RESEARCH ARTICLE

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Prognosis of Brain Metastases (BM) Patient Received Whole Brain Radiation Therapy (WBRT) alone or in combination with Surgery at Dharmais National Cancer Center, Indonesia

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Abstract

Purpose: WBRT and surgery are commonly used to improve the overall survival of BM patients. The study aims to evaluate the overall survival of patients treated with WBRT in combination with surgery or alone. **Methods:** This study is a cohort retrospective of 148 BM patients from January 1st, 2021, to December 31st, 2022, and our follow-up on their overall survival up to July 1st, 2023. We collected data on treatments received either in combination with WBRT and surgery or alone. Information for age, sex, primary tumor types, and sites of metastases were collected. Median survival time, Kaplan-Meier curves, and its' log-rank statistics were presented, including the results of Cox regression analysis. **Results:** The overall median survival of this sample was 4.3 months. Patients receiving WBRT exhibit higher survival rates than non-WBRT (median survival rates are 6.9 vs 1.5 months) but not surgery (4.0 vs 4.4 months). The primary tumors (breast, lung, and others) have no difference in the median survival rates. The survival rate using Kaplan-Meier showed a significant difference between patients with WBRT vs non-WBRT (log-rank p=0.0) but not for surgery. A Cox regression shows hazard ratio (HR) for patients receiving WBRT=0.34 [95% CI: 0.19–0.62; P<0.001] and when it is adjusted for surgery and other variables it exhibits only a small change. **Conclusion:** BM patients who received WBRT had better survival than non-WBRT patients, which could reduce HR, but surgery was not statistically significant. All BM patients should receive WBRT regardless of surgery.

Keywords: Brain Metastases- WBRT- brain surgery- overall survival- Indonesia

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Introduction

Solid metastases from any origins may spread into the brain, causing a range of signs and symptoms such as headache, focal neurological dysfunction, cognitive impairment, seizure, and stroke[1]. BM incidence rate ranges around 20-30% of solid cancer cases. It is particularly high in cancer patients with lung and breast origins[1-6]. Incidence in other primary tumors is relatively lower but remains a significant factor that might worsen the disease prognosis [5, 3, 2, 7]. The treatments of choice for BM are in general surgical removal or non-surgical approaches with radiotherapy, including WBRT [8, 4, 1]. However, some patients did not have the chance to receive either WBRT or surgery due to loss of follow-up or died before completing treatment. While chemotherapy and targeted therapy are considered effective in primary tumors outside the brain, for example, breast cancer, both treatments for BM are relatively ineffective due to the blood-brain barrier which most pharmaceutical agents cannot penetrate the barrier [9, 10].

Whole brain radiotherapy (WBRT), despite its controversy with the side effects weighing more than the benefits (with an average survival rate of 3-4 months with WBRT versus 2 months with palliative care alone) [6, 11-14], it remains the standard of care in many hospitals, including Indonesia. At the Dharmais National Cancer Center, this treatment is consistent with the ASTRO Clinical Practice Guideline. This guideline is based on a systematic review provided by the Agency for Healthcare Research and Quality [8].

A total dose of 30 Gy in 10 fractions is the most common schedule for BM treatment [2, 7, 12, 15]. However, the decision of the fractionation for a given patient is very complex. Many factors must be considered, including KPS, histology, age, GPA, and RPA[2]. Another

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consideration is the side effects of WBRT. Higher dosages of WBRT are associated with severe side effects such as cognitive impairment, while lower dosages reduce the effectiveness [11, 12, 16]. These side effects are generally mild and resolved with basic supportive care [14, 17]. In some cases, these side effects may lead to permanent brain damage, affecting both the cognitive function and the patient's quality of life [13, 18, 19, 16, 20].

Dexamethasone is administered for most BM patients to improve the overall patient conditions and compliance with radiotherapy [2, 12]. In our hospital, other drug treatments do not vary, and evaluating treatment variation for the BM patient is difficult. However, WBRT treatment and surgery vary among patients depending on the clinical pathway at our hospital. Furthermore, the change in treatments depends on the survival before treatment and loss of follow-up. The study aims to evaluate the overall survival of patients treated with WBRT in combination with surgery or alone. We hypothesized that WBRT can increase the overall survival of patients who received WBRT even when we considered surgery and other clinical conditions. This finding will be useful in providing information on BM patients' prognoses in Indonesia since no data is available for this condition.

Materials and Methods

Study Design

The design of this study is a cohort retrospective using data extracted from the electronic medical record (eMR) database at Dharmais National Cancer Center, Jakarta, Indonesia. This cancer hospital is the national referral hospital for all cancers, including brain cancer. The hospital has advanced brain operation facilities, expertise, and complete chemotherapy required for cancer patients, including for brain metastasis cases from many primary cancer origins.

Patient Enrollment

Utilizing a total sampling method, we include all patients above 18 years old diagnosed with BM from solid tumors between January 1st, 2021, and December 31st, 2022. Patients diagnosed with BM with brain magnetic resonance imaging (MRI) before January 1st, 2021, and those visiting the neurological department earlier are excluded. A total of 148 patients fulfilling the inclusion and exclusion criteria were applied in this study. We followed up with all patients on their survival until July 1st, 2023.

