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Original article

Impact of age at diagnosis of metastatic breast cancer on overall survival in the real-life ESME metastatic breast cancer cohort

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ABSTRACT

Background: Young age is a poor prognostic factor in early stage breast cancer (BC) but its value is less established in metastatic BC (MBC). We evaluated the impact of age at MBC diagnosis on overall survival (OS) across three age groups (<40, 40 to 60 and > 60 years(y)).
Methods: ESME MBC database is a national cohort, collecting retrospective data from 18 participating French cancer centers between January 01, 2008 and December 31, 2014.
Results: Among 14 403 women included, 1077 (7.5%), 6436 (44.7%) and 6890 (47.8%) pts were <40, 40 −60 and > 60 y respectively. Pts <40 had significantly more aggressive presentations than other age groups: more frequent HER2+ (25.7 vs 15.3% in >60y) and triple negative subtypes (27.4 vs 14.6% in >60y), and more frequent visceral involvement (36.3 vs 29.8% in >60y). At a median follow-up of 48 months, median OS differed across age groups: 38.8, 38.4 and 35.6 months for pts <40, 40–60 and > 60y, respectively ($p < 0.0001$). Compared to pts <40y, older pts had a statistically significant higher risk of

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Real-world data
Age

death (all causes of death included), although of limited clinical value (HR = 1.1, IC 95%:1.01–1.20). There was a significant trend for better OS in pts <40y with HER2+ and luminal diseases. A possible explanation is a greater use of anti-Her2 therapies as first-line treatments: 86.6, 81.9 and 74.9% for pts <40, 40–60 and > 60y, respectively (p < 0.0001).
Conclusion: Although young age seems associated with more aggressive presentations at diagnosis of MBC, it has no deleterious effect on OS in this large series.

1. Introduction

Breast cancer (BC) is the first female cancer and the leading cause of cancer death in women in France [1] and worldwide [2]. Latest French data show an estimated annual mortality rate of 11 833 women (2017) [3], and interestingly, overall survival (OS) at 5 years differs among age groups: 90% before 45 years old (y), 92% between 45 and 55y, 89% between 55 and 65y, 87% between 65 and 75y, and 58% after75y [1]. In early stage BC, young age is a known poor prognostic factor [4–6]. Aggressive subtypes, like triple negative, are more frequent in young patients. However, young age has been found to be an independent prognostic factor in most studies [4,7], sometimes only in luminal subtypes [8,9].

In metastatic breast cancer (MBC), recognized poor prognostic factors are short metastasis-free interval, visceral involvement and crisis, negative hormone receptor (HoR) and particularly triple negative subtype, primary endocrine resistance for luminal subtype and number of metastatic sites [10]. However, the prognostic impact of age remains unclear in this clinical setting. Several retrospective series have unexpectedly suggested that older women had a poorer prognosis than women under 50 years of age [11–13]. Nonetheless, international guidelines state that age should not guide the treatment strategy and the intensity of treatment, especially to avoid overtreatment in young patients [10,14].

Real-world data are important assets as they provide data from large data sets with long follow-up which usefully complements data from randomized clinical trials. The Epidemiological Strategy and Medical Economics (ESME) program is an academic initiative launched in 2014 by UNICANCER, the French network of cancer centers, to report exhaustive, high quality and centralized real-life data on different solid tumors including MBC. It allowed building a database of more than 16 000 MBC cases. The ESME Research program included 3 types of cancer: MBC, ovarian and lung cancers. It involves 18 academic cancer centers managing together over one-third of all BC cases nationwide; for MBC, other citations are available [15–18]. We used the ESME MBC database (NCT03275311) to evaluate the impact of age at MBC diagnosis on overall survival (OS).

2. Patients and methods

2.1. Study design

The ESME MBC database is a unique national cohort, collecting retrospective data using clinical trial-like methodology. It included all consecutive MBC patients (pts) who initiated at least one treatment in one of the 18 participating French cancer centers between January 01, 2008 and Decemeber 31, 2014. Follow-up data have been collected until October 11, 2016, death or date of latest news. Exclusion criteria were: patients treated for another cancer in the last 5 years before MBC diagnosis, with unknown ER/PR/Her2 status, or men (who will be analyzed in a separate study [19]).

