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Long-term prognosis of patients with local recurrence after conservative surgery and radiotherapy for early breast cancer

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Abstract

We have studied the long-term prognosis of 266 patients considered to have isolated local recurrence in the breast following conservative surgery and radiotherapy for early breast cancer. The median follow-up of the patients still alive after diagnosis of local relapse was 11.2 years. At 10 years from the date of salvage treatment, the overall survival rate for the 226 patients with invasive local recurrence was 39% (95% CI, 32–46), the distant recurrence-free survival rate was 36% (95% CI, 29–42), and the local control rate (*i.e.*, survival without subsequent local recurrence or local progression) was 68% (95% CI, 62–75). Among patients with a local recurrence at or near the original tumour site a better distant disease-free survival was observed for patients with recurrences measuring 1 cm or less, compared to those with larger recurrences. This suggests, though does not prove, that early detection of local recurrence can improve the treatment outcome but might as well point towards a different biologic behaviour, facilitating early detection.

Keywords: Breast carcinoma; Breast conservation; Local recurrence; Detection; Survival; Long-term prognosis

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1. Introduction

It is estimated that each year about 300,000 women with stages I and II breast cancer undergo breast-conserving therapy (BCT) worldwide [1]. Rates of local recurrence in the preserved breast vary between 2% and 10% after 5 years and between 5% and 15% at 10 years [1–10]. Considering the growing number of patients who have undergone BCT and the risk of local recurrence also extending after more than 10 years of follow-up, the number of patients experiencing a local recurrence is expected to increase considerably in the future.

Whilst the poor prognosis of patients with a local recurrence after modified radical mastectomy is well established, there has been considerable debate about the prognosis and salvage possibilities for patients with local recurrence after BCT. Earlier studies reported 5-year survival rates ranging from 70% to 84% after salvage treatment for patients with local recurrence after BCT, which is equal or only slightly worse compared with those without local recurrence [5,11–13]. More recent series, however, reported poorer 5-year survival rates, ranging from 55% to 68% after 5 years [3,14] and one study even reached the conclusion that the survival after treatment for an early loco-regional recurrence after modified radical mastectomy or BCT is similar [15]. The unfavourable prognostic effect of developing a local recurrence has been confirmed by other studies, that included local recurrence in a multivariate analysis as a time-dependent variable and showed it to be a strong independent predictor of the risk of developing distant metastatic disease [6,7,16–21]. Figures on the long-term prognosis of patients with local recurrence are scarce and based on small patient series. Interpretation and comparison of the results is also hampered by heterogeneity; some focused on prognosis after local recurrence treated with salvage mastectomy, whereas others studied prognosis after all local recurrences regardless of therapy. In some studies, patients were included who also had distant metastasis diagnosed before or simultaneously with local recurrence. Finally, studies on prognostic factors for patients with local recurrence made use of different end-points, some presenting overall survival and other distant disease-free or cause-specific survival.

This report describes the long-term prognosis of 266 patients with local recurrence after BCT as first event, *i.e.*, without clinical signs of distant metastases at the time of diagnosis of local recurrence. In a previous report, with a median follow-up time of 52 months, the distant recurrence free survival rate for all 266 patients was 61% (95% CI, 40–53%) at 5-years from the date of salvage treatment [22]. At that time, the survival curve showed no tendency of levelling off, indicating that distant recurrences continue to occur more than five years after diagnosis of local recurrence. For the current study, the median follow-up of the cohort has been extended to more than 11 years, which offered us the possibility to calculate the survival rates at 10 years after the diagnosis of local recurrence and identify subgroups with a good and a poor long-term prognosis.

