

Original Article

Non-Small Cell Lung Cancer Patients with Brain Metastases and Limited Access to Systemic Therapy

Kyrhatii Trikhirhisthit¹, Aniwa Berpan², Sunee Neesanun³¹Division of Radiation Oncology, Department of Radiology, Sawanpracharak Hospital, Nakhonsawan, Thailand²Division of Radiation Oncology, Department of Radiology, Faculty of Medicine Vajira Hospital, Navamindradhiraj University, Bangkok, Thailand³Division of Oncology, Department of Internal Medicine, Sawanpracharak Hospital, Nakhonsawan, Thailand

Cite this article as: Trikhirhisthit K, Berpan A, Neesanun S. Non-small cell lung cancer patients with brain metastases and limited access to systemic therapy. *Thorac Res Pract.* [Epub Ahead of Print]

ABSTRACT

OBJECTIVE: We aimed to identify prognostic factors associated with overall survival in patients with brain metastases from non-small cell lung cancer (BM-NSCLC) who had limited access to systemic therapy.

MATERIAL AND METHODS: We retrospectively analyzed 83 patients with BM-NSCLC. Data collected included age, sex, performance status, histology, neurologic symptoms, extracranial metastasis (ECM), and receipt of whole-brain radiotherapy (WBRT) and systemic treatment. Associations between these factors and time to death were assessed using Cox proportional hazards regression analysis.

RESULTS: The mean age of the patients was 63.1±8.9 years. Approximately 30% of patients had ECM, whereas 14% received systemic treatment. Three-quarters of the cohort underwent WBRT. The median survival time was 2.7 months [95% confidence interval (CI): 2.2–4.1 months]. The 6-month and 1-year survival probabilities were 26.5% (95% CI: 17.6%–36.3%) and 9.6% (95% CI: 4.5%–17.1%), respectively. Multivariable analysis demonstrated that ECM was significantly associated with an increased risk of death [adjusted hazard ratio (aHR): 4.22, 95% CI: 1.27–14.0, $P = 0.019$, for newly diagnosed lung cancer; aHR: 6.33, 95% CI: 1.62–24.79, $P = 0.008$, for controlled primary lung cancer with ECM; and aHR: 11.32, 95% CI: 2.89–56.1, $P = 0.003$, for uncontrolled primary lung cancer and ECM]. Receipt of systemic treatment was significantly associated with a lower risk of death (aHR: 0.39, 95% CI: 0.18–0.80, $P = 0.011$). WBRT was not significantly associated with improved survival (aHR: 0.79, 95% CI: 0.43–1.44, $P = 0.441$).

CONCLUSION: The presence of ECM and the absence of systemic treatment were significantly associated with shorter survival in patients with BM-NSCLC.

KEYWORDS: Overall survival, prognostic factors, systemic therapy

Received: 07.05.2026

Revision Requested: 04.06.2026

Last Revision Received: 22.07.2026

Accepted: 24.07.2026

Epub: 26.10.2026

INTRODUCTION

Brain metastases (BM) are the most common brain tumors, occurring approximately 10 times more frequently than primary malignant brain tumors.¹ Non-small cell lung cancer (NSCLC) is the most common primary source of BM, with intracranial spread occurring in approximately 9% of patients.² Despite advances in treatment, survival remains dismal, particularly in patients with BM.³ Historically, whole brain radiotherapy (WBRT) with or without surgery was the mainstay of treatment. However, advances in cancer therapy have shifted practice toward stereotactic radiosurgery (SRS) and systemic pharmacotherapy. The European Association of Neuro-Oncology-European Society for Medical Oncology 2021 guidelines recommend SRS or systemic therapy rather than WBRT for appropriate patients.⁴ In asymptomatic patients with NSCLC and BM, upfront immune checkpoint inhibitors with or without systemic chemotherapy are recommended in the absence of actionable oncogenic driver alterations, whereas targeted systemic therapy is preferred when such alterations are present. Nevertheless, in resource-limited settings, access to advanced radiotherapy and high-priced systemic agents remains restricted. Furthermore, approximately two-thirds of patients with BM from NSCLC die due to extracranial

Corresponding author: Aniwa Berpan, MD, e-mail: berpanmaster@hotmail.com



Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of Turkish Thoracic Society.
Content of this journal is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.

disease rather than intracranial progression,⁵ underscoring the importance of effective systemic treatment.

