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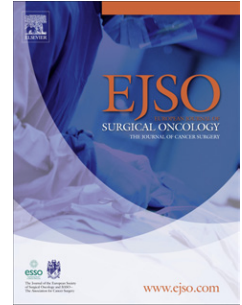
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# Accepted Manuscript

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**Factors influencing survival in patients with breast cancer and single or solitary brain metastasis.**

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**Abstract**

**Aim:** To perform a comprehensive analysis of patients with breast cancer and solitary or single brain metastasis and to analyze factors influencing survival from brain metastasis.

**Methods:** One hundred consecutive patients with single or solitary brain metastasis were treated in one institution in the years 2003-2009. Brain lesions were diagnosed by magnetic resonance imaging (MRI). A total of 57% of patients underwent resection of brain metastasis, 95% of patients received whole-brain radiation therapy (WBRT) and 67% were treated systemically after WBRT.

**Results:** Median survival from the detection of brain metastasis was 13 months and 28% of patients survived for 2 years. In 29 patients with solitary brain metastasis, median survival was 20 months (2–80 months) and in 71 patients with single brain metastasis it was 11 months (1–79 months)  $p = 0.01$ . Median survival from brain metastasis in patients with Recursive Partitioning Analysis Radiation Therapy Oncology Group (RPA RTOG) prognostic class I, II and III was 22 months (4–80 months), 13 months (2–79 months) and 6 months (0.4–28 months), respectively,  $p < 0.0001$ . Median survival from brain metastasis in triple-negative, HER2, luminal B and luminal A subtypes was 11 months, 13 months, 16 months and 15 months, respectively ( $p = 0.60$ ). Multivariate analysis revealed that RPA RTOG prognostic class I, neurosurgery and systemic therapy after WBRT were factors that correlated with survival.

**Conclusions:** In patients with one metastatic lesion in the brain, affiliation to RPA RTOG prognostic class I and intensive local and systemic treatment had a strong correlation with survival. There was no significant correlation between biological subtype of cancer and survival.

**Keywords:** breast cancer, RPA RTOG prognostic class, single brain metastasis, solitary brain metastasis, systemic therapy

**Introduction:**

Approximately 15–30% of patients with cancer will develop cerebral metastases over the course of their disease [1, 2], but in 30–40% of those patients, only one metastatic lesion in the brain will be detected [3]. “Solitary brain metastasis” is a relatively rare occurrence of a single parenchymal brain metastasis and it is the only known site of metastatic cancer in the body, with no systemic metastatic disease. The term “single brain metastasis” refers to a single cerebral lesion, without any implications connected to the extent of extracranial disease [3]. In the present study, it means the presence of cancer lesions outside the brain.

Current treatment approaches to local therapy of brain metastasis include surgery, whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) or a combination of these modalities [4]. Patients with single or solitary brain metastasis generally undergo more aggressive local treatment than those with multiple metastases. Despite this, majority of patients with breast cancer and single brain metastases die because of progressive extracranial disease [5], therefore, a continuation of systemic therapy after local treatment in patients with active systemic disease is justified. However, the role of systemic therapy after local treatment in patients with breast cancer and solitary brain metastasis has not been studied.

Due to the fact that survival of patients with brain metastases depends on many factors that are related to patient’s characteristics, breast disease and method of treatment, the aim of the study was to assess prognostic factors influencing survival from brain metastasis in 100 patients with breast cancer who had single or solitary brain lesion.

**Patients and Methods:**

Between 01.01.2003 and 31.12.2009, 441 patients with breast cancer and brain metastases, were treated in Breast Cancer Department at the Cancer Center and Institute of Oncology in Warsaw, Poland. Out of 441, one hundred patients had solitary or single brain metastasis. The prospective observation of patients started at the time of the detection of brain metastases and all data was collected in data base. In each case, treatment options were approved by team of medical oncologists, radiation oncologist (A.N.), neurologist and neurosurgeons and were performed after patients had signed written consent.