We carried out a retrospective, comparative study to assess overall survival of MBC patients selected from the ESME MBC database among 3 age groups (<40, 40 to 60 and > 60 y).

The ESME research program is handled by R&D Unicancer in accordance with current best practice guidelines and rules (Good pharmacoepidemiology pratices). The program is monitored by an independent scientific committee who approved the present work. The ESME MBC database [20] was authorised by the French data protection authority ([Registration ID 1704113 and authorisation N°DE-2013.-117], NCT03275311). All data are exclusively obtained retrospectively. The present analysis was approved by an independent ethics committee (Comité de Protection des Personnes Sud-Est II-2015-79). Considering the retrospective design of the study, no informed consent was deemed necessary. Nevertheless, all patients were informed about the re-use of their electronically recorded data.

Subtypes were defined according to the first histology available (primary tumor), otherwise on the metastasis. HoR + status was defined as ER+/PR+; ER+/PR- or missing; ER- or missing/PR+. HoR positivity was defined if nuclear staining was strictly superior to 10% in immunochemistry. HER2+ status was established if HER2 was found 3+ in IHC or 2+ with amplified FISH or CISH. De novo MBC was defined by the diagnosis of a metastasis within 90 days of the primary tumor. Among de novo MBC, loco-regional treatment was defined as breast surgery (mastectomy or lumpectomy) and/or loco-regional radiotherapy (including breast±regional lymph nodes) within the first year of diagnosis. OS was defined as the time between the diagnosis of metastasis and the date of death (from any cause), or censored to the date of latest news.

2.2. Objectives

The primary endpoint of this study was the evaluation of the impact of age at MBC diagnosis on OS, among 3 age groups (<40, 40 to 60 and > 60 y). Main secondary endpoints were the description of MBC features in each age group and evaluation of OS by breast cancer subtype in each age group.

2.3. Statistical analysis

Clinical, pathological and treatment characteristics were described overall and across age groups by their distribution for categorical data, and their mean and median for continuous data. Comparisons between age groups were performed using Chi-squared tests or Fisher's exact test for categorical data and non-parametric Wilcoxon's test for continuous data. A p-value <0.05 was considered statistically significant.

Median follow-up was calculated using reverse Kaplan-Meier estimation.

For OS, survival curves were determined using the Kaplan-Meier method; survival medians were given with their 95% confidence interval (CI). Survival curves were compared using log-rank tests. Hazard-ratio with their 95% CI were computed using a univariate Cox model; all significant factors were included in a multivariate Cox model. Survival analysis were conducted in the whole population and in each subtype group.

3. Results

Among 16 703 included pts, 1810 had no information available in the database on tumor receptors (ER/PR/HER2) and 490 had at least one exclusion criterion (unknown age, men, other cancer in the last 5y), leaving 14 403 for analysis (Fig. 1).

3.1. Patients <40y had more frequent aggressive features at both primary disease and first metastatic event

Data relative to TNM stage of the primary tumor were partly retrieved (Table 1). Tumors occurring in women aged <40y showed more aggressive features. Grade III tumors were recorded in 62.3%, 48.2% and 39.9% in patients <40, 40–60 and > 60 y respectively ($p < 0.0001$). HoR-/HER2-tumors were observed in 26.8%, 19.4% and 14.0% of patients <40, 40–60 and > 60 y respectively, and Her2+ subtype in 25.7%, 20.6% and 15.7% of patients <40, 40–60 and > 60 y respectively ($p < 0.0001$). Details of adjuvant treatments are described in Table 1.

At the onset of MBC, 1077 (7.5%), 6436 (44.7%) and 6890 (47.8%) pts were <40, 40–60 and > 60 y respectively. De novo metastatic disease occurred in 4124 patients (28.6%), more frequently in younger patients: 31.5%, 28.7 and 27.1% in patients <40, 40–60 and > 60 y respectively ($p = 0.003$). Younger patients had also a shorter time to first metastasis: 28.6% between 3 and 24 months versus 12.5% in patients >60y. Overall, median time to metastasis was shorter in younger patients: 18 months in <40y, 27 months in 40–60y and 42 months in >60y ($p < 0.0001$) which might be in line with subtype distribution.

