

Prognostic Factors in 77 Curative Chest Wall Resections for Isolated Breast Cancer Recurrence

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ABSTRACT

Background. Full-thickness chest wall resection (CWR) is the preferred treatment for breast cancer (BC) patients with extensive isolated locoregional recurrence. It remains a challenge to select patients that will benefit most from this treatment. The aim of this study was to define prognostic factors in patients who undergo CWR with curative intent.

Methods. BC patients who underwent a CWR with curative intent for recurrence of disease between 1986 and 2006 were included in this retrospective study. Twenty-two factors were studied in a univariate analyses, and multivariate stepwise Cox regression analyses was performed.

Results. Seventy-seven patients were included in this study. The 5-year overall survival was 25%. There was one post-operative death. Univariate analyses showed that three prognostic factors were significantly correlated with OS and disease-free survival: (1) interval between primary treatment and CWR ($P = .02$ and $.004$, respectively), (2) chemotherapy for recurrence ($P = .05$ and $.05$, respectively), and (3) resection specimen smaller than 150 cm^2 ($P = .03$ and $.009$, respectively). An interval lasting >10 years between primary treatment and CWR remained statistically significantly correlated with better overall survival and disease-free survival after multivariate analyses.

Conclusions. CWR is a safe treatment in patients who have isolated extensive BC recurrence. The best survival outcome was seen in patients after a disease-free interval of

≥ 10 years. Existing data show that adjuvant radiotherapy and adjuvant hormone therapy for estrogen-positive tumors improves overall survival. Neoadjuvant chemotherapy may be considered in individual patients.

Locoregional recurrence (LRR) after modified radical mastectomy (MRM) for breast cancer (BC) is a worrying event for both doctor and patient. Despite optimal local treatment with curative intent, 60% of the patients will develop distant metastases, although at the time of the first sign of LRR, two out of three patients have no any other signs of BC recurrence.^{1,2}

Recently, the results of a prospective series of 1957 patients who underwent MRM have been published after a median follow-up of 6 years. The LRR rate was 9%, and 3% of these patients had concomitant distant metastases.³ Early detection of LRR and small tumor size predicted better prognosis.⁴⁻⁷

Options for local treatment of LRR include wide local excision and/or radiotherapy whether or not in combination with hyperthermia.⁸ However, for small lesions, the type of local treatment did not affect the final outcome.⁹ Another study on the treatment of LRR after mastectomy concluded that surgery combined with radiotherapy was the best treatment option, with a 5-year disease-free survival (DFS) of 27%.¹⁰ In patients who initially underwent breast-conserving therapy (BCT) for BC, radiotherapy cannot be included in the multimodal treatment for LRR. Therefore, salvage mastectomy has to be performed, or even more extensive surgery when the chest wall is involved. In patients with LRR who were initially treated with BCT or MRM, the results are similar.^{2,9} After MRM and BCT, the 5-year survival rates were 58% and 59%, with subsequent local control rates of 61% and 63%. In this study, aggressive multimodal therapy with curative intent is recommended.

In the literature, adequate definitions for LRR, the extent of LRR and the type of treatment these patients received are lacking. Often it is unclear whether patients with extensive LRR underwent chest wall resection (CWR) or not.

As a result of the heterogeneity of LRR invading the chest wall and the scarcity of published data, there are no evidence-based guidelines for the best treatment results.

Radiotherapy as monotherapy for extensive LRR does not result in complete remission. Consequently, surgery may be the best treatment option, even if it means extensive surgical resection with reconstruction of the chest wall. CWR is expected to regain local control, improve the prognosis, and/or achieve good palliation, in combination with limited morbidity and mortality.

In 1907, Sauerbruch introduced an extensive thoracic wall resection procedure for recurrent breast carcinoma.¹¹ Since then, several reports have been published on these procedures. There are a few large series (approximately 15), and some of them were performed at the same institute—for example, M. D. Anderson Cancer Center in the United States, the Istituto Nazionale in Italy, and Kinki Hospital in Japan.^{12–20}

The present retrospective single-center study of CWR for recurrent BC aims to describe the outcome of treatment and to identify prognostic factors in patients who were treated with curative intent.

