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Breast Cancer

Measures of Outcome in Metastatic Breast Cancer: Insights From a Real-World Scenario

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Key Words. Outcome measure • Surrogate endpoint • Survival analysis • Breast neoplasms

Abstract

No gold standard treatment exists for metastatic breast cancer (MBC). Clinical decision making is based on knowledge of prognostic and predictive factors that are extrapolated from clinical trials and, sometimes, are not reliably transferable to a real-world scenario. Moreover, misalignment between endpoints used in drug development and measures of outcome in clinical practice has been noted. The roles of overall survival (OS) and progression-free survival (PFS) as primary endpoints in the context of clinical trials are the subjects of lively debate. Information about these parameters in routine clinical practice is potentially useful to design new studies and/or to interpret the results of clinical research. This study analyzed the impact of patient and tumor characteristics on the major measures of outcome across different lines of treatment in a cohort of 472 patients treated for MBC. OS, PFS, and postprogression survival (PPS) were analyzed. The study showed how biological and clinical characteristics may have different prognostic value across different lines of therapy for MBC. After first-line treatment, the median PPS of luminal A, luminal B, and human epidermal growth factor receptor 2 (HER2)-positive groups was longer than 12 months. The choice of OS as a primary endpoint for clinical trials could not be appropriate with these subtypes. In contrast, OS could be an appropriate endpoint when PPS is expected to be low (e.g., triple-negative subtype after the first line; other subtypes after the third line). The potential implications of these findings are clinical and methodological. ***The Oncologist*** 2014;19:608–615

Implications for Practice: Although randomized clinical trials are recognized as the highest level of scientific evidence to demonstrate the efficacy of a treatment, sometimes they do not reflect the clinical circumstances faced in a real-world scenario. The present study provides data about outcomes of consecutive metastatic breast cancer patients treated at an academic hospital. The findings support the importance of considering breast cancer in distinct subgroups with the aim of obtaining more precise information about prognosis and expected benefit from treatment. The study also provides insights for future clinical trial design.

Introduction

Breast cancer (BC) is the leading malignancy among women in both Europe and the U.S. and is becoming an emerging oncologic disease in developing countries [1, 2]. Approximately 30% of women with early stage BC will develop metastases, whereas metastatic breast cancer (MBC) occurs in approximately 6%–7% of newly diagnosed cases [3]. The 5-year relative survival for women with MBC is ∼25%, and the median overall survival (OS) is usually reported to be ∼24 months [4–6]. In contrast, single clinical trials tend to report different results in terms of outcome depending on the specific characteristics of the enrolled population. Some recent trials on first-line treatment of MBC report median values of OS that are notably longer than those observed in previous studies [7–12]. Although comparison across different trials needs to be performed with extreme caution, this source of information could be useful if the trial population is homogeneous enough and well defined at molecular, pathological, and clinical levels. Among the different disease- and patient-related variables that may influence the prognosis of patients with MBC, tumor subtypes, sites of metastatic involvement, burden of disease, and patient comorbidities are considered to be of value [13].

Despite great improvements in early diagnosis and the strict standardization of the adjuvant setting, no gold standard therapy has been defined or validated for MBC. Multiple effective options for treatment are available, and the choice should be tailored to the individual patient on the basis of specific factors that are key points of the therapeutic algorithm: hormone receptor status, human epidermal growth factor receptor 2 (HER2) status, tumor burden, and prior treatments. Only a percentage of patients who receive

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a specific treatment really benefit from it [14]. Accordingly, there is increasing scientific interest in the identification of prognostic and predictive factors that maximize survival, that save patients from unnecessary toxicity, and that maintain a good standard of quality of life.

