*Original Article*

# Outcome and Prognostic Factors of Brain Metastasis From Solid Organ Tumor: A 10-Year Follow-up

Jarin Chindaprasirt MD[1], Aumkhae Sookprasert MD[1]

[1] Medical Oncology Unit, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

***Objective:*** Brain metastasis is common in various solid organ tumors and the prognosis is unfavorable. The objectives were to characterize brain metastasis patients and to study the Recursive Partition Analysis (RPA) classification as a predictor of survival.

***Materials and Methods:*** This is a retrospective analytic study, which includes 213 adult patients diagnosed with brain metastasis from solid organ tumors in Srinagarind Hospital during 2006-2010. The clinical characteristics and treatment outcome were reviewed.

***Results:*** The median survival time was 3.5 months (95% CI: 2.75-4.35). The overall survival rates at 1, 2, and 5 years were 21.6%, 8.9%, and 4.2% respectively. The 10-year survival rate was 3.1%. The independent risk factors for having inferior survival were male gender and RPA class III.

***Conclusion:*** Brain metastasis is common in lung and breast cancer and the overall survival time is short. RPA class is a simple and important prognostic factor for survival.

***Keywords:*** brain neoplasm, brain metastasis, prognostic score, whole brain radiotherapy (WBRT), RPA

**J Med Assoc Thai 2018; 101 [Suppl. 7]: S101-S106**
**Website:** http://www.jmatonline.com

The most common intracranial tumor is brain metastasis (BM), with a higher rate of incidence than primary lesion[1]. It accounts for 20-40% cancer patients[2]. Not only shortening the survival, intracranial metastasis can potentially cause the affected person to experience a functional decline, increased dependency, and can complicate other health conditions. Furthermore, it can lead to substantial healthcare cost as well as socio-economic and disability burden.

The incidence of brain metastasis is expected to increase. Since many novel treatments have shown promising results to prolong survival, cancer patients will live with the disease for a longer period of time and this would increase the time for metastasis to occur. In addition, as new technology in imaging techniques has been widely used, asymptomatic small brain lesions are detected easier[3].

Whole brain radiation has been the main treatment for many decades[4]. Currently, newer methods for brain metastasis are being evaluated; brain surgery and stereotactic radiosurgery. However, the selection of the patient, the availability of each method and the cost-effectiveness are still the problem especially in the developing country as Thailand.

The prognosis also depends on many factors. The study from Gasper et al[5] showed that the recursive partitioning analysis [RPA] classes are major indicators of outcome following therapy in brain metastasis patients. Nevertheless, a study from Germany stated that the RPA class does not predict survival in patients with four or more brain metastases[6].

Herein, the present study aimed to characterize brain metastasis patients diagnosed with solid organ tumor according to RPA classification.

**Correspondence to:**
Chindaprasirt J. Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand.
**Phone:** +66-43-363664
**E-mail:** jarich@kku.ac.th

## Materials and Methods

### *Patient demographics and clinical characteristics*

This is a retrospective observational study. All adult patients diagnosed with or referred to

**How to cite this article:** Chindaprasirt J, Sookprasert A.Outcome and Prognostic Factors of Brain Metastasis From Solid Organ Tumor: A 10-Year Follow-Up. J Med Assoc Thai 2018;101;Suppl.7: S101-S106.

Srinagarind hospital for brain metastasis from solid organ tumor during January 2006 and December 2010 were included. Baseline characteristics including age, gender, type of cancer, and survival data were reviewed. Patients were grouped into the RTOG RPA classes (Table 1): Class I include patients with Karnofsky performance status [KPS] ≥70, age less than 65 years old, controlled primary tumor, and no extra-cranial metastases. Class III includes patients with a KPS <70. All other patients belong to class II[5].

Brain metastasis was diagnosed by either histology of metastasis from the surgical specimen or by CT/MRI brain confirmed by a radiologist. Overall survival was defined as the time from diagnosis of brain metastasis to death from any cause.

