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The Safety of Breast-Conserving Therapy in Patients With Breast Cancer Aged ≤40 Years

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BACKGROUND. The objectives of this study were to study the probability of local control after breast-conserving therapy (BCT) in a large population of patients with early-stage breast cancer aged ≤40 years and to determine which factors had prognostic value.

METHODS. All patients (n = 758) aged ≤40 years with clinical stage I or II breast cancer who underwent BCT in general hospitals in the southern part of the Netherlands between 1988 and 2002 were selected for the current analysis. BCT included local excision of the tumor followed by irradiation of the breast. Of 758 patients, 329 patients (43%) received adjuvant systemic treatment, and 36 patients (5%) underwent a microscopically incomplete excision. The median follow-up was 8.5 years.

RESULTS. During follow-up, 95 patients developed a local recurrence without evidence of distant disease at the time the recurrence was diagnosed. Contralateral breast cancer was diagnosed in 59 patients. The 5- and 10-year actuarial local recurrence rates were 9.0% (95% confidence interval [95% CI], 6.6–11.4%) and 17.9% (95% CI, 14.1–21.7%), respectively. In a multivariate analysis, adjuvant systemic treatment reduced the risk of local recurrence (hazards ratio [HR], 0.47; 95% CI, 0.28–0.78) and contralateral breast cancer (HR, 0.46; 95% CI, 0.24–0.87) by >50%.

CONCLUSIONS. The risk of local recurrence in young patients who underwent BCT was reduced strongly by using adjuvant systemic treatment. This finding may provide an argument if favor of advising the use of systemic treatment for all patients aged ≤40 years who undergo BCT. ***Cancer* 2007;109:1957–64.** © *2007 American Cancer Society.*

KEYWORDS: breast carcinoma, breast-conservation, local recurrence, radiotherapy.

In the Netherlands, 11,687 women were diagnosed with invasive breast cancer in 2003; and, in the same year, an estimated 211,300 new cases were diagnosed in the U.S.[1] Among those patients, 673 women (5.6%) and 11,500 women (5.5%), respectively, were aged <40 years at diagnosis. Several large, randomized clinical trials with long-term follow-up have reported equal survival rates after breast-conserving therapy (BCT) and after mastectomy for patients with early-stage breast cancer.[2–4] Consequently, BCT is now a generally accepted alternative to mastectomy for the treatment of early-stage breast cancer. It is estimated that approximately 300,000 women with stage I and II breast cancer undergo BCT worldwide each year.[4]

There is no solid proof of a better psychological adjustment after BCT compared with mastectomy. However, results with respect to body image and sexual functioning seem to be in favor of BCT,[5]

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which makes it an attractive treatment option for young women. Unfortunately, in many studies, young women also are those with the highest risk of developing local recurrence after BCT compared with older patients and with patients who undergo mastectomy. The reported 10-year actuarial rates of local recurrence for patients aged ≤40 years vary between 7% and 12% after mastectomy and between 19% and 35% after BCT.[6–11] In 2 studies that compared the risk of local recurrence after BCT in younger patients and older patients, a 9-times greater risk was observed in patients aged ≤35 years,[10] and a 5-times greater risk was observed in patients aged ≤40 years[9] compared with patients aged >60 years. Although younger patients are more likely to present with risk factors for local recurrence than older patients, including high tumor grade, vascular invasion, and an extensive intraductal component, these factors do not fully explain their greater risk of recurrence.[6] These observation have raised doubts among surgeons and radiation oncologists about the safety of BCT for young women. To evaluate the probability of achieving local control after BCT and to determine which factors have prognostic importance, we studied a cohort of 758 patients aged ≤40 years who underwent BCT between 1988 and 2002 according to regional treatment guidelines in general hospitals in the southern Netherlands.