Similarly, at metastatic disease onset, patients <40y also had significantly more aggressive presentations than other age groups (data are shown across age groups: <40, 40–60 and > 60 y respectively): more frequent visceral involvement (36.3%, 33.3% and 29.8%), more frequent HER2+ (26.6%, 21.2% and 16.1%), and HoR-/Her2- (25.3%, 17.7% and 12.1%) subtypes, (all p-value vs other age groups <0.0001) [Details are specified in Table 2].

3.2. First line treatments for metastatic breast cancer

First-line treatments for MBC differed across age groups among all subtypes. In HoR+/HER2-younger patients received more frequently chemotherapy (80.5%, 60.8% and 47.4% in the 3 age groups respectively; $p < 0.0001$) and less endocrine therapy (70.1%, 75.6% and 81.3%; $p < 0.0001$). In Her2+ subtype, chemotherapy as well as anti-Her2 treatments were more frequently administered to younger patients: 80.5%, 68.5% and 47.4% across age groups for chemotherapy ($p < 0.0001$); 87.1%, 81.7% and 75% for anti-Her2 treatments ($p < 0.0001$). A similar trend was observed in HoR-/HER2-patients. Details are shown in Table 3.

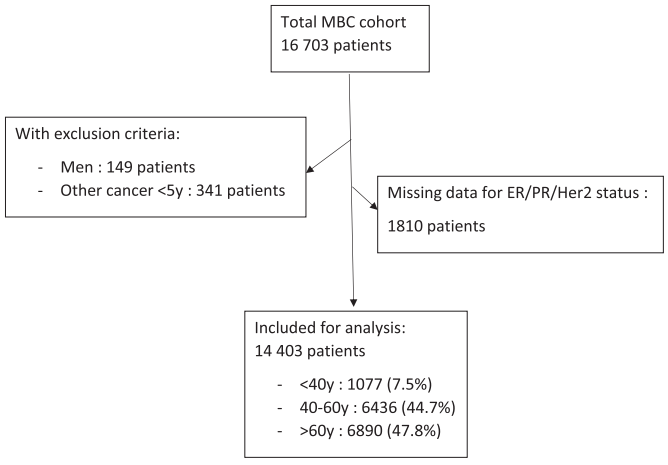

Fig. 1. Study flow diagram.

3.3. Loco-regional treatment of the primary tumor in de novo MBC

Among patients with de novo MBC, loco-regional treatment was more frequent in patients <40y: breast surgery (breast-conserving or mastectomy) was performed in 26.5% of patients <40y, 20.5% in the 40-60y group and 12.1% in >60y group; loco-regional radiotherapy was performed in 51% of patients <40y, 38.1% in the 40-60y group and 24.3% in the >60y group.

3.4. Overall survival differs after first metastatic event according to age and subtype

Median follow-up was 48 months. Median OS significantly differed across age groups, and was 38.8, 38.4 and 35.6 months for pts <40, 40–60 and > 60y, respectively ($p < 0.0001$). Compared to pts >60y, younger pts had a slightly significant lower risk of death (all causes of death included): HR = 0.91, CI 95% 0.83–0.99. This trend for a longer OS was confirmed in patients <40 in HoR+/HER2- and Her2+ subtypes, but not in HoR-/Her2- MBC [Fig. 2 and Table 4].

Univariate analysis suggested that young age was a favorable prognostic factor in MBC. Multi-variate analysis confirmed that young age was an independent prognostic factor when controlling for other factors in patients with MBC. Indeed, compared to patients >60y, hazard ratio for death was 0.75 (95% CI 0.69–0.82) in patients <40y and 0.84 (95% CI 0.80–0.88) in patients aged 40-60y ($p < 0.0001$). Other expected prognostic factors were confirmed: longer time to MBC and de novo disease [HR for death 1.88 (95% CI 1.77–1.99) for patients relapsing between 3 and 24 months, 0.84 (95% CI 0.80–0.89) for de novo MBC, all compared to patients relapsing after 24 months ($p < 0.0001$)], subtype [HR 2.48 (95% CI 2.34–2.63) for the HoR-/HER2-subset, 0.87 (95% CI 0.81–0.92) for Her2+ compared to HoR + HER2- ($p < 0.0001$)], number of metastatic sites [HR 1.40 (95% CI 1.32–1.48) for 2 sites, 1.99 (95% CI 1.88–2.11) for 3 or more sites compared to one ($p < 0.0001$)], and type of metastatic sites [HR 1.10 (95% CI 1.05–1.16) for visceral involvement, 0.77 (95% CI 0.71–0.84) for neither visceral nor bone compared to bone only ($p < 0.0001$)]. Details are shown in Table 4.

