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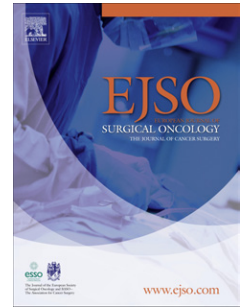
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Presence of symptoms and timing of surgery do not affect the prognosis of patients with primary metastatic breast cancer

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Abstract

Aims Though most studies on surgical resection of the breast tumor in patients with primary distant metastatic breast cancer (MBC) indicated that surgery is associated with prolonged overall survival, some state that this effect has been confounded by indication and timing of surgery. In this study we analysed these possible confounders and their relation to overall survival.

Methods To determine the impact of potential confounders, individual charts of 279 patients with primary MBC were reviewed.

Results The median survival in patients treated with surgery of the breast tumor was 39 months, compared to 15 months for those without surgery ($p < 0.0001$). The median survival of patients with symptomatic metastatic disease ($n=112$) was 19 months, compared to 22 months for those without symptomatic disease ($n=167$) ($p=0.15$). Patients who received surgery and whose metastases were detected before surgery of the breast tumor had taken place ($n=40$) had a median survival of 38 months, compared to 40 months for patients in whom the metastatic disease was diagnosed after surgery ($n=43$) ($p=0.81$).

Conclusion Presence of symptomatic metastatic disease was no significant prognostic factor for patients with distant metastasis at diagnosis, neither was the timing of surgery. It is unlikely that the prolonged survival after surgery is explained by these potentials confounders.

Introduction

In recent years, several studies have been published on the effect of surgical resection of the primary tumor in breast cancer patients with distant metastatic disease at initial presentation. Most of these studies indicate that surgery of the primary tumor is associated with prolonged overall survival in these patients.[1-7]

The decision to perform surgery of the primary tumor depends on many factors, such as age, tumor size, the number of metastatic sites, co-morbidity and performance status. Although the analyses were adjusted for these potential confounders, bias could not be ruled out completely because of the retrospective designs of all studies. Other researchers have investigated additional confounding factors and they concluded that the survival benefit, seen in patients who were treated with a surgical resection of the primary tumor, was not as strong as reported previously or could be fully explained by these additional confounders.[8-10] For instance, in one of these studies the authors concluded that the benefit of surgery is confined to patients operated upon before diagnosis of metastatic disease, as there was no survival advantage in patients who received an operation of the breast tumor after the diagnosis of the metastatic disease had taken place.[9]

So far, most studies have been performed with data from population-based or hospital-based cancer registries, which lack information on the timing of surgery or other potential confounders and which might suffer from missing values or coding errors.

Earlier we reported on 728 patients with distant metastatic breast cancer at diagnosis in the south of the Netherlands in the period 1993-2004, using data from the population-based Eindhoven Cancer Registry. A improved survival was demonstrated in patients treated with breast surgery.[6] We questioned if the aforementioned biases could be identified in our study and whether these might explain part of the positive effect of breast surgery. To answer this question we meticulously reviewed the individual charts of 279 patients with primary distant metastatic breast cancer. Among others, we recorded information on presence of symptoms of metastatic disease and timing of surgery (before or after diagnosis of metastatic disease). Furthermore, in some studies the effect of surgery on overall survival was smaller or even absent in patients with positive surgical margins.[1,3] To confirm these findings we also collected information on surgical margins for those patients who underwent surgical resection of the primary tumor.

Methods

Patients

The Eindhoven Cancer Registry (ECR) of the Comprehensive Cancer Centre South records data on all newly diagnosed patients with cancer in the south of the Netherlands. With these data we already performed a study on 728 patients with primary distant metastatic breast cancer.[6] The current study includes a selection of the patients, derived from four large teaching hospitals in the south of the Netherlands, resulting in 318 eligible patients diagnosed between 1995 and 2005 for whom extensive analysis was possible.

Definitions

Primary metastatic breast cancer was defined as diagnosis of distant metastases before or within one month after the diagnosis of the breast tumor. Presence or absence of symptomatic metastatic disease was recorded. Symptomatic metastases were defined as metastases causing complains before the primary tumor was diagnosed and therefore were the first sign of disease. Timing of surgery of the primary tumor related to timing of diagnoses of the metastases was defined as (1) surgery before diagnosis of the metastases (all within 60 days of diagnosis of the primary tumor); (2) surgery after diagnosis of the metastases; (3) delayed surgery in order to gain local control (in symptomatic local disease). The third group consisted of four patients, they were included and analyzed in the non surgical group.

