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Survival in Metastatic Recurrent Breast Cancer after Adjuvant Chemotherapy: Little Evidence for Improvement Over the Past Three Decades

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Abstract

Purpose—Population-based studies have shown improved survival for patients diagnosed with metastatic breast cancer (MBC) over time, presumably due to the availability of new and more effective therapies. The objective of this analysis was to determine if survival improved for patients who developed distant recurrence of breast cancer after receiving adjuvant therapy.

Methods—Adjuvant chemotherapy trials coordinated by the Eastern Cooperative Oncology Group (ECOG) that accrued patients between 1978–2002 were reviewed. Survival following distant recurrence was estimated for progressive time periods, and adjusted for baseline covariates in a Cox proportional hazards model.

Results—Of the 13,785 patients who received adjuvant chemotherapy in 11 trials, 3447 (24.4%) developed distant recurrence; median survival following recurrence was 20 months (95% confidence intervals: 19, 21). Factors associated with inferior survival included shorter distant recurrence free interval (DRFI), ER- and PR-negative disease number of positive axillary nodes at diagnosis and black race ($p<0.0001$ for all). When time-period of recurrence was added to the model, it was not significantly associated with survival for the general population with recurrence. Survival improved over time only in hormone-receptor negative patients with a DRFI ≤ 3 years, both among the 5 recent and entire trial datasets ($p=0.01$ and $p=0.05$ respectively).

Conclusions—In contrast to reports from population-based studies, we did not observe general improvement in survival over the last three decades for patients who developed distant recurrence

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after adjuvant chemotherapy after adjusting for DRFI. Improved survival for hormone-receptor negative patients with a short DRFI suggests benefit from trastuzumab.

Keywords

breast cancer; distant recurrence; survival; distant recurrence free interval; metastatic disease

Introduction

MBC remains the second leading cause of cancer death in women, with over 40,000 dying in the United States (US) and over 400,000 dying globally each year.[1] Although breast cancer mortality rates have declined in the US due to screening and improved systemic adjuvant therapy,[2] the disease remains incurable for those with distant metastases.[3] Evidence suggests survival has modestly improved in the era of modern systemic therapy,[4–6] implying further improvement may be possible with new therapeutic approaches. A potential secondary benefit is that identification of effective new agents for MBC may produce survival gains when used as adjuvant therapy for localized disease: notable examples include anthracyclines, taxanes, and trastuzumab.[7–9]

In order to determine whether survival has improved for patients who developed distant recurrence ***after*** receiving adjuvant therapy, we undertook a review of adjuvant phase III trials conducted by the Eastern Cooperative Oncology Group (ECOG) over a period of approximately three decades.

Methods

Population

Eleven phase III adjuvant breast cancer trials conducted by the ECOG that treated patients with adjuvant chemotherapy, and with at least 5 years of followup were identified and included in this analysis (Table 1). Participants who did not receive adjuvant chemotherapy were excluded from this analysis.

Analysis

The primary study endpoint was survival following distant recurrence, defined as time from date of distant recurrence to date of death (or date last known alive). Survival after distant recurrence was determined with adjustment for baseline covariates in a Cox proportional hazards model. The models included calendar year of (distant) recurrence, age at diagnosis of recurrence, estrogen receptor (ER) and progesterone receptor (PgR) status, number of positive axillary lymph nodes at diagnosis, primary tumor size at diagnosis, race and DRFI. HER2 was not available to include in the model. DRFI was defined as the time from study entry to the date of distant recurrence. Because DRFI is strongly associated with survival after recurrence and the potential for “gap time” bias,[10] logrank tests for other covariates were computed stratified on DRFI (0–3, >3–6, >6 years). Estimates of survival after distant recurrence were weighted averages of the Kaplan Meier estimates computed within DRFI groups. Therapeutic intervals of interest were identified between the first on-study date (1978) and the last point at which data was censored (2010). Recurrences were assigned to one of six time periods: 1978–1983, 1984–1988, 1989–1993, 1994–1998, 1999–2003, and 2004–2010. The most recent time period (2004–2010) was used as the comparator. Analyses are based on all 3447 patients with distant recurrence. We additionally examined the outcomes for 2237 patients receiving “recent” chemotherapy regimens (E3189, E5188, E2190, E2197, E1199) between 1989 and 2002, given that the type of adjuvant chemotherapy might influence resistance in the metastatic setting.

Results

Characteristics of Included Trials

The study population included 13,785 patients enrolled on 11 adjuvant ECOG trials between 1978 and 2002 (Table 1). Among the 13,785 enrolled, 3447 (24.4%) had distant recurrences, 814 (5.9%) had local recurrences only, and 20 (0.1%) had unknown sites of recurrence. Table 2 shows the characteristics of both all adjuvant participants and the subset with distant recurrence. Median survival following distant recurrence (n=3447) was 20 months (95% confidence intervals: 19, 21 months). Estimated 5 and 10-year survival rates were 16.3% and 6.4%.

Analysis of Distant Recurrence

Covariates significantly associated with inferior survival after distant recurrence included ER- and PR-negative disease (Figure 1a). However, DRFI was the most strongly associated with survival after recurrence (Figures 1b–c). Black race and increasing number of positive axillary nodes at diagnosis were also significant.

Table 3 shows the estimated hazard ratio (HR) from the Cox proportional hazards model. Patients with a shorter DRFI fared significantly worse than those with a longer DRFI (HR of 2.44 DRFI > 6 vs. ≤ 3 years, $p<0.0001$; and a HR of 1.43 DRFI of >6 years vs >3–6 years, $p<0.0001$.) Patients with ER- and PR-negative disease also had significantly shorter survival following recurrence (HR 1.35, $p<0.0001$; 1.33, $p<0.0001$ respectively), as did those of black race (HR 1.34, $p<0.0001$) and with more positive nodes at diagnosis (HR 1.17, 1–3 vs. 0 nodes; HR 1.35, 4–9 vs. 0 nodes; HR 1.33, >9 vs. 0 nodes; $p<0.0001$). Age, primary tumor size and year of recurrence were not significant.

