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ORIGINAL ARTICLE

Prognostic factors of brain metastases affecting survival: an Indonesian cohort

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ABSTRACT

BACKGROUND

Brain metastases (BMs) most frequently originate from primary tumors of the lung and breast, and significantly impact cancer patient prognosis. Metastases can be detected synchronously along with the primary tumor or metachronously, following treatment of localized disease. The objective of this study was to identify key prognostic factors influencing survival in synchronous metastases (SM) and metachronous metastases (MM), focusing on metastatic duration, tumor volume response, and gamma knife radiosurgery.

METHODS

A retrospective cohort study was conducted involving 100 patients with brain metastases (48 synchronous, 52 metachronous). Age, gender, primary tumor, gamma knife status, metastasis location, peritumoral index group, volume reduction, metastatic duration, metastasis characteristics, and intensity pattern based on MRI. A Cox proportional hazards regression was used to analyze the data. Based on the Cox regression coefficients, a prognostic index was constructed.

RESULTS

Calculated HR comprised MM (HR=0.49;95% CI :0.24–0.97], gamma knife treatment (HR = 0.15;95% CI: 0.07–0.29], and volume response (HR=0.40;95% CI: 0.16–0.99), all indicating a significantly reduced mortality risk. A prognostic index was calculated for all patients; those with scores ≤–1.513 were classified as low risk. Kaplan-Meier analysis showed that the low-risk group had a significantly longer mean survival period (75.52 months) compared to the high-risk group (31.43 months) ($p<0.001$).

CONCLUSION

Metachronous presentation, gamma knife therapy, and greater tumor volume reduction independently predict better survival. The developed prognostic index provides a clinically useful tool for personalized risk assessment and treatment planning in patients with brain metastases.

Keywords: Brain metastases, MRI, synchronous, metachronous, gamma knife, survival, prognostic factors

INTRODUCTION

Brain metastases (BM) occur in 15-20% of adults and 5-10% of children, with an annual incidence of 70,000 to 400,000 new cases in the United States.[1,2] In Indonesia, studies by Aninditha et al.[3] and Dewi et al.[4] found brain metastases in 13% and 45.1% of brain tumor patients, respectively.

Brain metastases are categorized as synchronous (SM), which are BM diagnosed within 2 months of primary cancer diagnosis, or metachronous (MM), which are BM diagnosed more than 2 months after primary cancer diagnosis. Late detection of either one commonly leads to late detection leading to increased mortality and morbidity.[5] Magnetic resonance imaging (MRI) remains the gold standard for BM detection, with advanced MRI techniques providing detailed characterization of tumor morphology and peritumoral features critical for prognosis.[6] However, prognostic factors influencing survival outcomes in BM patients show inconsistent findings across studies, reflecting heterogeneity in tumor biology, patient characteristics, and treatment modalities.[1–4,7]

Conflicting results have emerged regarding the determinants of survival in BM from different primary cancers. Li et al.[8] analyzed 400 patients with synchronous or metachronous BM from non-small cell lung cancer (NSCLC) and found that metachronous BM correlated with improved overall survival (OS), particularly in squamous cell carcinoma patients lacking epidermal growth factor receptor (EGFR) mutations. In contrast, an observational study examining the influence of patient, tumor, and treatment characteristics on overall survival after synchronous or metachronous CNS metastases, found no difference in survival between the two types of metastases.[9]

Similarly, Leone et al.[10] reported that human epidermal growth factor receptor 2 (HER2)-positive and triple-negative breast cancer subtypes carry a higher risk of BM development; however, receptor status was not an independent predictor of survival in patients undergoing surgery, radiation, and systemic therapy. Age and stage at diagnosis emerged as more consistent prognostic factors, with unclear impact from radiation type or initial recurrence site.

In the context of patients presenting with a single brain metastasis, Baumgart et al.[7] observed longer survival among those with solitary BM than among those with singular BM (one BM plus extracranial metastases). Notably, no significant survival differences were found between complete and incomplete tumor resection, a finding that contrasts with other reports favoring maximal cytoreduction. Postoperative radiotherapy, particularly stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (HSRT), was associated with significantly improved OS. Furthermore, Chu et al.[11] found that patients with anaplastic lymphoma kinase (ALK) rearranged NSCLC exhibiting metachronous BM had more favorable radiographic features (fewer and smaller lesions with less peritumoral edema) compared to synchronous BM patients, who tended to have more aggressive disease manifestations and neurological symptoms. These imaging distinctions inform treatment decisions, favoring SRS over prophylactic cranial irradiation (PCI) in metachronous BM cases, even though access to targeted therapies and timing of radiotherapy contribute to variable survival outcomes.