Data collection and follow-up

Details on surgical procedure, such as margin status, were noted. Type of systemic treatment was documented including hormonal treatment and chemotherapy. Radiotherapy was divided in loco-regional radiotherapy and radiotherapy in case of painful bone metastases or cerebral metastases. Based on the chart review 39 patients were excluded: 22 patients were excluded because they did not have primary distant metastatic disease according to our definition, 15 because they did not have breast cancer, but another primary tumor and 2 because they did not have metastatic disease. Thus 279 patients were eligible for analysis. Follow-up was completed until the 1st of January 2010. Data were collected by the ECR from the pathology reports and medical records. We collected information (JR) on age at diagnosis, TNM classification, receptor status, symptoms of metastases and specific information on site and number of metastases. Noted different sites were bone, liver, lung/pleurae, cutaneous, central nervous system and other sites.

Statistical analysis

The aim of this study was to analyze the effect of surgery on overall survival with respect to presence of symptomatic metastases, timing of surgery and margin status after surgery.

Survival time was defined as the period between the date of diagnosis of the primary tumor and the date of death or 1 January 2010 for the patients who were still alive. Crude survival rates were calculated using the life-table method. Characteristics of patients with symptomatic and asymptomatic metastatic disease were compared with respect to age, T-classification, receptor status, site of metastases, number of metastatic sites, symptomatic metastatic disease and

margin status by using Chi-square test or Fisher's Exact test for class variables and t-test for continuous variables. The same tests were used to compare the characteristics of patients treated with surgery versus those without surgery and of patients who had surgery before and after the diagnosis of metastatic disease. The log-rank test and Kaplan-Meier analyses were performed to compare the survival rates.

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

Results

Of the 279 patients with primary metastatic breast cancer, 84 underwent surgery of the breast tumor as part of their treatment. Patients who underwent surgery were somewhat younger (60 vs. 62 yrs), but this difference was not statistically significant. Patients undergoing surgery were more likely to have a tumor with a positive progesterone receptor status and less likely to have metastases at more than one site (9 vs. 45%) compared to patients who did not receive surgery. They were also less likely to have lung or pleural metastases (10 vs. 30%). No other significant differences were observed between both groups with respect to the site of metastatic disease.

General characteristics according to symptomatic or non-symptomatic metastases

Of the 279 patients with primary metastatic breast cancer 112 had symptomatic disease, related to their metastases (Table 1). Those patients were somewhat older than the patients without metastatic symptoms (median survival 65 vs. 60 years), but this was not statistically significant. No significant differences were observed between both groups with respect to tumor size (49 vs. 45% T1-2), the expression of oestrogen and progesterone receptors and Her2neu expression. Patients presenting with symptomatic metastatic disease were more likely to have cutaneous metastases (13 vs. 4%, $P=0.002$) and metastases of the central nervous system (4 vs. 1%, $P=0.03$). No other differences were observed between both groups with respect to the site of metastatic disease. The number of metastatic sites differed significantly; in patients with symptomatic disease 16% had three or more metastatic sites, compared to 5% in patients without

symptomatic disease ($P=0.006$). Regarding surgery only 16% of the patients with symptomatic metastases had an operation of the breast tumor, compared with 40% of the patients without symptomatic disease ($P<0.0001$). Patients with symptomatic metastases were less often treated with chemotherapy (46 vs. 60%, $P=0.02$) and with locoregional radiotherapy (8 vs. 21%, $P=0.004$). They were more likely to be treated with radiotherapy for bone metastases (46 vs. 34%, $P=0.03$). Treatment with hormonal therapy was comparable between the two groups.

General characteristics according to timing of surgery

Of the 84 patients whose primary tumor was removed surgically, 43 underwent surgery before metastatic disease was diagnosed and 40 after the diagnosis of metastatic disease. For one patient the timing of the surgical treatment was not known.

Of the 40 patients who had surgery after diagnosis of metastatic disease, the interval between the diagnosis of primary tumor and the date of surgery varied between 0 and 61 months, with a mean interval of 5 months. Eighteen patients received surgery within 2 months after the diagnosis of the primary tumor, in nine patients surgery was performed after good response of the tumor to systemic treatment and in the remaining thirteen patients information on the motivation for surgery was not available.