2. Patients and methods

2.1. Patients and data collection

Patient data were obtained from eight departments of radiotherapy, two cancer institutes and one department of surgery in the Netherlands, which maintained complete records on approximately 7000 patients with invasive breast cancer undergoing BCT. BCT generally consisted of wide local excision of the tumour with an attempted margin of at least 1 cm of healthy tissue and axillary dissection, followed by 45–50 Gy whole breast irradiation in fractions of 1.8 or 2.0 Gy five times a week. An additional boost was given to the tumour bed by an external beam technique, using either photons or electrons, or by the use of iridium 192 interstitial implants. Total boost doses varied between 15 and 25 Gy but were sometimes higher for iridium 192 implants. Adjuvant systemic therapy was given only to axillary node-positive patients; in general premenopausal patients received 6 cycles of adjuvant cyclophosphamide, methotrexate and 5-fluorouracil (CMF) combination chemotherapy, given after the completion of radiotherapy, whereas postmenopausal patients received 20 mg of tamoxifen daily for at least 1 year.

Together, the participating centres identified 360 patients with local recurrence after BCT, diagnosed before January 1994. Local recurrence was defined as a new tumour occurring in the preserved breast or overlying skin after complete loco-regional treatment. Of the 360 local recurrences, 28 (8%) were detected after the diagnosis of distant disease, and in 66 (18%) distant disease was diagnosed within three months after the diagnosis of local recurrence. The remaining 266 patients (74%) showed no signs of distant metastases or axillary recurrence, at least within the first three months after the diagnosis of local recurrence. These 266 patients were considered to have an 'isolated local recurrence' and constitute the study population. Of these, 248 (93%) had undergone BCT during the 1980s and 18 (7%) during the period 1990–1992. Three patients had not received a boost dose. At initial diagnosis, 150 (56%) had pathological stage I primary breast cancer ($T_1N_0M_0$), 83 patients (31%) stage IIA ($T_1N_1M_0$, $T_2N_0M_0$), 28 (11%) stage IIB ($T_3N_0M_0$, $T_2N_1M_0$) and four (1%) stage IIIA ($T_3N_1M_0$, $T_{1-3}N_2M_0$). Axillary lymph nodes were involved in 71 of the 266 patients (27%) at the time of primary treatment. The median age was 45 years (range 16–81 years) at the time of primary

treatment and 49 years (range 17–82) at diagnosis of the local recurrence. The median time between the date of breast-conservative surgery and diagnosis of local recurrence was 3.6 years (range: 0.3–13.1 years). Seventy-eight recurrences (29%) occurred within two years of BCT, 127 (48%) between two and five years, and 61 (23%) more than five years after BCT.

Further details on collection of information on the method of detection and the location, the extent, histologic type and treatment of the local recurrence have been described before [22]. Specimens of the primary tumour were available for review for 238 of the 266 patients (89%). Follow-up of the patients was updated until January 2003. The median follow-up time for surviving patients after diagnosis of local recurrence was 134 months.

2.2. Statistical analysis

Survival analysis, using the life-table method, was performed to evaluate the prognosis after local recurrence. End-points were overall survival, distant disease-free survival and survival without subsequent local recurrence, including local progression of disease. Survival curves were calculated from the date of salvage treatment of local recurrence or the date of the diagnosis of local recurrence when salvage treatment was not given. The following variables were analysed to assess their ability to predict distant recurrence-free survival: age at diagnosis of local recurrence; time interval from initial surgery to recurrence; mode of detection, location, size and histologic type of local recurrence; size, nodal status, histologic grade and microscopic margins of the original tumour; and presence of vascular invasion and extensive intraductal component (EIC) in the original tumour. Actuarial curves were compared by means of the two-tailed log-rank test. A multivariate analysis using the Cox proportional hazards model was performed to evaluate the independent predictive effect of the covariates. Hazard ratios (with 95% confidence intervals (95% CI) and P values) were estimated for each covariate in relation to the reference category. As the prognostic effect of the co-variates is likely to vary for patients with an early or a late local recurrence, separate analyses were performed for the group with a local recurrence within three years after diagnosis of the primary tumour and the group with a recurrence-free interval of more than three years after BCT.

