Chapter 2

Unfavourable pattern of metastases in M0 breast cancer patients during 1978-2008: a population-based analysis of the Munich Cancer Registry

C.J.G. van den Hurk, R. Eckel, L.V. van de Poll-Franse, J.W.W. Coebergh, J.W.R. Nortier, D. Holzel, W.P.M. Breed, J. Engel

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Abstract

Purpose

Little is known about time trends in metastases in patients treated in routine health care facilities without metastases at diagnosis (M0) and about survival after these metastases.

Methods

Data on 33,771 M0 patients with primary breast cancer diagnosed between 1978 and 2003 were obtained from the Munich Cancer Registry. Survival analyses were restricted to patients with metastases within 5 years of the initial diagnosis.

Results

The incident number of patients approximately doubled each period and 5-year overall survival increased from 77% in the first to 82% percent in the last period. 5490 (16%) M0 patients developed metastases within 5 years after the initial diagnosis. The hazard of developing metastases was lowest in the most recent period compared to the first period (HR=0.50, p<0.001). The hazard of dying after metastases was equal for patients diagnosed between 1978-1984 and 1995-2003 (HR 1.08, p=0.3). The percentage of patients that developed bone metastases decreased each time period, but the percentage primary liver and CNS metastases increased. Exclusion of site of metastases in the multivariate analysis led to a 20% (p=0.02) higher hazard of dying following metastases in the last versus the first period.

Conclusions

In the period 1978-2008, unfavourable changes in the pattern of metastases were exhibited and no improvement was observed in survival of patients after occurrence of metastases. An explanation might be the increased use of adjuvant systemic treatment, which has less effect on the highly lethal liver and CNS metastases than on bone metastases. The increased use also appeared to contribute to the overall prevention of metastases in breast cancer and therefore to improve overall survival.

2

Introduction

The prevalence of breast cancer patients without metastases at diagnosis (M0) has increased in industrialised countries. This increase can be explained by the rising incidence and decreasing overall mortality rate of breast cancer[1-4], which is attributed to earlier detection and therefore advantageous stage distribution, and improvements in treatment.[1] The early detection is largely due to breast cancer screening, developments in imaging and higher awareness of the disease amongst women. One would expect that these developments would influence the occurrence of metastases at diagnosis and in follow-up.

The reported percentage of M0 patients with metastases in follow-up is 20%-30%.[3] The proportion of patients with metastases at initial diagnosis (M1) remains stable at about 5%[1,5] or decreases minimally.[6] In M1 patients, pattern of metastases and survival are frequently described, but the progression patterns and time trends of occurrence of metastases after initial treatment in M0 patients are seldom investigated. The objective of this study was to describe the incidence of metastases and survival after metastases in M0 breast cancer patients since 1978. Therefore, this study will provide knowledge about the level of progress in medical management of metastases in these patients. Data were obtained from the Munich Cancer Registry (MCR), which uniquely documents metastases during follow-up.[7]

Patients and methods

Study population and data collection

Data on breast cancer patients diagnosed in the period 1978-1984, 1985-1994 and 1995-2003 were obtained from the population-based MCR. The MCR has in the last period a catchment area of 2.5 million residents (since 2002 3.9 million residents) and records data on all patients newly diagnosed with cancer.[8,9] The unequal subdivision into time periods of initial diagnosis marks steps in the changes from a hospital-based (up to 1984) to a population-based registry of Munich and surrounding areas. The MCR is for breast cancer population based since 1994, when the pathologists of the region started structural cooperation with the MCR. Data on primary diagnosis and progression were provided by the hospitals in the Munich region by means of tumour-specific reporting forms, doctors' letters and pathology reports and nowadays also through online documentation. Diagnosis of metastases was based on radiological imaging, physical evaluation or histological examination in regular oncological follow-up. Life status information was obtained from the population registration offices and death certificates until October 1, 2007 and is complete for more than 90% of the patients.[7] In the Munich catchment area screening for breast cancer has increased over time since the beginning of the 1990s, was initially opportunistic and at the end widespread, before programmed screening was started in 2004.

Between 1978 and 2003, the MCR registered 36,002 female patients diagnosed with primary invasive breast cancer. The data set did not include patients with secondary malignancies or sarcomas or with only a death certificate. Follow-up was complete up to October 30, 2008.

