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Trends in the prognosis of patients with primary metastatic breast cancer diagnosed between 1975 and 2002

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Summary   We performed a population-based study, including 1089 patients with primary metastatic breast cancer, diagnosed in South-East Netherlands between 1975 and 2002, and tried to give an answer to the question if prognosis of this patient group has improved or not. Follow-up was completed until 1 January 2005.

The median survival times for patients with primary metastatic disease were 18, 17 and 20.5 months for patients diagnosed in the periods 1975–1984, 1985–1994 and 1995–2002, respectively. A multivariate analysis, including age, tumour size and information on the localization of metastatic disease and the number of metastatic sites, showed that patients diagnosed in the period 1995–2002 had a 18% lower death risk (95% confidence interval 5–30) compared to those diagnosed in the period 1985–1994.

These data show that the prognosis of patients with primary metastatic breast cancer remained unchanged between 1975 and 1994 and that some progress has been made after 1994.

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Introduction

In the western world, about 11% of all women will develop breast cancer. This percentage has increased through the years, partly due to mammographic screening. About 3–10% of all breast cancer patients have distant metastases at initial presentation,[1–4] and this proportion has decreased only slightly during the last three decades.[5,6] In the same period, the treatment of metastatic breast cancer has undergone considerable changes, starting with the introduction of chemotherapy in the sixties and seventies, tamoxifen in the eighties, taxanes and aromatase inhibitors and trastuzumab in the second half of the nineties and later. Despite the continuing developments in the treatment of metastatic breast cancer it has been difficult to demonstrate the impact on survival rates in daily practice, with some being unable to demonstrate an improvement in survival after the introduction of systemic treatment,[7–9] and others being positive for a survival difference favoring the patients treated more recently.[10,11] All these studies were conducted in patients with recurrent metastatic breast cancer and not in patients with primary metastatic disease. Such studies are vulnerable to bias, as patients diagnosed with metastatic disease in more recent years tend to have a longer disease-free interval, which is associated with a better prognosis. Unfortunately, only few studies have addressed the trends in prognosis of patients with primary metastatic breast cancer.[12–14] In a recent study, describing the patients of three French cancer centres, it was concluded that remarkable progress has been made in the treatment of breast cancer patients with primary metastatic breast cancer between 1987 and 2000.[12] The 3-year overall survival rates of the patients improved from 27% to 44% and the median survival increased from 23 to 29 months.

We performed a population-based study, including all patients with primary metastatic breast cancer in South-East Netherlands between 1975 and 2002 and tried to give an answer to the question if prognosis of this patient group has improved or not.

Patients and methods

Patients

The Eindhoven Cancer Registry records data on all patients newly diagnosed with cancer in the southern part of the Netherlands, an area with about 2.4 million inhabitants and 16 general hospitals, but no academic centre. In the period 1975–2002, 20,522 patients with primary breast cancer were diagnosed and metastatic disease at initial presentation was detected in 1089 of these patients (5%). Data were collected by the Cancer Registry from copies of the pathology reports and the medical records. The patients were staged according to the TNM system of the UICC.[15] 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 localization of metastatic disease and the number of metastatic sites was only available since 1985. No information was available for the specific drugs used. Patients were divided into three groups, according to their date of diagnosis: 1975–1984, 1985–1994 and 1995–2002. This division largely corresponds with the changes in the systemic treatment of metastatic breast, as described in the introduction. The general characteristics of the patients and their disease and treatment are presented in Table 1, according to period of diagnosis.

Follow-up was completed until 1 January 2005. This information was obtained from the municipal registries in the area of the Eindhoven Cancer Registry 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 was less than 0.3%.

Statistical analysis

Survival time was defined as the period between the date of diagnosis and the date of death or 1 January 2005 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 in univariate analyses. Multivariate analyses were carried out using Cox proportional hazards regression models. The variables inserted into the proportional hazards model were: period of diagnosis (1985–1994 and 1995–2002 versus 1975–1984), age at diagnosis (50–69 and 70+ versus <50) and T-classification (T2, T3, T4 and Tx versus T1). A separate multivariate analysis was performed for the patients diagnosed in the period

Table 1 Characteristics of patients with primary metastatic breast cancer according to period of diagnosis ($n = 1089$).