### *Statistical analysis*

Baseline data were presented as percentage, mean, and standard deviation for normal distribution data. For those without normal distribution, the median and interquartile range was used. Patients were categorized by RPA status and compared by one-way ANOVA and Chi-square test. Survival analysis was performed using Kaplan-Meier method and log-rank test. Univariate and multivariate Cox regression analyses of factors affecting overall survival were used. For all statistical comparisons, a *p*-value of less than 0.05 was considered statistically significant. All data analyses were carried out using SPSS version 17.0 (Statistical Package for the Social Sciences, Chicago, IL, USA). This study was approved by the Khon Kaen University Faculty of Medicine Ethics Committee as insti-tuted by the Declaration of Helsinki.

## Results

Since 2006 to 2010, a total of 213 patients with brain metastasis from solid organ were included (95 males; 118 females). The median age at diagnosis

**Table 1.** Characteristics of brain metastasis patients according to RPA class

| Variables (n = 213) | RPA class I (n = 72, 33.8 %) | RPA class II (n = 19, 8.9 %) | RPA class III (n = 122, 57.3 %) | *p*-value |
|---|---|---|---|---|
| Age (years), median (IQR) | 51 (12) | 68 (6) | 57 (66) | <0.001* |
| Age group (years), n(%) | | | | <0.001* |
| <65 | 71 (98.6) | 0 (0) | 94 (77.0) | |
| 65 to 74 | 1 (1.4) | 17 (89.5) | 17 (13.9) | |
| ≥75 | 0 (0) | 2 (10.5) | 11 (9.0) | |
| Primary site of tumor | | | | |
| Lung | 43 (38.4) | 14 (12.5) | 55 (49.1) | 0.022* |
| Breast | 8 (29.6) | 1 (3.7) | 18 (66.7) | 0.454 |
| Gender | | | | 0.332 |
| Male | 34 (47.2) | 11 (57.9) | 50 (41) | |
| Female | 38 (52.8) | 8 (42.1) | 72 (59) | |
| KPS | | | | <0.001* |
| <70 | 0 (0) | 0 (0) | 98 (80.3) | |
| ≥70 | 72 (100) | 19 (100) | 24 (19.7) | |
| Number of metastasis | | | | 0.042* |
| Single | 34 (47.2) | 9 (47.4) | 37 (30.3) | |
| Multiple | 38 (52.8) | 10 (52.6) | 85 (69.7) | |
| Extra-cranial metastasis | | | | <0.001* |
| Yes | 19 (26.4) | 5 (26.3) | 74 (60.7) | |
| No | 53 (73.6) | 14 (73.7) | 48 (39.3) | |
| Treatment modality | | | | |
| WBRT | 59 (81.9) | 13 (68.4) | 77 (63.1) | 0.022* |
| Surgery | 17 (23.6) | 5 (26.3) | 12 (9.8) | 0.018* |
| Chemotherapy | 1 (1.4) | 0 (0) | 2 (1.6) | 1.000 |
| Palliative care | 5 (6.9) | 2 (10.5) | 21 (17.2) | 0.116 |

RPA = recursive partition analysis; IQR = interquartile range; KPS = Karnofsky performance status; WBRT = whole brain radiation

was 55 years (range 21 to 87). Nearly half of the cases were adults aged 45 to 60 years (44%). Primary lung tumors were the most common primary site of primary tumor. Only 34 (19%) patients were diagnosed by the surgical specimen.

Fifty-seven percent of the patients were classified as RPA class 3, while there were 33.8% and 8.9% in RPA class 1 and 2 respectively. Most of the patients in RPA class II aged 65 to 74 years old, while those with class I and III aged less than 65 years old. Patients with RPA class III suffered from extra-cranial metastasis and presented with multiple brain metastases more than those with class I and II (Table 1).

The most common presenting symptoms were headache (33%), weakness (29%), and seizure (13%). Only 4% of patients experienced no symptom (Figure 1).

### *Survival data*

At data cut-off time, 207 patients (97%) had died. The median follow-up time was 136.9 months (95% CI: 114.0 to 159.8) and the median survival time was 3.5 months (95% CI: 2.75 to 4.35). The overall survival rates at 1, 2, and 5 years were 21.6%, 8.9%, and 4.2% respectively. The survival curved dropped rapidly during the first two years compared to the time thereafter (Figure 2). Interestingly, the 10-year survival rate was 3.1%.

