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PII: S1526-8209(20)30272-X

DOI: https://doi.org/10.1016/j.clbc.2020.11.001

Reference: CLBC 1215

To appear in: *Clinical Breast Cancer*

Received Date: 5 April 2020

Revised Date: 9 October 2020

Accepted Date: 2 November 2020

Please cite this article as: La Verde NM, Collovà E, Blasi L, Pinotti G, Palumbo R, Bonotto M, Garrone O, Brunello A, Rimanti A, Bareggi C, Zaniboni A, Frassoldati A, Foglietta J, Berardi R, Moretti A, Farina G, Porcu L, Barni S, Overall survival in metastatic breast cancer patients in the third millennium: results of the COSMO study, *Clinical Breast Cancer* (2020), doi: https://doi.org/10.1016/j.clbc.2020.11.001.

Overall survival in metastatic breast cancer patients in the third millennium: results of the COSMO study

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INTRODUCTION

Metastatic breast cancer (MBC) is the cause of death of about 12000 women every year in Italy (1). The introduction of new drugs over the last twenty years, with the development of supportive care has the aim of improving survival. In literature, several studies were designed to better understand survival trends in patients with MBC and which factors affect prognosis.

Giordano et al. published in 2004 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 detection of the disease. (2) A similar trend over the decades was detected by Chia 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 positive breast cancer cases. (6)

To conclude, the literature shows a slight trend in survival improvement for MBC which has not been univocally 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. Secondary objectives were the identification of prognostic factors of OS.

MATERIAL METHODS

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

The COSMO network is a group made up of clinical oncologists, with expertise in breast cancer treatment, coming from different Italian Centers from all 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 features were collected: age at diagnosis of MBC, histotype, stage at diagnosis, presence (M1) or absence (M0) of synchronous metastasis at diagnosis, disease free interval (DFI), biological subtype, treatments performed, 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 1st January 2000 and 31st December 2008, were consecutively enrolled. OS was defined as the time from the diagnosis of MBC to death from any cause.

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

STATISTICAL ANALYSIS

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 using SAS software, version 9.4 [Copyright © 2002-2012 by SAS Institute Inc., Cary, NC, USA].

Survival functions were presented graphically via the STATA software (StataCorp 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP), version 12.1).

RESULTS

COSMO database was locked on 1st April 2017. 3930 patients were enrolled from 31 Italian oncological centers spread all over the country. 3721 patients were eligible and included in the analysis (193 were excluded because out of temporal range, 16 excluded because of lack of OS data). The patients were distributed over the three different periods as follows: 886 (23.8%), 1302 (35.0%) and 1533 (41.2%) in 2000-2002, 2003-2005, 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.

		TIME PERIOD			**TOTAL**
		2000-2002	**2003-2005**	**2006-2008**	
Age at first diagnosis	N	884	1300	1531	3715
	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	*N (%)*	*2 (0.2)*	*2 (0.1)*	*2 (0.1)*	*6 (0.1)*
STAGE AT DIAGNOSIS					
M0	N (%)	664 (77.0)	975 (77.1)	1121 (76.3)	2760 (76.8)
M1	N (%)	198 (23.0)	289 (22.9)	348 (23.7)	835 (23.3)
Missing data	*N (%)*	*24 (2.7)*	*38 (2.9)*	*64 (4.2)*	*126 (3.4)*
HISTOLOGICAL TYPE					
Ductal carcinoma	N (%)	651 (73.5)	960 (73.7)	1137 (74.2)	2748 (73.9)
Lobular carcinoma	N (%)	103 (11.6)	150 (11.5)	193 (12.6)	446 (12)
Mixed carcinoma	N (%)	30 (3.4)	64 (4.9)	79 (5.2)	173 (4.6)
Other histological type	N (%)	45 (5.1)	83 (6.4)	86 (5.6)	214 (5.8)
Missing data	*N (%)*	*57 (6.4)*	*45 (3.5)*	*38 (2.5)*	*140 (3.8)*
TUMOR BIOLOGY					
Hormone receptor positive	N (%)	401 (66.9)	597(58)	810 (58.1)	1808 (59.8)
HER2+	N (%)	122 (20.4)	300 (29.2)	384 (27.5)	806 (26.7)
Triple negative	N (%)	76 (12.7)	132 (12.8)	201 (14.4)	409 (13.5)
Missing data	*N (%)*	*287 (32.4)*	*273 (21.0)*	*138 (9.0)*	*698 (18.7)*

Table 1 - Patient and tumor characteristics.