Characteristic	Period of diagnosis						P-value*
	1975–1984 ($n = 221$)		1985–1994 ($n = 314$)		1995–2002 ($n = 554$)		
	N	%	N	%	N	%	
Age (years)							0.0007
<50	48	(22)	67	(21)	130	(23)	
50–69	117	(53)	159	(51)	217	(39)	
70+	56	(25)	88	(28)	207	(37)	
Metastatic sites[†]							
Bone	n.a.		149	(47)	303	(55)	0.04
Liver	n.a.		48	(15)	130	(23)	0.004
Lung/pleurae	n.a.		38	(12)	102	(18)	0.02
Brain	n.a.		8	(3)	15	(3)	0.88
Skin	n.a.		28	(9)	39	(7)	0.32
Unknown/not specified	n.a.		70	(22)	97	(18)	0.09
Multiple sites[†]							0.006
Yes	n.a.		83	(26)	171	(31)	
No			223	(71)	346	(62)	
Unknown			8	(3)	37	(7)	
Only non-visceral metastases[†]							0.02
Yes	n.a.		130	(41)	202	(36)	
No			176	(56)	315	(57)	
Unknown			8	(3)	37	(7)	
Histologic type							<0.0001
Ductal	158	(71)	218	(69)	445	(80)	
Lobular/mixed	20	(9)	55	(18)	98	(18)	
Other/not specified	43	(19)	41	(13)	11	(2)	
Clinical T classification (cT)							<0.0001
T1	15	(7)	33	(11)	110	(20)	
T2	37	(17)	83	(26)	161	(29)	
T3	26	(12)	21	(7)	30	(5)	
T4	119	(54)	156	(50)	212	(38)	
Unknown	24	(11)	21	(7)	41	(7)	
Surgery	142	(64)	185	(59)	268	(48)	<0.0001
Radiotherapy	139	(63)	116	(37)	107	(19)	<0.0001
Systemic treatment	115	(52)	259	(82)	447	(81)	<0.0001
Chemotherapy	94	(43)	88	(28)	190	(34)	0.0023
Hormonal therapy	30	(14)	202	(64)	329	(59)	<0.0001

n.a.: data not available.
  *Chi-squared test or Fishers' exact test, depending on the expected values.
  [†]Situation at the time of diagnosis of the primary tumour.

1985–2002, including information on the localization of metastatic disease and the number of metastatic sites, which was not available for the patients diagnosed before 1985. Hazard ratios (HR) with 95% confidence intervals (CI) and P-values were estimated with respect to the reference category for each covariate.

Survival in the general population decreases with age. Therefore, we also calculated the relative survival rates of the total group and each age group, which is the ratio of observed survival of the cancer patients divided by the expected survival of a group of individuals of closely similar age from the general population.[16] The SAS

computer package (version 8.2) was used for all statistical analyses (SAS Institute Inc., Cary, NC, USA, 1999).

Results

General characteristics

The proportion of patients with primary metastatic breast cancer decreased from 6.0% in the period 1975–1984 to 4.5% in the period 1995–2002. Table 1 shows the characteristics of the 1089 patients with primary metastatic breast cancer according to the period of diagnosis. The median age at diagnosis increased from 62 years in 1975–1984 to 64 years in 1995–2002 ($P = 0.24$). A large increase was observed in the proportion of patients of 70 years or older, whereas the proportion of patients younger than 50 did not change. The large majority of the patients had a tumour of the ductal type. The proportion with lobular breast cancer doubled, from 9% to 18%, and the proportion with an unknown or other histologic tumour type decreased

Table 2 Characteristics of patients with primary metastatic breast cancer according to age at diagnosis ($n = 1089$).

