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Fifteen-year trends in metastatic breast cancer survival in Greece

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Abstract In the metastatic setting, a detected time trend to improved prognosis could be attributed to the corresponding recent advances in the therapeutic approaches. The aim of the current study was to first assess, in a large cohort of well over a thousand patients, the time trends in survival in MBC for the last 15 years and second to explore its association to prognostic factors affecting outcome including therapeutic regimen. This meta-analysis uses individual patient data collected from all the trials on MBC (6 nonrandomized, 4 randomized) conducted by HeCOG from 1991 through 2006. Four 4-year time periods (1991–1994, 1995–1998, 1999–2002, and 2003–2006) were constructed for exploration of time trends in survival according to the patient's date of metastatic diagnosis. Different first line regimens in the 10 trials include anthracycline monotherapy (epirubicin, in the early 1990s) and taxane-containing regimens either as monotherapy or in different

combinations with anthracyclines or other drugs. In two phase II studies and in the last randomized study, trastuzumab was administered in all the patients with HER2 overexpressing tumors. In this study, information is based on a total of 1361 patients with a median follow up of 3.7 years and median survival of 1.9 years (median survival 1.28, 1.68, 2.20, and 2.57 years for 1991–1994, 1995–1998, 1999–2002, and 2003–2006, respectively). Survival improved significantly across diagnosis time periods, by 25, 44, and 51%, respectively, in each time period (1995–1998: HR = 0.75, $P = 0.004$; 1999–2002: HR = 0.56, $P < 0.001$; 2003–2006: HR = 0.49, $P < 0.001$) as compared to the first time period (1991–1994). The effect of metastatic diagnosis time period remains almost unchanged in the presence of the following significant prognostic factors: performance status, hormonal receptor status, previous adjuvant chemotherapy, previous adjuvant hormonal treatment, visceral metastasis at entry, and number of metastatic sites. When exploring the effect of new systemic treatment introduction, taking into account the same significant prognostic factors, the effect of diagnosis time period disappears, and the survival improvement is explained directly by the introduction of new agents (hormonal treatment for metastatic disease: yes vs. no: HR = 0.72, $P < 0.001$; taxanes at first line: yes vs. no: HR = 0.69, $P = 0.002$; trastuzumab at first line: yes vs. no: HR = 0.63, $P < 0.001$). The results of this study provide significant evidence of improvement in prognosis of MBC patients within the last 15 years, taking into account all the important significant prognostic factors, and this improvement can be attributed to the use of new systemic treatment agents in the management of the disease.

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Introduction

Recent advances in the management of Metastatic Breast Cancer (MBC) include a large variety of new palliative approaches [1]. A decrease in overall breast cancer mortality rates has been noted in the last two decades [2, 3]. This decrease is attributed to the combined impact of more effective screening and more effective therapeutic approaches both in the adjuvant and metastatic setting [4]. In the adjuvant setting the relative contribution of therapeutic advances and of more effective screening are confounded and thus not directly distinguishable.

In the metastatic setting, a detected time trend to improved prognosis could be more readily attributed to the corresponding advances in the therapeutic approaches, assuming that the characteristics and the expected natural course of the disease did not change across time. No indication to the contrary exists, rendering this assumption plausible.

Trends in survival prolongation in MBC have been explored previously [4–7]. In a study examining the prognosis of 834 patients diagnosed with MBC from 1974 to 2000, longer survival, possibly attributed to the new active more recent therapies, was documented in the more recent cohorts [5]. Data extracted from the Surveillance, Epidemiology and End Results registry (SEER), on 15,438 women with MBC diagnosed between 1988 and 2003 suggested a modest improvement in overall and breast-specific survival [4]. Similarly, in 640 MBC patients entered in 6 consecutive trials between 1983 and 2001, a reduction in hazard of death between the 1995–1997 and 1998–2001 cohorts was suggested [6]. An improvement in survival over time, was found in 724 patients treated in three centers for an initially MBC between 1987 and 2000 [7].

In Greece, a cancer registry is not available to provide the basis for following the trends in incidence and/or survival of women with any stage Breast Cancer. The only available data is collected within Clinical Trials. The advantage of using data extracted from consecutive Clinical Trials lies in the fact that all information including patient and tumor characteristics, treatment regimen, prognostic factors and progression event or death, is collected prospectively. On the other hand, the study population as defined by specific entry and exclusion criteria, is not necessarily representative of the whole MBC population. Nevertheless, it can still be used to explore time trends that can be extrapolated to the whole population cohort with similar demographics and disease/tumor characteristics.

The clinical trial setting allows for new compounds or novel administration strategies to be available to patients before they formally enter routine clinical care. Thus, patients participating in these trials have the advantage of gaining access to new therapeutic approaches earlier than

the general patient population. This means that any therapeutic advantage identified in the clinical trials setting would be expected to be reflected at a later time in the general population setting.

