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Local Recurrences After Conservative Treatment of Ductal Carcinoma-In-Situ of the Breast Without Radiotherapy: The Effect of Age

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Background: The main goal in treatment of ductal carcinoma-in-situ (DCIS) of the breast is to prevent local recurrences. Radiotherapy after breast-conserving surgery has been shown to decrease the recurrence rate, although whether all patients should be treated with radiotherapy remains a topic of debate. The aim of this study was to assess the local recurrence rate after conservative surgical treatment of DCIS without radiotherapy and to identify risk factors for local recurrence.

Methods: A total of 499 female patients with 502 DCIS lesions treated in the period 1989 to 2002 were retrospectively reviewed. Survival rates were calculated by the Kaplan-Meier method, and differences were tested by using the log-rank test. The association of variables with local recurrence was analyzed by using the χ^2 test.

Results: Treatment constituted of lumpectomy in 329 patients (65%). Thirty-eight patients (8%) had disease-positive margins, and for 41 patients (8%) the margin status was not known. Eighty tumors recurred, for a local recurrence rate of 13% after 4 years compared with 17% for patients treated with breast-conserving surgery only. Risk factors for ipsilateral recurrences were younger age (< 50 years), treatment with breast-conserving surgery only, and presence of disease-involved surgical margins.

Conclusions: Conservative treatment of DCIS results in high recurrences rates, and outcomes can be improved by performing more radical surgery. Because radiotherapy has been shown to be effective in preventing recurrent disease, and, to date, no subgroups have been identified in which radiation can be omitted, its use is recommended, especially in younger patients.

Key Words: Ductal carcinoma-in-situ—Breast—Surgical treatment—Local recurrences—Risk factors.

Since the introduction of mammographic screening programs for breast cancer, there has been a marked increase in the detection of ductal carcinoma-in-situ (DCIS).[1] Because of the noninvasive nature of DCIS, there is a potential cure rate of almost 100% if treated with a mastectomy.[2,3] With breast-conserving surgery proven to be a safe treatment option compared with mastectomy for patients with invasive breast cancer, breast-conserving surgery for DCIS is also assumed to be effective and is used widely.[1,2,4–6] However, breast-conserving therapy carries the risk for recurrent disease. Half of the local recurrences that occur

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after breast-conserving treatment of DCIS are invasive carcinomas with, thus, a risk for distant disease and subsequent death.[7–9] Although the risk of dying as a result of DCIS is low (2% after 10 years of follow-up), local recurrences are still a major concern in the treatment of patients with DCIS.[6,10]

An important treatment-related risk factor for local recurrences is the adequacy of surgical excision.[11,12] This is demonstrated by the fact that most recurrences after breast-conserving surgery occur at the same site of and are clonally related to their primary lesions.[13–15]

Recently, two large-scale randomized studies revealed that radiotherapy after breast-conserving surgery for DCIS decreased the incidence of local recurrences.[16–21] However, it has also been shown that radiotherapy cannot compensate for an inadequate excision in reducing the risk of local recurrence.[22–24] Therefore, a microscopically complete excision remains the cornerstone in treatment of DCIS. Whether all patients with DCIS should receive radiotherapy after breast-conserving surgery remains a topic of active debate.[11,21] The aim of this population-based study was to assess the outcome of conservative surgical treatment of patients with DCIS without radiotherapy and to identify subgroups of patients at increased risk for local recurrence.

PATIENTS AND METHODS

The Comprehensive Cancer Centre of the Middle Netherlands (Integraal Kanker Centrum Midden Nederland) is composed of seven hospitals, two of which are teaching hospitals and one of which is a university hospital (Appendix 1). Together, these hospitals treat all patients with DCIS who are living in the central part of The Netherlands. The Comprehensive Cancer Centre of the Middle Netherlands guidelines for treatment of DCIS recommend a microscopically complete excision of the lesion with either breast-conserving surgery or mastectomy for larger lesions (no specific size is recommended) or multifocal lesions. During the study period, the routine use of any adjuvant therapy was not recommended.

Through the Cancer Registry from the Comprehensive Cancer Centre of the Middle Netherlands, all patients with a first diagnosis of DCIS in the period between January 1989 and December 2002 were identified. Patients with a simultaneously occurring invasive breast lesion and/or other malignancies (except for nonmelanoma skin cancer) were excluded. A total of 604 patients were eligible, and their medical records were reviewed. For 36 patients, no medical record was available. Another 69 patients were excluded because of a microinvasive component of the initial DCIS lesion (12 patients), DCIS with lobular carcinoma-in-situ (8 patients), invasive breast carcinoma as an initial diagnosis (9 patients), simultaneous contralateral invasive breast carcinoma (3 patients), a history of breast cancer (6 patients), no further information or follow-up data (20 patients), or other criteria (no diagnosis of DCIS or an unknown malignancy elsewhere; 11 patients).

