


Original Research Article

Whole brain radiotherapy for patients with brain metastasis from lung cancer – Prognostic significance of RTOG-RPA score

S. Jeeva¹, K. Chandralekha^{2*}, V. Vanitha³, M. Sornam⁴, Balasubramaniam⁵, P. Vidya⁶

¹⁻⁶Department of Radiation Oncology, Tamil Nadu Govt. Multi Super Speciality Hospital, OMA Chennai & Department of computer science, University of Madras, India

*Corresponding author email: drchandralekhakmc@gmail.com

	International Archives of Integrated Medicine, Vol. 6, Issue 5, May, 2019.	
	Copy right © 2019, IAIM, All Rights Reserved.	
	Available online at http://iaimjournal.com/	
	ISSN: 2394-0026 (P)	ISSN: 2394-0034 (O)
	Received on: 08-04-2019	Accepted on: 16-04-2019
	Source of support: Nil	Conflict of interest: None declared.
How to cite this article: S. Jeeva, K. Chandralekha, V. Vanitha, M. Sornam, Balasubramaniam, P. Vidya. Whole brain radiotherapy for patients with brain metastasis from lung cancer – Prognostic significance of RTOG-RPA score. IAIM, 2019; 6(5): 32-39.		

Abstract

Background: Whole brain radiotherapy for patients with brain metastasis from lung cancer – prognostic significance of RTOG-RPA score.

Aim: To evaluate the prognostic significance of Recursive partition Analysis (RPA) score in predicting the survival in patients with brain metastasis from Non-Small Cell Lung Cancer (NSCLC).

Materials and methods: 35 patients diagnosed to have brain metastasis (BM) from primary NSCLC who had received palliative whole brain radiotherapy (WBRT) with or without chemotherapy from March 2014 to Mar 2017 were analyzed in this study. Data regarding the patient age, gender, performance status, histology, number of BM, time of metastasis, neurosurgical resection, radiotherapy details were collected and analyzed. Patients were divided into 3 groups according to RPA classification. The differences in clinical characteristics and treatment variables were analyzed by chi square test and overall survival analysis using Kaplan Mayer. The Cox proportional hazards regression model was used to determine statistically significant variables related to survival.

Results: In univariate analysis histology, number of BM, extra cranial metastases, KPS and RPA score were identified to have prognostic significance. The result of multivariate analysis by the Cox proportional hazard model showed that RPA, no of mets and Extra cranial mets were significant.

Conclusions: Our study showed that RPA is good prognostic indicator in assessing the prognosis of patients with brain metastasis in NSCLC.

Key words

Non-small cell Lung cancer, Brain metastases, RPA score, WBRT.

Introduction

Lung cancer is known to commonly metastasize to the brain, with a range of 10%–36% of all lung cancers developing BM during the course of their disease [1-3]. Among lung cancer histology, adenocarcinoma is a common source of BM [4, 5]. Whole brain radiotherapy (WBRT) is currently recommended as the standard treatment approach for multiple BM. Surgical resection, stereotactic radiosurgery (SRS), and combined treatment approaches are the other treatment options at present [12]. The median survival of patients with BM following WBRT is only 2.4–4.8 months which makes it crucial to identify the prognostic factors in this patient population for effective management [6, 7, 8]. Many prognostic scores are available to classify BM patients into different groups like Recursive partition analysis (RPA), Graded Prognostic Assessment (GPA) and Mini Mental Status Examination (MMSE) [9, 10, 11]. The aim of this retrospective study was to evaluate the prognostic significance of RPA scores in predicting the survival in patients with BM from NSCLC. RPA prognostic score by RTOG given in **Table - 1**.

Table – 1: RPA classes.

Classes	Variables
Class I	Age <65 years, KPS \geq 70, controlled primary tumor, no extra cranial metastasis
Class II	All patients not in Class I or III
Class III	KPS <70

(KPS: Karnofsky performance status.)

Materials and methods

We retrospectively reviewed 35 patients with BM from NSCLC treated in Department of Radiation Oncology at our hospital from Feb 2014 to April 2017. Inclusion criteria for this analysis were biopsy proven NSCLC, age more

than 18 years, patient who had received palliative WBRT with or without chemotherapy (CT). The diagnosis of NSCLC was based on histopathological evaluation in all patients. CT thorax was used to evaluate the primary tumor and extent of intra thoracic disease. BM was defined as synchronous if it appeared within 3 months of the diagnosis of the primary tumor. Diagnosis of single or multiple BM was based on the CT or MRI.