In order to record the improvement in survival, we conducted a meta-analysis based on the individual patient data available from all clinical trials run consecutively by the Hellenic Oncology Cooperative Group (HeCOG) during the 90s through 2007. The first aim for this meta-analysis is to describe the course of the disease under “up to date” care as this is reflected within the clinical trials’ regimen of the corresponding era and explore time trends in MBC outcome. The second is to access the prognostic factors affecting outcome in MBC using this large cohort of well over a thousand patients.

Patients and methods

Individual patient data from a total of 1361 patients diagnosed with metastatic disease from 1991 through 2006, with a median follow up of 3.7 years, were included in this meta-analysis. These patients participated in ten trials designed and run consecutively by HeCOG, exploring different first-line treatment options for patients with MBC [8–17]. Information was collected prospectively according to the corresponding trial protocol and deposited in the central HeCOG office database. Follow-up was updated periodically with the last update in September 2007 for the purposes of this meta-analysis. Four of the trials address a randomized comparison between different treatment options, while six trials are Phase II single arm studies. Their characteristics are described in Table 1, including design characteristics (phase II or III, randomized or single arm, the study treatments, and the number of eligible patients). Dose dense monotherapy, incorporation of paclitaxel and more recently of trastuzumab represent the concepts tested in the consecutive clinical trials. The most recent study starting in 2002, a randomized Phase III trial, compares three non-anthracycline containing regimens, shown in earlier studies of this group and others to have significant activity and manageable toxicity in MBC (HE1102) [17]. The ten trials span the experience of HeCOG in Greek patients with MBC and represent the treatment options and their evolution for over 15 years.

Eligibility criteria were used uniformly across all studies, including histologically proven MBC, performance status (PS) ≤ 2 on the ECOG scale, life expectancy at least 12 weeks (or 2 months in the two first studies), age > 18 , and signed informed consent. Prior radiotherapy or hormone therapy either in the adjuvant or the metastatic setting was allowed, while previous adjuvant chemotherapy was

Table 1 Studies included in the meta-analysis

Study	Phase	Treatment	No. of patients
HDEPI-GCSF [8]	II	Epirubicin: 110 mg/m ² 6 cycles q 4 weeks	38 ^b
HE1192 [9]	II	Epirubicin: 110 mg/m ² 6 cycles q 2 weeks	49
HE1193 [10]	II ^a	Epirubicin: Grp A: 110 mg/m ² 6 cycles q 4 weeks, Grp B: 110 mg/m ² 6 cycles q 2 weeks	167
HE11B96 [11]	II	Paclitaxel → Carboplatin: 175 mg/m ² → 6 AUC 6 cycles q 3 weeks	66
HE1197 [12]	II	Epirubicin → Paclitaxel: 110 mg/m ² 4 cycles → 225 mg/m ² q 2 weeks	41
HE11B97 [13]	II ^a	Epirubicin, Paclitaxel: Grp A: 110 mg/m ² → 225 mg/m ² , 4 cycles q 2 weeks, Grp B: 80 mg/m ² + 175 mg/m ² , 6 cycles q 3 weeks	183
HE1199 [14]	II	Paclitaxel → Herceptin: 90 mg/m ² 12 cycles, 4 mg/m ² , 2 mg/m ² q 30 min	34
HE11B99 [15]	III ^a	Grp A: Epirubicin → Paclitaxel Grp B: Paclitaxel → Carboplatin Grp A: 80 mg/m ² → 175 mg/m ² 6 cycles q 3 weeks, Grp B: 175 mg/m ² → 6 AUC 6 cycles q 3 weeks	327
HE1100 [16]	II	Gemcitabine + Paclitaxel Herceptin: 1000 mg/m ² q 2 weeks +80 mg/m ² q 1 week	40
HE1102 [17]	III ^a	Grp A: Paclitaxel → Carboplatin Grp B: Gemcitabine → Docetaxel Grp C: Paclitaxel Grp A: 175 mg/m ² → 6 AUC 6 cycles q 3 weeks Grp B: 1000 mg/m ² days 1,8 → 75 mg/m ² day 8 6 cycles q 3 weeks Grp C: 90 mg/m ² q 3 weeks	416

^a Randomized studies

^b Four patients registered in HDEPI-GCSF before 1991 were excluded from the present analysis

allowed if the interval between completion of chemotherapy and first recurrence was at least 12 months. Exclusion criteria were previous chemotherapy for advanced disease, symptomatic brain metastases, history of other malignancy (except curatively resected non-melanoma skin cancer or in situ cervical cancer), myocardial infarction within the last 6 months, or other serious illness that would impair the ability of the patient to receive protocol treatment. In two of the studies with trastuzumab administration (HE1199 and HE1100) [14, 16], eligibility criteria required histologically proven HER-2/neu overexpression [$>25\%$ positive cells by immunohistochemistry or fluorescent in situ hybridization (FISH)-positive]. The current analysis is performed both including and excluding the two trastuzumab studies.