Kerschbaumer et al.[12] examined 143 patients with brain metastases who underwent surgery. The amount of swelling around the brain tumors did not affect patient survival. Another study by Du et al.[13] reviewed 696 patients treated with stereotactic radiosurgery (SRS) and found that factors such as patient performance, control of cancer outside the brain, tumor size, and edema index were linked to treatment response. Phung et al.[14] studied 75 breast cancer patients with 1-5 brain metastases treated with gamma knife radiosurgery (GKRS) in Vietnam. The patients were mostly around 53 years old, had three or fewer brain lesions, and a median tumor size of 3.78 cm^3. The study showed that 92.5% of tumors were controlled at 6 months after GKRS, with a median survival of 17.2 months. Longer survival was associated with a smaller total tumor volume, hormone receptor negativity, fewer previous treatments, and controlled cancer outside the brain. Age and number of brain lesions were the key survival factors. Gamma knife radiosurgery was effective in selected breast cancer patients with brain metastases. Gupta et al.[15] analyzed the records of 116 patients with solid tumors and brain metastases. They found that patients with simultaneous brain metastases, certain recursive partitioning analysis (RPA) classes, and male sex had worse survival.

This study used MRI features and other factors to create a model for predicting survival. It compared simultaneous and later brain metastases in the same group, examining clinical, radiological, and treatment factors, including GKRS. This new prognostic index helps clinicians to assess the risk and manage brain metastases in Indonesia. Previous studies have examined fewer factors; for example, Kerschbaumer et al.[12] found that swelling did not affect survival after surgery. Du et al.[13] linked patient status, extracranial control, tumor size, and edema index to radiosurgery outcomes. Phung et al.[14] found that tumor size and extracranial disease predicted outcomes in patients with breast cancer treated with gamma knife radiosurgery. Gupta et al.[15] found that simultaneous metastases, RPA class, and male sex predicted worse survival. In contrast, this study combined clinical, imaging, and treatment factors into a validated index. This approach allows personalized risk assessment for Indonesian patients with brain metastases, combining imaging response and treatment into a useful tool for clinical decision-making.

The study aimed to identify key prognostic factors influencing survival in synchronous and metachronous brain metastases using MRI in an Indonesian cohort, focusing on the impact of metastatic duration, treatment response, and Gamma Knife treatment status.

METHODS

Research design

A retrospective cohort study was conducted at Siloam Hospitals Lippo Village, Tangerang, Indonesia, from January 2021 to December 2023.

Research subjects

We calculated the sample size with Lemeshow's [16] two-group comparison formula, based on anticipated differences between populations. Chu et al.[11] estimated that 50% of SBM patients (P_1=0.50) would have poor outcomes, versus 30% in the MBM group (P_2=0.30), yielding an effect size of 20 percentage points. The sample size calculation used a mean difference of 0.20, Type I error rate (α) of 0.05 for a two-tailed test, and 80% power ($1-\beta$), and each group had a minimum sample size of 43.

The study included 100 patients with brain metastases, 48 with synchronous brain metastases (SBM), and 52 with metachronous brain metastases (MBM). The inclusion criteria were patients diagnosed with brain metastases by histopathology report between January 2021 and December 2023, who were documented in electronic medical records, and aged 18-90 years. Patients with incomplete related medical record data or with other brain disorders were excluded from the study. Brain metastases are classified into two categories, namely synchronous and metachronous, based on their time of occurrence after diagnosis of the primary tumor. Synchronous brain metastases are defined as a diagnosis of brain metastases made less than six months after the primary tumor diagnosis. In contrast, metachronous brain metastases are defined as a diagnosis of brain metastases made more than six months after the primary tumor diagnosis.

Brain MRI protocol

All patients underwent a brain contrast MRI using a 1.5 Tesla MRI machine (Achieva, Philips, Amsterdam, Netherlands) at Siloam Hospitals Lippo Village, Tangerang, Indonesia. The MRI examinations included the following sequence: axial and sagittal T1-weighted, axial and coronal T2-weighted, axial T2 fluid-attenuated inversion recovery (FLAIR), axial T2 weighted fast field echo (FFE), axial echo planar diffusion weighted imaging (EP-DWI), and contrast axial, coronal, and sagittal T1 fat suppression. The scanners were operated by licensed technical staff and underwent daily quality assurance monitoring. Subjects with significant motion artifacts or those missing one or more of the required sequences on the brain MRI were excluded from the cohort. Three licensed radiologists (RS, RM, K) reached a consensus in determining the brain characteristics of metastases in the MRI brain contrast sequences.