Statistical analysis

Statistical analyses included time to metastases within 5 years of initial diagnosis and survival following the first metastasis amongst patients who developed a metastasis within 5 years of

initial diagnosis. Metastases were included in the analyses grouped by the most frequent sites of occurrence or combinations of these specific sites. These combinations were independent of sequence of metastatic sites and synchronous or metachronous detection and were only inserted if no additional metastases were present at rarer sites. Loco regional skin or lymph node recurrences were excluded. Event-free patients were censored on October 30, 2008 and patients who were lost to follow-up at their last date of contact. Survival times, time to metastases, and survival after metastases were described with the Life-Table method and tested with the log-rank test. For determining the importance of the independent variables Cox proportional hazards regression models were used, in which missing values were recoded into dummy variables. The enclosed variables were: period of diagnosis, age, tumour size (pT), lymph node status (pN), grade, receptor status and histological type. Analyses regarding time to metastases also included resection margins, initial radiotherapy and systemic therapy. Additional variables for survival following metastases were time to metastases and site(s) of metastases. When evaluating the proportional hazard assumption of the main objective of this study, namely period of diagnosis, the graphs of the survival function versus the survival time yielded parallel curves as did the graphs of the log[-log(survival)] versus log of survival time.

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

Results

General characteristics of M0 patients

The MCR comprised 33,771 M0 patients and 2231 (6%) M1 patients who were diagnosed with breast cancer between 1978 and 2003. For M0 patients, median follow-up time for patients alive or lost to follow-up ranged from 177 months in the period 1985-1994 (50% of patients were deceased on October 1, 2008) to 80 months in 1995-2003 (25% of patients were deceased on October 1, 2008) (Table 1). The incident number of patients approximately doubled each period and during follow-up 8183 (24%) patients developed a metastasis after M0 at diagnosis, 5490 (67%) of whom within 5 years of initial diagnosis. An increase in 5-year overall survival was observed for the last period (77% vs. 76% vs. 82%, $p<0.0001$) (Figure 1).

In time, the observed proportion of patients diagnosed with pT1 and lymph node-negative tumours increased, as did the proportion of older women (70+) (Table 1). About 80% of patients had a tumour of the ductal type and positive estrogen (ER) or progesterone (PR) receptors. Unknown receptor status decreased considerably from the second (46%) to the third study period (16%), whilst the ratio of positive to negative receptors hardly changed. The proportion of patients who underwent mastectomy decreased from 98% in the first to 35% in the last period and systemic treatment was used more often in recent periods (22% vs. 44% vs. 70%). A decrease in the proportion of patients undergoing radiotherapy was seen in period 1985-1994.

Table 1. Characteristics of M0 patients with breast cancer according to period of initial diagnosis (n=33,771).

Characteristic	Period of initial diagnosis						p-value
	1978-1984 (n=4978)		1985-1994 (n=10,201)		1995-2003[b] (n=18,592)		
	n	%[a]	n	%[a]	n	%[a]	
Median FU time after initial diagnosis of patients alive or lost to FU (mo)	148		177		80		<0.0001
Deceased (1 Oct. 2008)	2893	(58)	5123	(50)	4571	(25)	<0.0001
M0 at diagnosis, metastasis in FU	1785	(36)	2999	(29)	3399	(18)	<0.0001
M0 at diagnosis, metastasis within 5 years of FU	798	(16)	1159	(11)	1952	(10)	<0.0001
Age (yrs)							
<50	1909	(38)	3522	(35)	4649	(25)	
50 -69	2380	(48)	4731	(46)	9540	(51)	
70+	689	(14)	1948	(19)	4403	(24)	<0.0001
pT							
T1	978	(43)	4155	(47)	9358	(55)	
T2	958	(42)	3524	(40)	6224	(37)	
T3	202	(9)	436	(5)	723	(4)	
T4	149	(6)	693	(8)	747	(4)	<0.0001
Unknown	2691	(54)	1393	(14)	1545	(8)[c]	
pN							
Negative	1071	(48)	4413	(52)	9649	(59)	
Positive	1142	(52)	4114	(48)	6682	(41)	<0.0001
Unknown	2765	(56)	1674	(16)	2261	(12)	
Histological type							
Ductal	3533	(82)	7445	(80)	13,970	(78)	
Lobular/Mixed	419	(10)	1486	(16)	3678	(21)	
Other/n.o.s.	363	(8)	346	(4)	276	(1)	<0.0001
Unknown	663	(13)	924	(9)	668	(4)	
Grade							
1	-	-	485	(6)	1902	(11)	
2	-	-	4440	(58)	9311	(53)	
3+4	-	-	2748	(36)	6206	(36)	<0.0001
Unknown	-	-	2528	(25)	1173	(6)	
Receptor status (ER or PR)							
Positive	-	-	4336	(79)	13,120	(84)	
Negative	-	-	1140	(21)	2577	(16)	<0.0001
Unknown	-	-	4725	(46)	2900	(16)	