Median age at first diagnosis was 61.2 years with an interquartile range of 51.3-71.1 years. As expected, the most frequent histological type was ductal carcinoma, and most patients had non-metastatic disease at diagnosis (only 23,3% pts were metastatic at diagnosis).

Patients were classified in three subgroups, based on the biological characteristics of their tumor, expressed at the immunositochemical staining: HER2-positive group included all patients with HER2-positive breast cancer, regardless of hormone receptor status (oestrogen or progesterone). Hormone receptor positive group included patients with positive hormone receptors and negative HER2 status. Patients with both HER2-negative and hormone receptor negative breast cancers were classified as the triple negative (TN) group (8).

59.8% of patients had hormone receptor positive disease, 13.5% TN breast cancer and 26.7% 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 decreases during the three 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 non-visceral disease as shown in Table 2.
1744 patients (47.3%) had visceral disease. Of them 307 had central nervous system metastasis (8.3% of the overall population).
Non-visceral 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% patients. The subgroup of patients with only bone disease was made up of 825 women (22.4%).

		TIME PERIOD			**TOTAL**
		2000-2002	**2003-2005**	**2006-2008**	
Visceral disease	N (%)	439 (50.1)	649 (50.3)	853 (56.2)	1941 (52.7)
Non-visceral disease	N (%)	437 (49.9)	642 (49.7)	665 (43.8)	1744 (47.3)
Missing data	*N (%)*	*10 (1.1)*	*11 (0.8)*	*15 (1.0)*	*36 (1.0)*
SUBGROUPS DATA					
CNS metastasis subgroup of visceral disease	N (%)	54 (6.2)	108 (8.4)	145 (9.6)	307 (8.3)
Only bone disease subgroup of non-visceral disease	N (%)	217 (24.8)	292 (22.6)	316 (20.8)	825 (22.4)

Table 2 - Metastatic sites at diagnosis of metastatic disease

Median follow up was 9.3 years for the overall population, while in the 3 groups it was 12.8 (IQR 8.6-15.4) years, 10.2 (IQR 5.8-11.7) years, 8.5 (IQR 4.2-9.9) years for 2000-2002, 2003-2005, 2006-2008 respectively.
Follow-up maturity was estimated by the number of deaths and the completeness C index for alive patients (i.e. the percentage of the total observed person time of follow-up respect the potential time of follow-up), at the database closing date. The follow-up was found mature for all three cohorts. Deaths were 810/886 (91.4%) for 2000-2002, 1120/1302 (86%) for 2003-2005, 1179/1533 (76.9%) for 2006-2008 with a total of 3109 (83.6%) events. The *C* index for alive patients was 47.9% for 2000-2002, 49.2% for 2003-2005, 46.9% for 2006-2008, with a total of 48.2%.
Median OS was 2.8 years (95%CI: 2.7 – 2.9 years) from the diagnosis of MBC.
With a p value for trend of 0.563, no difference in OS was found over the three periods. Survival estimates are reported in Table 3. A non-homogeneous accrual performed by participating centers during the three periods in examination, could have introduced selection bias, making the comparison between the three cohorts not reliable. Figure 1 – OS in three cohorts.