Statistical methods

The primary goal of the study was to explore the temporal trend of the outcome of MBC as it is expressed primarily by survival and secondarily by time to disease progression (TTP). Survival was calculated from randomization or registration date to the date of death or to the date of last contact. TTP was defined as the time interval between randomization or registration date and disease progression

or death from the disease (in case of unknown date of disease progression), or death from any other cause. Overall follow-up was updated periodically with the last update in September 2007.

In order to evaluate the calendar time effect at the time of diagnosis, accrual time was grouped in consecutive 4-year periods starting in 1991, leading to four consecutive time cohorts (1991–1994, 1995–1998, 1999–2002 and 2003–2006). Survival probabilities were estimated by the Kaplan–Meier method and the log-rank test was used in the comparison of survival curves between time periods and between studies. The association between survival and time period of diagnosis, treatment evolution (use of taxanes, trastuzumab, and hormonotherapy), and other candidate prognostic factors was explored through multivariate Cox models. In addition, similar analyses regarding TTP and survival after failure of first-line chemotherapy, were performed.

The baseline factors examined, were performance status (PS, 1 vs. 0, 2 vs. 0), menopausal status (pre vs. post), hormonal receptor (HR) [estrogen/progesterone receptor (ER and/or PgR)] status (positive vs. negative), nodal status (positive vs. negative), adjuvant treatment [chemotherapy (CT), radiotherapy (RT), hormonal treatment (HT)], relapse free survival (RFS, <1 year vs. ≥ 1 year), number

of metastatic sites at diagnosis of advanced disease (2 vs. 1, ≥ 3 vs. 1), metastatic site (visceral vs. not, bones vs. not, soft tissue/distant nodes vs. not). Whenever deemed appropriate, the category “unknown” was also used versus the relevant reference category for the corresponding baseline factor.

The effects of study phase (phase III vs. II) and type of study (randomized study vs. non-randomized) were also explored by including them as independent prognostic factors in the Cox models. The analysis was repeated with the exclusion of the two studies with trastuzumab regimen at their design, and with censoring at 5 years.

A backward selection procedure with removal criterion $P \geq 0.10$ was used for the selection of the multivariate Cox model which best describes the association of outcome to diagnosis time period or to the use of new therapeutic approaches in this setting in the presence of confounding factors. The fit of the Cox models was examined by use of Cox-Snell residuals and Schoenfeld residuals.

In order to justify the combined use of data from all study participants we explored the heterogeneity of the data set for all important patient and tumor characteristics through methods common in meta-analysis [18, 19]. The statistical package “RevMan” from the Cochrane Collaboration was used [20]. The log hazard ratios of every study for survival and TTP were calculated using the individual patient data and then combined across studies using either fixed or random effect models. The selection of the random or the fixed effect models was based on the corresponding heterogeneity tests and funnel plots with 95% confidence boundaries [21]. The standard error of the estimates of the study effects was used as the measure of accuracy for funnel plots. Median follow-up is based on the reverse censoring method [22].

All analyses were conducted according to “intention to treat” and only ineligible patients were excluded.

Results

Patient and tumor characteristics

A total of 1361 patients with MBC are included in the pooled analysis of the ten consecutive studies, with 198 of them diagnosed with metastatic disease during the period 1991–1994, while 314, 485 and 364 in the periods 1995–1998, 1999–2002 and 2003–2006, respectively. The median age of these women at metastatic diagnosis is 58 years (range 26–84 years), 57.5% with PS equal to 0, 73% of them postmenopausal at initial diagnosis, 55% with HR status positive, and half with positive nodes (Table 2). HR status is known in only 30% of the first cohort, increasing steadily across time to 58, 90 and up to 93% in the last

cohort. Similarly, nodal status is known in 41, 62, 79 and 79% in the respective time cohorts. A significant trend was detected across time periods, with the more recent studies including higher proportion of patients with better PS ($P < 0.001$) and positive nodes ($P < 0.001$). Locoregional metastases were present in 38% of the patients while distant ones in the overwhelming majority of patients (91%), with visceral (70%) and bone metastasis (49%) the most common sites, and at least three metastatic sites involved in 37% of the patients. Only 18 patients, evenly distributed across time periods, presented with ipsilateral isolated supraclavicular lymph nodes.

Results from the chi-square tests for heterogeneity and corresponding funnel plots supported the lack of heterogeneity between studies on all important patient and tumor characteristics examined (chi-square test for heterogeneity P -value > 0.05) apart from PS ($P = 0.03$ for survival and $P = 0.01$ for TTP).

More frequent use of adjuvant CT ($P < 0.001$, Table 2) and first line HT, RT, taxane-containing CT as well as treatment with trastuzumab is apparent in the more recent time periods (all $P < 0.001$) (Table 3).

