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Prognostic Factors for Patients With Brain Metastases Treated With Single-fraction Gamma Knife Radiosurgery

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Abstract. *Background/Aim: The aim of this study was to identify prognostic factors for brain metastases treated with Gamma knife radiosurgery. Patients and Methods: Multivariate Cox proportional hazards regression analyses were conducted for patients who received treatment between June 2013 and March 2018. Results: A total of 131 consecutive patients were included. The median follow-up period was 16.0 months (range=1.5-61.5 months). Brain metastases [hazard ratio (HR)=0.42, 95%CI=0.27-0.67, p<0.001], history of systemic therapy (HR=2.23, 95%CI=1.28-3.89, p=0.005), and active extracranial disease (HR=2.49, 95%CI=1.30-4.76, p=0.006) were independent predictors of overall survival. Number of brain metastases (HR=0.39, 95%CI=0.26-0.59, p<0.001) and history of systemic therapy (HR=1.90, 95%CI=1.17-3.08, p=0.005) were independent predictors of intracranial progression-free survival. Conclusion: The number of brain metastases and the history of systemic therapy are associated with patient overall survival and intracranial progression-free survival.*

Symptomatic metastatic brain tumors are reported to occur in approximately 10% of cancer patients (1). The incidence of metastatic brain tumors is increasing as the survival of patients is prolonged by remarkable advances in systemic therapy and the use of magnetic resonance imaging (MRI) to detect tiny brain metastases (BM) (2). In addition to strongly impacting quality of life and survival (3), metastatic brain tumors cause various neurological manifestations, including headaches, focal symptoms, seizures, increased intracranial pressure, impairment in higher brain dysfunction, and psychiatric symptoms (4). In general, the median survival time after the diagnosis of metastatic brain tumors is approximately 1 month without intervention (5).

Several factors should be considered in determining the appropriate treatment for BM. These include the characteristics of the primary tumor, clinical symptoms, performance status of patients, life expectancy following systemic treatment, and the patients' clinical context. Predicting the prognosis of patients with metastatic brain tumors is essential, and several scoring systems have been investigated in the past. Gaspar *et al.* proposed the recursive partition analysis (RPA) index as a prognostic tool based on a retrospective analysis of data from 1,200 patients enrolled in the Radiation Therapy Oncology Group (RTOG) clinical trial in 1997 (6). However, the RTOG-RPA index has some limitations. For instance, it does not consider the primary tumor site and the number of metastases. Another index is the graded prognostic assessment (GPA), proposed by Sperduto *et al.* based on the results of a multivariable analysis of data from several RTOG clinical studies in 2008 (7). This method assigned scores to significant risk factors according to their importance and predicted the survival for each group. The GPA was later developed into the diagnosis-specific GPA (ds-GPA), which took the primary tumor site into account (8).

Local treatment options for BM include surgical resection, whole brain radiotherapy (WBRT), and stereotactic radiotherapy (SRT). Although WBRT has been used for a long time, it is well known to cause a decline in cognitive function after several months of therapy (9). Recent advancements in systemic therapy like molecular targeted therapies and immune checkpoint inhibitors contributed to the less frequent application of WBRT resulted in the avoidance of such late-phase adverse events in BMs (10). On the other hand, SRT is known to provide better local tumor control and fewer adverse events for patients with limited number of BM than WBRT (11). Gamma knife radiosurgery (GKRS), as a treatment option of SRT, has the benefit of targeting accuracy and a steep dose fall-off (12), which enables selective high-dose irradiation to the BM and reduces irradiation to the normal brain tissue around the BM.

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Key Words: Gamma knife radiosurgery, brain metastasis, prognostic factor.

To determine the optimal treatment for BM, it is necessary to identify prognostic factors. We conducted at single-institutional based retrospective study to identify prognostic and therapeutic factors for GKRS in the modern era. We analyzed the treatment outcome with GKRS regarding overall survival (OS) and intracranial progression-free survival (IPFS). Factors associated with clinical outcomes were also evaluated.