In recent years, several new drugs have been proposed for MBC, but too often, they do not show OS benefit. Some of the negative results appear to be related to the design of the randomized clinical trial (RcT) [15]. The primary measure of clinical benefit in MBC has traditionally been OS [16]. OS, defined as the time from randomization to death from any cause, addresses both safety and efficacy. Nonetheless, confounded by subsequent therapy and crossover, the value of OS as a primary endpoint in trials that evaluate new therapeutic agents for MBC has been questioned, especially in the context of first-line treatment. In fact, because of requirements for large sample sizes and long durations of follow-up, many RcTs cannot achieve the statistical power to detect a plausible increase in OS [17–19]. For these reasons, alternative event-driven endpoints that could act as predictive surrogates of OS have been proposed. Progression-free survival (PFS), defined as the time from randomization to tumor progression or death from any cause, is commonly adopted as an alternative endpoint to OS in first-line setting [19]. It requires a shorter follow-up period and a smaller sample size. PFS was informally accepted as a surrogate endpoint for OS in clinical cancer research [20, 21]. However, in several studies, treatment that demonstrated advantage in terms of PFS did not determine the same effect on OS [19]. The fact that PFS benefit was not translated into a statistically significant benefit in terms of OS, however, could not be interpreted as lack of improvement in OS as a whole. In particular, one possible explanation for the low correlation between PFS and OS is the observation of long postprogression survival (PPS). PPS is defined as the time from tumor progression to death from any cause. This relatively new measure of outcome has gained interest for understanding treatment effects. In fact, when examining the results of RcTs, the probability of detecting a statistically significant difference in OS depends on the length of the median PPS interval. In other words, the longer PPS is, there is less chance of detecting a statistically significant difference in OS between the treatment arms of an RcT. By using simulation methods to generate clinical trials, it has been shown that the sample size required for detecting a statistically significant difference in OS is directly correlated to the duration of PPS. When median PPS is short, the correlation between the hazard ratios (HRs) for PFS and OS is high, but when median PPS is longer than 12 months, the correlation between the two HR estimates decreases significantly. Accordingly, the notion that drugs that significantly prolong PFS should necessarily prolong OS is questionable [22]. To date, no data are available about PPS in patients treated outside of RcTs.

The aim of this study is to analyze the impact of patient and tumor characteristics on the outcome measures of a cohort of 472 patients with MBC. Results of this study are estimated to be potentially useful as a basis for the design of future clinical trials.

Materials and Methods

Study Design

We retrospectively reviewed a total of 472 consecutive MBC patients, treated at the Department of Oncology of the University Hospital of Udine, Udine, Italy, from January 2004 through July 2012.

For each patient, individual data and information on primary and advanced disease were collected from electronic health records. Based on this data set, the following BC subgroups were defined: "luminal A" (positive for estrogen receptor [ER] or progesterone receptor [PR], HER2 negative, Ki-67 $\leq$14%), "luminal B" (ER or PR positive, HER2 negative, Ki-67 $>$14%), "HER2 positive" (HER2 positive and any ER or PR status), "triple negative" (ER and PR negative, HER2 negative) [23, 24]. HER2-positive disease was further categorized according to the concomitant expression of hormone receptors (HER2 positive and ER or PR positive vs. HER2 positive and ER and PR negative). The cutoff point of 1% was used to define ER and/or PR positivity [25]. Time to development of MBC was defined as the interval between diagnosis of primary BC and diagnosis of MBC. OS was defined as the time elapsed between the start of treatment for metastatic disease and death or last follow-up. PFS was defined as the interval between the start of treatment for MBC and the occurrence of disease progression or death for any cause, whichever occurred first. PFS was calculated for the first four lines of treatment and were defined accordingly as PFS1, PFS2, PFS3, and PFS4. PPS was defined as the interval between progression and death or last follow-up. According to the starting point (evidence of progression after specific lines of treatment), PPS was defined as PPS1, PPS2, PPS3, and PPS4. The date of progression was defined as the date at which progression was first evident (e.g., imaging, biochemical examination, clinical visit), according to clinical practice.