MATERIALS AND METHODS

According to our retrospective database on CWRs for malignant tumors or radiation ulcers on the chest wall in the period 1986 to 2006, a total of 92 of 229 consecutive patients had undergone CWR for recurrent BC.

CWR was defined as either extended soft tissue resection with broad margins that required reconstruction of the soft tissue component, or full-thickness CWR that included at least one rib or part of the sternum (Fig. 1). Several types of inlay have been used for skeletal reconstruction over the 20-year study period. In the first few years, homologous dura mater has been used (Lyodura, B. Braun, Melsungen, FRG), later to be replaced by polyurethane (Neuropatch, B. Braun, Melsungen, FRG) as an artificial inlay. In some cases, polyglactin (Vicryl, Ethicon) was used. Patients operated on after 2004 received a double-layer polypropylene-polytetrafluoroethylene mesh (Composix). Standard soft tissue reconstruction was performed with pedicled omentoplasty unless primary closure could be achieved. Surgical aspects of the CWR technique at our hospital have been described previously.²¹

Fifteen of the 92 patients were excluded from this study because the CWR was for palliative reasons, such as

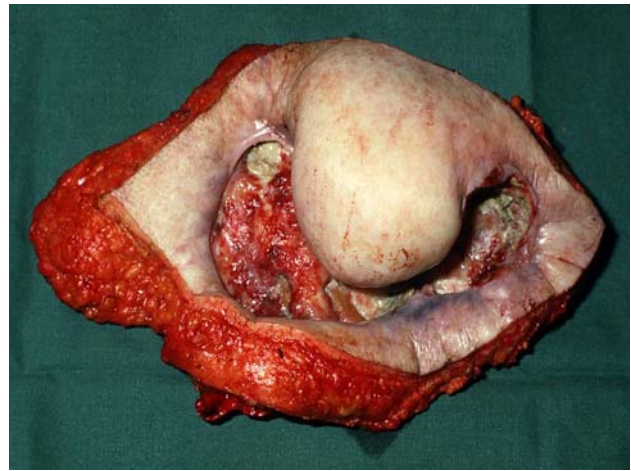


FIG. 1 Full-thickness chest wall resection for recurrent breast cancer, including the remaining breast and radiation ulcer with osteoradionecrosis of the costae

fungating ulcers or symptomatic progression of LRR, and the prognosis was reasonable despite the presence of distant metastases and limited life expectancy. The CWR was considered to be potentially curative when preoperative evaluation showed that the resection could be radical and the patient had no evidence of distant metastases. Therefore, at least a computed tomographic scan of the lung and of the liver, a bone scintigraphy, and mammography were performed. Patients who had received previous radiotherapy and/or systemic therapy for this LRR were not excluded from our analysis. Severe complications were defined as those that required prolonged hospitalization or resurgery.

Two clinical end points were set: (1) overall survival (OS) defined as the time from CWR to the date of death or the date of the last visit, whichever occurred first; (2) DFS, defined as the time from CWR to the date of local recurrence, or regional recurrence, or the date of death, or the date of the last visit, whichever occurred first.

Detailed clinical information was obtained from the medical records and pathology reports. Patient, tumor, and treatment characteristics at initial presentation with BC (Table 1) and treatment and outcome factors at the time of CWR (Table 2) were collected.

Univariate analysis was performed by the Kaplan-Meier method and the log rank test. Multivariate analysis was performed to determine the independent prognostic values of the statistically significant univariate factors by Cox's proportional hazard model (stepwise backward selection). Significance was set at a *P* value of $\leq .05$. All the statistical analyses were performed with Stata, version 9.2 (Stata-Corp, College Station, TX).