Survival

Median survival of MBC patients was 1.28, 1.68, 2.20 and 2.57 years for 1991–1994, 1995–1998, 1999–2002, and 2003–2006, respectively (Figs. 1, 2). Survival improved significantly across diagnosis time periods, by 25, 44 and 51% respectively in each time period as compared to the first (1991–1994), (1995–1998: HR = 0.75, $P = 0.004$; 1999–2002: HR = 0.56, $P < 0.001$; 2003–2006: HR = 0.49, $P < 0.001$). The respective 3-year survival rates were increased from 17.5% in 1991–1994, to 27% in 1995–1998, 38.5% in 1999–2002 and 42% in 2003–2006.

When only patients with HR positive tumors ($n = 754$) were considered, median survival was 1.55, 1.71, 2.37 and 2.62 years in 1991–1994, 1995–1998, 1999–2002 and 2003–2006 (log rank test for trend $P < 0.001$) while the 3-year survival rates were 16, 25, 43 and 41.5% respectively (Fig. 3). When patients with HR-negative tumors were considered ($n = 262$) median survival was 1.25, 1.49, 1.61 and 3.19 years in the four time periods (log rank test for trend, $P = 0.002$) while the 3-year survival rates were 20, 28, 24 and 54% respectively (Fig. 4).

In order to evaluate the independent impact of new systemic treatments or metastatic diagnosis time period on survival, two separate models were fitted after adjusting for the significant covariates among all candidate prognostic factors mentioned in the statistical analysis section (Table 4). Results suggested that the effect of time period remains almost unchanged in the presence of PS, HR status, previous adjuvant treatment (CT, HT), visceral

Table 2 Patient characteristics by time cohort

Time cohort	1991–1994	1995–1998	1999–2002	2003–2006	Total
<i>N</i>	198	314	485	364	1361
Age (years)					
Median	57	56	58	60	58
Range	30–73	26–77	27–78	27–84	26–84
Unknown	5	1	6	1	13
	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)
Performance status					
0	62 (31)	154 (49)	325 (67)	241 (66)	782 (57.5)
1	96 (48.5)	111 (35)	126 (26)	105 (29)	438 (32)
2	40 (20)	49 (16)	33 (7)	16 (4)	138 (10)
Unknown	–	–	1 (0.2)	2 (0.5)	3 (0.2)
Menopausal status (at initial diagnosis)					
Premenopausal	58 (29)	103 (33)	130 (27)	71 (19.5)	362 (27)
Postmenopausal	136 (69)	211 (67)	354 (73)	292 (80)	993 (73)
Unknown	4 (2)	–	1 (0.2)	1 (0.3)	6 (0.4)
HR status					
Negative	10 (5)	46 (15)	116 (24)	90 (25)	262 (19)
Positive	50 (25)	135 (43)	320 (66)	249 (68)	754 (55)
Unknown	138 (70)	133 (42)	49 (10)	25 (7)	345 (25)
Positive nodes					
Negative	11 (6)	40 (13)	140 (29)	73 (20)	264 (19)
Positive	69 (35)	154 (49)	244 (50)	215 (59)	682 (50)
Unknown	118 (60)	120 (38)	101 (21)	76 (21)	415 (30.5)
Sites of metastases					
Locoregional metastases	58 (29)	145 (46)	195 (40)	125 (34)	523 (38)
Distant metastases	185 (93)	280 (89)	444 (91.5)	330 (91)	1239 (91)
Visceral	138 (70)	196 (62)	357 (74)	264 (72.5)	955 (70)
Soft tissue/nodes	52 (26)	67 (21)	83 (17)	90 (25)	292 (21.5)
Bones	111 (56)	133 (42)	237 (49)	182 (50)	663 (49)
Other distant metastases	26 (13)	34 (11)	29 (6)	16 (4)	105 (8)
Unknown	6 (3)	–	2 (0.4)	2 (0.5)	10 (1)
Number of metastatic sites					
1	55 (28)	96 (31)	136 (28)	116 (32)	403 (30)
2	64 (32)	101 (32)	153 (31.5)	132 (36)	450 (33)
≥3	73 (37)	117 (37)	194 (40)	114 (31)	498 (37)
Unknown	6 (3)	–	2 (0.4)	2 (0.5)	10 (1)
Study					
HDEPI–GCSF	38 (19)	–	–	–	38 (3)
HE1192	49 (25)	–	–	–	49 (4)
HE1193	111 (56)	56 (18)	–	–	167 (12)
HE11B96	–	66 (21)	–	–	66 (5)
HE1197	–	41 (13)	–	–	41 (3)
HE11B97	–	150 (48)	–	–	183 (13)
HE1199	–	1 (0.3)	33 (7)	–	34 (2.5)
HE11B99	–	–	327 (67)	–	327 (24)
HE1100	–	–	40 (8)	–	40 (3)
HE1102	–	–	52 (11)	364 (100)	416 (31)

