Overall Survival in Metastatic Breast Cancer Patients in the Third Millennium: Results of the COSMO Study*

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Abstract

Metastatic breast cancer remains a deadly disease despite scientific progress. The COSMO study included 3721 patients and aimed to detect a temporal variation in overall survival during the period 2000-2008 that had not yet been demonstrated. Disease-free interval, metastatic site, age at diagnosis, and tumor biology remain important factors that affect prognosis.

Introduction: Metastatic breast cancer (MBC) is a life-threatening disease, and although some data suggest a trend in survival improvement, it has not yet been unequivocally demonstrated. This study aimed to evaluate the overall survival (OS) of MBC patients, assessing its correlation with prognostic factors. **Patients and Methods:** COSMO (Checking Overall Survival in a MBC Observational study) is an Italian longitudinal retrospective multicenter study that enrolled patients with MBC diagnosed between 2000 and 2008. The primary objective was to detect a temporal difference in OS; the secondary objective was to identify prognostic factors as causal factors of the temporal variation in OS. **Results:** A total of 3721 of 3930 patients from 31 centers were distributed in 3 periods: 886 (23.8%), 1302 (35.0%), and 1533 (41.2%) in 2000-2002, 2003-2005, and 2006-2008, respectively. With a median follow-up of 9.3 years, median OS was 2.8 years (95% confidence interval, 2.6-2.9). No difference in OS was found in the 3 cohorts (P for trend = .563). The worst prognosis was observed for patients with triple-negative MBC (OS, 1.5 years) and for those with central nervous system metastases (1.7 years); the best prognosis was observed in those with bone metastases or nonvisceral disease (3.4 and 3.2 years, respectively) and in patients with a disease-free interval, defined as the time between resection of the primary malignancy and diagnosis of MBC, of $>$ 2 years (3 years). **Conclusions:** The COSMO study found improvement in OS between 2000 and 2008. Molecular subtype remained the strongest prognostic factor, and the role of other prognostic factors was confirmed, in particular disease-free interval, site of metastasis, and age.

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Introduction

Metastatic breast cancer (MBC) is the cause of death of about 12,000 women every year in Italy.[1] The introduction of new drugs over the last 20 years, along with the development of supportive care, aimed to improve survival. In the literature, several studies were designed to better understand survival trends in patients with MBC and to determine which factors affect prognosis.

Giordano et al[2] in 2004 published a retrospective study exploring overall survival (OS) trends in MBC patients between 1974 and 2000. The results showed that median OS improved through the observed period, which was considered the consequence of improvement in treatments and early disease detection. A similar trend over the decades was detected by Chia's group in 2007.[3] Other authors detected a small improvement in prognosis only for patients treated with taxanes, starting from the late 1990s.[4,5]

More recent data based on a large French cohort showed a slight improvement in survival, limited to HER2 (human epidermal growth factor receptor 2)-positive breast cancer cases.[6]

The literature shows a slight trend in survival improvement for MBC that has not been unequivocally demonstrated, and the factors that influence prognosis are still unclear. In this setting, the primary objective of our study was to detect a temporal difference in OS for MBC patients in Italy. A secondary objective was to identify prognostic factors for OS.

Materials and Methods

COSMO is a spontaneous, longitudinal, retrospective, multicenter, nonpharmacologic Italian study. This retrospective observational study aimed to evaluate the OS of MBC patients, assessing its correlation with specific prognostic factors (demographic, clinical, pathologic, and biologic).

The COSMO network is a group made up of clinical oncologists with expertise in breast cancer treatment affiliated with different Italian treatment centers over the country. The study was approved by local ethics committees.

Patient data were retrospectively retrieved from medical charts in each participating center.

The following information was collected: age at diagnosis of MBC, disease histotype, disease stage at diagnosis, presence (M1) or absence (M0) of synchronous metastasis at diagnosis, disease-free interval (DFI), biologic subtype, treatments provided, and date of last contact or death. For patients who were still alive, a live status update was provided prospectively through a telephone call.

Female patients aged over 18 years with new cases of MBC diagnosed between January 1, 2000, and December 31, 2008, were consecutively enrolled. OS was defined as the time of diagnosis of MBC to death from any cause.

In order to detect a temporal trend, eligible patients were divided into 3 different cohorts depending on the date of MBC diagnosis: 2000-2002, 2003-2005, and 2006-2008.

