and 5% in the LE + RT group. A further analysis of the well-differentiated lesions according to architectural pattern demonstrated that four of 58 and eight of 99 patients with, respectively, clinging and micropapillary growth patterns developed an LR. If the well-differentiated DCIS had cribriform or a solid/comedo architecture, 24 of 115 and three of 10 women developed an LR, respectively.

Figure 2 shows in a Forrest plot that RT reduced the risk of LR in all subgroups, with the effect of RT being homogeneous across all risk factors.

At multivariate analysis, factors significantly associated with an increased risk of LR were young age, symptomatic detection of the lesion, intermediately or poorly differentiated DCIS (as opposed to well-differentiated DCIS), solid or cribriform growth pattern (as opposed to clinging/micropapillary subtypes), margins that were not free, and treatment by LE alone (Table 3).

The histologic type was related to the risk of DCIS and invasive LR, metastases, and death (Table 4). Well-differentiated DCIS had a lower risk of DCIS LR but not of invasive LR. Overall, the histologic type was not significantly related to the risk of distant metastases or death. Of note is that all causes of metastases and death are included in this analysis (eg, also resulting from CLBC). Twenty-three of 106 patients with an invasive recurrence developed metastasis; the corresponding Kaplan-Meier estimate of the metastasis-free rate at 10 years after an invasive recurrence is 74% (counting from the invasive recurrence).

DISCUSSION

With a median follow-up of 10.5 years, the results of this randomized trial continue to show that RT after LE of DCIS of the breast reduces the risk of LR as compared with LE alone. The magnitude of the reduction has become slightly larger compared with the analysis performed at 4.25 years (HR now = 0.53, HR then = 0.62). The EORTC 10853 trial is the second to publish its long-term results. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study, including 818 women, published long-term results at 10.8 years of follow-up.[4] The UK Co-ordinating Committee on Cancer Research (UKCCCR) DCIS trial, randomly assigning 1,701 patients to RT, tamoxifen, or both, presented its first results in 2003 at 4.4 years.[5] All three trials demonstrate a reduction in the risk of LR as a result of RT. The EORTC study demonstrates similar reductions by RT for DCIS and invasive LR: a 10-year DCIS LR rate reduction from 14% to 7% and from 13% to 8% of invasive LR. All three trials, as well as many