Characteristic	Age at diagnosis (years)						P-value*
	<50 ($n = 245$)		50–69 ($n = 493$)		70+ ($n = 351$)		
	N	%	N	%	N	%	
Metastatic sites[†]							
Bone	100	(51)	198	(53)	154	(52)	0.91
Liver	62	(31)	74	(20)	42	(14)	<0.0001
Lung/Pleurae	27	(14)	54	(14)	59	(20)	0.08
Brain	5	(3)	9	(2)	9	(3)	0.65
Skin	12	(6)	27	(7)	28	(9)	0.34
Unknown/not specified	40	(21)	76	(21)	50	(17)	0.58
Only non-visceral metastases[†]							0.20
Yes	64	(32)	140	(38)	126	(43)	
No	122	(62)	212	(56)	157	(53)	
Unknown	11	(6)	22	(6)	12	(4)	
Multiple sites[†]							0.66
Yes	62	(31)	111	(30)	81	(27)	
No	124	(63)	243	(65)	202	(68)	
Unknown	11	(6)	22	(6)	12	(4)	
Histologic type							<0.0001
Ductal	158	(71)	218	(69)	445	(80)	
Lobular/mixed	20	(9)	55	(18)	98	(18)	
Other/not specified	43	(19)	41	(13)	11	(2)	
Clinical T classification (cT)							0.002
T1	51	(21)	63	(13)	44	(13)	
T2	72	(29)	112	(23)	97	(28)	
T3	18	(7)	38	(8)	21	(6)	
T4	85	(35)	247	(50)	155	(44)	
Tx	19	(8)	33	(7)	34	(10)	
Surgery	156	(64)	280	(57)	159	(45)	<0.0001
Radiotherapy	89	(36)	190	(39)	83	(24)	<0.0001
Systemic treatment	191	(78)	375	(76)	255	(73)	0.23
Chemotherapy	138	(56)	192	(39)	42	(12)	<0.0001
Hormonal therapy	98	(40)	236	(48)	227	(65)	<0.0001

*Chi-squared test or Fishers' exact test, depending on the expected values.
[†]Information was only available for the patients diagnosed between 1985 and 2002 and reflects the situation at the time of diagnosis of the primary tumour.

from 19% to 2%, possibly due to improved documentation. The proportion of patients with a primary breast tumour of 5 cm or less (i.e., T1 or T2) increased from 24% to 49%, whereas the proportion with locally advanced breast cancer (i.e., T3 or T4) decreased from 66% to 43%.

Table 2 shows the characteristics of the patients according to age group. Patients younger than 50 years were more likely to have liver metastases and had a more favourable T-classification compared to older patients. Patients aged 70 years or older were less likely to receive radiotherapy or to undergo surgery and more likely to receive systemic treatment without receiving any other treatment.

Trends in survival

Univariate analysis of the crude survival rates showed that the prognosis of patients with primary metastatic disease differed significantly between the three periods of diagnosis. The median survival of the patients was 18 months for the period 1974–1984, 17 months for the period 1985–1994 and 20.5 months for the period 1995–2002. The prognosis of the patients diagnosed in the period 1995–2002 was significantly better than the prognosis of the patients diagnosed between 1985 and 1994 ($P = 0.02$). The relative survival rates for the total group and the separate age groups show similar trends as the crude survival rates (Figs. 1 and 2a–c).

A multivariate analysis, taking into account the age of the patients and T-classification at the time of diagnosis, showed that the risk of death for patients diagnosed in the period 1995–2002 tended to be lower than the risk for patients diagnosed between 1975 and 1985 ($P = 0.16$; Table 3a). Patients of 50–69 years of age and of 70 years or older had a significantly higher hazard ratio, as compared to patients younger than 50. Also, patients with a T3-tumour appeared to have an increased risk of death, as compared to patients with a T1-tumour. Stratified analyses according to age group and T-classification showed no different outcomes with respect to trends over time (data not shown).

A separate multivariate analysis for the patients diagnosed in the period 1985–2002, including information on the localization of metastatic disease and the number of metastatic sites (Table 3b), showed that patients diagnosed in the period 1995–2002 had a 18% lower risk of death compared to those diagnosed in the period 1985–1994 (HR 0.82, 95% CI 0.70–0.95). Patients with visceral metastases (HR 1.24, 95% CI 1.03–1.46) and those with multiple metastatic sites (HR 1.65, 95% CI 1.36–1.97) had a significantly higher risk of death, as compared to patients with no evidence of visceral metastases or a single metastatic site. Age remained a significant prognostic factor.