If survival after distant recurrence was evaluated *without* stratification for DRFI for all 11 studies, survival *did* significantly improve over time (Figure 2a). However, once stratified by DRFI, there was not significant improvement in survival over time (Figure 2b). The improvement observed in the unadjusted analysis for the entire population is likely reflects more favorable patients recruited by later adjuvant trials–recent adjuvant trials selected for more ER-positive disease. Table 4 illustrates this point. Survival after distant recurrence by time period of recurrence stratified by DRFI and receptor status is shown in Figures 3a–d. Only among hormone-receptor negative participants who recurred within 3 years does there appear to be any improvement in survival over time.

Analysis of Recent Trials Only

In the 5 most recent trials, factors associated with survival after distant recurrence included DRFI, ER/PR expression, and race (Figure 2c, Table 3). However, in contrast to the entire study population, older age at recurrence and time period of recurrence beginning in 1999 (compared with before 1994) *were* significantly associated with improved survival. However, this improvement over time was again confined to those patients with hormone-receptor negative disease who recurrent within 3 years of diagnosis (Figure 4a–e).

Discussion

Among the many phase III MBC trials performed over the past three decades, survival significantly improved in only of handful.[11–14] Despite difficulty in demonstrating improved survival in individual trials, population-based studies suggest that MBC patients now survive modestly longer than in the past.[4–6] This improvement observed in population-based studies could be due to the increased availability of drugs that when used individually have minimal effect in prolonging survival, but when used sequentially may produce modest

survival gains. Other suggested explanations include the impact of improved imaging.[4] Better imaging may lead to apparent prolongation in the interval between diagnosis of recurrence and death by identifying MBC at earlier time points. Better imaging also increases the percentage of women with *de novo* MBC (women with recurrent breast cancer have inferior survival compared to women with *de novo* disease.[15])

To determine whether the perceived improvement in survival demonstrated by population-based studies was also evident in clinical trial populations, we evaluated survival following recurrence among ECOG clinical trial participants who received adjuvant chemotherapy. Our analysis suggests that for women who develop distant recurrence following adjuvant chemotherapy, the availability of new cytotoxic and biologic agents has not broadly translated into improved survival. The exception appears to be among hormone-receptor negative patients who relapse within 3 years of diagnosis, where survival improved for the period of recurrence beginning in 1999 (compared with before 1994). We *hypothesize* that this may reflect an effect of trastuzumab rather than improved cytotoxic therapy: trastuzumab became commercially available in 1998, and HER2-positive disease is associated with early recurrence.

Table 5 summarizes characteristics of this and other reports evaluating trends in metastatic survival. There are several key differences between our analysis and the other reports.[4, 5, 16, 17] First, we included only patients who recurred after receiving adjuvant chemotherapy for early stage breast cancer and thus were more likely to have drug resistant disease (*de novo* disease was included in other analyses.) Second, we adjusted for multiple prognostic covariates in multivariate models, including DRFI. Giordano et al [4] noted large differences in outcome by the year of recurrence, which was not evident when adjusted for DRFI. However, not all prior analyses shown in Table 5 adjusted for DRFI and other covariates. This may contribute to the improved survival over time observed by others. Indeed, survival was improved over time in our dataset if the survival analysis was not stratified by DRFI, highlighting the importance of controlling for this variable when evaluating survival over time.

This analysis has several strengths and limitations. Strengths include the large sample size, long followup, conduct by the same group of investigators, and standardized treatment regimens and prospective data collection. The heterogeneity of the population over time is a limitation imposed by evolving eligibility criteria for the 11 adjuvant trials. To account for this, analysis was not based on time period of enrollment, but rather on time period of recurrence, while controlling for factors such as age, ER/PR expression and race. Other limitations include lack of information regarding sites of recurrence, treatments used after recurrence, and the potential for lead-time bias due to improved imaging. Additionally, information is absent about HER2 status and anti-HER2 therapy. Although we hypothesize that the survival benefit for those diagnosed with an early recurrence after 1999 was due to the availability of trastuzumab, it is not possible for us to determine with certainty that this reflects the improved survival for HER2+ disease demonstrated in prospective clinical trials.[11, 18, 19]

In conclusion, we found evidence over a 30-year time period for an improvement in survival among hormone-receptor negative patients who recurred within 3 years following adjuvant chemotherapy for localized disease, but not for the population as a whole. Survival seemed to improve over the past 30 years for the entire population, but this effect was not persistent when the survival analysis was adjusted for DRFI and other covariates. This suggests that survival improvements observed among population-based studies may not reflect outcomes for all subsets of women recurring after adjuvant chemotherapy. There remains a critical

need for developing more effective therapies for patients with MBC, especially those who have recurred after receiving adjuvant chemotherapy.

Acknowledgments

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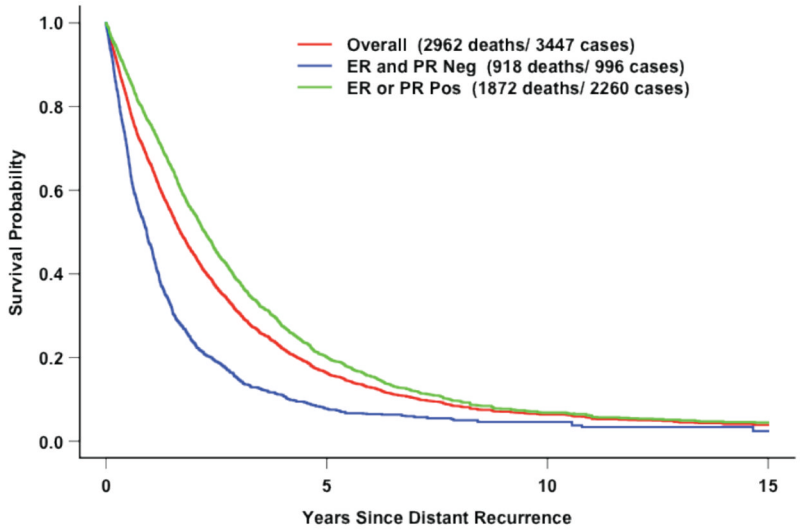
Figure 1a.



