Kasr El-Aini J. Clin. Oncol. Nucl. Med.
Vol. 7, No. 1-2, Jan.-April. 2011:12-16

Original article

Survival Analysis and Prognostic Factors of Whole Brain Radiotherapy for Brain Metastasis

Aboziada A. Mohamed and Elsayed I. Mohamed

Department of Radiation Oncology, South Egypt Cancer Institute, University of Assiut.

Purpose: The aim of this study is to evaluate survival and prognostic factors in patients with brain metastases (BM) who received whole brain radiotherapy (WBRT).
Methods and Methods: Patients (118) were retrospectively identified through the hospital data-base, patients' charts and imaging studies.
Results: Cancer breast was the most common primary site (38) followed by the lung (24). The median survival for all patients was 4 months. Higher Karnofsky score ($p = 0.04$), single metastases ($p = 0.04$) and systemic chemotherapy ($p = 0.01$) are associated with better survival. The recursive partitioning analysis showed strong relation with survival ($p < 0.01$). Different radiotherapy doses and fractionation schedules did not altered survival.
Conclusion: WBRT is an effective treatment in the management of BM. Multimodality treatments including surgery, radiosurgery and chemotherapy with WBRT should be used to improve survival mainly in those patients with single metastases, higher KPS and controlled extra cranial disease.

Key words: Brain metastases, Radiotherapy, Radiosurgery.
Corresponding author: Aboziada A. Mohamed Email: Maboziada70@yahoo.com

Original article

INTRODUCTION

Brain metastases (BM) are an important cause of morbidity and mortality and, occurring in approximately 10% to 30% of adult cancer patients. The risk of developing brain metastases varies according to primary tumor. The most common primary sites are the lung followed by the breast[1]. Whole brain radiotherapy (WBRT) and corticosteroid are the standard treatment to patients with brain metastases[2,3]. The use of adjuvant WBRT after resection or radiosurgery has been proven to be effective in terms of improving local control of brain metastases and thus, the likelihood of neurological death is decreased[4]. For most patients who present with multiple brain metastases, the goal of treatment is palliation. Specifically, the main expectations of therapy are an improvement in presenting neurological symptoms and prevention of neurological deterioration[5].

The prognosis of patients with brain metastases is poor; the median survival time of untreated patients is approximately 1 month. With WBRT, the overall median survival time after diagnosis is approximately 4 months[6]. Radiation Therapy Oncology Group (RTOG) showed that as many as 40% of high-risk patients do not survive more than 2 months. RTOG classified patients into three classes Table (1) based on recursive partitioning analysis (RPA)[7]. It provided a tool to identify the prognosis and patients who may not benefit from WBRT.

There is no consensus on the optimal radiation schedule for patients with brain metastases. Standard treatment regimen include all dose ranges which evaluated in the early RTOG studies and is dependent upon issues such as the severity of CNS symptoms, the extent of systemic disease and physician preference[8]. The aim of this study is to evaluate survival and prognostic factors in patients with BM who received WBRT.

PATIENTS AND METHODS

Patients, record were retrospectively identified through the hospital data-base, patients' charts and imaging studies. WBRT was performed in all patients with BM using 6 MV photons of a linear accelerator. The whole brain was irradiated by usual bilateral fields that encompassed the cranium with a 1 cm margin. Regarding radiation dose, patients were heterogeneously treated according to the physician's decision. During the study period three fractionation schemes were used: hypofractionation with daily fractions of 3 Gy, five days per week to a planned total dose of 30 Gy ($n = 95$), hypofractionation with daily fractions of 4 Gy, five days per week to a planned total dose of 20 Gy ($n = 14$) and conventional fractionation with daily fractions of 2 Gray (Gy), five days per week to a planned total dose of 40 Gy ($n = 9$). Boost dose was given in cases of single brain metastasis with different

fractionation schemes. No surgical resection was done. Systemic chemotherapy administered to the patients (n=28) with active systemic disease after WBRT. The supportive care (corticosteroid therapy) was introduced in the beginning of treatment and during radiotherapy.