The median overall survival was 8.1 months (95% CI, 1.5 to 11.6) and 7.8 months (95% CI, 3.9 to 11.7) in the RPA class I and II group respectively, as compared with 2.3 months (95% CI, 1.7 to 2.9) in the RPA class III group: hazard ratio 30.1, $p$<0.001 (Figure 3).

The survival time varied greatly among primary site of the tumor. Patients with primary thyroid cancer and germ cell tumor survived longer than those with other primary tumors significantly (hazard ratio [HR] 0.22, $p$<0.001). Patients with liver and esophageal cancer had the shortest median survival time, 1.94 and 1.64 months respectively.

Univariate survival analyses were performed

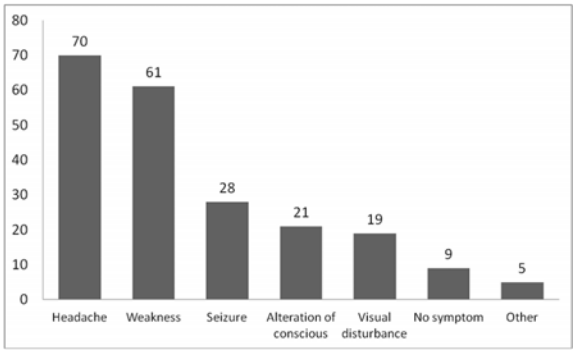


**Figure 1.** Presenting symptoms of brain metastasis (%).

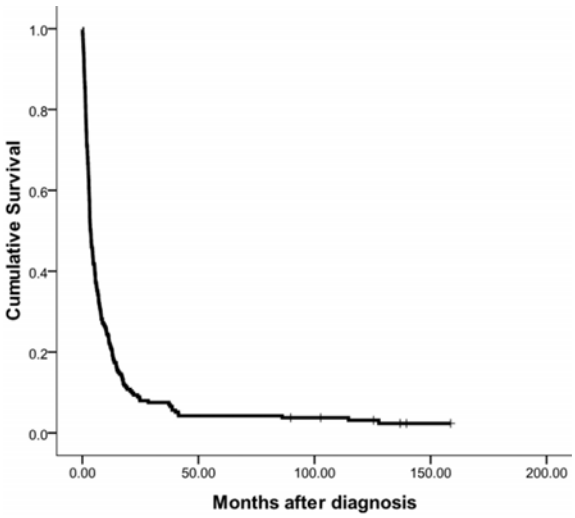


**Figure 2.** Kaplan-Meier curve of overall survival of all patients (n = 213).

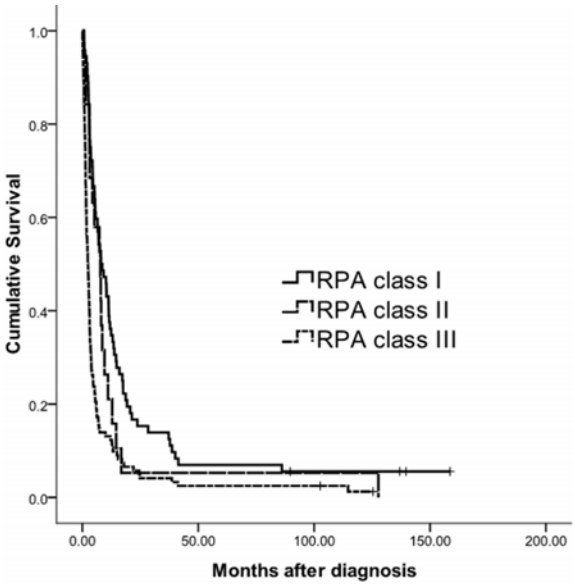


**Figure 3.** Overall survival of patients according to RPA class. Tick marks represent patients who had data censored at the last time that they were known to be alive.

to determine the correlations between clinical characteristics, primary tumor site, and treatment modality and overall survival (Table 2). No difference was found for patients with extra-cranial metastasis compared to patients without extra-cranial metastasis (Hazard ratio [HR] 1.02, 95% CI 0.78 to 1.35). Similarly, for those with multiple brain metastases versus those with single brain metastasis, the difference was not significant (HR 1.21, 95% CI 0.91 to 1.60).

