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The HERBA study: a retrospective multi-institutional Italian study on patients with brain metastases from HER2-positive breast cancer

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The HERBA study: a retrospective multi-institutional Italian study on patients with brain metastases from HER2-positive breast cancer

Abstract

Microabstract

In this retrospective, multi-institutional study we collected data of 154 HER2-positive, breast cancer patients diagnosed with brain metastases from 2005 to 2014 with the aim to assess the impact of local and systemic treatments on the outcome. We report better survival for patients receiving surgery or stereotactic radiosurgery as local treatment and for those receiving HER2-targeted therapy as systemic treatment.

Background: There is no sufficient evidence to establish a standard of care for patients with brain metastases (BM) from HER2-positive (HER2+) breast cancer (BC). The aim of this study was to assess the impact of local and systemic treatments on the outcome of patients diagnosed with BM from HER2+BC over a period of 10 years, from 2005 to 2014.

Methods: Data of 154 patients were retrospectively collected at 14 Italian institutions through a specifically designed database

Results: Median overall survival (OS) was 24.5 months. Patients receiving surgery/stereotactic radiosurgery (SRS) achieved longer OS compared with those receiving whole brain radiotherapy (WBRT) or no treatment (33.5 vs 11.4 months; HR 0.34, 95% CI 0.22-0.52, p<0.001). Interestingly, WBRT did not improve OS when compared with no treatment (11.4 vs 9.8 months, HR 0.99, 95% CI 0.62-1.62, *P*=0.99). HER2-targeted therapy was associated with better OS when compared with systemic therapy without HER2-targeted therapy or no systemic therapy (27.5 vs 5.4 months, HR 0.26, 95% CI 0.17-0.41, p<0.001). At multivariate analysis stratified by local treatments, systemic therapy, Karnofsky performance score (KPS) and neurological symptoms significantly affected the OS. Age, number of BM, steroidal therapy, number of previous lines of systemic therapy, status of extracranial disease and period of diagnosis had not a significant impact on OS.

Conclusions: Patients with BM from HER2+BC treated with surgery/SRS as local treatment and HER2-targeted therapy as systemic treatment achieved the best outcomes. Patients with low KPS and neurological symptoms had poor survival.

Clinical practice points:

There is no high-level evidence from randomized study on the optimal therapeutic approach for patients with HER2-positive breast cancer metastatic to the brain. In this retrospective study, among local treatments surgery or stereotactic radiosurgery were associated with better overall survival, as compared with whole brain radiotherapy or with no local treatment. Regarding systemic therapy, HER2-targeted agents provided longer survival compared with systemic therapy without HER2-targeted agents or no systemic therapy. No difference were observed between trastuzuma

and lapatinib. At multivariate analysis, Karnofsky performance score and neurological symptoms represented relevant prognostic factors.

Key words: HER2-positive; brain metastasis; metastatic breast cancer; trastuzumab; lapatinib; breast-GPA; SRS

Introduction

HER2-positive (HER2+) breast cancer (BC) has higher propensity to metastasize to the brain when compared with other intrinsic subtypes [1]. It is estimated that 35-55% of patients with HER2+ BC will develop brain metastases (BM) during the course of their disease [2.3]. Historically, prognosis of patients with BM from BC unselected for HER2 status was poor, with a median overall survival (OS) of about 4-6 months [4,5].

The advent of HER2 targeted therapies has prolonged survival of patients with HER2+ BC including those with BM, whose median OS has been estimated at approximately 12-24 months [2,6-10]. Retrospective studies showed that the administration of trastuzumab-based therapy after the diagnosis of BM improves OS, although such improvement seems to be due to a prolonged control of extracranial disease (ECD) rather than activity against BM [10-13]. Conversely, combination of lapatinib plus capecitabine demonstrated direct activity against BM, with an objective partial intracranial response of 65.9%, a median time to intracranial progression of 5.5 months and median OS of 17 months, as reported by the phase 2 LANDSCAPE study [14]. More recently, the armamentarium for the treatment of metastatic HER2+ BC has been further expanded by the introduction of pertuzumab and trastuzumab-emtansine (T-DM1). Pertuzumab, given in combination with trastuzumab and docetaxel in the phase 3 CLEOPATRA study, translated into a delay in the onset of BM and a trend toward an increased OS after diagnosis of BM [15]. There is accumulating evidence that T-DM1 has activity against BM [16], and an exploratory retrospective analysis of the EMILIA trial showed a survival benefit for patients with BM treated with T-DM1 compared to patients treated with lapatinib and capecitabine [17].