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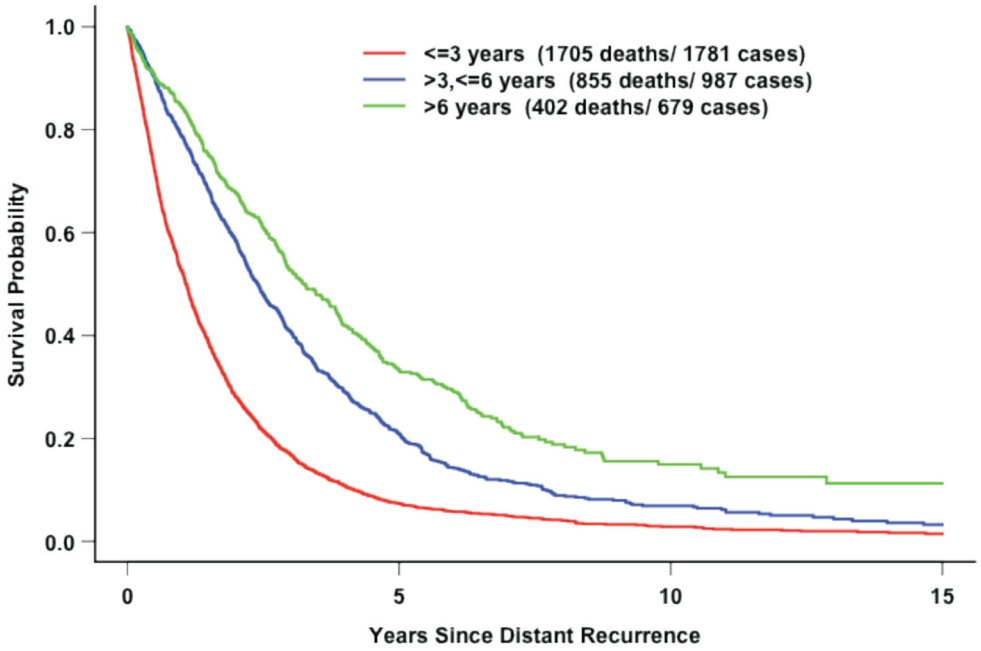

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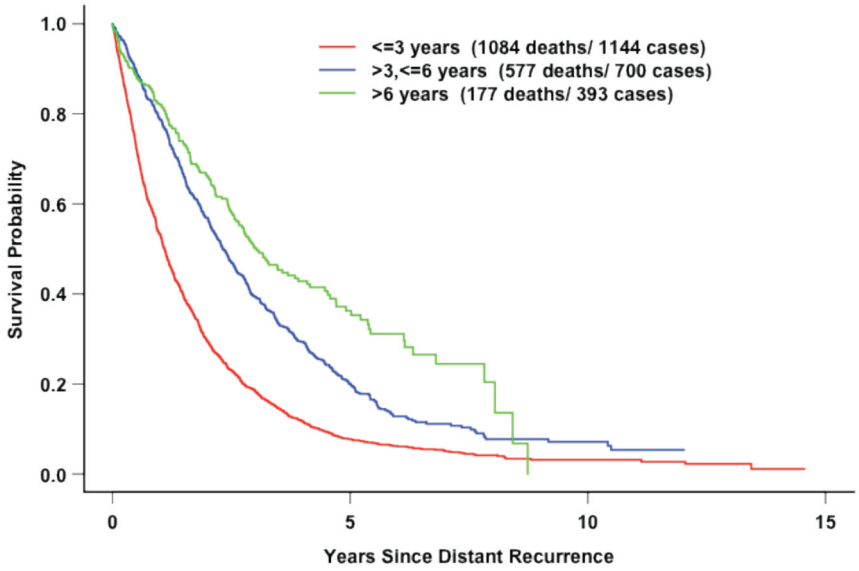


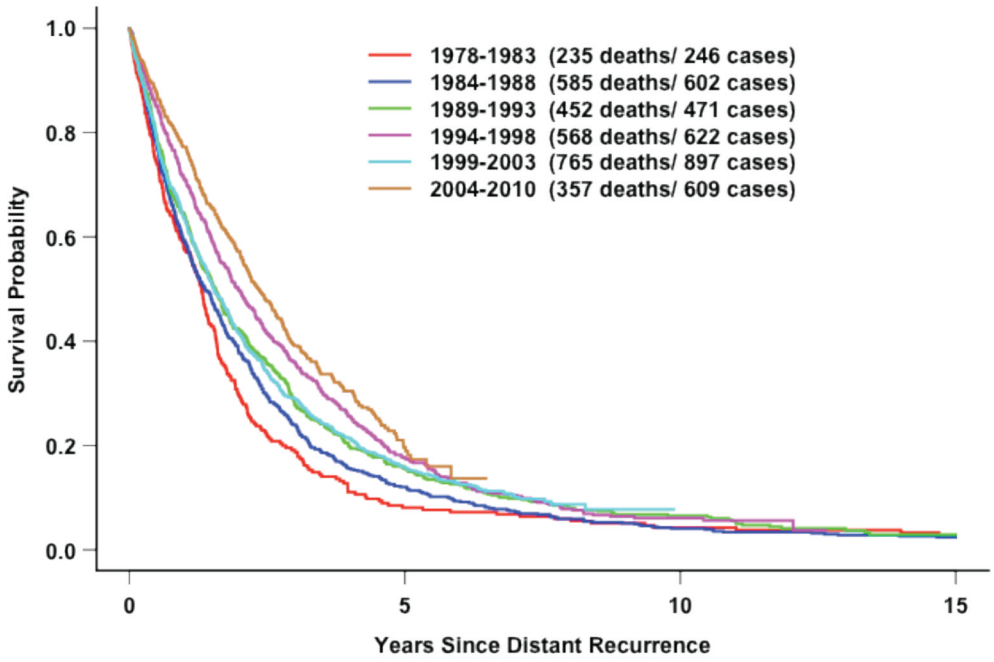
Figure 1.