Variables

The main outcome of this study was an overall survival time at the end of this study whether the patient survived or the loss of follow-up or death at the end of the study period (death or censored). Each patient was assessed according to the treatment received, i.e. received a combination of WBRT and surgery. Thus, patients are classified into four groups (WBRT, surgery, WBRT + surgery, and none). It should be noted that patients who received 10 doses of radiation or more during the study period we recorded received WBRT but if less than 10 doses we recorded not received WBRT. Similarly, patients were classified according to the surgery performed whether he/she had surgery or not, regardless of the type of surgery. In addition, we collected data from medical records variables encompassing patient demographics, signs, and symptoms upon first visiting the neurology department, primary tumor site, and metastatic characteristics (number, location, and extracranial metastases). We did not extract data on chemotherapy or other drug data since there are almost no variations and too many drugs given.

Statistical Analyses

We use survival analysis for patients' overall survival times in months based on the follow-up period from the date of diagnosed brain metastasis using MRI until the date of death or survival by July 1st, 2023, or at a loss to follow-up before or at the end of the study (administrative censored). We perform statistical analyses using Stata version 17 software [21]. The survival probability is illustrated using Kaplan-Meier curves, and the different lines are tested using the log-rank test with its' p-value. We explore possible other variables associated with the outcome that should be considered in the multivariable model. We used a Cox regression analysis to estimate the hazard ratio comparing received and non-received WBRT adjusted to variable surgery and other variables [22].

Results

Patient characteristics

Table 1 shows the demographic and clinical characteristics of the BM patients according to WBRT treatment status, including surgery performed. The total number of patients admitted to the hospital with BM was 148, with 95 (64.2%) receiving WBRT). Approximately one-third of patients undergo surgery (29.1%). Data on the demographics and clinical characteristics of those who received WBRT and those who did not indicate significant disparities. For example, more male patients received WBRT than females, but this discrepancy was not statistically meaningful. Other demographic characteristics such as age groups, nutritional status, and patient education levels also did not show notable variations.

Clinical findings presented, including primary cancer type, presence of multiple or solitary metastases, location of BM, and presence of extracranial metastases (e.g., lung, liver, bone, and others), showed no significant distinctions between the two groups. The location of the tumor at supratentorial is higher among those treated with WBRT compared to those not treated with WBRT (89.4% vs 79.2%); however, the difference is not statistically significant (χ^2 tests with p=0.09). Approximately one-third of the patients had a history of brain surgery, and this factor similarly did not differ significantly between the groups. In summary, patients who received WBRT and those who did not have similar demographic and clinical profiles.

Median survival time according to demographics and clinical characteristics

Table 2 presents the survival times of BM patients based on clinical characteristics at Dharmais National

Table 1. Demographic and Clinical Characteristics of the Brain Metastases Patients According to WBRT Treatment Admitted to the Dharmais National Cancer

Treated using WBRT	No	Yes	Total	P-value
n (%)	53 (35.8)	95 (64.2)	148 (100.0)	
Sex, n (%)				
Male	16 (30.2)	39 (41.1)	55 (37.2)	
Female	37 (69.8)	56 (58.9)	93 (62.8)	0.19
Age group, n (%)				
<40	6 (11.3)	13 (13.7)	19 (12.8)	
40-50	14 (26.4)	26 (27.4)	40 (27.0)	
50+	33 (62.3)	56 (58.9)	89 (60.1)	0.90
Educational Background, n (%)				
Secondary or below	9 (17.0)	21 (22.1)	30 (20.3)	
High School/diploma	34 (64.2)	54 (56.8)	88 (59.5)	
Post Graduated	10 (18.9)	20 (21.1)	30 (20.3)	0.66
Nutritional status, n (%)				
Normal	30 (57.7)	43 (45.7)	73 (50.0)	
Overweight	9 (17.3)	26 (27.7)	35 (24.0)	
Underweight	13 (25.0)	25 (26.6)	38 (26.0)	0.29
Type of primary cancer, n (%)				
Breast Cancer	22 (41.5)	30 (31.9)	52 (35.4)	
Lung Cancer	22 (41.5)	50 (53.2)	72 (49.0)	
Others	9 (17.0)	14 (14.9)	23 (15.6)	0.38
Multiple or Solitary metastases, n (%)				
Multiple	36 (69.2)	64 (68.1)	100 (68.5)	
Solitary	16 (30.8)	30 (31.9)	46 (31.5)	0.89
Location at supratentorial, n (%)				
No	11 (20.8)	10 (10.6)	21 (14.3)	
Yes	42 (79.2)	84 (89.4)	126 (85.7)	0.09
Location at infratentorial, n (%)				
No	23 (43.4)	47 (50.0)	70 (47.6)	
Yes	30 (56.6)	47 (50.0)	77 (52.4)	0.44
Extracranial metastases to lung, n (%)				
No	42 (79.2)	70 (73.7)	112 (75.7)	
Yes	11 (20.8)	25 (26.3)	36 (24.3)	0.45
Extracranial metastasis to liver, n (%)				
No	40 (76.9)	68 (71.6)	108 (73.5)	
Yes	12 (23.1)	27 (28.4)	39 (26.5)	0.48
Extracranial metastasis to bone, n (%)				
No	26 (49.1)	54 (56.8)	80 (54.1)	
Yes	27 (50.9)	41 (43.2)	68 (45.9)	0.36
Other extracranial metastases, n (%)				
No	49 (92.5)	88 (92.6)	137 (92.6)	
Yes	4 (7.5)	7 (7.4)	11 (7.4)	0.97
Brain Surgery, n (%)				
No	39 (73.6)	66 (69.5)	105 (70.9)	
Yes	14 (26.4)	29 (30.5)	43 (29.1)	0.60