From the remaining 499 patients with 502 DCIS lesions, all available clinical, pathologic, and follow up data were collected. The following data were noted: detection method (clinical diagnosis or mammographic detection), mammographic appearance (calcifications, architecture distortion, or both), age at diagnosis, family history of breast cancer (both first and second degree), location of primary DCIS (inner quadrant, outer quadrant, or central), size of DCIS lesion (according to mammographic or pathology reports, if specified), surgical treatment (including the performance of re-excision and the total number of surgical procedures), use of adjuvant radiotherapy, pathologic classification of the DCIS lesion, and final margin status (positive or negative, and margin width, if specified).

Follow-up started at the date of the first surgical procedure and ended at the last visit at the outpatient clinic. A local recurrence was defined as a pathology-proven carcinoma, both noninvasive and invasive, anywhere in the treated breast. Contralateral ''recurrences'' were not considered treatment failures.

Survival rates for ipsilateral recurrences were calculated by using the Kaplan-Meier method. Statistical significance of differences between survival curves of subgroups was tested by using the log-rank test. The association of clinical, pathologic, and treatment-related variables with recurrent disease was analyzed by using the χ^2 test. For continuous variables, Student's *t*-test was used. For all statistical analyses, a P value $< .05$ was considered statistically significant.

RESULTS

Table 1 lists patient and tumor characteristics of the study population. The median age at diagnosis was 56.4 years (range, 26.5–89.7 years), and the median follow-up length of the entire cohort was 50.6 months (range, 1.3–166.5 months). No differences were found for either age or follow-up length among different hospitals (data not shown).

TABLE 1. *Patient and tumor characteristics*

Characteristic	n	%
Age at diagnosis (y)		
<40	32	7
40–69	403	80
≥70	67	14
Family history of breast cancer		
Positive, first degree	72	14
Positive, degree unknown	28	6
Negative	233	46
Not specified	169	34
DCIS diagnosis		
Nipple discharge or palpable mass	103	21
Microcalcifications	334	66
Architecture distortion	24	5
Microcalcifications within distortion	41	8
Location of DCIS		
Inner quadrant	93	19
Outer quadrant	282	56
Central	121	24
Unknown	6	1
Initial treatment		
Lumpectomy	479	95
Mastectomy	23	5
Re-excision		
No	254	51
Yes, lumpectomy	98	19
Yes, mastectomy	150	30
No. of surgical procedures		
1	254	50
2	224	45
3	24	5
Final treatment		
Lumpectomy	329	65
Mastectomy	173	35
Postoperative therapy		
No adjuvant therapy	482	96
Radiotherapy	20	4
Tumor size (mm)		
Not specified	369	74
<15	82	16
15–40	47	9
≥40	4	1
Final margin status		
Negative	423	84
Positive[a]	38	8
Not specified	41	8
Margin width (mm)		
Not specified	361	72
<1	123	25
1–10	16	3
≥10	2	0

DCIS, ductal carcinoma-in-situ.
[a] Including 10 patients with disease-positive margins after mastectomy.

Most DCIS lesions were detected by mammography (80%), and most patients (95%) were treated by breast-conserving surgery initially. A complete excision on the first attempt was achieved in 233 patients (46%). No information on margin status was available from 47 patients (9%). Subsequently, a second or third surgical procedure was performed in 246 patients (49%), of whom 150 underwent mastectomy.

TABLE 2. *Four-year local recurrence–free survival calculated with the Kaplan-Meier method*

Event	n	4-y recurrence-free survival (%)
All recurrences	80	86.6
Noninvasive	44	92.4
Invasive	36	93.7

After 1 or more surgical procedures (mean, 1.54; median, 1.00), 329 patients (65%) were treated by lumpectomy, and 173 patients (35%) were treated by mastectomy. Twenty patients (4%) received postoperative radiotherapy as a result of inclusion in the European Organization for Research and Treatment of Cancer (EORTC) 10853 trial. At the start of follow-up, 38 patients (8%) had disease-involved margins (including 10 patients with disease-involved margins after mastectomy), and in 41 patients (8%), margin status was not specified.