4. Discussion

Our study analyzed real-world data on MBC across three commonly accepted age groups <40; 40–60 and > 60 years old. Our primary objectives were to describe metastatic breast cancer clinical characteristics according to age in order to evaluate its impact on overall survival, and to analyze the relationship between age and BC subtype at the metastatic stage.

This unique real-world database of a large cohort of patients with MBC demonstrated that young patients had not only, more aggressive presentations in primary tumors but also at the time of metastatic disease, most likely associated with subtype distribution. Indeed, patients under 40y exhibited more frequently three or more metastatic sites and visceral involvement, and had also more frequent HER2+ or triple negative subtypes (Table 2). These features had been identified as independent poor prognostic factors in a previous global report of the ESME MBC cohort [21]. Despite this poor risk presentation, and contrary to what is commonly observed in early breast cancer, OS was significantly longer in young patients in the present cohort: 38.8, 38.4 and 35.6 months for pts <40, 40–60 and > 60y, respectively ($p < 0.0001$). Specifically, OS was

Table 1
Characteristics of primary tumor and adjuvant treatment: overall and across age groups(*%/available data; **%/all patients).

	All N = 14403	Age at MBC						P value between age groups
		<40 N = 1077		40–60 years N = 6436		>60 years N = 6890		
	N	N	%	N	%	N	%	
Tumor size (cT)								**<0.0001**
T0	164	4	0.7%*	75	2.5%*	85	2.8%*	
T1	1297	75	13.4%*	548	17.9%*	674	22.4%*	
T2	2389	210	37.6%*	1119	36.6%*	1060	35.3%*	
T3	1192	156	28.0%*	617	20.2%*	419	13.9%*	
T4 global	1579	113	20.3%*	698	22.8%*	768	25.5%*	
Not avalaible	*7782*	*519*	*48.2%***	*3379*	*52.5%***	*3884*	*56.4%***	
Nodal status (cN)								**<0.0001**
N0	2740	183	34.7%*	1201	41.5%*	1356	48.6%*	
N1	2513	242	45.9%*	1235	42.6%*	1036	37.1%*	
N2	575	63	12.0%*	273	9.4%*	239	8.6%*	
N3	386	39	7.4%*	188	6.5%*	159	5.7%*	
Not available	8189	550	51.1%**	3539	55.0%**	4100	59.5%**	
Grade								**<0.0001**
I	915	26	2.6%*	346	5.9%*	543	8.8%*	
II	6247	352	35.1%*	2711	45.9%*	3184	51.3%*	
III	5947	624	62.3%*	2847	48.2%*	2476	39.9%*	
Not available	1294	75	7.0%**	532	8.3%**	687	10.0%**	
Histological type								**<0.0001**
Ductal	11317	973	97.0%*	5281	89.3%*	5063	80.8%*	
Lobular	1868	30	3.0%*	636	10.7%*	1202	19.2%*	
Other or Not available	1218	74	6.9%**	519	8.0%**	625	9.0%**	
Subtypes								**<0.0001**
HoR + Her2-	8391	502	47.5%*	3604	60.0%*	4285	70.3%*	
HoR-Her2-	2298	283	26.8%*	1163	19.4%*	852	14.0%*	
Her2+	2465	271	25.7%*	1238	20.6%*	956	15.7%*	
Not available	1249	21	1.9%**	431	6.7%**	797	11.6%**	
Adjuvant chemotherapy								**<.0001**
Yes	7502	699	64.9%*	3913	60.9%*	2890	42.1%*	
No	6870	378	35.1%*	2515	39.1%*	3977	57.9%*	
Not available	31	0	0.0%**	8	0.1%**	23	0.3%**	
Adjuvant radiotherapy								**0.1309**
Yes	8880	634	58.9%*	3997	62.2%*	4249	61.8%*	
No	5493	441	40.9%*	2429	37.8%*	2623	38.2%*	
Not avalaible	30	2	0.2%**	10	0.2%**	18	0.3%**	
Adjuvant endocrine therapy								**<.0001**
Yes	6695	380	35.3%*	2838	44.1%*	3477	50.5%*	
No	7677	695	64.5%*	3583	55.7%*	3399	49.3%*	
Not avalaible	31	2	0.2%**	15	0.2%**	14	0.2%**	

Table 2
Metastatic breast cancer characteristics according to age groups.