Cancer Center, Indonesia, regardless of WBRT treatment. Overall, the median survival time of the BM patients is 4.3 months. It is shown that females have a longer survival time than males. For example, around 25% of the male patients died at 1.63 months, while the female patients died at 2.16 months. The median survival for the males is much lower compared to the females (3.6 vs 5.2 months). Increasing age groups tend to increase the probability of dying, while those with the lowest education have the shortest survival times. The median survival time of primary breast cancer is the same as that of lung cancer (4.3 months), but for lung cancer, 75% died at 11.6 months, and for breast cancer at 13.8 months. Multiple metastases show a shorter median survival time than solitary BM (4.0 vs 6.9 months). The tumor location in the supratentorial region has a better median survival time than the non-supratentorial region (4.4 vs 2.8 months). Extracranial metastasis to the bone has a lower median survival time than the liver and lung (4.8 vs 7.0 and 7.7 months). The median survival time for the WBRT vs non-WBRT patients is 6.9 vs 1.5 months, respectively, indicating that WBRT-receiving patients have a relatively better prognosis around 4-5 times than the non-receiving counterparts. Looking at the patients who had brain surgery compared to those who did not, there is not much difference in median survival times (4.4 vs 4 months).

Survival curve using the Kaplan-Meier graph and log-rank test

Figure 1 shows the Kaplan-Meier graph with 4 lines representing the survival time of BM patients as the results of classifying the sample according to WBRT and surgery. These lines are samples of BM patients that received a) WBRT only, b) surgery only, c) both WBRT and surgery, and d) no WBRT and no surgery.

The figure suggests that combination surgery and WBRT or WBRT only resulted in the best median survival rate reaching up to 7 months. This is relatively the best overall survival among available treatment options. In contrast, the median survival time for the sample "performed surgery only" or "no surgery and no WBRT" have a low median survival time (less than 2 months). Comparing these 4 lines, the log-rank test is statistically significance (χ^2 =21.13 and p=0.000).

We analyzed survival rates using Kaplan-Meier graphs for patients treated with WBRT compared to those who did not receive them. Figure 2 shows higher survival rates among WBRT recipients compared to non-recipients. Within the first six months of BM diagnosis, 52% of WBRT recipients survived compared to 20% of non-recipients, with a log-rank test confirming significant differences in survival rates (log-rank with $\chi^2$2 =19.41 and p=0.000). The figure shows that the recipient WBRT has a higher probability of surviving than non-WBRT recipients.

In contrast, surgery for BM showed no improvements in overall survival rates (Figure 3). The 6-month overall survival rates were comparable between those who received surgery (49%) and those who did not (45%), with the log-rank test indicating that there are no significant differences in survival rates ($\chi^2$2 =0.67 and p=0.412).

Multivariable analysis

Table 3 utilized a Cox proportional hazard model to estimate the hazard ratio (HR) and identify the most relevant variables for multivariable analysis. The result in Model 1 showed that receiving WBRT combined with surgery significantly reduced the hazard ratio [HR] to: 0.34; with a 95% confidence interval [CI]: 0.19–0.62; P<0.001 compared to those none (baseline) indicating a 66% risk reduction. Similarly, receiving WBRT alone reduced the HR to 0.39 with a 95% CI: 0.24–0.62 and P<0.001 indicating a 62% risk reduction. If patients received only surgery, the HR is 0.71 with a 95% CI: 0.35–1.43 and P>0.05 which is not statistically significant.

In Model 2, adjusting for sex did not alter the HR for treatments significantly, but sex showed a significant HR=0.66 with a 95% CI: 0.44–0.98 and P<0.05. In Model 3 HR for WBRT and surgery adjusted for age group did not alter the HR for treatments and the age group did not

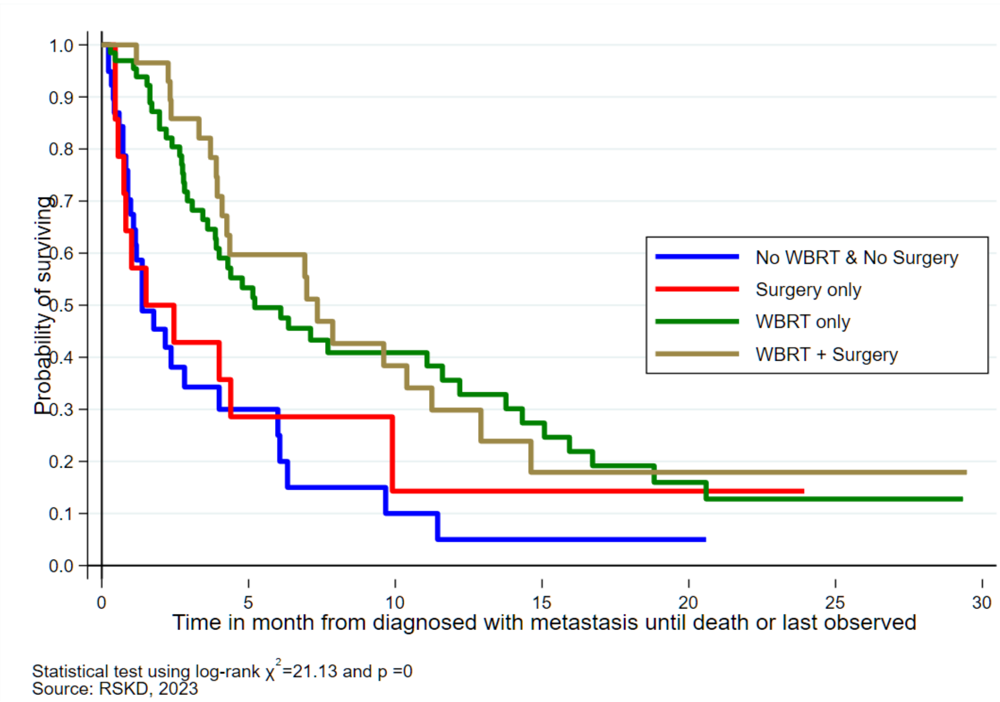

Figure 1. Kaplan Meie's Curve of brain metastasis patients according to WBRT treatment and Surgery admitted to the Dharmais Hospital, Jakarta From 1 January 2021 to-31-December, 2022