At the same time, local treatment for BM has undergone remarkable progress. Particularly, in the last 5-10 years, stereotactic radiosurgery (SRS) has been increasingly used as adjuvant treatment in the post-operative setting [18] or as a non-invasive alternative to surgical resection, and improvements in radiotherapy techniques now allows for treating patients with multiple BM using SRS [19-20].

However, there is currently no sufficient high-level evidence to establish a standard of care for patients with BM from HER2+ BC, and current recommendations suggest that treatment should be chosen on an individual basis [21]. Since data from randomized trials are lacking, observational studies may provide relevant information about the impact of different therapeutic strategies and prognostic factors in the era of modern treatments [6-10].

We performed this multi-institutional, retrospective study with the aim to assess the impact of local and systemic treatments on the outcome of a real-life population of patients diagnosed BM from HER2+ BC over a period of 10 years, from 2005 to 2014.

Patients and Methods

The HERBA study ("a study on HER2+ metastatic BC patients with BrAin metastases") was a retrospective study conducted in 14 centers in Italy. Patients were included if they had histologically proven BC with HER2-positive status tested with immunohistochemistry and/or fluorescent in situ hybridization according to period-appropriated guidelines [22,23], and if they had first occurrence of BM documented by computed tomography or magnetic resonance imaging from 1st January 2005 to 31st December 2014. The study protocol was approved by the Ethics Committee of Verona and Rovigo area and by the Institutional Review Board at each participating center.

Data collection

Data obtained through a retrospective chart review at each participating institution were collected on a specifically-designed database and included the following information: Ki67, estrogen receptor (ER) and progesterone receptor (PgR) status, date of initial diagnosis of BC, date of diagnosis of metastatic disease, date of diagnosis of BM, number of BM, Karnofsky performance score (KPS), presence of neurological symptoms, administration of steroids, status of ECD at the diagnosis of BM, type of first-line local treatment and first-line systemic treatment for BM, date of intracranial and ECD progression, type of local and systemic treatment received at the time of first intracranial disease progression, date of death or last follow-up for patients who were alive at the time of data cut-off. The class of breast-specific graded prognostic assessment (Breast-GPA) was determined for each patient based on the reported information about age and KPS at the time of BM diagnosis, and ER/PgR status of the primary tumor [24].

Statistical analysis

Patients were divided in 2 cohorts according to the period of BM diagnosis: period A (2005-2009) and period B (2010-2014). These cohort time intervals were selected because lapatinib was approved by Italian Medicines Agency (AIFA) in May 2009, and from 2010 it became widely available in routine clinical practice in Italy. Descriptive statistics were used to analyze clinical-pathologic characteristics. Association between variables were evaluated using Chi-square test or Fisher's exact test when appropriate for categorical variables, and Mann-Whitney test for continuous variables. Time to occurrence of BM was defined as the time from BC diagnosis to the first evidence of BM. Intracranial progression-free survival (iPFS) was defined as the time from BM diagnosis to intracranial disease progression defined according to RECIST 1.1 or death for any cause, whichever occurred first. OS was defined as the time from BM diagnosis to death due to any cause. The Kaplan-Meier method and log-rank test were used to estimate and compare survival times. Median follow-up time was estimated according to the reverse Kaplan-Meier method. Univariate Cox proportional hazards regression modeling and multivariate analysis were used to evaluate associations of clinical-pathological variables with OS.

All analyses were carried out from a data cut-off on 30th April 2016 using STATA/SE 14.2. A p-value < 0.05 was considered as statistically significant.

Results

Patient characteristics

A total of 154 patients with BM from HER2+ BC were included in the study, 63 (41%) with BM diagnosed in period A (2005-2009) and 91 (59%) with BM diagnosed in period B (2010-2014). Main characteristics of patients were summarized in table 1. There was no significant difference in terms of patient characteristics between the two periods, except for median KPS that was 100 for patients in period A, 80 for patients in period B (*P*=0.0011).

