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Prognosis of metastatic breast cancer: are there differences between patients with *de novo* and recurrent metastatic breast cancer?

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Background: We aimed to determine the prognostic impact of time between primary breast cancer and diagnosis of distant metastasis (metastatic-free interval, MFI) on the survival of metastatic breast cancer patients.

Methods: Consecutive patients diagnosed with metastatic breast cancer in 2007–2009 in eight hospitals in the Southeast of the Netherlands were included and categorised based on MFI. Survival curves were estimated using the Kaplan–Meier method. Cox proportional hazards model was used to determine the prognostic impact of *de novo* metastatic breast cancer *vs* recurrent metastatic breast cancer (MFI $\leqslant$24 months and $>$24 months), adjusted for age, hormone receptor and HER2 status, initial site of metastasis and use of prior (neo)adjuvant systemic therapy.

Results: Eight hundred and fifteen patients were included and divided in three subgroups based on MFI; 154 patients with *de novo* metastatic breast cancer, 176 patients with MFI $<$24 months and 485 patients with MFI $>$24 months. Patients with *de novo* metastatic breast cancer had a prolonged survival compared with patients with recurrent metastatic breast cancer with MFI $<$24 months (median 29.4 *vs* 9.1 months, $P<0.0001$), but no difference in survival compared with patients with recurrent metastatic breast cancer with MFI $>$24 months (median, 29.4 *vs* 27.9 months, $P=0.73$). Adjusting for other prognostic factors, patients with MFI $<$24 months had increased mortality risk (hazard ratio 1.97, 95% CI 1.49–2.60, $P<0.0001$) compared with patients with *de novo* metastatic breast cancer. When comparing recurrent metastatic breast cancer with MFI $>$24 months with *de novo* metastatic breast cancer no significant difference in mortality risk was found. The association between MFI and survival was seen irrespective of use of (neo)adjuvant systemic therapy.

Conclusion: Patients with *de novo* metastatic breast cancer had a significantly better outcome when compared with patients with MFI $<$24 months, irrespective of the use of prior adjuvant systemic therapy in the latter group. However, compared with patients with MFI $>$24 months, patients with *de novo* metastatic breast cancer had similar outcome.

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Despite progress in the treatment of early breast cancer, 20–30% of the patients will develop a distant recurrence (Harris *et al*, 1993). Once distant recurrence has occurred the disease remains largely incurable and median survival of patients with metastatic breast cancer ranges from 2 to 3 years (Cardoso *et al*, 2012).

The outcome of patients with metastatic breast cancer depends on several prognostic factors. Biological breast cancer subtypes based on hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status are associated with different outcomes once distant recurrence has occurred (Kennecke *et al*, 2010; Lobbezoo *et al*, 2013). Besides biological breast cancer subtype, other known prognostic factors are age, performance status and site and number of distant metastases (Yamamoto *et al*, 1998; Largillier *et al*, 2008).

Furthermore, the metastatic-free interval (MFI), which is defined as the time between primary breast cancer diagnosis and the development of distant recurrence, is a known strong prognostic factor for survival of patients with metastatic breast cancer. Metastatic-free interval <24 months is associated with a worse prognosis, as shown in several population-based studies of patients with metastatic breast cancer (Largillier *et al*, 2008; Puente *et al*, 2010; Llombart-Cussac *et al*, 2014). The importance of MFI is stressed by the incorporation of this prognostic factor in clinically relevant and validated prognostic models for patients with metastatic breast cancer (Yamamoto *et al*, 1998; Regierer *et al*, 2014).

Acknowledging separate prognostic groups based on MFI, patients with distant metastasis at initial breast cancer diagnosis can also be viewed as a distinct prognostic subgroup. This subgroup, called *de novo* metastatic breast cancer, could on the one hand be suggested to represent a poor prognostic group with early distant metastasis as a sign of more aggressive disease. On the other hand, one could hypothesise that patients with *de novo* metastatic breast cancer have a better prognosis because their disease is therapy-naive and thus less likely to show resistance to systemic therapy.