	All		Age at MBC						*P value between age groups*
			<40 years		[40–60] years		>60 years		
	N	%	N	%	N	%	N	%	
Time to first metastasis									<0.0001
De novo (< 3 months)	4058	28.2%	339	31.5%	1849	28.7%	1870	27.1%	
[3–24[months	2284	15.9%	308	28.6%	1114	17.3%	862	12.5%	
>= 24 months	8035	55.8%	429	39.8%	3461	53.8%	4145	60.2%	
NA	26	0.2%	1	0.1%	12	0.2%	13	0.2%	
Number of metastatic sites									0.02
One site	7976	55.4%	572	53.1%	3493	54.3%	3911	56.8%	
Two sites	3473	24.1%	267	24.8%	1586	24.6%	1620	23.5%	
Three or more sites	2954	20.5%	238	22.1%	1357	21.1%	1359	19.7%	
Type of metastasis									<0.0001
Bone only	8145	65.3%	562	52.2%	3587	55.7%	3996	58.0%	
Visceral	4584	15.6%	391	36.3%	2140	33.3%	2053	29.8%	
Other (neither visceral nor bone)	1674	19.1%	124	11.5%	709	11.0%	841	12.2%	
Tumor subtype									<0.0001
HoR + HER2-	9398	15.6%	519	48.2%	3934	61.1%	4945	71.8%	
HoR-HER2-	2247	19.1%	272	25.3%	1138	17.7%	837	12.1%	
HER2+	2758	65.3%	286	26.6%	1364	21.2%	1108	16.1%	
De novo MBC –treatment of primary tumor <1y from diagnosis									
Breast surgery	691	17.0%	90	26.5%	374	20.5%	227	12.1%	0.001
Loco-regional RT	1333	32.8%	173	51.0%	705	38.1%	455	24.3%	<0.0001

Table 3
First-line treatments according to tumor subtypes and age groups.

	All		Age groups (years)						P value between age groups
			<40		40–60		>60		
	N	%	N	%	N	%	N	%	
HoR+/HER2									
Chemotherapy	5456	58.1%	418	80.5%	2693	68.5%	2345	47.4%	<0.0001
Endocrine therapy	7358	78.3%	364	70.1%	2974	75.6%	4020	81.3%	<0.0001
Her2+									
Chemotherapy	2469	89.5%	273	95.5%	1257	92.2%	939	84.7%	<0.0001
Endocrine therapy	1131	41.0%	134	46.9%	494	36.2%	503	45.4%	<0.0001
Anti-Her2	2195	79.6%	249	87.1%	1115	81.7%	831	75.0%	<0.0001
HoR-/HER2-									<0.0001
Chemotherapy	2109	93.9%	262	96.3%	1092	96.0%	755	90.2%	<0.0001

