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Risk Factors of Developing Leptomeningeal Seeding After Resection of Brain Metastasis in Patients With Breast Cancer: Defining the Indication for Preoperative SRS

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Abstract

Background/Aim: This study aimed to identify the incidence and risk factors for leptomeningeal seeding (LMS) in patients with breast cancer following brain metastasis resection and radiotherapy (RT) and to determine potential candidates for preoperative stereotactic radiosurgery (SRS).

Patients and Methods: Between 2012 and 2022, 33 patients with breast cancer underwent surgical resection and postoperative RT for newly detected brain metastases. Twenty-one patients received whole-brain RT, while 12 patients were treated with SRS. Survival and incidence of LMS development were retrospectively analyzed. Several risk factors for the development of LMS were identified.

Results: After a median follow-up of 25.3 months, the 1- and 3-year overall survival (OS) rates were 81.2% and 58.1%, respectively. Development of LMS was the only significant factor affecting OS in multivariate analysis (Hazard ratio=3.08). Significant risk factors for LMS included age ≤45 years, triple-negative breast cancer (TNBC), and piecemeal resection. The 1-year LMS risk was 85.7% for younger patients, 46.2% for those with TNBC or piecemeal resection, and 11.1% for older patients without TNBC undergoing en-bloc resection.

Conclusion: Patients with breast cancer brain metastases who were ≤45 years old, had TNBC, or underwent piecemeal resection were at high risk of developing LMS, regardless of the postoperative RT technique used. Patients with these risk factors are essential candidates for alternative treatment approaches, such as preoperative SRS.

Keywords: Breast cancer, brain metastasis, stereotactic radiosurgery, radiotherapy.

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Introduction

Brain metastasis is a common and serious complication of advanced cancer that often leads to significant neurological impairment and reduced quality of life. Traditionally, surgical resection has been the preferred treatment for patients with accessible, solitary, or large brain metastases, offering immediate relief from mass effects and potential improvements in neurological symptoms. However, surgery alone is associated with high recurrence rates, necessitating the development of additional therapeutic strategies to enhance local control (1, 2).

Radiotherapy has long played a critical role in the management of brain metastases and has also been extensively used in the postoperative setting. Whole-brain radiotherapy (WBRT) has historically been used to reduce the risk of recurrence following surgery. Despite its effectiveness, WBRT is associated with notable cognitive side effects, prompting a shift towards more targeted approaches for treating the postoperative cavity, such as stereotactic radiosurgery (SRS) (3-6). With technological advancements, SRS has gained popularity as an adjuvant treatment that provides high-dose localized radiation to the surgical cavity while minimizing exposure to surrounding healthy brain tissue. This approach aims to balance effective disease control with the preservation of cognitive function, which is a crucial consideration, as systemic therapies continue to improve and extend patient survival.

However, the increased use of SRS in the postoperative setting has raised concerns about potential complications, including radiation necrosis and leptomeningeal spread (LMS), particularly in specific patient populations such as those with breast cancer (7-9). The risk factors contributing to LMS, such as the surgical technique, tumor characteristics, and primary cancer type, are yet to be determined. Notably, patients with breast cancer, especially those with aggressive subtypes, may be at an elevated risk of LMS, underscoring the need for further research in this area (7-10).

Given these complexities, this study aimed to explore the factors influencing the development of LMS in patients with breast cancer after surgical resection and post-operative SRS to provide insights that could guide future treatment strategies and improve patient outcomes.

Patients and Methods

Patient selection. Data of patients with breast cancer who underwent surgical resection of brain metastases and were treated with radiotherapy (RT) at Seoul St. Mary's Hospital were retrospectively reviewed. The inclusion criteria were as follows: 1) patients with breast cancer with brain metastasis diagnosed between 2012 and 2023; 2) patients who underwent surgical resection of brain metastasis and received postoperative RT. The exclusion criteria were as follows: 1) patients who received brain RT prior to surgery, 2) patients who received less than half of the planned RT schedule, and 3) patients who were lost to follow-up immediately after RT.