Multiple studies have evaluated prognostic factors in patients with BM who were treated with WBRT. Gilbride et al.⁶ developed a prognostic nomogram based on data from over 1,000 patients with various primary cancers. Nieder et al.⁷ identified key prognostic variables in NSCLC, including performance status, age, sex, primary cancer status, extracranial disease, number of BM, histology, lesion volume, neurological symptoms, steroid use, BM status, and molecular markers such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations. However, data from settings with restricted access to systemic therapy remain limited. Therefore, this study aimed to investigate prognostic factors associated with overall survival (OS) and evaluate survival outcomes in patients with BM-NSCLC in a resource-constrained healthcare environment.

MATERIAL AND METHODS

We conducted a retrospective cohort study of patients treated at a university-affiliated tertiary care center in Thailand between January 2019 and December 2019. Eligible patients were adults aged >18 years with histologically confirmed primary NSCLC and with BM verified by computed tomography or magnetic resonance imaging. Patients with concomitant malignancies were excluded. The study was approved by the Sawanpracharak Hospital Ethics Committee (COA NO. 66/2563) on October 29, 2020, for retrospective data analysis, and the requirement for informed consent was waived.

The primary outcome was OS, defined as the time from diagnosis of BM to death from any cause or last follow-up. Survival status was ascertained as of November 30, 2020, using a local death registry and hospital records. Patients who were alive at the cut-off date were censored in the survival analysis.

Clinical and treatment variables were collected as potential prognostic factors, including age, sex, Karnofsky performance status (KPS), histology, neurological symptoms, extracranial disease status, and receipt of further systemic therapy and WBRT. Definitions and scales were selected based on established literature and clinical practice. Patients were categorized into four groups according to the status of the primary lung tumor and extracranial metastases (ECM): (1) controlled primary lung cancer with no ECM, defined as controlled primary lung disease without evidence of extracranial metastatic disease; (2) controlled primary lung cancer with ECM, defined as controlled primary lung disease in the presence of ECM; (3) uncontrolled primary lung cancer and ECM, defined as uncontrolled primary lung disease and progressive extracranial

metastatic disease despite previous treatment; and (4) newly diagnosed primary lung cancer, defined as patients presenting with newly diagnosed primary lung cancer. Primary lung cancer was considered controlled if there was no radiographic or clinical evidence of progression at the time of BM diagnosis, as determined by the treating physician.

Statistical Analysis

Survival outcomes were estimated using Kaplan-Meier analysis. Associations between covariates and survival were evaluated using Cox proportional hazards regression. The proportional hazards assumption was assessed using Schoenfeld residuals. Survival rates at 1, 3, 6, and 12 months, as well as median survival time, were calculated. Hazard ratios (HRs) and adjusted hazard ratios (aHRs), with corresponding 95% confidence intervals (CIs), were reported for univariable and multivariable analyses, respectively. A *P* value <0.05 was considered statistically significant.

Adjusted survival functions from the multivariable Cox regression model were plotted for significant prognostic variables at representative covariate values. All statistical analyses were performed using Stata/SE version 17 (StataCorp LP, College Station, TX, USA).

RESULTS

Eighty-three patients with BM-NSCLC were included in the study, of whom 81 had died at the time of analysis. Clinical characteristics are summarized in Table 1. The mean age was 63.1±8.9 years. Most patients had adenocarcinoma histology and presented with significant neurological symptoms. Approximately half of the cohort were classified as class II by recursive partitioning analysis (RPA). The majority of patients (65%) had BM at the time of initial lung cancer diagnosis. Nearly 30% had ECM, whereas 14% received systemic treatment. Approximately three-quarters of patients underwent WBRT, and fewer than 15% of patients underwent genetic mutation testing.