Survival functions were estimated by the Kaplan-Meier method. The follow-up duration was estimated by the reverse Kaplan-Meier method. The completeness of follow-up was estimated by the *C* index.[7] The log-rank test for trend was used to detect a temporal trend. The Cox regression model was used to detect and estimate the statistical association between predictors and OS. Baseline characteristics were summarized by absolute and percentage frequencies for categorical variables and median and interquartile range (IQR) for continuous variables.

Statistical analysis was performed by SAS 9.4 software (SAS Institute, Cary, NC). Survival functions were presented graphically by Stata 12.1 software (StataCorp, College Station, TX).

Results

The COSMO database was locked on April 1, 2017. A total of 3930 patients were enrolled from 31 Italian oncologic centers spread all over the country; 3721 patients were eligible and were included in the analysis (193 were excluded because they were not within the temporal range under study, and 16 were excluded because of a lack of OS data). The patients were distributed over the 3 different periods as follows: 886 (23.8%), 1302 (35.0%), and 1533 (41.2%) in 2000-2002, 2003-2005, and 2006-2008, respectively. It should be noted that the first group is less represented than the other two, probably because of difficulties in accessing the oldest clinical reports.

Median (IQR) age at first diagnosis was 61.2 (51.3-71.1) years. As expected, the most frequent histologic type was ductal carcinoma, and most patients had nonmetastatic disease at diagnosis (only 23.3% of patients had metastatic disease at diagnosis). Table 1 lists the patient characteristics.

Patients were placed into one of 3 subgroups on the basis of the biologic characteristics of their tumor expressed via immunohistochemical staining. The HER2-positive group included all patients with HER2-positive breast cancer, regardless of hormone receptor (HR) status (estrogen or progesterone). The HR-positive group included patients with positive HR and negative HER2 disease. Patients with both HER2-negative and HR-negative breast cancers were classified as having triple-negative (TN) disease.[8] A total of 59.8% of patients had HR-positive disease, 13.5% had TN breast cancer, and 26.7% had HER2-positive disease.

This distribution reflects the real population of MBC patients, in which HER2-positive disease is found on average in 25% of cases. The missing data rate on tumor biology decreased during the 3 observed periods, especially regarding HER2 status assessment, reflecting how in Italy this test was introduced in clinical practice starting from 2001.

Metastatic sites were categorized as visceral disease and nonvisceral disease (Table 2). A total of 1744 patients (47.3%) had visceral disease. Of them, 307 had central nervous system (CNS) metastasis (8.3% of the overall population).

Table 1 Patient and Tumor Characteristics

Characteristic	Time Period			Total
	2000-2002	2003-2005	2006-2008	
N	884	1300	1531	3715
Age at first diagnosis				
Median	61.0	61.7	61.0	61.2
Q1-Q3	50.8-70.3	52.0-71.4	51.2-71.6	51.3-71.1
Missing data	2 (0.2)	2 (0.1)	2 (0.1)	6 (0.1)
Stage at diagnosis				
M0	664 (77.0)	975 (77.1)	1121 (76.3)	2760 (76.8)
M1	198 (23.0)	289 (22.9)	348 (23.7)	835 (23.3)
Missing data	24 (2.7)	38 (2.9)	64 (4.2)	126 (3.4)
Histologic type				
Ductal carcinoma	651 (73.5)	960 (73.7)	1137 (74.2)	2748 (73.9)
Lobular carcinoma	103 (11.6)	150 (11.5)	193 (12.6)	446 (12)
Mixed carcinoma	30 (3.4)	64 (4.9)	79 (5.2)	173 (4.6)
Other histologic type	45 (5.1)	83 (6.4)	86 (5.6)	214 (5.8)
Missing data	57 (6.4)	45 (3.5)	38 (2.5)	140 (3.8)
Tumor biology				
Hormone receptor positive	401 (66.9)	597 (58)	810 (58.1)	1808 (59.8)
HER2 positive	122 (20.4)	300 (29.2)	384 (27.5)	806 (26.7)
Triple negative	76 (12.7)	132 (12.8)	201 (14.4)	409 (13.5)
Missing data	287 (32.4)	273 (21.0)	138 (9.0)	698 (18.7)

Data are presented as n (%) unless otherwise indicated.

