**Original Article**
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# Different Fractionation in Whole Brain Irradiation for Multiple Brain Metastases

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## Abstract

**Background:** This study compared the efficacy of two commonly used fractionation schedules for palliative whole brain irradiation in patients with brain metastases, and assessed the association of the Radiotherapy Therapy Oncology Group (RTOG) Recursive Partitioning Analysis for brain metastases (RPA) to survival with each schedule.

**Methods:** Patients with multiple (more than three) brain metastases were assigned to receive whole brain irradiation in 20 Gy over 5 fractions (group 1) or 30 Gy over 10 fractions (group 2). Primary outcome was response and overall survival in each group. Secondary outcome was the RPA classification relation to overall survival and its possible role in the choice between schedules.

**Results:** There were 54 patients in group 1 and 39 in group 2. There was no significant difference in response ($P$=0.67) or overall survival between the two groups ($P$=0.55). However RPA 1 patients had significantly better overall survival than RPA 2 patients in both group 1 ($P$=0.02) and group 2 ($P$=0.0014), but no significant difference was found when overall survival of RPA 1 patients of both groups were compared ($P$=0.47) or that of RPA 2 patients in both groups ($P$=0.29).

**Conclusion:** The two schedules assessed are comparable in terms of response and overall survival. RPA 1 patients have better overall survival than RPA 2 patients regardless of the fractionation used. A schedule of 20 Gy over 5 fractions should be routinely considered for RPA 2 patients as they are less likely to experience late toxicity. This schedule may be considered for RPA 1 patients, however larger randomized trials are needed to confirm the results and assess differences in neurocognitive function.

***Keywords:*** Brain metastases, Radiotherapy, Fractionation, RP

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## Introduction

Brain metastases occur in 20%-40% of cancer patients.[1] Outlook is poor for these patients with a median survival of 1-2 months with corticosteroids[2] which may be improved to six months with whole brain radiation therapy (WBRT).[3,4] Protracted radiation schedules are obviously a burden for these

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patients.[5] In many cases priority should be given to controlling symptoms more than concerns of radiation-induced late effects.[6] Patients with multiple (more than three metastases) are rarely considered eligible for surgical removal or stereotactic treatment of the metastases.[7] These patients should particularly be considered as candidates for shorter courses of radiation because their treatment time depends primarily on the WBRT duration. The aim of this study is to compare 20 Gy WBRT over 5 fractions to 30 Gy over 10 fractions in patients with multiple metastases for differences in response and overall survival (OS). A secondary endpoint is to assess OS differences of patients when classified according to the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) classification for brain metastases and to identify a possible subgroup more suited for hypofractionation.

## Patients and Methods

The protocol was reviewed and accepted by the Institutional Review Board of the South Egypt Cancer Institute and written informed consent was obtained from all participating patients. Entry criteria included patients 18 years and older with confirmed systemic malignant disease. A contrast-enhanced MRI scan that showed more than three brain metastases was required. Patients with Karnofsky Performance Status (KPS) of 70 or more were allowed to participate. The patients were assigned to receive 20 Gy WBRT in 5 fractions (group 1) or 30 Gy in 10 fractions (group 2). WBRT was applied using standard techniques with the dose prescribed to the midline. Clinical evaluation and MRI scans were performed at three months, and the patients were followed up at three-month intervals. In accordance with RTOG definitions, disappearance of all lesions and a stable neurological examination after withdrawal of steroids was considered complete response (CR). Partial response (PR) was defined as a greater than 50% decrease in all lesions with stable neurological examination, and stable disease (SD) was considered 50% or less decrease in the size of all lesions, with stable neurological examination. Progressive disease (PD) was increase in the size of any lesion, development of new lesions, or deterioration in the neurological examination.[8] All patients were classified according to the RTOG RPA for brain metastases (Table 1).[9] Acute toxicities were those that occurred within 90 days of the start of radiotherapy, while late toxicities were those identified thereafter. Statistical analysis included the chi-square test for qualitative variables and t-test for continuous variables. The Kaplan-Meir method for generation of actuarial survival curves was used and comparison was via the log-rank test.