The median survival time was 2.7 months (95% CI: 2.2–4.1 months). Survival probabilities are shown in Figure 1. The 1-month, 3-month, 6-month, and 1-year survival rates were 78.3% (95% CI: 68.0%–88.6%), 47.0% (95% CI: 36.0%–57.2%), 26.5% (95% CI: 17.6%–36.3%), and 9.6% (95% CI: 4.5%–17.1%), respectively.

Both univariable and multivariable Cox proportional hazards regression analyses were performed, and the proportional hazards assumption was satisfied. In univariable analysis, age >65 years, receipt of systemic treatment, and receipt of WBRT were significantly associated with a reduced risk of death, whereas the presence of extracranial disease was significantly associated with an increased mortality risk. In multivariable analysis, systemic treatment remained a significant, favorable prognostic factor for OS (aHR: 0.39, 95% CI: 0.18–0.80, *P* = 0.011). Extracranial disease was identified as an unfavorable prognostic factor, with risk progressively increasing according to disease status (for newly diagnosed lung cancer: aHR: 4.22, 95% CI: 1.27–14.0, *P* = 0.019; for controlled primary lung cancer with ECM: aHR: 6.33, 95% CI: 1.62–24.79, *P* = 0.008; and for uncontrolled primary lung cancer ECM:

Main Points

- Extracranial metastasis and receipt of subsequent systemic treatment were significantly associated with overall survival (OS).
- Patients with newly diagnosed disease had better OS than those with uncontrolled cancer.
- Whole brain radiotherapy did not provide a significant OS benefit.

aHR: 11.32, 95% CI: 2.89–56.1, $P = 0.003$). Notably, WBRT was not significantly associated with improved survival in the multivariable model (aHR: 0.79, 95% CI: 0.43–1.44, $P = 0.441$) (Table 2). Estimated survival functions for key prognostic variables are shown in Figures 2 and 3.

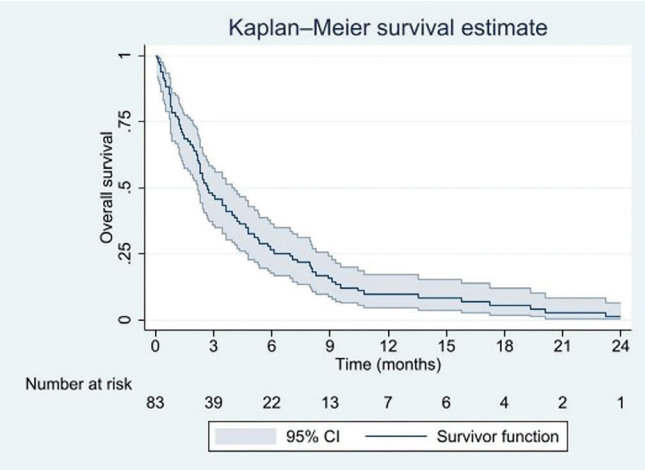


Figure 1. Overall survival
CI: confidence interval

Table 1. Clinical characteristics	
Characteristics	n = 83
Age (mean ± SD)	63.1±8.9
Age >65	37 (45%)
Female	36 (43%)
KPS ≥70	44 (53%)
Histology	
• Adenocarcinoma	61 (73%)
• Non-adenocarcinoma	22 (27%)
EGFR/ALK mutation	
• Positive	5 (6%)
• Negative	7 (8%)
• Unknown	71 (86%)
Neurological symptoms	
• None	3 (4%)
• Mild	10 (12%)
• Major	70 (84%)
Extracranial disease	
• Controlled primary lung cancer with no ECM	5 (6%)
• Controlled primary lung cancer with ECM	16 (19%)
• Uncontrolled primary lung cancer and ECM	8 (9%)
• Newly diagnosed lung cancer	54 (65%)
Further systemic treatment	12 (14%)
WBRT	62 (75%)
RPA	
• Class I	3 (4%)
• Class II	43 (52%)
• Class III	37 (44%)

ALK: anaplastic lymphoma kinase, ECM: extracranial metastasis, EGFR: epidermal growth factor receptor, KPS: Karnofsky performance status, WBRT: whole brain radiotherapy, SD: standard deviation, RPA: recursive partitioning analysis

DISCUSSION

In patients with BM-NSCLC who had limited access to anticancer therapy, the receipt of further systemic treatment and the presence of ECM were identified as significant favorable and unfavorable prognostic factors for OS, respectively. These findings highlight the critical role of extracranial disease control in BM-NSCLC; extracranial disease control is typically managed with systemic therapies.