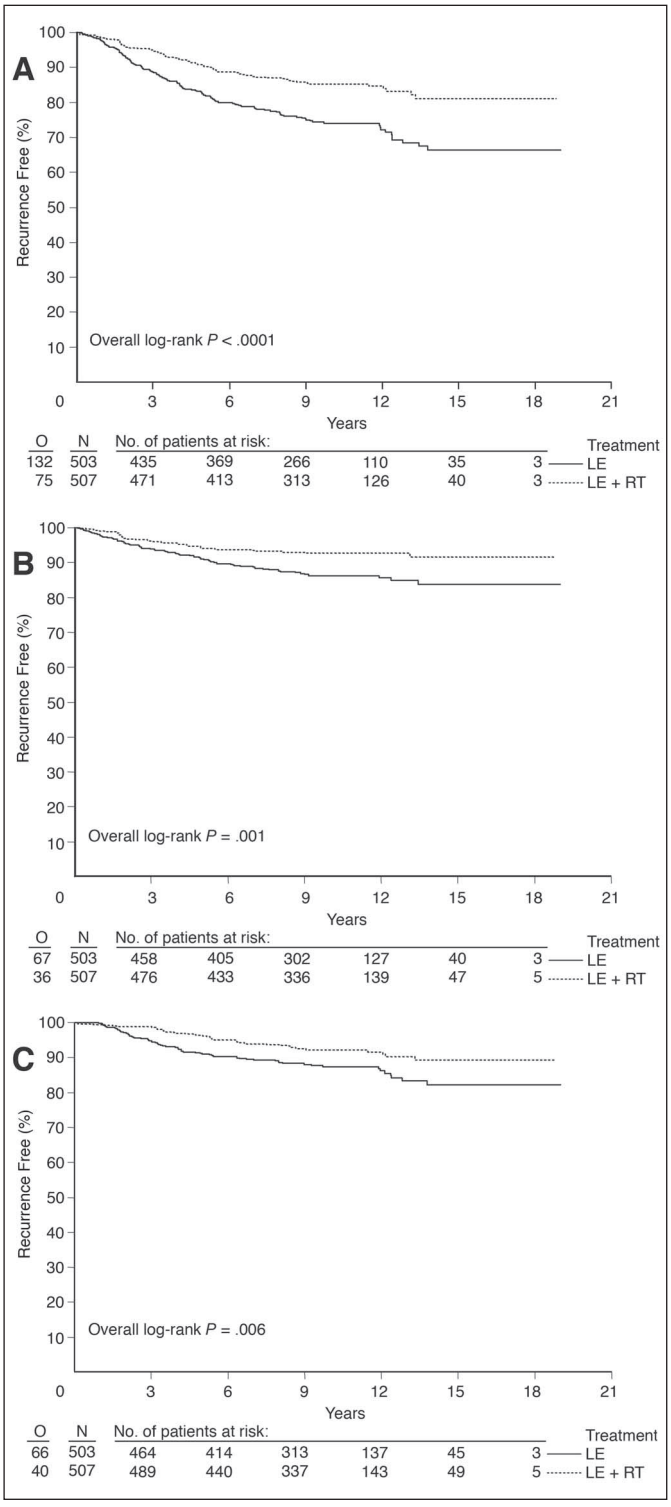

Fig 1. (A) Time to local recurrence by treatment arm; (B) time to ductal carcinoma in situ recurrence by treatment arm; and (C) time to invasive recurrence by treatment arm. O, observed; N, number of patients; LE, local excision; RT, radiotherapy.

nonrandomized studies,[12-14] show that in both treatment groups about half of the LRs are DCIS and half of them are invasive.

Whereas in the EORTC study, at the first analysis a surprisingly higher rate of CLBCs was found in the RT arm,[6] in the current update a significant difference could no longer be observed. As was assumed in the first analysis, this update seems to confirm that the original finding was a false positive.

Our analysis of risk factors for LR showed that young women ($\leq$ 40 years of age) are at a particularly high risk for LR. A similar phenomenon is seen for invasive breast cancer.[15-18] Other studies have also found that young age is an adverse prognostic factor for LR after BCT for DCIS.[12,14,19,20] The cases of DCIS in the young age group are a mixture of lesions detected in high-risk women who underwent individual screening, and of symptomatic lesions, which have been shown to grow more extensively.[21] Possible biologic differences of DCIS in young women are subject of research.[22] In our study, the young women did not have a higher frequency of poorly differentiated DCIS compared with the older women.

The completeness of excision of the DCIS remains one of the most important predictors for LR. Many studies have shown that margin status is an independent factor for LR after BCT for DCIS.[12-14,20,23] The current trial required excision margins to be free of tumor for trial entry. Thus, by review of the medical files, strictly, patients with involved margins would have become ineligible. However, only seven patients were entered while the pathologist stated the margins to be involved with tumor. When margins are really involved with tumor, one can expect even higher LR rates. Therefore, the performance of a complete excision with tumor-free margins is one of the mainstays of BCT for DCIS. In 1999, a retrospective series suggested that with a margin width of at least 10 mm, the risk of LR was very low, with possibly a limited absolute additional benefit of RT in BCT of DCIS. Recently, a prospective study of 158 patients with small ($\leq$ 2.5 cm) grade 1 or 2 DCIS, excised with margins of 10 mm or larger, still found a high LR rate after LE only of 12% at 5 years.[24] In our study, those patients who underwent a re-excision in which no residual DCIS was found (also considered $\geq$ 10 mm) did not have a lower LR rate compared with those who had free margins without further specification of the margin width. Currently, the Radiation Therapy Oncology Group (RTOG) 9804 study randomly assigns women with "good-risk" DCIS between RT plus tamoxifen and tamoxifen only.

The risk factor analysis of the NSABP study at 8 years of follow-up yielded the presence of comedo necrosis as the most important risk factor related to LR.[25] Although margin status was of borderline significance in this analysis, the authors still stressed the importance of a microscopic complete excision.

Current practice, to ensure complete removal of all microcalcifications, includes a postoperative mammogram that was not part of the protocol because, at the time this study was designed, there was limited experience with BCT for nonpalpable lesions.

