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Novel prognostic classification predicts overall survival of patients receiving salvage whole-brain radiotherapy for recurrent brain metastasis from breast cancer: A recursive partitioning analysis (KROG 16-12)

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ABSTRACT

Background: To investigate outcomes of salvage whole-brain radiotherapy (WBRT) for recurrent brain metastases (BM) from breast cancer (BC), to identify prognostic factors of overall survival (OS), and to propose a novel prognostic classification for OS in these patients.
Materials and methods: We identified 54 patients who had received salvage WBRT as the second brain-focused treatment for recurrent BM from BC (2000–2014). The median follow-up duration was 4.9 months. A recursive partitioning analysis (RPA) was conducted to develop a model to predict OS at the time of salvage WBRT.
Results: The median OS was 6.8 months. OS according to BC-specific graded prognostic assessment (breast-GPA), modified breast-GPA, and updated breast-GPA did not represent our cohort. In the multivariate analysis, a long time before salvage WBRT (≥16 months), control of primary BC or extracranial metastases, systemic treatment after salvage WBRT, and administration of a biologically effective dose for an α/β of 10 Gy (BED10) of salvage WBRT >37.5 Gy showed superior OS. We proposed three RPA classes based on the control of both primary BC and extracranial metastasis and BED10 of salvage WBRT: class I, class II, and class III. In this model, patients with class I experienced the best OS (34.6 months; class II, 5.0 months; class III, 2.4 months; $P < 0.001$).
Conclusions: In our RPA classification according to the control of both primary BC and extracranial metastasis and the dose of salvage WBRT, significant differences in OS were observed. The subsequent use of a systemic treatment showed better OS.

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1. Introduction

Breast cancer (BC) is the second-most common cause of brain metastases (BM); symptomatic BM develop in approximately 10–15% of patients with BC [1]. Unfortunately, the incidence of BM is expected to increase for several reasons. Although trastuzumab and pertuzumab are historically effective in treating extracranial disease and significantly improving patient survival [2,3], prolonged survival and insufficiently controlled intracranial spread have paradoxically increased the risk of BM [4]. Additionally, advances in neuroimaging techniques have also helped radiologists detect asymptomatic BM [5].

Whole-brain radiotherapy (WBRT) or surgical resection has been the treatment of choice for BM, historically, regardless of the type of primary tumor [6]. We previously reported the delivery of WBRT alone as a brain-focused treatment for initial BM to over 50% of patients with BM as a result of BC [7]. Another 20% of patients were treated with single-fraction stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) alone [7]. Unlike in our previous work, recent treatment guidelines now recommend SRS over WBRT because of the increased risk of neurocognitive dysfunction after WBRT, reserving WBRT as a salvage therapy [4].

In a randomized controlled trial, patients receiving SRS alone had poor local disease control compared with patients treated with SRS plus WBRT ($P = 0.002$) [8]. When SRS is widely recommended, many patients tend to experience recurrent BM and poor quality of life. The benefits of salvage WBRT after local brain radiotherapy including SRS is currently unknown. Considering the growing burden of recurrent BM, the potential benefits of salvage WBRT should be investigated in such patients. In addition, there is an unmet clinical need for a prognostic model for patients who are scheduled for salvage WBRT because most models such as breast cancer-specific graded prognostic assessment (breast-GPA) focus on patients with newly diagnosed BM [9–11].

In this study, we analyzed the survival outcomes for patients with BM caused by BC who were treated with salvage WBRT after an initial brain-focused treatment such as surgery and/or local brain radiotherapy. We also identified clinical factors affecting overall survival (OS). Furthermore, a novel prognostic model for these patients was developed to overcome the limitations of previous models.

2. Materials and Methods

2.1. Patients and tumor molecular subtypes

Seven hundred thirty patients with BM caused by BC treated at 17 institutions from 2000 to 2014 were included in the Korean Radiation Oncology Group (KROG) 16-12 study [7]. Among them, 54 patients received salvage WBRT for recurrent BM after brain-focused treatment for initial BM. The median follow-up duration from the date of last salvage WBRT was 4.9 months (range, 0.3–50.4). The institutional review boards of each institution approved this study. Because of the retrospective design of the analysis, obtaining informed consent from participants included in the study was not required.