Treatment. RT simulation was performed in the head-first supine position, and a U-frame mask was used for immobilization. Brain computed tomography (CT) images were obtained with 3-mm slices for WBRT and with 2-mm slices for SRS. Contrast enhancement was performed only in the patients who underwent SRS. Because a more accurate delineation of the targets is required for SRS, brain magnetic resonance imaging (MRI) scans of the T1 sequence with gadolinium enhancement were fused with simulated CT images. Radiation was delivered at 30 Gy in 10-12 fractions to the whole brain during WBRT. WBRT was delivered using bilateral opposing fields except in five patients who received hippocampal-avoidance WBRT. In patients with SRS, the clinical target volume (CTV) included the postoperative cavity and any residual enhancing lesion plus a 2-mm margin, with an additional 0-1-mm margin for the planning target volume. The prescription dose was 24 Gy in three fractions treated with Cyberknife (Accuray Inc., Sunnyvale, CA, USA) or 25-30 Gy in five

fractions treated with tomotherapy (Accuray Inc.). In patients with multiple brain lesions treated with SRS, any residual lesions were treated with 20 Gy in single fraction or 27 Gy in three fractions of SRS.

Follow-up evaluation. All patients were followed until death or the time of analysis. Patients received follow up MRI at intervals of three months after surgery. The primary endpoint was LMS development after RT. LMS was diagnosed based on histologic confirmation from cerebrospinal fluid (CSF) or by definite leptomeningeal enhancement observed on brain MRI (in the sulci of the cerebral hemispheres, subependymal areas, cranial nerves, folia of the cerebellum), or in the spinal cord. Although dural metastasis is technically distinct from LMS, the two are often difficult to differentiate clinically. Therefore, in this study, we did not distinguish between them and included dural metastases in the LMS. Local recurrence (LR) was defined as the development of new enhancing lesions within the resection cavity, whereas distant brain recurrence (DBR) was defined as the emergence of new metastatic nodules in the brain parenchyma, distinct from the resection cavity.

Statistical analysis. Baseline differences between the WBRT and SRS groups were analyzed using the Chi-square test or Fischer's exact test and the Mann-Whitney *U*-test. The risk of LMS and overall survival (OS) were calculated from the end of RT to the date of event occurrence. Survival curves were estimated using the Kaplan-Meier method and compared using the log-rank test. Statistical significance was set at $p<0.05$. The Cox proportional hazards model was used for multivariate analysis to identify factors associated with OS and LMS with hazard ratios (HR) and 95% confidence intervals (CI). The backward stepwise selection method was used to determine the final model. All statistical analyses were performed using SPSS Statistics 20.0.0. (IBM Corp, Armonk, NY, USA). This study was approved by our institutional review board (IRB, no: KC22RISI0209).

Results

Patient and treatment characteristics. Thirty-three patients met the inclusion criteria and were included in this study. The patient characteristics are shown in Table I. All patients underwent postoperative RT with WBRT (n=21) or SRS (n=12). The median patient age was 55 years (range=28-75 years). In the majority (69.7%) of patients, brain metastasis was diagnosed at the time of breast cancer recurrence. Only two patients were initially diagnosed with breast cancer with synchronous brain metastasis. Extracranial disease was present in 48.5% of the patients, with the majority having controlled disease (69.7%). The median size of the brain metastases was 3.3 cm (range=1.1-6.2 cm) with the majority located in the cerebrum (69.7%) rather than the cerebellum. Single brain metastases were observed in 63.6% of patients, and 36.4% of patients had multiple metastases. Gross total resection was performed in 84.8% of patients, while 15.2% underwent less extensive resection. En-bloc resection was performed in 57.6% of cases, whereas piecemeal resection was performed in 42.4% of cases. In terms of pathology, 36.4% of the patients were HER2-positive, and 39.4% had triple-negative breast cancer (TNBC). Postoperatively, most patients received systemic treatment, with 39.4%, 21.2%, and 21.2% receiving cytotoxic, hormonal, and anti-HER2 therapies, respectively. Baseline characteristics were not significantly different between the postoperative WBRT and SRS groups.