The RPA classification, introduced in 1997 and validated in 2000 by Gaspar et al.^{8,9}, was developed to estimate survival in patients with BM using variables such as performance status, age, control of the primary tumor, and ECM, and it stratifies patients into three prognostic classes. Subsequently, multiple prognostic scoring systems have been developed. The Score Index for Radiosurgery (SIR) in BM, which incorporates age, performance status, ECM status, number of brain lesions, and largest lesion volume, was derived from a cohort of 65 patients.¹⁰ In a larger study involving 110 patients, Lorenzoni et al.¹¹ developed the basic score (BS) for BM, which included performance status, primary tumor control, and ECM. Their analysis showed that SIR and BS-BM were significantly associated with survival, whereas RPA was not. Rades et al.¹² further identified age, performance status, ECM, interval from tumor diagnosis to radiotherapy, and number of BMs as significant prognostic factors in survival scoring systems. Lagerwaard et al.¹³ reported that performance status, systemic disease status, steroid response, and primary tumor site were significant predictors of survival. Barnholtz-Sloan et al.¹⁴ developed a nomogram incorporating primary site, histology, primary tumor status, metastatic spread, age, KPS, and number of brain lesions to estimate survival.

In BM-NSCLC specifically, Chao et al.¹⁵ found that only performance status and ECM were significant predictors of survival, whereas Golden et al.¹⁶ reported that age <65 years, absence of extracranial disease, and having ≤3 BM were favorable prognostic factors. Agarwal et al.¹⁷ identified factors such as sex, performance status, and EGFR mutation status as relevant in determining which patients may not benefit from WBRT. In the most recent NSCLC graded prognostic assessment (GPA), Sperduto et al.³ included programmed death-ligand 1 (PD-L1) expression as a prognostic variable and reaffirmed the importance of EGFR and ALK status, performance status, age, number of BM, and ECM. However, in the present study, molecular profiling was performed on only 14% of patients, and no PD-L1 testing was available, reflecting limited access to comprehensive diagnostic and therapeutic resources.

Across virtually all published prognostic models, ECM consistently appears as a key determinant of survival, underscoring its strong prognostic impact. This observation aligns with the present findings; ECM demonstrates a graded effect on mortality risk. In multivariable analysis, aHRs were 6.33 (95% CI, 1.62–24.79), 11.32 (95% CI, 2.89–56.1), and 4.22 (95% CI, 1.27–14.0) for controlled primary lung cancer with ECM, uncontrolled primary lung cancer with ECM, and newly diagnosed lung cancer, respectively. The severity was more pronounced in uncontrolled extracranial disease than in controlled or treatment-naïve disease. Despite limited systemic agents, uncontrolled extracranial disease tends to be treatment-resistant, particularly to radiation, and limits eligibility for other

Table 2. Multivariable analysis of predictors of OS		
Characteristics	aHR (95% CI)	P value
Age		
≤65	1	-
>65	0.68 (0.41–1.13)	0.139
Sex		
Male	1	-
Female	1.47 (0.87–2.48)	0.148
KPS score		
<70	1	-
≥70	0.82 (0.47–1.42)	0.469
Histology		
Adenocarcinoma	1	-
Non-adenocarcinoma	0.63 (0.34–1.16)	0.140
Neurological symptoms		
• None	1	-
• Mild	3.78 (0.59–24.2)	0.161
• Major	2.25 (0.44–11.5)	0.330
Extracranial disease		
• Controlled primary lung cancer with no ECM	1	-
• Controlled primary lung cancer with ECM	6.33 (1.62–24.79)	0.008
• Uncontrolled primary lung cancer and ECM	11.32 (2.89–56.1)	0.003
• Newly diagnosed lung cancer	4.22 (1.27–14.0)	0.019
Further systemic treatment		
No	1	-
Yes	0.39 (0.18–0.80)	0.011
WBRT		
No	1	-
Yes	0.79 (0.43–1.44)	0.441