Immunohistochemical staining of primary BC samples was used to determine the tumor molecular subtypes. Tumors that were hormone receptor-positive were classified as luminal A/B unless human epidermal growth factor receptor 2 (HER2) was positive; otherwise, these tumors were considered luminal HER2. Tumors positive for HER2 but not for hormone receptor were classified as the HER2 subtype. All negative immunohistochemical staining results were classified as triple negative.

2.2. Variables and response evaluation

Patient characteristics including age, performance status, neurologic symptoms, control of primary BC and extracranial metastasis, number and location of BM, and presence of leptomeningeal seeding were evaluated at the time of salvage WBRT. Interval to salvage WBRT was defined as the time interval between first brain-focused treatment and salvage WBRT.

Computed tomography or magnetic resonance imaging was performed after brain-focused treatment at time intervals determined by each institution. The response of the intracranial lesions to treatment was evaluated using the Response Evaluation Criteria in Solid Tumors 1.1 guidelines with follow-up imaging [12].

2.3. Statistical analysis

To compare baseline characteristics and treatment responses according to the use of WBRT as an initial brain-focused treatment, we used the chi-square test or Fisher's exact test for categorical data, and the independent Student's *t*-test for age at salvage WBRT. The cutoff value of the biologically effective dose for an α/β ratio of 10 Gy (BED10) of salvage WBRT was determined using the median value of BED10 of salvage WBRT. OS was measured from the last day of salvage WBRT to death from any cause. Survival curves were generated using the Kaplan-Meier method, and the log-rank test was performed to compare results between groups. Univariate and multivariate Cox proportional hazard models were used to report hazard ratios (HRs) and 95% confidence intervals (CIs). All variables with *P* levels less than 0.100 in the univariate analysis were adjusted in the multivariate analysis.

The “rpart” package of R was used to perform the recursive partitioning analysis (RPA) with significant prognostic factors for OS identified from the multivariate analysis. We excluded the variable of systemic treatment after salvage WBRT to generate a prognostic model at the time of salvage WBRT. A recursive decision tree was generated based on the terminal nodes where bifurcation of the tree required at least 15 patients and a *P* value less than 0.01 using the log-rank test. If there were no significant differences in OS between the terminal nodes, the nodes were combined, and 10-fold cross-validation was performed internally. We calculated the concordance index to compare the predictive power of breast-GPA, modified breast-GPA, updated breast-GPA, and our novel RPA classification.

The statistical significance of a reported two-sided *P* value was set at 5%. All analyses were performed in R, version 4.0.4 (https://www.rproject.org/).

3. Results

3.1. Characteristics of patients with BM

Baseline characteristics of patients with BM, categorized into two groups according to the initial use of WBRT, are summarized in

Table 1. There was no difference in age ($P = 0.902$) and tumor subtype distribution ($P = 0.605$) between the two groups. Performance status was worse in patients who received WBRT initially ($P = 0.004$). However, no differences were observed between the two groups in terms of intra- and extracranial tumor burden. Patients receiving WBRT initially tended to have a longer time from an initial brain-focused treatment until salvage WBRT (median salvage WBRT-free duration, 6.9 vs. 8.7 months, $P = 0.058$, Figure A1).

3.2. Treatment

Twenty-four patients (initial WBRT group) were treated with whole-brain reirradiation (Table 1). The median dose of WBRT for initial BM was 30 Gy over 10 fractions (range, 12–35 Gy). The median dose of salvage WBRT was 20 Gy over 10 fractions for patients previously treated with WBRT (n = 24; range, 4–30 Gy) and 30 Gy over 10 fractions for patients who had not been previously treated with WBRT (n = 30; range, 9–37.5 Gy). In terms of BED10, it ranged from 4.8 Gy to 46.9 Gy. A higher BED10 (>37.5 Gy) was delivered to 23 WBRT-naïve patients (76.7%) and four WBRT-treated patients (16.7%, $P < 0.001$). We compared baseline characteristics according to the BED10 (Table A1). Patients with a higher BED10 had a low intracranial tumor burden and better performance status. After salvage WBRT, diverse systemic therapies were used in 40 patients (74.1%): endocrine therapy in three patients, HER2-targeted therapy in 11 patients, and chemotherapy in 36 patients.