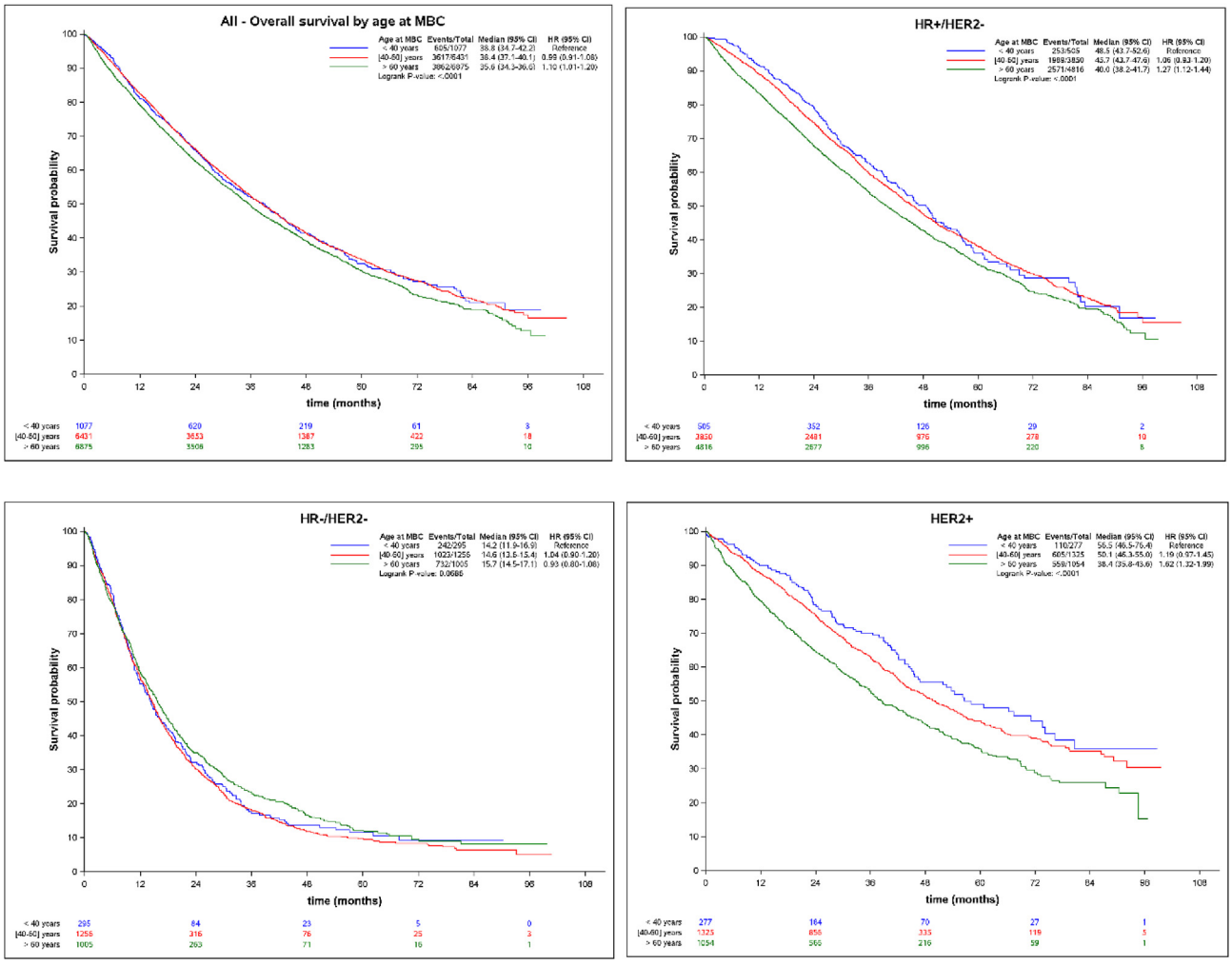

Fig. 2. Overall survival according to age and tumor subtypes.

significantly better for young patients with HoR+/Her2-or Her2+ subtypes: HR comparing <40y to >60y was 1.27 (95%CI 1.12–1.44) and 1.62 (95%CI 1.32–1.99) respectively (Fig. 2). No difference was found in the triple negative subtype, where patients suffered a poor survival rate in all age groups. The multivariate analysis demonstrated that age <40y, HER2+ subtype and de novo metastatic disease were all independent favorable prognostic factors, along with disease limited to one site or neither visceral/nor bone sites (Table 4).

The independent favorable impact of young age on overall survival in metastatic breast cancer has been previously reported. One of the main ESME MBC report, which focused on overall survival time trends, showed that each incremental year of age was independently and significantly associated with a higher hazard ratio for death: HR 1.02 per additional year in the HoR+/HER2-and HER2+ subsets ($p < 0.001$) [21]. Similarly, in a large cohort of metastatic breast cancer from the SEER database, age under 50 was also found to be a favorable prognostic factor among 4932 patients

Table 4
Uni- and multi-variate analysis of factors impacting on overall survival.