MATERIALS AND METHODS

Data were derived from 2 radiotherapy departments in the south of the Netherlands, the Dr. Bernard Verbeeten Institute in Tilburg and the Department of Radiotherapy of the Catharina Hospital in Eindhoven. Together, these institutes currently serve a population of approximately 2.4 million inhabitants. Data provided by the 2 radiotherapy departments were compared with data from the population-based Eindhoven Cancer Registry (ECR), which has been recording data on all patients with newly diagnosed cancer since 1955 in an area that largely overlaps the area served by the 2 radiotherapy departments. According to data from the ECR, 18,393 patients were diagnosed with invasive breast cancer in the period from 1988 to 2002, including 1554 patients (8.4%) aged ≤40 years. Of those 1554 patients, 774 (49.8%) underwent breast-conserving surgery, and 747 of those 774 patients (96.5%) also received postoperative radiotherapy. No clear trend could be observed in the proportion of patients aged ≤40 years who underwent BCT during the period of our study (Fig. 1). From the 2 radiotherapy departments, we received files that contained data from 780

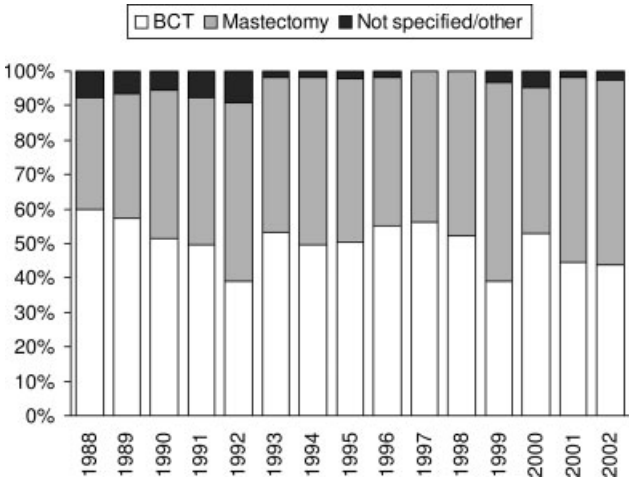

FIGURE 1. Proportion of patients of aged ≤40 years who underwent breast-conserving therapy (BCT) or mastectomy in the period from 1988 to 2002 (n = 1554 patients). BCT included local excision of the tumor followed by irradiation of the breast. Source: Eindhoven Cancer Registry.

patients aged ≤40 years who were diagnosed during the period from 1988 to 2002 and who received BCT. The clinical charts of these patients were reviewed to collect information with respect to tumor stage, treatment, and outcome.

After the completion of data collection, it appeared that 13 of the 780 patients had locally advanced breast cancer (ie, T3 or T4 tumor classification), 7 patients had ductal carcinoma in situ, 1 patient had not received radiotherapy, and 1 patient presented with distant disease at the time the primary tumor was diagnosed. After excluding these 22 patients, 758 patients with pathologic stage I and II breast cancer (T1-T2, N0-N2, M0)[12] remained available for the current analysis.

All patients underwent a wide excision of the tumor and either a sentinel lymph node procedure or an axillary lymph node dissection followed by radiotherapy. Radiotherapy was given to a dose from 46 grays (Gy) to 50 Gy to the whole breast and was delivered by using a tangential-field technique in 2-Gy to 2.3-Gy fractions 4 or 5 times per week. Six hundred sixty patients (87%) received a boost to the primary tumor bed of 14 Gy to 16 Gy, in 2-Gy to 2.5-Gy fractions, 4 or 5 times per week, delivered by external photon or electron beam therapy. Twenty-three patients (3%) received an iridium implantation with a dose of 15 Gy at a low dose rate, and 75 patients (10%) did not receive a boost.

Before 1998, adjuvant systemic treatment was based on regional guidelines and was recommended only for patients who had positive axillary lymph

nodes. In 1998, the Dutch National Breast Cancer Platform and the Dutch Society for Medical Oncology published a new guideline[13] based on the St. Gallen guidelines[14,15] in which lymph node-negative patients with high-risk breast cancer were advised to receive adjuvant systemic treatment, depending on the size, grade, and hormone receptor status of their tumor. In 2001, the guideline was updated, so that patients aged $\leq$35 years always were recommended to receive adjuvant systemic treatment, irrespective of their lymph node status or primary tumor characteristics. However, in the most recent update of the guideline, which was published in 2005, adjuvant systemic treatment no longer was advised for patients who had well-differentiated tumors that measured $\leq$1 cm. The standard chemotherapy regimen consisted of cyclophosphamide, methotrexate, and fluorouracil in the early years of the study period and of an anthracycline-containing regimen thereafter. From 1998, hormone therapy (tamoxifen at a dose of 20 mg daily for 5 years) was recommended for patients who had positive lymph nodes and for lymph node-negative, high-risk patients who had estrogen or progesterone receptor-positive tumors.