CI: confidence interval, ECM: extracranial metastasis, aHR: adjusted hazard ratio, KPS: Karnofsky performance status, WBRT: whole brain radiotherapy, OS: overall survival

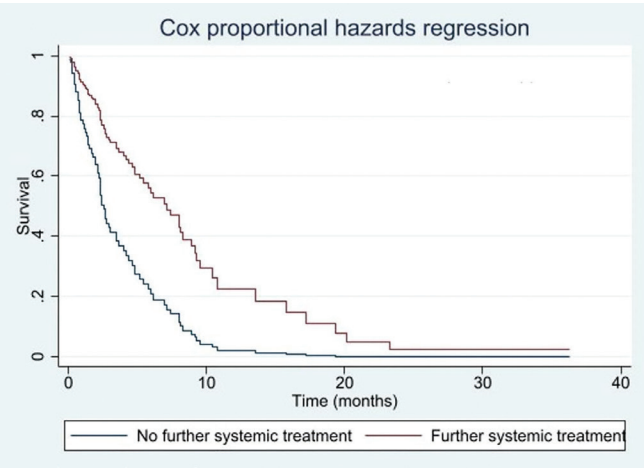


Figure 2. Adjusted OS functions derived from the Cox proportional hazards regression model comparing patients who did and did not receive further systemic treatment. Adjusted survival functions estimated from the multivariable Cox proportional hazards regression model. The following covariates were held constant: age, sex, Karnofsky performance status, histology, neurological symptoms, extracranial metastasis status, and receipt of whole-brain radiotherapy

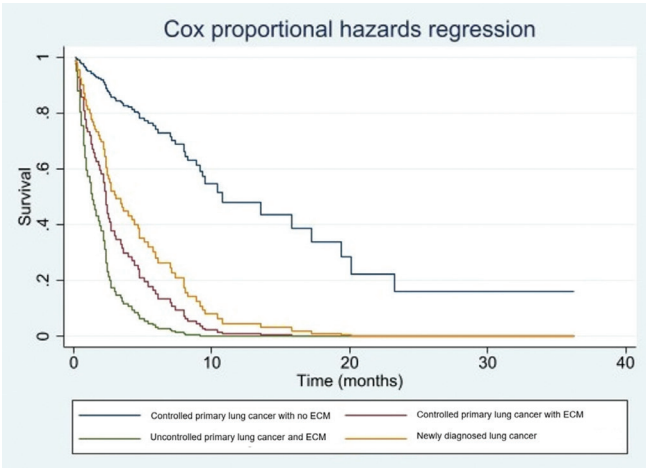


Figure 3. Adjusted OS functions derived from the Cox proportional hazards regression model according to extracranial metastasis status. Adjusted survival functions estimated from the multivariable Cox proportional hazards regression model. The following covariates were held constant: age, sex, Karnofsky performance status, histology, neurological symptoms, receipt of further systemic treatment, and receipt of whole-brain radiotherapy

ECM: extracranial metastasis

interventions, such as surgery or ablation therapy, because of the number, size, or location of the tumor. Therefore, this disease stage is likely to have a poorer prognosis. Meanwhile, the treatment-naïve disease tends to be sensitive to radiation and to possess characteristics amenable to other local treatments. Hence, the stage is associated with better survival than controlled disease. However, the nature of these disease stages requires further study to elucidate the underlying mechanisms thoroughly, enabling better assignment of treatments to each stage.