Initial treatment of BM and intracranial PFS

Pattern of initial treatment for BM is listed in table 2. In the overall population, 81% of patients received local treatment and 80% of patients received systemic therapy at the time of BM diagnosis. There was no difference between the two periods in terms of distribution of local treatments. As anticipated, regarding systemic therapy there was an increased use of lapatinib (26% vs 17%) and other HER2 targeted agents (8% vs 0%) with a consequent reduced use of trastuzumab (34% vs 44%) in period B compared with period A, although this difference was not statistically significant (p=0.084). Percentage of patients who received lapatinib in first-line or subsequent lines of therapy was the same (42%) in both periods (data not shown).

Median iPFS was 8.68 months in the overall population, without significant difference between period A and B (9.86 vs 7.50 months; HR 1.16, 95% CI 0.83-1.64; *P*=0.368). Patients treated with surgery/SRS had longer median iPFS compared to those who received WBRT or no local treatment (13.52 vs 6.18 months; HR 0.54, 95% CI 0.38-0.76; *P*=0.001).

Interestingly, median iPFS was significantly longer for patients receiving trastuzumab-based therapy or other HER2 targeted therapy, compared with patients who did not receive HER2 targeted therapy (10.4 vs 9.8 vs 3.5 months, respectively; HR for trastuzumab vs no HER2 targeted therapy: 0.41, 95% CI 0.27-0.64; HR for other HER2 targeted therapy vs no HER2 targeted therapy: 0.42, 95% CI 0.27-0.67; *P*<0.001). Median iPFS was 7.04 months for patients who had received ≥ 3 lines of systemic therapy, and 8.79 months for those who had received 0-2 lines of systemic therapy before the diagnosis of BM (HR: 1.18, 95% CI 0.76-1.81, p = 0.467).

Treatment of BM at first intracranial progression

Among 93 patients who experienced intracranial disease progression, 45% received a local treatment, and 76% received systemic therapy (table 3). More patients diagnosed in period B received HER2 targeted agents after intracranial disease progression than those diagnosed in period A, although this difference was not statistically significant (74% vs 60%, *P*=0.38).

Overall Survival

At the time of data cut-off, 107 patients were dead. After a median follow-up of 58 months (IQR 22-87), median OS from the diagnosis of BM was 24.5 months, with no significant difference between the two periods (period B vs period A: 25.9 vs 21.5 months; HR 1.18, 95% CI 0.79-1.74, *P*=0.422 - figure 1).

Patients who were treated with surgery and/or SRS as initial local treatment achieved a longer median OS than those receiving WBRT or no local treatment (33.5 vs 11.4 months; HR 0.34, 95% CI 0.22-0.52, *P*<0.001 - figure 2). No significant difference in median OS was observed between patients treated with surgery compared to those treated with SRS (35.8 vs 32.5 months, HR 0.95, 95% CI 0.46-1.98, *P*=0.90), and between patients treated with WBRT compared to those who did not receive local treatment (11.4 vs 9.8 months, HR 0.99, 95% CI 0.62-1.62, *P*=0.99).

Regarding systemic therapy, patients who received HER2 targeted agents at the diagnosis of BM achieved longer median OS than those receiving systemic therapy without HER2 targeted agents (27.5 vs 13.8 months, HR 0.44, 95% CI 0.25-0.78, *P*=0.004) or no systemic therapy (27.5 vs 2.1 months, HR 0.09, 95% CI 0.05-0.16, *P*<0.001 – figure 3), with no significant difference between patients treated with trastuzumab compared with those treated with lapatinib (28.2 vs 24.5 months, HR 0.78, 95% CI 0.47-1.29, *P*=0.333 – figure 4).

Treatment given at the time of first intracranial progression had a significant impact on survival. Patients who received surgery and/or SRS at first progression compared with those who received WBRT or no local treatment had longer median OS (25.8 vs 11.3 months, calculated from first evidence of intracranial progression; HR 0.35, 95% CI 0.19-0.65, p=.001). Similarly, patients who received HER2 targeted agents at first progression achieved longer median OS than patients who received systemic therapy without HER2 targeted agents or no systemic therapy (19.2 vs 1.7 months; HR 0.23, 95% CI 0.13-0.42; p<.001).