We categorized the reasons for administering salvage WBRT for local intracranial progression with or without new BM (i.e., distant intracranial failure). In WBRT-naïve patients, the major failure pattern was distant intracranial failure [12 (40.0%) patients without local progression and 14 (46.7%) with local progression]. Only four (13.3%) patients were treated with salvage WBRT due to local progression only. However, 17 (70.8%) patients who were previously administered WBRT experienced local progression. Among them, nine (37.5%) patients were accompanied with new BM. Distant intracranial failure without progression of the initial lesion was found in the other seven (29.2%) patients.

Table 1
Baseline characteristics at salvage whole-brain radiotherapy.

Characteristics	Patients without initial WBRT, N = 30		Patients with initial WBRT, N = 24		*p*-value
	N	% or IQR	N	% or IQR	
Age (year, median)	49.6	40.7–54.5	50.1	41.2–54.8	0.902
Tumor subtypes					0.605
Luminal A/B	8	26.7	3	12.5	
Luminal HER2	7	23.3	8	33.3	
HER2	9	30.0	8	33.3	
Triple negative	6	20.0	5	20.8	
ECOG performance status[a]					0.004
0-1	20	80.0	8	34.8	
2-3	5	20.0	15	65.2	
Symptom					0.270
No	7	23.3	2	8.3	
Yes	23	76.7	22	91.7	
Primary breast cancer control					0.793
No	2	6.7	3	12.5	
Yes	28	93.3	21	87.5	
Extracranial metastasis					0.337
No	7	23.3	2	8.3	
Yes - uncontrolled	15	50.0	14	58.3	
Yes - controlled	8	26.7	8	33.3	
Number of BM					0.117
≤4	12	40.0	4	16.7	
>4	18	60.0	20	83.3	
Location of BM					0.652
Supra-/infra-tentorial	9	30.0	5	20.8	
Both tentorial	21	70.0	19	79.2	
Leptomeningeal seeding					0.687
No	25	83.3	18	75.0	
Yes	5	16.7	6	25.0	
Initial brain-focused treatment					<0.001
WBRT alone	0	0	22	91.7	
SRS or FSRT alone	23	76.7	0	0	
Op alone	4	13.3	0	0	
Op/SRS/FSRT → WBRT	0	0	2	8.3	
Others	3	10.0	0	0	

Abbreviation: BM, brain metastasis; ECOG, Eastern Cooperative Oncology Group; FSRT, fractionated stereotactic radiotherapy; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; Op, operation; SRS, single-fraction stereotactic radiosurgery; WBRT, whole-brain radiotherapy.
[a] Available data only.

4. Treatment response and survival outcome

The best responses after an initial brain-focused treatment and after salvage WBRT are described in Table 2. Regardless of whether or not a patient received WBRT initially, about 50% of patients experienced a complete or partial response. Among 45 patients who suffered from symptoms before salvage WBRT, 29 (64.4%) patients experienced symptom improvement, and only 7 (15.6%) patients experienced worsening of symptoms after salvage WBRT (Table 2).

Fig. 1a shows the survival curve of the entire cohort after salvage WBRT and an estimated median OS of 6.8 months (95% CI 5.0–24.0). We assessed breast-GPA, modified breast-GPA, and updated breast-GPA scores for each patient using previously defined criteria (Table A2) [9–11]. Patients were then classified into four groups based on their GPA scores: 0–1.0, 1.5–2.0, 2.5–3.0, and 3.5–4.0, respectively. No GPA scoring system correlated with OS (Fig. 1b–d). The c-indices of breast-GPA, modified breast-GPA, and updated breast-GPA were 0.555, 0.475, and 0.566, respectively. The OS of patients receiving a second round of WBRT was similar to that of patients receiving a single round of WBRT (median OS, 6.8 vs. 7.0 months, $P = 0.350$, Figure A2).