Treatment outcome. After a median follow-up of 25.3 months (range=2.8-70.6 months), the 1- and 3-year OS rates were 81.2% and 58.1%, respectively (Figure 1A). In univariate analysis, significant factors influencing OS were as follows: the timing of brain metastasis diagnosis (initial or recurrence in stage IV *vs*. during stage IV treatment, $p=0.046$), the presence of extracranial disease ($p=0.032$), and the occurrence of LMS ($p=0.034$). The OS difference according to the development of LMS is shown in Figure 1B. In multivariate analysis, only the development of LMS remained a significant factor (HR=3.08, 95%CI=1.07-8.83, $p=0.037$) (Table II).

Table I. *Patient characteristics.*

	Postop WBRT (n=21)	Postop SRS (n=12)	Total (% of total)	*p*-Value
Age (years) median 55 (range=28-75)				0.261
≤55 age	13 (72.2%)	5 (27.8%)	18 (54.5%)	
>55 age	8 (53.3%)	7 (46.7%)	15 (45.5%)	
Brain mets diagnosis time				0.404
Initially	2 (100.0%)	0 (0%)	2 (6.1%)	
Recurrence in stage IV	15 (65.2%)	8 (34.8%)	23 (69.7%)	
During stage IV treatment	4 (50%	4 (50%)	8 (24.2%)	
Extracranial disease status				0.978
None	11 (64.7%)	6 (35.3%)	17 (51.5%)	
Oligo (1-5)	2 (66.7%)	1 (33.3%)	3 (9.1%)	
Poly (>5)	8 (61.5%)	5 (38.5%)	13 (39.4%)	
Extracranial disease controlled				0.283
Controlled	16 (69.6%)	7 (30.4%)	23 (69.7%)	
Not controlled	5 (50.0%)	5 (50.0%)	10 (30.3%)	
Brain mets size median 3.3 (1.1-6.2)				0.947
≤3.5 cm	12 (63.2%)	7 (36.8%)	19 (57.6%)	
>3.5 cm	9 (64.3%)	5 (35.7%)	14 (42.4%)	
Brain mets location				0.775
Cerebrum	15 (65.2%)	8 (34.8%)	23 (69.7%)	
Cerebellum	6 (60.0%)	4 (40.0%)	10 (30.3%)	
Brain mets number median 1 (range,1-4)				0.305
Single	12 (57.1%)	9 (42.9%)	21 (63.6%)	
Multiple	9 (75.0%)	3 (25.0%)	12 (36.4%)	
Surgery extent				0.854
GTR	18 (64.3%)	10 (35.7%)	28 (84.8%)	
None-GTR	3 (60.0%)	2 (40.0%)	5 (15.2%)	
Surgery type				0.132
En-bloc	10 (52.6%)	9 (47.4%)	19 (57.6%)	
Piecemeal	11 (78.6%)	3 (21.4%)	14 (42.4%)	
Pathology type				0.735
ER+/HER2-	6 (75.0%)	2 (25.0%)	8 (24.2%)	
HER2+	7 (58.3%)	5 (41.7%)	12 (36.4%)	
TNBC	8 (61.5%)	5 (38.5%)	13 (39.4%)	
Ki-67 index				0.741
≤50%	11 (61.1%)	7 (38.9%)	18 (54.5%)	
>50%	10 (66.7%)	5 (33.3%)	15 (45.5%)	
Post-surgery systemic treatment				0.141
None	6 (100%)	0 (%)	6 (18.2%)	
Anti-HER2	3 (42.9%)	4 (57.1%)	7 (21.2%)	
Hormone Tx	5 (71.4%)	2 (28.6%)	7 (21.2%)	
Cytotoxic	7 (53.8%)	6 (46.2%)	13 (39.4%)	

WBRT: Whole brain radiotherapy; SRS: stereotactic radiosurgery; mets: metastasis; GTR: gross total resection; ER: estrogen receptor; HER2: human epidermal growth factor receptor-2; TNBC: triple-negative breast cancer; Tx: treatment.