The following variables were studied as possible prognostic factors for specific clinical outcome: ER status, PR status, HER2 status, Ki-67 status, previous adjuvant endocrine therapy (ET) and/or chemotherapy (CT) (yes vs. no), visceral metastatic site involved (yes vs. no), pulmonary sites involved (yes vs. no), brain (yes vs. no), and liver metastasis (yes vs. no), bone-only localizations (yes vs. no), age at diagnosis ($<$35 years, 65–70 years, or $>$70 years vs. 35–65 years), performance status according to the Eastern Cooperative Oncology Group (ECOG) scale (ECOG $\geq$2 vs. ECOG 1 and ECOG $\geq$2 vs. ECOG 0) [26–28].

Statistical Analysis

Descriptive analysis of clinical and pathological characteristics was performed. For categorical variables, such as age, histotype, grade, ER, PR, HER2 status, Ki-67, the frequency distribution was calculated. For the continuous variables, 25th, 50th, and 75th percentiles were calculated.

Outcome measures analyzed were OS, PFS, and PPS. In particular, the analyses were performed considering every type of therapy (OS_tot, PFS_tot, PPS_tot), ET lines only (OS_ET, PFS_ET, PPS_ET) and CT lines only (OS_CT, PFS_CT, PPS_CT).

We estimated HR, with a 95% confidence interval (CI), using uni- and multivariate Cox's proportional hazards regression model. The selection of covariates in the final model was based on both clinical relevance and statistical significance. The significance level was set at $p = .05$. All variables that showed statistical significance in univariate analysis were included in multivariate analysis. Kaplan-Meier analysis and the log-rank test were performed to compare survival curves among different population subgroups.

Table 1. Patient and disease characteristics

Characteristic	Sample size (missing value)[a]	Subgroup	*n*	%
Age at diagnosis (years) Median value: 58 years	*n* = 472 (0 missing)	<35	17	3.6
		35-65	295	62.5
		65-70	44	9.3
		> 70	116	24.6
Age at diagnosis of MBC (years) Median value: 63 years	*n* = 472 (0 missing)	<35	7	1.5
		35-65	248	52.5
		65-70	66	14.0
		> 70	151	32.0
Histotype	*n* = 463 (9 missing)	NOS	351	75.8
		Lobular	82	17.7
		Other	30	6.4
Histological grade	*n* = 413 (59 missing)	Grade 1	26	6.3
		Grade 2	214	51.8
		Grade 3	173	41.9
ER status	*n* = 433 (39 missing)	Positive	339	78.3
		Negative	94	21.7
PgR status	*n* = 434 (38 missing)	Positive	275	63.3
		Negative	159	36.6
Ki-67	*n* = 348 (124 missing)	≤14%	111	31.9
		>14%	237	68.1
HER2 (IHC and/or FISH)	*n* = 420 (52 missing)	Positive	89	21.2
		Negative	328	78.1
Immunophenotype	*n* = 359 (113 missing)	Luminal A	88	24.5
		Luminal B	138	38.4
		Triple negative	44	12.3
		HER2 positive	89	24.8
Adjuvant therapy	*n* = 302 (0 missing)	Anthracycline	176	57.3
		Taxane	103	34.1
		Trastuzumab	22	7.3
		Tamoxifen	156	51.7
		Aromatase inhibitor	110	36.4
Sites of metastasis	*n* = 472 (0 missing)	Bone only	123	26.1
		Visceral	243	51.5
		Lung	114	24.2
		Brain	21	4.4
		Liver	117	24.8
Menopausal status	*n* = 434 (38 missing)	Postmenopausal	393	90.6
		Premenopausal	66	15.2
		Male	5	1.2
ECOG performance status at first line	*n* = 425 (47 missing)	≥2	44	10.3
		1	146	34.4
		0	235	55.3
ECOG performance status at second line	*n* = 325 (10 missing)	≥2	38	11.7
		1	124	38.1
		0	163	50.2
ECOG performance status at third line	*n* = 241 (5 missing)	≥2	32	13.3
		1	98	40.7
		0	111	46
ECOG performance status at fourth line	*n* = 153 (5 missing)	≥2	20	13.1
		1	71	46.4
		0	62	40.5

[a]Total sample sizes and numbers missing may differ due to missing values for selected variables.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MBC metastatic breast cancer; PR, progesterone receptor; NOS, not otherwise specified.