Patients who underwent surgery of the primary tumor before metastatic disease was diagnosed had significantly smaller tumors (74 vs. 33% T1-2), were less likely to have hormone receptor positive tumors (70 vs. 95% ER and/or PR positive) and tended to be more likely to have liver metastases, were less likely

to have bone metastases (56 vs. 75%) and less likely to have symptomatic metastases at diagnosis (5 vs. 40%) (Table 2).

Survival

The median survival in patients treated with surgery of the breast tumor was 39 months, compared to 15 months for those without surgery ($p < 0.0001$) (Figure 1). The median survival of patients with symptomatic metastases ($n=112$) was 19 months, compared to 22 months for those without symptomatic disease ($n=167$) ($p=0.15$) (Figure 2). Patients who underwent surgery of the breast tumor and whose metastases were detected before surgery ($n=40$) had a median survival of 38 months, compared to 40 months for the patients with metastatic disease diagnosed after surgery ($n=43$) ($p=0.81$) (Figure 3).

Margin status

Of the patients who underwent surgery, 61 had a complete resection of the primary tumor and 15 were reported by the pathologist to have tumor-positive resection margins. For 11 patients information on margin status was not available. The median survival of patients with a complete resection was 41 months, compared to 28 months for those with tumor-positive margins ($p=0.06$).

Discussion

In the present study, based on detailed chart review, we showed a similar benefit of breast surgery on overall survival as has been reported in previous studies in patients with primary metastatic breast cancer.[1-7] Also, the presence of symptomatic metastatic disease and timing of surgery were very unlikely to be important confounders of this association. Finally, the median survival of patients treated with a complete resection of the breast tumor tended to be better than of patients who had tumor-positive margins.

Patient differences

In line with our current observations, other studies showed that patients who were selected for surgery of the primary tumor were significantly younger, [2-6,8,10-13] had smaller tumors,[3-7,11] were less likely to have metastases at more than one site,[1-3,5-7,9] and were less likely to have visceral metastases,[1-3,5,6,9,11,13] compared to patients who were not treated with surgery of the breast tumor. Information from our detailed chart review also indicated that patients who were treated with surgery, were less likely to have symptomatic metastases and less likely to have lung or pleural metastases.

Symptomatic metastases

Our study is the first one examining the differences between patients with and without symptomatic primary metastatic breast cancer. Patients with symptomatic metastases were more likely to have three or more metastatic sites and less likely to receive surgery of the breast tumor as part of their treatment.

These differences are in line with what one would expect regarding the presentation and clinical management of patients with symptomatic metastases.

Timing of surgery

A distinction was made between patients whose metastases were detected before and after surgery of the primary tumor. It appeared that half of the patients were diagnosed with metastases after surgery. Our results showed no significant difference in median survival between both groups. This is an interesting finding, because the patients who underwent surgery before the diagnosis of metastatic disease had smaller tumors and were less likely to have hormone receptor positive tumors, compared with patients who had surgery after metastatic disease was diagnosed. One would expect that this first patient group would have a better prognosis, but the median survival between both groups was comparable. A possible explanation is that the first group had more aggressive tumors with a higher metastatic potential, which had a negative influence on their survival, compared to those who had surgery after diagnosis of the metastases. It should be noted, however, that patient numbers in the subgroups were relatively small, thus decreasing the power to detect clinically relevant differences. Three other studies compared patients who were diagnosed with metastasis preoperatively to those diagnosed postoperatively and also found no significant differences between these two subgroups in overall survival.[7,9,12]

Resection margins

We observed that patients who had a complete resection of the tumor tended to have a better survival than patients with positive tumor margins. These results are in agreement with other studies.[1,3,14] Only one study did not report a survival advantage for patients treated with a complete resection of the primary tumor.[7] The association between margin status and survival in patients with primary distant metastatic breast cancer seems to indicate that tumors with positive margins have a more aggressive behaviour or that the primary tumor is in some way controlling the growth of the metastatic sites. Other investigators have found a significant relationship between margin involvement in patients with localized breast cancer and the risk of subsequent distant disease, which indicates that margin involvement in some way may be a marker of the aggressiveness of the tumor.[15] Further research, for example on circulating tumor or endothelial cells in blood and the immune response and angiogenic potential of metastases, should be performed in order to provide an answer to the question which mechanism is causing the survival benefit in the patients with tumor-free surgical margins of the primary tumor.