3. Results

3.1. Diagnosis and treatment

Local recurrence was diagnosed by mammography alone in 47 cases (25%), by physical examination (*i.e.*, on the basis of signs or symptoms) in 102 cases (54%) and by both physical examination and mammography in 40 cases (21%). 225 patients (85%) underwent salvage mastectomy and 20 (8%) local excision, 11 (4%) only received systemic treatment and 8 patients (3%) remained untreated. Treatment was unknown for one patient. Detailed results on the detection and treatment of LR have been described elsewhere [22].

3.2. Outcome

Of the 266 patients with local recurrence, 226 had an invasive and 25 a non-invasive recurrence. Information on the invasiveness of the recurrence was lacking for 15 patients. Of the 226 patients with invasive local recurrence 148 (65%) had died. Distant metastases were observed in 145 patients (64%) and subsequent local recurrence or local progression in 66 (31%). Of the 145 distant metastases, 88 (61%) were detected within 2.5 years after diagnosis of local recurrence, 126 (87%) occurred within 5 years and 139 (96%) within 10 years. At 10 years from the date of salvage treatment, the overall survival rate for the 226 patients with invasive local recurrence was 39% (95% CI, 32–46), the distant recurrence-free survival rate was 36% (95% CI, 29–42), and the local control rate (*i.e.*, survival without subsequent local recurrence or local progression) was 68% (95% CI, 62–75) (Fig. 1).

Univariate analysis showed the following factors to be significantly associated with the occurrence of distant metastases following an invasive local recurrence: the mode of detection, the type and size of local recurrence, the axillary lymph node status of the primary tumour and the presence of vascular invasion in the primary tumour (Table 1). Patients with a local recurrence that had been detected by mammography alone were less likely to develop distant disease than those with a palpable recurrence ($P = 0.038$). When making a subdivision accord-

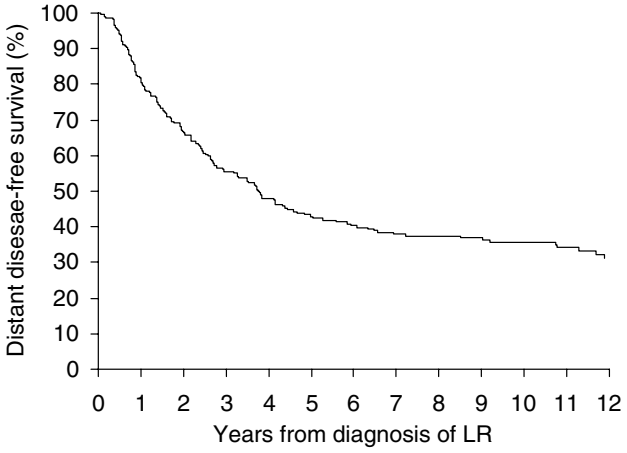

Fig. 1. Distant-recurrence-free survival of 226 patients with invasive local recurrence (LR) following breast-conserving therapy.

ing to the type and the size of local recurrence, the prognosis of patients with a recurrence elsewhere in the breast appeared to be similar to the prognosis of those with a recurrence of 1 cm or less located at or near the site of the original tumour and significantly better than the prognosis of the patients with larger recurrences (Fig. 2). A very poor prognosis was observed for patients with a recurrence involving the skin (Fig. 2). The proportion of patients developing distant metastases varied between 62% and 78% in the five institutes that contributed at least 25 patients with local recurrence to the study ($P = 0.47$).

Of the 25 patients with a non-invasive recurrence, 4 developed distant metastases and their time to distant disease varied between 53 and 79 months.

The results of the multivariate Cox regression analyses of prognostic factors for distant recurrence-free survival, overall survival and local control are presented in Table 2.

