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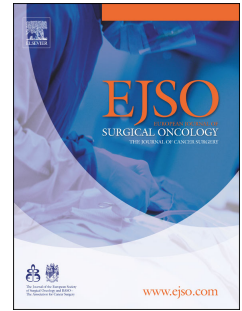


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**Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis.\***

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**Abstract**

*Objective:* Recent studies indicate that removal of the primary tumour may have a beneficial effect on mortality risk of patients with primary distant metastatic breast cancer (stage IV), although most of them did not rule out confounding by the presence of comorbidity. In this retrospective study the impact of surgical resection of the primary tumour on the survival of patients with primary distant metastatic disease is investigated, taking into account the presence of comorbidity and other potential confounders.

*Methods:* Between 1993 and 2004 15 769 patients with breast cancer were diagnosed in the South of the Netherlands. This study included the patients with distant metastatic disease at initial presentation, which was 5% of all patients. Of them, 40% had surgery of the primary tumour. Follow-up was completed until 1 July 2006.

*Results:* Median survival of the patients who had surgery of their primary tumour was significantly longer than for the patients who did not have surgery (31 vs. 14 months). The 5-year survival rates were 24.5% and 13.1%, respectively ( $p < 0.0001$ ). In a multivariable Cox regression analysis, adjusting for age, period of diagnosis, T-classification, number of metastatic sites, comorbidity, use of loco-regional radiotherapy and use of systemic therapy, surgery appeared to be an independent prognostic factor for overall survival (HR=0.62; 95% CI 0.56-0.71).

*Conclusion:* Removal of the primary tumour in patients with primary distant metastatic disease was associated with a reduction of the mortality risk of around 40%. The association was independent of age, presence of comorbidity and other potential confounders, but a randomized controlled trial will be needed to rule out residual confounding.

**Key words:** Breast cancer, Metastasis, Surgery, Prognosis, Comorbidity

## Introduction

Distant metastatic breast cancer is considered to be an incurable disease and therefore is only treated with palliative intent. Local treatment is recommended only if the primary tumour is symptomatic. In contrast to the current treatment strategy, recent studies indicate that (complete) resection of the primary tumour significantly may prolong survival of patients with primary distant metastatic breast cancer.<sup>1-6</sup> Most of these studies did not rule out confounding of their findings by the presence of comorbidity. Patients with comorbidity may be less likely to undergo surgery, which might explain part of the difference in prognosis between patients with and without surgery. In this retrospective study the impact of surgical resection of the primary tumour on the survival of patients with primary distant metastatic breast cancer is investigated, taking into account the presence of comorbidity and other potential confounders.

## Patients and Methods

### *Patients*

The Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South records data on all patients newly diagnosed with cancer in the South of the Netherlands. The region covered by the ECR comprises 2.3 million inhabitants and 16 general hospitals, but no academic centre. Ten hospitals and the 2 radiotherapy institutes participate in the ECR. In these hospitals 15 769 patients were diagnosed with breast cancer in the period 1993-2004. This study included the 728 patients with distant metastatic disease at initial presentation (4.6%). Data were collected by the ECR from copies of the pathology reports and the medical

records. Primary treatment (as planned within 6 months of diagnosis) was recorded, including surgery, loco-regional radiotherapy, chemotherapy (with or without targeted therapy) or hormonal therapy, as well as details on the surgical procedure, such as breast-conserving surgery, mastectomy and axillary dissection. The patients were staged according to the TNM system of the UICC.<sup>7</sup> For patients who did not undergo surgery and/or for whom the postoperative tumour size was unknown, we used the clinical tumour size as measured on the mammogram or at palpation, to determine the T-classification. Information on the dominant localization of metastatic disease and the number of metastatic sites was also recorded. Noted different sites were bone, liver, lung/pleurae, brain, skin and unknown/not specified sites. Also a separation was made between patients with only non-visceral metastases and patients with visceral metastases.