Table 2. Survival Times of BM Patients based on Clinical Characteristics at Dharmais National Cancer Center, Indonesia

Characteristics	Time at risk	Incidence Rate	Number of Subjects	Survival times		
				25%	50%	75%
Total	857.8	0.12	148	2.0	4.3	11.6
Sex						
Male	254.5	0.16	55	1.63	3.6	9.7
Female	603.4	0.10	93	2.16	5.2	14.6
Age groups						
< 40	86.1	0.14	19	1.2	2.4	18.8
40- 50	243.8	0.12	40	2.8	6.0	12.2
> 50	527.9	0.12	89	1.6	4.0	11.5
Education						
Secondary	131.5	0.17	30	1.5	2.7	7.3
High School	491.4	0.12	88	1.8	5.2	11.6
Graduate	234.9	0.09	30	2.8	5.2	15.9
Nutritional status						
Normal	387.4	0.14	73	1.6	4.0	11.3
Overweight	272.5	0.08	35	3.4	7.3	15.1
Underweight	189.0	0.14	38	1.5	4.4	11.1
Type of primary cancer						
Breast Cancer	285.5	0.12	52	2.7	4.3	13.8
Lung Cancer	443.7	0.12	72	1.6	4.3	11.6
Others	121.7	0.14	23	1.5	3.9	7.1
Solitary or Multiple metastases						
Multiple	521.7	0.14	100	1.6	4.0	10.4
Solitary	327.8	0.09	46	2.4	6.9	14.6
Location at supratentorial						
No	110.6	0.13	21	1.2	2.8	14.6
Yes	743.0	0.12	126	2.0	4.4	12.2
Location at infratentorial						
No	476.1	0.10	70	2.2	4.8	14.3
Yes	377.5	0.15	77	1.6	3.9	10.4
Extracranial metastases to lung						
No	599.3	0.13	112	1.6	3.9	11.3
Yes	258.6	0.09	36	2.8	7.7	15.9
Extracranial metastasis to the liver						
No	587.2	0.13	108	2.2	4.1	11.1
Yes	268.9	0.10	39	2.0	7.0	13.8
Extracranial metastasis to bone						
No	448.6	0.12	80	2.0	4.0	11.1
Yes	409.3	0.12	68	2.0	4.8	13.8
Extracranial metastasis to other organs						
No	743.9	0.13	137	1.8	4.3	11.3
Yes	114.0	0.08	11	2.0	5.2	20.6
Brain Surgery						
No	554.8	0.13	105	1.6	4	12.2
Yes	303.1	0.10	43	2.3	4.4	11.3
Receiving WBRT						
No	166.7	0.24	53	0.8	1.5	6.1
Yes	691.1	0.09	95	3.1	6.9	14.6

Note: The Incidence rate is the number of failures divided by the total analysis time at risk under observation. For example, the total incidence rate is 102/857,836 = 0.118903846423, or 0.12, as presented in the first row of the table.

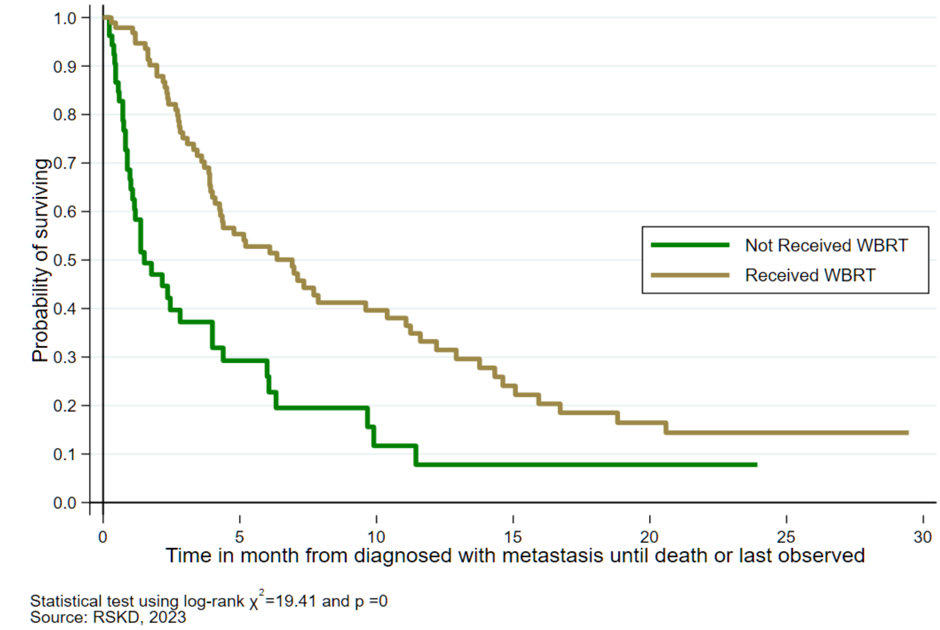

Figure 2. Kaplan Meie's Curve of Brain Metastasis Patients According to WBRT Treatment and Admitted to the Dharmais Hospital, Jakarta From 1 January 2021 to-31-December 2022

show a significant HR of 0.59 with a 95% CI: 0.29–1.19 and P>0.05 for the age group 40-50 and age group 50+ is 0.65 with a 95% CI: 0.34–1.24 and P>0.05 compared to ages 40 and below. This indicates that the younger ages have a higher risk of dying even though statistically not significant. Thus, adjusting to the age group did not change the HR of treatments.