Figure 1a. All Eleven Trials: Survival after distant recurrence

Figure 1b. All Eleven Trials: Survival following recurrence by DRFI ($p<0.0001$)

Figure 1c. Five Recent Trials: Survival following recurrence by DRFI ($p<0.0001$)

Figure 2a:



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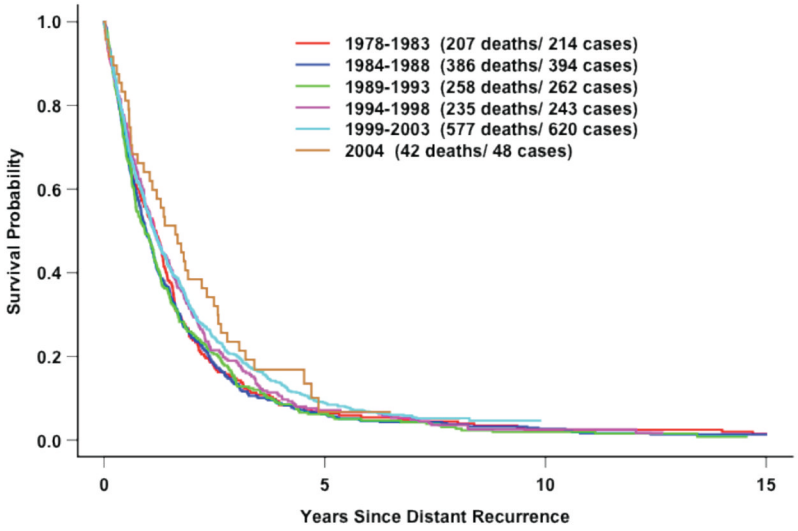

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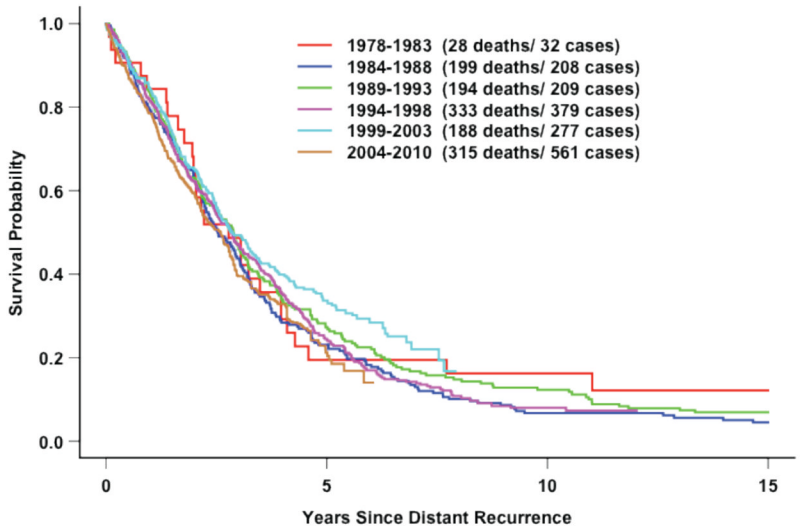


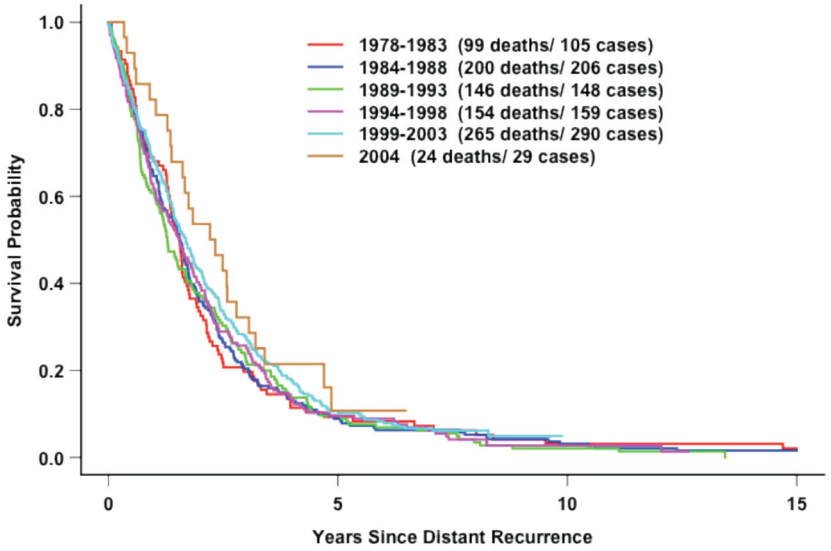
Figure 2.

Figure 2a: All Eleven Trials: Survival following distant recurrence by time period WITHOUT adjustment for DRFI ($p<0.0001$, logrank test without stratification)

Figure 2b. All Eleven Trials: Survival following recurrence by time period of recurrence in patients WITH DRFI≤ 3 Years ($p=0.04$)

Figure 2c. All Eleven Trials: Survival following recurrence by time period in patients WITH DRFI> 3 Years ($p=0.47$)

Figure 3a.



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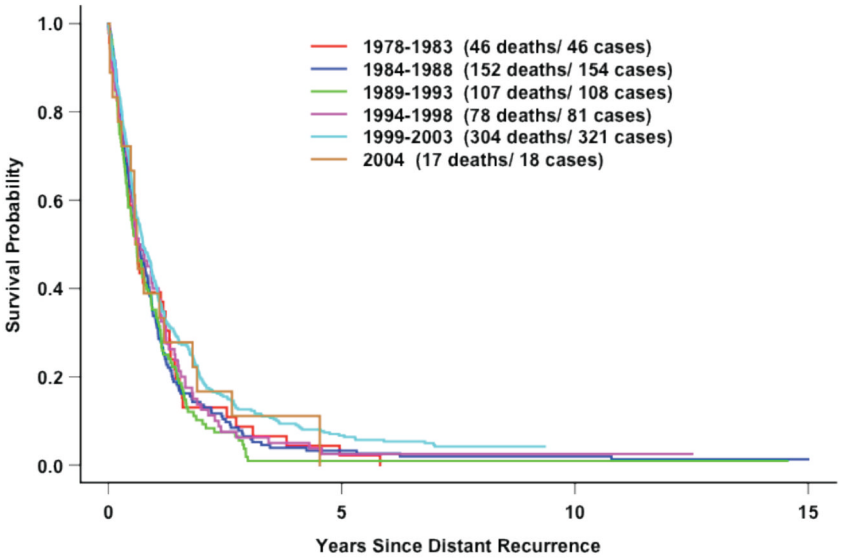