Patients and Methods

Data collection. A retrospective review was performed at our institution. The inclusion criteria were as follows: 1) Patients with radiographic evidence of BM on pretreatment MRI or CT, 2) Patients treated with single-fraction GKRS, and 3) Patients treated between June 2013 and March 2018. Three patients without any follow-up medical records were excluded. The clinical conditions of patients were prospectively collected at the time of the hospital visit, whereas data for patients who dropped out of our follow-up or returned to the referral hospital were collected by telephone. Approval was obtained from our institutional review board, and written informed consent was obtained from all patients for the treatment.

Details of GKRS techniques and Post-GKRS management. All treatments were performed using the Leksell Gamma knife 4C (Elekta Instruments, Stockholm, Sweden). On the day of treatment, the Leksell stereotactic frame (Elekta Instruments) was applied under local anesthesia, supplemented with intravenous conscious sedation. The patient then underwent stereotactic imaging of gadolinium-enhanced MRI or CT (if MRI was contraindicated) to define the precise shape, volume, and three-dimensional coordinates of tumors. Image-based planning was performed using the Leksell GammaPlan (Elekta Instruments). A dose of 20 Gy was generally prescribed to the 50% isodose line. However, doses were occasionally changed, depending on the tumor location, tumor diameter, histology of primary site or the patient's performance status. A follow-up brain MRI was usually performed at 3-month intervals depending on patient's condition. The follow-up images were evaluated by independent neurosurgeons and radiologists.

Statistical analysis. OS was defined as the intervals from the date of GKRS until the date of death and IPFS was defined as the intervals from the date of GKRS until the date of death or intracranial progression such as local recurrence, parenchymal or leptomeningeal metastasis. Survival curves were calculated using the Kaplan–Meier method. The following dichotomized covariates were collected for analysis: age (<67 years compared with ≥67 years), gender (male compared with female), primary organs (lung compared with others), number of treated tumors (1 compared with ≥2), maximal diameter of BM (<17 mm compared with ≥17 mm), prescription dose (<20 Gy compared with ≥20 Gy), history of resection (yes compared with no), history of WBRT (yes compared with no), history of systemic therapy (yes compared with no), active extracranial disease (yes compared with no), and pretreatment Karnofsky performance score (KPS, <80% compared with ≥80%). Continuous variables (age, number of treated tumors, maximal diameter of BM, and prescription dose) were dichotomized using a median split technique.

Log-rank test was used to compare survival curves stratified by the covariates. Univariate and multivariate Cox proportional hazards regression analyses were used to calculate the hazard ratios of the factors associated with OS and IPFS. Multivariable Cox regression analysis was conducted using Bayesian information criterion for model selection. Differences were considered statistically significant at p-values <0.05. All data analyses were performed using R software (version 2.4-0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinical characteristics of the patients. A total of 131 consecutive patients were included in this study, of which 66 were male (50%). Patient characteristics are provided in Table I. Median follow-up period was 16.0 months (range=1.5-61.5 months). The median KPS was 90 (range=30-100). The most common primary site was the lung (N=55, 42%), followed by the breast (N=21, 16%), kidney (N=14, 11%), the upper gastrointestinal tract (N=10, 8%), the lower gastrointestinal tract (N=10, 8%), and the gynecologic organ (N=7, 5%). Other primary sites included the melanoma, pancreas, maxillary sinus, bladder, prostate, and peritoneum.

Survival analysis. The OS and IPFS curves calculated using the Kaplan–Meier method are shown in Figures 1 and 2, respectively. For the entire patient cohort, the median OS was 13.4 months [95% confidence interval (CI)=7.7-17.8 months]. The 1-year and 2-year OS rates were 51.1% and 34.1%, respectively. The median IPFS was 5.5 months (95%CI=4.1-7.0 months). The 1-year and 2-year IPFS rates were 29.7% and 15.1%, respectively.

Stratified by GPA score, the median OS was 2.5 months for GPA 0.0-1.0, 8.4 months for GPA 1.5-2.5, 44.1 months for GPA 3.0, and 18.0 months for GPA 3.5-4.0 (Figure 3).

Log-rank test confirmed that the following categorized factors were associated with worse OS rate: male (41.4% *vs*. 61.3% at 1 year, p=0.036), 2 or more BMs (36.3% *vs*. 67.1% at 1 year, p<0.001), history of systemic therapy (45.5% *vs*. 67.8% at 1 year, p=0.035), and active extracranial disease (45.9% *vs*. 70.6% at 1 year, p=0.004). The OS curves stratified by these factors are shown in Figures 4, 5, 6, and 7, respectively. Based on the multivariable Cox proportional hazards regression analyses, increased number of BMs [hazard ratio (HR)=0.42, 95%CI=0.27-0.67, p<0.001], history of systemic therapy (HR=2.23, 95%CI=1.28-3.89, p=0.005), and active extracranial disease (HR=2.49, 95%CI=1.30-4.76, p=0.006) were independent prognostic factors influencing OS (Table II).

