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Using loco-regional recurrence as an indicator of the quality of breast cancer treatment

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Abstract

The aim of our study was to compare the loco-regional recurrence (LRR) rates after breast-conserving surgery and mastectomy between the time periods of 1985–1992 and 1993–1999. The first period reflects the early experiences with breast conservation. The second period covers the years when a mammographical screening programme was introduced for women 50–69 years of age. We collected data on 1212 patients with 1264 resectable breast cancers (i.e. stage I, IIA, IIB and IIIA), of which 385 were removed by breast conserving surgery and 879 by mastectomy. During follow-up, 47 loco-regional recurrences developed after breast conservation, and 67 after mastectomy. The 5- and 10-year loco-regional recurrence rates were 5.7% (95% Confidence Interval (CI) 4.0–7.4) and 11.0% (95% CI 8.0–14.0), respectively, after mastectomy and 7.3% (95% CI 4.5–10.1) and 15.8% (95% CI 11.2–20.4), respectively, after breast conservation. The 8-year loco-regional recurrence rate after breast conservation decreased from 20.1% (95% CI 14.7–26.5) in the period of 1985–1992 to 5.4% (95% CI 1.8–9.0) in the period of 1993–1999 ($P=0.0018$). Despite the more favourable stage distribution of the patients undergoing mastectomy, no significant decrease was observed in the LRR risk in the latter period ($P=0.18$). Improvements in patient selection and treatment techniques are the most likely explanations of the decreasing LRR rate after breast conservation in our teaching hospital.
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Keywords: Breast carcinoma; Quality; Local control

1. Introduction

The first randomised clinical trials providing evidence for the safety of breast-conserving surgery for patients with tumours less than 2–4 cm in diameter were published in the early 1980s [1–3]. From that time on, surgeons in general hospitals in The Netherlands started offering patients the choice between modified radical mastectomy and breast-conserving treatment, resulting in a significant increase in the use of the latter [4].

After publication of the randomised trials, an increasing number of observational studies was published on risk factors for local recurrence after breast conservation [5–12]. In these studies, the most consistent risk factors were young age (i.e. <35 or <40 years), infiltrating tumour with an extensive intraductal component (EIC), vascular invasion, and microscopic involvement of the excision margins. The risk factors were used to define evidence-based guidelines for the use of breast conservation to support the surgeons and their patients in the decision-making process. However, local recurrence cannot always be prevented and remains a major concern of those involved in breast cancer treatment. It can be considered an important indicator for the quality of breast cancer surgery within a hospital, not only after breast conservation, but also after mastectomy.

Using data of all breast cancer patients, diagnosed and treated in a large general hospital, we compared the

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loco-regional recurrence (LRR) rates after breast-conserving surgery and mastectomy between the time periods of 1985–1992 and 1993–1999. The first period reflects the early experiences with breast conservation. The second period covers the years when a mammographical screening programme was introduced for women 50–69 years of age.

2. Patients and methods

2.1. Patients

Between 1 January 1985 and 31 December 1999, 1520 breast cancers were diagnosed in 1448 patients in the St. Elisabeth Hospital in Tilburg. The tumours were staged according to the TNM system of the International Union Against Cancer (UICC) [13]. After exclusion of 54 tumours of an unknown size, 80 cases of ductal carcinoma *in situ* and 122 tumours with direct extension to the chest wall or skin, inflammatory cancer (T4 classification) or clinical signs of distant metastases (M1 classification), 1212 patients with 1264 resectable breast cancers (i.e. stage I, IIA, IIB and IIIA) remained available for our analysis.

A mammographical screening programme, offering biannual screening for women 50–69 years old, was first introduced in this part of The Netherlands in 1992 and reached total coverage in 1996.

2.2. Treatment

Of the 1264 invasive breast cancers, 385 were removed by breast-conserving surgery and 879 by mastectomy. Breast-conserving surgery generally consisted of wide local excision of the tumour with an attempted margin of at least 1 cm of healthy tissue, 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 the iridium 192 implants. Irradiation took place at the Dr. Bernard Verbeeten Institute in Tilburg, which was one of the largest contributors to the European Organisation for Research and Treatment of Cancer (EORTC) boost–no boost trial between 1989 and 1996 (some of the patients will not have received the boost dose). Mastectomy was of the modified radical type, according to Madden or Patey. Postmastectomy radiotherapy to the chest wall (50 Gy) was recommended only for high-risk groups showing locally incomplete operation and/or more than three positive axillary lymph nodes. Both mastectomy and breast-conserving surgery included complete axillary dissection, except for patients with tumours <0.5 cm and the very old patients, for whom it was considered optional. Adjuvant systemic therapy was given only to axillary node-positive patients; premenopausal patients received six 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.