#### *Comorbidity*

Since 1993, the registry also records comorbidity according to a slight adaptation of the list of serious diseases drawn up by Charlson and colleagues.<sup>8</sup> In short, the following important conditions were recorded: chronic obstructive pulmonary diseases (COPD), cardiovascular and cerebrovascular diseases, other malignancies (excluding basal cell carcinoma of the skin), and diabetes mellitus. Connective tissue diseases, rheumatoid arthritis, kidney, bowel, and liver diseases, dementia, tuberculosis and other chronic infections were also recorded.<sup>9</sup>

#### *Follow-up*

Follow-up was completed until 1 July 2006. This information was obtained from the municipal registries in the area of the ECR and the Central Bureau for Genealogy. The latter is an institution that collects data on all deceased Dutch citizens via the municipal registries. In this way, information on patients who had moved outside the registry area was also

obtained. Patients who died outside the Netherlands were wrongly considered as 'being alive'. However, the estimated proportion of these patients is less than 0.3%.

### *Statistical analyses*

Survival time was defined as the period between the date of diagnosis and the date of death or 1 July 2006 for the patients who were still alive. Crude survival rates were calculated using the life-table method. The log-rank test was performed to evaluate significant differences between survival curves of surgically and non-surgically treated patients in univariate analyses. Stratified analyses were performed to compare surgically and non-surgically treated patients in subgroups defined by age (<50, 50-69 or 70+ years), T-classification (T1-2 or T3-4), number of metastatic sites (1 or >1), presence of visceral metastases (yes or no) and comorbidity (present or absent). To examine the independent contribution of surgery of the primary tumour, a multivariable Cox regression analysis was performed, including the following variables: age, period of diagnosis, T-classification, number of metastatic sites, presence of visceral metastases, comorbidity, use of loco-regional radiotherapy and use of systemic therapy.

Information on clinical and postoperative axillary nodal status was missing for more than 30% of the patients and was therefore not included in the univariate and multivariable analysis.

Hazard ratios (HR) with 95% confidence intervals (CI) and P values were estimated with respect to the reference category for each co-variate.

The SAS computer package (version 9.1) was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA, 1999).

## Results

### *Patient, tumour, and treatment characteristics*

Of the 728 patients diagnosed with primary metastatic breast cancer, diagnosed in the period 1993-2004, 288 had surgery of the primary tumour. Patient, tumour and treatment characteristics for surgically and non-surgically treated patients are listed in Table 1. The patients who had surgery of the primary tumour were younger than the patients whose primary tumour remained in situ. They were also less likely to have metastatic involvement of multiple sites or visceral metastases and had smaller primary tumours. Patients who had surgery were also less likely to have concomitant diseases; 54% of the surgically treated patients had no comorbidity versus 37% in the non-surgically treated patients, and the proportion of patients with 2 or more concomitant diseases was smaller (11% vs. 19%). The use of loco-regional radiotherapy was higher among the patients who had surgery (34% vs. 10%) as was the use of systemic therapy (89% vs. 79%). The proportion of patients who had surgery decreased from 55% in the period 1993-1996, to 39% in the period 1997-2000 and to 30% in the period 2001-2004 ( $p < 0.0001$ ).

Of the 288 patients who received surgery, 85 had breast-conserving surgery and 189 mastectomy. Type of surgery could not be retrieved for 14 patients. Axillary dissection was performed in 190 patients, of whom 44 had breast-conserving surgery and 146 mastectomy.

### *Univariate analyses*

Median survival of the patients who had surgery of their primary tumour was significantly longer than for the patients who did not have surgery (31 vs. 14 months) and the 5-year survival rates were 24.5% (95% CI 18.9-30.1) and 13.1% (95% CI 9.5-16.7), respectively (Fig. 1). A stratified analysis according to age, tumour size, number of metastatic sites, and

localization of metastases (non-visceral or visceral) and presence of concomitant diseases showed that surgery was strongly associated with a prolonged survival in all strata ( $p < 0.01$ ). A somewhat weaker, but still statistically significant, association was found for patients with more than one metastatic site, where the median survival was 16 months for the patients with surgery, compared to 10 months for the patients without surgery ( $p = 0.02$ ). For the patients who had surgery, no significant difference in overall survival was observed between those with breast-conserving surgery or mastectomy ( $p = 0.80$ ). Patients undergoing axillary dissection tended to have a better overall survival than those without axillary dissection, but this difference was restricted to the first year after treatment.