Nonvisceral disease was defined as the presence of bone and/or soft tissue metastasis (including lymph nodes, skin, pleural, peritoneal, or subcutaneous involvement) without visceral metastasis. This issue was present in 46.9% of patients. The subgroup of patients with only bone disease comprised 825 women (22.4%). Median follow-up was 9.3 years for the overall population, while median (IQR) in the 3 groups was 12.8 (8.6-15.4) years, 10.2 (5.8-11.7) years, and 8.5 (4.2-9.9) years for 2000-2002, 2003-2005, and 2006-2008, respectively.

Follow-up maturity was estimated by the number of deaths and the completeness *C* index for patients who were still alive (ie, the percentage of the total observed person-time of follow-up reflects the potential time of follow-up) at the time we closed the database. The follow-up was found to be mature for all 3 cohorts. Deaths occurred in 810 (91.4%) of 886 patients for 2000-2002, 1120 (86%) of 1302 for 2003-2005, and 1179 (76.9%) of 1533 for 2006-2008, with a total of 3109 events (83.6%). The *C* index for patients who remained alive was 47.9% for 2000%-2002%, 49.2% for 2003%-2005%, and 46.9% for 2006-2008, with a total of 48.2%.

Median OS was 2.8 years (95% CI, 2.7-2.9) from the diagnosis of MBC. With a *P* value for trend of .563, no difference in OS was found for the 3 periods. Survival estimates are reported in Table 3. A nonhomogeneous accrual performed by participating centers during the 3 periods under examination could have introduced selection bias, making a comparison between the 3 cohorts unreliable. Figure 1 shows the OS in the 3 time cohorts.

Regarding biologic subtype, median OS for HER2-positive patients was 3.1 years (95% CI, 2.8-3.4), for HR-positive disease was

Table 2 Metastatic Sites at Diagnosis of Metastatic Disease

Characteristic	Time Period			Total
	2000-2002	2003-2005	2006-2008	
Visceral disease	439 (50.1)	649 (50.3)	853 (56.2)	1941 (52.7)
Nonvisceral disease	437 (49.9)	642 (49.7)	665 (43.8)	1744 (47.3)
Missing data	10 (1.1)	11 (0.8)	15 (1.0)	36 (1.0)
Subgroup data				
CNS metastasis subgroup of visceral disease	54 (6.2)	108 (8.4)	145 (9.6)	307 (8.3)
Only bone disease subgroup of nonvisceral disease	217 (24.8)	292 (22.6)	316 (20.8)	825 (22.4)

Data are presented as n (%).

Table 3 Survival Estimates

Survival	Point Estimate (95% CI) for:			
	Time Period 2000-2002	Time Period 2003-2005	Time Period 2006-2008	Total
Median (years)	2.8 (2.6-3.0)	2.9 (2.8-3.1)	2.6 (2.4-2.7)	2.8 (2.6-2.9)
OS at 1 year	0.81 (0.79-0.84)	0.83 (0.81-0.85)	0.80 (0.78-0.82)	0.81 (0.80-0.83)
OS at 2 years	0.63 (0.60-0.66)	0.64 (0.62-0.67)	0.60 (0.58-0.63)	0.62 (0.61-0.64)
OS at 5 years	0.26 (0.24-0.29)	0.27 (0.24-0.29)	0.24 (0.21-0.26)	0.26 (0.24-0.27)

Abbreviations: CI = confidence interval; OS = overall survival.

3.0 years (95% CI, 2.8-3.1), and for TN disease was 1.5 years (95% CI, 1.3-1.7) (Figure 2A).

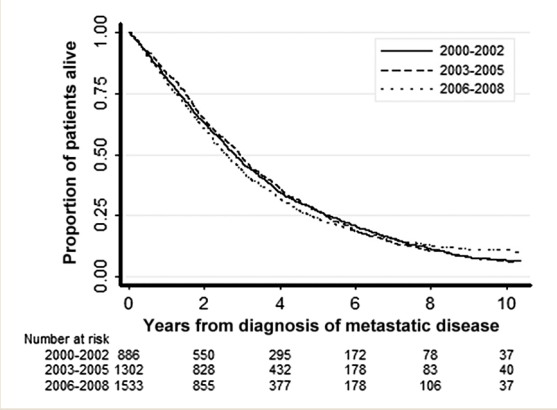
Median (IQR) DFI was 3.2 (1.7-6) years, and it was calculated from diagnosis to first relapse only for M0 patients, excluding patients with de novo metastasis. Figure 2B shows how DFI affects prognosis: median OS was 2.1 years for patients with a DFI of ≤ 2 years (95% CI, 1.8-2.2) and was 3.0 years (95% CI, 2.9-3.2) for patients with a DFI of > 2 years. Patients with a DFI of < 2 years have shorter OS.