Multivariate Cox proportional hazard model including age, gender, RPA class, the primary site of thyroid or germ cell tumor, WBRT, and surgery was performed. Male gender, RPA class III, thyroid cancer or germ cell tumor, WBRT, and surgery are independent prognostic factors of overall survival (Table 3). Age was not an independent predictor of survival.

## Discussion

Brain metastasis occurs frequently in cancer patients with short survival time. The survival time in this study was comparable to other studies during the same period. Lutterbach et al[7] reported the median survival of 3.4 months and a review of more than 700 patients by Hall et al[8] reported median survival of 4.0 months. The characteristics of patients with predominant lung and breast cancers are concordant

**Table 2.** The median survival time according to the primary site of the tumor

| Primary site | n | % | Median survival (months) | (95% CI) |
|---|---|---|---|---|
| Lung | 112 | 52.6 | 3.19 | (2.70 to 3.67) |
| Breast | 27 | 12.7 | 4.70 | (3.25 to 6.15) |
| CUP | 20 | 9.4 | 2.86 | (2.09 to 3.63) |
| Liver | 18 | 8.5 | 1.94 | (0.85 to 3.03) |
| Colon-rectum | 9 | 4.2 | 3.09 | (2.51 to 3.66) |
| Cervix | 6 | 2.8 | 8.6 | (0.01 to 17.68) |
| NPC | 5 | 2.3 | 5.26 | (3.78 to 6.74) |
| Thyroid | 4 | 1.9 | 22.05 | (0.01 to 57.66) |
| Germ cell tumor | 4 | 1.9 | 41.30 | - |
| Melanoma | 4 | 1.9 | 2.53 | (0.01-14.48) |
| RCC | 3 | 1.4 | 5.36 | (0.01-11.72) |
| Esophagus | 1 | 0.5 | 1.64 | - |

**Table 3.** Univariate and multivariate Cox regression analyses of factors affecting overall survival in brain metastasis patients

| Variables | Univariate model | | | Multivariate model | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | (95% CI) | *p*-value | Hazard ratio | (95% CI) | *p*-value |
| Age | 1.02 | (1.00 to 1.03) | 0.011* | 0.99 | (0.98 to 1.01) | 0.746 |
| Male | 1.29 | (0.98 to 1.69) | 0.072 | 1.54 | (1.15 to 2.07) | 0.004* |
| RPA | | | | | | |
| Class I | 1 | | | - | | |
| Class II | 1.32 | (0.78 to 2.20) | 0.287 | 0.89 | (0.50 to 1.57) | 0.686 |
| Class III | 2.26 | (1.67 t 3.06) | <0.001* | 2.19 | (1.58 to 3.04) | <0.001* |
| Thyroid cancer/ | 0.22 | (0.09 to 0.54) | 0.001* | 0.21 | (0.08 to 0.53) | 0.001* |
| Extra-cranial metastasis | 1.02 | (0.78 to 1.35) | 0.874 | - | | |
| Germ cell tumor | | | | | | |
| Multiple metastasis | 1.21 | (0.91 to 1.60) | 0.18 | - | | |
| WBRT | 0.55 | (0.41 to 0.74) | <0.001* | 0.51 | (0.37 to 0.71) | <0.001* |
| Surgery | 0.60 | (0.41 to 087) | 0.007* | 0.57 | (0.38 to 0.83) | 0.004* |

The *p*-value was significant at $p<0.05$
RPA = recursive partitioning analysis; WBRT = whole brain radiation

with other series[1, 7].

Median overall survival in RPA class I, II, and III was 8.1 months, 7.8 months, and 2.3 months respectively. This compares well with a survival reported by RTOG for class I and class III of 7.1 months and 2.3 months[5]. For class II, however, the survival in this series was longer than other reports. This could be due to less extra-cranial metastasis and a high proportion of single metastasis in class II patient. It was shown that survival outcome was better in RPA class II with a single metastasis compared with RPA class I patients with multiple brain metastases[7].