TABLE 1 Demographics at the time of initial treatment before chest wall resection for recurrent breast cancer

Factor	n (%)
Age (y)	
<40	14 (18)
≥40	63 (82)
Treatment	
BCT	47 (61)
MRM	27 (35)
Radiotherapy alone	3 (4)
T status	
T1	19 (25)
T2	45 (58)
T3	6 (8)
T4	6 (8)
Tx	1 (1)
N status	
N0	45 (58)
N1	28 (37)
N2	3 (4)
N3	0 (0)
Nx	1 (1)
Adjuvant chemotherapy	
Yes	11 (14)
No	66 (86)
Adjuvant hormone therapy	
Yes	19 (25)
No	58 (75)
Adjuvant radiotherapy	
Yes	44 (57)
No	33 (43)
Receptor status ^a	
ER positive	41 (53)
ER negative	27 (35)
ER unknown	9 (12)
PR positive	28 (36)
PR negative	33 (43)
PR unknown	16 (21)

BCT breast-conserving therapy, MRM modified radical mastectomy, ER estrogen receptor, PR progesterone receptor

^a Not tested in univariate analysis because too much data are missing

RESULTS

In 77 patients CWR was performed for recurrent BC that fulfilled our above-described curative-intent criteria. Indications were local recurrence in the chest wall (n = 41) and regional recurrence in the axillary lymph nodes (n = 9), or in the internal mammary lymph nodes (n = 27). The last group of patients is described in detail elsewhere.²²

TABLE 2 Characteristics of 77 patients at the time of chest wall resection for recurrent breast cancer

Factor	n (%)
Age (y)	
<60	43 (56)
≥60	34 (44)
Interval since primary treatment for CWR	
≤10 y	49 (64)
>10 y	25 (33)
Unknown	3 (4)
Pre-CWR hyperthermia	
No	67 (87)
Yes	10 (13)
Pre-CWR hormone therapy	
No	62 (81)
Yes	15 (19)
Pre-CWR chemotherapy	
No	66 (86)
Yes	11 (14)
Pre-thorax radiotherapy	
No	63 (82)
Yes	14 (18)
Recurrence rate	
First	55 (65)
Second	10 (13)
Third	8 (10)
Fourth	3 (4)
Seventh	1 (1)
Resected specimen	
Skin + soft tissue	14 (18)
Bone (with or without lung)	63 (82)
Size of resection surface	
<150 cm ²	62 (81)
≥150 cm ²	15 (19)
Radicality	
No	28 (36)
Yes	49 (64)
Bone invasion	
No	32 (42)
Yes	45 (58)
Ulceration	
No	67 (87)
Yes	10 (13)
Reconstruction of bone	
No	17 (22)
Yes	60 (78)
Reconstruction of skin	
No	51 (66)
Yes	26 (34)

TABLE 2 continued

Factor	n (%)
Adjuvant treatment	
No	37 (48)
Yes	40 (52)
CWR chest wall resection	

Factors at the Time of Primary Treatment

Table 1 shows the demographic data at the time of initial treatment for BC. Age at the time of diagnosis was 28 to 86 (median 46) years, and 18% of the patients were younger than 40 years. MRM had been performed in 61%, BCT in 35%, and radiotherapy in combination with chemotherapy for T4 tumors in 4%. Postoperative radiotherapy was given in 19 of the 47 MRM patients and in 25 of the 27 BCT patients. Initial T1–T2 tumors were present in 83% of the patients, and axillary lymph nodes were negative in 59%. Estrogen receptor–positive tumors were found in 53%. Various schedules of adjuvant systemic treatment after MRM or BCT had been applied to 19 patients (25%), according to the guidelines at that time.

Factors at the Time of CWR

Table 2 shows the demographic data at the time of CWR. The interval between initial treatment and CWR ranged from 0 to 33 years, with a median of 7 years. This interval was >10 years in 34%.