Without having the possibility to perform gene expression profiling, biological subtypes of brain metastases were defined based on the expression of estrogen (ER), progesterone (PgR) and HER2 receptors, which were proposed by Hugh et al [6]. Immunohistochemistry (IHC) was performed in order to evaluate the level of ER, PgR and

HER2 expression. Fluorescence in situ hybridization (FISH) analysis for HER2 amplification was performed in the case of IHC 2+. Four biological subtypes were selected: triple-negative (ER/PgR negative, HER2 negative), HER2 (HER2 positive, ER/PgR negative), luminal B (HER2 positive, ER/PgR positive) and luminal A (ER/PgR positive, HER2 negative). Triple-negative and luminal A subsets were HER2-negative. HER2 and luminal B subsets were HER2-positive.

Overall survival (OS) was calculated from the diagnosis of breast cancer to a death from any cause. Disease free survival (DFS) was calculated from the diagnosis of breast cancer to distant or local-regional cancer recurrence or to a death from any cause, whichever occurred first. DFS and OS were calculated in the entire group and within 4 biological subgroups. Survival calculated from the detection of brain metastasis was analyzed in the entire group, including 4 biological subgroups, in three Recursive Partitioning Analysis Radiation Therapy Oncology Group (RPA RTOG) prognostic classes, and in both solitary and single brain metastasis subsets. RPA RTOG prognostic class I included patients below 65 years of age, with Karnofsky Performance Status (KPS) score of 70 or more and with controlled disease at the primary site without metastases outside the brain. Prognostic class III included patients with a KPS score below 70, regardless of other factors, while prognostic class II included all the remaining patients [7].

#### Statistical analysis:

Descriptive statistics were determined for the patient demographics and clinical characteristics. All hypotheses tests were conducted at the  $\alpha = 0.05$  level with a 95% confidence interval. In order to compare categorical tumor features in 4 biological subgroups of patients, the chi-square test was used. For those categorical variables in which the chi-square test was inappropriate because of small numbers, the Fisher exact test was used. In order to determine factors influencing survival from brain metastases multivariate Cox proportional hazards model was developed. Proportional hazards assumption for the final Cox model was tested using Schoenfeld's residuals. The following factors were analyzed: RPA RTOG prognostic class (III vs I and III vs II), biological subtype of breast cancer (triple-negative vs luminal A; triple-negative vs luminal B and triple-negative vs HER2), localization of brain lesion (infratentorial vs supratentorial), leptomeningeal carcinomatosis appearing as a relapse after definitive treatment (yes vs no), neurosurgery (yes vs no), WBRT (40Gy vs 30Gy vs 20Gy) and systemic treatment after WBRT (yes vs no). Survivals were estimated using the Kaplan-Meier method and compared using the log-rank test.

**Results:**

## Patients' demographics and treatment

In all patients, brain metastases were detected in magnetic resonance (MR) after clinical symptoms appeared. In 57% of patients neurosurgery with curative intention was performed. In 95% of patients WBRT was performed, using 4–6 MV photon beam by two lateral opposed standard fields covering all intracranial contents. In 5 patients neither surgery nor WBRT was performed because of poor performance status. After local treatment of brain metastases, systemic treatment was ordered in 67% of patients. Stereotactic radiosurgery was performed in 3 patients, after local recurrence.

A comparison of clinicopathological features between patients with single and solitary brain metastasis is presented in Table 1. Solitary brain metastasis (one lesion within the brain without any extracranial metastatic site) was detected in 29% of patients and single brain metastasis (one lesion in the brain with any extracranial metastases) was detected in the remaining 71% of patients. Patients with solitary brain metastasis were more likely to be HER2-negative and belonged to RPA RTOG prognostic class I. They were often treated with neurosurgery and WBRT on schedule 40 Gy in 20 fractions. Systemic treatment was ordered less frequently and in most cases, hormonal therapy was given.

A comparison of clinical features of four biological subsets is presented in Table 2. Almost half of patients were HER2-positive (HER2 and luminal B subtypes). Biological subsets of patients did not differ in relation to age at initial diagnosis, initial TNM stage, KPS, rates of neurosurgery, WBRT and systemic treatment after WBRT. The only difference was the pattern of metastatic spread. In HER2-positive breast cancer patients (HER2 and luminal B subtypes), metastases in many organs were detected and strong correlation between brain metastases and metastases to the viscera was observed. In 42% of patients with triple-negative breast cancer, the first site of dissemination of breast cancer could be found in the brain. In luminal A subtype, bones were the most frequent site of metastasis. Locoregional failure was observed in all biological subtypes, but it was the most frequent in luminal B subset of patients.