Table 1. continues on next page

Initial surgery							
Lumpectomy	49	(2)	2660	(39)	10,835	(65)	
Mastectomy	1920	(98)	4248	(61)	5841	(35)	<0.0001
Unknown/ Other[d]	3009	(60)	3293	(32)	1916	(10)	
Initial radiotherapy	2729	(59)	4534	(44)	10,910	(59)	<0.0001
Resection margins							
Negative	-	-	2923	(29)	12,833	(69)	
Positive	-	-	152	(1)	590	(3)	
Unknown	-	-	7126	(70)	5169	(28)	<0.0001
Initial systemic treatment							
Chemotherapy	673	(13)	1959	(19)	4345	(23)	
Hormonal therapy	375	(8)	2324	(23)	6271	(34)	
Both	59	(1)	217	(2)	2394	(13)	
No	3871	(78)	5701	(56)	5582	(30)	<0.0001

FU=follow-up, n.o.s.= not otherwise specified, ER=estrogen receptor, PR=progesterone receptor

[a] percentage of sub-categories related to the sum of each item with available data; missing values not taken into account

[b] the population based cohort

[c] pT missing in 4% out of 8% because of neo-adjuvant systemic therapy

[d] no differentiation for surgical method in the 1970's and early 1980's. 'Other' is for example surgery following neo-adjuvant systemic therapy

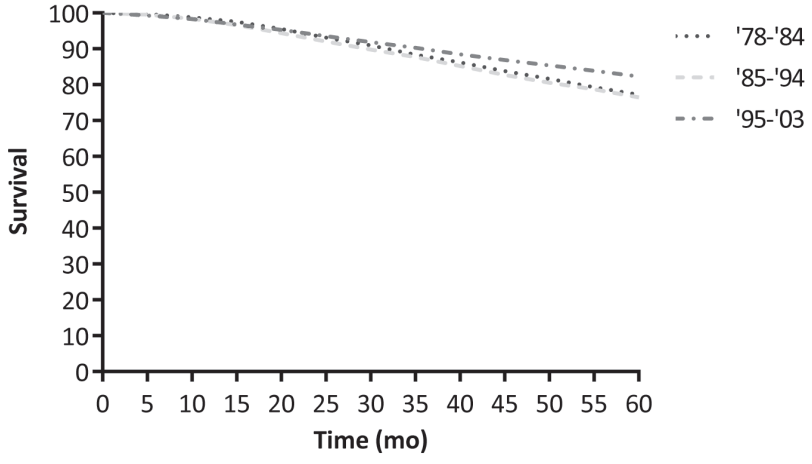

Figure 1. 5-year overall survival of M0 breast cancer patients diagnosed between 1978 and 2003 (n=33,771).

Patterns of metastases

In the cohort of 5490 M0 patients with metastases within 5 years of initial diagnosis, 59% developed the first metastasis within 2.5 years (Table 2). Overall 56% of the patients developed metastases at 2 or more sites and the proportion of metachronously diagnosed metastases increased in time from 66 to 82%. The proportion of bone metastases declined (69% vs. 62% vs. 47%) whilst the proportion of liver, central nervous system (CNS) and less common occurring sites of metastases increased. In time, trends were comparable for the first detected metastases. In the first period, 85% of patients died within 5 years of the first metastases versus 95% in the last period. Of patients alive or lost to follow-up, median follow-up was 29 months in the first period, 11 months in 1985-1994 and 50 months in 1995-2003. The patients who developed metastases within 5 years had a positive lymph node status at initial diagnosis more often and had a higher pT status than M0 patients in general.

Time from diagnosis to first metastasis

The proportion M0 patients who developed metastases within 5 years of initial diagnosis declined significantly from 27% in 1978-1984 to 15% in 1995-2003 ($p<0.0001$) (Figure 2a). Overall, the risk of occurrence of metastases was highest in the first 2.5 years of initial diagnosis (65% vs. 60% vs. 56%), as also indicated by the steepness of the curves in Figure 3. For the specified metastatic sites, only small differences emerged in time to detection during 5 years of follow-up, except for skin metastases that appeared later. Detection of metastases occurred within 5 years of initial diagnosis in 76% of patients who developed a combination of bone, liver and lung metastases and in 52% of patients with skin metastases only.