DFI results were strongly associated with disease biology. Interestingly, patients who experienced late disease recurrence (DFI > 2 years) had mostly HR-positive disease (971 patients, 67.0%), versus 23.3% for HER2-positive disease (n = 338) and 9.7% for TN disease (n = 141). On the contrary, the group that experienced early relapse (DFI ≤ 2 years) included a higher rate of HER2-positive (30.7%) and TN breast cancer (24%) versus HR-positive disease (45.3%) (χ^2 test, $P < .001$).

All HR-positive patients received hormone treatment. The overall HER2-positive population received trastuzumab in the metastatic setting in 81.1% of cases (565 patients). As expected, the use of trastuzumab increased during the observed period for this cohort (69.4% in 2000%-2002%, 78.8% in 2003%-2005%, and 81.1% in 2006-2008). This may justify the good prognosis of patients with HER2-positive disease in our population.

The outcome correlates with age (Figure 2C). We divided patients into 4 groups according to age (<45 years, 45-55 years, 55-65 years, and $\geq$ 65 years) at the time of onset of metastatic disease.

Figure 1 Overall Survival at 3 Different Time Periods



Patients aged $\geq$ 65 years had the worst prognosis, with a median OS of 2.2 months (95% confidence interval [CI], 2.1-2.4, $P < .001$).

Regarding metastatic sites, we collected data on the site of first relapse, identifying two groups of patients: those with only nonvisceral disease (including bone and/or soft tissue metastasis, lymph nodes, skin, pleural, peritoneal, or subcutaneous involvement) and those with disease at least one visceral site. We also identified two subgroups: the first with only bone disease (subgroup of nonvisceral disease) and the second with CNS involvement (subgroup of visceral disease).

Figure 2D shows the OS trends for these 4 groups and shows how nonvisceral disease correlates with a median OS of 3.2 months (95% CI, 3.1-3.4) versus visceral involvement (median OS, 2.4; 95% CI, 2.3-2.5; $P < .001$). With a median OS of 1.7 years (95% CI, 1.6-1.9), the worst prognosis is for patients with CNS metastasis, while the best prognosis is for patients with only bone disease, with a median OS of 3.4 years (95% CI, 3.1-3.6).

Median OS for ductal carcinoma was 2.8 months (95% CI, 2.7-2.9), versus 2.8 (95% CI, 2.5-3.0), 2.9 (95% CI, 2.5-3.5), and 2.8 (95% CI, 2.5-3.3) months for lobular, mixed, and other histotypes, respectively.

At multivariate analysis, biologic subtype, age, and metastatic site were the only characteristics that were independently correlated with OS (Table 4). No difference in prognosis was found for patients with synchronous (M1) versus metachronous (M0) metastasis ($P = .899$), considering that we calculated OS since the diagnosis of metastatic disease.