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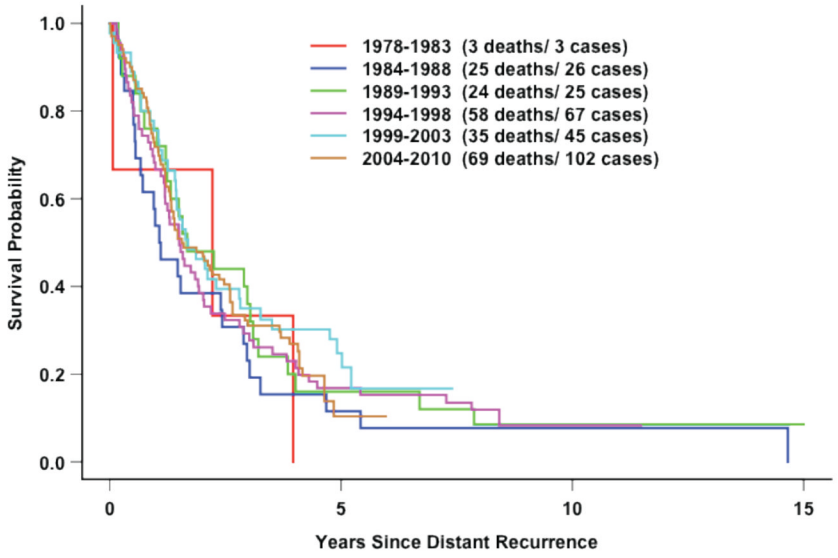

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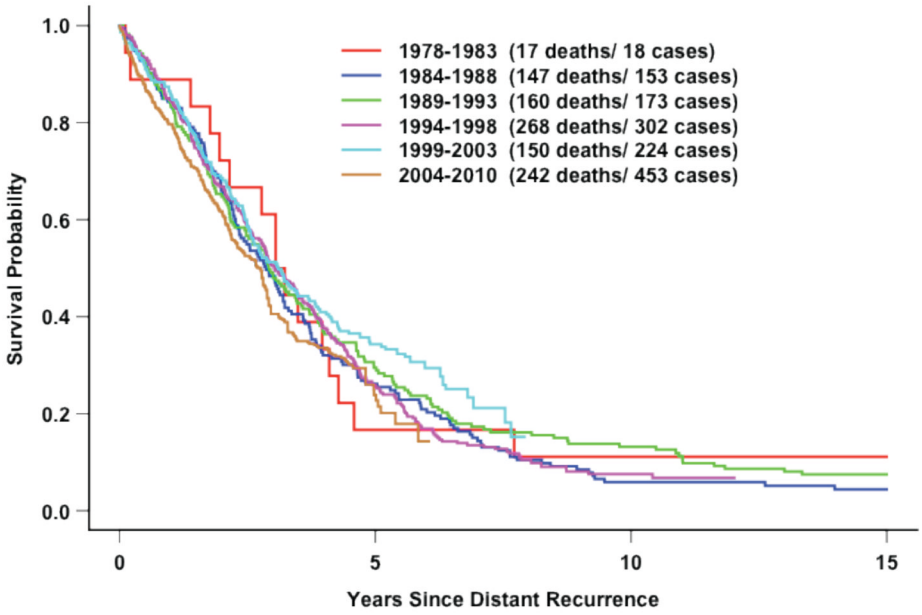


Figure 3.

Figure 3a. All Eleven Trials: Survival following recurrence by time period for hormone-receptor positive patients with DRFI≤ 3 Years (p=0.41)

Figure 3b. All Eleven Trials: Survival after recurrence by time period in hormone-receptor negative patients with DRFI≤ 3 Years (p=0.05)

Figure 3c. All Eleven Trials: Survival following recurrence by time period in hormone-receptor negative patients with DRFI > 3 Years. (p=0.94)

Figure 3d. Five Recent Trials: Survival following distant recurrence by time period in hormone-receptor positive patients with DRFI > 3 Years (p=0.46)

Figure 4a.

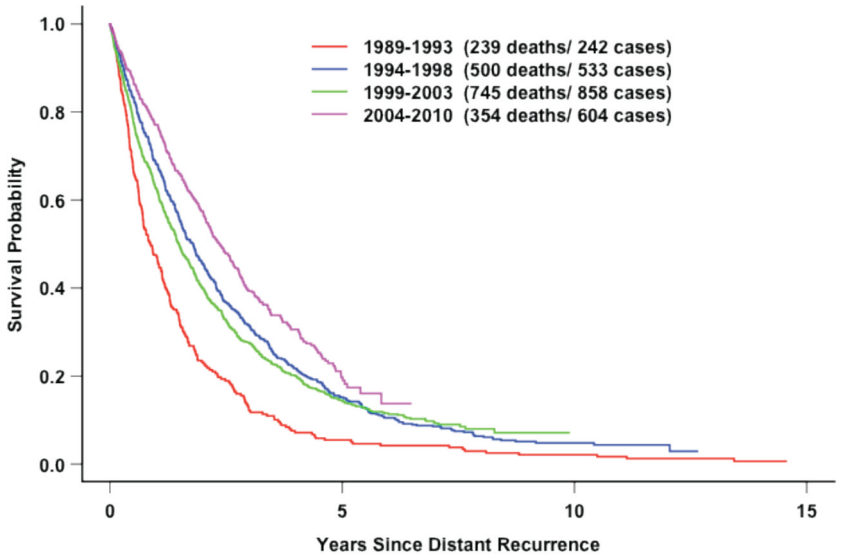
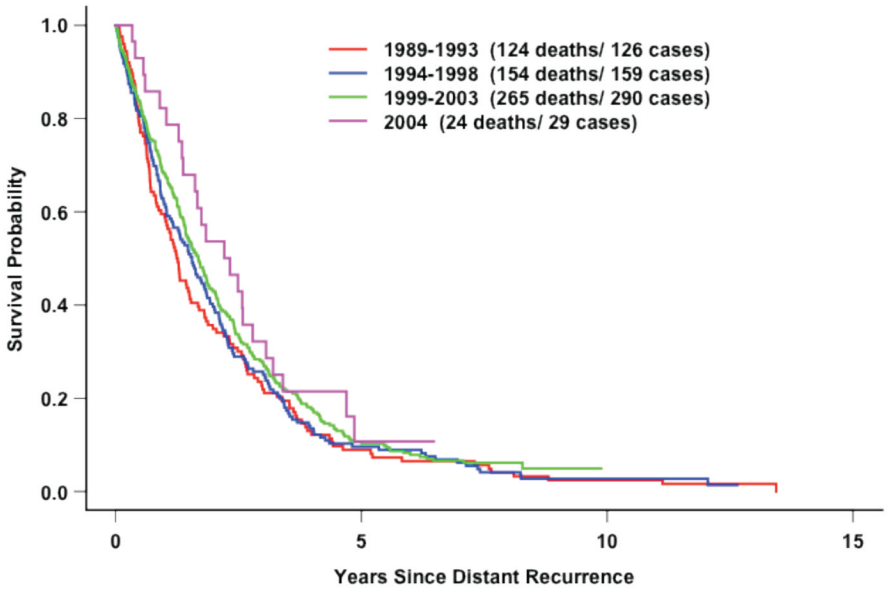