4.1. Prognostic factors affecting OS after salvage WBRT and novel RPA classification

We selected variables with P values less than 0.100 for the multivariate analysis (Table 3), which revealed that the time to salvage WBRT (≥16 months), control of the primary BC, uncontrolled extracranial metastasis, BED10 of salvage WBRT greater than 37.5 Gy, and subsequent administration of a systemic treatment were prognostic factors that significantly influenced OS (all $P < 0.005$).

Based on these results, the time to salvage WBRT (<16 months vs. ≥16 months), status of the primary BC (controlled vs. uncontrolled), status of extracranial metastasis (controlled vs. uncontrolled), and BED10 of salvage WBRT (≤37.5 Gy vs. >37.5 Gy) were chosen for RPA to predict OS at the initiation of salvage WBRT. The primary factor resulting in a bifurcation of the recursive decision tree was the control of primary BC, which resulted in five terminal nodes (Fig. 2a). After amalgamation, three RPA classes were finally identified; 17 patients were categorized into class I, 32 patients were categorized into class II, and 5 patients were categorized into class III (Fig. 2b). The median OS of classes I, II, and III was 34.6, 5.0, and 2.4 months, respectively ($P < 0.001$, Fig. 3a). The OS for each class significantly differed ($P < 0.001$ for class I vs. class II, class I vs.

Table 2
Treatment response.

Characteristics	Patients without initial WBRT, N = 30		Patients with initial WBRT, N = 24		p-value
	N	%	N	%	
Best response after initial brain-focused treatment					0.770
Complete response	3	10.0	1	4.2	
Partial response	13	43.3	11	45.8	
Stable disease	3	10.0	4	16.7	
Progressive disease	11	36.7	8	33.3	
Symptom relief after salvage WBRT[a]					0.542
No change	2	9.1	5	23.8	
Improvement	16	72.7	13	61.9	
Aggravation	4	18.2	3	14.3	
Best response after salvage WBRT[b]					0.138
Complete response	0	0	0	0	
Partial response	13	46.4	9	50.0	
Stable disease	11	39.3	4	22.2	
Progressive disease	4	14.3	5	27.8	

Abbreviation: WBRT, whole-brain radiotherapy.
[a] Patients who had symptoms before salvage whole-brain radiotherapy (WBRT) were included: 22 patients in the initial WBRT(−) group and 21 patients in the initial WBRT(+) group with available information.
[b] Available data only.