Discussion

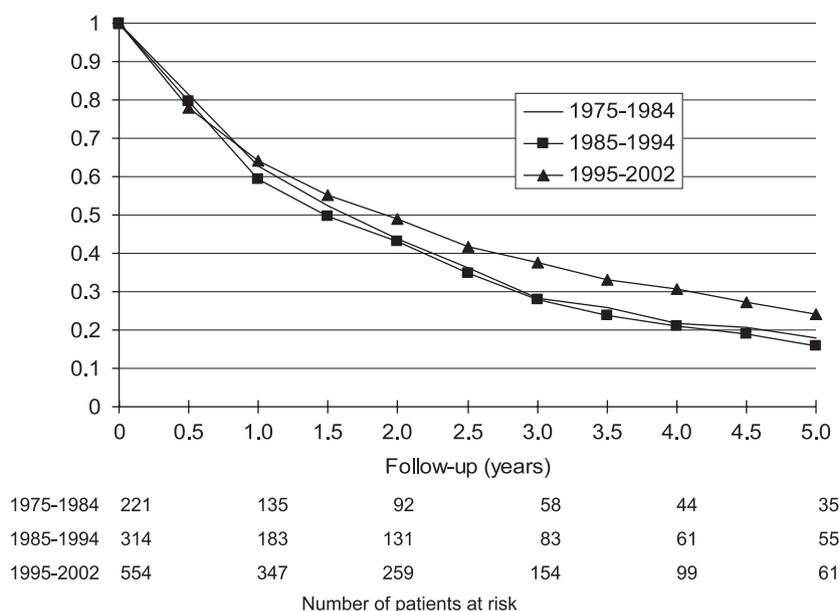The prognosis of patients with primary metastatic breast cancer in the South-East Netherlands started

1975–1984	221	135	92	58	44	35
1985–1994	314	183	131	83	61	55
1995–2002	554	347	259	154	99	61

Number of patients at risk

Figure 1 Relative survival of patients with primary metastatic breast cancer, according to period of diagnosis ($n = 1089$).
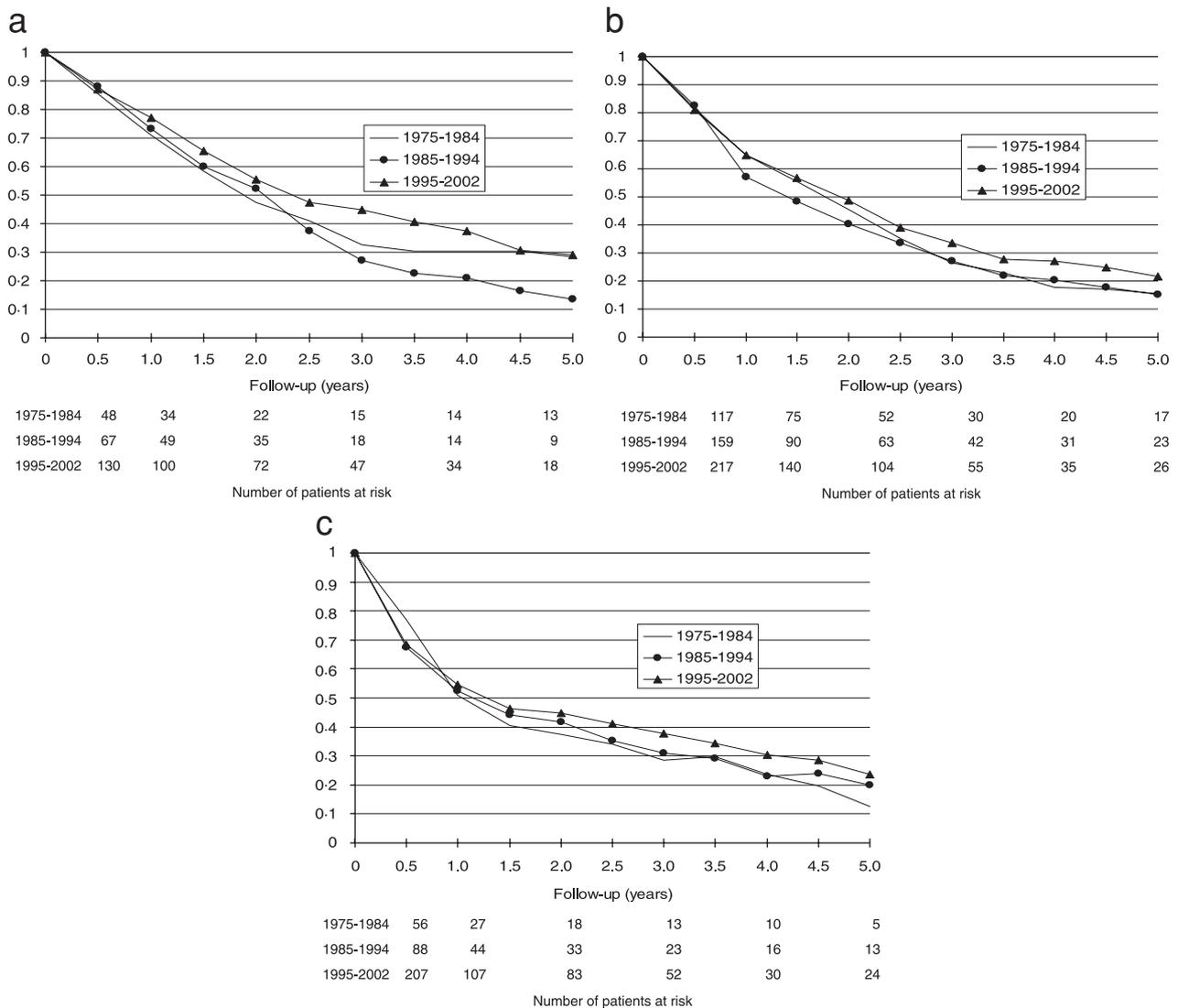
a