Univariate and Multivariate analysis for overall survival

In univariate analysis, younger age (<60), better KPS (>70), a limited number of BM (≤3), absence of neurological symptoms, no needs for steroidal therapy and high breast-GPA score were significantly associated with better OS, whereas hormone receptor status and ECD status did not

affect the outcome. However, it should be noticed that in this study only 4 patients out of 154 had uncontrolled ECD at the time of BM diagnosis, therefore no definitive conclusion can be drawn on the prognostic impact of ECD (table 4).

In the multivariate analysis, Breast-GPA was not included but it was separated into the single items (age, KPS, and genetic subtypes defined as it follows: HER2 if tumor was ER and PgR negative, luminal B if tumor was ER and/or PgR positive). The multivariate analysis with backward selection identified four variables that significantly affected the OS: local treatment, systemic therapy, KPS and neurological symptoms. Since local treatment did not meet the proportional hazards assumption, it was considered as a stratification factor in the final model (table 5).

Discussion

In the HERBA study, median OS of patients diagnosed with BM from HER2+ BC from 2005 to 2014 was approximately 24 months. This survival time is consistent with that reported across other series [2,6-10] and confirms an improvement in terms of life expectancy over time, going from few months in historical series of patients unselected for HER2 status [4,5] to 18-24 months in more recent series of patients with HER2+ status in the era of modern multimodal treatments.

However, there is not a meaningful difference in terms of survival when comparing data of patients diagnosed in early 2000s [2] with those of patients diagnosed in more recent years [7-9], including patients enrolled in the present study. This observation suggests that median OS might have now reached a plateau, despite the introduction of novel HER2 targeted therapy beyond trastuzumab, such as lapatinib and, more recently, pertuzumab and T-DM1. In fact, a recent retrospective study on 123 patients conducted at the University of North Carolina [9], that compared 3 cohorts of patients defined on the basis of year of HER2 targeted therapy approval by US Food and Drug Administration (1998-2007 for trastuzumab, 2008-2012 for lapatinib, and 2013-2015 for pertuzumab and TDM-1), did not show any significant difference in terms of OS among the 3 cohorts. Similarly, among 100 consecutive patients with BM from HER2+ BC treated at the Memorial Sloan Kettering Cancer Center (MSKCC) from 2001 to 2011 [8], lapatinib was not associated with a clear survival advantage since, at multivariate analysis, HR for survival was similar for patients who received lapatinib and for those treated with non-lapatinib HER2 targeted therapy, when compared with patients who did not continued HER2 targeted therapy.

Consistently with these data, we did not observe significant survival difference between patients diagnosed in 2005-2009 (period A) and those diagnosed in 2010-2014 (period B). This might be explained by the fact that, actually, there was no significant difference in terms of treatment among the two periods. Although there was a trend toward a more frequent use of front-line lapatinib for patients diagnosed in period B, the percentage of patients receiving lapatinib at some point during

the course of their disease was the same for both periods. Patients in period B had a significantly worse median KPS than patients in period A, and this imbalancement might have potentially hidden a positive impact of front-line lapatinib on survival. Therefore, based on these observations, no definitive conclusion can be drawn about the impact of lapatinib on OS of patients with BM from HER2+ BC.

Although in the HERBA study it was not possible to assess the impact of each HER2 targeted agent, in general the administration of HER2 targeted therapy significantly extended median OS (27.5 months) when compared with no HER2 targeted therapy (13.8 months) or no systemic therapy (2.2 months); the positive impact of HER2 targeted therapy on OS was also confirmed at multivariate analysis (HR 0.30). The association of HER2 targeted therapy with better OS is consistent with data already reported by other authors [6-8]. Interestingly, in this study HER2 targeted therapy was also associated with a better iPFS, suggesting that the positive impact on OS may be due not only to an effective control of ECD but also to a possible role in delaying intracranial progression.