Log-rank test also showed that the following factors were significantly worse prognostic factors for IPFS: 2 or more BMs (15.7% *vs*. 45.0% at 1 year, p<0.001) and active extracranial disease (25.5% *vs*. 45.1% at 1 year, p=0.034).

Table I. *Patient characteristics of 131 consecutive patients treated in our institution by single-fraction gamma knife radiosurgery.*

Variables	Number (percent)
Sample size	131
Age (y. o.)	Median 67 (range=39-89)
KPS (%)	Median 90 (range=30-100)
Gender	
Male	66 (50%)
Female	65 (50%)
Primary	
Lung	57 (44%)
Breast	21 (16%)
Kidney	14 (11%)
Upper gastrointestinal tract	10 (8%)
Lower gastrointestinal tract	10 (8%)
Gynecologic organ	7 (5%)
Others	12 (9%)
Dose (Gy)	Median 20 (range=15-24)
Number of treated tumors	
1	62 (47%)
2	20 (15%)
3 or more	43 (37%)
Diameter (mm)	Median 16 (range=3–45)
Resection	
Yes	6 (5%)
No	125 (95%)
WBRT	
Yes	15 (11%)
No	116 (89%)
Systemic therapy	
Yes	99 (76%)
No	32 (24%)
Extracranial disease	
Yes	102 (78%)
No	29 (22%)

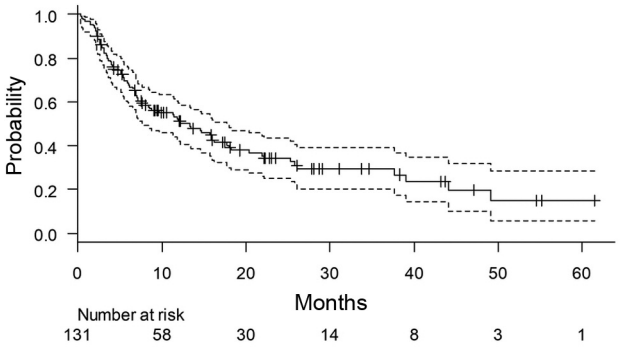

Figure 1. *Patients' overall survival curve estimated by the Kaplan–Meier method. The dashed lines illustrate 95% confidence intervals.*

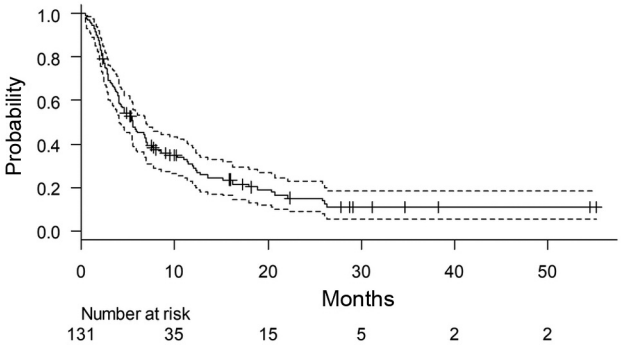

Figure 2. *Patients' intracranial progression-free survival curve estimated by the Kaplan–Meier method. The dashed lines illustrate 95% confidence intervals.*

Multivariable Cox proportional hazards regression analyses showed that 2 or more BMs (HR=0.39, 95%CI=0.26-0.59, $p<0.001$) and history of systemic therapy (HR=1.97, 95%CI=1.23-3.19, $p=0.005$) had a significantly poor IPFS as independent factors (Table III).

Discussion

The present study showed a median survival of 13.4 months, a result compatible with those of previous studies (13-16). Our study also revealed prognostic factors for OS and IPFS.