Table 2 continued

Time cohort	1991–1994	1995–1998	1999–2002	2003–2006	Total
Adjuvant CT					
No	28 (14)	132 (42)	232 (48)	162 (44.5)	554 (41)
Yes	71 (36)	151 (48)	251 (52)	200 (55)	673 (49)
Unknown	99 (50)	31 (10)	2 (0.4)	2 (0.5)	134 (10)
Anthracycline-containing	18 (25)	64 (42)	132 (53)	135 (67.5)	349 (52)
CMF-like	30 (42)	43 (28.5)	136 (54)	117 (58.5)	326 (48)
Taxanes-containing	1 (1.4)	2 (1.3)	25 (10)	63 (31.5)	91 (13.5)
Adjuvant HT					
No	98 (49.5)	101 (32)	199 (41)	184 (50.5)	582 (43)
Yes	55 (28)	135 (43)	248 (51)	176 (48)	614 (45)
Unknown	45 (23)	78 (25)	38 (8)	4 (1)	165 (12)
Adjuvant RT					
No	98 (49.5)	207 (66)	321 (66)	220 (60)	846 (62)
Yes	55 (28)	105 (33)	161 (33)	140 (38.5)	461 (34)
Unknown	45 (23)	2 (1)	3 (1)	4 (1)	54 (4)
Relapse free interval (RFI)					
<1 year	42 (21)	74 (24)	148 (30.5)	102 (28)	366 (27)
1–3 years	38 (19)	75 (24)	122 (25)	87 (24)	322 (24)
3–5 years	31 (16)	46 (15)	87 (18)	65 (18)	229 (17)
>5 years	26 (13)	62 (20)	99 (20)	96 (26)	283 (21)
Unknown	61 (31)	57 (18)	29 (6)	14 (4)	161 (12)

metastasis at entry and number of metastatic sites. Also the effect of these significant confounders is almost identical in the presence of either MBC new therapeutic options (use of taxanes, trastuzumab and HR) or diagnosis time period in the multivariate Cox model. When both new first line agents and diagnosis time period are included in the same model, the effect of time disappears while the effect of first line treatments remains significant ($P < 0.001$, $P = 0.017$ and $P < 0.001$ for HT, taxanes and trastuzumab, respectively). Analysis where the diagnosis time period was treated as a continuous variable (year of diagnosis) converged with the same final model as the one in Table 4, with a 4% decrease in hazard of death per consecutive year of metastatic diagnosis (HR = 0.96, $P < 0.001$).

The results of multivariate analysis were consistent and similar when the analysis was repeated by (a) excluding the two studies with trastuzumab in their design, (b) adjusting for phase or (c) type of study, (d) using censoring at 5 years.

Time to disease progression (TTP)

Median TTP improved significantly over time (log rank test for trend $P < 0.001$, (Figs. 1, 5). The median TTP estimates were 0.60, 0.75, 0.85 and 0.88 years for 1991–1994, 1995–1998, 1999–2002, and 2003–2006, respectively. In

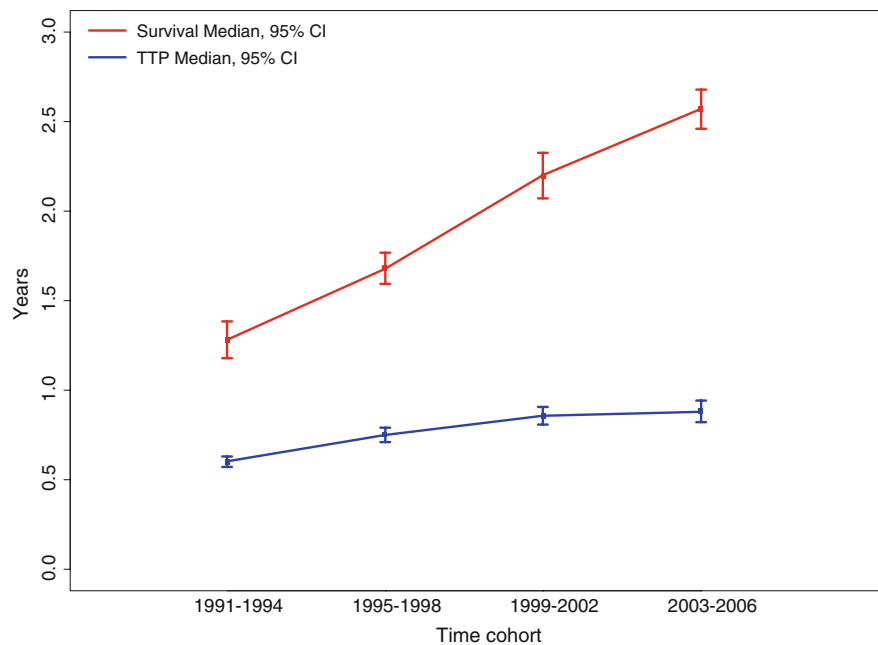
multivariate analysis, adjusting for the same confounders as for survival, in the model including the diagnosis time period, significant effect of the diagnosis time cohort was detected (HR = 0.87, 0.73 and 0.69; $P = 0.22$, 0.008 and 0.003, respectively for 1995–1998, 1999–2002, and 2003–2006 compared to 1991–1994), while in the model including first line treatment, HR = 0.73, $P < 0.001$ for HT (yes vs. no), HR = 0.81, $P = 0.055$ for taxanes and HR = 0.84, $P = 0.057$ for trastuzumab. When including in the multivariate model, both the diagnosis time cohort and first line treatment, the diagnosis time cohort effect is non-significant while the only significant first line treatment is HT ($P = 0.009$).