In terms of local treatment, surgery/SRS were associated with significantly longer OS (35 months) when compared with WBRT (11.4 months) or no local treatment (9.8 months). Clearly, this data should be interpreted cautiously, given that the choice of local treatment is generally based on the prognostic assessment of the patient and on the extent of intracranial disease. Generally, SRS/surgery is offered in case of good prognosis and limited intracranial disease (1-3 BM), whereas WBRT is given for multiple BM. Therefore, the difference in OS between SRS/surgery and WBRT/no treatment observed in the present study may possibly reflect a different distribution of prognostic factors or number of BM among patients receiving different local treatments, rather than a different efficacy of local treatments. Regarding the number of BM, however, in this study it was not associated with OS at multivariate analysis. In fact, the prognostic role of the number of BM in BC is still controversial, and the Breast-GPA Index that does not include number of BM in the prognostic assessment [25]. Accumulating evidence suggest that the outcome of patients, especially those treated with SRS, may be affected more by the cumulative intracranial tumor volume than by the number of BM [20,26,27]. Unfortunately, data about the cumulative intracranial tumor volume was not collected in this retrospective study.

Interestingly, we observed no significant difference in terms of OS between WBRT (11.4 months) and no treatment (9.8 months). These data are consistent with the results of the QUARTZ trial, a non-inferiority phase 3 study comparing best supportive care (BSC) plus WBRT with BSC alone in 538 patients with non-small cell lung cancer and BM unsuitable for surgery or SRS and with uncertainty by the physician or the patients about the potential benefit of WBRT: this trial showed no difference in OS between the 2 arms, although in a subgroup analysis a potential benefit from radiotherapy was observed in younger patients, those with a good KPS and no extracranial

disease [26]. These data suggest that, when surgery/SRS are not feasible, the administration of WBRT may be questionable for patients with HER2+ BC and BM.

Local and systemic treatments given at the first intracranial progression were significantly associated with the outcome. Again, even when given as salvage therapy, SRS/surgery and HER2 targeted therapy were associated with the longest survival. Based on these data, we can speculate that, in the era of modern multimodal treatment for BM, front-line approach is important but it should be integrated into a comprehensive therapeutic strategy involving multiple local and systemic treatments, given sequentially at each disease progression.

In the HERBA study, we also explored the role of prognostic factors. Although older age (>60 years), low KPS (≤70), multiple BM (>3), presence of neurological symptoms, need for steroidal therapy and lower Breast-GPA score (Groups 1-3) were associated with shorter survival at univariate analysis, only KPS and neurological symptoms maintained a prognostic role at multivariate analysis. This may suggest that Breast-GPA is not an optimal prognostic tool in the specific setting of patients with BM from HER2+ BC, and that other important factors, such as HER2 targeted therapy, should be incorporated, as suggested by other authors [12]. Particularly, a possible prognostic role of neurological symptoms was recently observed also in the MSKCC series [8] and the authors concluded that, although routine screening for BM in asymptomatic patients with HER2+ metastatic BC is not currently recommended [21], this finding represents an argument for early detection of BM [8].

We recognize that the HERBA study has several limitations. First, it is a retrospective study, therefore results should be interpreted cautiously, especially due to potential selection bias. However, since data from randomized trials are lacking in this setting, we believe that data from retrospective studies may still provide relevant information. Second, a central review of CNS imaging was not planned and this could have affected the response assessment and the evaluation of iPFS. However, the lack of central review has no impact on OS analysis, given the objective nature of this endpoint. Third, because only patients diagnosed from 2005 to 2014 were enrolled in the study, the majority of patients received trastuzumab and/or lapatinib as HER2 targeted therapy and no conclusion can be drawn about the role of novel HER2 targeted agents, such as pertuzumab and T-DM1. At this regard, a prospective observational study on patients with HER2+ BC and BM diagnosed from 2016 to 2018, the pro-HERBA study, is currently ongoing at the same institutions that participated to the retrospective HERBA study.