	TIME PERIOD			**TOTAL** Point estimate (95%CI)
	2000-2002	**2003-2005**	**2006-2008**	

	Point estimate (95%CI)	Point estimate (95%CI)	Point estimate (95%CI)	
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-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-2 year	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-5 year	0.26 (0.24-0.29)	0.27 (0.24-0.29)	0.24 (0.21-0.26)	0.26 (0.24-0.27)

Table 3 - Survival estimates by time period and overall

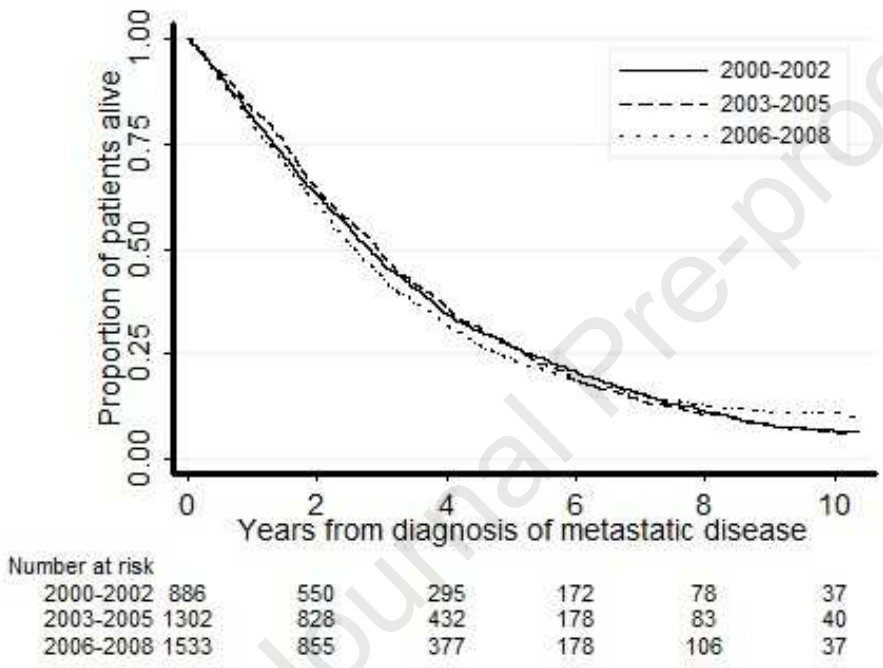

Figure 1- OS in three different periods

Regarding the biological subtype, median OS for HER2 positive patients was 3.1 years (95%CI: 2.8-3.4), for hormone receptor positive disease was 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 DFI was 3.2 years (interquartile range 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 DFI≤2 (95%CI: 1.8 – 2.2), and 3.0 years (95%CI: 2.9-3.2) for patients with DFI>2 years. Patients with DFI shorter than 2 years, show a shorter OS.

DFI resulted strongly associated with disease biology. Interestingly, patients who have a late recurrence (the group of DFI>2 years) are mostly hormone receptor positive (971 pts, 67.0%) versus 23.3% HER2+(338) and 9.7% (141) Triple negative. On the contrary, the group of early relapse (DFI≤2 years) includes a higher rate of HER2+ (30.7%) and TNBC (24%) versus hormone receptor positive (45.3%), p-value (Chi2-square test) < 0.001

All hormone receptor positive patients received hormonal treatment. The overall HER2+ population received trastuzumab in the metastatic setting in 81.1% of cases (565 pts). As expected, the use of trastuzumab increased during the observed period for this cohort (69.4% in 2000-2002, 78.8% in

2003-2005, 81.1% in 2006-2008). This may justify the good prognosis of HER2 patients in our population.

The outcome correlates with age, as showed in Figure 2C. We divided patients into four groups (< 45 years, 45-55 years, 55-65 years, ≥ 65 years), based on age at onset of metastatic disease.

Patients aged ≥ 65 years have the worst prognosis with a median OS of 2.2 months (95%CI 2.1-2.4, p<0.001).

Regarding metastatic sites, we collected data on the site of first relapse, identifying as previously mentioned two groups of patients: those with only non-visceral disease (including bone and/or soft tissue metastasis, lymph nodes, skin, pleural, peritoneal or subcutaneous involvement) and those with at least one visceral site.

We also identified two subgroups: the first with only bone disease (subgroup of non-visceral disease) and the second with the involvement of central nervous system (CNS) (subgroup of visceral disease).

Figure 2D shows OS trends for these four groups, and indicates how non-visceral 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-value <0.001). With a median OS of 1.7 (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 (95%CI 3.1-3.6).