Model 4 considered multiple nodules that might affect the HR of treatment. The result shows after adjusting to the number of nodules the treatment effect did not change significantly. Multiple nodules have increased HR to 1.23 with a 95% CI: 0.78–1.94 but it is not statistically significant (P>0.05). Finally, Model 5 shows the HR of treatment adjusted to types of primary cancer that did change the treatment effects. There are no significant differences between the primary cancer types. In conclusion, WBRT is associated with reduced mortality, whereas surgery alone does not significantly

Table 3. Hazard ratios (HR) of Survival Prediction for BM Based on Treatment Received (WBRT or Surgery) and adjusted for Sex, Age Group, clinical characteristics (multiple nodules), and primary cancer types presented in exponentiated coefficients; 95% confidence intervals in brackets

	Model 1	Model 2	Model 3	Model 4	Model 5
Treatment Received					
No WBRT + No Surgery	1 [1,1]	1 [1,1]	1 [1,1]	1 [1,1]	1 [1,1]
Surgery only	0.71[0.35,1.43]	0.78[0.39,1.59]	0.78[0.38,1.58]	0.80[0.38,1.66]	0.76[0.35,1.65]
WBRT only	0.38***[0.24,0.62]	0.39***[0.24,0.64]	0.37***[0.22,0.60]	0.37***[0.23,0.61]	0.37***[0.22,0.63]
WBRT + Surgery	0.34***[0.19,0.62]	0.34***[0.19,0.60]	0.32*** [0.18,0.58]	0.35*** [0.19,0.65]	0.34***[0.18,0.65]
Sex					
Male		1 [1,1]	1 [1,1]	1 [1,1]	1 [1,1]
Female		0.66*[0.44,0.98]	0.65*[0.43,0.98]	0.65*[0.43,1.00]	0.62 [0.38,1.02]
Age group					
<40			1 [1,1]	1 [1,1]	1 [1,1]
40-50			0.59 [0.29,1.19]	0.60 [0.30,1.21]	0.58 [0.29,1.17]
50+			0.65 [0.34,1.24]	0.65 [0.34,1.25]	0.70 [0.36,1.37]
Multiple					
No				1 [1,1]	1 [1,1]
Yes				1.23 [0.78,1.94]	1.32 [0.81,2.16]
Primary Cancer					
Breast Cancer					1 [1,1]
Lung Cancer					0.86 [0.49,1.53]
Others					1.34 [0.68,2.64]

* p < 0.05, ** p < 0.01, *** p < 0.001

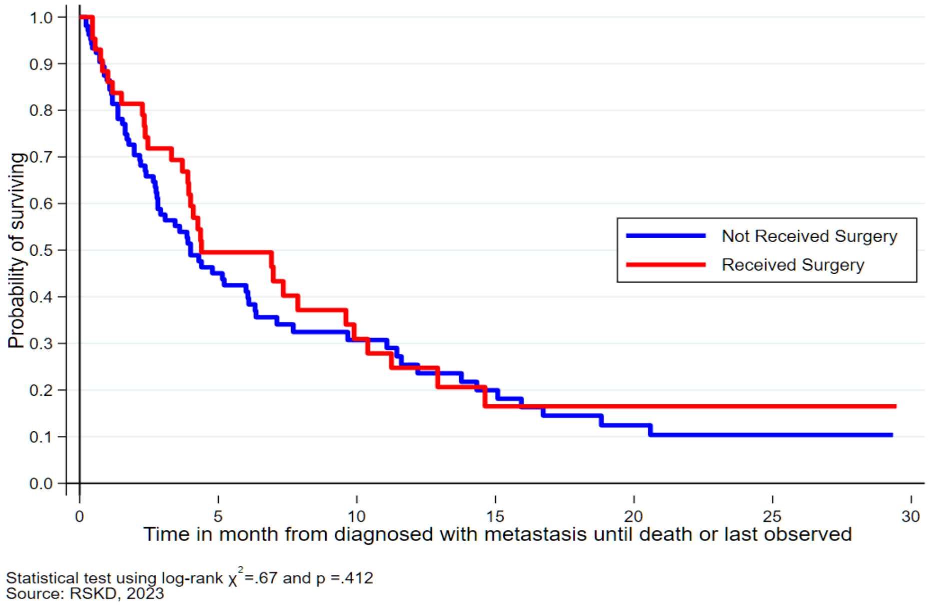

Figure 3. Kaplan Meie's Curve of Brain Metastasis Patients According to Status for Surgery Admitted to the Dharmais Hospital, Jakarta From 1 January 2021 to-31-December 2022

Table 4. Pseudo R^2 and AIC of the Model

	Model 1	Model 2	Model 3	Model 4	Model 5
Pseudo R^2	0.021	0.025	0.028	0.029	0.031
AIC	842.6	840.6	842.5	824.9	825.4
df_m	3	4	6	7	9
Observations	148	148	148	146	145

AIC, Likelihood Ratio (LR) of Akaiki Criterion; df_m, Degrees of freedom of the model; Source of data, RKSD, 2023

affect survival. Patients after surgery need to receive WBRT (Table 4).