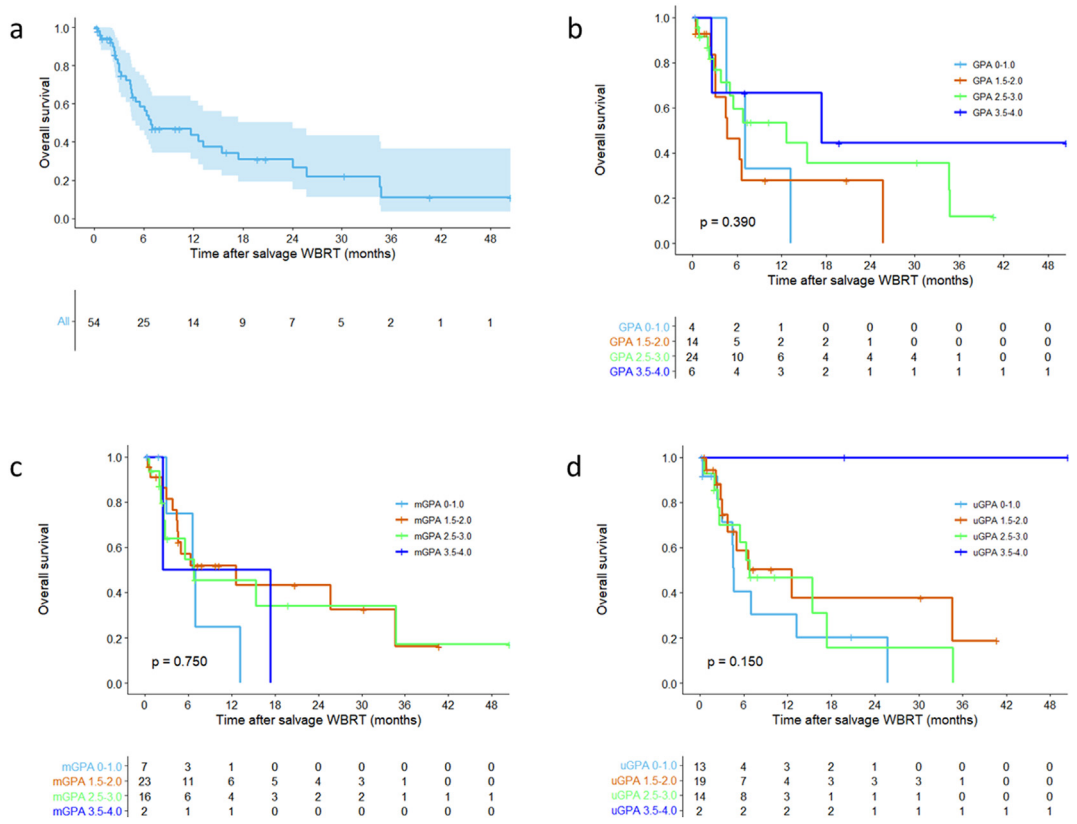

Fig. 1. Overall survival after salvage whole-brain radiotherapy (WBRT) (a) in all patients and according to (b) breast cancer-specific graded prognostic assessment (breast-GPA), (c) modified breast-GPA, and (d) updated breast-GPA.
Abbreviation: CI, confidence interval; mGPA, modified graded prognostic assessment; GPA, graded prognostic assessment; uGPA, updated graded prognostic assessment; WBRT, whole-brain radiotherapy.

class III, and class II vs. class III). The c-index of our RPA classification was 0.735.

The effects of a subsequent systemic treatment after salvage WBRT on OS were analyzed according to the above classification scheme. The median OS of class I patients treated with (n = 15) or without (n = 2) a systemic agent was 6.1 and 34.6 months, respectively ($P = 0.016$, Figure A3a). For patients in RPA class II, the median OS was longer when a systemic treatment was used (6.8 vs.

Table 3
Univariate and multivariate Cox proportional hazards model for overall survival.

Variables	1-year OS (vs. reference)	Univariate		Multivariate	
		p-value	HR (95% CI)	p-value	HR (95% CI)
Interval to salvage WBRT ≥16 months	80.0% (vs. 39.7%)	0.092	0.180 (0.024–1.321)	0.025	0.087 (0.010–0.736)
Luminal subtype[a]	51.9% (vs. 37.8%)	0.575	0.820 (0.409–1.641)		
Triple negative subtype[a]	30.0% (vs. 48.0%)	0.283	1.536 (0.702–3.360)		
ECOG performance status 2-3	42.9% (vs. 48.7%)	0.220	1.646 (0.743–3.645)		
Symptom present	40.9% (vs. 59.3%)	0.826	1.114 (0.427–2.908)		
Controlled primary breast cancer	47.7% (vs. 0%)	<0.001	0.051 (0.012–0.210)	<0.001	0.041 (0.007–0.235)
Uncontrolled extracranial metastasis	25.4% (vs. 63.9%)	0.003	3.282 (1.479–7.283)	0.008	3.070 (1.343–7.018)
Number of BM > 4	46.7% (vs. 36.1%)	0.331	0.702 (0.344–1.433)		
BM in both tentorial regions	46.7% (vs. 39.7%)	0.898	0.952 (0.451–2.012)		
Leptomeningeal seeding	51.9% (vs. 41.4%)	0.717	0.857 (0.371–1.979)		
Initial WBRT	49.0% (vs. 42.2%)	0.350	1.416 (0.683–2.933)		
BED10 of salvage WBRT >37.5 Gy	53.8% (vs. 33.9%)	0.017	0.422 (0.207–0.857)	0.017	0.393 (0.183–0.844)
Systemic treatment after salvage WBRT	54.4% (vs. 0%)	<0.001	0.146 (0.058–0.366)	<0.001	0.093 (0.031–0.282)
Aggravation of symptoms	25.0% (vs. 47.8%)	0.331	1.695 (0.584–4.920)		
Progression after salvage WBRT	37.5% (vs. 48.5%)	0.604	1.298 (0.485–3.475)		

Abbreviation: BED10, biologically effective dose ($\alpha/\beta = 10$ Gy); BM, brain metastasis; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; WBRT, whole-brain radiotherapy.
[a] Compared with other subtypes.