From 214 DCIS lesions (43%), a histopathologic classification could be obtained from pathology reports: 29 lesions (19%) were classified as grade 1, or well differentiated; 45 lesions (29%) were classified as grade 2, or moderately differentiated; and 79 lesions (52%) were classified as grade 3, or poorly differentiated. A total of 52 DCIS tumors were classified as comedo type, whereas 9 were classified as non–comedo type DCIS. Pathology reports noted "ductal carcinoma-in-situ" only in 288 patients (57%).

During follow-up, five non–breast cancer–related deaths were recorded, for an overall survival rate of 98.7%. Ninety-eight patients (20%) developed a breast cancer–related failure in either the treated or contralateral breast. One patient developed an ipsilateral recurrence and contralateral breast tumor simultaneously.

Eighty tumors (16%) recurred in the treated breast and thus were considered treatment failures. The median interval from surgery to ipsilateral recurrence was 30 months (range, 1–130 months). Approximately half of these recurrent tumors (45%) were invasive breast carcinomas.

Table 2 presents the 4-year local recurrence–free survival rates calculated according to the Kaplan-Meier method. The cumulative incidence of all local recurrences after 4 years was 13%, whereas the cumulative incidence for invasive local recurrences after 4 years was 6%.

An analysis was performed for a number of potential factors related to ipsilateral recurrences Table 3. No differences in 4-year local recurrence–free survival rates were found between hospitals

TABLE 3. *Four-year local recurrence–free survival rates for selected patient and treatment characteristics*

Characteristic	Patients (n)	Recurrences (n)	4-y local recurrence–free survival (%)	*P* value[a]
Age (y)				
< 50	114	27	80.7	
≥ 50	388	53	88.3	.02
Family history breast cancer[b]				
Positive	100	22	79.7	
Negative	233	35	87.3	.10
DCIS diagnosis				
Mammographic	399	62	87.8	
Clinical	99	18	81.6	.50
Tumor size (mm)[b]				
< 15	82	12	90.4	
≥ 15	51	8	83.8	.48
Histopathologic grading				
Non–high grade	74	8	84.8	
High grade	79	10	88.4	.65
Initial treatment				
Lumpectomy	479	80	86.1	
Mastectomy	23	0	100.0	.06
Re-excision				
Yes	248	33	89.7	
No	254	47	83.5	.12
Final treatment				
Lumpectomy	329	67	83.1	
Mastectomy	173	13	93.3	< .01
Final margin status				
Positive	38	9	62.2	
Negative	423	64	87.8	.04
Unknown	41	7	91.4	
Radiotherapy				
Yes	20	2	100.0	
No	482	78	86.0	.40

DCIS, ductal carcinoma-in-situ.
[a] Log rank.
[b] Excluding unknown values.

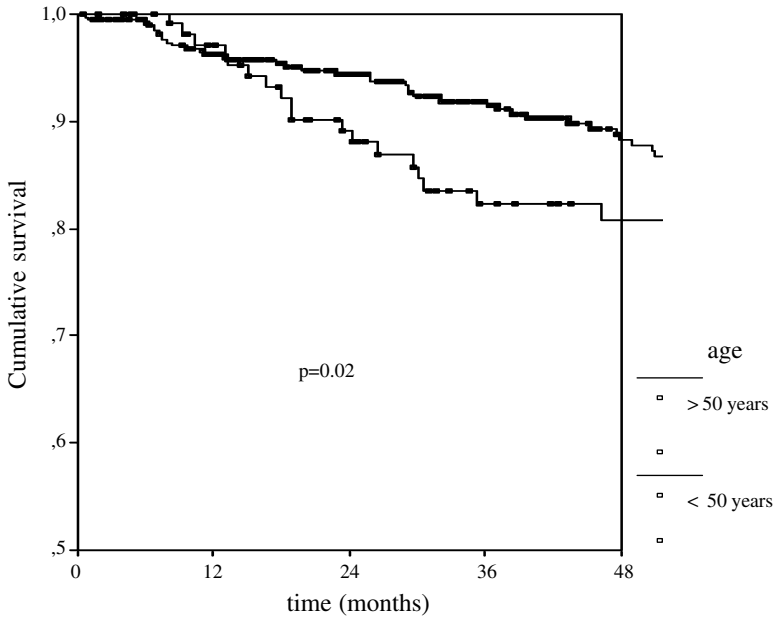
(P = .39). When patients treated with radiotherapy were compared with those not treated with adjuvant therapy, no significant difference in 4-year local recurrence–free survival was found, mainly because of the small number of patients (n = 20) who received radiotherapy.