Age at the time of CWR was younger than 60 years in 56%. In 65% of the patients who underwent CWR, it was their first recurrence of BC. In the other 22 patients, CWR was performed because two or more episodes of recurrence had been treated unsuccessfully in the past with systemic therapy and/or radiotherapy. None of the patients had surgery of the LRR before. Full-thickness CWR with bone resection was performed in 63 patients (82%) and bone reconstruction in 60 patients. Primary skin closure could be achieved in 66% of the patients, most of whom (84%) underwent bone reconstruction. Soft tissue reconstruction was indicated in 33%: in all but one patient, pedicled omentoplasty and split skin grafting were performed, while 17 patients needed soft tissue reconstruction combined with bone reconstruction.

The pathology reports described tumor-free margins (R0 resection) in 64% of the CWR specimens. Adjuvant treatment had been applied to 58% of the patients after intensive discussion in a multidisciplinary team (Table 3). Of the patients with no tumor-free margins, 18% received adjuvant systemic treatment, and 54% radiotherapy and/or hyperthermia.

TABLE 3 Adjuvant treatment after chest wall resection for recurrent breast cancer (n = 37)

Adjuvant treatment	n (%)
Chemotherapy	5 (13)
Hormone treatment	8 (22)
Radiotherapy	18 (49)
Hyperthermia	3 (8)
Hormone treatment and radiotherapy	2 (5)
Radiotherapy and hyperthermia	1 (3)

Complications

Recovery without any complications was seen in 48 (62%) of 77 patients. The remaining 29 patients (38%) had moderate or severe complications. Complications that could be treated conservatively occurred in 12 patients, while 16 patients (22%) had severe complications that required resurgery or prolonged hospitalization. One patient died within 30 days due to respiratory failure caused by pulmonary embolism.

OS, DFS, Local Recurrence, and Metastases

Median OS of the patients who underwent CWR for recurrent BC with curative intent was 40 months. The 1-year and 5-year OS rates were 94% and 25%, respectively (Fig. 1).

The 1-year and 5-year local recurrence-free rates were 81% and 51%, respectively.

Median DFS was 14.5 months. The 1-year and 5-year DFS rates were 56% and 12%, respectively. Median interval until (regional and distant) metastases was 18.0 months. The 1-year and 5-year metastases-free rates were 63% and 19%, respectively.

Univariate and Multivariate Analyses

Univariate analysis showed that three prognostic factors were significantly related with OS and DFS: (1) interval between primary treatment and CWR ($P = .02$ and $.004$, respectively), (2) chemotherapy for treatment of LRR at any time before or after CWR ($P = .05$ and $.05$, respectively) and (3) resection specimen $< 150 \text{ cm}^2$ ($P = .03$ and $.009$, respectively) (Table 4).

Stepwise Cox regression analysis was performed on interval, chemotherapy, and size simultaneously. Only an interval of >10 years between primary treatment and CWR remained highly correlated with better OS and DFS.

TABLE 4 Univariate analyses of 77 patients with chest wall resection for recurrent breast cancer

Factor	Overall survival			Disease-free survival		
	HR	95% CI	P value	HR	95% CI	P value
Age at initial treatment						
<40 y	1			1		
≥40 y	1.01	0.99–1.03	.50	0.99	0.98–1.01	.50
Initial surgery						
BCT	1			1		
MRM	0.69	0.33–1.44	.32	0.84	0.43–1.62	.60
T status						
T1	1			1		
T2	1.22	0.51–2.94	.65	1.00	0.49–2.05	.99
T3–T4	1.09	0.40–2.95	.87	1.47	0.63–3.46	.37
N status						
N0	1			1		
N1	0.67	0.32–1.40	.29	0.79	0.43–1.46	.46
N2–N3	0.90	0.21–3.84	.88	0.64	0.15–2.69	.54
Initial adjuvant chemotherapy						
No	1			1		
Yes	1.65	0.58–4.72	.35	2.47	0.92–6.61	.06
Initial adjuvant hormone therapy						
No	1			1		
Yes	0.52	0.20–1.34	.17	0.72	0.35–1.51	.39
Initial adjuvant radiotherapy						
No	1			1		
Yes	1.26	0.63–2.54	.52	1.46	0.80–2.64	.21
Age at CWR						
<60 y	1			1		
≥60 y	0.99	0.97–1.01	.18	0.99	0.97–1.00	.056
Interval prim–CWR						
≤10 y	1			1		
>10 y	0.32	0.12–0.84	.02	0.37	0.19–0.74	.004
Pre-CWR hyperthermia						
No	1			1		
Yes	1.17	0.45–3.02	.75	1.31	0.58–2.94	.51
Pre-CWR hormones						
No	1			1		
Yes	0.72	0.33–1.60	.42	0.97	0.50–1.88	.93
Pre-CWR chemotherapy						
No	1			1		
Yes	2.29	0.99–5.34	.05	2.26	0.99–5.13	.05
Pre-CWR radiotherapy						
No	1			1		
Yes	0.68	0.30–1.56	.36	0.99	0.50–1.97	.99
Recurrence rate						
First	1			1		
Second or more	0.86	0.42–1.73	.66	1.44	0.79–2.61	.23