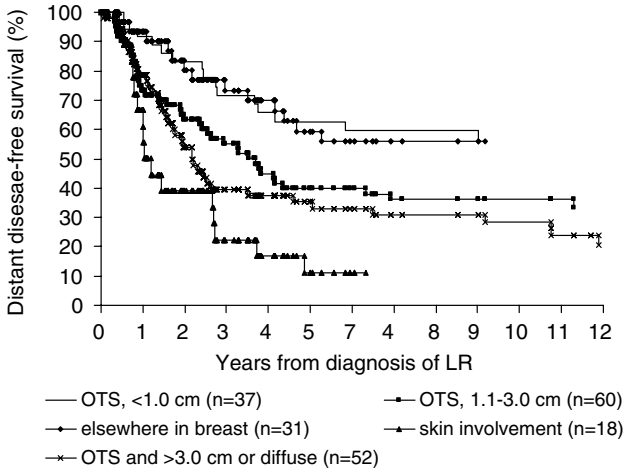

Fig. 2. Distant-recurrence-free survival of 226 patients with invasive local recurrence (LR) following breast-conserving therapy, according to the type of LR (OTS: at or near the original tumour site).

Table 1
Univariate analysis of factors related to distant recurrence in patients with invasive local recurrence after breast-conserving therapy ($n = 226$)

Variable	No. of patients	Distant recurrence-free survival		
		No.	Five-year actuarial rate (SE)	*P*-value (log-rank)
Age at diagnosis of LR (years)				
<45	81	56	43 (5)	0.405
45–64	121	75	49 (4)	
≥65	24	14	55 (9)	
Time interval to LR (years)				
≤2.0	68	45	43 (6)	0.746
2.1–5.0	107	69	39 (5)	
>5.0	51	31	53 (7)	
Mode of detection of LR				
Mammography alone	38	20	58 (8)	0.038
Signs and symptoms	125	85	36 (4)	
Type of LR				
At or near OTS and ≤1.0 cm	37	15	63 (8)	<0.0001
At or near OTS and 1.1–3.0 cm	60	40	40 (6)	
Elsewhere in breast	31	14	60 (9)	
At or near OTS and >3.0 cm or diffuse	52	38	35 (7)	
Skin involvement	18	17	11 (7)	
Lymph node status of primary tumour				
Negative	173	105	48 (4)	0.020
Positive	53	40	29 (6)	
Size primary tumour (cm)				
≤2.0	169	109	44 (4)	0.997
>2.0	55	34	42 (7)	
Vascular invasion (primary)				
No	131	85	50 (4)	0.017
Yes	55	48	33 (6)	
Extensive intraductal component (primary)				
No	149	91	43 (4)	0.857
Yes	49	34	51 (7)	
Histologic grade (primary)				
Low/intermediate	90	53	49 (6)	0.339
High	120	72	43 (5)	

Table 2
Cox regression analysis: distant recurrence, death, and subsequent local recurrence (LR) or local progression

Variable	Distant recurrence			Death			Subsequent LR or local progression		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Type of LR									
At or near OTS and ≤1.0 cm	1 (Ref)			1 (Ref)			1 (Ref)		
At or near OTS and 1.1–3.0 cm	1.86	1.15–3.00	0.012	1.70	1.06–2.74	0.028	1.56	0.73–3.32	0.247
At or near OTS and >3.0 cm or diffuse	2.53	1.55–4.15	0.0002	2.39	1.49–3.83	0.0003	2.17	1.23–3.82	0.007
Elsewhere in breast	1.04	0.49–2.19	0.218	0.90	1.30–6.03	0.775	1.52	0.48–4.81	0.478
Skin involvement	4.24	2.30–7.82	<0.0001	5.89	3.24–10.73	<0.0001	3. 56	1.67–7.63	0.001
Lymph node status of primary tumour									
Negative	1 (Ref)			1 (Ref)			1 (Ref)		
Positive	1.70	1.14–2.54	0.010	1.96	1.32–2.92	0.0009	1.68	0.94–2.99	0.08

HR: hazard ratio; OTS: original tumour site; CI: confidence interval.