MRI brain contrast was reviewed based on variables reflecting radiologic information including i) the number of metastatic nodules, divided into solitary (one brain metastasis), oligometastases (two to three brain metastases), and multiple (more than three brain metastases; ii) maximum diameter of brain metastases on T1-weighted gadolinium-enhanced; iii) peritumoral brain index (Figure 1); iv) primary tumor, divided into lung, breast, and others; v) diffusion weighted imaging, divided into restricted and unrestricted;[17] vi) localization of metastatic nodules, divided into supratentorial and infratentorial; vii) signal intensity of the T1, T2, and FLAIR sequences, divided into hypointense, isointense, and hyperintense; viii) T1 enhancement characteristics (Figure 2), divided into four categories: rim-enhancing (strong rim image with extensive central necrosis), spherical (clear boundary, solid, not strong, and small necrosis area), breakout (clear boundary with at least one side having an indistinct boundary, solid, not strong, and small necrosis area), and diffuse (indistinct boundary, diffuse (without strong edges); ix) tumor borders; x) intratumoral bleeding; xi) tumor-induced mass effect; xii) intratumoral cysts or necrosis.[6,18,19]

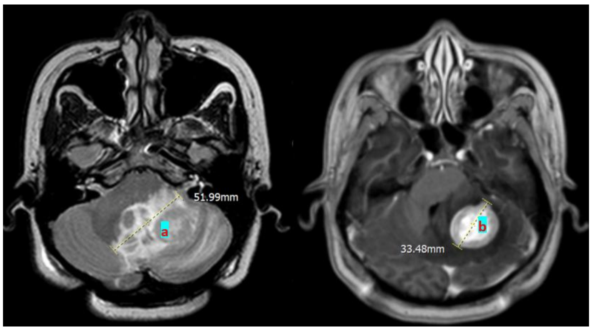

Figure 1. Peritumoral brain index is obtained by dividing the size of peritumoral edema (maximum diameter of edema obtained from T2-weighted image (a) minus the maximum diameter of tumor on T1-weighted gadolinium-enhanced (b)) by the maximum diameter of tumor on T1-weighted gadolinium-enhanced ((a-b)/b)

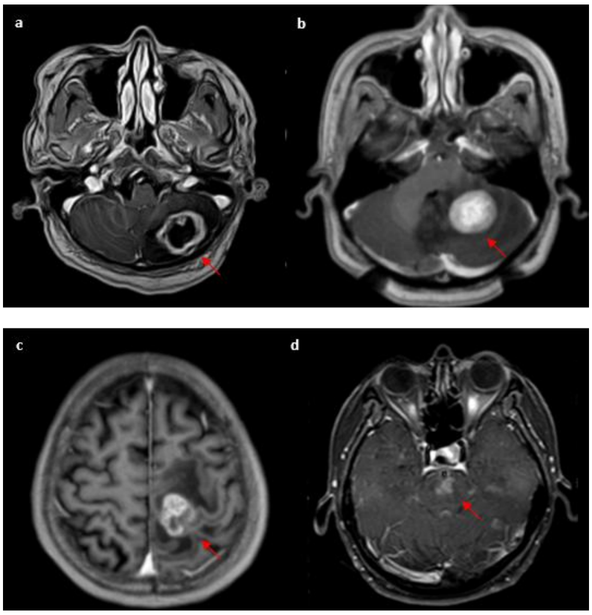

Figure 2. The T1 enhancement characteristics are divided into four categories (red arrows): rim-enhancing: strong rim image with extensive central necrosis (a), spherical: clear boundary, solid, not strong, and small necrosis area (b), breakout: clear boundary with at least one side having an indistinct boundary, solid, not strong, and small necrosis area (c), and diffuse: indistinct boundary, diffused without strong edges (d)

Data collection

The researchers collected data on independent variables including demographics, primary tumor origin, radiological information, volume reduction, and gamma knife status. The dependent variable was brain metastases duration (synchronous/metachronous).