Time from progression to death

In order to explore whether the survival benefit could be attributed to treatment beyond first line, an analysis of time from progression to death was performed for patients with a disease defining event. Survival after failure of first-line chemotherapy significantly improved with time (log rank test $P = 0.001$). Median time from progression to death was 0.59, 0.75, 0.80, and 0.97 years in the cohorts 1991–1994, 1995–1998, 1999–2002, and 2003–2006 respectively. However, in the multivariate analysis, in contrast to the results for TTP and survival, when adjusting for the

Table 3 Treatment for metastatic disease (MD)

Time cohort	1991–1994	1995–1998	1999–2002	2003–2006	Total
<i>N</i>	198	314	485	364	1361
Treatment for MD	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)
HT at 1st line					
No	83 (42)	189 (60)	196 (40)	158 (43)	626 (46)
Yes	33 (17)	125 (40)	282 (58)	201 (55)	641 (47)
Unknown	82 (41)	–	7 (1)	5 (1)	94 (7)
RT at 1st line					
No	94 (47.5)	220 (70)	297 (61)	242 (66.5)	853 (63)
Yes	25 (13)	93 (30)	159 (33)	117 (32)	394 (29)
Unknown	79 (40)	1 (0.3)	29 (6)	5 (1)	114 (8)
Taxanes at 1st line					
No	198 (100)	58 (18.5)	9 (2)	14 (4)	279 (20.5)
Yes	–	256 (81.5)	476 (98)	350 (96)	1082 (79.5)
Trastuzumab (at any time)					
No	175 (88)	191 (61)	84 (17)	255 (70)	705 (52)
Yes	–	5 (2)	115 (24)	108 (30)	228 (17)
Unknown	23 (12)	118 (38)	286 (59)	1 (0.3)	428 (31)
Trastuzumab at 1 st line					
No	198 (100)	312 (99)	393 (81)	272 (75)	1175 (86)
Yes	–	2 (1)	92 (19)	92 (25)	186 (14)



		1991-1994	1995-1998	1999-2002	2003-2006
Survival (yrs)	Events/Total cases	177/198	253/314	318/485	185/364
	Median (95% C.I.)	1.28 (1.08-1.48)	1.68 (1.51-1.85)	2.20 (1.95-2.45)	2.57 (2.35-2.79)
TTP (yrs)	Events/Total cases	188/198	282/314	410/485	280/364
	Median (95% C.I.)	0.60 (0.54-0.66)	0.75 (0.67-0.82)	0.855 (0.76-0.95)	0.88 (0.77-1.00)