Follow-up was completed until the patient's death or until the date of last contact with the surgeon, radiation-oncologist, or general practitioner. The median duration of follow-up for all 758 patients was 8.5 years (range, 0.9–16.9 years). Forty-two patients (5.2%) were lost to follow-up, which meant that their last contact date was before January 1, 2005. The median follow-up for those 42 patients was 7.6 years.

The endpoints that were addressed in the study were local recurrence, regional recurrence, distant recurrence, contralateral breast cancer, and death. Local recurrence was defined as any reappearance of tumor growth in the treated breast or overlying skin. Regional recurrence was defined as any recurrent tumor growth in the axillary, internal mammary, or supraclavicular lymph node areas. The time to local, regional, and distant recurrence; contralateral breast cancer; and death were estimated by using the life-table method. For each endpoint, the time to event was defined as the interval between primary treatment and occurrence of the event of interest. In the absence of the event of interest, observation time was censored at the last contact date of the patient. Comparisons between subgroups with respect to the occurrence of local recurrence were made by using the log-rank test. Multivariate analyses were carried out using Cox proportional hazards models to identify factors that were associated with an increased risk of local recurrence.

Only local recurrences that occurred as a first event were included in the survival analyses. For several reasons, local and regional recurrences and contralateral breast cancers that were diagnosed after distant metastases or with synchronous distant disease were not counted in the survival analyses, because they are considered less important clinically, and the risk of underreporting is greater.

RESULTS

Patient and Treatment Characteristics

Table 1 shows the patient, tumor, and treatment characteristics of the study population. The median age at diagnosis was 37.5 years (range, 23.9–40.9 years) at the time of primary diagnosis. The primary excision was reported as incomplete in 105 patients (14%) and in 36 patients (5%) when taking into account the results of reexcision, which was undergone by 89 patients (12%). No differences were detected between the 3 time periods (ie, 1988–1992, 1993–1997, and 1998–2002) with respect to age, tumor size, histologic grade and type, estrogen and progesterone receptor status, the proportion of patients who underwent reexcision, or the proportion of patients who achieved positive resection margins. All patients received radiotherapy, as described above. From 1989 to 1996, a number of patients participated in the European Organization for Research and Treatment of Cancer (EORTC) 'boost versus no boost' trial,[16] which partially explains why 75 patients had not received a boost dose. Chemotherapy was administered to 218 patients (29%), and hormone therapy was administered to 25 patients (3%), whereas 86 patients (11%) received both. The proportion of patients that received adjuvant systemic treatment was 30% during the period from 1988 to 1992, 33% during the period from 1993 to 1997, and increased to 68% during the period from 1998 to 2002. This increase could be attributed largely to the growing proportion of patients with negative axillary lymph nodes who received systemic treatment; for patients with negative lymph node status, the proportions of patients in the subsequent periods were 4%, 10%, and 48% ($P < .0001$), respectively; whereas, for patients with positive lymph node status, these proportions were 71%, 96%, and 99% ($P < .0001$), respectively.

Local Recurrence

During follow-up, a local recurrence was diagnosed in 95 patients without evidence of metastatic disease. Seventeen additional local recurrences were diagnosed either after distant metastases or at the same

TABLE 1
Actuarial Risks of Local Recurrence According to Patient, Tumor, and Treatment Characteristics (n = 758 patients)