TABLE 4 continued

Factor	Overall survival			Disease-free survival		
	HR	95% CI	P value	HR	95% CI	P value
Resected specimen						
Skin + soft tissue	1			1		
Bone (+other)	0.86	0.38–1.98	.73	0.99	0.48–2.06	.99
Size resection surface						
<150 cm ²	1			1		
≥150 cm ²	2.32	1.08–4.98	.03	2.4	1.22–4.70	.009
Radicality						
No	1			1		
Yes	1.82	0.85–3.89	.12	0.84	0.46–1.53	.57
Bone invasion						
No	1			1		
Yes	1.32	0.67–2.59	.42	1.19	0.65–2.20	.57
Ulceration						
No	1			1		
Yes	1.67	0.64–4.37	.29	1.06	0.44–2.50	.90
Reconstruction bone						
No	1			1		
Yes	0.99	0.46–2.12	.97	1.1	0.57–2.15	.77
Reconstruction skin						
No	1			1		
Yes	1.53	0.79–2.98	.21	1.73	0.97–3.10	.06
Adjuvant treatment						
No	1			1		
Yes	0.59	0.28–1.22	.15	0.87	0.49–1.56	.65

HR hazard ratio, 95% CI 95% confidence interval, BCT breast-conserving therapy, MRM modified radical mastectomy, CWR chest wall resection

Bold indicates significant values

DISCUSSION

Extensive isolated BC recurrence in the chest wall is difficult to manage. It is a challenge to choose the best local treatment. Evidence-based guidelines for multimodality treatment are not yet available for this heterogeneous group of BC patients. A few reports focus on radiotherapy for all kinds of LRRs after BC and mainly in patients who underwent some type of surgery before radiotherapy was provided.²³ In 43% to 68% of the patients, radiotherapy can provide local control, with a reported 5- and 10-year OS of 36% to 61% and 21% to 35%, respectively.^{5,23–25} In our opinion, these percentages are relatively high because a large number of patients with a small scar recurrence are included, although prognosis seems to be worse when CWR is performed after the failure of radiotherapy for BC

recurrences.²⁶ No differences in outcome were found between surgery and radiotherapy for small isolated lesions of local recurrence, but aggressive multimodality treatment was usually advised.^{9,10} According to Dutch evidence-based guidelines, surgery is recommended in combination with hormone treatment for estrogen receptor- or progesterone receptor-positive tumors, but the indication for chemotherapy is still unclear.^{27,28} Several reports showed that CWR is a safe and justifiable procedure with low mortality (0 to 4.5%) and morbidity.^{12,29–31} Differences in the type of complications recorded, together with the wide range of scoring systems in the literature, make it difficult to compare the 38% complications found in this study—which varied from slight wound infection that could be treated by antibiotics, to omental necrosis and pyothorax that required additional surgery—with other studies. Mortality in this study is <1% and comparable to data reported in the literature.