Conclusions

The HERBA study reported a median OS of approximately 24 months in patients with BM from HER2+ BC. We did not observe survival difference between patients diagnosed in 2005-2009 and

those diagnosed in 2010-2014. Surgery/SRS and HER2 targeted agents, given both as upfront and as salvage treatment, were associated with better outcomes, with median OS exceeding 2.5 years in selected patients. When interpreting this data, it must be kept in mind that candidates to surgery/SRS or active systemic treatments including HER2-targeted agents generally have more favorable prognostic features than patients treated with WBRT or best supportive care alone. Notwithstanding these limitations, our results suggest that, when feasible, surgery/SRS and HER2 targeted therapy should be considered as the preferred therapeutic approach.

Breast-GPA may be not an optimal tool to assess the prognosis of patients with HER2+ BM from BC. KPS and the presence of neurological symptoms are relevant prognostic factors and should be considered when planning the therapeutic strategy, whereas age, number of metastases, steroidal therapy or number of previous lines of systemic therapy should only have a secondary role in the choice of treatment.

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Tables

Table 1: Patients characteristics

Characteristic	All	Year of diagnosis		*P*
		2005-2009	2010-2014	
***N* of patients**	154 (100%)	63 (41%)	91 (59%)	
Median age (range) at diagnosis of brain metastases, year	53 (29-79)	53 (29-71)	54 (30-79)	0.237
IHC subtype:				0.669
ER/PgR positive	60 (39%)	23 (37%)	37 (41%)	
ER/PgR negative	86 (56%)	36 (57%)	50 (55%)	
Missing data	8 (5%)	4 (6%)	4 (4%)	
***N* of brain metastases**				0.150
Median (range)	3 (1-20)	3 (1-20)	3 (1-20)	
1	47 (30%)	30 (32%)	27 (30%)	
2-3	37 (24%)	12 (19%)	25 (27%)	
> 3	66 (43%)	28 (44%)	38 (42%)	
Missing data	4 (3%)	3 (5%)	1 (1%)	
KPS				0.0011
Median (range)	80 (30-100)	100 (40-100)	80 (40-100)	
≤ 50	12 (8%)	4 (6%)	8 (9%)	
60	8 (5%)	1 (2%)	7 (8%)	
70-80	58 (38%)	16 (25%)	42 (46%)	
90-100	74 (48%)	40 (64%)	34 (37%)	
Missing data	2 (1%)	2 (3%)	-	
Breast-GPA				0.268

Group 1 (score 0-1.0)	0 (0%)	0 (0%)	0 (0%)	
Group 2 (score 1.5-2.0)	11 (7%)	3 (5%)	8 (9%)	
Group 3 (score 2.5-3.0)	53 (35%)	18 (29%)	35 (38%)	
Group 4 (score 3.5-4.0)	88 (57%)	40 (63%)	48 (53%)	
Missing data	2 (1%)	2 (3%)	0 (0%)	
Neurological symptoms				0.145
Present	86 (56%)	30 (48%)	56 (62%)	
Absent	62 (40%)	29 (46%)	33 (36%)	
Missing data	6 (4%)	4 (6%)	2 (2%)	
Steroidal therapy				0.168
Yes	110 (71%)	41 (65%)	69 (76%)	
No	38 (25%)	19 (30%)	19 (21%)	
Missing data	6 (4%)	3 (5%)	3 (3%)	
***N* of lines of systemic therapy received before brain metastases**				0.502
Median (range)	1 (0-8)	1 (0-8)	1 (0-8)	
0-2	114 (74%)	45 (71%)	69 (76%)	
≥ 3	28 (18%)	13 (21%)	15 (16%)	
Missing data	12 (8%)	5 (8%)	7 (8%)	
Time from diagnosis of BC to brain metastases				0.111
Median (IQR), months	39.1 (20.3-62.4)	45.7 (29.1-62.1)	34.9 (16.6-63.0)	
Time from diagnosis of metastatic disease to brain metastases				0.772
Median (IQR), months	12.5 (2.0-24.0)	13.0 (0.9-25.8)	12.3 (3.1-22.3)	
Status of extracranial disease				0.750
No evidence of extracranial disease	18 (12%)	6 (10%)	12 (13%)	
Controlled extracranial disease	128 (83%)	53 (84%)	75 (82%)	
Uncontrolled extracranial disease	4 (2.5%)	2 (3%)	2 (2%)	
Missing data	4 (2.5%)	2 (3%)	2 (2%)	