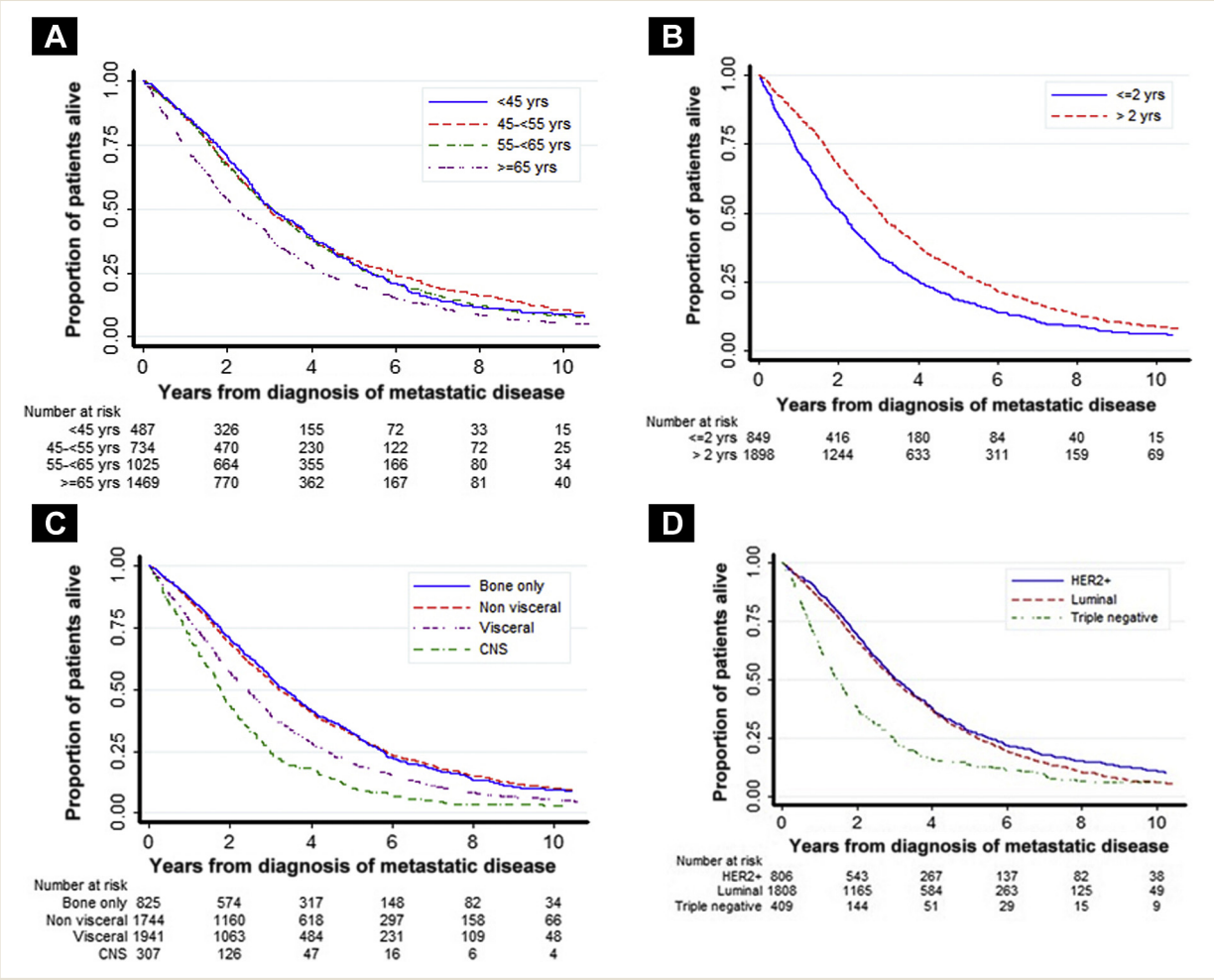
Discussion

With a total of 3930 patients enrolled in 31 centers throughout Italy, the COSMO study provides a large overview of Italian clinical data on MBC between 2000 and 2008, providing new insight into the patients' prognosis.

First, no change in OS was observed during the decade under study. This result could be considered unreliable because of the nonhomogeneous number of patients in the 3 different periods enrolled. Nevertheless, this finding was consistent with the Italian tumor registry,[1] which reports a reduction in mortality observed only starting in 2008 (−2.2% per year) despite an increase in the incidence of breast cancer cases, probably due to a higher adherence to screening programs.

Data from other studies reported different conclusions.[2,4,5] In 2004 Giordano et al[2] published an observational study on 834 patients with MBC diagnosed between November 1974 and December 2000 that aimed to explore the correlation between year of relapse and OS. The overall population was divided into 5 groups

Figure 2 Overall Survival According to (A) Biologic Subtype, (B) Disease-Free Survival, (C) Age, and (D) Metastatic Site With $P = .534$, No Difference in Prognosis Was Found For Different Histotypes



according to year of relapse. The authors found an improvement in OS in the more recent cohorts. Despite this result, the authors declared that the patients who experienced relapsed in the earlier periods were treated with adjuvant chemotherapy, probably because they were at a higher risk of relapse than the more recent cohorts.[2]

Another study, conducted by Andre et al[5] in 2004, showed an OS benefit in patients with MBC diagnosed after 1994, a period of introduction of taxanes and new aromatase inhibitors, versus patients diagnosed before this year, especially in HR-positive breast cancer. The authors concluded that this benefit could be attributed to the introduction of new treatments for metastatic disease.