Indeed, in a large study on metastatic breast cancer diagnosed in the period 1992–2007, outcome of patients with *de novo* metastatic breast cancer was superior compared with patients with recurrent metastatic breast cancer (Dawood *et al*, 2010b). This favourable outcome was also demonstrated for patients with *de novo* HER2 positive metastatic breast cancer, as compared to those with recurrent HER2 positive metastatic breast cancer (Yardley *et al*, 2014). However, in another analysis on HER2-positive patients all treated with first-line palliative trastuzumab-based therapy no difference in outcome between *de novo* and recurrent metastatic breast cancer was found (Rossi *et al*, 2014).

This led to our study investigating the prognosis and prognostic factors, including HR and HER2 status, for patients with *de novo* metastatic breast cancer compared with patients with recurrent metastatic breast cancer in a large multicentre study. All patients were diagnosed with metastatic breast cancer in the period 2007–2009 and were treated according to modern treatment strategies, including targeted therapy.

PATIENTS AND METHODS

Patients and data collection. All consecutive patients diagnosed with metastatic breast cancer in 2007–2009 in eight hospitals in the Southeast of the Netherlands were identified. Patients were included irrespective of the date of diagnosis of the primary tumour with the exception of patients with a diagnosis of primary breast cancer before 1990, due to the limited available data on the primary tumour characteristics and the initial treatment.

Data on all included patients was obtained from medical files by specially trained registration clerks, after approval from the Medical Research Ethics Committee of Maastricht University Medical Centre. Information was collected on patient and tumour characteristics, treatment information (surgery, radiotherapy and systemic treatment, both adjuvant and palliative), number and sites of distant metastases and survival time. Initial metastatic sites were registered as single or multiple and were categorised as: bone, visceral (including lung, liver, pleural, peritoneal, pericardial and lymphangitic carcinomatosis), brain (including leptomeningeal and central nervous system), skin and lymph nodes and multiple metastases (more than one of the aforementioned metastatic sites). Tumours were characterised by the sixth edition of the TNM classification of malignant tumours (Greene *et al*, 2002) and Scarff Bloom Richardson (SBR) histological grading (Elston and Ellis, 1991). We used pathological TNM also for the small amount of patients with neoadjuvant systemic therapy (9% of all patients treated with (neo)adjuvant therapy). Oestrogen receptor and progesterone receptor positivity was defined as positive nuclear staining of $\geqslant 10\%$ and HR positivity was defined as Oestrogen receptor- and/or progesterone receptor-positive breast cancer. HER2 positivity was defined as immunohistochemistry score of $3+$, or $2+$ with a positive fluorescence *in situ* hybridisation result. In case of missing HER2 status a dedicated pathologist centrally reviewed missing data when material was available.

Data analysis. We categorised the total of 815 included metastatic breast cancer patients based on MFI. Metastatic-free interval was defined as time between date of diagnosis of primary breast cancer and date of diagnosis of first distant metastatic recurrence. On the basis of the cutoff points used in other studies and their demonstrated differential impact, patients were divided in three categories; patients with *de novo* metastatic breast cancer (MFI <3 months), patients with recurrent metastatic breast cancer with MFI $\leqslant 24$ months and patients with recurrent metastatic breast cancer with MFI of >24 months.

The primary aim of our study was to assess differences in survival of patients with *de novo* metastatic breast cancer compared with those with recurrent metastatic breast cancer. Survival of patients with distant metastasis was defined as time between date of diagnosis of first distant metastasis and date of death. All patients still alive were censored at the date of last follow-up of each individual patient. Survival curves were obtained using the Kaplan–Meier method.