	Cox univariate		Cox multivariate	
	HR (95% CI)	p	HR (95% CI)	p
Age at MBC				
>60 years	1	<0.0001	1	<0.0001
[40–60]	0.90 (0.86–0.94)		0.84 (0.80–0.88)	
<40 years	0.91 (0.83–0.99)		0.75 (0.69–0.82)	
Time to MBC				
≥24 months	1	<0.0001	1	<0.0001
[3–24[months	2.00 (1.89–2.12)		1.88 (1.77–1.99)	
De novo (<3 months)	0.83 (0.79–0.88)		0.84 (0.80–0.89)	
Subtype				
HoR + HER2-	1	<0.0001	1	<0.0001
HoR-HER2-	2.72 (2.58–2.88)		2.48 (2.34–2.63)	
HER2+	0.89 (0.83–0.94)		0.87 (0.81–0.92)	
Number of metastatic sites				
One site	1	<0.0001	1	<0.0001
Two sites	1.40 (1.33–1.48)		1.40 (1.32–1.48)	
Three or more sites	1.93 (1.82–2.03)		1.99 (1.88–2.11)	
Metastatic site				
Bone	1	<0.0001	1	<0.0001
Visceral	1.19 (1.13–1.25)		1.10 (1.05–1.16)	
Other (neither visceral nor bone)	0.80 (0.74–0.86)		0.77 (0.71–0.84)	

including 850 patients (5%) under 50 years old [22]. Of note, aggressive phenotypes were also more frequent in younger patients in this cohort, again showing no negative impact on OS. On the contrary, overall and breast-cancer specific survivals were significantly better in younger patients compared to middle-aged patients (50–69 y): HR 0.77 (95%IC 0.68–0.87; $p < 0.001$) and HR 0.81 (95%IC 0.71–0.92; $p = 0.002$) respectively. In other cohorts as well, younger age was significantly associated with better prognosis, in uni- and multi-variate analysis [11–13].

A possible explanation for the difference in prognosis across age groups could be the less frequent use of chemotherapy. in older patients. Especially in Her2+ MBC chemotherapy as well as anti-Her2 treatments was less frequently used in older patients, possibly due to comorbidities, and could explain the negative impact on OS in patients >60y.

However, in HoR+/Her2-subtype, a dedicated analysis of the same ESME cohort showed that endocrine therapy as first line treatment was not associated with a significant impact on OS and PFS in the entire cohort [23] as well as in patients ≤45 years old [24]. Furthermore, young age is less frequently associated with comorbidities and frailty. Conversely, older age may limit the possibility to prescribe and sustain treatments, and be associated with more frequent competitive causes of death [9,25,26].

For patients with de novo metastatic disease, a potential explanation for the impact of age on OS, is a higher rate of loco-regional treatments in younger patients. Loco-regional treatments are known to be more frequently performed in younger patients and to be associated with better outcomes [17,27–29]. Furthermore, recent prospective data also suggested that locoregional treatment of de novo MBC may improve long term prognosis [30].

This study has several limitations. Causes of death were mostly unknown (52.1% of the total cohort, probably due to the retrospective collection of data), and this hampers our interpretation of overall survival. This is particularly true in the elderly population, where underlying comorbidities and other medications may limit the use of cancer treatments, and/or favor more severe and potentially lethal adverse events, again limiting therapeutic options. Competitive causes of death in elderly patients may also blur the meaning of overall survival, and breast cancer specific survival might be a more suitable endpoint. Another important limitation is the absence of information on the biology of metastatic disease. It has been widely demonstrated that the biological subtype may differ between the primary tumor and the metastatic tissue, notably for HoR + breast cancer [31]. Of note, age did not impact overall survival in HoR-/HER2-patients, and triple negative disease is the less prone to subtype change. Finally, follow-up was collected until on October 2016, before wide use of novel therapeutic agents having shown positive impact on OS (e.g. CDK4/6 inhibitors). These targeted agents are widely prescribed also in elderly women, which may positively impact outcomes, warranting future real-life evaluations.

5. Conclusion

Although young age seems to be associated with a more aggressive presentation at diagnosis of MBC, it does not affect OS in this large serie. On the contrary, young age was associated with a better prognosis, particularly among HoR+/Her2-and Her2+ subtypes, possibly linked to a more frequent use of chemotherapy and anti-Her2 treatments. Further studies should question the possible under-treatment of older patients, and try tailoring treatments to compensate for poor prognosis.

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Declaration of competing interest

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