We also compared the recurrence rate in non–high-grade lesions (grade I, or well differentiated, and grade II, or moderately differentiated; n = 74) and high-grade lesions (grade II, or poorly differentiated; n = 79) but found no significant differences (P = .65).

At 4 years of follow-up, younger patients (< 50 years) had worse local recurrence–free survival rates compared with older patients (Fig. 1; 4-year local recurrence–free survival, 81% vs. 88%, respectively; P = .02). The mean follow-up time was comparable for both age groups (P = .56). The mean age in the ipsilateral recurrence group was 54 years, compared with 58 years in the nonrecurrent or contralateral recurrence group (P = .01). Although younger patients underwent more surgical procedures (mean, 1.70 vs. 1.49 in older patients; *t*-test; P < .01), the results on margin status did not differ between age groups (negative margins vs. positive or unknown margin status; P = .76). Furthermore, younger patients were treated with a mastectomy less frequently compared with older patients (48% vs. 30%; P < .01). In patients for whom the histopathologic classification was known, high-grade DCIS lesions were found in 83% of younger patients compared with 71% in older patients, but this difference reached no statistical significance (P = .25).

Patients treated by lumpectomy had a 4-year local recurrence–free survival of 83% vs. 93% for the group treated with mastectomy (Fig. 2; P < .01). This difference could not be attributed to age differences: the mean age in the lumpectomy group was 58 years compared with 56 years in the mastectomy group (P = .07).

No differences in local recurrence–free survival were found between re-excised and non–re-excised cases: the mean number of surgical procedures was 1.45 for the ipsilateral recurrence group versus 1.56 for the nonrecurrent or contralateral recurrent group (P = .13). Patients with disease-involved surgical margins had worse 4-year local recurrence–free sur-



	Time (months)	6	12	18	24	30	36	42	48
Age <50 years	**Cumulative events**	0	3	8	11	15	17	17	18
	Number at risk	109	100	91	82	73	66	62	59
Age >50 years	**Cumulative events**	2	14	17	20	26	27	31	35
	Number at risk	375	342	306	282	254	232	196	179

FIG. 1. Local recurrence–free survival of patients <50 and ≥50 years of age.

vival compared with those with surgical margins free of disease (88% vs. 62%; $P = .01$; Fig. 3).

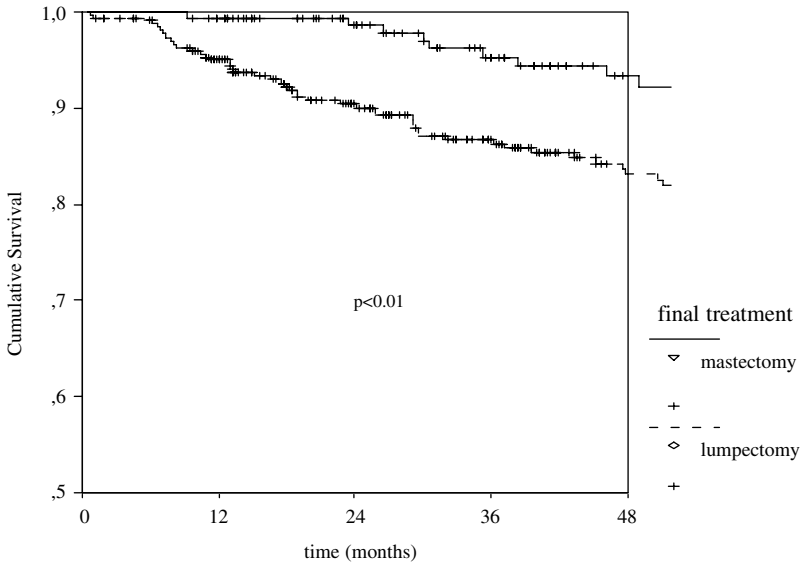
DISCUSSION

This retrospective multicenter review presents the outcome of conservative treatment of DCIS by breast-conserving surgery or mastectomy without radiotherapy in the Comprehensive Cancer Centres of the Middle Netherlands. The overall local recurrence rate was 13%, whereas for patients conservatively treated with breast-conserving surgery only, the recurrence rate was 17%.