All our patients received palliative WBRT 20-30 Gy in 5-10 fractions by parallel opposing laterals with Cobalt-60 machine. Data regarding the following prognostic variables were collected: patient age, gender, performance status, histology, number of BM, time of metastasis, tumor stage, primary disease status, neurosurgical resection. The survival time is defined as the time of diagnosis of brain metastases to death. Follow up data was collected from medical case records and telephonic contact whenever necessary.

All of the analyses were performed using the SPSS statistical software program package (SPSS version 11.5 for Windows, SPSS Inc., Chicago, IL, USA). The differences in the clinical characteristics were analyzed by Chi-square tests, and overall survival (OS) was calculated from the date of diagnosis of brain metastases to the date of death from any cause or the date of the last follow-up. OS was estimated using the Kaplan-Meier method. The Cox proportional hazards regression model was used to determine statistically significant variables related to survival. Differences were considered significant when $P < 0.05$.

Results

Patient and treatment characteristics

The median patient age was 58 years (range: 20–95) with 20 (57%) males and 15 (43%) females. Adenocarcinoma was the most common histologic type (n= 26). Most of the patients had extra cranial metastasis (N=18) and T4 disease status (N= 18) at the time of diagnosis of BM. All patients received whole brain radiotherapy with or without chemotherapy. 30 Gy in 10 fractions was the most common regime (N=30). Though systemic therapy forms an integral part of patient management for metastatic lung cancer, only 54% of them received it due to poor performance status. According the RPA classification – only one patient was classified in the class I (2.8%), 23 patients belonged to class II (65.7%) and 11 patients belonged to class III (31.5%). The baseline patient and tumor characteristics are given in **Table - 2**. Treatment details were as per **Table – 3**.

Table - 2: Distribution of Patient and Tumor characteristics (Total n=35).

Variables	No. of pts	%
Male	20	57
Female	15	43
T1	-	
T2	2	5.7
T3	15	42.8
T4	18	51
N Stage		
N0	3	8.5
N1	13	37
N2	17	48.5
N3	2	6
Pathology		
Adenocarcinoma	26	74.2
Squamous carcinoma	9	25.7
No of Brain metastases		
1	7	20
1-3	11	31.5
>3	17	48.5
Primary lesion		
Present	30	86
Absent	5	14
Extra cranial metastases		
Present	18	51.5
Absent	17	48.5

Brain metastases		
Synchronous	24	68.5
Metachronous	11	31.5

Table - 3: Treatment details.

Variables	No of patients	%
WBRT		
Dose 30 Gy	30	85.7%
Dose 20 Gy	5	14.3%
Chemotherapy		
Received	19	54%
Not received	16	66%

Outcomes

The median survival of the patients in our study population was 3.6 months (95 % CI- 2.6 to 5.3 months). Out of 35 patients, 4 patients were alive at the time of analysis. In the univariate analysis better overall survival was associated with the adenocarcinoma histology (p=0.016), KPS > 70 (P= 0.047), RPA 1 and 2 (p=0.004), only 1 to 3 brain metastases (p = 0.010), absence of extra cranial metastases at the time of WBRT, synchronous metastases (p=0.05). The result of univariate analysis for overall survival were summarized in the **Table - 4**.

In multivariate analysis of overall survival by Cox proportional hazard model and Kaplan Meir survival curve showed that RPA (p= 0.023), No. of brain mets (p=0.025), extracranial mets (p=0.047), synchronous mets (p=0.047) was found to be significant. These results are showed in **Table - 5**.

Discussion

In patients with brain metastasis the median overall survival is poor in spite of multimodality treatment [13]. Studies showed that resection of cranial metastases and SRS are treatment option for selected patients with a solitary metastasis [14, 15]. In spite of aggressive treatment the evidence for improved overall survival is lacking except in patients who have undergone resection of brain metastasis [17, 18]. Hence the prognostic factors help the clinician to select the patients who may benefit from more aggressive

treatment. Several scoring systems exist to estimate the survival prognosis of patient with BM [16]. The RPA prognostic index of RTOG by Gasper, et al., the first scoring system, for patients with BM to assess the survival outcome was published in 1997 [7]. It was again validated

in 2000, from RTOG 91-04 trial [19]. In this study, younger age, better performance status, lack of extra cranial metastases, lower RPA class and a longer interval from tumor diagnosis to treatment of BM were significant prognostic factors for patient survival.