The central nervous system (CNS) control outcomes are summarized in Table III. The 1- and 3-year LR rates were 7.2% and 16.5%, respectively. All local recurrences were observed in the WBRT group. The 1- and 3-year DBR rates (excluding LMS) were 8.3 and 15.9%, respectively. There was no difference in DBR between the WBRT and SRS groups. The 1- and 3-year risks of developing LMS after surgery were 43.8% and 51.4%, respectively, which indicates that the majority of failures in the CNS were LMS. Most cases of LMS developed in the first year (Figure 2).

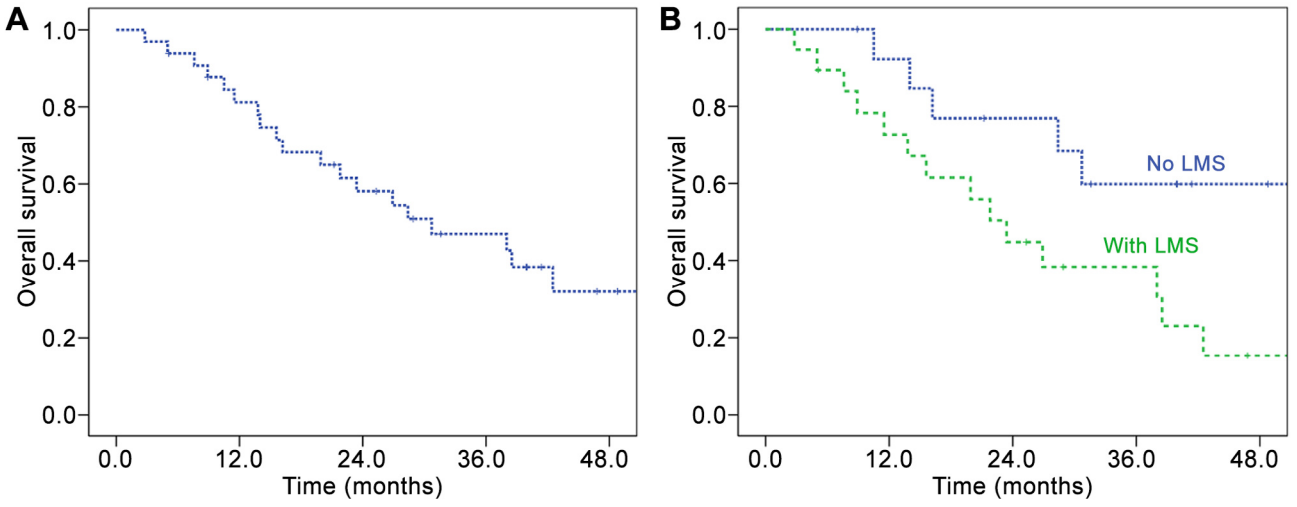

Figure 1. *Overall survival (OS). The Kaplan-Meier plot for (A) overall survival (OS) and (B) OS differences based on the development of leptomeningeal seeding (LMS).*

Table II. *Multivariate cox regression analysis of significant factors affecting survival.*

Variables	HR [Exp(B)]	95%CI for Exp(B)	*p*-Value
Brain mets diagnosis timing (initial or recur *vs.* during stage IV)	1.504	0.496-4.559	0.471
Extracranial disease (no *vs.* yes)	2.131	0.755-6.014	0.153
Development of LMS	3.078	1.073-8.833	0.037

HR: Hazard ratio; CI: confidence interval; mets: metastasis; LMS: leptomeningeal seeding.

Table III. *Central nervous system control outcomes.*

Outcome	1-year rate (%)	3-year rate (%)	Notes
Local recurrence (LR)	7.2	16.5	All occurred in WBRT
Distant brain recurrence (DBR)	8.3	15.9	No difference between WBRT and SRS (p=0.869)
Risk of LMS development	43.8	51.4	No difference between WBRT and SRS (p=0.951)

WBRT: Whole brain radiotherapy; SRS: stereotactic radiosurgery; LMS: leptomeningeal seeding.