Data collection

This study contains detailed information from clinical charts, compared to many other studies relying on databases of cancer registries without information on the timing of surgery and margin status. The charts also revealed some coding errors and missing information in the original database, provided by the cancer registry. This indicates that studies based on existing databases may benefit from chart review to complete missing information and check the quality of the data.

Conclusions

There were several differences between the patients who had surgery before or after the diagnosis of the metastases. Patients who had their operation before the diagnosis of the metastases had smaller tumors, were less likely to have hormone positive tumors, were less likely to have bone metastases and were less likely to have symptomatic metastases at diagnosis. Still, there was no significant difference in median survival between both groups. This leads to the conclusion that both timing of surgery and detection method of metastases are no important confounders. A future randomized controlled trial (RCT) that investigates the effect of surgery of the breast tumor in patients with primary metastatic breast cancer should include a protocol for (pre-operative) screening for metastases and pre-stratification for important confounders, such as age, dominant location of distant metastases, hormonal receptor status and HER2Neu status. Currently, studies are running in India (RCT, ongoing, not recruiting), Turkey (RCT, recruiting at the moment, no results published), United States (observational study, recruiting at the moment) and Austria (RCT, ongoing).[16] In the Netherlands we will start a RCT on this very interesting subject Autumn 2011.

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Table 1: general characteristics of patients with symptomatic and with asymptomatic primary metastatic breast cancer (n=279)

	<i>Symptomatic (n=112)</i>	<i>Asymptomatic (n=167)</i>	<i>P-value</i>
	<i>n</i>	<i>n</i>	
Age at diagnosis (years)			0.74
< 50	24	40	
50-69	49	76	
≥ 70	39	51	
Median age [range]	65.0 [27.1 – 89.1]	60.3 [29.4 – 93.6]	
T-classification			0.46
T1	24	28	
T2	31	47	
T3	6	14	
T4	32	58	
Unknown	19	20	
Oestrogen receptor status			
ER positive	81	115	0.50
ER negative	20	39	
ER other/unknown	11	13	
Progesterone receptor status			
PR positive	62	88	0.67
PR negative	39	66	
PR other/unknown	11	13	
Her2neu			0.53
Overexpression	5	13	
No overexpression	36	50	
Unknown	71	104	
Site of metastases			
Bone	75	104	0.42
Liver	34	52	0.89
Lung/pleural	29	38	0.55
Cutaneous	15	6	0.002
CNS	5	1	0.03
Other/unknown	15	18	0.51
Number of metastatic sites			0.006
1	62	112	
2	31	39	
≥ 3	18	9	
Unknown	1	7	
Treatment			
Surgery	18	66	<0.0001
Hormonal therapy	86	124	0.63
Chemotherapy	51	100	0.02
Radiotherapy, loco-regional	9	35	0.004
Radiotherapy, bone	52	56	0.03
Radiotherapy, cns	7	9	0.76

Table 2: characteristics of patients who had surgery before or after the diagnosis of the metastases (n=83)

	<i>Surgery before (n=43)</i>	<i>Surgery after (n=40)</i>	<i>P-value</i>
	<i>diagnosis of the metastases</i>		
	<i>n</i>	<i>n</i>	
Age at diagnosis (years)			0.53
< 50	15	10	
50-69	17	16	
≥ 70	11	14	
Median age [range]	54.6 [32.6-88.7]	64.8 [27.1-92.1]	
T-classification			0.0001
T1-2	32	13	
T3-4	5	21	
Unknown	6	6	
Hormone receptor status			0.01
ER and/or PR positive	30	38	
ER and PR negative	11	2	
ER/PR unknown	2	0	
Site of metastases			
Bone	24	30	0.07
Liver	14	6	0.06
Lung/pleural	3	5	0.39
Cutaneous	2	1	0.30
CNS	0	1	0.60
Other/unknown	3	3	0.93
Number of metastatic sites			0.52
1	39	35	
≥2	3	5	
Unknown	1	0	
Symptomatic metastases			<0.0001
Yes	2	16	
No	41	24	
Margin status			0.86
Complete resection	33	28	
Positive margins	7	8	
unknown	3	4	