Table 2. Number of lines received across different immunophenotypes

Lines	Median	Minimum	Maximum
Overall lines			
Luminal A	3	1	9
Luminal B	3	1	12
HER2 positive	2	1	11
Triple negative	2	1	6
Endocrine therapy lines			
Luminal A	2	0	4
Luminal B	1	0	6
HER2 positive	0	0	4
Triple negative	0	0	0
Chemotherapy lines			
Luminal A	1	0	7
Luminal B	1.5	0	7
HER2 positive	2	0	8
Triple negative	2	1	6

Results

Median age at diagnosis was 58 years, and median age at diagnosis of MBC was 63 years; 147 patients presented de novo metastatic disease.

Most patients (78.3%) had ER-positive disease. Eighty-eight patients (24.5%) had a luminal A disease, 138 (38.4%) had a luminal B disease, 89 (24.8%) had a HER2-positive disease, and 44 (12.3%) had a triple-negative phenotype. Distributions of patient personal data and primary and advanced disease characteristics are shown in Table 1.

The median number of therapeutic lines for metastatic disease was 3 (range: 1–12 therapeutic lines). Specifically, the median number of CT lines was 1 (range: 0–9 CT lines), and the median number of ET lines was 1 (range: 0–6 ET lines). The number of lines among different breast cancer subtypes is presented in Table 2.

Median time to development of MBC from initial diagnosis of BC was 21.7 months (range: 0–175 months); median OS was 34 months (25th–75th percentile: 13.7–58.5). In patients with hormone receptor-positive disease, no statistically significant difference in OS was observed according to the type of first-line treatment (CT vs. ET, log-rank test $p = .83$; median, 38 months and 36.7 months, respectively).

Table 3 summarizes outcome estimates for each line of therapy. Distinct analysis of chemotherapy and endocrine therapy lines is also shown. Median PFS and PPS progressively decreased in the different lines of therapy beyond the first. Different outcomes were observed among BC subtypes (Table 4, Fig. 1). Patients with luminal A and HER2-positive disease experienced the best prognoses. In the HER2-positive group, outcomes varied on the basis of concomitant expression of hormone receptors (Fig. 2). In particular, among HER2-positive cases, a better outcome was noted for hormone receptor positive disease versus hormone receptor negative disease (OS: 55.3 months vs. 26.0 months; PFS: 17.5 months vs. 8.1 months; PPS: 27.8 months vs. 14.0 months).

Table 3. Outcome estimates according to the line of therapy

Outcome	*n*	Median (months)	IQR (25th–75th percentile)
OS			
All treatment	472	34	13.7–58.5
Endocrine therapy	331	36.5	17.7–65.3
Chemotherapy	367	24.1	10.3–48.4
PFS, all treatment			
First line	472	9.0	4.2–18.2
Second line	335	4.4	2.5–10.6
Third line	246	4.0	2.2–8.4
Fourth line	158	3.0	2.0–6.1
PFS, endocrine therapy			
First line	332	9.5	3.7–19.7
Second line	181	4.7	2.7–10.4
Third line	76	3.9	2.4–7.3
Fourth line	23	4.2	1.5–10.6
PFS, chemotherapy			
First line	367	7.1	3.5–14.4
Second line	234	3.7	2.1–8.4
Third line	160	3.3	2.1–5.7
Fourth line	87	2.5	1.8–4.2
PPS, all treatment			
First line	472	18.3	5.1–36.2
Second line	335	12.2	4.3–27.4
Third line	246	8.2	2.7–18.9
Fourth line	158	7.0	2.1–14.9
PPS, endocrine therapy			
First line	332	21.0	7.6–39.1
Second line	181	14.2	4.6–31.5
Third line	76	7.5	0.8–30.6
Fourth line	23	6.7	1.2–32.9
PPS, chemotherapy			
First line	367	12.7	3.1–28.2
Second line	234	7.8	2.5–17.4
Third line	160	5.6	1.6–12.2
Fourth line	87	5.3	0.76–9.6

Abbreviations: IQR, interquartile range; OS, overall survival; PFS, progression-free survival; PPS, postprogression survival.