Discussion

The main objective of this study is to investigate the effectiveness of treatments for BM patients on their overall survival rate. In addition to WBRT and surgery treatments, demographic and clinical characteristics were considered for this analysis. The median survival of the patients receiving WBRT reaches 6.9 months vs 1.5 months for non-receiving WBRT. The surgery was not associated with the overall survival time (median survival 4.4 vs 4.0 months). Further analysis using multivariable analysis confirmed that HR for WBRT protects about 66% of the risk of dying but surgery only did not. Other demographic and clinical characteristics were not associated with the overall survival. Only females have a lower HR than males.

We created 5 models based on the bivariate analysis between survival time and treatment evaluated, including using the Kaplan-Meier graph and log-rank statistic. In addition to treatment (WBRT and surgery), sex, age group, and multiple nodules were considered for our modeling. In addition to examining the proportionality assumption, we also explore the possibilities of interaction among treatments and clinical features. Given there are no interactions between WBRT, surgery, sex, age group, multiple nodules, and primary cancer types (Model 5) we prefer a model with statistical significance independent variables (Model 2). Thus, the effect of treatment should consider patients' ages.

This analysis is based on retrospective cohort studies with some possible sources of bias. This study is based on the electronic medical record available at our hospital. Therefore, some important variables might not be available. For example, the survival status of some patients was known at the last follow-up more than 3 months of the visit schedule. In this case, we made follow-up by telephone, especially when other data was complete but survival status. However, the result of telephone follow-up was not possible to confirm the cause of death, but we tried to ask his/her family in detail. For example, if the cause of death was due to a traffic accident it should be excluded from death data. Nevertheless, the telephone follow-up is only a small fraction of this dataset (less than 5%). Its difference with deaths was recorded in the hospital. Even so, we depend on the final diagnosis made by the medical provider which might have more than one cause of death. If there is more than one of the causes of death, we select the first listed in the medical record. Some possibilities of causes of death are vague, especially during the Covid-19 pandemic but we were relying on the existing electronic medical record.

Another source of bias is multiple providers collected the data. Although we have advocated standardized clinical guidelines [15], the variation in data collection and clinical management can vary according to clinical providers. This is true for the treatment of BM other than WBRT and surgery. For example, the use of chemotherapy and dexamethasone, including other palliative drugs, is difficult to analyze. Even though this chemotherapy and palliative drug treatment might be associated with overall survival, we excluded them from our study by assuming these treatments do not vary between BM patients. So, if this assumption is not close to reality, then it becomes one of the sources of bias for this study.

The decision to define whether BM patients received WBRT or not might become a source of classification bias. BM patients classified as receiving WBRT should meet the criteria at least 10 times received radiation before defining the outcome of the study [15]. This means that BM patients who receive 9 times radiation have been classified as not receiving WBRT. Ideally, the number of radiations is evaluated for BM patients, but it is not our study objective. Similarly, we did not categorize the type of brain surgery that might vary between patients. Therefore, variables included in the final analysis are more objective measures, such as multiple or single nodules of the BM tumor. Thus, the classification bias cannot be overlooked in this study.

Considering the objectivity of the data collected and the negligible bias of this study, our analysis has shown that the WBRT is significantly associated with the overall survival of BM patients. These findings can be compared with other studies among patients with BM who received WBRT and surgery. Our result is relatively better than studies conducted by Khan and Dicker (median survival 4 to 6 months) [11]. The median survival of WBRT vs non-WBRT patients is comparable to the study by Trikhirhisthit et al. (4.4 months and 2.3 months, respectively) [23].

Tumor origins such as breast and lung have similar median survival rates. The finding contrasts with the BM studies by Jeene et al. [7], which shows that BM from breast cancer has a better median survival rate than that of patients with lung cancer origins. This difference might be related to the types of lung cancers among the observed subjects. Demographically, about 90% of lung cancer patients at Dharmais Cancer Center have non-small-cell-lung cancer (NSCLC) type and about half of NSCLC patients have a positive EGFR mutation (in the form of single, double, or triple variant) [24]. This mutation is associated with targeted therapy availability to control the primary tumor, such as tyrosine-kinase inhibitors (TKIs) [25]. Compliance with TKI indicates a better prognosis, with a reduction in HR of up to 83% compared to non-compliant individuals [25]. Conversely, the best predictor for targeted therapy in breast cancer, HER2 receptor positivity, in Asian women is about 30% [9, 26]. Therefore, the median survival of both lung cancer and breast cancer might be similar, but the overall survival is likely to be higher for breast cancer.

The results also align with studies on BM and their survival rates in other studies [27, 7, 4]. People aged 40-50 years old have the best median survival rate, while people aged 40 years or younger tend to have a worse prognosis in the age group. In terms of survival rates according to gender, females show relatively better median survival rates [28]. Additionally, multiple BM and infratentorial locations indicate a worse prognosis for a median survival rate. Solitary BM has a better median survival rate of 6.9 months than multiple BM with 4.0 months. This result is also shown by Hazuka et al in 1993 (12 months for solitary BM versus 5 months for multiples BMs) [29].

According to EANO and ESMO, patients with solitary BM are recommended to undergo surgical resection with the level of evidence 1A (EANO) and IIA (ESMO) [15]. The use of Radiotherapy (WBRT) or the newer Stereotactic Radiosurgery (SRS) is preferred for tumor diameter >3 cm or in patients with >3 BMs [15, 5, 8]. WBRT alone is mainly used as the primary modality for unresectable tumors due to location, many BMs, or as an adjuvant modality [5, 8, 15]. Female and supratentorial regions of BM remain indicating factors for a better prognosis in most studies related to BM [28, 30, 27, 31-33]. Nevertheless, the clinical profiles in this study were found to be statistically insignificant with a p-value >0.09.