1975–1984	48	34	22	15	14	13
1985–1994	67	49	35	18	14	9
1995–2002	130	100	72	47	34	18

Number of patients at risk

b

1975–1984	117	75	52	30	20	17
1985–1994	159	90	63	42	31	23
1995–2002	217	140	104	55	35	26

Number of patients at risk

c

1975–1984	56	27	18	13	10	5
1985–1994	88	44	33	23	16	13
1995–2002	207	107	83	52	30	24

Number of patients at risk

Figure 2 (a) Relative survival of patients with primary metastatic breast cancer, <50 years at diagnosis, according to period of diagnosis ($n = 245$); (b) relative survival of patients with primary metastatic breast cancer, 50–69 years at diagnosis, according to period of diagnosis ($n = 493$); (c) relative survival of patients with primary metastatic breast cancer, 70 years or older at diagnosis, according to period of diagnosis ($n = 351$).

to improve after 1994. The median survival of patients diagnosed in the period 1995–2002 was 20.5 months, compared to 17 months for those diagnosed in the period 1985–1994.

In most studies, the prevalence of distant metastases at the time of primary diagnosis varies between 3% and 10% (1–4). In the South-East Netherlands, the proportion of patients with metastatic breast cancer has remained rather stable during the period 1975–2002. However, a significant increase was observed in the proportion of elderly patients among those with primary metastatic disease, which most probably is just a reflection of the ageing of the general population. A more remarkable finding was the decreasing

proportion of patients with primary metastatic disease presenting with T3 or T4 tumours, which occurred more frequently in the seventies and eighties than in the nineties. The increasing proportion of patients with T1 and T2 tumours is thought to reflect the more widespread use of mammography, the introduction of mammographic screening for women of 50–75 years of age and the greater knowledge and awareness of women of the early signs of breast cancer. Not only in the Netherlands, but also in many other countries, the growing use of mammography during the eighties and the introduction of breast cancer screening programs in the nineties have led to the diagnosis of breast cancer tumours in an earlier stage. An

Table 3 Results of the multivariate analysis.