## Survivals

In the entire group, median disease free survival (DFS) was 2 years and overall survival (OS) was 4.8 years. Median survival from the detection of brain metastasis was 13 months and 28% of patients survived for 2 years. Median survival from brain metastasis in

patients with RPA RTOG prognostic class I, II and III was 22 months, 13 months and 6 months, respectively,  $p < 0.0001$ . Median survival from brain metastasis in 29 patients with solitary brain metastasis was 20 months and in 71 patients with single brain metastasis was 11 months,  $p = 0.01$  (Figure1). Median survival in patients with solitary brain metastasis, treated and not treated systemically after WBRT, was 34 months and 8 months, respectively and in patients with single brain metastasis it was 13 months and 4 months, respectively,  $p < 0.001$ . Median survival from brain metastases in triple-negative, HER2, luminal B and luminal A subtypes was 11 months, 13 months, 16 months and 15 months, respectively ( $p = 0.60$ ) and 2-year-survival was 12%, 20%, 17% and 32%, respectively. Median survivals of patients are presented in Table 3.

#### Factors influencing survival after WBRT – multivariate analysis

The Cox multivariate analysis revealed that patients with RPA RTOG prognostic class I as well as those who underwent neurosurgery and those who were treated systemically after WBRT, were at a lower risk of death. On the contrary, RPA RTOG prognostic class III, lack of surgical resection and systemic treatment as well as central nervous system relapse in the form of carcinomatous meningitis correlated with poor survival. Biological subtype of breast cancer (triple-negative vs luminal A,  $p = 0.51$ ; triple-negative vs luminal B,  $p = 0.51$ , and triple-negative vs HER2,  $p = 0.78$ ), localization of the lesion in the brain ( $p = 0.34$ ) and the schedule of WBRT ( $p = 0.41$ ) did not correlate with survival. The results of final model are presented in Table 4.

#### Discussion

Survival from brain metastases depends on factors related to patient's characteristics (age, performance status), the disease (biological subtype of breast cancer, number of brain metastases, presence and advancement of extracranial disease) and type of treatment given (surgery, WBRT, SRS and systemic treatment after WBRT).

#### Patient-related factors

In the present study, affiliation to the RPA RTOG prognostic class was an important prognostic factor influencing survival from the detection of brain metastasis. Our results are



comparable to the results that had been already published [8, 9] and to our previous study concerning survival of patients with operated brain metastases [10].

Tendulkar et al [8] analyzed 271 patients with a single brain metastasis who underwent surgical resection and adjuvant therapy. Survival of patients in RPA class I was 21.4 months, in RPA class II – 9.0 months and in RPA class III – 8.9 months. This analysis supported the prognostic significance of the RPA classification in patients with a single/solitary brain metastasis who underwent surgical resection and adjuvant therapy.

## Cancer-related factors

### Biological subtypes

Biological subtypes of breast cancer are prognostic factors that give information about natural history of the disease. The survival of HER2-positive (HER2 and luminal B) and triple-negative breast cancer patients was the worst while survival for luminal A subtype was the best [11], however, new therapeutic approaches can improve the outcome of patients with poor prognosis. In the post-trastuzumab era, the survival of HER2-positive breast cancer patients is comparable or even better, than that observed in patients with luminal A subtype [12, 13]. In the present study, the rate of HER2-positive (HER2 and luminal B), triple-negative and luminal A subsets was comparable to our previous study concerning the whole group of 420 patients with brain metastases treated in the years 2003-2009 [12].

We failed to demonstrate the influence of biological subtype of breast cancer on survival in single or solitary brain metastasis. The possible explanation of this result is that the extent of metastatic disease of those patients was relatively small and intensive local and systemic treatment could be effective enough to overcome poor prognosis attributed to particular biological subtype. However, two-year survival from brain metastases in triple-negative, HER2, luminal B and luminal A subtypes was 12%, 20%, 17% and 32%, respectively. Although the difference is not statistically significant ( $p = 0.60$ ), this suggests, that triple-negative breast cancer remains the worst and that luminal A is the best biological subtype. Unfortunately, the presented subgroups are too small to definitively solve this problem.