The hazard of developing metastases within 5 years of diagnosis was lowest in the most recent period (HR=0.50, $p<0.001$) (Table 3). A positive receptor status (HR=0.61, $p<0.001$) and the combination of chemotherapy and hormonal therapy (HR=0.69, $p<0.001$) were associated with a lower risk of metastases. Age and radiotherapy were not significantly associated with the occurrence of metastases within 5 years.

Time from first metastasis to death

If only the death certificate or a post mortem report indicated metastases, the date of first metastasis was similar to the date of death and these patients were excluded from survival analyses (n=6251).

In M0 patients with metastases within 5 years of initial diagnosis, 5-year actuarial survival rates after occurrence of first metastasis decreased and differed significantly between the time periods (17% vs. 12% vs. 8%, $p=0.0001$) (Figure 2b).

Multivariate regression analysis showed that patients who developed a metastasis within 5 years of diagnosis in the period 1985-1994 had a 20% increased hazard of dying compared to those in 1978-1984 and 1995-2003; this first and last period showed no difference in survival (Table 4). However, when site of metastases was removed from the model, then the hazard ratios became 1.24 ($p=0.003$) and 1.21 ($p=0.02$) for the last two periods. Mortality risk increased with the increase in age and a higher pT, positive lymph nodes and differentiation grade. The hazard of dying for patients with metastases was 35% lower for receptor status-

positive patients and decreased 7% in each additional year between initial diagnosis and first metastasis.
Prognosis for patients after metastases varied for the site(s) of metastasis (Table 3). Up to 5 years after detection of metastases, patients with bone metastases or skin metastases alone exhibited best survival (Figure 5). From 5 to 10 years, skin alone and distant lymph node alone had best prognosis up to 10 years after detection of metastases (data not shown).

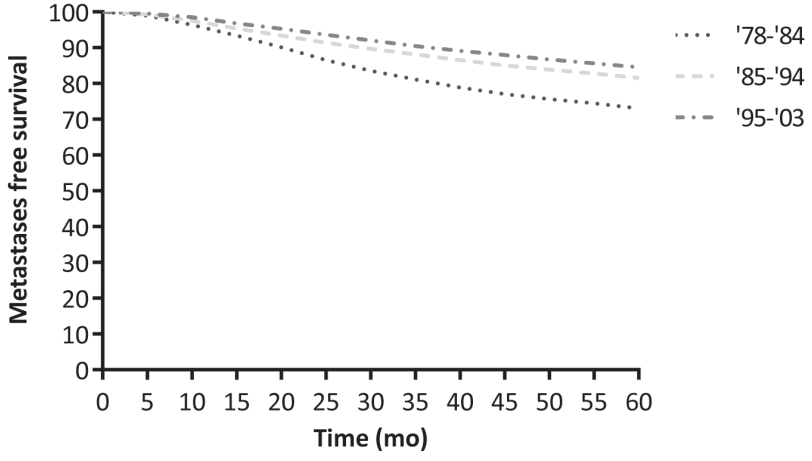

Figure 2a. 5-year actuarial rate of occurrence of first metastases in M0 breast cancer patients according to period of diagnosis of initial tumour.

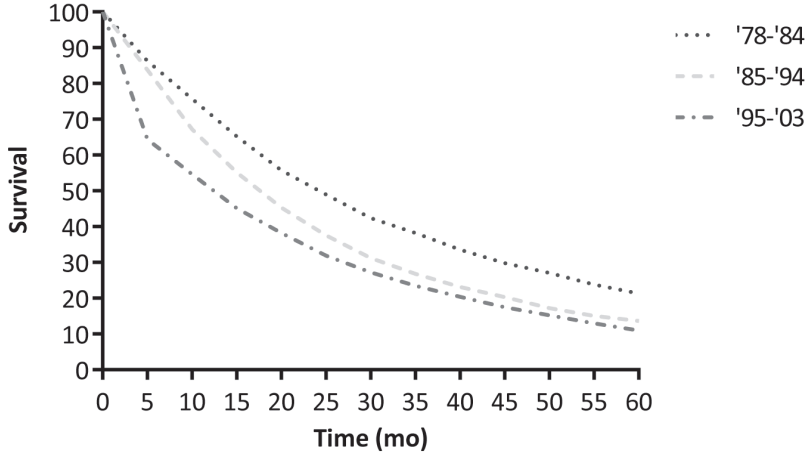

Figure 2b. Survival following first metastasis in M0 breast cancer patients who developed metastasis within 5 years of diagnosis according to period of diagnosis of initial tumour.