We selected prognostic factors based on clinical importance rather than by statistical significance and included the following factors in the model; age at metastatic breast cancer diagnosis, HR and HER2 status and initial number and site of metastases. First, a Cox proportional hazards model was used to assess whether the prognostic impact of these factors differed between the three subgroups based on MFI by statistical testing of the interaction between the prognostic factors and MFI with a likelihood ratio test. Second, the ratios of the hazard rates comparing *de novo* metastatic breast cancer with recurrent metastatic breast cancer were adjusted for these factors in a Cox regression model. To evaluate the effect of (neo)adjuvant therapy we repeated this model when excluding patients with (neo)adjuvant systemic therapy.

All reported P-values were two-sided and a P-value <0.05 was considered of statistical significance.

RESULTS

Characteristics. A total of 815 metastatic breast cancer patients were included in the study, of which 154 patients (19%) were diagnosed with *de novo* metastatic breast cancer and 661 patients (81%) had recurrent metastatic breast cancer (Table 1). Of the patients with recurrent metastatic breast cancer, 176 patients (27%) had MFI <24 months and 485 patients (73%) had MFI >24 months.

Median age at diagnosis of metastatic breast cancer was 61 years (range 25–89 years) for patients with *de novo* metastatic breast cancer and 64 years (range 25–93 year) for patients with recurrent metastatic breast cancer, irrespective of MFI ($P = 0.06$).

Pathological tumour and lymph node status was missing for the majority of patients with *de novo* metastatic breast cancer, as surgical removal of the primary tumour was not routinely performed after diagnosis of metastatic breast cancer (83% of patients with *de novo* metastatic breast cancer did not have surgery of the primary tumour).

Hormone receptor-positive breast cancer was most frequently seen in patients with *de novo* metastatic breast cancer (81%) and recurrent metastatic breast cancer with MFI >24 months (83%), but less in patients with recurrent metastatic breast cancer with MFI <24 months (55%) ($P < .0001$). Human epidermal growth factor receptor 2-positive status was not different between patients with *de novo* metastatic breast cancer (23%), recurrent metastatic breast cancer with MFI >24 months (18%) ($P = 0.21$) and recurrent metastatic breast cancer with MFI <24 months (21%; $P = 0.76$).

The percentage of patients with visceral or brain metastasis as initial metastatic site for recurrent metastatic breast cancer with MFI <24 months was, respectively, 33% and 10%. These percentages were lower for patients with *de novo* metastatic breast cancer (respectively, 24% and 0%) and for patients with recurrent metastatic breast cancer with MFI >24 months (respectively, 27% and 2%).

For all patients with recurrent metastatic breast cancer, 46% had received prior (neo) adjuvant chemotherapy and 51% prior (neo-) adjuvant endocrine therapy.

Of patients with *de novo* metastatic breast cancer 57% received at least one-line of palliative chemotherapy *vs* 53% of patients with recurrent metastatic breast cancer ($P = 0.35$). Also the use of any palliative endocrine therapy was not different between *de novo* and recurrent metastatic breast cancer (respectively, 69% *vs* 62%; $P = 0.10$).

Survival and prognostic factors. Median follow-up after diagnosis of metastatic disease was 37.1 months (range 2.1–55.4), with 302 patients (37%) being alive at the end of the follow-up period.

The median survival of patients with *de novo* metastatic breast cancer was 29.4 months (95% CI 19.3–35.0 months) compared with 21.1 months (95% CI 18.7–24.4 months) for patients with recurrent metastatic breast cancer ($P = 0.14$).

When looking at the patients with recurrent metastatic breast cancer stratified by MFI, survival of those with *de novo* metastatic breast cancer was significantly better than for patients with MFI <24 months (median, 29.4 *vs* 9.1 months, $P < .0001$) (Figure 1). Survival of *de novo* metastatic breast cancer patients was not significantly different from the survival of recurrent metastatic breast cancer patients with MFI of >24 months (median, 29.4 *vs* 27.9 months, $P = 0.73$) (Figure 1).

The prognostic impact of the prognostic factors did not differ significantly for the three MFI groups (test for interaction $P = 0.98$). Therefore, the results could be pooled to obtain the final Cox proportional hazards model (Table 2).