#### *Multivariable analyses*

The results of the multivariable Cox regression analysis are listed in Table 2. Due to missing values for one or more of the co-variables, 174 of the 728 patients could not be included in the multivariable model. Surgery appeared to be an independent prognostic factor associated with overall survival (HR=0.62; 95% CI 0.56-0.71). Other independent prognostic factors, besides surgery, were the number of metastatic sites, use of systemic treatment and age, with patients with one metastatic site and with systemic treatment having a better survival, and older age being associated with worse survival. The presence of concomitant diseases was associated with a worse survival, but this association was not statistically significant ( $p = 0.06$ ). Prognosis did not improve over time. No statistically significant interaction was found between surgery and any of the co-variables included in the multivariable model.

To reduce the number of missing values, a separate multivariable model was run, not including concomitant diseases as a co-variate. This model included 626 patients, but did not substantially alter the risk estimates for the other co-variables, and surgery was still associated with a significantly reduced risk of death (HR=0.66; 95% CI 0.55-0.80).

Finally, a separate multivariable analysis for the patients undergoing surgery, adjusting for the same factors as demonstrated in Table 2, did not demonstrate a significant association between the type of surgery (i.e., breast-conserving surgery versus ablation) or use of axillary dissection on overall survival ( $p=0.59$  and  $p=0.35$ , respectively).

## Discussion

Our results demonstrate that patients with primary distant metastatic breast cancer who underwent surgical removal of the primary tumour had a median survival that was 16 months longer than for patients who did not undergo surgery. This result is difficult to interpret, as the patients with surgery were younger, had smaller tumours, were less likely to have comorbidity, more than one metastatic site or visceral metastases and were more often treated in combination with loco-regional radiotherapy and/or systemic treatment. However, the impact of surgical resection of the tumour persisted in a multivariable analysis adjusting for these potential confounders, with a hazard ratio of 0.62 and a 95% confidence interval ranging from 0.56 to 0.71. Among the surgically treated patients, no difference in overall survival was observed between those who underwent lumpectomy or mastectomy. In our study, the proportion of patients with primary distant metastatic breast cancer undergoing surgery decreased from 55% in the period 1993-1996 to 30% in the period 2001-2004. At the same time, no improvement was observed in the prognosis of these patients, despite the introduction of more effective drugs, such as trastuzumab, taxanes and aromatase inhibitors. A careful conclusion might be that the life-prolonging effects of these new drugs have been counterbalanced by the decrease in the use of surgery.

### *Type of surgery and surgical margins*

All studies conducted to analyze the impact of local surgical therapy in women presenting with stage IV disease and an intact primary tumour show that surgical resection of the tumour is associated with a better prognosis.<sup>1-6</sup> Hazard ratios for mortality vary from 0.53 to 0.63 and are thus comparable with the result from our study. However, some studies taking into account surgical resection margins, indicated that the improved survival remained limited to or was larger for those patients whose primary breast lesion had been removed with free surgical margins.<sup>1,3</sup> In our study, no information on margin status was available. It could be argued that clear margins were more likely to be obtained in patients who underwent mastectomy. Thus, type of surgery could be interpreted as a proxy for margin status, but no difference in overall survival could be observed between patients who underwent lumpectomy or mastectomy. Axillary dissection also did not appear to have an additional benefit, which is in line with the study by Khan et al., which also took into account this factor, as well as the number of involved axillary nodes.<sup>1</sup>

#### *Comorbidity and performance status*

Our study is the second, in which an attempt was made to control for bias due to an unequal distribution of comorbidity among the patients with and without surgery. A direct comparison with the results from the study by Field and colleagues is hampered by the lack of information on the results of the multivariable analysis in their study.<sup>11</sup> Adjusting for presence of comorbidity and age at the same time had little additional effect on the risk estimates, when compared to adjusting for age alone. As was illustrated by the hazard ratios in Table 2, the association of overall survival with comorbidity was much weaker than with age. It could be that comorbidity is not a very accurate descriptor of the general condition of a patient. Measures of general performance, such as the WHO-scale or the Karnofsky score may be

more suitable for that, but will also not be sufficient to rule out the risk of residual confounding by other factors.