Table 2. Characteristics of M0 breast cancer patients with first metastasis within 5 years of initial diagnosis, according to period of initial diagnosis (n=5490)

Characteristic	Period of initial diagnosis						p-value
	1978-1984 (n=1214)		1985-1994 (n=1677)		1995-2003 (n=2599)		
	n	%	n	%	n	%	
Metastasis within 2.5 years	791	(65)	999	(60)	1449	(56)	<0.0001
Deceased within 5 years of first metastasis	1031	(85)	1484	(88)	2464	(95)	<0.0001
Median FU time after initial diagnosis of patients alive or lost to FU (mo)	29		11		50		<0.0001
Multiple synchronous	603	(50)	862	(51)	1592	(61)	<0.0001
Multiple metachronous	399	(66)	637	(74)	1300	(82)	<0.0001
Metastatic sites at first progression/ all metastases during follow-up[a]							
Bone	719 (60) /	838 (69)	881 (53) /	1047 (62)	980 (38) /	1226 (47)	
Lung	286 (24) /	376 (31)	372 (22) /	533 (32)	514 (20) /	783 (29)	
Liver	168 (14) /	286 (24)	266 (16) /	484 (29)	587 (23) /	961 (35)	
CNS	55 (5) /	123 (10)	81 (5) /	232 (14)	265 (10) /	630 (22)	
Skin	92 (8) /	149 (12)	109 (7) /	177 (11)	171 (7) /	290 (11)	
Distant lymph node	74 (6) /	104 (9)	189 (11) /	273 (16)	284 (11) /	413 (15)	
Other	164 (14) /	287 (24)	219 (13) /	427 (25)	630 (24) /	1267 (51)	
Total	1558 /	2163	2117 /	3173	3431 /	5579	
Mean number of metastases per patient	1.28 /	1.78	1.26 /	1.89	1.32 /	2.14	
Age (yrs)							<0.0001
<50	506	(42)	653	(39)	723	(28)	
50 -69	576	(47)	794	(47)	1245	(48)	
70+	132	(11)	230	(14)	631	(24)	

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pT							0.0004
T1	132	(28)	411	(29)	612	(28)	
T2	234	(49)	688	(49)	1118	(51)	
T3	72	(15)	122	(9)	213	(10)	
T4	40	(8)	184	(13)	234	(11)	
Unknown (%)	736	(61)	272	(16)	422	(16)	
pN							0.9
Negative	137	(30)	433	(31)	650	(31)	
Positive	320	(70)	949	(69)	1463	(69)	
Unknown (%)	757	(62)	295	(18)	486	(19)	
Receptor status (ER or PR)							0.7
Negative	-	-	228	(29)	605	(30)	
Positive	-	-	562	(71)	1441	(70)	
Unknown (%)	-	-	887	(53)	553	(21)	

FU= follow-up, M0=no metastases at diagnose, CNS= central nervous system, ER=estrogen receptor, PR=progesterone receptor

[a] Since one patient can have more than one site of metastasis, percentages are more than 100%

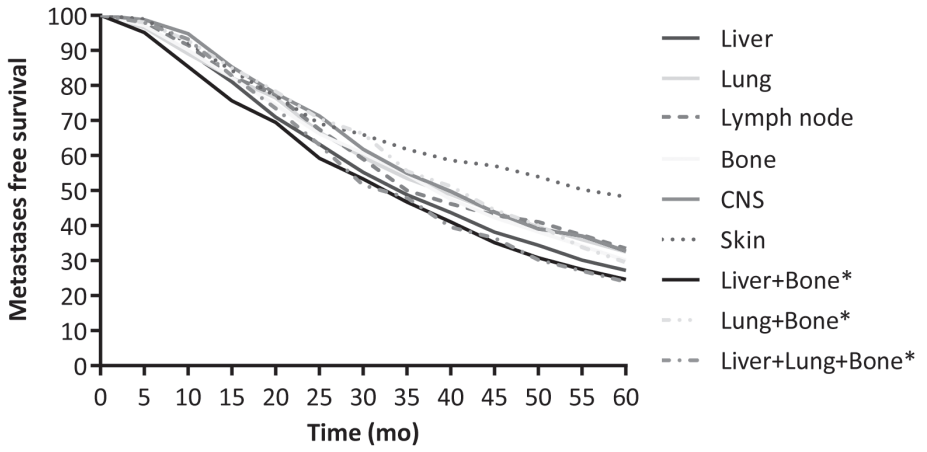

Figure 3. Time from diagnosis of primary tumour to first metastasis at the most common single sites and combinations of sites in M0 breast cancer patients with metastases.