## Treatment-related factors

### Surgery

In the present study, neurosurgery positively correlated with survival.

The publication of several prospective studies established the value of combining surgical resection and radiation therapy for brain metastases. In the trial by Patchell et al. [14], median survival for patients who received surgery and WBRT was 9.2 months as compared to 3.5 months for patients who received WBRT alone. In the trial by Vecht et al. [15] median survival was 10 months as compared to 6 months. The difference in survival was most robust in a subgroup of patients with stable or absent extracranial disease (median survival 12 versus 7 months). No significant survival difference was observed in patients with active extracranial disease (median survival 5 months in both treatment groups). In the trial by Mintz et al. [16] median survival between the surgery plus WBRT arm and the WBRT only arm was not statistically different (5.6 months and 6.3 months, respectively). In this study, the systemic extent of primary disease was identified as a major contributing factor and predictor of mortality. The results of the above mentioned studies suggests that surgical excision should be considered for patients with good performance status, with minimal or lack of extracranial disease, and in cases where single brain metastasis can be amenable to complete excision.

#### WBRT

In the present study the analysis of survival from brain metastasis revealed the same equivalence for all radiotherapy schedules used. The dose of 40 Gy in 20 fractions was not better than a dose of 30 Gy in 10 fractions and 20 Gy in 5 fractions.

In the study by Patchell et al [5] the role of WBRT in 95 patients with single brain metastasis after surgical resection was assessed. Patients, who received treatment with surgical resection and WBRT, had fewer recurrences in the brain (18% vs 70%) and were less likely to die due to neurological causes (14% vs 44%). There was no difference in overall survival between two groups (48 vs 43 weeks). The study confirms the opinion, that postoperative WBRT should be considered in patients who underwent resection of a single brain metastasis in order to reduce the risk of tumor recurrence.

Currently, there is no consensus on the optimal radiation scheme for patients with brain metastases. The optimal dose-fractionation schedules for patients with brain metastases have been evaluated in randomized trials conducted by the RTOG [17, 18]. The overall response and median survival rates were equivalent in arm of 40 Gy in 4 weeks, 30 Gy in 2 weeks and 20 Gy in 1 week. There were no survival benefits regardless of which fractionation scheme was used. The results of the present study confirm the above mentioned data. Long term side effects of WBRT are a significant issue in the treatment of patients with single or solitary brain metastases because of the relatively long survival time of these patients. In some

previous reports, increased risk of neurotoxicity after daily fractions 3–6 Gy was shown [19], but recent class I evidence suggests that, altered dose/fractionation schedules of WBRT do not result in significant differences in neurocognitive function when compared to 30 Gy in 10 fractions [20].

#### Systemic treatment

In the present study, the Cox multivariate analysis revealed, that systemic treatment ordered after WBRT statistically significantly correlated with survival.

Based on the recent publication, systemic therapy is not a standard treatment in patients with brain metastases; however, this recommendation was established mostly by the analysis of patients with non small cell lung cancer [21]. Breast cancer cells are relatively sensitive to chemotherapy, hormonal therapy and targeted therapy and tailored treatment can be effective in particular biological subsets of patients after WBRT [12]. Moreover, about 46% –71% of patients with brain metastases and active extracranial disease die because of progression in the viscera and not due to neurological causes [5, 15, 16, 17], therefore, continuation of systemic treatment after WBRT in patients with active systemic disease is justified [9, 11, 22].

Unexpectedly, in the present study, a strong correlation between systemic therapy and survival of patients with solitary brain metastasis has been shown. One possible explanation of this phenomenon is that systemic therapy can control occult metastatic lesions outside the brain and, in this way, it can prevent distant recurrence. The second explanation can be the fact, that WBRT disrupts the blood-brain barrier. The level of systemic drugs in central nervous system after WBRT can be high enough, to control brain lesions. To our knowledge, this is the first data demonstrating the activity of systemic therapy in patients with solitary brain metastasis from breast cancer, however, this study has some limitations and the results require confirmation by other authors.