Statistical Design: This was a retrospective study and bias can not be excluded. There was a difficulty to determine the accurate date of death because there is no available mortality registration. We contact with the family of patients to know the mortality date. The endpoint of the study was overall survival. Survival was calculated from the first day of radiotherapy using the method of Kaplan Meier. Survival curves were compared using the log-rank test. The covariates examined in all cases were: age, sex, primary tumor type, extent of disease, initial Karnofsky score, dose and fractionation radiotherapy schedule and recursive partitioning analysis (RPA) class. All factors with a P-value ≤ 0.05 were significant.

RESULTS

During the period of 2006 to 2009, 118 patients with brain metastases, who were treated with WBRT at our institution in the department of radiation Oncology, University of Assiut. Brain metastases were detected by contrast-enhanced cerebral computed tomography and/or magnetic resonance imaging. Age of patients ranged from 17-82 years (Median = 47 years). Sixty one patients were female and fifty seven patients were male. Cancer breast was the most common primary site (n = 38) followed by the lung (n = 24) Table (2).

The median survival time for all patients was 4 months Figure (1). The significant prognostic factors associated with better survival were: Higher KPS (p = 0.04), single metastases (p = 0.04) and systemic chemotherapy (p = 0.01) showed in Table (3) and Figures (2, 3, 4). The RPA class analysis showed strong relation with survival ($p < 0.01$) and the median survival time by RPA class in months was: class I: 5, class II: 4 and class III: 1.5 Figure (5).

DISSCUSION

Brain metastases are the most common intra-cranial tumor accounting significantly more than one- half of brain tumors in adults. WBRT is essential for most cases of multiple BM. The benefit with the use of WBRT over supportive care alone, in terms of symptom control, quality of life, or survival remains unclear, particularly in patients with poor performance status and/or active extracranial disease[8]. The goal of postoperative WBRT in patients with solitary BM is to destroy microscopic residual cancer cells at the site of resection and others localizations within the brain. Two of the three randomized trials (WBRT versus surgery plus WBRT) reported a statistically significant improvement in overall median survival for surgery plus WBRT[9,10,11]. This improvement demonstrated in patients with good performance status and absence of extracranial disease (RPA class I). In our trial, no patient performed surgery or sterotactic radiotherapy but conventional boost dose was given in cases of single BM. A larger trial (RTOG 95-08)[12] provides compelling evidence for the use of stereotactic radiosurgery (SRS) boost following WBRT in patients with newly diagnosed one to three BM. In our study, patients with multiple brain metastases had poorer survival than patients with single brain metastases (P = 0.04). We should encourage our patients for referral to receive SRS.

Most of our patients received a common standard dose-fractionation schedule (3000 cGy in 10 fractions), however, there is no difference in survival compared with other dose-fractionation schedules (P=0.2). RTOG attempted several randomized controlled trials[13,14,15] to evaluate the use of altered dose-fractionation schedules. However, there was no benefit in terms of overall survival or neurologic function improvement with altered dose-fractionation schedules as compared to a standard dose-fractionation schedule (3000 cGy in 10 fractions). None of the negative trials commented on confidence intervals or power calculations. As 2000 cGy in 5 fractions is most commonly employed in Canada and this is the second most commonly employed standard regimen[16].

Prognostic criteria determined by RPA of 1200 patients in RTOG trials[7]. RPA showed that poor prognostic features also included active extracranial metastases and an uncontrolled primary tumor. Gerrard et al,[17] performed three studies between 1997 and 2001. They revealed that three poor prognostic features, such as KPS < 70, over 60 years of age and primary other than breast cancer. All these prognostic factors were demonstrated in our study and by other authors[8,11]. Patients with poor performance status and progressive extracranial disease, treatment interventions may fail to achieve benefits and associated with side effects[18]. Our data demonstrate that the use of RPA class may identify patients most likely to benefit from WBRT.

The role of chemotherapy in BM is controversial. Most of trials found no survival advantage with chemotherapy[19,20,21]. We found chemotherapy improved the median survival like Shenglin[22] who found that gefitinib improved the median survival and quality of life in non small lung cancer. Nicolas and colleagues[23] also found chemotherapy improved the median survival in non small lung cancer. A number of studies[24,25] have, however, demonstrated favorable response rates and survival benefit in breast patients with BM receiving combination chemotherapy. This needs further investigations to demonstrate the value of chemotherapy.