CNS= central nervous system
*Independent of sequence of detection per site, synchronous or metachronous, no additional metastases at other sites

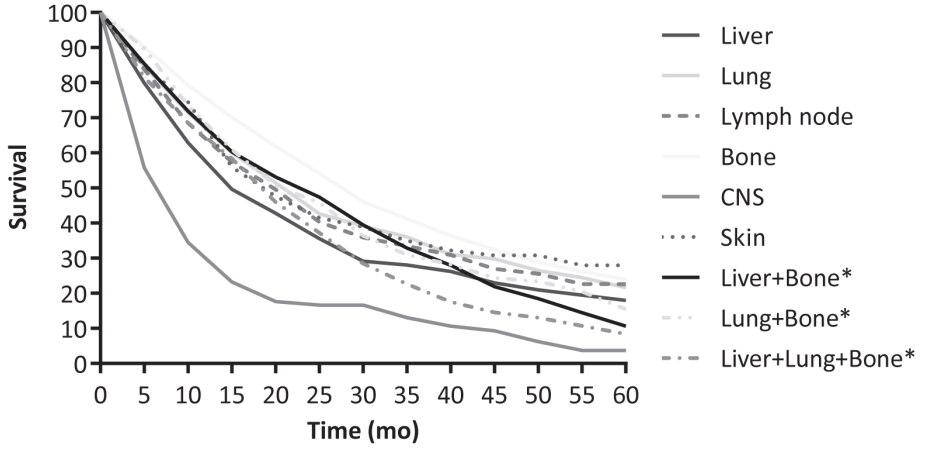

Figure 4. 5-Year survival after first metastasis in most common single sites and combinations of sites of metastases in M0 breast cancer patients with metastases within 5 years of diagnosis.

CNS= central nervous system
*Independent of sequence of detection per site, synchronous or metachronous, no additional metastases at other sites

Table 3. Determinants of time to first metastasis in M0 breast cancer patients, within 5 years of initial diagnosis.

Characteristics[b]	HR Univariate	HR[a] Multivariate	95% CI	p-value
Period of diagnosis				
1978-1984	1.00	1.00	-	
1985-1994	0.67	1.15	(0.98-1.35)	0.09
1995-2003	0.39	0.50	(0.42-0.61)	<0.0001
Age (yrs)				
<50	1.00	1.00	-	
50-69	0.83	0.98	(0.89-1.07)	0.7
70+	0.82	0.98	(0.85-1.12)	0.7
pT				
T1	1.00	1.00	-	
T2	1.60	1.80	(1.63-2.00)	<0.0001
T3	2.21	1.84	(1.58-2.15)	<0.0001
T4	2.98	2.32	(1.99-2.70)	<0.0001
pN				
Negative	1.00	1.00	-	
Positive	3.29	2.11	(1.91-2.34)	<0.0001
Grade				
1	1.00	1.00	-	
2	6.20	3.60	(2.37-5.46)	<0.0001
3/4	12.96	5.21	(3.43-7.91)	<0.0001
Receptor status (ER/PR)				
Negative	1.00	1.00	-	
Positive	0.40	0.61	(0.55-0.69)	<0.0001
Histological type				
Ductal	1.00	1.00	-	
Lobulair	0.62	0.90	(0.79-1.02)	0.1
Other	1.42	1.11	(0.90-1.38)	0.3
Resection margins				
Negative	1.00	1.00	-	
Positive	1.84	1.37	(1.08-1.73)	0.009
Unknown	2.48	1.59	(1.22-2.07)	0.0006
Initial radiotherapy	0.75	0.94	(0.86-1.02)	0.1
Initial systemic therapy				
No	1.00	1.00	-	
Chemotherapy	1.01 (NS)	0.95	(0.85-1.06)	0.4
Hormonal therapy	0.50	0.92	(0.81-1.04)	0.2
Both	0.47	0.69	(0.59-0.82)	<0.0001

HR= hazard ratio, 95% CI= 95% confidence interval, ER= estrogen receptor, PR=progesterone receptor, NS= not significant

[a] variables included if univariately significantly associated

[b] pT n=1867 missing, pN n=1959 missing, Differentiation grade n=2193 missing, Receptor status n=3046 missing, Resection margins n=4391 missing, Histological type n=533 missing

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Discussion

In the period 1978-2008, the hazard of developing metastases during follow-up decreased markedly and overall survival improved amongst women diagnosed with M0 breast cancer. Concurrently, we observed a change in the anatomic pattern of metastasis, without improvement in survival after occurrence of these metastases. There might be several explanations for our observations.