The following variables were included in the multivariate model: age at diagnosis of local recurrence, time interval to local recurrence, type of local recurrence and lymph node status and size of the primary tumour. Due to missing information on one or more of these variables, 30 patients had to be excluded from the multivariate analyses. The prognosis of these patients with respect to the three end-points appeared to be similar to the prognosis for the 196 left for the multivariate model, indicating that there was not a selective drop-out of patients from the multivariate analysis. The results of the multivariate analyses showed only slight differences with respect to the three end-points. Patients with positive axillary lymph nodes at the time of diagnosis of the primary tumour had a significantly higher risk of dying or developing distant disease, compared to patients with a negative lymph node status. Patients with a local recurrence at or near the original tumour site measuring 1.0 cm or less had a lower risk of dying or developing distant disease compared to patients with a larger recurrence. Skin involvement of local recurrence was the strongest prognostic factor for the occurrence of distant disease, subsequent local recurrence or local progression and for death. Adding vascular invasion and mode of detection to the model significantly lowered the statistical power of the model without improving its prognostic value.

Multivariate analyses were also performed according to the time to recurrence (Table 3). A positive lymph node status of the primary tumour was significantly associated with an increased risk of developing distant disease in patients with a local recurrence within three years after BCT but not for patients with a local recurrence more than three years after BCT. For both early and late recurrences, a larger diameter and involvement of the skin were unfavourable prognostic factors, although the effect of the skin involvement was only statistically significant for the early recurrences.

4. Discussion

The current study is one of the largest describing the long-term prognosis of patients with recurrence in the

Table 3
Cox regression analysis: distant recurrence, according to the time interval between the diagnosis of the primary tumour and the diagnosis of local recurrence

Variable	Time interval between primary tumour and local recurrence					
	<=3.0 years			>3.0 years		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Type of LR						
At or near OTS and ≤1.0 cm	1 (Ref)			1 (Ref)		
At or near OTS and 1.1–3.0 cm	1.83	0.88–3.81	0.109	1.93	1.06–3.50	0.032
At or near OTS and >3.0 cm or diffuse	1.92	1.06–3.48	0.032	2.32	1.19–4.52	0.014
Elsewhere in breast	0.62	0.18–2.10	0.443	1.53	0.52–4.50	0.441
Skin involvement	3.34	1.67–6.71	0.0007	2.74	0.90–8.32	0.075
Lymph node status of primary tumour						
Negative	1 (Ref)			1 (Ref)		
Positive	1.88	1.05–3.34	0.033	1.20	0.64–2.25	0.578

HR: hazard ratio; OTS: original tumour site; CI: confidence interval.

treated breast following BCT and indicates that about two third ultimately develops distant metastases. Not only the site of the recurrence but also its size provided important information about the risk of developing distant disease. Patients with recurrences $\leqslant$1 cm had a lower distant recurrence risk compared to patients with local recurrences >1 cm. Although this seems to point towards a potential benefit of early detection of local recurrence, it can also be explained by a different biological behaviour, associated with certain clinical and mammographic features that facilitate detection. Prognostic factors were almost similar for patients with a local recurrence within three years after diagnosis of the primary tumour and the group with a recurrence-free interval of more than three years, except for the axillary nodal status of the primary tumour that was only of importance for the first group.