Adjusted for other prognostic factors, patients with MFI <24 months had a significantly increased risk in mortality (hazard ratio 1.97; 95% CI 1.49–2.60) compared with patients with *de novo* metastatic cancer (Table 2). Recurrent metastatic breast cancer patients with MFI >24 months had no increased risk in mortality compared with *de novo* metastatic breast cancer patients (hazard ratio of 0.89, 95% CI 0.70–1.14) (Table 2).

Older age at diagnosis of metastatic breast cancer, HR-negative breast cancer, HER2-negative breast cancer, multiple initial metastatic sites as well as brain or visceral metastases as initial site compared with bone metastases were all associated with a worse prognostic impact on outcome (Table 2).

Performing the multivariable analysis when excluding patients with (neo)adjuvant systemic therapy, thereby comparing the therapy-naive patients with recurrent metastatic breast cancer and *de novo* metastatic breast cancer, the increased mortality risk for patients with MFI <24 months compared with *de novo* metastatic breast cancer remained statistically significant (adjusted hazard ratio 1.69, 95% CI 1.11–2.58) (Table 2).

DISCUSSION

We present survival and prognostic factors of patients with *de novo* metastatic breast cancer compared with patients with recurrent metastatic breast cancer in a multi-centre, unselected cohort of patients. As all patients were diagnosed with metastatic breast cancer between 2007 and 2009, this cohort reflects a time period in which HER2 status was routinely performed and treatment included targeted therapy.

There was no significant difference in prognosis between patients with *de novo* and recurrent metastatic breast cancer irrespective of MFI.

The median overall survival of 29 months for patients with *de novo* metastatic breast cancer in this cohort was comparable to the survival found in other cohort studies on patients with *de novo* metastatic breast cancer (Andre *et al*, 2004; Dawood *et al*, 2010b; Pal *et al*, 2012).

However, when stratifying patients with recurrent metastatic breast cancer according to the MFI differences in survival between *de novo* and recurrent metastatic breast cancer became apparent. Patients with *de novo* metastatic breast cancer had a similar outcome when compared with patients with late distant recurrent metastatic breast cancer. However, patients with *de novo* metastatic breast cancer had a significant better outcome when compared with patients with an early distant recurrence, also after exclusion of the patients receiving (neo)adjuvant systemic treatment.

We defined early distant recurrence as MFI shorter than 24 months, based on the cutoff points used in other studies and the demonstrated prognostic impact (Yamamoto *et al*, 1998; Largillier *et al*, 2008; Puente *et al*, 2010; Llombart-Cussac *et al*, 2014; Regierer *et al*, 2014).

When looking closer at this subgroup, patients with an early distant recurrence were more likely to have HR-negative breast cancer. It is known that breast cancer subtypes, based on HR and HER2 status, have different prognostic impact and different patterns of distant recurrence, with HR-negative subgroups having earlier recurrence and unfavourable prognosis compared with HR-positive subgroups (Kennecke *et al*, 2010; Lobbezoo *et al*, 2013). However, even when adjusting for HR-negative status, the difference in survival between *de novo* and early distant recurrent metastatic breast cancer remained present.

Another hypothesis explaining the better outcome of *de novo* metastatic breast cancer compared with early recurrent metastatic breast cancer is the use of adjuvant systemic therapy in patients with recurrent metastatic breast cancer. This could lead to more resistant metastatic disease compared with patients with therapy-naive *de novo* metastatic breast cancer. But, when we excluded patients with recurrent metastatic breast cancer with (neo)adjuvant systemic therapy, the difference in survival between *de novo* and early distant recurrent metastatic breast cancer remained present. Hence, in our cohort there was no evidence that the administration of systemic therapy in early breast cancer could explain the better outcome of *de novo* metastatic breast cancer when compared with patients with an early distant recurrence.