2.3. Statistical analysis

Follow-up information was collected from the patient records and included the site and date of any recurrence and the date of death. When data were missing, the family doctors were contacted. 2 patients could not be traced after the date of primary treatment and were considered lost to follow-up. The median follow-up of the surviving patients was 8.0 years (range 1.6–18.3 years). The endpoint was LRR. Local recurrence was defined as *any re-appearance of tumour growth in the preserved breast or overlying skin* for patients who underwent BCS and as *any new tumour growth involving the ipsilateral chest wall* for patients who underwent mastectomy. Regional recurrence was defined as any recurrent tumour growth in the axillary or parasternal nodal areas.

The time to LRR and distant recurrence for the treatment groups were estimated by the Kaplan–Meier method and compared by means of the logrank test. The event time was defined as the interval between primary treatment (i.e. breast-conserving surgery or mastectomy) and the occurrence of LRR. In the absence of LRR, the observation time was censored at the date on which follow-up ended (i.e. the date of death or last follow-up).

3. Results

3.1. Patient and treatment characteristics

Patient and treatment characteristics are presented in Table 1, according to type of surgery.

Patients undergoing breast-conserving surgery were significantly younger ($P<0.001$), had smaller tumours ($P<0.001$) and were less likely to have positive axillary lymph nodes ($P<0.001$), compared with those who underwent a mastectomy (Table 1). The proportion of patients undergoing axillary dissection was larger after mastectomy than after breast conservation (98% versus 90%; $P<0.001$). The use of axillary dissection was dependent on age; for patients $\geqslant 70$ years of age, 42% (24/57) underwent breast conservation without axillary dissection and 6% (12/194) mastectomy without axillary dissection. Ninety-one percent of the patients undergoing breast conservation and 30% of those undergoing mastectomy received radiotherapy. After breast conservation, 40% of the patients ⩾70 years (23/57) did not receive radiotherapy. After mastectomy, radiotherapy was given to 59% (221/372) of the patients with positive axillary lymph nodes and to 8% (41/486) of those with negative nodes. The proportion of patients with positive nodes receiving adjuvant systemic treatment (i.e. hormonal therapy and/or chemotherapy) was 90% after breast-conserving therapy and 91% after mastectomy. For patients with negative lymph nodes, these percentages were 0.4 and 2%, respectively.

When comparing the time periods of 1985–1992 and 1993–1999, no differences were observed for the patients undergoing breast conservation with respect to age, tumour size, pathological nodal status and use of radiotherapy or axillary dissection (Table 2). Of the patients who underwent mastectomy, those treated in the time period of 1993–1999 had smaller tumours and were less likely to have positive axillary lymph nodes (Table 2). The use of radiotherapy following mastectomy for patients with positive nodes decreased from 66 to 53% ($P=0.01$). No significant differences were observed in the use of adjuvant systemic therapy between the two time periods, either after breast-conserving therapy or after mastectomy. The proportion of patients undergoing breast-conserving surgery decreased from 33% (i.e. 186/563) in the period of 1985–1992 to 28% in the period of 1993–1999 (i.e. 199/701) ($P=0.07$). At the same time, the reporting of an *in situ* component in patients with invasive breast cancer increased from 8.9% in the first period to 20.4% in the second period ($P<0.0001$). In the period of 1985–1992, the presence of *in situ* breast carcinoma did not affect the choice for breast conservation; i.e. 33.7% of the patients without and 26.0% of the patients with an *in situ* component underwent breast conservation

Table 1
Characteristics of patients with operable breast cancer, diagnosed in the period 1985–1999, according to type of surgery ($N=1264$[a])

Characteristic	Breast conservation ($N=385$)		Mastectomy ($N=879$)		P value
	N	(%)	N	(%)	
Age (years)					
<50	148	(38)	239	(27)	<0.001
50–69	180	(47)	446	(51)	
70+	57	(15)	194	(22)	
Mean (range)	54.6	(21–85)	58.3	(23–92)	
Pathological tumour size (pT)					
pT1	282	(73)	365	(42)	<0.001
pT2	98	(25)	4645	(53)	
pT3	5	(1)	49	(6)	
Pathological nodal status, pN					
pN−	250	(65)	486	(55)	<0.001
pN+	98	(25)	372	(42)	
Unknown	36	(10)	21	(2)	
Axillary lymph node dissection					
Yes	348	(90)	859	(98)	<0.001
No	37	(10)	20	(2)	

[a] Number of breast cancers.