This study has limitations regarding the side effects and comparison studies with the newer technique, SRS [5, 8, 15, 34, 3], which are not widely available in cancer centers in Indonesia. Although many of the studies show limitations related to the quality of life in terms of side effects of WBRT, compliance with WBRT shows a relatively good quality of life for BM patients receiving WBRT [2, 35, 27, 32, 36].

In conclusion, BM patients who received WBRT had better overall survival than non-WBRT patients, but surgery alone was not statistically significant. WBRT reduces HR to 0.34, meaning WBRT protects patients from mortality up to 66%. In addition, if this surgery was not followed by WBRT, the surgery only performed at this hospital did not make a difference in BM patients' survival. This study implies that all BM patients should receive WBRT regardless of surgery since patients who did not receive WBRT have lower survival or higher HR.

Author Contribution Statement

Conception and design of study: Andriani R; Data analysis and interpretation: Wilopo SA; Data acquisition: Hanggrainy OS, Susilodinata A, Tjiptoningsih UM.

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Ethics Committee Approval

The institutional Ethics Committee of the Dharmais Cancer Center Hospital, Jakarta, Indonesia, gave ethical approval to one of our co-authors (Dr. Octavia So Hanggrainy) in August 2023.

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Ethical approval and consent to participate

Ethical approval was given by the Institutional Ethics Committee of the Dharmais Cancer Center Hospital, Jakarta, Indonesia, ethical approval was given to one of our co-authors (Dr. Octavia $o Hanggrainy) on 10 August 2023. The Ethical Approval Number is No.: 268/KEPKA/VII/2023.

Declaration of conflict of interest

The Authors declare that they have no competing financial or other conflict of interest.

References

1. Sas-Korczynska B, Rucinska M. Wbrt for brain metastases from non-small cell lung cancer: For whom and when?-contemporary point of view. J Thorac Dis. 2021;13(5):3246-57. https://doi.org/10.21037/jtd-2019-rbmlc-06.
2. Bassi S, Engelman A, Nichols E, Kwok Y. The risks and advantages of whole brain radiation therapy in patients with brain metastases. In: Hayat MA, editor. Brain metastases from primary tumors: Epidemiology, biology, and therapy of melanoma and other cancers. Amsterdam: Academic Press is an imprint of Elsevier; 2016. p. 197-211.
3. Gavrilovic IT, Posner JB. Brain metastases: Epidemiology and pathophysiology. J Neurooncol. 2005;75(1):5-14. https://doi.org/10.1007/s11060-004-8093-6.
4. Okada Y, Kobayashi M, Shinozaki M, Abe T, Kanemaki Y, Nakamura N, et al. Survival time and prognostic factors after whole-brain radiotherapy of brain metastases from of breast cancer. Acta Radiol Open. 2020;9(7):2058460120938744-. https://doi.org/10.1177/2058460120938744.
5. Schiff D, Messersmith H, Brastianos PK, Brown PD, Burri S, Dunn IF, et al. Radiation therapy for brain metastases: Asco guideline endorsement of astro guideline. J Clin Oncol. 2022;40(20):JCO2200333-2276. https://doi.org/10.1200/JCO.22.00333.
6. Stelzer K. Epidemiology and prognosis of brain metastases. Surg Neurol Int. 2013;4(4):S192-S202. https://doi.org/10.4103/2152-7806.111296.
7. Jeene PM, de Vries KC, van Nes JGH, Kwakman JJM, Wester G, Rozema T, et al. Therapy for brain metastases from lung cancer and breast cancer is poor in 6325 dutch patients treated between 2000 and 2014. Acta Oncol. 2018;57(5):637-43. https://doi.org/10.1080/0284186X.2017.1418534.
8. Gondi V, Bauman G, Bradfield L, Burri SH, Cabrera AR, Cunningham DA, et al. Radiation therapy for brain metastases: An astro clinical practice guideline. Pract Radiat Oncol. 2022;12(4):265-82. https://doi.org/https://doi.org/10.1016/j.prro.2022.02.003.
9. Dawood S, Broglio K, Buzdar AU, Hortobagyi GN, Giordano SH. Prognosis of women with metastatic breast cancer by her2 status and trastuzumab treatment: An institutional-based review. J Clin Oncol. 2010;28(1):92-8. https://doi.org/10.1200/JCO.2008.19.9844.
10. Mauri D, Polyzos NP, Salanti G, Pavlidis N, Ioannidis JPA. Multiple-treatments meta-analysis of chemotherapy and targeted therapies in advanced breast cancer. J Natl Cancer Inst. 2008;100(24):1780-91. https://doi.org/10.1093/jnci/djn414.
11. Khan AJ, Dicker AP. On the merits and limitations of whole-brain radiation therapy. J Clin Oncol. 2013;31(1):11-3. https://doi.org/10.1200/jco.2012.46.0410.
12. Shih HA. Epidemiology, clinical manifestations, and diagnosis of brain metastases. Up to Date. 2024.
13. Nogi S, Nakayama H, Tajima Y, Okubo M, Mikami R, Kanesaka N, et al. Significance of the number of brain metastases for identifying patients who don't need whole brain radiotherapy: Implication as oligometastases of the brain. J Radiosurg SBRT. 2013;2(2):119-26.
14. Yan Q, Li R, Yang J, Bai X, Guo X, Yang X, et al. Efficacy and safety evaluation of combined therapies incorporating whole-brain radiotherapy in patients with brain metastases: A systematic review and meta-analysis. Clin Transl Oncol. 2024. https://doi.org/10.1007/s12094-024-03525-1.
15. Le Rhun E, Weller M, Brandsma D, Van den Bent M, de Azambuja E, Henriksson R, et al. Eano–esmo clinical practice guidelines for diagnosis, treatment and follow-up of patients with leptomeningeal metastasis from solid tumours†. Ann Oncol. 2017;28:iv84-iv99. https://doi.org/https://doi.org/10.1093/annonc/mdx221.
16. Ardhini R, Aninditha T, Andriani R, Sofyan H. R. Cognitive function after whole brain radiotherapy in brain metastases in two cancer referral hospital in indonesia (fungsi kognitif pada pasien tumor otak metastasis pasca radiasi whole brain radiotherapy di dua rs rujukan kanker indonesia). Neurona. 2020;38(1):62-8.
17. McClelland S, 3rd. Early experience with biologically effective dose-comparable short-course whole brain radiation therapy for metastatic intracranial disease. Am J Clin Oncol. 2024;47(8):397-8. https://doi.org/10.1097/coc.0000000000001099
18. Shih HA. Overview of the treatment of brain metastases. Up to Date. 2024.
19. Popp I, Hartong NE, Nieder C, Grosu AL. Pro: Do we still need whole-brain irradiation for brain metastases? Cancers. 2023;15(12):3193. https://doi.org/10.3390/cancers15123193.
20. Shih HA. Prognosis assessment. Up to Date. 2023.
21. StataCorp. Stata statistical software: Release 17. College Station, TX: StataCorp LLC.; 2021.
22. Cox DR. Regression models and life-tables. Journal of the Royal Statistical Society: Series B (Methodological). 1972;34(2):187-202.
23. Trikhirhisthit K, Setakornnukul J, Thephamongkhol K. Added survival benefit of whole brain radiotherapy in brain metastatic non-small cell lung cancer: Development and external validation of an individual prediction model. Front Oncol. 2022;12:911835-. https://doi.org/10.3389/fonc.2022.911835.
24. Hanafi AR, Hanif MA, Pangaribuan MTG, Ariawan WP, Sutandyo N, Kurniawati SA, et al. Genomic features of lung cancer patients in indonesia's national cancer center. BMC Pulm Med. 2024;24(1):43-. https://doi.org/10.1186/s12890-024-02851-y.
25. Andriani R, Rosewitasari J, Hanif MA, Mulawarman A, Kurniawati SA, Fachri A. Factors affecting 2-year survival in patients with non–small cell lung cancer brain metastases: Evidence from indonesia's national cancer center, jakarta, indonesia. Clin Med Insights Oncol. 2023;17:11795549231178172-. https://doi.org/10.1177/11795549231178172.
26. Telli ML, Chang ET, Kurian AW, Keegan THM, McClure LA, Lichtensztajn D, et al. Asian ethnicity and breast cancer subtypes: A study from the california cancer registry. Breast Cancer Res Treat. 2011;127(2):471-8. https://doi.org/10.1007/s10549-010-1173-8.
27. Hügel M, Stöhr J, Kuhnt T, Nägler F, Papsdorf K, Klagges S,