#### Conclusions

In our study, clear difference in survival between single and solitary brain metastasis was demonstrated. RPA RTOG prognostic class was the most reliable indicator of survival in patients with one metastatic lesion in the brain. Neurosurgery as a part of multidisciplinary approach and systemic therapy used after local treatment prolonged survival in both subgroups. Although the proportion of particular biological subsets is comparable to the one,

observed in patients with multiple brain metastases, we failed to show significant correlation between biological subtype of breast cancer and the outcome.

### **Conflict of interest statement**

There have been no involvements that might raise the question of bias in the work reported.

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**Table legends:**

Table 1. A comparison of clinicopathological features between patients with single and solitary brain metastasis.

Table 2. Differences in clinical features depending on biological subtype.

Table 3. Survival from the detection of brain metastasis.

Table 4. Factors influencing survival from brain metastasis: multivariate analysis, final model.

**Figure legends:**

Figure 1. Survival from brain metastasis in patients with solitary and other single brain metastasis.

December 18, 2010

**Manuscript: Factors influencing survival in patients with breast cancer and single/solitary brain metastasis.**

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**Conflict of interest statement**

There have been no involvements that might raise the question of bias in the work reported

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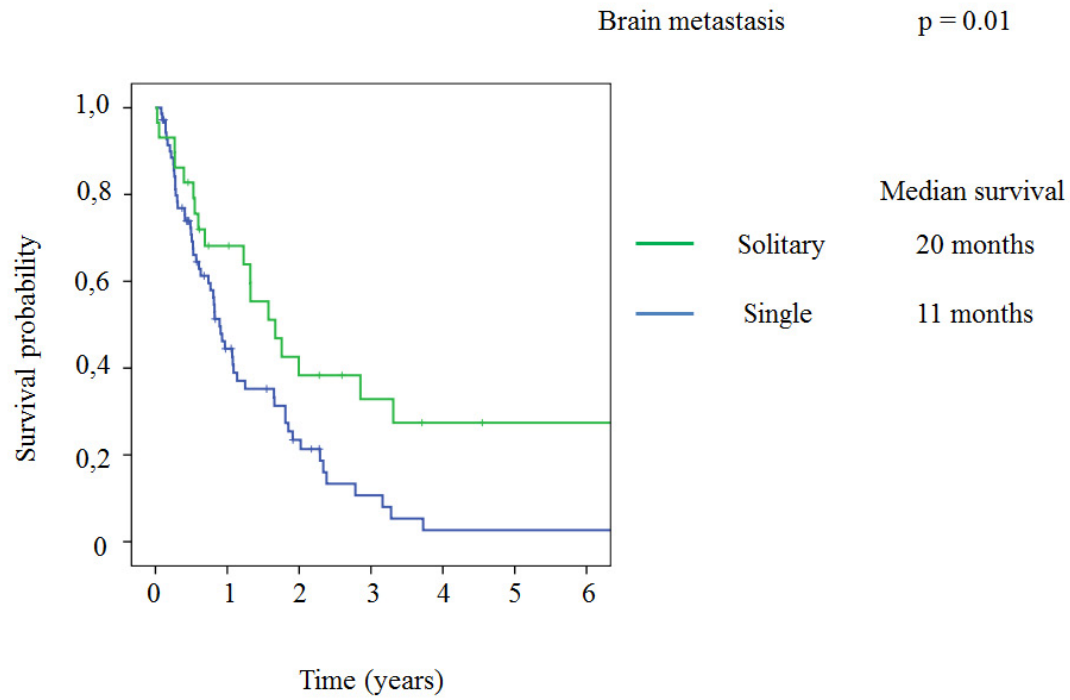




Table1. A comparison of clinicopathological features between patients with single and solitary brain metastasis.