Table 1: RTOG recursive partitioning analysis.

Class	Variables	Median survival (months)
Class I	<65 years of age; KPS ≥70; controlled primary tumor; metastases to brain only.	7.1
Class II	KPS ≥70, but uncontrolled primary tumor; KPS ≥70, primary controlled, but age ≥65; KPS ≥70, primary controlled, age <65, but metastases to brain and other sites.	4.2
Class III	KPS <70	2.3

KPS, Karnofsky performance status.

Table 2: Patient characteristics.

Variables	Number (%)
Age	
< 60	91 (77)
≥ 60	27 (23)
Sex	
Male	57 (48)
Female	61 (52)
KPS	
<70	26 (22)
>=70	92 (78)
Primary site	
Breast	38 (32)
Lung	24 (20)
MUP	15 (13)
Others	41 (35)
Number Lesions	
Single	32 (27)
Multiple	86 (73)
Extracranial metastasis	
Yes	65 (55)
No	53 (45)
Chemotherapy	
Yes	28 (24)
No	90 (76)
RPA class	
Class I	39 (33)
Class II	53 (45)
Class III	26 (22)

KPS, Karnofsky performance status; MUP, metastasis of unknown primary; RPA, recursive partitioning analysis.

Table 3: Factors affecting overall survival.

Factors	Median survival (months)	P. value
Age		
< 60	2	0.06
≥ 60	4	
Sex		
Male	4	0.3
Female	4	
KPS:		
<70	3	0.04
≥ 70	4	
lesions number:		
Single	6.5	0.04
Multiple	4	
Chemotherapy:		
Yes	5	0.015
No	3	
Extracranial lesions:		
Yes	4	0.6
No	4	
RPA class:		
Class I	4	
Class II	4	0.012
Class III	1.5	
Dose fractionation:		
30 Gy/10 fractions	4	0.2
Other fractions	4	

KPS, Karnofsky performance status; RPA, recursive partitioning analysis.

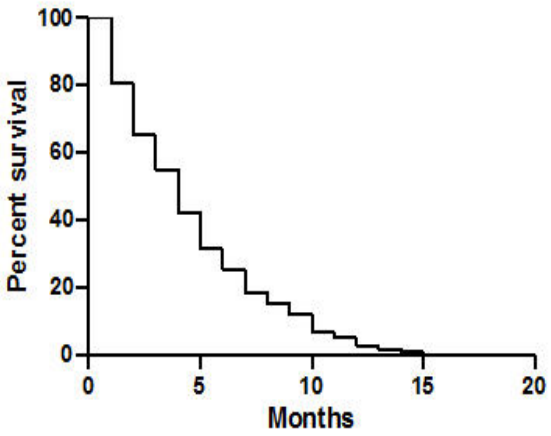

Figure 1: Overall survival of whole group.

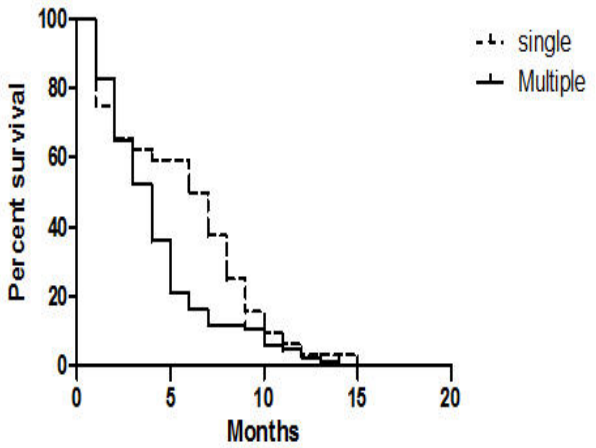

Figure 2: Overall survival by lesions.