Multivariate analysis was performed to test the independent association between variables and measures of outcome overall and for each line of treatment (Table 5). Better prognosis in terms of OS was observed in patients with ER-positive and HER2-positive disease. In contrast, having pulmonary or hepatic localizations at diagnosis of metastatic disease was associated with an unfavorable outcome.

HER2-positive disease was associated with longer PFS1_tot (HR: 0.42 [95% CI: 0.3–0.6], $p < .0001$) and PFS2_tot (HR: 0.63 [95% CI: 0.46–0.88], $p = .01$). Bone-only disease was associated with longer PPS1_tot (HR: 0.56 [95% CI: 0.31–0.92], $p = .02$), whereas liver metastasis (HR: 1.75 [95% CI: 1.09–2.79], $p = .02$) and lung metastasis (HR: 2.09 [95% CI: 1.3–3.35], $p = .002$) at the diagnosis of metastatic disease had

Table 4. Outcome estimates according to breast cancer subtypes

Outcome	*n*	Median (months)	IQR (25th–75th percentile)
OS			
Luminal A	88	45.3	21.9–56
Luminal B	138	29.7	13.9–52.4
HER2 positive	89	43.5	18.3–81.1
Triple negative	44	10.2	4.9–18.2
PFS1			
Luminal A	88	15.1	5–28.2
Luminal B	138	9.3	4.5–14.7
HER2 positive	89	10.0	5.9–21.4
Triple negative	44	3.9	2.5–6.1
PPS1			
Luminal A	88	24	6.3–39.8
Luminal B	138	18.9	5.2–33.1
HER2 positive	89	19	6.9–38.9
Triple negative	44	6.1	0.8–12.2

Abbreviations: IQR, interquartile range; OS, overall survival; PFS1, progression-free survival at first line of treatment; PPS1, postprogression survival after first line of treatment.

an unfavorable impact on PPS1_tot. Worse performance status (ECOG ≥2) remained a significant unfavorable prognostic factor in terms of PFS2_tot (HR: 1.92 [95% CI: 1.29–2.86], $p = .001$) and PFS3_tot (HR: 2.05 [95% CI: 1.32–3.2], $p = .001$). It was also independently associated with PPS1_tot (HR: 2.44 [95% CI: 1.44–4.16], $p = .001$), and it maintained the association with PPS after subsequent therapeutic lines.

Regression analysis was conducted to evaluate the prognostic value of different immunophenotypes (the luminal A phenotype was used as a reference). On multivariate analysis, the triple-negative phenotype conferred a significantly poorer outcome in terms of OS_tot (HR: 3.1 [95% CI: 1.9–5.04], $p = .0001$), OS_CT (HR: 1.8 [95% CI: 1.04–3.16], $p = .0353$), PFS1_tot (HR: 3.6 [95% CI: 2.35–5.48], $p < .0001$), PFS2_tot (HR: 2.77 [95% CI: 1.68–4.57], $p < .0001$), PFS1_CT (HR: 2.17 [95% CI: 1.36–3.46], $p = .0011$), and PPS1_tot (HR: 2.09 [95% CI: 1.2–3.65], $p = .009$). HER2-positive disease was associated with better prognosis in terms of OS_tot (HR: 0.65 [95% CI: 0.42–0.99], $p = .0488$), OS_CT (HR: 0.51 [95% CI: 0.31–0.83], $p = .0065$), and PFS1_ET (HR: 0.48 [95% CI: 0.3–0.79], $p = .0035$). The luminal B subgroup showed an unfavorable outcome in terms of PFS1_tot (HR: 1.41 [95% CI: 1.03–1.93], $p = .0312$) and PFS1_ET (HR: 1.52 [95% CI: 1.1–2.09], $p = .0109$).