Characteristic	Solitary brain metastasis	Single brain metastasis	p-value
Number of patients	29 (29%)	71 (71%)	
Age at initial diagnosis, years			
Median	51	52	0.380
Range	40–78	26–73	
Initial TNM stage:			
I	1 (3%)	6 (9%)	0.151
II	12 (43%)	31 (44%)	
III	15 (52%)	22 (31%)	
IV	1 (3%)	11 (16%)	
Histological type:			
Ductal carcinoma	19 (66%)	54 (77%)	0.569
Lobular carcinoma	2 (7%)	5 (7%)	
Papilar or neuroendocrine carcinomas	1 (3%)	2 (3%)	
Cancer cells or invasive cancer after chemotherapy	7 (24%)	9 (13%)	
Estrogen/Progesterone-receptor status:			
Positive	12 (43%)	37 (52%)	0.329
Negative	17 (57%)	34 (48%)	
HER2 status:			
Positive	10 (34%)	39 (56%)	0.063
Negative	19 (66%)	32 (44%)	
Biological subtype:			
Triple-negative	11 (42%)	15 (21%)	0.219
HER2	6 (24%)	19 (27%)	
Luminal B	4 (16%)	20 (28%)	
Luminal A	8 (32%)	17 (24%)	
RPA RTOG class:			
I	20 (69%)	0	<0.001
II	4 (14%)	57 (80%)	
III	5 (17%)	14 (20%)	
Karnofsky Performance Status:			
≥70	24 (83%)	57 (80%)	1
<70	5 (17%)	14 (20%)	

Schedule of WBRT:			
40 Gy/20 fractions	16 (55%)	16 (22%)	
30 Gy/10 fractions	11 (39%)	35 (49%)	
20 Gy/5 fractions	1 (3%)	16 (23%)	
No radiotherapy	1 (3%)	4 (6%)	0.002
Neurosurgery of brain metastasis:			
Yes	25 (86%)	32 (45%)	
No	4 (14%)	39 (55%)	<0.001
Systemic therapy after brain metastasis:			
Yes	14 (48%)	53 (75%)	
No	15 (52%)	18 (25%)	0.011
Type of systemic therapy <sup>a</sup>			
Hormonal therapy	10/14 (71%)	14/53 (26%)	0.002
Chemotherapy	5/14 (36%)	41/53 (77%)	0.003
Targeted therapy	2/14 (14%)	23/53 (43%)	0.045
Type of chemotherapy; schedules with <sup>a</sup>			
Taxanes	2/5 (40%)	10/41 (24%)	0.453
Anthracycline	2/5 (40%)	5/41 (12%)	0.102
Capecitabine	2/5 (40%)	4/41 (12%)	0.058
Vinorelbine	1/5 (20%)	5/41 (12%)	0.625
Platinum	1/5 (20%)	7/41 (17%)	0.869
Fluorouracil	1/5 (20%)	5/41 (12%)	0.625
Cyclophosphamide	1/5 (20%)	2/41 (5%)	0.196
Type of endocrine therapy			
Aromatase inhibitors	7/10 (70%)	10/12 (83%)	
Tamoxifen	2/10 (20%)	2/12 (17%)	0.507
Megestrol acetate	1/10 (10%)	0	
Type of targeted therapy			
Trastuzumab	1/2 (50%)	21/22 (95%)	
Lapatinib	1/2 (50%)	1/22 (5%)	0.026

a- In some patients more than one line of systemic therapy was ordered

Abbreviations: HER2, human epidermal growth factor receptor 2; RPA RTOG, recursive partitioning analysis of Radiation Therapy Oncology Group; WBRT, whole-brain radiotherapy.

Table 2. Differences in clinical features depending on biological subtype.