## Results

A total of 93 patients participated in this study from June 2011 to June 2014. Patients' characteristics are summarized in Table 2. There were 54 patients in group 1 who received the short course radiotherapy and 39 patients in group 2 who

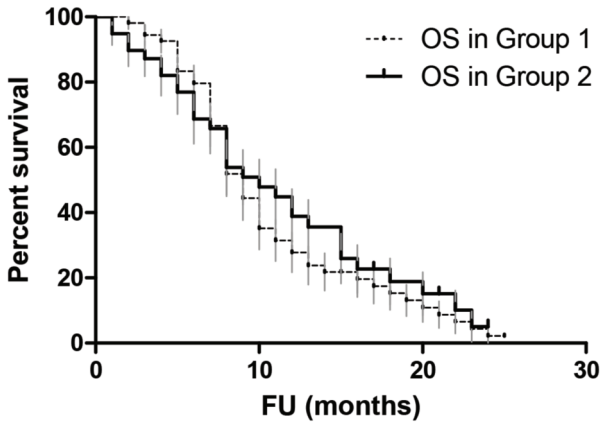


**Figure 1.** OS in group 1 *vs* group 2.

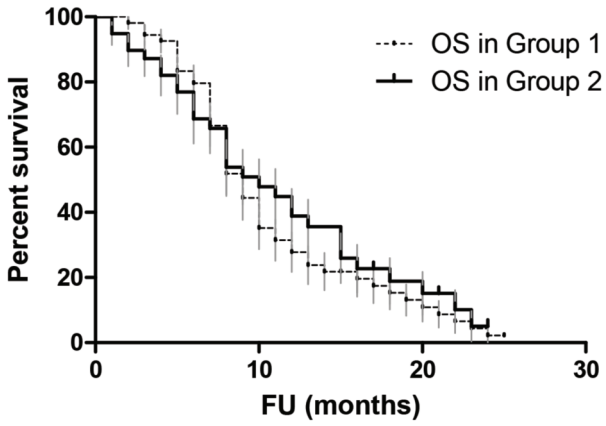


**Figure 2.** OS in group 1 according to RPA.

**Table 1.** Recursive Partitioning Analysis (RPA) for brain metastases.

| | Class 1 | Class 2 | Class 3 |
|---|---|---|---|
| KPS* | ≥70 | ≥70 | <70 |
| Primary status | Controlled | Uncontrolled | |
| Age (years) | <65 | ≥65 | |
| Extracranial disease status | Brain only | Brain plus other sites | |

*KPS: Karnofsky Performance Status

received the longer course which is still considered standard by many institutions. The two groups were well-matched with no statistical significance in terms of baseline characteristics. When assigned RPA classes, 27 (50%) patients in group 1 and 24 (61%) in group 2 were considered RPA 1; the rest were classified as RPA 2.

Response as assessed by MRI at three months is shown in Table 3. There were no cases of CR. Partial response and SD were achieved in 46 (85%) patients from group 1 and 34 (87%) patients from group 2. There was no statistically significant difference between responses in the two groups. Toxicity was limited in both groups. Acute toxicity was in the form of grade 1 nausea and vomiting in 5 (9.3%) patients from group 1 and in 2 (5%) patients in group 2 ($P$=0.51). Acute grade 1 skin toxicity occurred in 18 (33%) patients in group 1 and in 19 (49%) patients in group 2 ($P$=0.13). Late toxicity was observed only in the skin and was seen in 4 (7%) patients in group 1 and in 5 (13%) from group 2 ($P$=0.38). There was no higher grade toxicity observed.

Overall survival of the two groups is shown in figure 1. We observed no statistically significant difference in the survival of the two groups ($P$=0.55). The median survival was 9 months in group 1 and 10 months in group 2. However, when the patients in group 1 were compared according to RPA, those who were classified as RPA 1 had significantly better survival compared to patients who were RPA 2 ($P$=0.02; Figure 2). The median survival was 11 months for RPA 1 patients and 8 months for RPA 2 patients. Similarly, when the patients in group 2 were compared according to RPA, the RPA 1 patients had better OS ($P$=0.0014) compared to those who were RPA 2 (Figure 3). In group 2, the median survival was 15 months for RPA 1 patients and 8 months for RPA 2 patients. In order to further assess the effect of RPA on OS, we compared survival of RPA 1 patients in group 1 to that of RPA 1 patients in group 2. There was no statistically significant difference in OS of RPA 1 patients, regardless of the fractionation they received ($P$=0.47, Figure 4). Similar findings were encountered when comparing the OS of RPA 2 patients in group 1 with RPA 2 patients in group 2, which was not statistically significant ($P$=0.29; Figure 5).