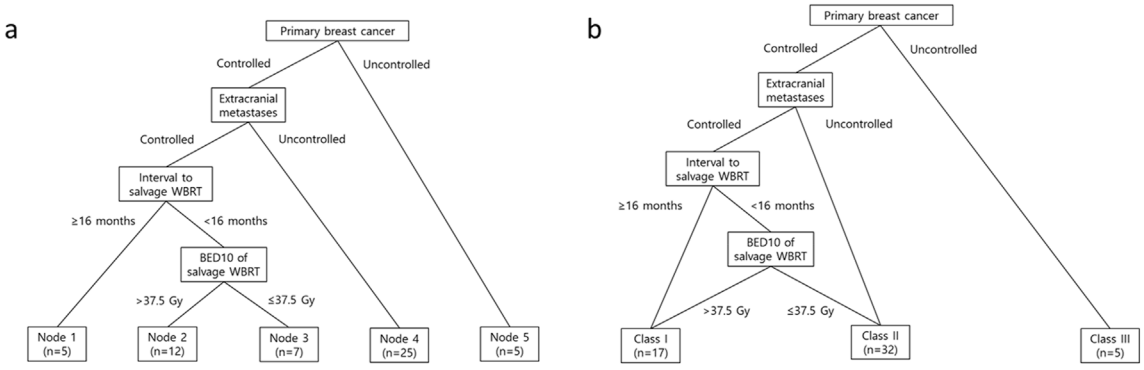

Fig. 2. Diagrams of recursive partitioning analysis (RPA). (a) Five terminal nodes before amalgamation. (b) Final three RPA classes after amalgamation.
Abbreviation: BED10, biologically effective dose ($\alpha/\beta = 10$ Gy); WBRT, whole-brain radiotherapy.

3.0 months, $P = 0.001$, Figure A3b). However, when the Cox proportional hazard model was used, only patients in class II who received a systemic treatment following salvage WBRT had prolonged OS (HR 0.184, 95% CI 0.061–0.555, $P = 0.003$, Fig. 3B).

Abbreviation: CI, confidence interval; HR, hazard ratio; WBRT, whole-brain radiotherapy.

5. Discussion

Salvage WBRT would be expected to generally increase under circumstances where patients with BM live longer and more patients experience intracranial failure after an initial treatment for BM. However, few reports of patients in these circumstances are available. In this study, we retrospectively analyzed 54 patients who underwent salvage WBRT for recurrent BM after a failed initial brain-focused treatment.

Thirty patients who had been treated without WBRT underwent salvage WBRT. Our previous report demonstrated that patients without initial WBRT had a low intracranial tumor burden. In these patients, only 14.5% had more than 4 BM, and BM located in both tentorial regions in 20.9% [13]. However, at the time of salvage WBRT, patients with BM more than 4 accounted for 60% of WBRT-naive patients. Also, in 70% of patients, BM was present in both supra- and infra-tentorial regions. Although the exact reason for selecting WBRT rather than repeating SRS or FSRT was not clear considering the multicenter retrospective design of this study, salvage WBRT seemed to be preferred in cases of increasing intracranial tumor burden after initial brain-focused local treatment. However, except for cases of symptomatic BM or progressive extracranial disease without an option for additional systemic therapy, repeating SRS or FSRT might be a currently feasible option [14–16].

In our cohort, at the time that salvage WBRT was administered, only performance status differed in patients who had been categorized into two groups according to the initial use of WBRT. More patients were assessed as Eastern Cooperative Oncology Group performance status 2–3 in the initial WBRT group. There were no differences in the indicators representing tumor burden. After the initial brain-focused treatment, performance status might worsen, but considering that patients with poor performance from the beginning tend to be treated with WBRT, the difference in performance between the two groups appears reasonable. Apart from this finding, no other differences were noted, suggesting that salvage WBRT was performed in the same situation regardless of the initial treatment.