Figure 4b.



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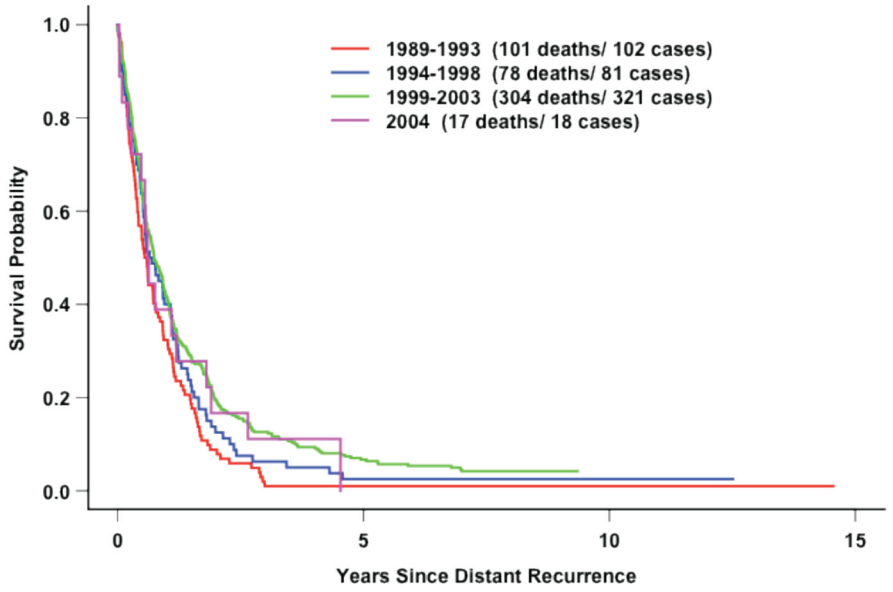

Figure 4d.

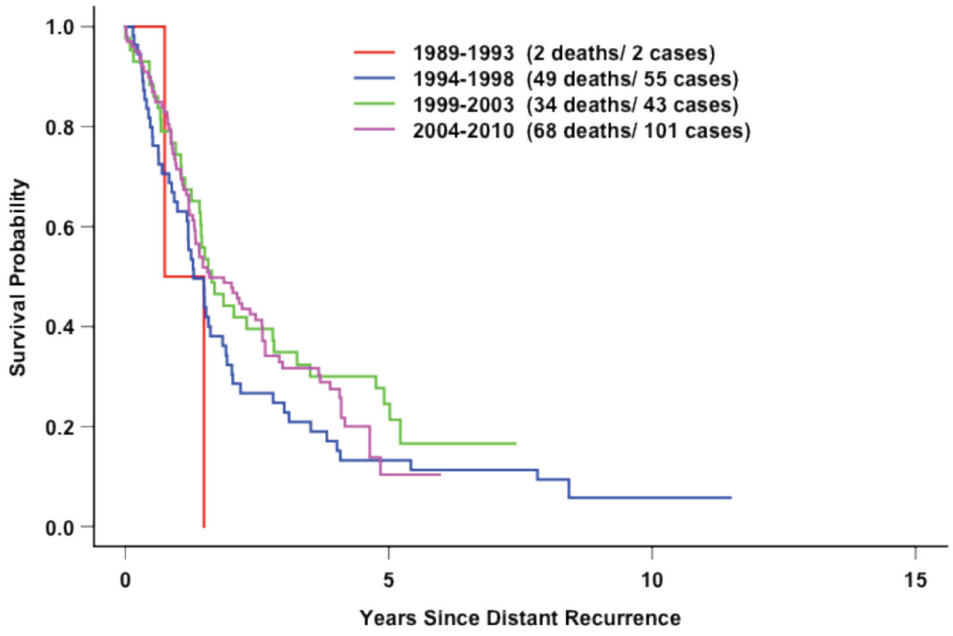

Figure 4e.

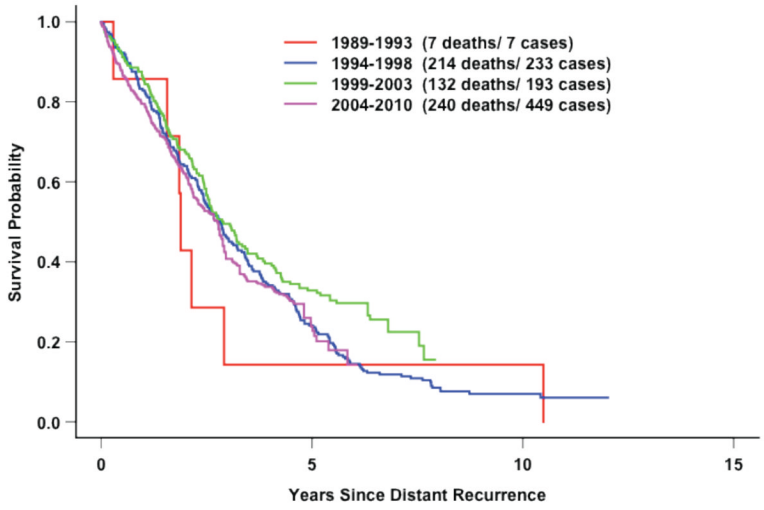

Figure 4.