A further confirmation of this hypothesis was reached the next year by Gennari et al,[4] who studied patients whose disease relapsed between 1983 and 2001, finding an OS benefit evident from 1994. In this study, the use of taxanes was significantly associated with an improved OS, suggesting once again that the use of these drugs was the only contributing factor to the prognosis.

The authors of the aforementioned studies, which enrolled patients with relapsed disease within a large time period, identified a benefit in OS due to the new drugs introduced in clinical practice. It is likely that our choice to identify 3 cohorts in only 9 years could have hidden the differences in survival rates because the new drugs were available over the period explored, and eventually in different lines of treatment. Moreover, the benefit of new drugs in this setting is evident after several years since its introduction. For example, taxanes and aromatase inhibitors, which arrived in clinics in the 1990s, led to a survival benefit in the second half of that decade.

Regarding the secondary objectives of the study, some prognostic factors were identified. Notably, when we focus on biologic subtype, the median OS for the HER2-positive group was 3.1 years, which is significantly higher than that of patients with TN breast cancer. Given that HER2-positive status historically correlates with more aggressive disease, we hypothesize that the inclusion in this subgroup of all patients with HER2-positive disease, regardless of hormone receptor status, and the progressive introduction of trastuzumab in clinical practice could explain the fairly good prognosis, which is similar to that of HR-positive patients. Similar data were reported by Gobbini et al,[6] who published a real-life survival

Table 4 Predictors of Overall Survival

Characteristic	Category or Regression Term	Univariate Analysis			Multivariate Analysis		
		Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Biologic subtype	HER2 positive	1	—	<.001	1	—	<.001
	Hormone receptor positive	1.02	0.94-1.10		1.08	1.00-1.17	
	Triple negative	1.76	1.56-1.98		1.84	1.62-2.08	
Age (every 10 years)	Linear	0.50	0.41-0.62	<.001	0.49	0.39-0.61	<.001
	Quadratic term	1.07	1.05-1.09		1.08	1.06-1.10	
M stage at diagnosis	M0	1	—	.422	1	—	.899
	M1	1.04	0.95-1.13		0.99	0.91-1.09	
Histotype	CDI	1	—	.534	1	—	.054
	CLI	1.08	0.97-1.20		1.12	1.01-1.26	
	Mixed	0.98	0.83-1.16		1.08	0.91-1.29	
	Other	0.97	0.83-1.13		0.89	0.75-1.05	
Site of metastasis	Nonvisceral	1	—	<.001	1	—	<.001
	Visceral	1.39	1.29-1.49		1.51	1.40-1.63	

Abbreviations: CDI = ductal invasive carcinoma; CI = confidence interval; CLI = lobular invasive carcinoma.

analysis in a large cohort of French MBC patients, demonstrating that the slightly improvement of OS is confined to HER2-positive cases.

Age ≥ 65 years clearly correlates with poor prognosis, independent of biologic subtype. This finding consolidates some data reported in the literature[9,10] that support the hypothesis of elderly patients having the worst OS. The idea of a better prognosis in older patients is probably an assumption from studies in early breast cancer, where younger age is an independent negative prognostic factor.[11] In our opinion, metastatic disease in the older population has a worse outcome probably because of few treatment opportunities, due to both the fear of toxicities and the presence of comorbidities. On the other hand, we cannot express any conclusion about very young patients, those under 35, because of their small number in this study.

A 2018 study conducted in the United States demonstrated an improvement in OS and cancer-specific survival in young breast cancer patients, including patients diagnosed from 1975 to 2015. The authors attributed this event to treatment rather than screening. Furthermore, the improvements appeared to reach a plateau after 2005, except among young women with metastatic breast cancer, in whom survival continued to improve throughout the period; this result seems to be a specific effect of new drugs.[12]

Our multivariate analysis revealed that the first metastatic site is an important independent prognostic factor. Visceral disease (vs. nonvisceral disease), and in particular disease with CNS involvement, correlates with a poor outcome in terms of OS. The best prognosis is seen in the subgroup of patients with only bone metastases, which made up 22.4% of the overall population in our study, who reached a median survival of 3.4 years. This good outcome is consistent with other reports in the literature.[13,14]

The study of Chen et al,[13] which was based on analysis of the Surveillance, Epidemiology, and End Results database, found that patients with only bone disease showed the best prognosis, both in terms of median OS and median breast cancer–specific survival. These data were also confirmed by the survival rates reported at the first and second year after diagnosis.