Our analysis shows that well-differentiated DCIS had a lower risk of LR than intermediately and poorly differentiated subtypes. Nevertheless, also in the well-differentiated group, RT reduced the risk of LR (Fig 2). As can be seen in Table 4, well-differentiated DCIS had a lower risk of DCIS LR but not of invasive LR. From our data, high-grade DCIS does not seem to progress into invasive carcinoma more rapidly than low-grade DCIS. Table 4 shows that a higher number of women (n = 12) with poorly differentiated DCIS died as a result of invasive LR, compared with three women with a well and three with an intermediately differentiated DCIS.

The groups with an exceptionally low risk of recurrence were those with well-differentiated DCIS with a clinging or micropapillary growth pattern, with, in both groups, overall less than 10% LRs at 10

Table 2. Univariate Analyses of Clinical and Histologic Characteristics Related to Local Recurrence

Characteristic	No. of Patients	No. of Events	10-Year Event-Free %	Hazard Ratio	95% CI	Log-Rank *P*
Age, years						.0021
> 40	945	184	81	1		
≤ 40	65	23	66	1.95	1.26-3.01	
Method of detection						.0095
X-ray finding only	723	134	82	1		
Clinical symptoms	275	72	74	1.46	1.09-1.94	
Size,* mm						.12
<10	134	25	82	1		
10-20	42	11	79	1.37	0.67-2.80	
>20	17	7	59	2.37	1.02-5.47	
Histologic type*						.0001
Well	284	39	86	1		
Intermediate	199	57	73	2.26	1.50-3.39	
Poor	292	77	74	2.08	1.41-3.05	
Architecture*						< .0001
Clinging/micropapillary	204	20	91	1		
Cribriform	269	69	74	2.83	1.72-4.65	
Solid/comedo	299	83	73	3.13	1.92-5.10	
Margins*						.0001
Free	578	110	81	1		
Not free	163	55	68	1.89	1.37-2.63	

*In ductal carcinoma in situ-confirmed patients.

years. In these groups, although the relative benefit of RT is similar to that in the other groups, the absolute benefit of RT on the LR risk will become very small.

The reduced risk of LR caused by RT has, at 10 years of follow-up, not resulted in a survival difference between the two arms. The death rate attributable to metastasized breast cancer after an invasive LR is with 2% the same in both arms and is, with this time of follow-up, similar to death rates reported after mastectomy.[26] However, this study was not powered for finding a difference in metastasis or survival. Perhaps only long-term follow-up from combined clinical trials can give answer to these questions. For women with DCIS who are at a high risk of invasive LR, such as those 40 years of age or younger or those with lesions that cannot be excised with tumor-free margins, the

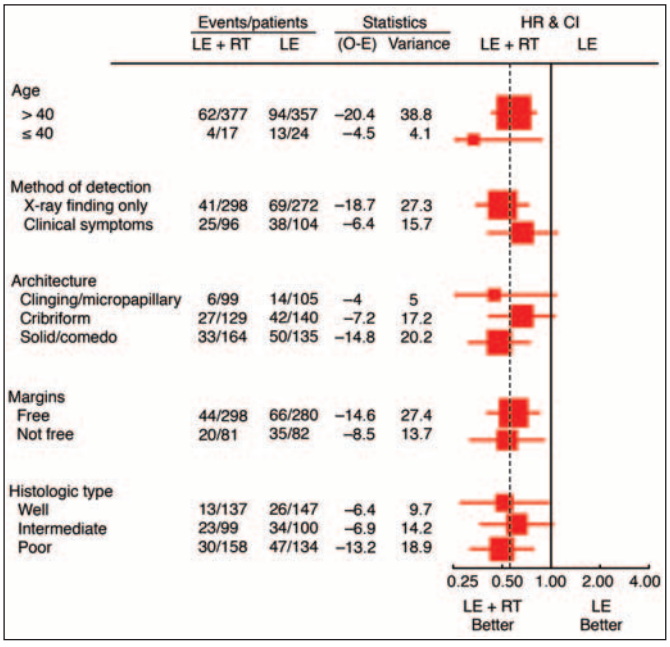

Fig 2. Effect of radiotherapy on local control by subgroup. LE, local excision; RT, radiotherapy; HR, hazard ratio; CI, 95% CI.