Characteristic	Total no.	Local recurrence (SE), %			P
		No.	5-Year rate	10-Year rate	
Age, y					.36
≤30	57	4	4.7 (3.4)	14.1 (7.1)	
31–35	213	33	10 (2.3)	22.6 (3.8)	
36–40	488	58	9 (1.4)	15.9 (2.2)	
Year of BCT					.06*
1988–1992	254	50	13 (2.3)	21.2 (3)	
1993–1997	254	31	7.3 (1.8)	16.5 (2.8)	
1998–2002	250	14	5.9 (1.6)	NA	
Pathologic tumor classification†					.74
pT1	529	65	8.8 (1.4)	17.1 (2.2)	
pT2	213	25	6.6 (1.9)	17.9 (3.8)	
Pathologic lymph node classification‡					.001
pN0	479	78	11.2 (1.6)	21.5 (2.4)	
pN1-pN2	264	15	4 (1.3)	8.4 (2.3)	
Histologic type§					.88
Ductal	678	85	8.6 (1.2)	17.5 (2)	
Lobular or mixed	54	5	9.5 (5.3)	18.9 (8)	
Other	19	3	10.7 (7.1)	21.9 (11.7)	
Histologic grade‖					.61
Good	32	3	7.8 (5.4)	19.4 (11.8)	
Moderate	101	14	10 (3.2)	29 (8.2)	
Poor	177	20	7.9 (2.2)	14.3 (3.5)	
Estrogen receptor status¶					.45
Positive	241	31	9.5 (2.2)	19.6 (3.7)	
Negative	122	12	7.8 (2.7)	14.4 (4.2)	
Progesterone receptor status#					.82
Positive	274	34	7.7 (1.8)	16.7 (3)	
Negative	102	12	10.5 (3.4)	18.4 (5.5)	
Boost					.10
Yes	683	78	8.8 (1.2)	17.2 (2.1)	
No	75	17	11 (4)	23.3 (5.5)	
Adjuvant systemic therapy**					.002
Yes	329	20	4.4 (1.3)	10.5 (2.6)	
No	427	74	12 (1.7)	21.6 (2.5)	
Microscopic completeness of tumor excision††					.005
Complete	708	83	8.3 (1.2)	16.4 (1.9)	
Incomplete	36	9	23.8 (8.8)	40.9 (12.6)	

SE indicates standard error; BCT, breast-conservation therapy; NA, not available.
* Test for trend.
† Data were missing for 16 patients.
‡ Data were missing for 15 patients.
§ Data were missing for 7 patients.
‖ Data were missing for 448 patients.
¶ Data were missing for 395 patients.
# Data were missing for 382 patients.
** Data were missing for 2 patients.
†† Includes results of reexcision (data were missing for 14 patients).

TABLE 2
Characteristics of Patients With Local Recurrence After Breast-Conserving Therapy (n = 95 patients)

Characteristic	No. (%)
Age at diagnosis of LR, y	
≤ 40	40 (42)
41–45	41 (43)
>46	14 (15)
Time to LR, y	
≤ 2.5	27 (28)
2.6–5	29 (31)
5.1–10	30 (32)
>10	9 (10)
Individual who detected LR	
Patient	42 (44)
Surgeon or radiation oncologist	45 (47)
General practitioner	2 (2)
Unknown	6 (6)
Mode of detection of LR	
Palpation	59 (62)
Mammography only	27 (28)
Echography only	1 (1)
MRI only	1 (1)
Unknown	1 (1)
Other	6 (5)
Localization of LR	
At site of primary tumor	58 (61)
Near site of primary tumor	14 (15)
Elsewhere in the breast	7 (7)
Diffuse	4 (4)
Unknown	12 (13)
Histologic type of LR	
Ductal	83 (87)
Lobular or mixed	10 (11)
Other	1 (1)
Unknown	1 (1)
Invasiveness of LR	
DCIS	13 (14)
Invasive	60 (63)
Invasive and DCIS	19 (20)
Unknown	3 (3)

LR indicates local recurrence; MRI, magnetic resonance imaging; DCIS, ductal carcinoma in situ.

time as distant disease. These 17 recurrences were not included in the current analyses. Forty-five of 95 isolated local recurrences (47%) were detected by the physician during routine control visits, 2 local recurrences (2%) were detected by the general practitioner, and 42 local recurrences (44%) were detected by the patients themselves (Table 2). Other characteristics of the local recurrences also are presented in Table 2.