However, initial WBRT extended the duration before salvage WBRT was needed. The interval between the first and second rounds of WBRT has been reported to be one of the prognostic factors for OS after whole-brain reirradiation [17,18]. Lai et al. reported that patients receiving a second round of WBRT more than 9

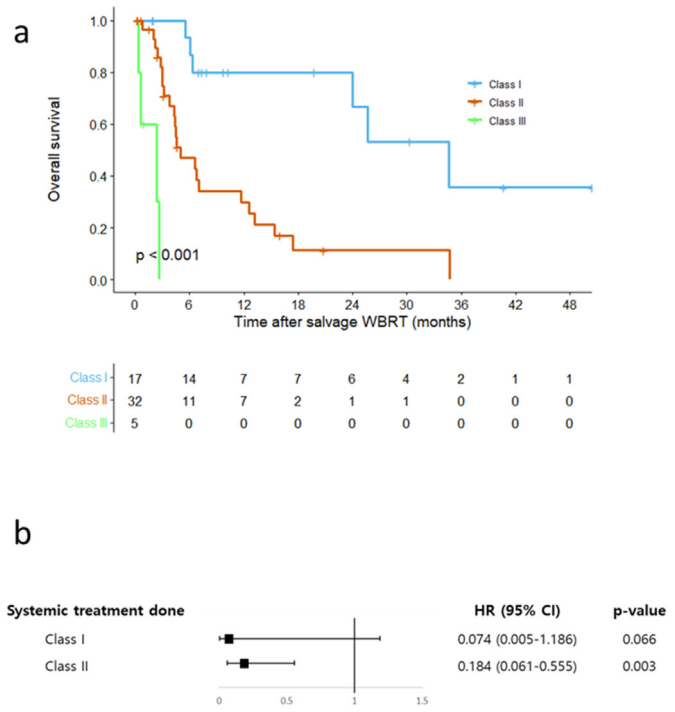

Fig. 3. (a) Overall survival (OS) according to the novel recursive partitioning analysis (RPA) class. (b) The effect of systemic treatment after salvage whole-brain radiotherapy according to the RPA class.

months after the first round of WBRT showed better OS (HR 0.45, $P = 0.041$) [18]. Our results are consistent with those findings. In our study, the cut-off time was 16 months after the initial brain-focused treatment. There have been concerns about neurocognitive dysfunction due to initial WBRT, but improvements in OS may be achieved by delaying salvage WBRT. Therefore, clinicians should carefully select patients who may benefit from WBRT.

The median OS in our study was 6.8 months, representing a dismal prognosis. The median survival time after whole-brain reirradiation in previous studies ranged from 2.93 months to 10.8 months [18–20]. The reason for such a large difference in survival may reflect differences in the study population examined. In our analysis, the survival of patients who received salvage WBRT after a previous non-WBRT treatment did not differ from those who received initial WBRT.

Salvage WBRT was able to alleviate symptoms satisfactorily in more than 50% of patients. After salvage WBRT, 22 (40.7%) patients and 15 (27.8%) patients had a partial response and stable disease as the best response, respectively. Although we did not collect toxicity profiles, a previous study found a comparatively low rate of acute toxicities [18]. Combining these results, WBRT may be a feasible and effective salvage treatment option for patients with recurrent BM, conferring a better quality of life to patients.

Stable extracranial lesions have been reported to be significant factors in improved survival in patients with recurrent BM [20,21]. Multivariate analyses demonstrated that a longer OS correlated with the control of extracranial metastases as well as of primary BC. Contrary to our expectations, intracranial tumor burden, represented by the number and location of BM and leptomeningeal seeding, did not affect OS. Although a direct relationship between treatment dose and OS was found, neither the worsening of initial symptoms nor intracranial progression after salvage WBRT was associated with poor OS. These findings, while preliminary, suggest that in patients receiving salvage WBRT, control of extracranial disease was more important than intracranial tumor burden. The fact that the use of systemic therapy following salvage WBRT improves survival despite the limited ability of the therapy to penetrate the blood-brain barrier further supports this hypothesis.