The median survival time of 2.7 months (1-year survival rate of 9.6%) in the present cohort was comparable to ones reported in the QUARTZ trial¹⁸ which were 9.2 weeks for the group with WBRT and 8.5 weeks for the group without WBRT. Half of the patients had a KPS of at least 70, and about 30% had active extracranial disease; however, only 14% received further systemic treatment in the present study. In contrast, in the QUARTZ trial, approximately two-thirds had KPS ≥ 70 with 55% having ECM, and systemic anticancer treatment was allowed, particularly after WBRT, suggesting that the present study's survival outcome was fair even with poor prognostic factors. In contrast, Kim et al.¹⁹ reported that patients with BM-NSCLC receiving chemotherapy after WBRT had a median OS of 7 months (range, 0.9–25.3 months) with a 1-year survival rate of 23%. Conversely, compared with an NSCLC GPA update,³ the least median survival was 6 months for an adenocarcinoma cohort with GPA of 0.0–1.0, which was analyzed in populations in three developed countries, provided with abundant treatment resources. Historically, systemic chemotherapy was the standard treatment for advanced NSCLC. In 16 randomized controlled trials (RCTs), chemotherapy increased 12-month survival by 9% (from 20% to 29%) and produced an absolute median survival gain of 1.5 months compared with best supportive care alone, as demonstrated in a Cochrane review in 2010.²⁰ No strong evidence suggested a survival benefit of chemotherapy in patients with BMs, which may be explained by the inability of cytotoxic chemotherapy to cross the blood-brain barrier. Currently, immunotherapy with or without chemotherapy is recommended for patients without actionable driver alterations, depending on PD-L1 expression, whereas targeted therapy is recommended for patients with actionable driver mutations.^{21,22} The aforementioned statement referred to patients with BMs.^{4,23} Although no phase III RCT has demonstrated that systemic anticancer therapy improves OS in patients with BM-NSCLC, several studies have shown potential CNS efficacy of specific agents. For example, a longer median CNS progression-free survival was reported among patients with untreated EGFR-mutated advanced NSCLC who received osimertinib than among those who received gefitinib or erlotinib, based on a preplanned exploratory analysis of the FLAURA study.²⁴ In the ALEX study, patients with stage III–IV ALK-positive NSCLC were randomized to receive alectinib or crizotinib. Notably, among patients with baseline CNS metastases, OS was significantly longer in the alectinib group.²⁵ Furthermore, most patients with BM had extracranial diseases. According to German data, ECM sites were observed in 60% of 5,074 patients with BM, and 50% of patients had lung cancer.²⁶ Meanwhile, 32%, 55%, and 62% of patients had active extracranial disease in JLGK0901 (76% lung cancer),²⁷ QUARTZ (100% NSCLC),¹⁸ and NRG CC001

(60% lung cancer)²⁸ trials. Around 70% of the patients in the present cohort had controlled extracranial disease, indicating that some patients experienced delayed treatment or limited access to treatment resources, particularly systemic therapy in this setting. The role of systemic treatment was given marked consideration in patients receiving intracranial radiation who had an active extracranial tumor, to control the disease outside the brain or even to improve survival.

Study Limitations

This study has limitations. First, its retrospective single-center design may limit the generalizability of the findings. Second, only a small proportion of patients received systemic treatment, reflecting the limited availability of these therapies during the study period; this may have reduced the statistical power to detect treatment effects. Third, molecular profiling was not routinely available, precluding analyses based on actionable genomic alterations that may influence prognosis and treatment selection. Fourth, treatment-selection bias is inherent in this retrospective study, as patients receiving systemic therapy may have had more favorable baseline characteristics despite adjustment for measured covariates. In addition, residual confounding from unmeasured factors cannot be excluded. Several estimates were associated with wide CIs, reflecting the relatively small sample size. These limitations should be considered when interpreting the results.

CONCLUSION

Among patients with BM-NSCLC, the presence of extracranial disease and the absence of systemic treatment were significantly associated with reduced OS. The poor outcomes observed in this cohort likely reflect the limited availability and accessibility of contemporary systemic therapies in resource-constrained settings. These findings should be interpreted in the broader context of global disparities in cancer care, where substantial gaps in access continue to contribute to unequal outcomes between high- and low-income countries.