Table 2
Characteristics of patients with operable breast cancer according to type of surgery and period of diagnosis ($n=1264$[a])

Characteristic	Breast conservation ($n=365$)				P value	Mastectomy ($n=879$)				P value
	1985–1992 ($N=186$)		1993–1999 ($N=199$)			1985–1992 ($N=377$)		1993–1999 ($N=502$)		
	N	(%)	N	(%)		N	(%)	N	(%)	
Age (years)										
<50	73	(39)	75	(37)	0.92	97	(26)	142	(28)	0.11
50–69	85	(46)	95	(48)		184	(49)	262	(52)	
70+	28	(15)	29	(15)		96	(25)	98	(19)	
Mean (range)	54.5	(26–85)	54.7	(21–83)		58.7	(24–85)	58.0	(23–92)	
Pathological tumour size (pT)										
pT1	137	(74)	145	(73)	0.84	125	(33)	240	(5)	<0.0001
pT2	46	(25)	52	(26)		228	(60)	237	(47)	
pT3	3	(2)	2	(1)		24	(6)	25	(5)	
Pathological nodal status, pN										
pN−	115	(62)	135	(68)	0.40	183	(49)	303	(61)	<0.0001
pN+	53	(28)	45	(23)		189	(50)	183	(36)	
Unknown	18	(10)	19	(10)		5	(1)	16	(3)	
Axillary lymph node dissection										
Yes	168	(90)	180	(90)	0.97	372	(99)	487	(97)	0.10
No	18	(10)	19	(10)		5	(1)	15	(3)	

[a] Number of breast cancers.

Table 3
Characteristics of loco-regional recurrence (LRR) after breast conservation or mastectomy in patients with T1-3;M0 breast cancer

Characteristics	LRR after breast conservation ($N=47$)		LRR after mastectomy ($N=67$)		P value
	N	(%)	N	(%)	
Type of LRR					
Axilla	1	(2)	6	(9)	0.31[a]
Local	43	(91)	58	(88)	
Local + axilla	1	(2)	0	(0)	
Unknown	2	(4)	3	(5)	
Age (years)					
< 50	18	(38)	15	(22)	0.03[b]
50–69	22	(47)	27	(40)	
70 +	7	(15)	25	(37)	
Mean (range)	55.6	(35–83)	62.0	(39–86)	
Interval until LRR (years)					
< 2	7	(15)	27	(40)	0.01[b]
2–5	19	(40)	19	(28)	
> 5	21	(45)	21	(31)	
Median (years)	4.4	(0.3-12.1)	2.4	(0.4–11.5)	
Timing of LRR					
LRR as first event	41	(87)	46	(69)	0.08[b]
LRR after distant disease	2	(4)	8	(12)	
LRR at same time as distant disease	4	(9)	13	(19)	
Size of primary tumour (pT)					
pT1	34	(72)	13	(19)	< 0.0001[a]
pT2	12	(26)	49	(73)	
pT3	1	(2)	5	(7)	
Nodal status of primary tumour (pN)					
pN−	34	(72)	42	(63)	0.24[a]
pN +	11	(23)	24	(36)	
Unknown	2	(4)	1	(1)	

[a] Fisher's exact test.
[b] Chi-square test.

($P=0.27$). However, in the period of 1993–1999, the proportion of patients with an *in situ* component undergoing breast-conserving surgery was 19.6% compared with 30.5% for patients without an *in situ* component ($P=0.0096$).

3.2. Loco-regional recurrence

During follow-up, 47 LRR developed after breast conservation, and 67 after mastectomy (Table 3). Only 8 patients had a recurrence in the axilla and all of them had undergone axillary dissection before. The median interval until the development of LRR was 4.4 years after BCS (range 0.3–12.1) and 2.4 years after mastectomy (range 0.4–11.5) ($P=0.018$; Wilcoxon rank-sum test). The patients with LRR after mastectomy were older and had larger primary tumours compared with those with LRR following breast-conserving therapy. The 5- and 10-year LRR rates were 5.7% (95% Confidence Intervals (CI): 4.0–7.4) and 11.0% (95% CI 8.0–14.0), respectively, after mastectomy and 7.3% (95% CI 4.5–10.1) and 15.8% (95% CI 11.2–20.4), respectively, after breast conservation.