We found that BED10 of salvage WBRT was one of the significant factors associated with a prognosis. Although patients with BED10 > 37.5 Gy were clustered in the initial WBRT(−) group, BED10 of salvage WBRT was more prominently prognostic than initial WBRT. BED10 of salvage WBRT was correlated with the intracranial tumor burden in terms of BM number and location, but it was also determined based on the use of initial WBRT, time interval to salvage WBRT, patients' performance status, and so on. Therefore, each factor might have a smaller impact on OS, as shown in the univariate analysis, but the dose of salvage WBRT (i.e., BED10) which synthetically reflected them, had a significant correlation with OS.

Several predictive models of OS in patients with BM have been developed, and GPA systems have been widely used [7,9–11]. We previously suggested a model using the KROG 16-12 study population [7]. Since these models were developed using newly diagnosed patients with BM, it is not yet clear whether they could be applied to patients with recurrent BM. Lai et al. identified an association between breast-GPA and survival outcomes in patients retreated with WBRT [18]. They found that patients with breast-GPA scores of 0–2.0 and 2.5–4.0 had a median survival of 1.57 and 4.37 months after WBRT reirradiation, respectively ($P < 0.005$) [18]. However, in our analysis, breast-GPA, modified breast-GPA, and updated breast-GPA scores did not predict patient prognosis and had low c-indices. These results emphasize the need for a new prognostic model for these patients.

The current GPA scoring system has several limitations. First, it was developed using the patient population who were newly diagnosed with BM. Considering the fact that the mismatch of BC subtypes between primary and metastatic sites has been reported [22–24], there might be several changes in tumor characteristics of recurrent BM after brain-focused treatment for initial BM. Besides, other factors which could be introduced after initial brain-focused treatment, such as time interval to salvage WBRT, should be evaluated for predicting OS. Therefore, prognostic factors for patients with recurrent BM might be different from those with an initial diagnosis of BM. Second, these models, except for the updated breast-GPA, did not consider extracranial disease, which is known to be an important prognostic factor [20,21]. Third, no GPA scoring systems included factors related to the previous and/or planned treatment. Surrogate factors for the response to initial treatment and the impact of scheduled treatment on prognosis should be considered. To address these shortcomings, we proposed a new RPA classification to predict the prognosis of patients when salvage WBRT is administered. To the best of our knowledge, this is the first study to suggest prognostic modeling by RPA in patients with recurrent BM. Our three classifications were based on the status of primary BC, the status of extracranial metastasis, the time to salvage WBRT, and the BED10 of salvage WBRT. Compared to previous classification systems, ours was a better predictor of OS. Moreover, while the small number of patients studied requires careful interpretation of the findings, in patients categorized as RPA class II, an additional systemic treatment was shown to improve survival. This novel RPA classification could play an informative role in daily practice for determining the dose of WBRT and whether to proceed with a systemic treatment after salvage WBRT.

There were limitations in our study. First, the nature of the study's retrospective design should be considered, as a selection bias may exist. Another limitation is that our cohort was too small to draw definite conclusions. Nevertheless, this was the first study to suggest the need for a model to predict the prognosis in patients

receiving salvage WBRT. The patients included in this study span a total of 15 years from 2000 to 2014 and there have been changes in the treatment paradigm during that period, which might also have affected the model. In addition, only internal validation was performed. Most of high-volume institutions in Korea were included in this KROG 16-12 study. External validation using a larger patient population outside of Korea is needed. Finally, our analysis did not include an investigation of the side effects of salvage WBRT. Although a few side effects have been reported in other studies, information on toxicity is important to evaluate a patient's quality of life after salvage WBRT.

In conclusion, we successfully developed an RPA classification of patients who were administered salvage WBRT by incorporating four simple clinical factors: status of both primary BC and extracranial metastasis and salvage WBRT interval and dose. This classification allowed patients to be stratified into three different groups that powerfully predicted their survival. Such a system could help clinicians evaluate a patient's prognosis and select patients who might benefit from a higher dose of salvage WBRT and subsequent systemic treatment. Further external validation is needed.

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Data sharing statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of competing interest

None.

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none.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.11.005.

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