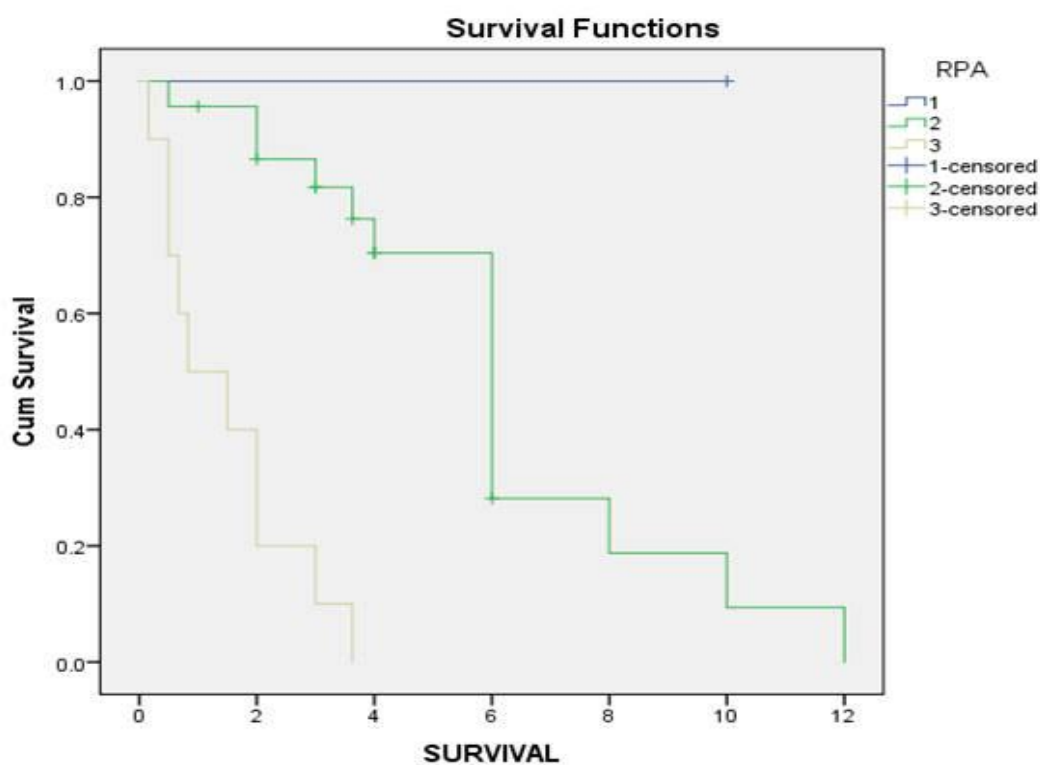
Table - 4: Univariate analysis of median overall survival.

Variable	Median OS in months (95% CI)	p-Value
Age		0.678
≤56	3.6(1.0-6.2)	
>56 and <65	3.8(0.0-7.7)	
>65	3(1.4-4.6)	
Gender		0.629
Male	3(1.9-4.1)	
Female	4(3.3-4.7)	
KPS		0.047
<70	4(2.8-5.2)	
>70	1.5(0.5-2.5)	
RPA		0.004
1	Not Applicable	
2	4(3.4-4.5)	
3	1(0.0-2.1)	
T Stage		0.347
T3	3.6(2.3-4.9)	
T4	3(1.4-4.6)	
N Stage		0.133
N1	3.6(1.02-6.2)	
N2	4(2.3-5.7)	
N3	3(1.6-4.4)	
Histology		0.016
Adeno ca	3.6(2.8-4.5)	
Squamous ca	0.8(0.1-1.5)	
Metastases No.		0.010
1-3	6(4.9-7.1)	
>3	2(0.7-3.3)	
Primary Disease		0.376
Yes	3(1.9-4.7)	
No	4(1.9-6.1)	
Extra Mets		0.046
	2.1(0.0-4.1)	
	2.2(0.0-4.4)	
Syn/Met		0.05
Synchronous	3.6(2.7-4.6)	
Metachronous	3(2.0-4.1)	

Table - 5: Multivariate analysis of median overall survival (multivariate cox regression analysis).

Variable	p-value	Hazard ratio	Confidence interval
KPS(>70)	0.000	0.326	0.052-2.041
KPS(<70)	0.000	---	---
RPA1	0.149	0.000	---
RPA2	0.003	0.400	0.025-6.366
RPA3	0.000	---	274-34.353
Squamous ca	0.470	0.532	146-1.940
Adeno ca	0.05	1.957	303-12.653
Brain mets(1-3)	0.03	0.342	039-3.085
Brain mets(>3)	0.5	0.768	0.385-3.647
Synchronous	0.72	1.413	494-4.040
Metachronous	0.72	1.413	494-4.040
Extracranial mets	0.021	4.467	1.254-15.911

Figure - 1: Kaplan-Meier survival curves for patients with BM stratified by RPA.