Preventing local recurrences is the main goal in treatment of patients with DCIS. Two large-scale randomized studies have been performed to compare conservative treatment of DCIS by breast-conserving surgery only with excision followed by radiotherapy in reducing local recurrences.[16–21] The National Surgical Adjuvant Breast and Bowel Project (NSABP) B17 trial, published in 1998, revealed after 90 months of follow-up that 27% of patients treated with breast-conserving surgery alone developed local recurrence, compared with 12% when surgery was followed by radiotherapy.[17]

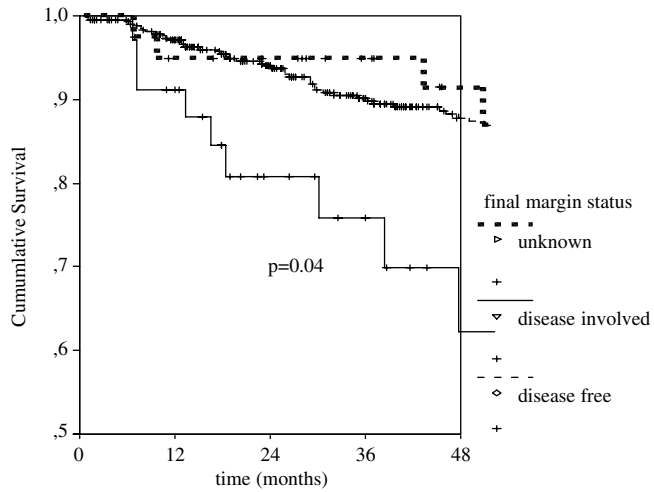
The EORTC 10853 trial, which included patients with DCIS lesions up to 5 cm and excluded patients ≥70 years, revealed a 4-year local recurrence rate of 16% in the surgery-only group, compared with 9% in patients treated by postoperative radiotherapy.[19] However, a comparison of a subgroup of patients treated with lumpectomy followed by radiotherapy outside and inside the trial showed significantly worse 4-year local recurrence–free rates: 83% outside the trial versus 98% inside the trial ($P = .03$).[21] For eligible patients treated with breast-conserving surgery only outside the trial, the 4-year recurrence-free rate was 93%, compared with 89% for randomized patients ($P = .45$).[21] Neither the NSABP nor EORTC trial revealed a beneficial effect of radiotherapy on either distant recurrences or breast cancer–related mortality.

Besides the use of radiotherapy, other risk factors have been identified that are associated with an increased risk of local recurrences. Histopathologic factors associated with increased recurrence rates are a high nuclear grade of DCIS and the presence of necrosis.[3,18,20,25–29] In our analysis, no differences in recurrence rates for non–high-grade and high-grade lesions were found. This can be mainly attributed to the small number of lesions for which a histopatho-



	Time (months)	6	12	18	24	30	36	42	48
Lumpectomy	**Cumulative events**	3	16	24	29	37	38	41	45
	Number at risk	318	288	255	234	209	191	164	151
mastectomy	**Cumulative events**	0	1	1	2	4	6	7	8
	Number at risk	163	154	142	130	117	106	94	87

FIG. 2. Ipsilateral disease-free survival of patients finally treated with lumpectomy and mastectomy.



	Time (months)	6	12	18	24	30	36	42	48
Disease-free margin	**Cumulative events**	3	12	18	23	32	35	38	41
	Number at risk	407	377	339	312	280	255	221	206
Disease-involved margin	**Cumulative events**	0	3	5	6	7	7	8	9
	Number at risk	34	29	23	18	15	13	10	8
Unknown margin	**Cumulative events**	0	2	2	2	2	2	2	3
	Number at risk	40	36	35	34	31	29	27	24

FIG. 3. Ipsilateral disease-free survival of patients with disease-involved margins, disease-free margins, and unknown margin status.

logic classification was known and to the use of different histopathologic classification systems in the various hospitals over time.

As has been outlined, a microscopically complete removal of DCIS is an important factor in preventing recurrent disease. However, in daily practice, it can

be difficult to obtain surgical margins free of DCIS. Excision of a screening-detected DCIS lesion has to be performed with a localization procedure without the guidance of a palpable mass. Furthermore, mammographic estimates of DCIS size frequently do not correlate with the histological DCIS size.[30] It has been shown that 43% of patients with initially clear margins, defined as a rim of normal breast tissue of ≥1 mm, had residual DCIS at re-excision or mastectomy.[22]