Table 3. Multivariate Analysis of Risk Factors Related to Local Recurrence

Variable	Hazard Ratio	95% CI	*P*
Age, years			
> 40	1		
≤ 40	1.89	1.12 to 3.19	.026
Method of detection			
X-ray finding only	1		
Clinical symptoms	1.55	1.11 to 2.16	.012
Histologic type			
Well	1		
Intermediate	1.85	1.18 to 2.90	.024
Poor	1.61	0.93 to 2.79	
Architecture			
Clinging/micropapillary	1		
Cribriform	2.39	1.41 to 4.03	.002
Solid/comedo	2.25	1.21 to 4.18	
Margins			
Free	1		
Not free	1.84	1.32 to 2.56	.0005
Treatment			
LE + RT	1		
LE	1.82	1.33 to 2.49	.0002

Abbreviations: LE, local excision; RT, radiotherapy.

Table 4. Histologic Type Related to DCIS/Invasive Recurrence, Metastasis, and Death

Event	No. of Patients	Events		Hazard Ratio	95% CI	*P*
		No.	%			
DCIS recurrence						.0006
Histologic type						
Well	284	15	5	1		
Intermediate	199	31	16	3.13	1.69 to 5.80	
Poor	292	41	14	2.82	1.56 to 5.09	
Invasive recurrence						.35
Histologic type						
Well	284	26	9	1		
Intermediate	199	26	13	1.45	0.84 to 2.51	
Poor	292	36	12	1.35	0.81 to 2.23	
Distant metastasis*						.24
Histologic type						
Well	284	8	3	1		
Intermediate	199	8	4	1.47	0.55 to 3.91	
Poor	292	17	6	2.04	0.88 to 4.73	
Death†						.17
Histologic type						
Well	284	11	4	1		
Intermediate	199	10	5	1.35	0.57 to 3.18	
Poor	292	23	8	1.96	0.95 to 4.02	

Abbreviation: DCIS, ductal carcinoma in situ.
*As a result of ipsilateral breast cancer: four well, five intermediate, 13 poorly-differentiated.
†As a result of ipsilateral breast cancer: three well, three intermediate, 12 poorly-differentiated.

subsequent risk of eventually dying from metastasized disease after an invasive LR could become unacceptably high.

Both the NSABP B-17 and the EORTC 10853 trials show relatively high 10-year LR rates of approximately 15% after RT. In the RT arms of these trials, the whole breast was irradiated to a dose of 50 Gy, without a boost dose administered to the original tumor bed. Recently, a large randomized trial has demonstrated that, in invasive breast cancer, an additional dose of 16 Gy directed at the tumor bed further reduced the risk of LR, with a HR of 0.59.[27] This additional dose to the tumor bed might also further reduce the risk of LR in DCIS.

The joint randomized trial NSABP B-39/RTOG 0413 compares whole-breast RT with partial breast RT in patients with early stage breast cancer, including DCIS. Because of the sometimes discontinuous spread of DCIS within the branching ducts, residual disease may not be in the immediate vicinity of the biopsy cavity. Therefore, women with DCIS might not be good candidates for partial-breast RT.

Two randomized trials have investigated tamoxifen in the treatment of DCIS.[5,28] The UKCCCR reported only a slight effect of tamoxifen on the reduction of DCIS LR and concluded that there is little evidence for treatment with tamoxifen in women with DCIS. The NSABP B-24 study showed a reduction of mainly invasive LRs and CLBCs caused by tamoxifen. In neither the UKCCCR nor the NSABP B-24 trial was information available on the estrogen receptor (ER) of the DCIS. Our data demonstrate that patients with a higher risk of metastases are those with a poorly differentiated DCIS. These lesions lack ER overexpression in 52% to 61%.[29-31] Tamoxifen is known to be ineffective for preventing recurrence in ER-negative breast tumors. The NSABP B-35 study, comparing tamoxifen with anastrozole in post menopausal women with DCIS, is ongoing.

In summary, the updated results of our trial confirm that, at long-term follow-up, the effectiveness of RT in BCT for DCIS persists. In addition, we have observed that RT reduced the risk of LR in all clinical and pathologic subgroups of patients, with a homogeneous treatment effect of RT across the levels of all factors considered. Hence, RT should be considered in all women treated with BCT for DCIS. However, some subgroups are at very low risk for LR; patients with clinging/micropapillary well-differentiated DCIS might be offered excision without additional irradiation in view of their excellent prognosis with surgery alone. In contrast, some women are, even after RT, at high risk of LR, such as young women and/or those with involved excision margins; in these patients, conservation of the breast should be weighted against a relatively high risk of developing distant metastases caused by an invasive LR from a curable disease.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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