The 5-year OS in our study is 25%. Most series reported a 5-year OS of 40% to 60%.^{16,29,32–34} The DFS at 5 years is 12% and only a very few series mention their results, varying from 26% to 67% (Table 5).³⁵ The reason for this difference remains unclear, but patient selection could be an explanation. Also, our study covers a large time period, during which aspects of BC treatment changed.

Larger series about CWR for BC make no difference between T4 BC invading the chest wall, local recurrence after mastectomy, axillary lymph node recurrence, internal mammary chain recurrence, or solitary sternal metastasis.^{5,20,36,37} On the other hand, our median survival of 40 months is comparable with other data. Also in this series, neither the T and N stage nor type of primary surgery, BCT or MRM, were statistically significant prognostic factors. In all series, the survival curve is slightly declining after 5 years.

Fifty-one percent of our patients do not develop local recurrence within 5 years; this result has been confirmed in another study (56%).¹⁶

Few authors studied the influence of prognostic factors. Age of <35 years, lymph node-negative status at initial presentation, and an interval between initial treatment and CWR of 2 years or 5 years were described as statistically significantly negative prognostic factors for OS and DFS.^{9,12,16,20,29,30,32,33,35,38,39} The multivariate analysis in this study confirmed prognostic significance of interval (alone) with the best results after 10 years.

If a radical (R0) resection can be expected, CWR should be considered. In this study, the pathologically confirmed R0 resection rate was 64%, which is comparable with another report.³⁰ In the literature, correlations between R1 and R0 resection and DFS or OS never reached significance.^{25,29} This was probably the result of postoperative radiotherapy in patients with a R1 resection. In discussions on the best local treatment, CWR is preferable to radiotherapy as the first choice because unsuccessful radiotherapy proved to be an important predictive factor for complications at the time of CWR.⁴⁰ Also, the effect of radiotherapy is less in extended and multifocal LRR, reflected in decreased survival.⁴¹

The role of adjuvant systemic therapy after CWR remains unclear, but it may be worth consideration. In 1992, a matched control study on all types of LRR treated with excisional surgery and radiotherapy, whether or not followed by chemotherapy or hormone therapy, showed that OS and DFS were greatly prolonged by adjuvant hormone therapy, but not by chemotherapy.⁵ Because the previously mentioned study was an older study, it can be expected that with the availability of new drugs and more effective chemotherapy schedules, the prognosis of patients with CWR for LRR of BC will improve.

TABLE 5 Literature review of overall survival after curative chest wall resection for locoregional breast cancer recurrence

Study	n	5-y survival (%)	Local control (follow-up)	Prognostic factors ^a
Kluiber ⁴²	12	27 m med*		
Soysal ¹⁴	10	33		
Faneyte ²⁹	30	45		Age 35 y, interval 2 y
Toi ³³	15	47		Interval 5 y ^b
Ohuchi ³²	16	57		Interval 5 y ^b
Kolodziejski ⁴³	13	62		
Lequaglie ¹⁹	18	30		
Miyauchi ¹⁶	23	48	56% (5 y)	
Pfannschmidt ³¹	33	41 m med*	85% (3 y)	Interval 2 y, no adjuvant chemotherapy
Downey ¹²	38	18		Initial node status
Warzelhan ³⁴	22	58		
Pameijer ³⁰	22	71		
Van Geel (this series)	77	25	82% (5 y)	Interval, ^c chemotherapy before CWR, size

* Months median

^a Univariate analysis

^b After mastectomy only

^c Multivariate interval 10 years

To our knowledge, this is the largest study on prognostic factors in CWR performed with curative intent for recurrent BC. Our results confirm that CWR is a safe surgical procedure. Surgery is indicated in patients who have isolated BC recurrence, even when surgery means a CWR. The longer the disease-free interval, the better the survival outcome. Adjuvant radiotherapy, and for estrogen receptor-positive tumors adjuvant hormone therapy, is indicated. Neoadjuvant systemic therapy may be taken into consideration on a case-by-case basis. With this regimen, it should be possible to obtain local tumor control in approximately half of the patients and even cure at least 25% of the patients with an isolated extensive recurrence of BC in the chest wall.

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