In our study population, 35% of patients were ultimately treated with mastectomy because of tumor-involved surgical margins after initial excision. This percentage of mastectomies in our population is comparable to results published from a large population-based study performed in the United States (34% mastectomy rate).[1] Furthermore, at the start of follow-up, 38 patients (8%) had positive margins, and in 41 patients (8%) margin status could not be specified. It is noteworthy that 6% of patients treated with mastectomy had disease-involved margins. From both the NSABP and EORTC trials, results on margin status were reported, and these are comparable to our data. An analysis of 77% of patients from the NSABP cohort showed that 16% of patients had uncertain or involved surgical margins. A comparable analysis of 85% of patients from the EORTC cohort revealed that from 12% of patients no information on margins was available and that 9% had close (margin width ≤1 mm) or involved margins.[16–21]

The difficulty of achieving a complete excision of DCIS can be explained by three-dimensional studies of growth patterns of DCIS. These studies showed that most lesions involve a single duct system and that gaps between DCIS rarely exceeded 10 mm.[30–32] According to this growth pattern, complete eradication of the lesion could be achieved in approximately 90% of cases if the lesion were excised with a rim of at least 10 mm of healthy breast tissue. Silverstein et al.[23] showed that excision of DCIS with a margin of ≥10 mm obtained excellent local control with or without radiotherapy (3 [2.3%] local recurrences out of 133 patients after a median follow-up of 72 months). Furthermore, this study showed that if DCIS was excised with a margin of ≤ 1 mm, adjuvant radiotherapy indeed decreased the rate of local recurrence from 58% to 30% in 8 years, but this still is an unacceptably high rate of local failure.[23] Clearly, radiotherapy does not compensate for surgical margins not free of disease.[22,23]

Although a margin width of 10 mm has been recommended, obtaining such a margin is difficult (only two of our patients had a margin width of ≥10 mm). Furthermore, widespread recommendation of this margin width could give rise to the performance of more mastectomies, which could be considered as overtreatment of noninvasive DCIS.

Another important risk factor for local recurrence in this study is age: patients < 50 years of age had an increased risk for local recurrence. For invasive breast carcinoma, younger age has found to correlate with local recurrence.[33] The EORTC trial revealed patient age < 40 years as a risk factor for recurrence.[16] In retrospective series, younger age also has been identified as a risk factor for ipsilateral recurrence.[34–38] Our data confirm these findings: younger patients (< 50 years) were more likely to develop a local recurrence. This age difference could not be attributed to different treatment strategies: no difference in mean age was found in the mastectomy and breast-conserving surgery groups. It can be hypothesized that DCIS lesions in younger patients have a worse biological behavior. Indeed, in our population, younger patients had lesions of higher grade, but this difference did not reach statistical significance. Otherwise, surgeons treating younger patients could be more likely to perform less radical excisions to obtain a better cosmetic outcome.[39] However, the volume of excised tissue is inversely related to cosmetic outcome but directly related to residual DCIS and, therefore, the risk of local recurrence.[39,40] Indeed, we found more surgical procedures in younger patients, although no difference in final margin status was found.

The previously mentioned risk factors for local recurrences (histopathologic grading, margin width of excision, tumor size, and age) have been summarized by Silverstein[11] in the University of Southern California/Van Nuys Prognostic Index scoring system. The goal of this classification system is to identify certain subgroups of patients with DCIS who have an increased risk of local recurrences, thereby guiding the treatment strategy. For example, some patients probably require no adjuvant treatment after complete local excision (older patients with small, low-grade lesions excised with a wide margin width), whereas others are at such an increased risk for local recurrence that mastectomy could be a reasonable treatment option. Still, the validity of this classification system has to be prospectively confirmed in large groups of patients.

In conclusion, we showed that treatment of DCIS with conservative surgical treatment without radiotherapy results in relatively high recurrence rates. Clearly, this treatment option for all patients with DCIS is not sufficient. Because the cornerstone in the treatment of DCIS remains radical excision, more

efforts should be made to perform radical surgery, because 8% of our patients had involved margins at the start of follow-up. On the basis of randomized trials, one could expect lower recurrence rates if patients were treated with radiotherapy after breast-conserving surgery. However, it is not clear whether all patients with DCIS will benefit from radiotherapy. Prospectively validated data to identify subgroups of patients at such a low risk for local recurrence that radiation can be omitted safely are not available yet. However, because younger patients (< 50 years) have an increased risk for local recurrence, the adjuvant use of radiotherapy in this group of patients is recommended strongly.

APPENDIX 1. *Members of the Comprehensive Cancer Centre Middle Netherlands Surgical Oncology Group*

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