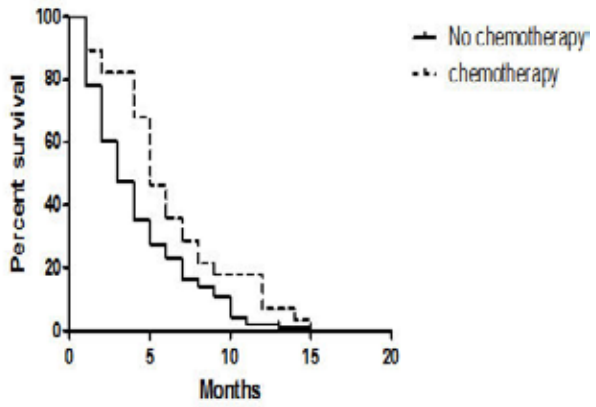

Figure 3: Overall survival by chemotherapy.

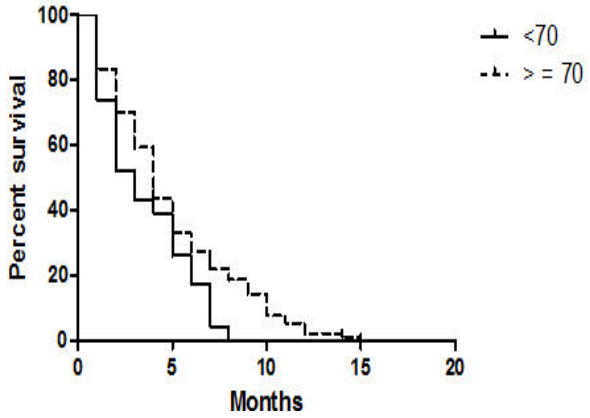

Figure 4: Overall survival by KPS.

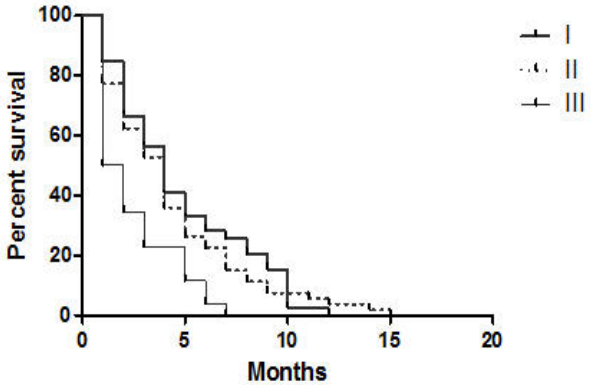

Figure 5: Overall survival by RPA class.

CONCLUSION

WBRT is an effective treatment in the management of BM. Despite the use of WBRT, outcomes are still poor and more efforts should be made to incorporate multimodality treatments including surgery, radiosurgery, chemotherapy and radiotherapy sensitizers to improve survival. Patients with RPA class I may be effectively treated with local resection or radiosurgery followed by WBRT, mainly in those patients with single metastases, higher KPS and controlled extra cranial disease.