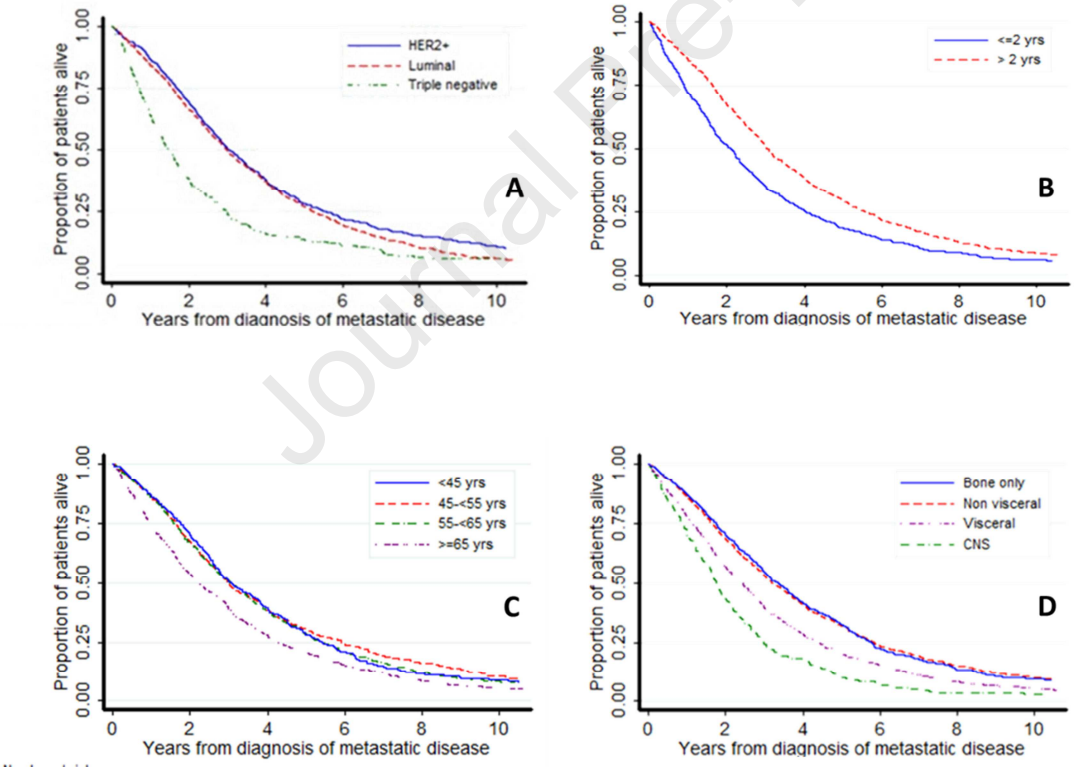

Figure 2 - Overall survival according to: biological subtype (2A); disease free survival (2B); age (2C); metastatic site (2D)

With a p-value of 0.534, no difference in prognosis was found for the different histotypes.

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) for lobular, mixed and other histotypes respectively.

At multivariate analysis, biological subtype, age and metastatic site were the only characteristics that independently correlated with OS (Table 4). No difference in prognosis was found for patients

with synchronous metastasis (M1) versus metachronous (M0) (p value 0.899), considering that we calculated OS since diagnosis of metastatic disease.

CHARACTERISTICS	CATEGORY or REGRESSION TERM	Univariate analysis			Multivariate analysis		
		HR	95%CI	P-VALUE	HR	95%CI	P-VALUE
Biological subtype	HER2+	1	-	<0.001	1	-	<0.001
	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	<0.001	0.49	0.39-0.61	<0 .001
	Quadratic term	1.07	1.05-1.09		1.08	1.06-1.10	
M stage at diagnosis	M0	1	-	0.422	1	-	0.899
	M1	1.04	0.95-1.13		0.99	0.91-1.09	
Histotype	CDI	1	-	0.534	1	-	0.054
	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	Non visceral	1	-	<0.001	1	-	<0.001
	Visceral	1.39	1.29-1.49		1.51	1.40-1.63	

Table 4 - OS predictors

DISCUSSION

With a total of 3930 patients, enrolled in 31 centers throughout the national territory, the COSMO study provides a large overview of the Italian clinical data on MBC between 2000 and 2008, adding insights about the patients' prognosis.