Risk factors affecting the development of LMS. The risk factors for the development of LMS are listed in Table IV. In the univariate analysis, patient age with a cutoff of 45 years, surgery type (en-bloc *vs*. piecemeal re-section), and subtype (TNBC *vs*. others) were significant risk factors for developing LMS. In all six patients who received the HER2-target agent after surgery, LMS did not develop at the time of the last follow-up. The type of postoperative RT (WBRT *vs*. SRS) did not affect the development of LMS. The 2-year risk of developing LMS in the WBRT and SRS groups was 60.7% and 63.5%, respectively (p=0.951). In multivariate analysis, age was the most significant factor, followed by subtype and surgery type (Table V).

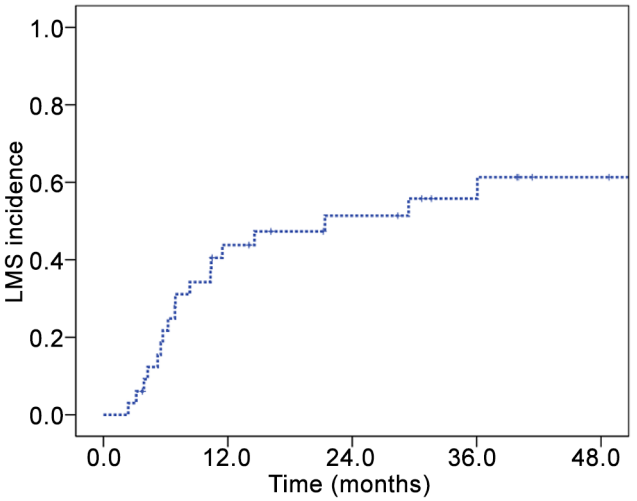

Figure 2. Leptomeningeal seeding (LMS) risk. The Kaplan-Meier plot for LMS development over time (months).

The risk of developing LMS by grouping risk factors is shown in Figure 3. Younger patients (aged ≤45 years) were found to be at a significantly higher risk, with 85.7% developing LMS within 1 year. Among older patients (aged >45 years), those with TNBC or who underwent piecemeal resection were at intermediate risk (46.2% at 1 year), whereas those with non-TNBC or who underwent en-bloc resection were considered low-risk, with only an 11.1% chance of developing LMS at 1 year.

Discussion

Traditionally, patients with solitary or large brain metastases have undergone surgical resection, but surgery alone results in a high local recurrence rate. To address this, postoperative WBRT has been commonly used, though it is associated with significant cognitive side effects (1-3, 11). With advancements in technology, postoperative SRS has emerged as an alternative, aiming to reduce cognitive decline while delivering higher doses to the surgical cavity (4, 5). A phase 3 randomized trial (NCCTG N107C/CEC·3) demonstrated a 52% *vs*. 85% overall cognitive function decline rate at six months in favor of postoperative SRS compared to WBRT without compromising OS (3).

Table IV. *Factors affecting the development of leptomeningeal seeding (LMS).*

	1-year LMS	3-year LMS	*p*-Value (log-rank)
Age (years)			
≤45	85.7%	85.7%	0.012
>45	30.8%	46.1%	
Extracranial disease status			
None	43.7%	57.1%	0.836
Positive	44.4%	65.3%	
Extracranial disease controlled			
Controlled	40.7%	58.9%	0.675
Not controlled	52.0%	64.0%	
Brain mets size			
≤3.5 cm	39.4%	63.6%	0.709
>3.5 cm	50.0%	57.1%	
Brain mets location			
Cerebrum	45.7%	57.7%	0.606
Cerebellum	40.0%	76.0%	
Brain mets number			
Single	42.9%	64.4%	0.993
Multiple	45.5%	56.4%	
Surgery extent			0.091
GTR	40.8%	51.9%	
None-GTR	60.0%	100%	
Surgery type			0.054
En-bloc	32.0%	38.2%	
Piecemeal	61.0%	88.3%	
ER status			0.490
Positive	41.7%	53.3%	
Negative	44.7%	63.3%	
HER2 status			0.153
Positive	25.0%	53.1%	
Negative	54.8%	67.0%	
TNBC			0.048
Non-TNBC	35.4%	50.8%	
TNBC	57.7%	77.4%	
Ki-67 index			0.151
≤50%	33.8%	47.9%	
>50%	56.7%	74.0%	
RT technique			0.951
WBRT	44.7%	60.7%	
SRS	41.7%	63.5%	
Systemic Tx			0.005
HER2 target	0%	0%	
Others	56.2%	76.0%	

LMS: Leptomeningeal seeding; mets: metastasis; GTR: gross total resection; ER: estrogen receptor; HER2: human epidermal growth factor receptor-2; TNBC: triple-negative breast cancer; RT: radiotherapy; WBRT: whole brain radiotherapy, SRS: stereotactic radiosurgery; Tx: treatment.