We attribute the generally improved survival of M0 patients in the last period to adjuvant, especially hormonal, treatment which was routinely administered at that time. In addition, patients recorded by the MCR showed advantageous stage distribution over the periods, which also contributed to improved prognosis. Time from initial diagnosis to metastasis is prolonged for pT1 versus pT2[8], but changes in adjuvant systemic treatment will also have lengthened the time.[10,11] The adjuvant treatment prevents the development of metastases or at least postpones it. However, if dormant tumour cells start growing again, whether due to resistance against the continued systemic therapy or not, then the survival time of the metastasized patients remained as poor as before. Over time, the proportional anatomic distribution of metastasis shifted from bone, with long survival times, towards CNS and liver, which are much more lethal. This shift has also been reported by others, but only for the first site of metastasis.[12] The increased use of hormonal treatment might cause the shift since ER-positive tumours tend to metastasize to bone; ER and PR negativity are commonly associated with visceral metastases, especially liver and CNS.[13-18] The increased proportion of CNS metastases might also reflect improvement in adjuvant systemic treatment; CNS is regarded as a sanctuary site that is less affected by most therapeutics than other sites.[19] In this study liver metastases, alone or in combination, occurred earliest during follow-up and were like CNS metastases, the most lethal. So, the largest benefit in the survival of patients with breast cancer will most likely come from the prevention and better treatment of CNS and liver metastases. In patients with over expression of HER2 major improvements have been reached with trastuzumab[20] and recently lapatinib.[21,22] Bisphosphonates of the third generation seem to have also an anti-tumour effect in the adjuvant setting.[23] In addition poly[adenosine diphosphate (ADP)-ribose] polymerase (PARP) inhibitors are likely to be beneficial for patients with triple-negative tumours.[24] Therefore, the incidence and pattern of metastases will change further in the future. Overall, sites of metastases appeared to contribute largely to the period effect, since exclusion of site of metastases in the multivariate analysis increased the mortality hazard ratio for the last versus the first period to 21%. Unfortunately, no information was available about the type of treatment of the metastasized cancer in the MCR region.

The worse outcome after occurrence of metastases in patients without metastasis at diagnosis might be related to less sensitive tumour cells that developed resistance after adjuvant systemic therapy. This is supported by recent observations of M1 patients who, in particular when the primary tumour had been removed completely, had a more favourable prognosis compared to M0 patients with subsequent metastases.[13,25-28] However, contradictory results have been reported of M1 patients, who sometimes had worse survival compared to M0 patients who developed metastases in follow-up.[29-32]

Table 4. Determinants of survival after first metastasis in M0 breast cancer patients with metastases within 5 years during follow-up.

Characteristics[a,b]	HR Univariate	HR[c] Multi variate	95% CI	p-value	HR Multi variate	95% CI	p-value
Period of diagnosis							
1978-1984	1.00	1.00	-		1.00	-	
1985-1994	1.31	1.24	(1.08-1.43)	0.003	1.20	(1.04-1.38)	<0.01
1995-2003	1.38	1.21	(1.04-1.40)	0.02	1.08	(0.93-1.26)	0.3
Age (yrs)							
<50	1.00	1.00	-		1.00	-	
50-69	1.13	1.12	(1.04-1.22)	0.004	1.14	(1.05-1.24)	0.001
70+	1.58	1.51	(1.34-1.69)	<0.0001	1.57	(1.40-1.75)	<0.0001
pT							
T1	1.00	1.00	-		1.00	-	
T2	1.20	1.14	(1.05-1.25)	0.003	1.14	(1.04-1.24)	0.004
T3	1.26	1.19	(1.04-1.37)	0.01	1.19	(1.04-1.36)	0.01
T4	1.46	1.23	(1.07-1.41)	0.003	1.22	(1.06-1.40)	0.004
pN							
Negative	1.00	1.00	-		1.00	-	
Positive	1.29	1.21	(1.12-1.32)	<0.0001	1.22	(1.13-1.33)	<0.0001
Grade							
1	1.00	1.00	-		1.00	-	
2	1.70	1.70	(1.21-2.40)	0.002	1.64	(1.17-2.31)	0.005
3/4	2.39	2.17	(1.54-3.06)	<0.0001	2.05	(1.46-2.89)	<0.0001
Receptor status (ER/PR)							
Negative	1.00	1.00	-		1.00	-	
Positive	0.58	0.62	(0.56-0.69)	<0.0001	0.65	(0.59-0.72)	<0.0001