Recent international initiatives, including the World Health Assembly resolution on precision medicine, have emphasized the need to improve equitable access to cancer innovations.²⁹ Potential strategies to reduce these disparities include sharing manufacturing knowledge and technology, implementing differential pricing policies, expanding international funding mechanisms, strengthening primary healthcare systems, and adopting cost-effective screening and early detection programs.³⁰ This study provides insight into the natural history of BM-NSCLC in a resource-limited setting and highlights the urgent need to improve equitable global access to effective systemic therapies.

Ethics

Ethics Committee Approval: The study was approved by the Sawanpracharak Hospital Ethics Committee (COA NO. 66/2563) on October 29, 2020.

Informed Consent: The requirement for informed consent was waived due to the retrospective nature of the study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: K.T., A.B., S.N., Concept: K.T., Design: K.T., Data Collection or Processing: K.T., Analysis or Interpretation: K.T., Literature Search: K.T., A.B., Writing: K.T., A.B., S.N.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

Data Availability Statement: The data underlying this study were obtained from Sawanpracharak Hospital. The datasets are controlled by the institution and are not publicly available because access is restricted under institutional policy to protect patient confidentiality. De-identified data may be made available from the corresponding author upon reasonable request, subject to approval by Sawanpracharak Hospital and the relevant institutional ethics requirements.