We calculated the tumor volume by manual segmentation and quantification using 3D Slicer's Segment Statistics module.[20] Volume response was calculated using the formula [(Pre-Treatment Volume−Post-Treatment Volume)/ Pre-Treatment Volume) x100%]. The volume response was categorized using a threshold of -30%, dividing patients into reduction ≤-30% (greater reduction), reduction >-30% (less reduction). This cutoff likely follows established Response Assessment in Neuro-Oncology for Brain Metastases (RANO-BM) guidelines, which typically define partial response as ≥30% reduction in tumor measurement.[21]

Data analysis

The analysis classified variables as continuous (age, tumor diameter, peritumoral index) and categorical (gender, primary tumor type, gamma knife status, volume response, radiological characteristics). All continuous variables were tested for data normality with the Kolmogorov-Smirnov test. We dichotomized age using a 60-year threshold based on the mean of each group, then created two groups, i.e. patients <60 years and patients ≥60 years for survival analysis. Peritumoral index group was dichotomized using cutoff value of 1.547 to categorize patients into low (≤1.547) and high (>1.547) peritumoral index groups based on mean from each group. Bivariate analysis compared synchronous and metachronous metastasis using various tests: unpaired t-test for normally distributed continuous variables, Mann-Whitney test for non-normally distributed continuous variables, chi-square test for categorical variables with two groups (if requirements were met), and Fisher exact test for unmet chi-square requirement. Univariable survival analysis identified factors associated with survival outcomes. Variables with $p<0.05$ were included in multivariable Cox Regression Analysis to determine prognostic factors. Survival analysis by risk group stratified patients based on prognostic scores. The regression coefficients (β) derived from significant predictors (metastatic timing, gamma knife treatment, and volume response) were employed to calculate an individual prognostic risk score for each patient. This was achieved through a weighted linear combination: Risk Score = β1 × Metastatic Timing + β2 × Gamma Knife Status + β3 × Volume Response. Utilizing the mean risk score value of -1.513 as a threshold, patients were categorized into two distinct groups: those with risk scores less than or equal to -1.513 were designated as the low-risk group, whereas those with scores exceeding this threshold were classified as the high-risk group. All statistical analyses were performed with SPSS 25.0 statistical software, and differences were considered statistically significant at $p<0.05$.[22]

Ethical clearance

This study obtained ethical clearance from the Ethics Committee of Pelita Harapan University, Tangerang, Indonesia, under number 057/K-LKJ/ETIK/I/2024.

RESULTS

A review of 100 patients with brain metastases was conducted, comprising 48 synchronous and 52 metachronous cases. Patients with synchronous brain metastases were significantly older than those with metachronous metastases, with a mean age of 58.83 ± 10.62 years in the synchronous group compared to 52.71 ± 11.90 years in the metachronous group (p=0.008). The distribution of primary tumor type was also significantly associated with the timing of brain metastases, particularly for lung and breast carcinoma (p=0.007).

The distribution of primary tumor types between synchronous and metachronous brain metastases is summarized in Table I. Among synchronous cases, lung cancer was significantly more prevalent (65.1% in synchronous vs. 34.9% in metachronous), while breast cancer occurred more often in metachronous cases (70.6% in metachronous vs. 29.4% in synchronous). The "other" tumor group showed less pronounced differences (43.5% synchronous vs. 56.5% metachronous). A chi-square test revealed a statistically significant association between primary tumor type and metastasis timing (p=0.007), indicating that the likelihood of lung or breast cancer being the primary site differs depending on whether brain metastases occur synchronously or metachronously. The location of metastases differed significantly based on timing. Supratentorial metastases were mostly synchronous, while infratentorial metastases were predominantly metachronous. No statistically significant differences were observed in gender, tumor diameter, peritumoral index, DWI, gamma knife status, volume response, number of metastatic nodules, T1 intensity, T1 contrast, T2, FLAIR, tumor border, intratumoral hemorrhage, and intratumoral cyst/necrosis.

Table 2 delineates the prognostic variables influencing overall survival in patients with brain metastases, as assessed using both univariate and multivariate Cox regression models. Age (≥60 years) did not significantly affect survival compared with the younger cohort (<59 years), with a HR of approximately 1 in both analyses. Regarding metastatic duration, individuals with MBM demonstrated a significantly reduced risk of mortality relative to those with SBM, indicating a protective effect with an HR of 0.49 (95% CI: 0.24–0.97, p=0.041) in the multivariate model. A volume reduction exceeding 30% was correlated with a significantly elevated risk of mortality, with an HR of 2.50 (95% CI: 1.01–6.23, p=0.048) in the multivariate analysis, suggesting a poor prognosis. Gamma knife treatment status also markedly affected survival; patients who did not receive gamma knife therapy exhibited a substantially higher risk of mortality than those who did, with an HR of 6.82 (95% CI: 3.45–13.50, p<0.001) in the multivariate model. Regarding the peritumoral index groups, no significant difference in survival was observed between patients with index values exceeding 1.547 and those with values less than or equal to 1.547, with a non-significant HR of 1.10 (95% CI: 0.70–1.75, p=0.625). Collectively, these findings underscore the importance of metastatic duration, volume reduction, and gamma knife status as significant independent predictors of overall survival in this patient cohort.