Fig. 1 Median Survival and TTP across time periods

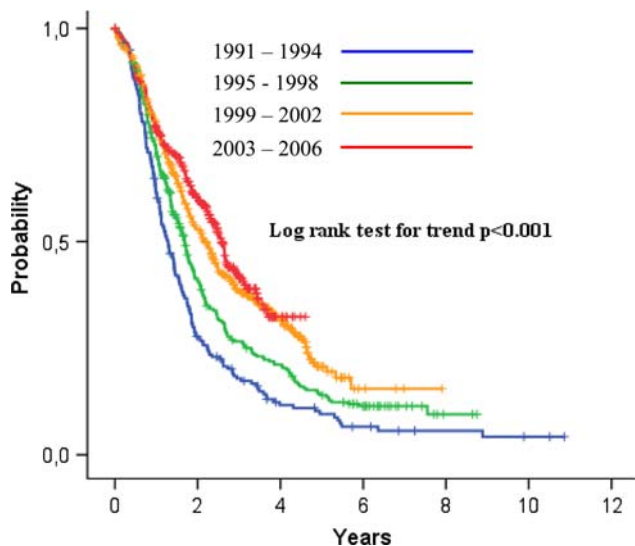


Fig. 2 Kaplan–Meier estimates of Survival by time cohort

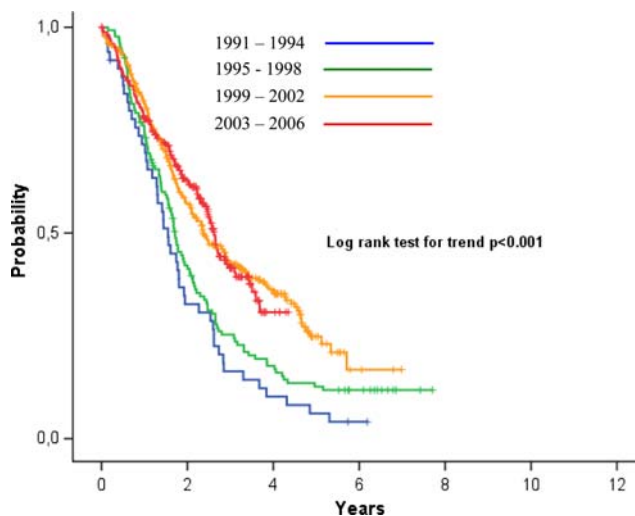


Fig. 3 Kaplan–Meier estimates of survival by time cohort in HR-positive patients

prognostic factors, the detected across time improvement on time from progression to death is not significant anymore. This result suggests that changes across time of the 2nd, 3rd and higher lines of treatment do not account for the survival improvement detected across consecutive diagnosis time cohorts.

Discussion

In the current meta-analysis, improvement across time was observed in the survival of 1361 women, participating in the HeCOG clinical trials, with MBC diagnosed in the period from 1991 to 2006. The median survival estimates

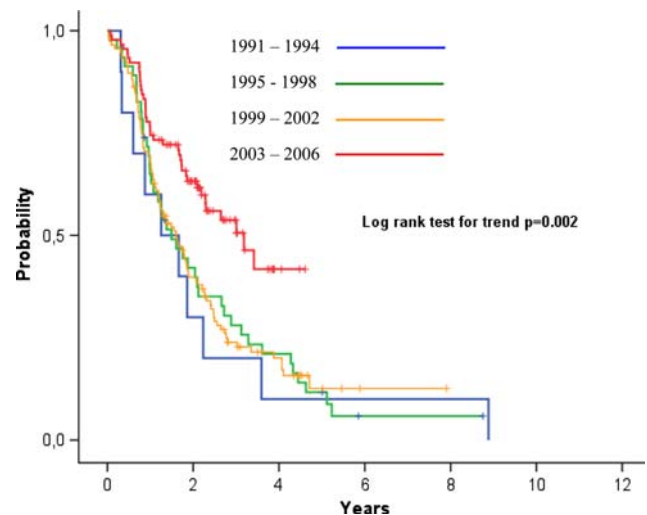


Fig. 4 Kaplan–Meier estimates of survival by time cohort in HR-negative patients

of 1.28, 1.68, 2.20 and 2.57 years for 1991–1994, 1995–1998, 1999–2002, and 2003–2006, observed here, reflect the ones already reported in the literature [1, 6]. Survival improved significantly across diagnosis time periods, by 25, 44 and 51% respectively in each time period as compared to the first (1991–1994). The prognostic factors across all time periods significantly associated with improved survival were good PS, positive HR status, previous adjuvant treatment (CT, HT), absence of visceral metastasis at entry and lower number of metastatic sites.

The observed increase in survival in the current study could be attributed to different factors such as (1) improvement in the effectiveness of new anticancer agents, (2) lead time bias stemming from either more intensive follow-up policies in operated BC patients and/or use of more effective diagnostic tools, (3) better control of toxicities leading to optimal chemotherapy dose delivery and improvement in supportive care [6].

In the current study, the significant time trend in survival improvement observed first in univariate analysis, persisted in multivariate analysis where adjustment for all important prognostic factors was performed. This wasn't the case in a retrospective analysis by Gennari et al. [6], exploring temporal trends between 1983 and 2001 based on individual data from 640 patients from six consecutive studies that suggested a reduction in hazard of death in only two cohorts (1995–1997 and 1998–2001) where taxane was added to first-line CT.

In another series of 834 women diagnosed with MBC between 1974 and 2000 and treated previously at the M.D. Anderson Cancer Center within adjuvant anthracycline chemotherapy protocols, a significant survival improvement was associated with more recent period of recurrence [5]. Again, although the univariate analysis showed a

Table 4 Cox model for OS with confounders

	With treatment			With time cohort		
	HR	95% C.I.	<i>P</i>	HR	95% C.I.	<i>P</i>
Performance status						
1 vs. 0	1.54	1.33–1.79	<0.001	1.55	1.34–1.79	<0.001
2 vs. 0	2.72	2.19–3.37	<0.001	2.84	2.29–3.52	<0.001
Receptor status						
Positive vs. Negative	0.785	0.65–0.94	0.009	0.74	0.62–0.88	0.001
Unknown vs. Negative	0.88	0.71–1.09	0.25	0.85	0.68–1.04	0.12
Adjuvant CT						
Yes vs. No	1.18	1.02–1.38	0.03	1.22	1.05–1.42	0.008
Unknown vs. No	0.785	0.59–1.04	0.095	0.91	0.70–1.18	0.46
Adjuvant HT						
Yes vs. No	1.26	1.08–1.47	0.004	1.16	1.0–1.36	0.052
Unknown vs. No	1.57	1.26–1.95	<0.001	1.40	1.14–1.73	0.001
Visceral						
Yes vs. No	1.44	1.24–1.68	<0.001	1.42	1.22–1.66	<0.001
Number of metastatic sites						
2 vs. 1	1.21	1.02–1.44	0.03	1.22	1.02–1.45	0.03
≥3 vs. 1	1.62	1.37–1.92	<0.001	1.61	1.36–1.91	<0.001
Treatment for MD						
HT						
Yes vs. No	0.72	0.62–0.83	<0.001	–	–	–
Unknown vs. No	0.83	0.61–1.13	0.23	–	–	–
Treatment with taxanes in 1st line						
Yes vs. No	0.69	0.55–0.87	0.002	–	–	–
Herceptin during first line treatment						
Yes vs. No	0.63	0.50–0.80	<0.001	–	–	–
Time cohort						
1995–1998 vs. 1991–1994	–	–	–	0.76	0.60–0.95	0.02
1999–2002 vs. 1991–1994	–	–	–	0.63	0.50–0.81	<0.001
2003–2006 vs. 1991–1994	–	–	–	0.60	0.46–0.78	<0.001