#### *Timing of surgery and systemic treatment*

No information on timing of surgery was available for our study. Distant metastases could have been found directly following surgery with curative intent, after the metastatic work-up was completed, or could already have been identified at the time of surgery, with the primary aim of surgery being loco-regional tumour control. The first group is probably small, as it was generally accepted and recommended in the treatment guidelines that there is no need for peri-operative screening for metastases in patients with a pre-operative diagnosis of early stage breast cancer without clinical signs of distant tumour spread, unless the post-operative tumour stage appears to be poorer than anticipated. Chest X-ray, bone scanning and liver ultrasound were generally recommended for patients with tumours larger than 5 cm (i.e. T3), tumours with direct extension to the chest wall or skin (i.e. T4a-d) and/or patients with evidence of extensive regional disease at clinical examination.

Information was also lacking on the timing of systemic treatment in the patients who underwent surgery. In a recent study by Cady et al., it is suggested that most of the survival advantage for patients undergoing surgery is explained by case selection bias, meaning that patients with a good response to initial systemic therapy also more likely to undergo surgery than those with a poor response.<sup>10</sup>

Review of the individual charts of the patients would be indicated, to analyse if such biases are also likely to have taken place in our study.

#### *Biological rationale behind the findings*

One possible explanation for the beneficial effect of surgery is that lowering the tumour load will reduce the number of circulating tumour cells in the blood, which are an important source of new metastatic deposits. Number of circulating tumour cells is known to be an independent predictor of progression-free survival and overall survival in patients with metastatic breast cancer.<sup>11</sup> In that view, the removal of the primary tumour should be considered as part of a multimodal strategy to prevent dissemination of tumour cells, also including radiotherapy and systemic treatment. Other positive effects of removal of the primary tumour have also been postulated, such as the restoration of the immune system and improvement of the nutritional status of the patient.

## **Conclusion**

In summary, our results are in line with previous studies and provide additional evidence that surgical removal of the primary tumour is associated with a significantly longer survival time in patients with distant metastatic breast cancer at diagnosis. The main limitation of our study, which it has in common with all other retrospective studies on this subject, is that surgery has not been assigned by randomisation. Even the adjustment for the presence of concurrent diseases at the time of diagnosis, as was done in our study, does not rule out residual confounding by other, unrecorded prognostic factors.<sup>12</sup> The only way to overcome this problem is to perform a well-designed prospective study. More specific questions of such a trial are the optimal sequencing of systemic treatment and surgery and the prognostic value of the response the primary tumour to systemic treatment, with or without surgery. Finally, translational research, assessing the role of circulating tumour cells, should also be integrated, to understand the tumour biological mechanism underlying a potentially beneficial effect of surgical excision of the primary tumour in women with stage IV breast cancer.

### Conflict of interest

The authors state that they have no conflict of interest.

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**Table 1**

Comparison of characteristics of surgically versus non-surgically treated patients with distant metastatic breast cancer at diagnosis (n=728).

	Surgical removal of primary tumour				p-value
	Yes (N=288)		No (N=440)		
	No.	(%)	No.	(%)	
Age (years)					0.003
<50	74	(26)	81	(18)	
50-69	126	(44)	172	(39)	
70+	88	(31)	187	(43)	
Mean (range)	60.2	(24-92)	64.8	(28-93)	
Period of diagnosis					<0.0001
1993-1996	109	(38)	89	(20)	
1997-2000	92	(32)	145	(33)	
2001-2004	87	(30)	206	(47)	
T classification					<0.0001
T1	61	(21)	56	(13)	
T2	112	(39)	106	(24)	
T3	20	(7)	32	(7)	
T4	91	(32)	188	(43)	
Missing	4	(1)	58	(13)	
More than 1 distant metastatic site*					<0.0001
No	213	(74)	249	(57)	
Yes	60	(21)	164	(37)	
Missing	15	(5)	27	(6)	
Visceral metastases*					0.09
No	120	(42)	148	(34)	
Yes	153	(53)	265	(60)	
Missing	15	(5)	27	(6)	

**Table 1 (continued)**

	No.	(%)	No.	(%)	p-value
Number of concomitant diseases					<0.0001
0	155	(54)	163	(37)	
1	72	(25)	140	(32)	
≥2	32	(11)	82	(19)	
Missing	29	(10)	55	(13)	
Loco-regional radiotherapy					<0.0001
No	190	(66)	396	(90)	
Yes	98	(34)	44	(10)	
Systemic treatment					0.0003
No	32	(11)	94	(21)	
Yes	256	(89)	346	(79)	

\*situation at the time of first presentation

**Table 2**

Multivariable Cox' regression analysis predicting overall survival in patients with distant metastatic breast cancer at diagnosis (n=554).