Utilizing the multivariable Cox regression analysis (Table 2), a prognostic index was developed by aggregating the weighted values of three significant predictors: metastatic timing, Gamma Knife radiosurgery, and tumor volume response. The prognostic index for each patient was computed as follows: Prognostic Index = (0.719 × Metastatic Timing [SM=0, MM=1]) + (1.920 × Gamma Knife Status [No=0, Yes=1]) + (0.918 × Volume Response [≤–30%=0, >–30%=1]). The mean index value (–1.513) served as the threshold to categorize patients into low- and high-risk groups, with survival analyses by risk group detailed in Table 3.

Table 1. Characteristics of patients with brain metastases, grouped by timing of metastases

Variables	Synchronous brain metastases (n=48)	Metachronous brain metastases (n=52)	p value
Age (years) ∞	58.83 ± 10.62	52.71 ± 11.90	0.008
Gender*			
Male	20 (55.6)	16 (44.4)	0.355
Female	28 (43.8)	36 (56.3)	
Primary tumor*			
Lungs	28 (65.1)	15 (34.9)	0.013
Breast	10 (29.4)	24 (70.6)	
Other (besides lungs and breast)	10 (43.5)	13 (56.5)	
Tumor diameter (mm)∞	27.98 ± 12.67	30.10 ± 12.16	0.395
Peritumoral index, median (min-max) Δ	2.32 (0.0-23.33)	1.8 (0.0-11.62)	0.253
DWI type*			
Unrestricted	19 (42.2)	26 (57.8)	0.321
Restricted	29 (52.7)	26 (47.3)	
Number of metastatic nodules*			
Singular	20 (43.5)	26 (56.6)	0.676
Oligometastases	15 (50.0)	15 (500)	
Multiple	13 (54.2)	11 (45.8)	
Metastases location*			
Infratentorial	10 (30.3)	23 (69.7)	0.008
Supratentorial	38 (56.7)	29 (43.4)	
T1 intensity*			
Hyperintense	6 (33.3)	12 (66.7)	0.241
Isointense	14 (63.6)	8 (36.4)	
Hypointense	28 (46.7)	32 (53.3)	
T1 contrast intensity*			
Spherical	18 (45.0)	22 (55.0)	0.952
Rim enhancing	12 (48.0)	13 (52.0)	
Breakout	9 (47.4)	10 (52.6)	
Diffuse	9 (56.3)	7 (43.8)	
T2 intensity+			
Hyperintense	4 (66.7)	2 (33.3)	0.108
Isointense	0	0	
Hypointense	44 (46.8)	50 (53.2)	
FLAIR intensity+			
Hyperintense	3(60.0)	2(40.0)	0.200
Isointense	0	0	
Hypointense	45 (47.4)	50 (52.6)	
Tumor border*			
Well defined	39 (47.6)	43 (52.4)	1.000
Ill defined	9 (50.0)	9 (50.0)	
Mass Effect *			
Yes	24 (44.4)	30 (55.6)	0.568
No	24 (52.2)	22 (47.8)	
Hemorrhage*			
Yes	14 (40.0)	21 (60.0)	0.287
No	34 (53.1)	30 (46.9)	
Intratumoral cyst or necrosis *			
Yes	20 (51.3)	19 (48.7)	0.749
No	28 (45.9)	33 (54.1)	
Volume reduction*			
≤ - 30%	11(36.7)	19 (63.3)	0.106
>- 30%	38 (54.3)	32 (45.7)	
Gamma knife status*			
With gamma knife	33(45.2)	40(54.8)	0.212
Without gamma knife	16 (59.3)	11 (40.7)	

Note: Data presented as n (%), except for age and tumor diameter (mean ± SD) and peritumoral index (median, range) * Chi-square; + Fisher exact test; ∞ T-test; Δ Mann-Whitney test; DWI: diffusion weighted imaging