REFERENCES

1. Wen PY, Black PM, Loeffler JS: Cancer: Principles and Practice of Oncology (ed 6). In Metastatic Brain Cancer Edited by: DeVita V, Hellman S, Rosenberg SA. Philadelphia, PA, Lippincott, WIlliams, & Wilkins; 2001:2655-2670.
2. Coia LR, Aaronson N, Linggood R, et al. A report of the consensus workshop panel on the treatment of brain metastases. Int J Radiat Oncol Biol Phys 1992; 23:223-227.
3. Paszat L, Shenouda G, Blood P, et al. The role of palliative radiotherapy for brain metastases. Can J Oncol 1996; 6(suppl 1):48-53.
4. Patchell RA, Regine WF: The rationale for adjuvant whole brain radiation therapy with radiosurgery in the treatment of single brain metastases. Technol Cancer Res Treat 2003, 2:111-115.
5. Lock M, Chow E, Pond GR, Do V, Danjoux C, Dinniwell R, Lea J, Bezjak A. Prognostic Factors in Brain Metastases: Can We Determine Patients Who Do Not Benefit from Whole-brain Radiotherapy? Clinical Oncology 2004:16, 332-338
6. Sundstrom JT, Minn H, Lertola KK, et al.: Prognosis of patients treated for intracranial metastase with whole-brain irradiation. Ann Med 1998, 30:296-299.
7. 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, 37:745-754.
8. Elisa Y Saito, Gustavo A Viani, Robson Ferrigno, Ricardo A Nakamura, et al., Whole brain radiation therapy in management of brain metastasis:results and prognostic factors. Radiation Oncology 2006, 1:20.
9. Mintz AH, Kestle J, Rathbone MP,et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with single brain metastasis. Cancer 1996; 78:1470–6.
10. Noordijk EM, Vecht CJ, Haaxma-Reiche H, et al. The choice of treatment of single brain metastasis should be based on extracranial tumour activity and age. Int J Radiat Oncol Biol Phys 1994; 29:711–7.
11. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322:494–500.
12. Andrews DW, Scott CB, Sperduto PW, Flanders L, Gaspar M, Schell M, Werner-Wasik W, Demas J, Ryu J, Bahary: 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. Perez CA, Hendrickson FR: The palliation of brain metastases. Final results of the first two studies by the Radiation Therapy Oncology group. Int J Radiat Oncol Biol Phys 1980, 6:1-9.
14. Vermeulen SS: Whole brain radiotherapy in the treatment

of metastatic brain tumors. Semin Surg Oncol 1998, 14:64-71.

15. Berk L: An overview of radiotherapy trials for the treatment of brain metastases. Oncology (Huntingt) 1995, 9:1205-1212.
16. May N. Tsao, Nancy S. Lloyd, Rebecca K.S. Wong, Eileen Rakovitch, Edward Chow, Normand Laperriere. Radiotherapeutic management of brain metastases: A systematic review and meta-analysis. Cancer treatment reviews 2005, 31, 256–273.
17. Gerrard G. E., Prestwich R. J., Edwards A., Russon L. J., Richards F., Johnston C. F., Kwok-Williams M. C. Investigating the Palliative Efficacy of Whole-brain Radiotherapy for Patients with Multiple-brain Metastases and Poor Prognostic Features. Clinical Oncology 2003, 15: 422–428.
18. Edward Chow, Lori Davis, Lori Holden, May Tsao, and Cyril Danjoux. Prospective Assessment of Patient-Rated Symptoms Following Whole Brain Radiotherapy for Brain Metastases. Journal of Pain and Symptom Management 2005, 30:18-23.
19. Robinet G, Thomas P, Breton JL, et al. Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination inoperable brain metastasis of non-small cell lung cancer: Groupe Franc¸aise de Pneumo-Cancerologie (GFPC) protocol 95-1. Ann Oncol 2001, 12:59–67.
20. Antonadou D, Coliarakis N, Paraskevaidis M, et al. Whole brain radiotherapy alone or in combination with temozolamide for brain metastases. A phase III study. Int J Radiat Oncol Biol Phys 2002, 54:93.
21. Mornex F, Thomas L, Mohr P, et al. Randomized phase III trial of fotemustine versus fotemustine plus whole brain irradiation in cerebral metastases of melanoma. Cancer Radiother 2003, 7(1):1–8.
22. Shenglin Ma, Yaping Xu, Qinghua Deng, Xinmin Yu. Treatment of brain metastasis from non-small cell lung cancer with whole brain radiotherapy and Gefitinib in a Chinese population. Lung Cancer 2009, 65: 198–203.
23. Nicolas Penel, Anne Brichet, Bernard Prevost, Alain Duhamel, Richard Assaker, Franc¸ois Dubois, Jean-Jacques Lafitte. Prognostic factors of synchronous brain metastases from lung cancer. Lung Cancer 2001, 33: 143–154.
24. Cocconi G, Lottici R, Bisagni G, et al. Combination therapy with platinum and etoposide of brain metastases from breast carcinoma. Cancer Invest 1990; 8: 327-334.
25. Boogerd W, Dalesio O, Bais EM, van der Sande JJ. Response of brain metastases from breast cancer to systemic chemotherapy. Cancer 1992; 69:972- 980.