Table 4. continues on next page

Characteristics[a,b]	HR Univariate	HR[c] Multi variate	95% CI	p-value	HR Multi variate	95% CI	p-value
Histological type							
Ductal	1.00	-			-		
Lobular	0.93 (NS)	-			-		
Other	1.03 (NS)	-			-		
Time to first metastasis[d]	0.91	0.93	(0.91-0.96)	<0.0001	0.93	(0.90-0.96)	<0.0001
Site(s) of Metastases							
Bone alone	1.00	-			1.00	-	
Liver alone	1.39	-			1.38	(1.15-1.67)	<0.0008
Lung alone	1.09 (NS)	-			1.20	(0.97-1.47)	0.1
CNS alone	3.16	-			2.81	(2.20-3.57)	<0.0001
Skin alone	1.01 (NS)	-			0.97	(0.71-1.33)	0.9
Distant lymph nodes alone	1.13 (NS)	-			0.94	(0.72-1.23)	0.6
Liver, Bone	1.38	-			1.50	(1.25-1.79)	<0.0001
Lung, Bone	1.28	-			1.18	(0.92-1.50)	0.2
Bone, Liver, Lung	1.66	-			1.67	(1.33-2.10)	<0.0001

HR= hazard ratio, 95% CI= 95% confidence interval, ER= estrogen receptor, PR=progesterone receptor, NS= not significant, CNS= central nervous system

[a] variables included if they were univariate significantly associated

[b] pT n=1334 missing, pN n=1413 missing, Grade n=1720 missing, Receptor status n=2379 missing, site of metastases 'Other' n=2646

[c] HR when site of metastases is excluded

[d] in years

Higher incidence of more aggressively growing tumours might be an additional explanation of the unimproved survival after metastases, since the increasing use of breast cancer screening mainly eliminates the slowly growing tumours. This is also reflected by the highly significant relationship between time to first metastasis and survival after occurrence of metastases, which remained after correction for period of diagnosis and site(s) of metastases. More aggressive growth might also be partly attributed to the lack of effective therapies for aggressive subtypes of breast cancer, such as triple negative, non-basal and basal-like subtypes.[33] These subtypes are known to influence the growth rate, site of metastases, time to occurrence and survival after metastases.[12,34] In this study, the majority of metastases became manifest within 2.5 years of initial diagnosis, as observed by others.[11,13,35,36]

The MCR hosts unique data on clinically evident metastases in follow-up, but the prevalence of metastases in the MCR is slightly underdocumented. Surgically treated and histopathologically confirmed metastases are obtained from pathology reports and are therefore nearly complete. However, not histopathologically confirmed metastases will be documented in about 70% of cases, based on estimations of tumour-specific survival and relative survival that should equalize the proportion of metastases.[7,37] Some of the metastases are likely to remain unreported by physicians to the MCR and some might never be detected because there were no clinical manifestations before death. The MCR's completeness is difficult to check with literature, whilst proportions of metastatic sites in breast cancer vary considerably, both within clinical and within autopsy studies.[18,26,38-43] Only a few studies were population based, and the subdivision of metastatic sites and follow-up times differed. The most adequate comparisons should be based on patients with breast cancer as the cause of death. It is likely that for the period 1995-2003, data on metastases in the MCR were more complete and most representative, whilst at that time the database became approximately population based. In time, methods of detection have improved and indications for diagnostics have changed, as exhibited by the decreased proportion of missing data on pT, pN and receptor status. In addition, the last period showed an increased number of metastases per patient, as well as increased detection of metastases at rarer sites. Nevertheless, the observed change in pattern of metastases can be considered to be a mirror for general specialised care in a variety of hospitals, whilst there were no systematic or specific diagnostics for metastases in the MCR region.

In conclusion, the enhanced use and extensive developments in systemic treatment of patients with breast cancer might have prevented development of metastases in breast cancer. It changed the anatomic distribution of sites of metastases, but did not improve survival after occurrence of metastases. The most important reason seems to be the shift from bone metastases towards CNS and liver metastases. Furthermore, there might have been a natural selection of more aggressively growing tumours in the recent period. So, at the time metastases became manifest, treatment possibilities remained insufficient, at least up to 2008. It seems that therapies for liver and CNS metastases might yield the largest gains in survival of M0 breast cancer patients. And finally, changes in patterns of metastases as a result of new treatments, illustrate the importance of including registration of metastases and secondary treatment in cancer registries. They can be used to study long term effects in the population and the usefulness of new treatment strategies.

2

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