A significant prognostic factor that remained for both IPFS and OS after multivariable analysis was the number of BMs. Previously, the number of BMs has been identified as a prognostic factor in a multi-institutional prospective study (JLGK0901) (14). The study found a median OS time of 12.0 months for all patients after GKRS, and only 1 BM was a statistically significant better prognostic factor compared to 2 or more BMs ($p<0.001$). The JLGK0901 study also revealed that in terms of OS, patients with 5-10 BMs were not inferior to patients with 2-4 BMs under GKRS treatment. This indicated that GKRS could also be an effective treatment for patients with more than 4 BMs, not only 1-3.

History of systemic therapy was also a significant predictor of worse OS and IPFS in the present study. This might be explained by the fact that the systemic therapy group included more patients with advanced-stage disease. Most cytotoxic chemotherapies have very limited therapeutic efficacy for brain tumors due to the blood-brain barrier (17). Research on the molecular environment of cancer in recent years has led to molecular targeted therapy and immunotherapy (which target molecules specific to cancer cells) playing a major role in systemic treatment (18). The effects of these novel systemic therapies on intracranial lesions have also been reported. Osimertinib, a third-generation irreversible epidermal growth factor receptor

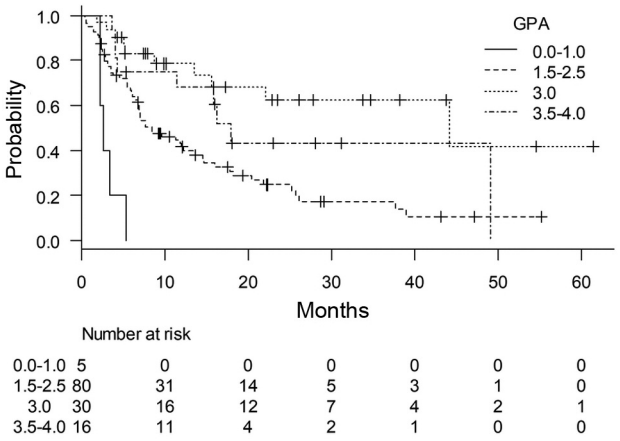

Figure 3. *Overall survival curve estimated by the Kaplan–Meier method for each level of the graded prognostic assessment (GPA).*

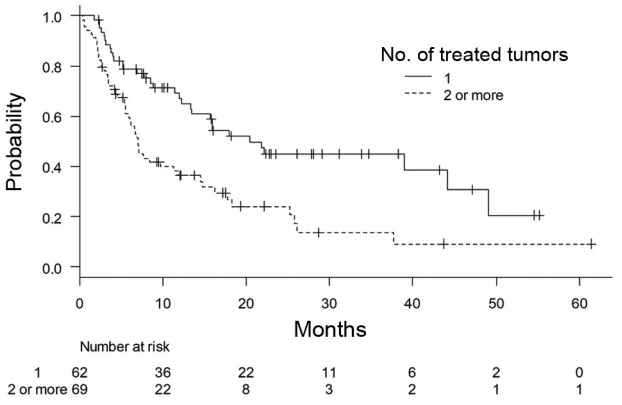

Figure 5. *Overall survival curve estimated by the Kaplan–Meier method stratified by the number of treated tumors.*

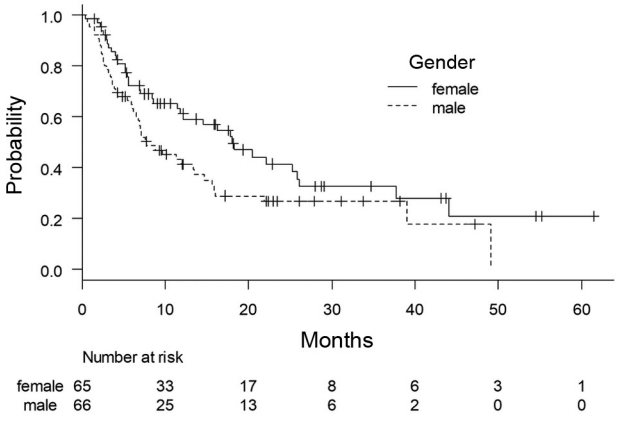

Figure 4. *Overall survival curve estimated by the Kaplan–Meier method stratified by gender.*