First, no change in OS was observed during the decade under study. This result could be considered unreliable due to a non-homogeneous number of patients in the three different periods enrolled. Nevertheless, this finding was consistent with the Italian tumor register (1), that reports a reduction in mortality, observed only starting 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 in fact published an observational study on 834 patients with MBC diagnosed in the period between November 1974 and December 2000, aimed to explore the correlation between year of relapse and OS.

The overall population was divided into 5 groups, depending of the year of relapse, and the authors found an improvement of OS in the more recent cohorts. Despite this result, the authors declared that the patients who relapsed in the first 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 Andrè in 2004, showed an OS benefit in patients with MBC diagnosed after 1994, period of introduction of taxanes and new aromatase inhibitors, versus patients diagnosed before this year, especially in hormone-receptor positive breast cancer. The authors concluded that this benefit could be attributed to the introduction of new treatments for the metastatic disease. (5).

A further confirmation of this hypothesis was reached the next year by Gennari, who studied patients 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. (4)

The authors of the aforementioned studies, which enrolled patients relapsed within a large period, identified a benefit in OS due to the new drugs introduced in clinical practice. Probably our choice

to identify three cohorts in only 9 years could have hidden the differences in survival rates, because the new drugs were available over the period explored, 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, in the case of taxanes and aromatase inhibitors, that arrived in clinics in the nineties, this led to a benefit in the second half of that decade.
Regarding the secondary objectives of the study, some prognostic factors were identified.
Notably, focusing on biological subtype, median OS for the HER2+ group was of 3.1 years, which is significantly higher than that of patients with TN breast cancer.
Given that the HER2+ status historically correlates with a more aggressive disease, we hypothesize that the inclusion in this subgroup of all patients with HER2 positive disease, regardless of the hormonal receptors status, and the progressive introduction of trastuzumab in clinical practice could explain the fairly good prognosis, similar to hormone receptor positive patients. A similar data was reached by Gobbini, who recently published a real-life analysis of survival among a large cohort of French MBC patients, demonstrating that the slightly improvement of OS is confined to HER2+ cases. (6)
An age ≥ 65 year clearly correlates with a poor prognosis, independently from the biological subtype. This finding consolidates some data of literature (9, 10) that support the hypothesis of a worst OS in elderly patients. The idea of a better prognosis in older patients is probably an assumption from studies in early breast cancer, where a younger age is an independent negative prognostic factor (11). In our opinion the metastatic disease in the elder 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 the very young patients, under 35, due to their small number in this study.
A recent study, conducted in US, has demonstrated that an improvement on overall and cancer specific survival in young breast cancer patients, including from 1975 to 2015. The authors attributed this event to treatments rather than screening. Furthermore, the improvements appeared to have reached a plateau after 2005, except among young women with metastatic breast cancer, in whom survival continued to improve throughout the period, and this seem a specific effect of new drugs (12).
The multivariate analysis revealed that the first metastatic site is an important independent prognostic factor. Visceral disease, in fact, and in particular CNS involvement, correlates with a poor outcome in term of OS, versus non-visceral disease. The best prognosis is seen in the subgroup of patients with only bone metastases, which makes up 22.4% of the overall population in study, that reaches a median survival of 3.4 years. This good outcome is consistent with other literature data (13, 14).
In a study of Chen, based on the analysis of the SEER database, patients with only bone disease showed the best prognosis, both in terms of median OS and median breast cancer specific survival. This data was confirmed also by the survival rates reported at 1st and 2nd year from the diagnosis (13).
Indeed, the different behavior of different metastatic patterns could be explained through biological 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. 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.
Nowadays the treatment of patients with brain metastasis remains a challenge; the integration between surgery, radiotherapy and pharmacological therapy are still object of study. (13)

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

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

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

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

Finally, the information obtained from the COSMO study can be an interesting benchmark of what happens in clinical practice and it can be useful when a real-life study is conducted. In this perspective, it will be interesting to observe the impact of new drugs (e. g. everolimus, cyclin inhibitors, anti-Her2, PARP inhibitors, etc…) on OS in MBC patients of the second decade of the 21st century.