Table 2. Prognostic variables affecting overall survival in brain metastasis patients

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p value	HR (95% CI)	p value
Age group (years)				
<59	Reference	0.905		
≥60	1.06 (0.49–2.29)			
Metastatic duration (months)				
SBM	Reference	0.036	Reference	0.041
MBM	0.67 (0.47–0.96)		0.49 (0.24–0.97)	
Volume reduction				
≤ - 30%	Reference	0.007	Reference	0.048
>- 30%	1.84 (1.17–2.88)		2.50(1.01–6.23)	
Gamma knife status				
With Gamma knife	Reference	<0.001	Reference	<0.001
Without Gamma knife	4.63 (2.84–7.54)		6.82 (3.45–13.50)	
Peritumoral index group				
≤1.547	Reference	0.625		
>1.547	1.10 (0.70–1.75)			

Note: SBM: synchronous brain metastases; MBM: metachronous brain metastases; HR: hazard ratio; CI: confidence interval. Reference denotes comparator category. p values from Cox regression

Based on the regression coefficients, a prognostic index was calculated using the mean value (-1.513) as the cutoff point for risk stratification. Kaplan-Meier analysis revealed significant survival differences between these groups (p<0.001). Patients in the low risk group demonstrated substantially longer mean survival (75.52 ± 5.48 months) compared to those in the high risk group (31.43 ± 4.95 months).

DISCUSSION

This study examined 100 patients with brain metastases, categorized into 48 synchronous brain metastases (SBM) and 52 metachronous brain metastases (MBM). Significant differences were observed between SBM and MBM patients in age, primary tumor origin, and metastatic location. Lung cancer was the primary source of SBM, while breast cancer was most common in MBM. Supratentorial lesions were more prevalent in SBM, and infratentorial lesions in MBM.

The examination of brain metastases (BM), particularly distinguishing between synchronous (SBM) and metachronous (MBM) presentations, has revealed clinically significant factors impacting patient survival and outcomes. Diverse studies consistently highlight differences in prognosis between SBM and MBM patients relative to the timing of metastasis, the primary tumor source, and the anatomical location of brain lesions. Clinically, lung cancer has been established as a predominant source of SBM, while breast cancer is more frequently associated with MBM.(23,24) This categorization aligns with prior findings indicating that the biological characteristics of primary tumors can influence metastatic behavior and subsequent clinical outcomes. For instance, the expression of specific biomarkers differs between primary tumors and their associated metastases, impacting prognosis; breast cancer, particularly, demonstrates variances in biomarker expression when metastasizing to the brain, which might theoretically correlate with the more favorable outcomes observed in MBM.(24) Moreover, patterns of metastasis reveal a propensity for SBM to present predominantly with supratentorial lesions, in contrast to the infratentorial lesions more commonly seen in MBM patients.(23) The location and number of metastases have profound implications for treatment decisions and prognosis, where studies have articulated that patients with fewer, isolated lesions typically present with a more favorable outcome than those with extensive metastasis, underscoring the impact of the metastatic load.(23)

Table 3. Survival analysis by risk group based on Cox regression model

Risk Group	n	Survival (months)	95% CI	p-value
High risk (≤-1.513)	50	31.43 ± 4.95	21.72 - 41.13	<0.001
Low risk (>-1.513)	50	75.52 ± 5.48	64.76 - 86.27	
Overall	100	49.14 ± 4.77	39.78 - 58.49	

Note: data presented as Mean ± SD

Survival analyses provide further evidence of significant prognostic disparities driven by the timing of metastasis. Research indicates that MBM patients exhibit longer mean survival rates, with recorded values such as 58.94 ± 6.84 months for MBM compared to 39.72 ± 6.31 months for SBM patients. This finding corroborates the observations noted in diverse cohorts demonstrating better survival outcomes linked to the characteristics of the metastasis timing. Different treatment responses based on the timing of the metastasis have also been implicated in these survival differences. For instance, studies indicate that MBM patients might respond better to systemic therapies than their SBM counterparts, affecting overall survival projections.(23,25,26) These survival discrepancies have been attributed to various biological mechanisms. For example, patients with MBM tend to have a different immune landscape compared to those with SBM, which can influence tumor progression and response to treatment.(26) This immune response divergence shapes the clinical management and outcome trajectories for patients facing brain metastasis, suggesting further exploration into tailored treatment strategies based on the nature of metastasis. In conclusion, substantial evidence supports the notion that differences between SBM and MBM patients significantly influence clinical outcomes, survival rates, and treatment responses. Research consistently illustrates how factors such as primary tumor origin, metastatic timing, and anatomical location contribute to these outcomes, marking a pivotal area for ongoing investigation in oncology.(7–10)