Many studies have been performed to distinguish the local recurrences associated with a good or a poor prognosis and to identify risk factors for the development of distant metastases. The question is whether salvage mastectomy is sufficient treatment or should it be followed by systemic treatment, depending on the risk for distant relapse? There is currently no good evidence that adjuvant systemic treatment is effective in patients with local recurrence. In a recent Cochrane systematic review of three randomised-controlled trials comparing systemic therapy *versus* observation for women with loco-regional recurrence following mastectomy or breast-conserving treatment who did not have previous or synchronous distant metastases, provided insufficient evidence for an improvement in the overall survival [23]. However, when overlooking the available evidence for its effectiveness in primary breast cancer, it is our opinion that adjuvant systemic (re-)treatment should be considered in patients with unfavourable prognostic factors. Local recurrence at or near the site of the original tumour [22,24–26], skin involvement [22,27], diffuse growth of recurrence [22,24], a short disease-free interval [3,4,8,12,13,15,20,28–30] and an unfavourable initial tumour stage [22,31] have been found to be predictors of a poorer prognosis in more than one study. Patients with a recurrence remote from the primary tumour appear to have a better prognosis than those with a recurrence at or near the site of the primary tumour [22,24–26]. The most likely explanation for this finding is that the first group consists largely of new primary tumours, whereas the recurrences that are located at or near the site of the primary tumour are true recurrences, originating from tumour tissue not removed by the primary excision. In the literature on the subject of local recurrence, the entities 'new primary tumour' and 'true recurrence' play an important role. The distinction between a true recurrence and a new primary is not always a clear-cut case. In most studies, the diagnosis 'new primary' was applied when the recurrence was located elsewhere in the breast, had a different histology, or DNA flow cytometry converted from an aneuploid primary to a diploid recurrence [14,25,26]. In the search for reliable distinction between new primary tumours and true recurrences, genetic techniques have been developed [32,33]. Schlechter [33] recently described a quantitative scoring system based on so-called allele imbalance (AI) or loss of heterozygosity (LOH). These DNA abnormalities, that are present in nearly all breast cancers, are traceable in archival specimens. They concluded that their approach is a potentially valuable tool in distinguishing new primary cancer from true recurrent disease, but further testing with a larger sample size is necessary to draw conclusions about the potential prognostic and therapeutic value of this technique.

In many studies, patients with a local recurrence within two or three years after the original treatment appeared to have a poorer overall and distant disease-free survival compared to those with a local recurrence occurring later [3,4,8,12,13,15,20,28–30]. True recurrences tend to have a shorter interval from BCT than the recurrences that are considered to be new primary tumours. This may explain why the proportion of patients with new primary tumours is generally larger in studies with longer follow-up after BCT and why the late recurrences are reported to have a better prognosis than the early recurrences. In our study the prognosis for patients with a local recurrence more than two years after BCT was similar to that for patients with a local recurrence within two years, which is in agreement with some other studies [31,34]. The number of patients with a recurrence more than five years after BCT was too small to estimate their prognosis accurately.

Hardly any study is available that performed a review of the histology slides of the local recurrence to identify prognostic factors [30,35]. In a series of 38 patients, DNA ploidy and S-phase fraction as measured by flow-cytometry techniques, showed some promising results as a tool in determining prognosis [35]. In another study of 68 patients, a high mitotic count was found to be associated with a higher risk of distant metastases [30].

Overall and distant recurrence-free survival and local control of disease were very poor for patients with recurrence in the skin of the breast, which was in accordance with the findings of Gage [27]. Such recurrences are likely to be markers of the metastatic potential of the tumour.

Although the 25 patients with a purely non-invasive local recurrence had a much better prognosis than the 225 with an invasive recurrence, distant metastases occurred in four of them. This is high risk when compared to patients with primary non-invasive breast cancer and suggests that the force of mortality remains present from the primary invasive cancer. In contrast to patients with invasive recurrences all distant metastases became clinically apparent more than four years after diagnosis of the local recurrence.

Finally, the prognosis of patients with a local recurrence also tends to be related to the risk of local recurrence as such. This observation comes from the patients undergoing breast-conserving surgery without radiotherapy; the high risk of local recurrence within this group is accompanied with a significantly better breast-cancer-specific survival following the diagnosis of local recurrence compared to the patients with local recurrence following breast-conserving surgery with radiotherapy [3].

In our large and unselected series of patients with local recurrence following conservative surgery and radiotherapy, long-term prognosis was poor, with a 10-year distant disease-free survival of only 36%. Lymph node status at the time of diagnosis of the primary tumour and location and size of breast cancer recurrence are predictors of this outcome. Although the latter finding suggests that follow-up directed at early detection of local recurrences might be worthwhile, it would require a large randomised study, comparing follow-up strategies with differing intensities, to confirm this.

Conflict of interest

None to declare.

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