The RTOG RPA was able to stratify patients with brain metastases into distinct prognostic groups similar to earlier studies[9-12]. In the present study, known extra-cranial metastasis and number of metastasis did not prove to be poor prognostic factors unlike other reports[9]. Since most of the cases in this reviewed was diagnosed by using CT scan, the small brain metastasis might not be detected as compared to MRI brain and led to a high false negative rate of multiple metastases. The long follow-up time in the present study made it possible to detect long-term survivors which whom the details of clinical data and treatment should be further studied. However, there are a few limitations that cannot be neglected in the present study. First, the study was conducted in the 2006 to 2010 period which was before the widely used PET/CT scan for staging. By detecting the intracranial metastasis at asymptomatic phase could significantly increase the survival time from diagnosis of brain metastasis. Second, the treatment was limited only to WBRT and surgery. Radiosurgery was not used in the cohort and there was no data regarding small molecule tyrosine kinase inhibitors at that time[13,14]. Third, the present study was performed in the tertiary care referral center, in which the number of patients with brain metastasis could be overestimated.

## Conclusion

The present study showed that the survival of brain metastasis is poor and is common in lung and breast cancer. RPA class is a simple and important prognostic factor for survival.

## What is already known on this topic?

The authors can use the clinical characteris tics of patients to predict the prognosis of brain metastasis by using the RPA classification with Karnofsky performance status [KPS] ≥70, age less than 65 years old, controlled primary tumor, and no extra-cranial metastases

## What this study adds?

The present study showed the clinical manifestations of the patients presenting with brain metastasis at our center and validated the prognostic role of RPA classification in Thai patients. Male gender, RPA class III, thyroid cancer or germ cell tumor, WBRT, and surgery were independent prognostic factors of overall survival while age was not.

## Acknowledgements

The authors would like to acknowledge Thailand Research Fund (number IRG 5780016) for the support of the present study.

## Potential conflicts of interest

The authors declare no conflict of interest.

## References

1. Nussbaum ES, Djalilian HR, Cho KH, Hall WA. Brain metastases. Histology, multiplicity, surgery, and survival. Cancer 1996;78:1781-8.
2. Patchell RA. The management of brain metastases. Cancer Treat Rev 2003;29:533-40.
3. Fabi A, Felici A, Metro G, Mirri A, Bria E, Telera S, et al. Brain metastases from solid tumors: disease outcome according to type of treatment and therapeutic resources of the treating center. J Exp Clin Cancer Res 2011;30:10.
4. Khuntia D, Brown P, Li J, Mehta MP. Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 2006;24:1295-304.
5. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, 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;37:745-51.
6. Nieder C, Andratschke N, Grosu AL, Molls M. Recursive partitioning analysis (RPA) class does not predict survival in patients with four or more brain metastases. Strahlenther Onkol 2003;179:16-20.
7. Lutterbach J, Bartelt S, Ostertag C. Long-term survival in patients with brain metastases. J Cancer Res Clin Oncol 2002;128:417-25.
8. Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long-term survival with metastatic cancer to the brain. Med Oncol 2000;17:279-86.
9. Golden DW, Lamborn KR, McDermott MW,

Kunwar S, Wara WM, Nakamura JL, 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.
10. Kano H, Morales-Restrepo A, Iyer A, Weiner GM, Mousavi SH, Kirkwood JM, et al. Comparison of prognostic indices in patients who undergo melanoma brain metastasis radiosurgery. J Neurosurg 2018;128:14-22.
11. Li H, Lian J, Jin H, Wang W, Cao J, Zhang X, et al. Assessment of prognostic scores of brain metastases from lung adenocarcinoma with EGFR mutations. J Neurooncol 2017;133:129-35.
12. Pojskic M, Bopp MHA, Schymalla M, Nimsky C, Carl B. Retrospective study of 229 surgically treated patients with brain metastases: Prognostic factors, outcome and comparison of recursive partitioning analysis and diagnosis-specific graded prognostic assessment. Surg Neurol Int 2017;8:259.
13. Linskey ME, Andrews DW, Asher AL, Burri SH, Kondziolka D, Robinson PD, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:45-68.
14. Li SH, Liu CY, Hsu PC, Fang YF, Wang CC, Kao KC, et al. Response to afatinib in treatment-naive patients with advanced mutant epidermal growth factor receptor lung adenocarcinoma with brain metastases. Expert Rev Anticancer Ther 2018;18:81-9.