The role of surgery of the primary breast tumour on the outcome of metastatic breast cancer patients remains controversial. Initial retrospective studies and meta-analyses of these data

Table 1. Baseline characteristics

	De novo		Recurrent all			Recurrent with MFI ⩽24 months			Recurrent with MFI >24 months		
	n = 154		*n* = 661			*n* = 176			*n* = 485		
Characteristics	**No.**	**%**	**No.**	**%**	***P*-value**	**No.**	**%**	***P*-value**	**No.**	**%**	***P*-value**
Age at diagnosis of metastatic disease											
Median, (range)	61	25–89	64	25–93	0.06	62	25–93	0.40	64	32–90	0.04
<40 years	10	6	18	3		12	7		6	1	
40–70 years	100	65	408	62		98	56		310	64	
>70 years	44	29	235	35		66	37		169	35	
Primary tumour stage[a]											
T1	9	25	240	44		38	31		202	48	
T2	22	63	265	48		73	58		192	45	
T3	2	6	29	5		8	6		21	5	
T4	2	6	16	3		6	5		10	2	
Unknown	119		111			51			60		
Regional lymph node stage primary tumour[a]											
N0	6	17	230	41		46	37		184	43	
N1	13	37	187	34		32	25		155	36	
N2	6	17	82	15		26	21		56	13	
N3	10	29	57	10		22	17		35	8	
Unknown	119		105			50			55		
Histological grade of primary tumour											
SBR 1	8	11	55	11	0.26	10	6	0.01	45	14	0.59
SBR 2	39	53	212	44		57	37		155	47	
SBR 3	26	36	219	45		89	57		130	39	
Unknown	81		175			20			155		
Hormone receptor status											
Positive	121	81	490	76	0.21	96	55	<0.0001	394	83	0.43
Negative	29	19	156	24		78	45		78	17	
Unknown	4		15			2			13		
HER2 status											
Positive	34	23	122	19	0.29	37	21	0.76	85	18	0.21
Negative	116	77	524	81		137	79		387	82	
Unknown	4		15			2			13		
Prior (neo)adjuvant chemotherapy											
Yes	—		306	46		85	48		221	46	
No			355	54		91	52		264	54	
Prior (neo) adjuvant endocrine therapy											
Yes	—		339	51		64	36		275	57	
No			322	49		112	64		210	43	
Prior (neo) adjuvant anti-HER2 therapy											
Yes	—		44	7		17	10		27	6	
No			617	93		159	90		458	94	
No. of metastatic sites											
1	103	67	426	64	0.57	123	70	0.56	303	62	0.32
⩾2	51	33	235	36		53	30		182	38	
Site of metastases											
Bone	60	39	202	31	0.04	41	23	0.002	161	33	0.19
Visceral	37	24	188	28	0.27	58	33	0.07	130	27	0.49
Brain	0	0	26	4	0.01	18	10	<0.0001	8	2	0.11
Skin and lymph nodes	9	6	46	7	0.62	16	9	0.27	30	6	0.88
Multiple	48	31	199	30	0.80	43	25	0.17	156	32	0.82
Any palliative chemotherapy											
Yes	88	57	350	53	0.35	84	48	0.09	266	55	0.62
No	66	43	311	47		92	52		219	45	
Any palliative endocrine therapy											
Yes	106	69	408	62	0.10	67	38	<0.0001	341	70	0.73
No	48	31	253	38		109	62		144	30	
Any palliative targeted therapy											
Yes	33	21	121	18	0.37	23	13	0.04	98	20	0.74
No	121	79	540	82		153	87		387	80	

Abbreviation: SBR = Scarff Bloom Richardson.
[a]Pathological TNM according to the sixth edition of the TNM classification of malignant tumours.

supported the idea that surgery of the primary tumour in *de novo* metastatic breast cancer could have a positive impact on outcome (Ruiterkamp *et al*, 2010; Ali and Le Scodan, 2011; Harris *et al*, 2013). However, data on randomised clinical trials could not show a survival advantage for surgery of the primary tumour and palliative systemic therapy compared with palliative systemic therapy alone (Badwe *et al*, 2013; Soran *et al*, 2013). Furthermore, when looking at the current views on molecular models of metastasis and tumour dormancy, some hypothesise that surgery of the primary tumour can be the systemic event that interrupts the dormant state of metastatic cancer cells, and thereby even have an unfavourable effect on outcome (Dillekas *et al*, 2014).