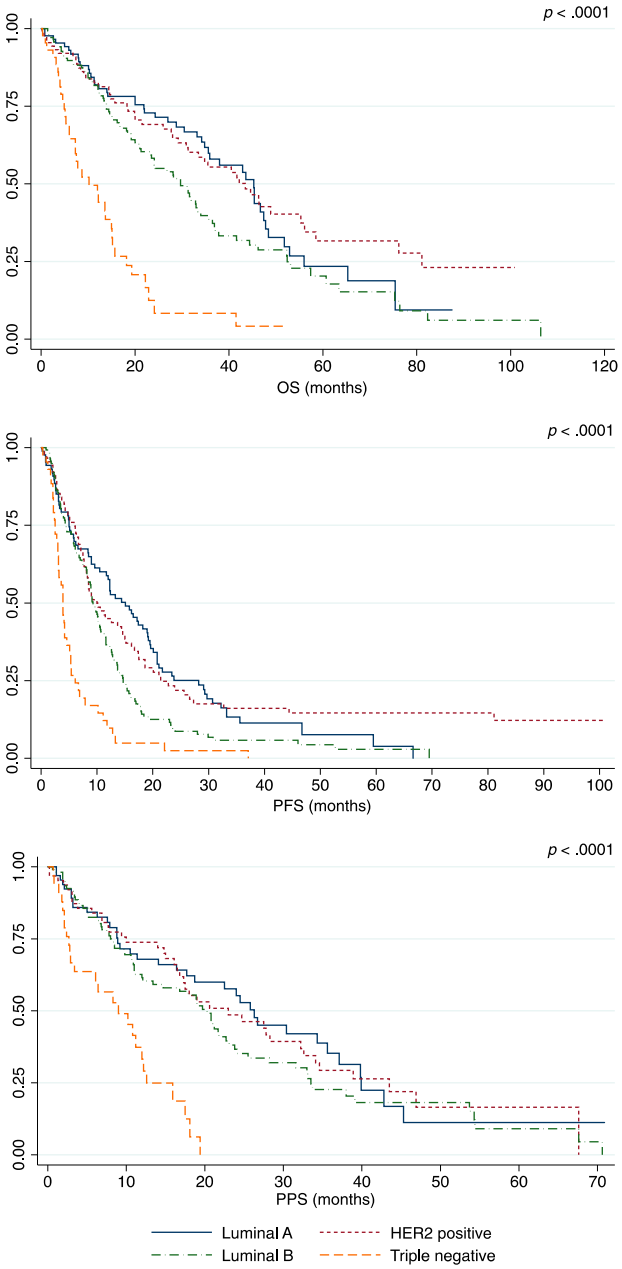

Figure 1. Comparison of OS, PFS at first line of treatment, and PPS after the first line of treatment between different immunophenotypes.

Abbreviations: OS, overall survival; PFS, progression-free survival; PPS, postprogression survival.

Discussion

There is a growing interest in the role and interpretation of the main measures of outcome used as endpoints in clinical cancer research. Traditionally, OS has been considered the most objective measure of efficacy in trials that test the value of anticancer agents. PFS has been proposed as a potential surrogate for OS that could allow faster evaluation of a new drug. Pros and cons have been raised about the use of PFS and OS [19, 29–31], the latter being considered the most objective; however, the use of OS as a measure of efficacy could be confounded by treatment beyond the first line. In fact, in clinical trials, the probability of pointing out differences in OS between two or more treatment arms is inversely related to the duration of PPS, a recently introduced measure of outcome that may offer insights into the interpretation of study results [22].