The 5- and 10-year actuarial local recurrence rates were 9% (95% confidence interval [95% CI], 6.6–11.4%) and 17.9% (95% CI, 14.1–21.7%), respectively (Fig. 2). Univariate analyses showed that the following factors were associated significantly with

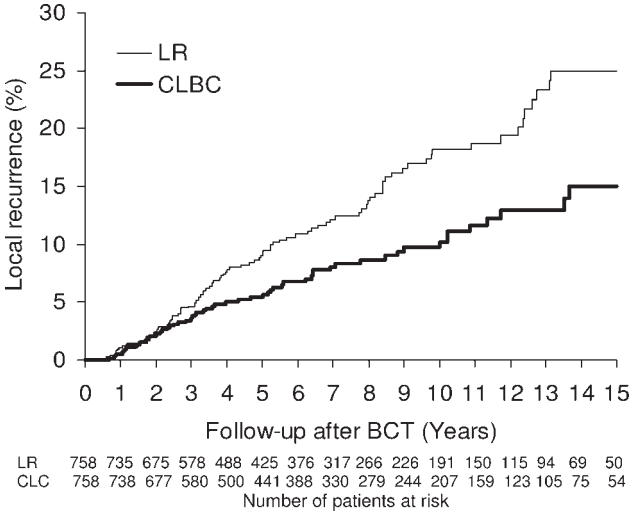

FIGURE 2. Actuarial risk of local recurrence (LR) and contralateral breast cancer (CLBC) in patients aged ≤40 years who underwent breast-conserving therapy (BCT) (n = 758 patients).

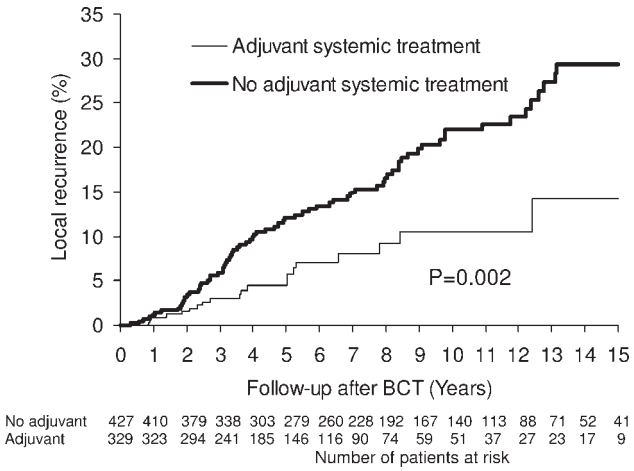

FIGURE 3. Actuarial risk of local recurrence in patients aged ≤40 years who underwent breast-conserving therapy (BCT) according to the use of adjuvant systemic treatment.

the occurrence of local recurrence: pathologic lymph node status ($P = .001$), microscopic resection margin ($P = .005$), and adjuvant systemic treatment ($P = .002$) (Table 1 and Fig. 3). A nonsignificant trend toward better local control was observed during the study period (test for trend: $P = .06$) and for patients who received a boost dose to the tumor bed ($P = .10$).

The results of the multivariate Cox regression analysis of prognostic factors for local recurrence-free survival are presented in Table 3. Because data on estrogen and progesterone receptor status and histologic grade were missing for >50% of patients,

TABLE 3
Results of Multivariate Analysis for Local Recurrence After Breast-Conserving Therapy (n = 727 patients)

Characteristic	HR	95% CI	*P*
Period of diagnosis			.28*
1988–1992	1 (Ref)		
1993–1997	0.83	0.52–1.32	.43
1998–2002	0.74	0.37–1.51	.41
Age at diagnosis, y			
36–40	1 (Ref)		
31–35	1.27	0.82–1.98	.29
≤30	0.73	0.26–2.02	.54
Pathologic tumor classification			
pT1	1 (Ref)		
pT2	1.07	0.66–1.74	.79
Tumor type			
Ductal	1 (Ref)		
Lobular or mixed	0.71	0.26–1.96	.51
Other	0.76	0.19–3.10	.70
Boost			
No	1 (Ref)		
Yes	0.67	0.39–1.15	.14
Microscopic completeness of tumor excision†			
Complete	1 (Ref)		
Incomplete	2.98	1.42–6.22	.004‡
Adjuvant systemic therapy			
No	1 (Ref)		
Yes	0.47	0.28–0.78	.004‡

HR indicates hazard ratio; 95% CI, 95% confidence interval; Ref, reference category.
* Test for trend.
† Includes result of reexcision.
‡ Significant *P* value for factors that were included in the final Cox regression model.