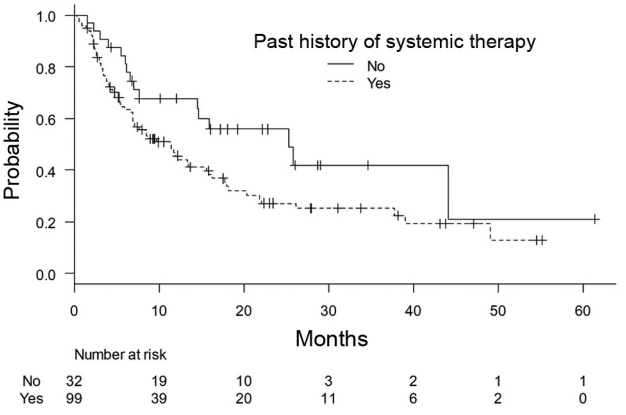

Figure 6. *Overall survival curve estimated by the Kaplan–Meier method stratified by the existence of history of systemic therapy.*

(EGFR) tyrosine kinase inhibitor, exerts clinical activity against central nervous system (CNS) metastases (19). In a meta-analysis of 15 studies involving 324 patients with metastatic EGFR mutation-positive non-small-cell lung carcinoma with intracranial metastatic disease, the osimertinib treatment group had a CNS objective response rate of 64 % (95%CI=53-76%) and a CNS disease control rate of 90% (95%CI=85-93%) (20). The past few years have also seen the wide clinical use of immunotherapy, leading to new approaches to cancer treatment. A recent phase II trial revealed the efficacy of the immune checkpoint inhibitor pembrolizumab for BMs in patients with advanced non-small cell lung cancer (21). The primary endpoint of the study was metastatic brain tumor overall response rate (ORR), which was 29.7% (N=11/37 patients, 95%CI=15.9%-47.0%) in the

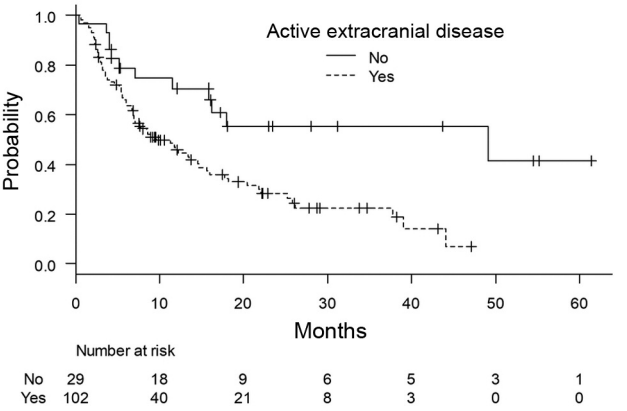

Figure 7. *Overall survival curve estimated by the Kaplan–Meier method stratified by the existence of active extracranial disease.*

Table II. *Univariate and multivariate Cox proportional hazards regression analysis of overall survival.*

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Age (<66 y.o. *vs.* ≥67 y.o.)	0.84 (0.54-1.30)	0.429		
Gender (Male *vs.* Female)	1.60 (1.03-2.47)	0.036		
Primary (Lung *vs.* Others)	1.23 (0.79-1.90)	0.354		
Number of treated tumors (1 *vs.* ≥2)	0.45 (0.29-0.70)	<0.001	0.42 (0.27-0.67)	<0.001
Diameter (<17 mm *vs.* ≥17 mm)	0.92 (0.60-1.42)	0.702		
Peripheral dose (<20 Gy *vs.* ≥20 Gy)	1.34 (0.84-2.15)	0.222		
Resection (Yes *vs.* No)	0.64 (0.16-2.61)	0.535		
WBRT (Yes *vs.* No)	1.44 (0.79-2.61)	0.229		
Systemic therapy (Yes *vs.* No)	1.78 (1.03-3.07)	0.035	2.23 (1.28-3.89)	0.005
Extracranial disease (Yes *vs.* No)	2.60 (1.37-4.94)	0.004	2.49 (1.30-4.76)	0.006
KPS (<80% *vs.* ≥80%)	1.42 (0.90-2.23)	0.137		

Table III. *Univariate and multivariate Cox proportional hazards regression analysis of intracranial progression free survival.*