Figure 4a. Five Recent Trials: Survival following distant recurrence by time period WITHOUT adjustment for DRFI ($p<0.0001$, logrank test without stratification)

Figure 4b. Five Recent Trials: Survival following recurrence by time period of distant recurrence in hormone-receptor positive patients with DRFI≤ 3 Years ($p=0.22$)

Figure 4c. Five Recent Trials: Survival following recurrence by time period hormone-receptor negative patients with DRFI≤ 3 Years ($p=0.01$)

Figure 4d. Five Recent Trials: Survival following recurrence by time period in hormone-receptor negative patients with DRFI > 3 Years ($p=0.64$)

Figure 4e. Five Recent Trials: Survival after recurrence by time period in hormone-receptor positive patients with DRFI > 3 Years ($p=0.57$)

Table 1

ECOG-coordinated adjuvant breast cancer trials included in analysis

Trial	Treatment Arms	Key Characteristics	Enrollment Dates (month/year)	Enrolled (n)	Received Chemo-therapy (n)	Distant Recurrence (n)
E5177[20]	CMF/P/PT	Premenopausal	2/78 to 2/82	662	662	284
E6177[21, 22]	CMFP vs. CMFPT vs. Observation	Postmenopausal	2/78 to 7/81	265	170	92
E1180[23, 24]	CMFP vs. Observation	Node-negative	5/81 to 5/88	541	276	47
E4181[25]	CMFPT 4 vs. 12 vs. 12 + continued T	Postmenopausal	2/82 to12/86	961	961	392
E5181[26]	CMFPT vs. Alternating chemo with Continued T vs. Observation	Premenopausal	2/82 to 7/87	658	658	224
E3181[27]	CAFTH with RT vs. Observation	Locally Advanced Resectable	1/82 to 2/87	332	332	171
"Recent" adjuvant trials						
*E3189[28]	CAF vs Multi-drug	ER-negative	8/89 to 4/93	646	646	212
*E5188[29]	CAF vs. CAF+Z vs. CAF+ZT	Premenopausal, ER-positive, Node-positive	7/89 to 2/94	1536	1536	533
*E2190[30]	CAF vs. CAF plus high dose chemotherapy	10+ positive axillary nodes	8/91 to 8/98	540	540	246
*E2197[31]	AC vs AD	0–3 positive axillary nodes	7/98 to 1/00	2952	2952	293
*E1199[32]	AC + Taxanes	Positive nodes or high-risk node-negative	10/99 to 1/02	5052	5052	953
			Total numbers	**14,145**	**13,785**	**3,447**

A: Adriamycin (doxorubicin), C: cyclophosphamide, M: methotrexate, F: 5-fluorouracil, T: tamoxifen, Z: Zoladex (goserelin), D: docectaxel, P: prednisone, H: Fluoxymesterone.

*All patients received "modern" chemotherapy: anthracyclines, or sequential/concurrent anthracycline-taxane therapy

Table 2

Characteristics of Adjuvant Trial Population and Subsets with Distant Recurrence

	Entire Adjuvant Study Population Treated with Chemo	**Cases with Distant Recurrence from Adjuvant Study Population**	**Cases with Distant Recurrence from Recent Trials Only**
Number of adjuvant trials	11	11	5 most recent: E3189, E5188, E2190, E2197, E1199
Number of Patients	13,785	3,447	2,237
Age at Initial Diagnosis, Median (range)	49 (19, 85)	48 (19, 80)	47 (19, 80)
Age at Distant Recurrence, Median (range)	--	52 (21, 85)	50 (22, 83)
Hormone Receptor Status			
ER Positive	8822 (64%)	2093 (61%)	1388 (63%)
PgR Positive	7977 (62%)	1794 (59%)	1359 (62%)
Tumor Size at Diagnosis			
Unknown	121	19	16
0–2.0 cm	5261 (39%)	933 (27%)	613 (28%)
2.1–5.0cm	7103 (52%)	1994 (58%)	1285 (58%)
5.1cm or greater	1300 (10%)	501 (15%)	323 (15%)
Number of Positive Axillary Nodes at Diagnosis			
Unknown	76	12	6
0 positive	2771 (20%)	275 (8%)	225 (10%)
1–3 positive	6400 (47%)	1281 (37%)	843 (38%)
4–9 positive	2746 (20%)	981 (29%)	560 (25%)
10 or more positive	1792 (13%)	898 (26%)	603 (27%)
Race			
Unknown	301	45	43
While	11817 (88%)	2972 (87%)	1873 (85%)
Black	1137 (8%)	298 (9%)	221 (10%)
Other	530 (4%)	132 (4%)	100 (5%)
DRFI			
≤3 years	--	1781 (52%)	1144 (51%)
3–6 years	--	987 (29%)	700 (31%)
> 6 years	--	679 (20%)	393 (18%)

Note: Information was missing for some variables in some patients in the entire cohort and relapsed cohort, including age at initial diagnosis (33 entire adjuvant/4 recurrent/0 recent study and recurrent), age at distant recurrence (--/4/0); ER expression (85/22/21), PR expression (932/386/33), tumor size (121/22/19), nodal status (76/12/6) and race (301/45/43).