significant survival improvement across time, in multivariate analysis the reported reduction in risk of approximately 1% for each increasing year was not found to be statistically significant in the presence of the important prognostic factors (number of involved nodes, site of disease recurrence and size of primary tumor).

Another study on patients from three French centers, did not address which intervention leads to survival improvement. Survival was compared between only two time-periods, 1994–2000 versus 1987–1993, and a significant improvement was found in the more recent period, (adjusting for visceral involvement, HR status, and involvement of multiple organs), for 724 patients treated for an initially MBC [7]. First line treatments were not included in the multivariate models, and thus only an indirect suggestion that new treatments account for the survival improvement should be considered feasible.

In a population-based study on 2150 patients, diagnosed from 1991 to 2001, the more recent cohorts (1999–2001 and 1997–1998), were associated with improved survival compared to the first cohort (1991–1992). In this study, although this temporal improvement in survival is attributed to “new chemotherapeutic and hormone agents” for MBC, no attempt is made to include these agents as predictors in the multivariate Cox models that include the time cohorts. Thus, this study also can be considered at best a surrogate to suggest that systemic therapy is associated with improved survival [23].

In contrast to all above reports, in our study the observed consistent survival improvement across time, holds in the presence of prognostic factors while it disappears when introducing into the model the effect of new systemic therapy agents, i.e., taxanes and/or trastuzumab and/or HT for metastatic disease. This fact along with the results on

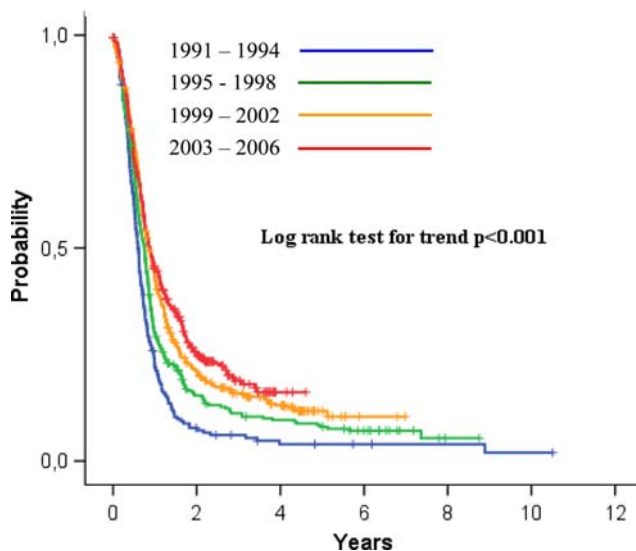


Fig. 5 Kaplan–Meier estimates of TTP by time cohort

the effect of the important prognostic factors that remain almost identical in the final multivariate model, strongly supports the hypothesis that the major improvement shown in survival can be attributed to the introduction of improved systemic therapeutic alternatives. The similar, although weaker results presented regarding TTP, an endpoint prone to ascertainment bias, do not contradict this hypothesis.

The 31% reduction in death rate (HR = 0.69, 95% C.I. 0.55–0.87) attributed to taxanes after taking into account all other significant predictors, falls within the 95% C.I. of the benefit previously reported [6]. The 37% reduction in death rate attributed to trastuzumab (HR = 0.63, 95% C.I. 0.50–0.80), is a dramatic benefit, higher than the original benefit of 20% reported in MBC in the pivotal trial of Herceptin [24]. Lastly, hormonal therapy has also a significant beneficial effect of a 28% magnitude (HR = 0.72, 95% C.I. 0.62–0.83).

In conclusion, this study provides significant evidence of improvement in prognosis of MBC patients within the last 15 years, while taking into account the beneficial effect of all significant prognostic factors [good PS, positive HR status, previous adjuvant treatment (CT, HT), absence of visceral metastasis at entry and lower number of metastatic sites]. In addition, there is considerable evidence strongly suggesting that this improvement can be attributed to the use of new systemic therapy agents in the management of the disease.

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