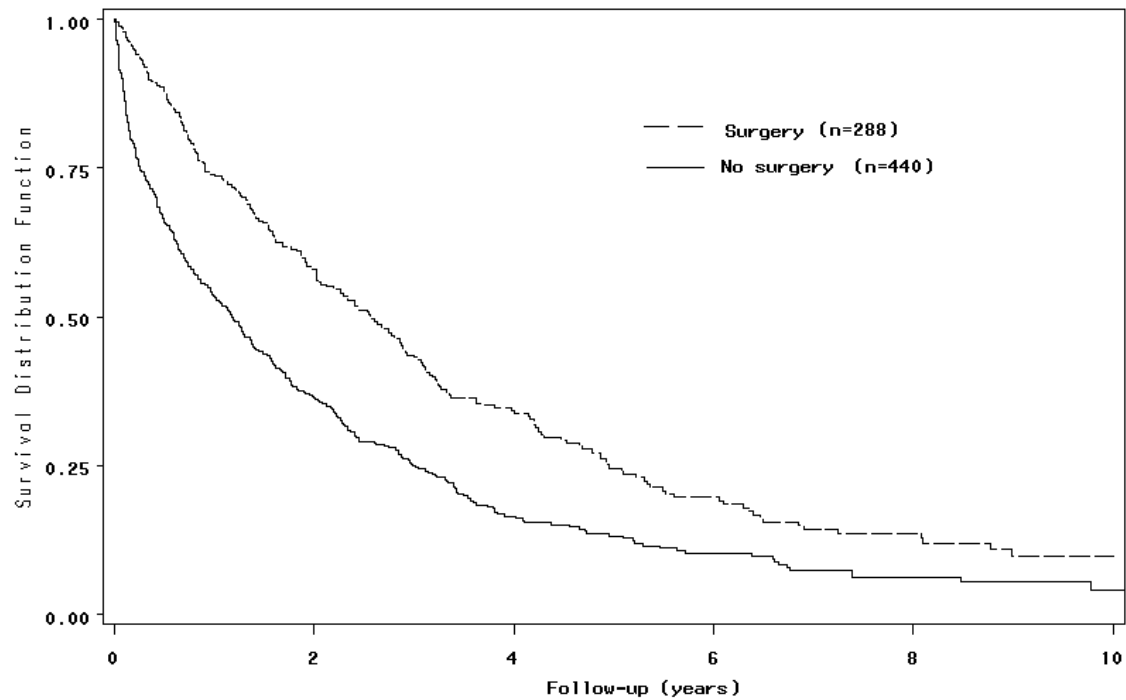
Characteristic	HR	(95% CI)	p-value
<b>Surgery</b>			
No	1 (Ref)		
Yes	0.62	(0.51-0.76)	<0.0001
<b>Age at diagnosis</b>			
<50	1 (Ref)		
50-69	1.32	(1.02-1.70)	0.03
70+	1.71	(1.23-2.11)	0.0005
<b>Period of diagnosis</b>			
1993-1996	1 (Ref)		
1997-2000	0.91	(0.72-1.14)	0.41
2001-2004	1.00	(0.77-1.28)	0.98
<b>Tumour classification</b>			
T1-T2	1 (Ref)		
T3-T4	1.07	(0.89-1.30)	0.47
<b>More than one distant metastatic site*</b>			
No	1 (Ref)		
Yes	1.58	(1.24-2.01)	0.0002
<b>Visceral metastases</b>			
No	1 (Ref)		
Yes	1.13	(0.90-1.42)	0.30
<b>Concomitant disease(s)</b>			
No	1 (Ref)		
Yes	1.21	(1.00-1.48)	0.06
<b>Radiotherapy</b>			
No	1 (Ref)		
Yes	1.00	(0.79-1.27)	0.98
<b>Systemic therapy</b>			
No	1 (Ref)		
Yes	0.45	(0.34-0.58)	<0.0001

HR: hazard ratio; 95% CI: 95% confidence interval

**LEGENDS TO FIGURES****Figure 1**

Relative survival of patients with primary distant metastatic breast cancer, according to surgical removal of the primary tumour.

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