Our study showed that tumor volume response and gamma knife radiosurgery were also significant predictors of survival. Patients achieving greater volume reduction and those treated with gamma knife radiosurgery demonstrated longer mean survival times. Multivariable Cox regression analysis identified three independent prognostic factors: metastatic timing, gamma knife treatment, and favorable volume response. These factors were used to calculate a prognostic index for risk stratification. Kaplan-Meier analysis of the resulting risk groups showed significant survival differences, with the low-risk group demonstrating substantially longer mean survival (75.52 months) compared to the high-risk group (31.43 months). This study provides valuable insights into the prognostic factors and treatment outcomes for patients with brain metastases. The findings highlight the importance of metastatic timing, tumor volume response, and gamma knife radiosurgery in predicting and potentially improving survival outcomes. The developed prognostic index offers a tool for risk stratification, which could aid in treatment planning and patient management.

The importance of tumor volume response and gamma knife radiosurgery as significant predictors of survival in patients with brain metastases has been consistently demonstrated across various studies.(13,27,28) Research indicates that tumor volume reduction serves as a crucial prognostic indicator, with a more favorable volume response correlated with improved survival rates.(29)

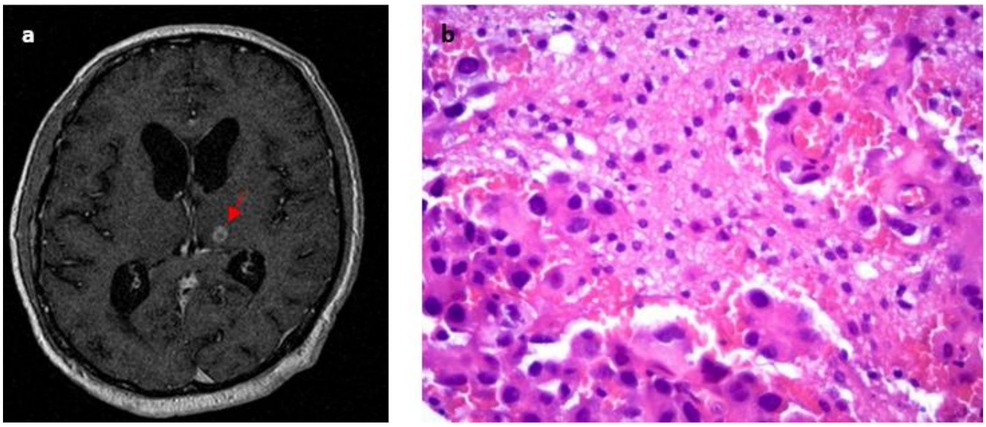

Figure 3. A 58-year-old male with synchronous brain metastases (red arrow) after diagnosis of lung carcinoma. Multiple ring enhancing lesions located mostly in supratentorial areas on T1 weighted imaging (a). Histopathology of brain metastases from lung carcinoma (hematoxylin and eosin staining; magnification, x 400) showing lung carcinoma cells arranged in groups, some of which form acini and grow infiltratively among the reactive glial tissue (b)