The recent literature has several examples of clinical trials in which, although a PFS benefit was observed, no improvement in OS was documented. In such cases, a long median PPS may explain the lack of statistical difference in OS [32]. This is

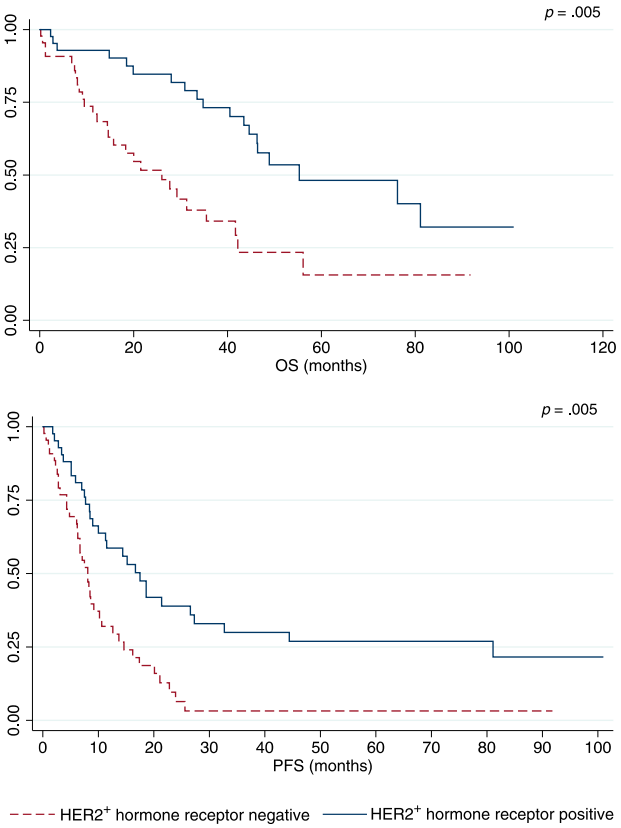

Figure 2. HER2+ population, comparison between hormone receptor-positive and -negative subgroups.

Abbreviations: OS, overall survival; PFS, progression-free survival.

Table 5. Multivariate Cox proportional hazards regression model

Variable	HR	95% CI	*p* value
OS, all treatment			
ER positive	0.41	0.26–0.66	.0003
HER2 positive	0.34	0.22–0.52	<.0001
Lung metastases	1.81	1.16–2.84	.01
Liver metastases	2.17	1.39–3.38	.0006
PFS1, all treatment			
ER positive	0.47	0.32–0.69	.0001
HER2 positive	0.42	0.3–0.6	<.0001
Ki-67 >14%	1.55	1.16–2.06	.003
Chemotherapy for early cancer (yes vs. no)	1.28	1.01–1.64	.04
Liver metastases	1.43	1.03–1.99	.03
PFS2, all treatment			
HER2 positive	0.63	0.46–0.88	.01
ECOG PS at second line 1	1.35	1.04–1.76	.03
ECOG PS at second line ≥2	1.92	1.29–2.86	.001
PFS3, all treatment			
Lung metastases	2.05	1.20–3.51	.008
ECOG PS at third line ≥2	2.05	1.32–3.2	.001
PPS1, all treatment			
Bone-only MBC	0.56	0.31–0.92	.02
Lung metastases	2.09	1.3–3.35	.002
Liver metastases	1.75	1.09–2.79	.02
ECOG PS at first line 1	1.88	1.31–2.68	.0006
ECOG PS at first line ≥2	2.44	1.44–4.16	.001
PPS2, all treatment			
Liver metastases	1.91	1.16–3.12	.01
ECOG PS at second line 1	2.03	1.46–2.83	<.0001
ECOG PS at second line ≥2	4.00	2.49–6.43	<.0001
PPS3, all treatment			
ECOG PS at third line 1	1.94	1.35–2.78	.0003
ECOG PS at third line ≥2	7.23	4.20–12.45	<.0001
PPS4, all treatment			
ER positive	0.39	0.19–0.82	.01
ECOG PS at fourth line 1	2.33	1.48–3.67	.0003
ECOG PS at fourth line ≥2	4.39	2.42–7.97	<.0001

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; PPS, postprogression survival.

a potential confounding factor in interpreting the results of first-line trials and could be occurred in studies that tested the combination of chemotherapy with the antiangiogenic agent bevacizumab [7–9]. In contrast, the EMBRACE study, which analyzed the role of eribulin in heavily treated patients with MBC, had more chances to observe benefit for OS because of the short PPS [33].