Table V. *Multivariate cox regression analysis of significant factors affecting the development of leptomeningeal seeding.*

Variables	HR [Exp(B)]	95%CI for Exp(B)	*p*-Value
Age (>45 *vs.* <45)	5.173	1.643-16.280	0.005
Surgery type (En-bloc *vs.* piecemeal)	2.563	0.992-6.623	0.052
TNBC (non-TNBC *vs.* TNBC)	3.279	1.186-2.840	0.022

HR: Hazard ratio; CI: confidence interval; TNBC: triple-negative breast cancer.

However, postoperative SRS has some disadvantages (12). The first is the risk of radiation necrosis of the brain. It is challenging to accurately define and contour the postoperative cavity; therefore, a few millimeter CTV margin is usually applied. In addition, when attempting to include the surgical tract in the treatment field, a larger volume of normal brain tissue is exposed to high-dose radiation than that in SRS for intact brain metastases. This typically increases the risk for necrosis. A careful approach based on these guidelines is essential (6, 13).

The second disadvantage is the increased likelihood of an LMS. During surgery, there is a potential for spillage of viable tumor cells, which can subsequently lead to LMS. Even though some studies have shown conflicting results, several publications have reported that postoperative SRS is associated with a 45% higher risk of LMS than WBRT (14, 15). A meta-analysis by Lamba *et al.* showed that SRS has a higher risk ratio of 2.99 than WBRT (14).

Additionally, these studies identified piecemeal resection, tumor size, and posterior fossa location as risk factors for the development of LMS after surgery (16). Notably, primary breast cancer tumors are consistently reported to have a higher risk than other cancers (7, 17). Atala *et al.* evaluated the risk of LMS after postoperative SRS in 165 patients and found that breast cancer histology was the sole risk factor of developing LMS, with an HR of 2.96 and a 1-year risk of 24% (7). However, not all breast cancer brain metastases result in LMS following surgery, which prompted the current study. No study has evaluated the risk factors for the development of LMS in patients with breast cancer after surgery.

In this study, LMS was found to be the main CNS failure pattern in patients with breast cancer with brain metastasis, followed by surgery. LR and DBR are relatively rare when adjuvant RT is administered. The OS was compromised if LMS developed. Poor prognosis is well known; therefore, preventing the development of LMS is essential for these patients (8, 18).