CONCLUSIONS

In summary, the present analysis provides insights about MBC. Although the introduction of new drugs in clinical practice, in the period 2000-2008 no advancements in OS have been observed.,
This study provides a very large amount of real-life clinical data, useful for better understanding of prognostic factors in MBC. The study stated that biological 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 blacklist of the "big killers".

Clinical practice points

- MBC is a life-threatening disease, and the literature shows slight trend of improvement in survival which has not been univocally demonstrated, and the factors that influence prognosis are still unclear.
- Our study aimed to detect a temporal difference in OS between 2000 and 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 pts prognosis.
- Consistent with data of Italian tumor register no survival improvement was observed in the period explored.
- Biological subtypes, DFI and site of metastasis affect prognosis.
- HER 2-positive positive subtype has the best outcome, while TN subtype has the shorter OS. A longer DFI from diagnosis (> 2years) correlates with a better prognosis.
- Visceral involvement correlates with poor prognosis and in particular pts with CNS metastasis represent the worst subgroup, while pts with only bone disease have the best prognosis.
- With a large number of patients, and a distribution of participant throughout the whole national territory, the COSMO study provides a large overview of the Italian clinical data on MBC between 2000 and 2008

Authors contributions

SB designed the study and provided methodological and statistical expertise; NML and EC wrote the first draft of the paper; LB and GP designed the study provided methodological and statistical expertise; RP, MB, OG, AB, AR, JF and CB assisted with data collection and interpretation; AZ and AF designed the study and provided trainee collaborative expertise; RB and AM collaborated with the manuscript editing and writing; LP analyzed data, providing methodological and statistical expertise for the study; All authors read and approved the final manuscript.

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Conflict of interest statement

The authors and collaborators certify that they have no affiliations with or involvement in any organization or entity with any financial or non-financial interest in the subject matter discussed in this manuscript.

Funding Source

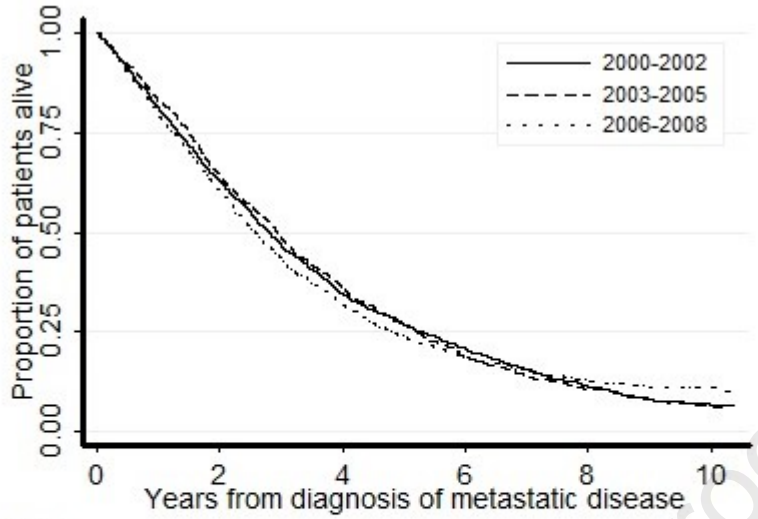
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Ethical Approval