these factors were not included in the multivariate model. The multivariate analysis also was complicated by the strong concordance between axillary lymph node status and adjuvant systemic treatment: 231 of 263 lymph node-positive patients (88%) had received systemic treatment compared with only 93 of 478 lymph node-negative patients (19%). In a model that included both systemic treatment and lymph node status, the prognostic effect of adjuvant systemic treatment was obscured by the effect of axillary lymph node status. In this model, patients with positive lymph node status appeared to have a 60% lower risk of developing local recurrence (hazards ratio [HR], 0.40; 95% CI, 0.23–0.72). Separate multivariate analyses for patients who did and did not receive adjuvant systemic treatment demonstrated that lymph node status was not associated with the risk of local recurrence, which implies that lymph node status was not an independent prognostic factor for local recurrence. Therefore, we opted for a model that excluded axillary lymph node status (Table 3). In this model, the use of adjuvant systemic treatment

appeared to reduce the risk of local recurrence by >50% (HR, 0.47; 95% CI, 0.28–0.78). The only other significant prognostic factor was the completeness of the tumor excision.

Of the 95 patients who had local recurrences, 34 patients developed distant metastases. The 5-year distant disease-free survival rate for this group was 66.3% (95% CI, 55.5–77.1%), as calculated from the date the local recurrence was diagnosed.

Survival, Contralateral Breast Cancer, Regional Recurrence, and Distant Recurrence

During follow-up, 22 of the 758 patients developed regional recurrences (including 8 patients who had supraclavicular recurrences), 209 patients developed distant metastases, 59 patients developed contralateral breast cancer (Fig. 2), and 174 patients died. The 10-year actuarial rates of these endpoints were 3.5% (95% CI, 1.8–5.2%), 30.4% (95% CI, 26.6–34.2%), 9.6% (95% CI, 6.8–12.4%) (Fig. 2), and 26.9% (95% CI, 23.1–30.7%), respectively. The 10-year disease-free survival rate (ie, survival without local, regional, or distant recurrence and without contralateral breast cancer) was 55.8% (95% CI, 51.6–60%). In multivariate analyses, a significantly lower risk of contralateral breast cancer was identified for patients who received adjuvant systemic treatment compared with patients who did not receive systemic treatment (HR, 0.46; 95% CI, 0.24–0.87).

DISCUSSION

The objective of the current study was to evaluate the results of BCT in patients aged ≤40 years. Our population-based study included 758 patients who received treatment between 1988 and 2002. The 5- and 10-year actuarial local recurrence rates were 9% and 17.9%, respectively. Patients who received adjuvant systemic therapy had a >50% lower risk of developing a local recurrence compared with patients who did not receive adjuvant systemic therapy, and a similar reduction in the risk of breast cancer in the contralateral breast was observed. The use of adjuvant systemic treatment also explained the lower risk of local recurrence in the patients with positive axillary lymph nodes, as illustrated by the finding that lymph node status was no longer an independent prognostic factor in the subgroups of patients who did and did not receive adjuvant systemic treatment.

Many studies on local recurrence after BCT were performed in the 1980s, directly after the introduction of BCT when adjuvant systemic treatment generally was not considered for patients who had negative axillary lymph nodes.[17–21] Therefore, the absolute risks reported in those studies from the 1980s may not have been representative of the results obtained in more recent years. Moreover, in most of those studies, the number of young patients was much smaller than in our study, which decreased the accuracy of their risk estimates and limited the possibility to study risk factors for local recurrence in young patients. Our rates appear to be lower than those of other recent reports for patients aged ≤40 years, which varied between 8% and 16% at 5 years after BCT and were >20% at 10 years.[7–11] However, a direct comparison with those other studies is complicated by their different definitions of local recurrence, which sometimes included regional recurrences or local recurrences that occurred with previous or synchronous distant metastases.