Characteristics	HR	95% CI	P value
(a) For death in patients diagnosed in the period 1975–2002 (n = 1003)			
Period of diagnosis			
1975–1984	1.03	(0.86–1.21)	0.73
1985–1994	1	—	
1995–2002	0.88	(0.74–1.04)	0.16
Age group			
50	1	—	
50–69	1.23	(1.03–1.44)	0.02
70+	1.42	(1.17–1.68)	<0.01
Clinical T			
T1	1	—	
T2	1.09	(0.88–1.37)	0.43
T3	1.35	(1.00–1.83)	0.05
T4	1.16	(0.94–1.42)	0.18
(b) For death in patients diagnosed in the period 1985–2002 (n = 765)			
Period of diagnosis			
1985–1994	1	—	
1995–2002	0.82	(0.70–0.95)	0.01
Age group			
<50	1.00	—	
50–69	1.24	(1.01–1.49)	0.04
70+	1.53	(1.23–1.87)	<0.01
Clinical T			
T1	1	—	
T2	0.99	(0.78–1.24)	0.91
T3	1.03	(0.71–1.50)	0.89
T4	0.99	(0.78–1.23)	0.89
Presence of visceral metastases			
No	1	—	
Yes	1.24	(1.03–1.46)	0.02
Number of metastatic sites			
Single site	1	—	
Multiple sites	1.65	(1.36–1.97)	<0.01

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

earlier detection of the primary tumour might have resulted in an earlier detection of metastatic disease and give the false impression of a longer survival-time. To rule out the effect of such lead-time bias we adjusted for changes in tumour size (i.e., T-classification) in the multivariate analysis. However, our data do not provide convincing evidence for a relationship between the size of the primary tumour and the mortality risk of patients with primary metastatic breast cancer. This observation is in accordance with a study of Engel and colleagues, who also compared overall survival after metastasization according to the size of the primary tumour and concluded that survival after metastasization appears to be independent of T-status, indicating an almost homogeneous growth of metastases.[17]

To be able to make a truly valid analysis of the time trends in the prognosis of patients with primary metastatic breast cancer and rule out lead-time bias would not only require adjustment for changes in tumour stage, but also for changes in the staging procedures. Unfortunately, information on the routine staging applied during the study period and changes over time were not available for our patients. Chest X-ray, bone scanning, abdominal ultrasound evaluation and a panel of haematological tests and liver function assays used to be part of staging procedures for newly diagnosed breast cancer patients. Nowadays, it is generally accepted and recommended in most guidelines that there is no need for peri-operative screening for metastases in patients without clinical signs of distant tumour spread. The reasons not to screen a-symptomatic patients are clear: a high rate of false positive findings, missing therapeutic consequences and high costs. However, despite the strong arguments against routine screening, many still do so.[18]

We noticed an increase in the proportion of patients with bone-, liver- and lung-metastases during the period 1985–2002. It is possible that underreporting of the number of metastatic sites by the cancer registry in the period 1985–1994 accounts for this phenomenon. However, another explanation might be the improvement of the imaging and laboratory techniques to detect such metastases. This explanation seems more likely, as no increase was observed in the proportion of skin metastases, of which the detection is not dependent on the use of imaging techniques. Stage migration is, therefore, a possible confounding variable in patients treated more recently.

Studies on trends in survival of patients with primary metastatic breast cancer are rare and show contradictory results.[12,14] The most recent one is a population-based study by Rapiti and colleagues, based on data of the Geneva Cancer Registry of 300 patients diagnosed between 1977 and 1996.[14] In these two decades no improvement was observed, as was illustrated by in the multivariate analysis of their data, in which period of diagnosis was not a significant prognostic factor. In another recent study of Andre and colleagues, including 724 patients diagnosed between 1987 and 2000, median survival improved from 23 months in the period 1987–1993 to 29 months in the period 1994–2000, which is about 9 months longer than the median survival rates of the patients diagnosed in the

period 1995–2002 in our study.[12] In the discussion of their paper Andre and colleagues attribute part of the improvement to the increased use of taxanes and aromatase inhibitors, which was administered to 10% of patients diagnosed in the period 1987–1993 and to 58% of the patients treated in the period 1994–2000. The lack of information on the type of systemic treatment limits the interpretation of our results. It is possible that the French data reflect the current standard in specialized clinics, which is difficult to compare with the practice of general hospitals where the introduction of new drug is generally somewhat later or more gradual. We therefore expect further improvements to become visible in our patient population in the next few years.

In summary, since 1994 the prognosis of patients with primary metastatic breast cancer has improved significantly. Considering the recent developments in the treatment of metastatic disease, especially the increased use of taxanes and aromatase inhibitors and the introduction of trastuzumab in human epidermal growth factor 2 (HER-2)-positive patients, the full impact of these drugs on a population-based level should become evident in the next few years.

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