The LRR rate after breast conservation appeared to be significantly lower for the patients treated in the period of 1993–1999, compared to those treated in the period of 1985–1992; the 8-year recurrence rate was 20.1% (95% CI 14.7–26.5) for the earlier period versus 5.4% (95% CI 1.8–9.0) for the later period ($P=0.0018$) (Fig. 1a). No significant improvement in loco-regional control between the two time periods of diagnosis was observed for patients who underwent mastectomy ($P=0.18$) (Fig. 1b). The improvement in loco-regional control after breast-conservation surgery was much more pronounced for patients aged 50–69 years ($P=0.0045$) than for patients < 50 years ($P=0.16$) or $\geqslant$70 years of age ($P=0.28$) (Fig. 2a and b).

4. Discussion

By studying the trends in the rates of LRR after breast conservation and mastectomy, we have tried to

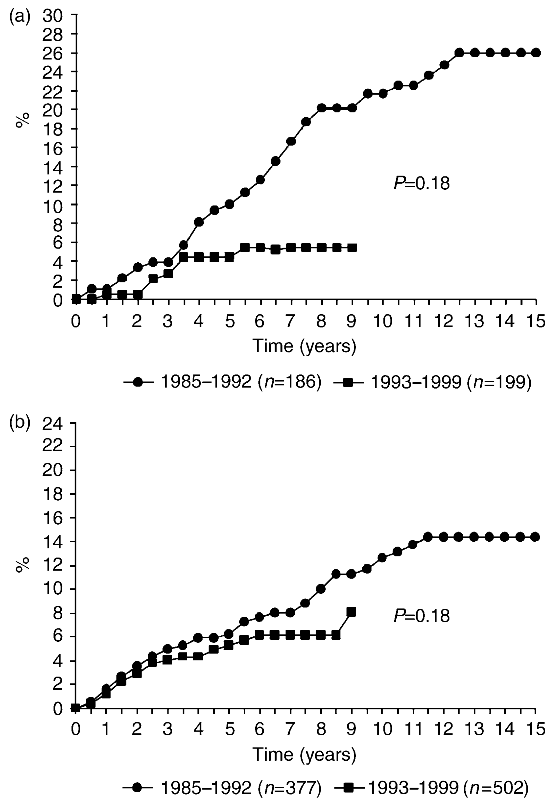

Fig. 1. (a) Loco-regional recurrence (LRR) after breast conservation in patients with invasive breast cancer stage pT1-3;M0, according to the period of diagnosis; (b) LRR after mastectomy in patients with invasive breast cancer stage pT1-3;M0, according to the period of diagnosis.

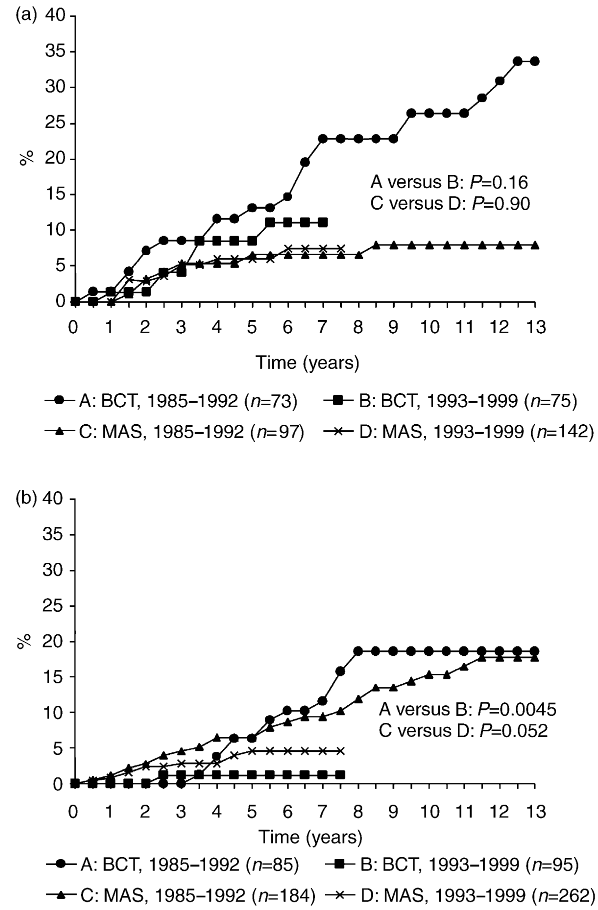

Fig. 2. (a) Loco-regional recurrence (LRR) after breast conservation (BCT) and mastectomy (MAS) in patients <50 years of age with invasive breast cancer stage pT1-3;M0, according to the period of diagnosis; (b) LRR after breast conservation (BCT) and mastectomy (MAS) in patients 50–69 years of age with invasive breast cancer stage pT1-3;M0, according to the period of diagnosis.

get a picture of the quality of breast cancer treatment in our hospital. A significant reduction was observed in the LRR risk after breast conservation.