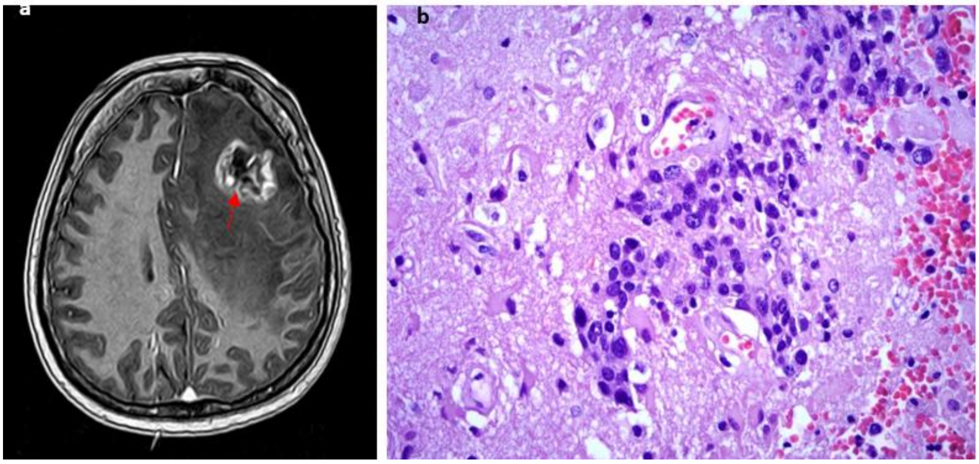

Figure 4. A 47-year-old female with metachronous brain metastases (red arrow) after diagnosis of breast cancer. Solitary ring enhancing lesion located in frontal lobe on T1 weighted imaging (a). Histopathology of brain metastases from breast cancer (hematoxylin and eosin staining; magnification, x 400) showing breast carcinoma tumor cells arranged in groups and individually, as infiltrative growth between reactive glial tissue (b)

Gamma knife radiosurgery has emerged as a key therapeutic modality for treating brain metastases, with its efficacy in achieving local tumor control and improving overall survival outcomes well-documented.[30] The development of a prognostic index based on factors including gamma knife treatment, metastatic timing, and volume response has led to significant survival stratification, with Kaplan-Meier analyses showing marked differences in mean survival between low-risk and high-risk groups.[31] The underlying mechanisms through which gamma knife radiosurgery and tumor volume response affect survival outcomes are multifaceted, with gamma knife radiosurgery acting primarily on the tumor microenvironment to induce apoptosis and necrosis while sparing adjacent healthy tissue.[32] The timing of metastatic spread can also influence therapeutic responses and the inherent biology of the tumors involved, emphasizing their crucial role in determining outcomes.[33] Noyama et al.[28] have further validated these findings, with gamma knife radiosurgery demonstrating improved survival rates and significant tumor volume reduction across various patient cohorts. Our study developed a prognostic index combining metastatic timing, gamma knife radiosurgery treatment status, and tumor volume response, effectively stratifying patients into distinct risk groups with significant value. These findings align with prior research validating risk stratification tools, such as recursive partitioning analysis (RPA) classes and tumor stability metrics.[34] However, our prognostic index advances existing models by incorporating dynamic treatment response parameters (e.g., volume reduction ≤-30%) alongside metastatic timing and treatment modality, offering a more granular and actionable framework for survival prediction.

This study's limitations include radiologist subjectivity in determining enhancement patterns and the lack of a universal cut-off for synchronous and metachronous metastases. The findings suggest considering brain MRI screening, especially for lung and breast cancer patients and the elderly. Future research should focus on identifying cut-off points for synchronous and metachronous metastases, developing screening timelines, and examining primary cancer staging, histopathology, survival rates, mortality, and functional outcomes. The study highlights the importance of metastatic timing, Gamma knife radiosurgery, and tumor volume response in brain metastasis management. Prioritizing Gamma knife radiosurgery for eligible patients, particularly those with metachronous metastases or achieving ≥30% volume reduction, could significantly improve survival. The developed prognostic index enables risk stratification, guiding tailored treatment strategies. The prevalence of lung cancer in synchronous metastases and breast cancer in metachronous cases emphasizes the need for primary tumor-specific surveillance protocols. These findings support integrating MRI biomarkers into clinical workflows to enhance prognostic accuracy and personalize care.

CONCLUSION

Advanced age, lung cancer, and supratentorial localization are associated with synchronous brain metastases. Metachronous metastases, gamma knife treatment, and favorable volume response predict better survival. Regular screening is crucial, especially for lung and breast cancer patients. The developed prognostic index aids in risk stratification and treatment planning.

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Conflict of Interest

The authors state that there are no conflicts of interest.

Author Contributions

K was responsible for the study's conceptualization and design, supervised data collection, conducted the analysis, and wrote the initial draft of the manuscript. RM played a role in designing the study, interpreting the data, and revising the manuscript. RS offered radiological analysis expertise and assisted in editing the manuscript. LH contributed to the neurosurgical elements of the study and provided significant revisions. EK was involved in pathology analysis and manuscript development. CF aided in data acquisition and statistical analysis. JC supported the literature review and the overall preparation of the manuscript. All authors have read and approved the final manuscript.

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Data Availability Statement

The data that underpin this study can be accessed by contacting the corresponding author, Koesbandono(koesbandono.raduph@gmail.com), upon reasonable request.

Declaration of Use of AI in Scientific Writing

No artificial intelligence tools were employed in the drafting or editing of this manuscript. All content was created through the efforts of the authors listed above.

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