The model of metastasis in breast cancer has evolved over the years and the knowledge gathered by genomic assays supports the idea that the capacity of metastasis is acquired early in the life of primary breast cancer (Weigelt *et al*, 2005; Chiang and Massague, 2008). Therefore, the assessment of recurrence risk is not only dependent on classical clinicopathological factors, but also on detection of metastatic potential of the primary breast tumour. This also leads to newer insights into relevant prognostic factors in early breast cancer to determine risk of recurrence, amongst others gene-expression profiling and the detection of disseminated tumour cells. However, once metastatic breast cancer is present, the need for clinical prognostic factors remains and is of importance to guide further treatment decision and to provide prognostic information to patients.

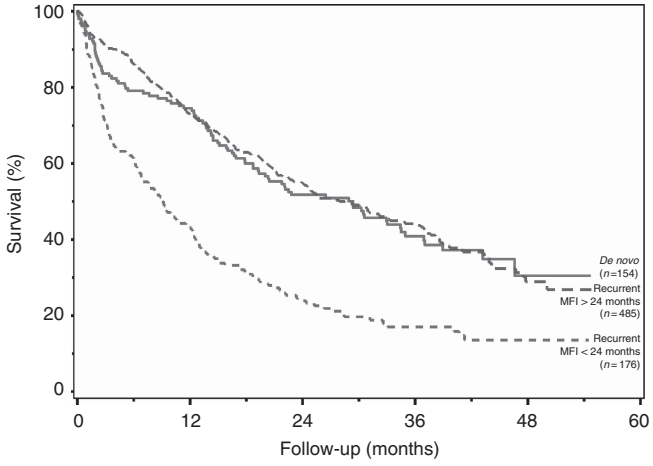

Figure 1. Survival after diagnosis of metastatic breast cancer for patients with *de novo* metastatic breast cancer and recurrent metastatic breast cancer with MFI <24 months and recurrent metastatic breast cancer with MFI >24 months.

In this analyses, prognostic factors that influenced survival besides MFI were age at diagnosis of metastatic breast cancer, HR and HER2 status and initial site of metastases. This is in accordance with other studies investigating prognostic factors in metastatic breast cancer (Andre *et al*, 2004; Largillier *et al*, 2008; Dawood *et al*, 2010b; Lobbezoo *et al*, 2013). As expected, we found a favourable impact of HR-positive breast cancer, with a hazard ratio of 0.57 ($P<0.0001$) compared with HR-negative breast cancer in our cohort, which is similar to that found in a large study on survival between *de novo* and recurrent metastatic breast cancer (Dawood *et al*, 2010b). Hormone receptor-positivity is a known favourable prognostic factor as well as a predictive factor for response to endocrine therapy. The hazard ratio as calculated in our model is not only reflecting the favourable prognostic influence but also the strong predictive influence for response to endocrine therapy.