For patients with an operable, non-metastasised breast tumour $\leqslant 5$ cm undergoing breast-conserving treatment, a maximum risk of local recurrence of 1–1.5% per year during the first 5 years of follow-up and 0.5–1% risk thereafter seems feasible, according to hospital-based series with long-term follow-up [12,14–16]. Thus, the risk should be somewhere between 3 and 7% at 5 years and between 5 and 15% at 10 years after treatment. In the guidelines of the European Society of Mastology, containing outcome measures for the quality control in the loco-regional treatment of breast cancer, it is stated that the (actuarial) breast relapse rate for invasive cancer after breast conservation should not exceed 15% at 10 years [17]. In our hospital, the actuarial local recurrence rates appeared to be higher for the patients undergoing breast conservation in the period 1985–1992. It was satisfying to see that the rate has improved significantly for the patients treated in the period 1993–1999 and is now within the above-mentioned range.

Greater knowledge about the risk factors for local recurrence, such as age <40 years, extensive intraductal component (EIC) and positive margins, has improved the selection of patients for breast conservation, and may be one explanation for the improved local control rate in our study. Patients with an unfavourable risk profile, who might have undergone breast conservation in the early years, are now more likely to be advised to undergo a mastectomy. The presence of an (extensive) intraductal component and microscopic margin involvement, which warranted little attention in the 1980s, are now extensively assessed by the pathologist. In our hospital, the quality of the pathology reports has increased significantly with respect to the reporting of *in situ* disease in and around the invasive tumour, and this has had a significant impact on the choice between breast conservation and mastectomy. However, the retrospective review of the pathology reports did not allow us to make a reliable assessement of the extent of the intraductal component. The retrospective nature of the study also explains why information on margin involvement was difficult to retrieve. In the future, careful and prospective registration might overcome this problem.

Not only the greater awareness of potential risk factors for local recurrence, but also the growing experience with breast-conserving surgery and specialisation among surgeons in our hospital will have contributed to a lower LRR risk in the second time period. The favourable effect of sub-specialisation among surgeons on disease-free survival and recurrence rates has been demonstrated in a study by Golledge and colleagues [18]. Finally, the better loco-regional control after breast conservation could be related to advancements in radiotherapy techniques and the participation in the 'boost–no boost' trial, which was preceded by the implementation of a quality assurance programme to guarantee that breast irradiation was performed in a standardised manner [19,20]. Adjuvant chemotherapy has also been demonstrated to lower the risk of local recurrence [21,22]. In our study, no increase in the use of chemotherapy was observed, which makes it an unlikely explanation for the observed improvement in loco-regional control after breast conservation.

In our hospital, the proportion of patients undergoing breast-conserving surgery was low compared with the proportion in other hospitals in an adjacent region and elsewhere [23–25]. It was expected that the introduction of mass mammographic screening in 1992 would have increased the proportion of patients undergoing breast conservation. Instead, a small, but significant, decrease was observed. A future goal should be to increase the proportion of patients undergoing breast conservation, without increasing the risk of LRR.

Despite the more favourable stage distribution of the patients undergoing mastectomy, no reduction was observed in the LRR risk in the period of 1993–1999. This lack of improvement might be related to the smaller proportion of patients with positive lymph nodes receiving postmastectomy irradiation, which has been demonstrated to reduce the risk of LRR [26,27].

Elderly patients were found to be more likely to receive less aggressive treatment, as reflected by the omission of axillary dissection and radiotherapy after breast-conserving surgery. Possible reasons for the omission of axillary dissection are comorbidity preventing general anaesthesia and the subsequent morbidity associated with this procedure. Deviation from the standard does not necessarily mean inadequate treatment; some adjustments in the treatment of elderly patients might improve their quality of life. In our study, the selective avoidance of axillary dissection and radiotherapy after breast conservation was not associated with an increased risk of LRR. However, randomised clinical trials and a recent cohort study from Sweden show that women treated with breast-conserving surgery, without radiotherapy, have local recurrence rates of more than 25% after 5 years, and that it is not yet possible to define subgroups with breast-conserving surgery who do not need radiotherapy [28–32]. Based on these results, omission of radiotherapy following breast-conserving surgery should only be considered for patients with serious comorbidities.

Based on the findings of the current study, we conclude that the continuous monitoring of loco-regional tumour control is a useful method for quality control in the loco-regional treatment of breast cancer. The decreasing LRR rate after breast conservation in our hospital is considered to be the result of improvements in patient selection and treatment techniques.

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