Characteristic	Luminal A (HER2-negative, ER/PgR-positive)	HER2-positive N = 49		Triple-negative (HER2-negative, ER-negative, PgR-negative)	p-value
		Luminal B (HER2-positive, ER/PgR-positive)	HER2/neu (HER2- positive, ER/PgR- negative)		
Number of patients	25	24	25	26	-
Age at initial diagnosis (years):					
Median	51	51.5	54	50	0.850
Range	(36–73)	(33–67)	(26–73)	(28–78)	
Initial TNM stage:					
I	2 (8.3%)	2 (8.3%)	0	3 (11.5%)	0.909
II	12 (50%)	10 (41.7%)	11 (44%)	10 (38.5%)	
III	8 (33.3%)	8 (33.3%)	11 (44%)	10 (38.5%)	
IV	2 (8.3%)	4 (16.7%)	3 (12%)	3 (11.5%)	
Histological type:					
Ductal carcinoma grade 3	5 (20.8%)	6 (26.1%)	12 (48%)	16 (64%)	0.015
Lobular carcinoma	7 (29.2%)	1 (4.3%)	0	0	
Other types	12 (50%)	16 (69.6%)	13 (52%)	9 (36%)	
Localization of other metastases:					
Brain as only site	9 (36%)	4 (16%)	7 (28%)	11 (42%)	0.235
Liver	6 (24%)	5 (20.8%)	9 (36%)	4 (15.4%)	0.367
Lung	5 (20%)	14 (58.3%)	9 (36%)	7 (26.9%)	0.030
Bone	11 (44%)	9 (37.5%)	10 (40%)	2 (7.7%)	0.021
Local recurrence	4 (16%)	13 (54.2%)	5 (20%)	7 (26.9%)	0.015
Systemic treatment after recurrence:					
Yes	17 (68%)	19 (79.2%)	18 (72%)	13 (50%)	0.151
No	8 (32%)	5 (20.8%)	7 (28%)	13 (50%)	
Karnofsky performance status					
≥70	20 (80%)	19 (80%)	20 (80%)	22 (85%)	0.975
<70	5 (20%)	5 (20.8%)	5 (20%)	4 (15%)	
Leptomeningeal carcinomatosis					
Yes	1 (4%)	1 (4.2%)	0	2 (7.7%)	0.579
No	25 (96%)	23 (95.8%)	25 (100%)	24 (92.3%)	

Localization of brain metastasis					
Supratentorial	19 (76%)	18 (75%)	17 (68%)	21 (80.8%)	0.01
Infratentorial	6 (24%)	6 (25%)	8 (32%)	5 (19.2%)	
Operation of brain metastasis					
Yes	13 (52%)	14 (58.3%)	14 (56%)	16 (61.5%)	0.919
No	12 (48%)	10 (41.7%)	11 (44%)	10 (38.5%)	
Radiotherapy - WBRT					
Rth<4000cGy	16 (64%)	18 (75%)	19 (76%)	15 (57.7%)	0.435
Rth=4000cGy	9 (36%)	6 (25%)	6 (24%)	11 (42.3%)	

Abbreviations: HER2, human epidermal growth factor receptor 2; ER, estrogen receptor; PgR, progesterone receptor; Rth, radiotherapy; WBRT, whole-brain radiotherapy.

Table 3. Survival from the detection of brain metastasis.

	Number of patients	Median (range), months	p-value
<b>Disease Free Survival:</b>			
All patients	100	24 (0–319)	0.61
Triple-negative	26	22 (0–319)	
HER2	25	14 (0–183)	
Luminal B	24	26 (0–135)	
Luminal A	25	32 (0–184)	
<b>Overall Survival:</b>			
All patients	100	58 (4–353)	0.63
Triple-negative	26	36 (6–330)	
HER2	25	50 (17–353)	
Luminal B	24	61 (4–174)	
Luminal A	25	60 (15–246)	
<b>Survival From Brain Metastasis:</b>			
All patients	100	13 (0.3–116)	0.60
Triple-negative	26	11 (0.6–109)	
HER2	25	13 (3–55)	
Luminal B	24	16 (1–38)	
Luminal A	25	15 (0.3–116)	
RPA RTOG prognostic class:			
I	21	22 (3–116)	<0.001
II	60	13 (2–78)	
III	19	6 (0.3–27)	
Solitary brain metastasis	29	20 (0.3–116)	0.01
Other single brain metastasis	71	11 (1–78)	

Abbreviations: HER2, human epidermal growth factor receptor 2; RPA RTOG, recursive partitioning analysis of Radiation Therapy Oncology Group

Table 4. Factors influencing survival from brain metastasis: multivariate analysis, final model.

Factor	Hazard Ratio	95% Confidence Interval	p-value
RPA RTOG prognostic class III vs I	6.32	2.58–15.50	<0.0001
RPA RTOG prognostic class III vs II	2.85	1.33–6.15	0.007
Surgical excision (yes vs no)	0.56	0.32–0.97	0.039
Systemic treatment after WBRT (yes vs no)	0.28	0.16–0.49	<0.0001
Leptomeningeal carcinomatosis (yes vs no)	5.17	1.17–22.81	0.030

Abbreviations: RPA RTOG, recursive partitioning analysis of Radiation Therapy Oncology Group; WBRT, whole-brain radiotherapy.