et al. Long-term survival in patients with brain metastases—clinical characterization of a rare scenario. Strahlenther. Onkol. 2024;200(4):335-45. https://doi.org/10.1007/s00066-023-02123-4.
28. Cioffi G, Ascha MS, Waite KA, Dmukauskas M, Wang X, Royce TJ, et al. Sex differences in odds of brain metastasis and outcomes by brain metastasis status after advanced melanoma diagnosis. Cancers. 2024;16(9):1771. https://doi.org/10.3390/cancers16091771.
29. Hazuka MB, Burleson WD, Stroud DN, Leonard CE, Lillehei KO, Kinzie JJ. Multiple brain metastases are associated with poor survival in patients treated with surgery and radiotherapy. J Clin Oncol. 1993;11(2):369-73. https://doi.org/10.1200/JCO.1993.11.2.369.
30. Rastogi K, Bhaskar S, Gupta S, Jain S, Singh D, Kumar P. Palliation of brain metastases: Analysis of prognostic factors affecting overall survival. Indian J Palliat Care. 2018;24(3):308-12. https://doi.org/10.4103/ijpc.Ijpc_1_18.
31. Anis SB, Hani U, Yousaf I. Predictors of survival in patients with metastatic brain tumors: Experience from a low-to-middle-income country. Asian J Neurosurg. 2023;18(1):139-49. https://doi.org/10.1055/s-0043-1764120.
32. Park K, Bae GH, Kim WK, Yoo CJ, Park CW, Kim SK, et al. Radiotherapy for brain metastasis and long-term survival. Sci Rep. 2021;11(1):8046-. https://doi.org/10.1038/s41598-021-87357-x.
33. Lamba N, Kearney RB, Catalano PJ, Hassett MJ, Wen PY, Aizer AA. Population-based estimates of survival among elderly patients with brain metastases. Neuro Oncol. 2021;23(4):661-76. https://doi.org/10.1093/neuonc/noaa233.
34. Li J, Ludmir EB, Wang Y, Guha-Thakurta N, McAleer MF, Settle SH, et al. Stereotactic radiosurgery versus whole-brain radiation therapy for patients with 4-15 brain metastases: A phase iii randomized controlled trial. Int J Radiat Oncol Biol Phys. 2020;108(3):S21-S2. https://doi.org/10.1016/j.ijrobp.2020.07.2108.
35. Shih HA. Acute complications of cranial irradiation. In: Uptodate. Up to Date. 2024.
36. Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An american society for radiation oncology evidence-based guideline. Pract Radiat Oncol. 2012;2(3):210-25. https://doi.org/10.1016/j.prro.2011.12.004.