BC: breast cancer; GPA: graded prognostic assessment; IQR (interquartile range); KPS: Karnofsky performance score

Table 2: Initial treatment for brain metastases from HER2-positive breast cancer

Treatment	All	Year of diagnosis		*P*
		2005-2009	2010-2014	
***N* of patients**	154	63	91	
Local treatment				
Surgery	**26 (17%)**	**10 (16%)**	**16 (17%)**	0.952
Surgery alone	7 (5%)	4 (6%)	3 (3%)	
Surgery + WBRT	15 (10%)	5 (8%)	10 (11%)	
Surgery + SRS	4 (2%)	1 (2%)	3 (3%)	
SRS	**33 (21%)**	**14 (22%)**	**19 (21%)**	
SRS alone	32 (20%)	13 (20%)	19 (21%)	
SRS + WBRT	1 (1%)	1 (2%)	-	
WBRT alone	**66 (43%)**	**26 (41%)**	**40 (44%)**	
No local treatment	**29 (19%)**	**13 (21%)**	**16 (18%)**	
Systemic therapy at the time of brain metastases diagnosis				
HER2 targeted agents	**102 (66%)**	**39 (61%)**	**63 (69%)**	0.084
Trastuzumab	59 (38%)	28 (44%)	31 (34%)	
Lapatinib	35 (23%)	11 (17%)	24 (26%)	
Others	8 (5%)	-	8 (9%)	
Chemotherapy/Endocrine therapy alone	**20 (13%)**	**10 (16%)**	**10 (11%)**	
No systemic therapy	**22 (14%)**	**9 (14%)**	**13 (14%)**	
Missing data	**10 (6%)**	**5 (8%)**	**5 (5%)**	

SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy.

Table 3: Treatment for brain metastases at the time of first intracranial progression in patients with HER2-positive breast cancer

Treatment	All	Year of diagnosis		*P*
		2005-2009	2010-2014	
***N* of patients (%)**	93 (100%)	40 (43%)	53 (57%)	-
Local treatment				
Surgery	**5 (5%)**	2 (5%)	3 (6%)	0.310
SRS	**21 (23%)**	6 (15%)	15 (28%)	
WBRT alone	**15 (16%)**	9 (22%)	6 (11%)	
No local treatment	**52 (56%)**	23 (58%)	29 (55%)	
Systemic therapy at the time of BM diagnosis				
HER2 targeted agents	**63 (67%)**	**24 (60%)**	**39 (74%)**	0.038
Trastuzumab	38 (41%)	11 (27%)	27 (51%)	
Lapatinib	19 (20%)	10 (25%)	9 (17%)	
Others	6 (6%)	3 (8%)	3 (6%)	
Chemotherapy/Endocrine therapy alone	**8 (9%)**	**6 (15%)**	**2 (4%)**	
No systemic therapy	**14 (15%)**	**8 (20%)**	**6 (11%)**	
Missing data	**8 (9%)**	**2 (5%)**	**6 (11%)**	

SRS: stereotactic radiosurgery; WBRT: whole brain radiotherapy.

Table 4: Univariate analysis for overall survival

Variable	Median OS (months)	HR (95% CI)	*P*
Age at diagnosis of brain metastases			0.004
≥60	13.0	1.00	
<60	27.3	0.55 (0.36-0.82)	
HR status			0.470
ER and PgR negative	20.0	1.00	
ER and/or PgR positive	23.0	0.86 (0.58-1.29)	
***N* of brain metastases**			0.030
>3	14.1	1.00	
1-3	27.4	0.64 (0.43-0.96)	
KPS at diagnosis of brain metastases			<0.001
≤70	7.6	1.00	
>70	27.3	0.34 (0.22-0.54)	
Neurological symptoms			<0.001
Present	13.8	1.00	
Absent	27.5	0.39 (0.26-0.61)	
Steroidal therapy			0.001
Yes	16.4	1.00	
No	38.6	0.44 (0.27-0.73)	
***N* of lines of previous systemic therapy**			0.6
≥3	13.6	1.00	
0-2	20.33	0.88 (0.53-1.45)	