The strength of this study is the incorporation of HER2 status, due to a very low rate of missing results for HER2 status (only 2%) because all missing HER2 results were centrally determined whenever possible. Interestingly, HER2 positive breast cancer was found to have a favourable influence on outcome of metastatic breast cancer. Even though in the pretrastuzumab era, the amplification of HER2 in breast cancer was demonstrated to be a strong unfavourable prognostic factor (Slamon *et al*, 1987). However, with the availability of anti-HER2 therapy this unfavourable prognostic factor has also become a favourable predictive factor for response to anti-HER2 therapy. And with the implementation of anti-HER2 therapy, outcome of HER2-positive breast cancer has changed to the extent that HER2-positive status is nowadays a prognostic factor associated with a favourable outcome in breast cancer (Dawood *et al*, 2010a; Lobbezoo *et al*, 2013). Numbers were too low to look at outcome of biological subtypes based on HR and HER2 in the three separate subgroups, but previous studies investigated differences in outcome between HER2-positive *de novo* metastatic breast cancer and HER2-positive recurrent metastatic breast cancer. In an unplanned analysis from the registHER observational study, a better survival was found for patients with HER2 positive *de novo* metastatic breast cancer compared with patients with HER2-positive recurrent metastatic breast cancer (Yardley *et al*, 2014). This difference in survival was seen regardless of adjuvant systemic therapy for patients with recurrent breast cancer. However, only 9% of patients with HER2-positive recurrent breast cancer had received anti-HER2 therapy in

Table 2. Multivariable analysis for survival after diagnosis of metastatic breast cancer

	All patients			Patients without (neo)adjuvant systemic therapy		
	n = 815			*n* = 318		
	Hazard ratio	95% CI	*P*-value	Hazard Ratio	95% CI	*P*-value
Recurrent with MFI <24 months *vs de novo*	1.97	1.49–2.60	<0.0001	1.69	1.11–2.58	0.015
Recurrent with MFI >24 months *vs de novo*	0.89	0.70–1.14	0.358	0.89	0.64–1.24	0.498
Age at diagnosis of metastatic breast cancer	1.02	1.01–1.02	<0.0001	1.02	1.00–1.03	0.008
Hormone receptor negative *vs* positive	1.74	1.40–2.17	<0.0001	2.21	1.58–3.11	<0.0001
HER2 negative *vs* positive	1.44	1.13–1.83	0.003	1.27	0.88–1.86	0.207
Visceral metastases as initial metastatic site *vs* bone	1.80	1.41–2.31	<0.0001	1.56	1.03–2.36	0.037
Brain metastases as initial metastatic site *vs* bone	2.31	1.40–3.80	0.001	4.50	1.49–13.64	0.008
Skin/lymph nodes as initial metastatic site *vs* bone	1.06	0.71–1.59	0.783	1.37	0.71–2.67	0.350
Multiple initial metastatic sites *vs* 1 metastatic site	2.30	1.81–2.93	<0.0001	2.66	1.83–3.87	<0.0001

Abbreviations: CI = confidence interval; MFI = metastatic-free interval.

adjuvant setting. Another study investigating the outcome of patients with HER2-positive *de novo* metastatic breast cancer did not demonstrate a difference in outcome compared with patients with HER2-positive recurrent metastatic breast cancer (Rossi *et al*, 2014).

Besides low number of patients when dividing the total cohort according to biological breast cancer subtype, there are other limitations of this study owing to its retrospective nature. Lead-time bias due to improved imaging could be a confounder in this study. However, all patients were diagnosed with metastatic breast cancer (either *de novo* or recurrent) during the same recent and relatively short time period so the availability of imaging techniques was probably equal. Even so, with the inclusion of all patients with metastatic breast cancer diagnosed in eight different hospitals we feel this cohort is a good representation of the actual diagnosis and treatment of patients with metastatic breast cancer in the Netherlands. With the availability and implementation of more advanced and sensitive diagnostic techniques, for example, positron emission tomography, the subgroup of patients with *de novo* metastatic breast cancer will probably increase. Therefore, prognostic information on this subgroup is of relevance for oncology practice.

In conclusion, we confirm that MFI is a strong prognostic indicator for outcome of metastatic breast cancer patients, with a short MFI being prognostic unfavourable. However, *de novo* metastatic breast cancer, which can be considered as a group with a 'very short' MFI was not found to be a very poor prognostic subgroup. In real life, patients with *de novo* metastatic breast cancer had a clearly better outcome, similar to what was seen in patients with metastatic breast cancer with MFI >24 months, compared with patients with MFI <24 months who had a nearly two-fold increased mortality risk.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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