Table 3

Estimated hazard ratios from Cox proportional hazards multivariate models

		All 11 studies (n=3431)			5 Recent Studies (n=2231)		
Factor	**Comparison**	**HR**	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
DRFI (years)	≤3 vs. >6	2.44	2.16–2.76	<0.0001	2.22	1.87–2.63	<0.0001
	>3, ≤6 vs. >6	1.43	1.26–1.62		1.38	1.16–1.63	
ER status	Negtv vs. Postv	1.35	1.23–1.49	<0.0001	1.34	1.16–1.56	<0.0001
	Unk vs. Postv	0.88	0.52–1.48		0.54	0.24–1.21	
PR status	Negtv vs. Postv	1.33	1.20–1.47	<0.0001	1.27	1.09–1.47	0.007
	Unk vs. Postv	1.04	0.90–1.21		1.43	0.78–2.62	
Number of positive axillary nodes *	1–3 vs. 0	1.17	1.01–1.36	<0.0001	1.05	0.89–1.25	0.15
	4–9 vs. 0	1.35	1.16–1.58		1.16	0.97–1.40	
	>9 vs. 0	1.33	1.14–1.56		1.17	0.97–1.40	
Race	Black vs. White	1.34	1.18–1.53	<0.0001	1.38	1.19–1.60	<0.0001
	Other vs. White	0.88	0.72–1.07		0.82	0.65–1.03	
	Unk vs. White	0.95	0.68–1.33		1.06	0.75–1.50	
Age at Distant Recurrence (years)	40–49 vs. <40	0.95	0.85–1.07	0.30	0.96	0.83–1.11	<0.0001
	50–59 vs. <40	0.99	0.88–1.11		1.06	0.91–1.23	
	60–69 vs. <40	1.01	0.89–1.16		1.20	1.00–1.43	
	>69 vs. < 40	1.13	0.95–1.33		1.68	1.31–2.15	
Tumor Size (cm)	2.1–5.0 vs. ≤2.0	1.11	1.01–1.21	0.12	1.13	1.02–1.27	0.07
	>5.0 vs. ≤2.0	1.07	0.95–1.21		1.19	1.03–1.39	
	Unk vs. ≤2.0	0.87	0.53–1.44		0.96	0.56–1.64	
Time period of Distant Recurrence	1978–83 vs. 2004–10	0.93	0.76–1.14	0.24	--	--	
	1984–88 vs. 2004–10	0.99	0.85–1.15		--	--	
	1989–93 vs. 2004–10	1.02	0.87–1.18		1.29	1.06–1.58	0.005
	1994–98 vs. 2004–10	0.97	0.84–1.12		1.13	0.97–1.31	
	1999–2003 vs. 2004–10	0.89	0.77–1.02		0.98	0.84–1.14	

Abbreviations: NS = not significant, HR = Hazard Ratio, CI = confidence interval, Negtv = negative, Postv = positive, Unk = unknown

* Cases with age or number of positive nodes unknown excluded (16 cases for all 11 studies, 6 cases for 5 recent studies); 'unknown' included as a separate category for other factors with unknown cases.

Interaction test for Time Period of Distant Recurrence vs. Five Recent Studies = 0.38

Table 4

Characteristics of patients with distant recurrence based on time period of recurrence

		Calendar Year of Recurrence					
		1978–1983	**1984–1988**	**1989–1993**	**1994–1998**	**1999–2003**	**2004–2010**
No. Patients		246	602	471	622	897	609
Age at Initial Diagnosis, Median (range)		47 (23, 73) [4 Unk]	52(20,79)	47(25,78)	44(24,77)	48(24,80)	50(19,77)
Age at Distant Recurrence, Median (range)		49 (25, 74) [4 Unk]	55(21,81)	50(25,83)	48(28,85)	52(25,82)	57(22,83)
ER status	ER Negative	129(52%)	278(46%)	191(41%)	217(35%)	394(44%)	123(20%)
	ER Positive	117(48%)	323(54%)	278(59%)	403(65%)	493(56%)	479(80%)
	Unknown	0	1	2	2	10	7
PR status	PgR Negative	61(56%)	266(58%)	194(45%)	198(33%)	411(47%)	137(23%)
	PgR Positive	48(44%)	192(42%)	238(55%)	394(67%)	461(53%)	461(77%)
	Unknown	137	144	39	30	25	11
Tumor Size	≤ 2cm	59(24%)	156(26%)	110(23%)	194(31%)	235(26%)	179(30%)
	>2, ≤ 5 cm	140(57%)	354(59%)	279(59%)	337(55%)	523(59%)	361(60%)
	>5 cm	45(18%)	91(15%)	80(17%)	85(14%)	134(15%)	66(11%)
	Unk	2	1	2	6	5	3
Number of positive axillary nodes at diagnosis	0	1(0%)	31(5%)	11(2%)	5(1%)	147(16%)	80(13%)
	1–3	83(34%)	199(33%)	159(34%)	214(34%)	354(40%)	272(45%)
	4–9	94(39%)	205(34%)	185(39%)	174(28%)	172(19%)	151(25%)
	>9	65(27%)	165(28%)	116(25%)	229(37%)	220(25%)	103(17%)
	Unk	3	2	0	0	4	3
Race	White	219(89%)	543(90%)	398(85%)	520(84%)	767(88%)	525(89%)
	Black	18(7%)	40(7%)	48(10%)	64(10%)	76(9%)	52(9%)
	Other	8(3%)	19(3%)	22(5%)	36(6%)	32(4%)	15(3%)
	Unk	1	0	3	2	22	17
DRFI	< 3 yrs	214(87%)	394(65%)	262(56%)	243(39%)	620(69%)	48(8%)
	3–6 yrs	32(13%)	167(28%)	97(21%)	246(40%)	125(14%)	320(53%)
	>6 yrs	0(0%)	41(7%)	112(24%)	133(21%)	152(17%)	241(40%)

Unk= unknown

Table 5

Comparison of trials examining survival over time

Author	Number with MBC* (and % with *de novo* Stage IV)	Time Period Examined	Source	Median Survival	DFI or DRFI in model	Survival over time
Chia et al[5]	2,150 (21.4%)	1991–2001	Population- based registry	15–22 months#	No	Improved
Dabakuyo et al[33]	1459 (12%)	1982–2005	Population- based registry	Relative survival reported	No	Improved
Dawood et al[16]	2,091 (22.4%)	1991–2007	Single institution database	28.6 months	No	Improved$
Dawood et al[6]	15,438 (100%)	1988–2003	Population- based registry	23 months	No	Improved
Giorodano et al[4]	834 (0%)	1974–1994	Single institution database	21 months	Yes	Not Improved^
Largillier et al[17]	1,038 (0%)	1975–2005	Single institution database	23.1 months	Yes	Not improved
This analysis	3477 (0%)	1978–2010	Multi- institution database	20 months	Yes	Not improved overall

DFI = disease-free interval; MBC=metastatic breast cancer

*MBC includes both de novo Stage IV and recurrence after operable disease;

#Based on time period of recurrence, 30-day/month;

$HER2 status and trastuzumab use known and included in model;

^In multivariate analysis adjusting for tumor size, nodes, stage, DFI, ER status and site of metastases, p-value =0.09. In an alternate, unstratified model including DFI, p=0.04.