REFERENCES

- Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep*. 2012;14(1):48-54. [\[Crossref\]](#)
- Goncalves PH, Peterson SL, Vigneau FD, et al. Risk of brain metastases in patients with nonmetastatic lung cancer: analysis of the Metropolitan Detroit Surveillance, Epidemiology, and End Results (SEER) data. *Cancer*. 2016;122(12):1921-1927. [\[Crossref\]](#)
- Sperduto PW, De B, Li J, et al. Graded Prognostic Assessment (GPA) for patients with lung cancer and brain metastases: initial report of the small cell lung cancer GPA and update of the non-small cell lung cancer GPA including the effect of programmed death ligand 1 and other prognostic factors. *Int J Radiat Oncol Biol Phys*. 2022;114(1):60-74. [\[Crossref\]](#)
- Le Rhun E, Guckenberger M, Smits M, et al.; EANO Executive Board and ESMO Guidelines Committee. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. *Ann Oncol*. 2021;32(11):1332-1347. [\[Crossref\]](#)
- Thawani R, Fakhoury K, Becker K. Cause of mortality in patients with lung cancer and brain metastasis. *J Clin Oncol*. 2020;38(Suppl 15):e21743-e21743. [\[Crossref\]](#)
- Gilbride L, Siker M, Bovi J, Gore E, Schultz C, Hall WA. Current predictive indices and nomograms to enable personalization of radiation therapy for patients with secondary malignant neoplasms of the central nervous system: a review. *Neurosurgery*. 2018;82(5):595-603. [\[Crossref\]](#)
- Nieder C, Bremnes RM, Andrasschke NH. Prognostic scores in patients with brain metastases from non-small cell lung cancer. *J Thorac Oncol*. 2009;4(11):1337-1341. [\[Crossref\]](#)
- Gaspar L, Scott C, Rotman M, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys*. 1997;37(4):745-751. [\[Crossref\]](#)
- Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys*. 2000;47(4):1001-1006. [\[Crossref\]](#)
- Weltman E, Salvajoli JV, Brandt RA, et al. Radiosurgery for brain metastases: a score index for predicting prognosis. *Int J Radiat Oncol Biol Phys*. 2000;46(5):1155-1161. [\[Crossref\]](#)
- Lorenzoni J, Devriendt D, Massager N, et al. Radiosurgery for treatment of brain metastases: estimation of patient eligibility using three stratification systems. *Int J Radiat Oncol Biol Phys*. 2004;60(1):218-224. [\[Crossref\]](#)
- Rades D, Dziggel L, Haatanen T, et al. Scoring systems to estimate intracerebral control and survival rates of patients irradiated for brain metastases. *Int J Radiat Oncol Biol Phys*. 2011;80(4):1122-1127. [\[Crossref\]](#)
- Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys*. 1999;43(4):795-803. [\[Crossref\]](#)
- Barnholtz-Sloan JS, Yu C, Sloan AE, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol*. 2012;14(7):910-918. [\[Crossref\]](#)
- Chao ST, Elson P, Angelov L, et al. New classification scheme to predict survival in patients with brain metastases from non-small cell lung cancer treated with upfront stereotactic radiosurgery. *Int J Radiat Oncol Biol Phys*. 2008;72:S214-S215. [\[Crossref\]](#)
- Golden DW, Lamborn KR, McDermott MW, et al. Prognostic factors and grading systems for overall survival in patients treated with radiosurgery for brain metastases: variation by primary site. *J Neurosurg*. 2008;109 Suppl:77-86. [\[Crossref\]](#)
- Agarwal JP, Chakraborty S, Laskar SG, et al. Applying the QUARTZ trial results in clinical practice: development of a prognostic model predicting poor outcomes for non-small cell lung cancers with brain metastases. *Clin Oncol (R Coll Radiol)*. 2018;30(6):382-390. [\[Crossref\]](#)
- Mulvenna P, Nankivell M, Barton R, et al. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet*. 2016;388(10055):2004-2014. [\[Crossref\]](#)
- Kim JH, Kim HS, Kwon JH, et al. Systemic chemotherapy after cranial irradiation in patients with brain metastases from non-small cell lung cancer: a retrospective study. *Lung Cancer*. 2009;63(3):405-409. [\[Crossref\]](#)
- Non-Small Cell Lung Cancer Collaborative Group. Chemotherapy and supportive care versus supportive care alone for advanced non-small cell lung cancer. *Cochrane Database Syst Rev*. 2010;2010(5):CD007309. [\[Crossref\]](#)
- Singh N, Temin S, Baker S Jr, et al. Therapy for stage IV non-small-cell lung cancer with driver alterations: ASCO living guideline. *J Clin Oncol*. 2022;40(28):3310-3322. Update in: *J Clin Oncol*. 2023;41(5):e10-e20. Update in: *J Clin Oncol*. 2023;41(11):e31-e41. Update in: *J Clin Oncol*. 2023;41(15):e42-e50. Update in: *J Clin Oncol*. 2023;41(24):e63-e72. [\[Crossref\]](#)
- Planchard D, Popat S, Kerr K, et al.; ESMO Guidelines Committee. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv192-iv237. Erratum in: *Ann Oncol*. 2019;30(5):863-870. [\[Crossref\]](#)
- Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO Guideline. *J Clin Oncol*. 2022;40(5):492-516. Erratum in: *J Clin Oncol*. 2022;40(12):1392. [\[Crossref\]](#)

24. Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. *J Clin Oncol*. 2018;36(33):3290-3297. [\[Crossref\]](#)
25. Mok T, Camidge DR, Gadgeel SM, et al. Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol*. 2020;31(8):1056-1064. [\[Crossref\]](#)
26. Vuong DA, Rades D, Vo SQ, Busse R. Extracranial metastatic patterns on occurrence of brain metastases. *J Neurooncol*. 2011;105(1):83-90. [\[Crossref\]](#)
27. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol*. 2014;15(4):387-395. [\[Crossref\]](#)
28. Brown PD, Gondi V, Pugh S, et al.; for NRG Oncology. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG oncology CC001. *J Clin Oncol*. 2020;38(10):1019-1029. [\[Crossref\]](#)
29. World Health Assembly endorses resolution on precision medicine. WHO. Accessed June 5, 2026. [\[Crossref\]](#)
30. Tfayli AH, El-Halabi LN, Khuri FR. Global disparities in cancer care: bridging the gap in affordability and access to medications between high and low-income countries. *Cancer*. 2025;131(1):e35590. [\[Crossref\]](#)