The role of routine follow-up in the detection of local recurrence remains a matter of debate. In our study, in which follow-up included annual mammography and a clinical examination at each visit, approximately 50% of local recurrences were detected by the physician during routine control visits, and the other 50% were detected by the patients themselves (Table 2). These proportions are in accordance with the results from a systematic review by de Bock et al. showing that approximately 40% of isolated locoregional recurrences after the treatment of early-stage invasive breast cancer were diagnosed during routine visits and routine tests in asymptomatic patients.[22] More research is needed to determine which diagnostic strategies are able to improve the detection of asymptomatic, isolated recurrences and to assess their impact on the potential for cure and on the quality of life.

Of the local recurrences that were identified in our study, the large majority occurred at or near the site of the primary tumor, and only 7% developed elsewhere in the breast. This suggests that, at least in young women, most local recurrences are not new primary tumors but are more likely to be true recurrences, originating from residual tumor tissue or from genetic alterations in apparently normal breast tissue at the margins of the surgically excised tumor.[23] The decision to deliver an additional localized dose of irradiation to the tumor bed is motivated by the finding that most local recurrences occur within the vicinity of the primary tumor. It has been demonstrated that patients aged ≤40 years benefit more from an additional boost treatment; the cumulative 5-year rate of local recurrence was 19.5% without and 12% with an additional dose in a large, randomized, controlled trial that was designed by the EORTC.[16] Although the risk estimate did not reach

statistical significance, the results of our study, in which 75 of 758 patients did not receive a boost dose, are in line with the findings of the EORTC-trial: The boost treatment reduced the local recurrence rate by 33% (HR, 0.67; 95%CI, 0.39–1.15).

A trend toward increasing local control was identified over the study period, although it did not reach statistical significance. The first years of our study, between 1988 and 1992, covered the early experiences with BCT, which was introduced during the first half of the 1980s.[24,25] The later years were characterized by more frequent use of adjuvant systemic therapy (ie, nearly a doubling of the proportion of patients receiving systemic treatment after 1998) and increased knowledge of the importance of achieving a complete excision of the tumor, especially in the presence of an extensive intraductal component. It is believed that this resulted in a more careful evaluation of the tumor margins and a more evidence-based selection of patients for BCT.[26] These supposed changes also have been mentioned by others to explain similar trends of improving local control.[27,28]

Similar to other studies, the current study demonstrated that patients who achieve a microscopically incomplete tumor excision have a significantly higher risk of local recurrence than patients who achieve a complete excision. However, it should be noted that only 36 patients (5%) in our study had positive resection margins (taking into account the reexcision), and 9 of those patients developed a local recurrence, and that 83 of 95 recurrences occurred in patients who had achieved negative margins. Therefore, as reported previously by Schnitt, the identification of risk factors for local recurrence among patients who achieve a microscopically complete excision is of particular interest and importance.[29]

Several studies have confirmed the possible benefit of adjuvant systemic therapy on local control after BCT.[28,30–36] The risk reductions observed in those studies appeared to be of the same magnitude for both lymph node-positive patients and lymph node-negative patients and varied between 50% and 70%, proportions that are comparable to the reductions observed in our study. It is only since 1998 that the Dutch guidelines have recommended adjuvant systemic treatment for lymph node-negative patients, depending on the size, grade, and steroid receptor status of the tumor. The indications for the use of systemic treatment underwent additional changes in 2001 and 2005, as discussed above. Considering the recent modifications of the guidelines, the length of follow-up in our patients still is too short to evaluate the potential impact of the increased use of systemic treatment on local tumor control.

A recent review of the Early Breast Cancer Trialists' Collaborative Group indicated that locoregional recurrence also can affect long-term breast cancer mortality; it was estimated that the prevention of 4 local recurrences after BCT would avoid approximately 1 death from breast cancer over the next 15 years.[37] Our data indicate that the 10-year local recurrence rate in patients aged $\leq$40 years is reduced from $>$20% to approximately 10% by adjuvant systemic treatment, which would mean that, for every 100 patients who receive BCT, 10 patients are spared ablative surgery, and 2 or 3 supplementary patients may be cured. These are convincing reasons to consider the use of adjuvant systemic treatment for all patients aged $\leq$40 years who receive BCT. However, to be able to define the most effective treatment regimen for preventing local recurrence, larger studies still are needed with detailed information on the type, dose, timing, and duration of adjuvant systemic treatment that also include the role of ovarian function suppression and that take into account the possible side effects of the treatment and the personal wishes of the patient.

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