In patients with MBC, outcome is dependent on the presence of several prognostic factors and benefit of treatment, with the latter ultimately related to predictive factors. Because earlier clinical trials were conducted in heterogeneous populations that were not differentiated for prognostic and predictive factors, information about estimate of outcome is not reliably transferable to real clinical practice [34].

The present study investigated the different measures of outcome (OS, PFS across subsequent lines of therapy, PPS) in a real-world scenario, including both patients with MBC enrolled in clinical trials and patients with MBC treated in the context of routine clinical practice.

Interestingly, median OS was 34 months for the whole population, suggesting that prognosis of patients with MBC is better than expected based on the results of the earliest clinical trials testing chemotherapy agents [6]. The observation of incremental improvement of survival over time has been documented by several analyses of retrospective series [35–37]. Although only inferred, the advances in OS documented in more recent years have been attributed to the introduction of active anticancer agents administered sequentially across different lines of treatment [38].

In the present series, the highest median OS has been observed for patients with luminal A or HER2-positive phenotype confirming the best prognosis for these subgroups, with the outcome of the HER2-positive group being favorably influenced by anti-HER2 therapy.

The present analysis also confirmed the observation that median PFS usually decreases across subsequent lines. This clinical finding probably reflects the occurrence of resistance

to anticancer agents but also could be related to clinical conditions that may preclude optimal access to therapy (e.g., deterioration of performance status, cumulative side effects of therapy). The observation that, in HER2-positive disease, the therapeutic benefit is maintained longer than in the other subgroups supports the role of anti-HER2 agents beyond first-line treatment.

Interestingly, similar results were recently reported by Seah et al., who analyzed a series of 199 consecutive patients with MBC at the Dana-Farber Cancer Institute in Boston, Massachusetts [34]. The authors observed that tumor subtypes were differently associated with number of therapeutic lines, duration of chemotherapy, and OS. Patients with HER2-positive disease experienced the longest duration of chemotherapy and received the highest number of lines. In contrast, in patients with triple-negative BC, the duration of treatment was always the shortest, regardless of the line examined.

The analysis of PPS in a real-world scenario showed interesting findings. From a methodological point of view, it is important to note that although PPS can be defined simply as the difference between OS and PFS (i.e., PPS = OS − PFS), it is a time-to-event measure. Interestingly, the PPS value observed in our series has been evaluated by using standard methods of survival analysis. After the first and second lines of treatment, PPS was 18.3 months and 12.2 months, respectively. In both cases, the figure is over the 12-month threshold that could decrease the chance to point out OS differences in the context of a hypothetical clinical trial [22]. Accordingly, in similar scenarios, PFS should be favored over OS as a primary endpoint in trials testing anticancer agents in first- or second-line setting.

On the other hand, PPS after first line treatment was particularly short in patients with the absence of ER, PR and HER2 receptors, suggesting that a clinical trial conducted on a population selected for a triple-negative phenotype could adopt OS as a valid primary endpoint.

Although this study is affected by the limits that are typical of a retrospective design (e.g., heterogeneity in the method and intervals of disease assessment, variation in the choice of treatment lines over time), it analyzed a consecutive series of patients with MBC treated in a real-world scenario. In addition, a detailed review of the electronic health records guaranteed the accuracy of information about clinical and pathological findings. Results confirmed the prognostic role of specific disease and patient characteristics and were in line with data in the literature, suggesting that outcome is largely dependent on immunophenotype as defined in a sample of the primary tumor [39]. Furthermore, the study analyzed outcome through different measures and across sequential lines of treatment.

Conclusion

The observation of distinct values for PFS and PPS according to disease and patient variables underscores the importance of defining endpoints for clinical trials on the basis of characteristics of the study population. In other words, in the era of tailored treatment, the new concept of "tailored endpoints" should be taken into account when designing clinical trials. For this purpose, data acquired from consecutive series of patients treated in clinical practice may represent an added value to the development of novel anticancer drugs.

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Disclosures

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