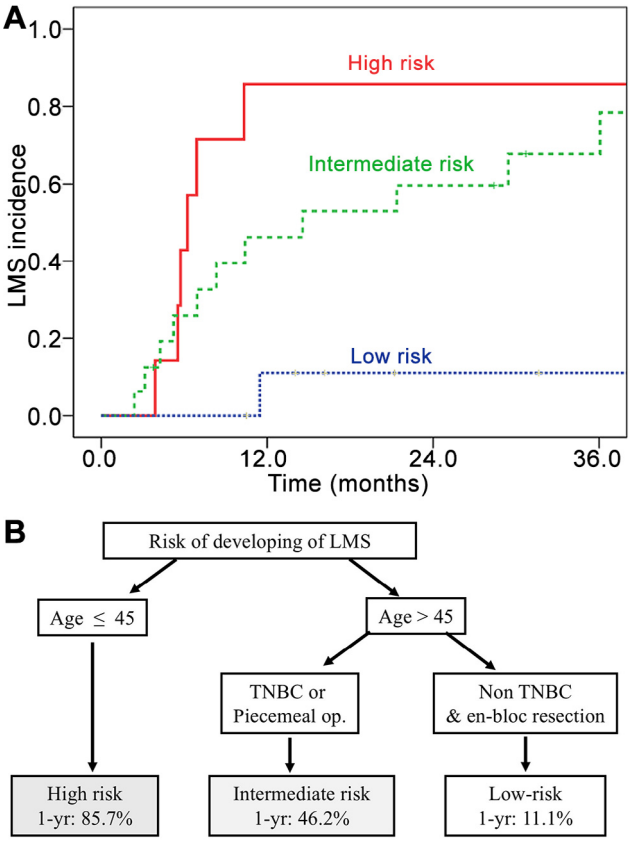

Figure 3. *Risk stratification for leptomeningeal seeding (LMS). (A) Risk stratification for the development of LMS based on clinical factors. (B) Kaplan-Meier plot of LMS incidence stratified by risk group.*

Younger age, TNBC, and piecemeal resection were the major factors contributing to LMS development in our

study. None of the patients treated with HER2-targeted agents after brain surgery developed LMS. These results are consistent with those of other studies (16, 19).

In our study, WBRT did not reduce the risk of LMS compared to postoperative SRS. This finding differs from the results of Ha *et al*., who reported a significantly higher leptomeningeal carcinomatosis or dural metastasis-free survival rate at 18 months for patients treated with WBRT compared to those receiving partial radiotherapy, particularly in breast cancer patients (77.5% *vs*. 30.0%) (9). These contradictory findings may be due to the small sample size of our study or the undetected confounding factors inherent to the limitations of the retrospective design. Additionally, the standard WBRT dose may be insufficient to prevent seeding in patients with breast cancer brain metastasis, which may explain these discrepancies.

Recent studies have focused on preoperative SRS to overcome these limitations (20, 21). This approach could theoretically reduce both the risk of cognitive decline compared with WBRT and the risk of LMS compared with postoperative SRS, although no randomized trials have yet been conducted. However, several retrospective studies have reported promising results suggesting that this method may be effective (22). Nonetheless, because surgery is typically performed in patients with large symptomatic metastases, the time required for planning and quality assurance of SRS may not always be feasible. Therefore, it is crucial to identify the specific subgroup of patients, particularly those at high risk for LMS, who would benefit the most from preoperative SRS.

This study has several limitations, the most significant being the small sample size and retrospective nature of the analysis. The small number of patients requires caution when interpreting the statistical results, as they may lack sufficient power to detect small but clinically meaningful differences. Additionally, the retrospective design inherently introduces potential biases such as selection bias and the presence of un-measured confounding factors.

Specifically, no LMS cases were observed in the six patients who received HER2-targeted therapy; however, owing to the small sample size, it was not possible to establish statistical significance. Therefore, this group was excluded from further analysis. These findings highlight the need for additional research to better understand the impact of HER2-targeted agents on LMS development. Several studies have demonstrated the efficacy of controlling CNS diseases in breast cancer (23, 24).

Another limitation of this study is the difficulty in determining whether the LMS observed in the patients developed solely as a result of surgery or if it would have occurred without surgery. More than 5% of patients with breast cancer develop LMS without surgery. Jung *et al.* reported 11% rate of LMS in breast cancer patients treated with WBRT alone without surgery (25). Therefore, some LMS cases in this study may have occurred independent of surgery or RT. Distinguishing between these two causes is a challenging task. Given that most LMS cases develop within the first year, and the incidence after surgery is significantly high, this factor may be of less concern.

In conclusion, although this analysis was based on a small patient cohort, young age, TNBC, and piecemeal resection are significant risk factors for the development of LMS following surgery. Furthermore, even with WBRT, the risk of LMS is not significantly reduced. Future studies should explore alternative treatment approaches such as preoperative SRS for patients with these risk factors.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

Authors' Contributions

All Authors contributed to the conception and design of the study. JH Hong and JE Lee contributed equally to this work. Material preparation and data collection were performed by JH Hong, BO Choi, and JS Park, and the analyses were performed by JH Song and JE Lee. JH Hong and JH Song wrote the first draft of the manuscript, and

all the authors commented on the previous versions of the manuscript. All Authors have read and approved the final version of the manuscript.

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