Variable	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Age (<66 y.o *vs.* ≥67 y.o)	0.98 (0.66-1.44)	0.906		
Gender (Male *vs.* Female)	1.47 (0.99-2.17)	0.054		
Primary (Lung *vs.* Others)	1.07 (0.72-1.57)	0.753		
Number of treated tumors (1 *vs.* ≥2)	0.45 (0.31-0.68)	<0.001	0.39 (0.26-0.59)	<0.001
Diameter (<17 mm *vs.* ≥17 mm)	0.96 (0.65-1.42)	0.852		
Peripheral dose (<20 Gy *vs.* ≥20 Gy)	1.04 (0.67-1.59)	0.876		
Resection (Yes *vs.* No)	0.98 (0.36-2.66)	0.965		
WBRT (Yes *vs.* No)	1.10 (0.62-1.95)	0.738		
Systemic therapy (Yes *vs.* No)	1.56 (0.98-2.48)	0.063	1.97 (1.23-3.19)	0.005
Extracranial disease (Yes *vs.* No)	1.72 (1.04-2.83)	0.034		
KPS (<80% *vs.* ≥80%)	1.19 (0.79-1.79)	0.408		

cohort for patients with a PD-L1 expression of ≥1%. Recently, the combination of immune checkpoint inhibitors and radiotherapy has shown promise (22). The remarkable development of these systemic therapies could essentially improve the OS and IPFS of BM patients; however, the history of systemic therapy was rather the worse predicting factor. Differences in patient background and the effects of selection bias could not be denied. Recruitment of more BM patients with longer follow-up periods is desirable.

In the present study, we analyzed the treatment modality of GKRS alone. The addition of WBRT to GKRS is controversial in the treatment of BMs. In a meta-analysis by Sahgal *et al*., there was no significant difference in OS rate between the stereotactic radiosurgery (SRS) group and the WBRT plus SRS group (OS=86% and 85%, respectively; HR=1.01, 95%CI=0.93-1.10, p=0.94) (15). They also found a statistically significant difference in the intracranial exacerbation rate: 57% in the SRS group and 24% in the SRS plus WBRT group (HR=2.35, 95%CI=1.78-3.11, p<0.001). While the addition of whole-brain irradiation can reduce intracranial recurrence without a favorable impact on OS, WBRT + SRS can cause significant cognitive decline compared to SRS alone. A randomized phase III clinical trial examined 213 patients with 1 to 3 BMs who were randomly assigned to the WBRT + SRS arm or SRS alone arm. At 3 months post-irradiation, 91.7% of the patients in the WBRT + SRS arm had cognitive decline, compared to 63.5% of the patients in the SRS arm. The quality of life was also better in patients treated with SRS alone (16). Since no significant difference in OS was found, they concluded that patients with a limited number of BMs should be treated with SRS alone. However, Sperduto *et al*. found that for patients in the good prognosis group, SRS + WBRT had a significantly more favorable effect on OS rate compared to SRS alone,

according to a subset analysis of the RTOG 9508 trial (23). These results show that the addition of WBRT to GKRS should be carefully evaluated before execution.

The present study has some limitations. Because of its retrospective nature, patient selection bias is possible. For patients who were censored due to transfer to other hospitals, information about their disease after transfer has become unknown. We attempted to contact these hospitals via telephone to obtain information about these patients; however, some information could not be obtained. Another potential limitation is the difficulty involved in accurately distinguishing among local failure, tumor pseudo-progression, and radiation necrosis. We made these clinical diagnoses based on the clinical course and radiological imaging studies. However, these clinical diagnoses are not always correct, and they contribute to the inaccuracy of IPFS. Differential diagnosis between radiation necrosis and local recurrence is an important clinical issue; however, it is difficult to differentiate them, even with the use of gadolinium-enhanced MRI or positron emission tomography (24).

In conclusion, this study identified that the number of BM and the history of systemic therapy are associated with patient OS and IPFS, which provides insight into a more appropriate treatment strategy for patients with BM. These parameters could be a practical tool for predicting patient prognosis or avoiding over-treatment. Further prospective studies are needed to validate the prognostic value of these parameters.

Conflicts of Interest

The Authors declare no competing interests in relation to this study.

Authors' Contributions

Acquisition of data: T.N.; Analysis and interpretation of data: T.N and A.K.; Drafting the article: T.N.; Critically revising the article: A.K, Y.S, and M.K.; Study supervision: M.S, N.S, and H.Y.; All Authors participated in this study approved the final version of the manuscript.

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