Median Survival based on RPA 1: 11 months
 Median Survival based on RPA 2: 5.4 months
 Median Survival based on RPA 3: 0.9 months

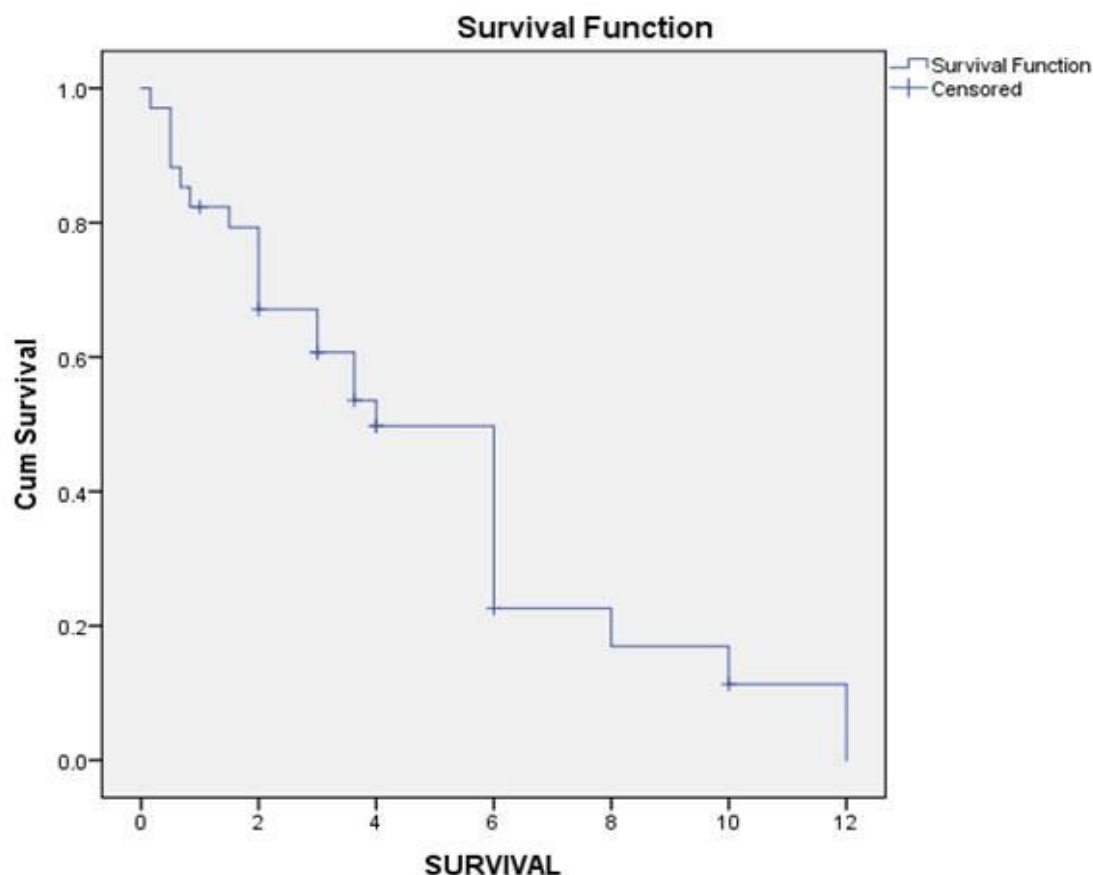
Studies showed that patients who had adenocarcinoma had better overall survival as compared to the non-adenocarcinoma histology. Patients with 1-3 brain metastasis had better implication on overall survival [13, 14]. In our retrospective study, patients who had adenocarcinoma and those with 1-3 brain

metastases were significant on univariate analysis for overall survival.

Extra cranial metastases are a prognostic factor used by RPA is one of the significant factors for predicting overall survival [10]. In our study, only one patient came under the RPA class I and majority of the patients fell under the class II and

III. It was conferred in our study that patients in class I and II had better survival than class III. We had 7 patients with solitary brain metastases but surgery could not be done because of poor performance status.

Figure – 2: Kaplan-Meier survival for overall survival.



In our study the multivariate analysis for overall survival showed, that lower RPA class, one to three BM, absence of extra cranial metastases are independent prognostic factors impacting the survival of NSCLC with BM. The prognostic classes of RPA and the results showed that the Kaplan Meir survival curves of subgroups were significantly different. The median survival based on RPA 1 to 3 is 11, 5.4, 0.9 months respectively. These findings may facilitate pre-treatment prediction of survival in patients with BM in NSCLC and help to select subgroup of patients for more aggressive treatment. The results of Kaplan Meir curve are given in **Figure – 1** and **Figure - 2**.