Extracranial disease			0.75
Uncontrolled	28.4	1.00	
Absent/controlled	23.0	1.19 (0.38-3.79)	
Breast-GPA			<0.001
Groups 1-3	12.6	1	
Group 4	27.4	0.48 (0.32-0.72)	
Period of diagnosis			0.422
Period A (2005-2009)	25.9	1.00	
Period B (2010-2014)	21.5	1.18 (0.79-1.74)	
Local treatment			<0.001
WBRT/No treatment	11.4	1.00	
Surgery[a]/SRS[b]	33.5	0.34 (0.22-0.52)	
Systemic treatment			<0.001
No HER2 targeted therapy/no therapy	5.4	1.00	
HER2 targeted therapy	27.5	0.26 (0.17-0.41)	

ER: estrogen receptor; GPA: graded prognostic assessment; HR: hormone receptors; KPS: Karnofsky performance score; PgR: progesterone receptor; SRS: sterotactic radiosurgery; WBRT: whole brain radiotherapy

a. Surgery includes surgery alone or surgery followed either by SRS or WBRT;
b. SRS includes

SRS alone or SRS followed by WBRT

Table 5: Multivariate analysis for overall survival

Initial Cox model with all covariates	HR (95% CI)	*P*
Local treatment		<0.001
WBRT/No treatment	1.00	
Surgery/SRS	0.26 (0.15-0.46)	
Systemic treatment		<0.001
No HER2 targeted therapy/no therapy	1.00	
HER2 targeted therapy	0.33 (0.20-0.52)	
Age at diagnosis of brain metastases		0.254
≥60	1.00	
<60	0.76 (0.47-1.22)	
KPS at diagnosis of brain metastases		0.077
≤70	1.00	
>70	0.63 (0.38-1.05)	
***N* of brain metastases**		0.875
>3	1.00	
1-3	0.96 (0.59-1.56)	
Neurological symptoms		0.073
Present	1.00	
Absent	0.58 (0.31-1.05)	
Steroidal therapy		0.465
Yes	1.00	
No	0.75 (0.35-1.61)	
Final Cox model [§]	**HR (95% CI)**	***P***
Systemic treatment		<0.001
No HER2 targeted therapy/no therapy	1.00	
HER2 targeted therapy	0.30 (0.19-0.47)	
KPS at diagnosis of brain metastases		0.026
≤70	1.00	
>70	0.58 (0.36-0.94)	
Neurological symptoms		0.005
Present	1.00	
Absent	0.50 (0.31-0.81)	

§ Cox model after backward selection, stratified by Local treatment since this variable did not meet the proportional hazards assumption.

Figures

Figure 1. – OS according to period of brain metastases diagnosis

Kaplan Meier OS curves according to period of brain metastases diagnosis. Period B (2004-2009) vs Period A (2010-2014): median OS 25.9 vs 21.5 months; HR 1.18 (95% CI 0.79-1.74), *P*=0.422.

Figure 2 – OS according to local treatments

Kaplan Meier OS curves according to local treatments. Median OS was: 35.8 months for surgery, 32.5 months for SRS, 11.4 months for WBRT, 9.8 months for no local treatment. HR was: surgery vs no treatment, 0.38 (95% CI 0.20-0.75), *P*=0.005; SRS vs no treatment, 0.33 (95% CI 0.18-0.63), *P*=0.001; WBRT vs no treatment, 1.10 (95% CI 0.68-1.78), *P*=0.703.

Figure 3 – OS according to systemic therapy

Kaplan Meier OS curves according to systemic therapy. Median OS was: 2.1 months for no systemic therapy (HR: 1.00), 13.8 months for systemic therapy without HER2 targeted agents (HR 0.20, 95% CI 0.10-0.40; *P*<0.001), 27.5 months for systemic therapy with HER2 targeted agents (HR 0.09, 95% CI 0.05-0.16, *P*<0.001).

Figure 4 – OS according to HER2 targeted agents (trastuzumab vs lapatinib)

Kaplan Meier OS curves for patients treated with trastuzumab-based and lapatinib-based systemic therapy. Median OS was 28.2 and 24.5 months for trastuzumab-based and lapatinib-based, respectively (HR 0.78, 95% CI 0.47-1.29, *P*=0.333).