Indeed, the different behavior of different metastatic patterns could be explained through biologic features. Furthermore, the availability of several specific treatment options for bone disease, such as bisphosphonates and radiotherapy, may be of benefit for this subgroup of patients. On the contrary, the worst prognosis seen for patients with CNS involvement could be explained by the limited number of effective therapies able to cross the blood–brain barrier. When observing the differences in prognosis, clinical studies, which are aimed to evaluate the impact of new drugs, should likewise consider the evaluation of the activity on different metastatic sites.

Today, the treatment of patients with brain metastasis remains a challenge; the integration of surgery, radiotherapy and pharmacologic therapy remains an object of study.[13]

Finally, a DFI of < 2 years correlates with the worst prognosis in terms of OS. All patients received adjuvant treatment according to standard guidelines from 2000 till 2010. Probably patients with a short DFI, regardless of tumor biology, have an illness resistant to drugs, and so they experience relapse early and have the worst possibility to obtain disease control with chemotherapy, hormone therapy, or biologic drugs such as trastuzumab.

The present analysis may be affected by several limitations. The study is retrospective, and it shares all the limitations of all retrospective analysis, both in terms of data collection and in terms of interpretation of the results. Nevertheless, today MBC is one of the cancers with higher survival rates compared to other tumors, so the prospective collection of real-life survival data would be difficult for the wide range of time that ought to be considered. Indeed, all the studies about OS trends in MBC are based on retrospective data collections.[2,3,6,15]

Data were collected from 31 centers, which results in a wide cohort of patients but at the same time results in a lack of uniformity in data interpretation, as happens with every retrospective multicenter study.

Moreover, another limit of this study is the lack of exhaustive data about the treatment administered, which limited our evaluation on the real impact of therapies on prognosis.

Finally, the information obtained from the COSMO study should be considered an interesting benchmark of what happens in clinical practice, making it useful when a real-world study is conducted. From this perspective, it will be interesting to observe the impact of new drugs (eg, everolimus, cyclin inhibitors, anti-HER2, PARP [poly(ADP-ribose) polymerase] inhibitors) on OS in MBC patients during the second decade of the 21st century.

Conclusion

The present analysis provides insights about MBC. Although the introduction of new drugs in clinical practice, during the period 2000-2008, no improvements in OS have been observed.

This study provides a large amount of real-life clinical data, which is useful for better understanding the prognostic factors in MBC. We found that biologic subtype, DFI, sites of metastasis, and age are the most relevant known prognostic factors. Unfortunately, MBC remains a lethal disease, and the improvement of OS remains the challenge that oncologists must face. Further research must consider these prognostic factors in order to develop studies that seek to eliminate breast cancer from the list of big killers.

Clinical Practice Points

- Metastatic breast cancer (MBC) is a life-threatening disease. The literature shows a slight trend of improvement in survival that has not been unequivocally demonstrated, and the factors that influence prognosis remain unclear.
- Our study aimed to detect a temporal difference in overall survival (OS) during 2000-2008 and the identification of prognostic factors as causal factors of the temporal variation in OS.
- The COSMO study provides an overview of the Italian clinical data on MBC between 2000 and 2008, adding new insights about patient prognosis.
- Consistent with the data of an Italian tumor registry, no survival improvement was observed in the period explored.
- Biologic subtype, disease-free interval (DFI), and site of metastasis affect prognosis.
- The HER2-positive subtype has the best outcome, while the TN subtype has the shortest OS. A longer DFI from diagnosis (>2 years) correlates with better prognosis.
- Visceral involvement correlates with poor prognosis; in particular, patients with CNS metastasis represent the subgroup with the worst OS, while patients with only bone disease have the best prognosis.
- With a large number of patients, as well as nationwide distribution of participants, the COSMO study provides a broad overview of the Italian clinical data on MBC between 2000 and 2008.

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