The study was approved by local ethics committees

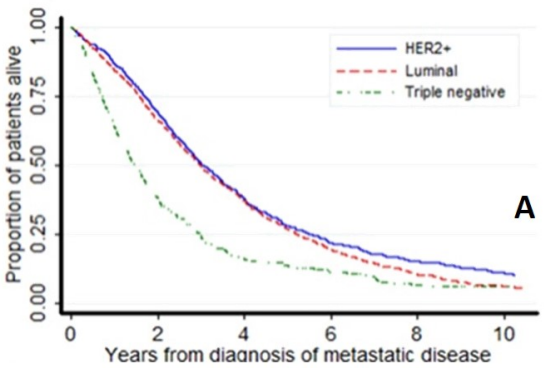
REFERENCES

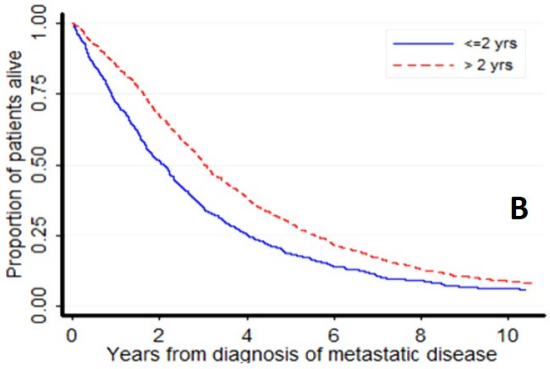
1. AIOM I numeri del cancro in Italia 2019 https://www.aiom.it/wp-content/uploads/2019/09/2019_Numeri_Cancro-operatori-web.pdf
2. Giordano SH, Buzdar AU, Smith TI, et al. Is breast cancer survival improving? *Cancer* 2004;100:44-52. DOI: 10.1002/cncr.11859
3. Chia SK, Speers CH, D'yachkova Y, Kang A, Malfair-Taylor S, Barnett J, Coldman A, Gelmon KA, O'reilly SE, Olivotto IA. The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 2007 Sep 1;110(5):973-9. DOI: 10.1002/cncr.22867
4. Gennari A, Conte PF, Rosso R, et al. Survival of Metastatic Breast Carcinoma Patients over a 20-Year Period. A Retrospective Analysis Based on Individual Patient Data from Six Consecutive Studies. *Cancer* 2005;104:1742-1750. DOI: 10.1002/cncr.21359
5. Andre F, Slimane K, Bachelot T, Dunant A, Namer M, Barrelier A, Kabbaj O, Spano JP, Marsiglia H, Rouzier R, Delaloge S, Spielmann M. Breast cancer with synchronous metastases: trends in survival during a 14-year period. *J Clin Oncol.* 2004 Aug 15;22(16):3302-8. DOI: 10.1200/JCO.2004.08.095
6. Gobbini E, Ezzalfani M, Dieras V, Bachelot T, Brain E, Debled M, Jacot W, Mouret-Reynier MA, Goncalves A, Dalenc F, Patsouris A, Ferrero JM, Levy C, Lorgis V, Vanlemmens L, Lefeuvre-Plesse C, Mathoulin-Pelissier S, Petit T, Uwer L, Jouannaud C, Leheurteur M, Lacroix-Triki M, Cleaud AL, Robain M, Courtinard C, Cailliot C, Perol D, Delaloge S. Time trends of overall survival among metastatic breast cancer patients in the real-life ESME cohort. *Eur J Cancer*. 2018 Jun;96:17-24. DOI: 10.1016/j.ejca.2018.03.015
7. Clark TG, Altman DG, De Stavola BL. Quantification of the completeness of follow-up *Lancet* 2002; 359: 1309–10. DOI: 10.1016/s0140-6736(02)08272-7
8. Perou et al. Cancer Genome Atlas Network. Comprehensive molecular portraits of human breast tumors *Nature*. 2012 October 4; 490(7418): 61–70. DOI: 10.1038/nature11412
9. Chen HL, Zhou MQ, Tian W, Meng KX, He HF. Effect of Age on Breast Cancer Patient Prognoses: A Population-Based Study Using the SEER 18 Database. *PLoS One.* 2016 Oct 31;11(10). DOI: 10.1371/journal.pone.0165409
10. Brandt J, Garne JP, Tengrup I, Manjer J. Age at diagnosis in relation to survival following breast cancer: a cohort study. *World J Surg Oncol*. 2015 Feb 7;13:33. DOI: 10.1186/s12957-014-0429-x
11. Narod SA, Sun P, Wall C, Baines C, Miller AB. Impact of screening mammography on mortality from breast cancer before age 60 in women 40 to 49 years of age. *Curr Oncol.* 2014 Oct;21(5):217-21. DOI: 10.3747/co.21.2067
12. Guo F, Kuo YF, Shih YCT, Giordano SH, Berenson AB. Trends in Breast Cancer Mortality by Stage at Diagnosis Among Young Women in the United States. *Cancer*. 2018 Sep 1;124(17):3500-3509. DOI: 10.1002/cncr.31638
13. Chen MT, Sun HF, Zhao Y, Fu WY, Yang LP, Gao SP, Li LD, Jiang HL, Jin W. Comparison of patterns and prognosis among distant metastatic breast cancer patients by age groups: a SEER population-based analysis. Sci Rep. 2017 Aug 23;7(1):9254.
14. Rogoz B, Houzé de l'Aulnoit A, Duhamel A, Houzé de l'Aulnoit D. Thirty-Year Trends of Survival and Time-Varying Effects of Prognostic Factors in Patients With Metastatic Breast Cancer-A Single Institution Experience. *Clin Breast Cancer*. 2018 Jun;18(3):246-253. DOI: 10.1016/j.clbc.2017.08.012
15. Ufen MP, Köhne CH, Wischneswky M, Wolters R, Novopashenny I, Fischer J, Constantinidou M, Possinger K, Regierer AC. Metastatic breast cancer: are we treating the same patients as in the past? *Ann Oncol.* 2014 Jan;25(1):95-100. DOI: 10.1093/annonc/mdt429