The limitation of our study was that it was retrospective in nature and less number of

patients. Therefore, a prospective trial and larger clinical trials are needed. In this retrospective analysis of patients with BM in NSCLC lung at our hospital, median overall survival calculated were relevant to the existing data. Majority of the patients belonged to RPA class II or III. Patients with the most favourable RPA class, KPS of the patient at diagnosis of BM and status of primary lung cancer had a significantly longer median OS compared to other patient.

Conclusion

Our study showed that RPA is good prognostic indicator in assessing the prognosis of patients with brain metastasis in NSCLC.

References

1. Komamicky L.T., Phillips T.L., Martz K., Asbell S., Isaacson S., Urtasun R. A randomized Phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG79-16). *Int. J. Radiat. Oncol. Biol. Phys.*, 1991; 20: 53-58.
2. Phillips T.L., Scott C.B., Leibel S.A., Rotman M., Weigensberg I.J. Results of a randomized comparison of radiotherapy and bromodeoxyurine to radiotherapy alone for brain metastases: Report of RTOG trial 89-05. *Int. J. Radiat. Oncol. Biol. Phys.*, 1994; 30: 215.
3. Sause W.T., Crowley J.J., Morantz R., Rotman M., Mowry P.A., Bouzaglou A., Borst J.R., Selin H. Solitary brain metastasis: Results of an RTOG/SWOG protocol evaluation- surgery + RT versus RT alone. *Am. J. Clin. Oncol. (CCT)*, 1990; 13: 427-432.
4. Mujoomdar A, Austin JH, Malhotra R, et al. Clinical predictors of metastatic disease to the brain from non-small cell lung carcinoma: primary tumor size, cell type, and lymph node metastases. *Radiology*, 2007; 242(3): 882–888.
5. Fox BD, Cheung VJ, Patel AJ, et al. Epidemiology of metastatic brain tumors. *Neurosurg Clin N Am.*, 2011; 22(1): 1–6.
6. Langer CJ, Mehta MP. Current management of brain metastases, with a focus on systemic options. *J Clin Oncol.*, 2005; 23: 6207-19.
7. Khuntia D, Brown P, Li J, Mehta MP. Whole-brain radiotherapy in the management of brain metastasis. *J Clin Oncol.*, 2006; 24: 1295-304.
8. Eichler AF, Loeffler JS. Multidisciplinary management of brain metastases. *Oncologist*, 2007; 12: 884-98.
9. Gaspar LE, Scott C, Murray K, et al. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *Int J Radiat Oncol Biol Phys.*, 2000; 47: 1001-6.
10. Sperduto PW, Berkey B, Gaspar LE, et al. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys.*, 2008; 70: 510-4.
11. Pan HC, Sheehan J, Stroila M, et al. Gamma knife surgery for brain metastases from lung cancer. *J Neurosurg.*, 2005; 102(Suppl): 128-33.
12. Andrews D.W., Scott C.B., Sperduto P.W., Flanders A.E., Gaspar L.E., Schell M.C., Werner-Wasik M., Demas W., Ryu J., Bahary J.P., et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomised trial. *Lancet*, 2004; 363: 1665–1672.
13. Sakamoto J, Sonobe M, Kobayashi M, Ishikawa M, Kikuchi R, Nakajima D, et al. Prognostic factors for patients in postoperative brain metastases from surgically resected non-small cell lung cancer. *Int J Clin Oncol.*, 2014; 19: 50-6.
14. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. *JAMA*, 2006; 295: 2483-91.
15. Serizawa T, Saeki N, Higuchi Y, Ono J, Iuchi T, Nagano O, et al. Gamma knife surgery for brain metastases: Indications for and limitations of a local treatment protocol. *Acta Neurochir (Wien)*, 2005; 147: 721-6.
16. Peters S, Adjei AA, Gridelli C, Reck M, Kerr K, Felip E. ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis,

- treatment and follow-up. *Ann Oncol.*, 2012; 23 Suppl 7: vii56-64.
17. Griffioen GH, Toguri D, Dahele M, Warner A, de Haan PF, Rodrigues GB, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): Patient outcomes and prognostic factors. *Lung Cancer*, 2013; 82: 95-102.
 18. De Ruyscher D, Wanders R, van Baardwijk A, Dingemans AM, Reymen B, Houben R, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: Long-term results of a prospective phase II trial (Nct01282450). *J Thorac Oncol.*, 2012; 7: 1547-55
 19. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. *International journal of radiation oncology, biology, physics*, 2000; 47(4): 1001-6.