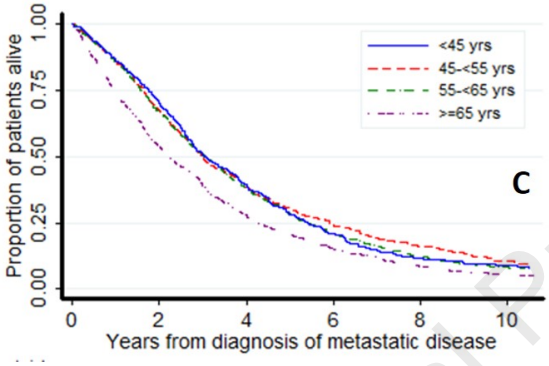


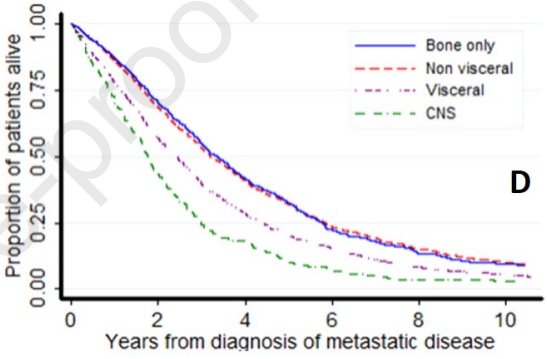
Number at risk

2000-2002	886	550	295	172	78	37
2003-2005	1302	828	432	178	83	40
2006-2008	1533	855	377	178	106	37









MICROABSTRACT

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

Clinical practice points

- MBC is a life-threatening disease, and the literature shows slight trend of improvement in survival which has not been univocally demonstrated, and the factors that influence prognosis are still unclear.
- Our study aimed to detect a temporal difference in OS between 2000 and 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 pts prognosis.
- Consistent with data of Italian tumor register no survival improvement was observed in the period explored.
- Biological subtypes, DFI and site of metastasis affect prognosis.
- HER 2-positive positive subtype has the best outcome, while TN subtype has the shorter OS. A longer DFI from diagnosis (> 2years) correlates with a better prognosis.
- Visceral involvement correlates with poor prognosis and in particular pts with CNS metastasis represent the worst subgroup, while pts with only bone disease have the best prognosis.
- With a large number of patients, and a distribution of participant throughout the whole national territory, the COSMO study provides a large overview of the Italian clinical data on MBC between 2000 and 2008