## Discussion

Brain metastases outnumber primary neoplasms by at least 10 to 1, occurring in up to

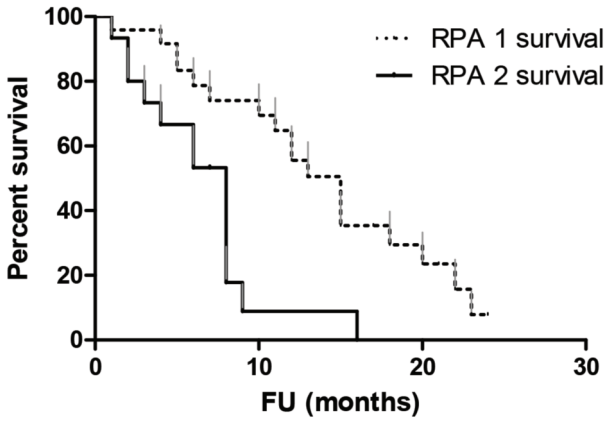


**Figure 3.** OS in group 2 according to RPA.

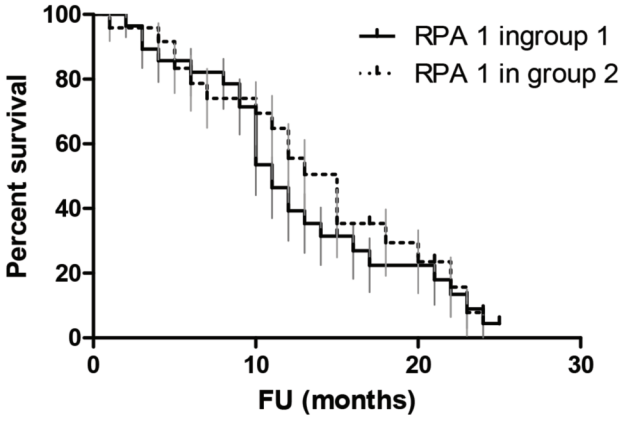


**Figure 4.** OS of RPA 1 patients in each group.

**Table 2.** Patients' characteristics.

| | Group 1 (54 patients) | Group 2 (39 patients) | *P*-value |
|---|---|---|---|
| Age (years) median (range) | 52 (20-73) | 53 (23-71) | 0.87 |
| **Sex** | | | |
| Male | 25 (46%) | 19 (49%) | 0.82 |
| Female | 29 (54%) | 20 (51%) | |
| **Histological status** | | | |
| Adenocarcinoma | 26 (48%) | 17 (44%) | 0.98 |
| Squamous cell carcinoma (SCC) | 15 (28%) | 12 (31%) | |
| Nonsmall cell lung cancer (NSCLC) | 6 (11%) | 5 (13%) | |
| Renal | 5 (9%) | 3 (7%) | |
| Spindle | 2 (4%) | 2 (5%) | |
| **Primary tumor** | | | |
| Breast | 13 (24%) | 11 (28%) | 0.99 |
| Lung | 10 (19%) | 9 (23%) | |
| MUO | 9 (17%) | 5 (13%) | |
| Bladder | 6 (11%) | 4 (10%) | |
| Renal | 5 (9%) | 3 (7.5%) | |
| Colon | 5 (9%) | 3 (7.5%) | |
| Esophagus | 2 (4%) | 1 (3%) | |
| Sarcoma | 2 (3.5%) | 2 (5%) | |
| Ovarian | 2 (3.5%) | 1 (3%) | |
| **Neurological function** | | | |
| Deficit | 20 (37%) | 12 (31%) | 0.53 |
| No deficit | 34 (63%) | 27 (69%) | |
| **RPA class** | | | |
| 1 | 27 (50%) | 24 (61%) | 0.26 |
| 2 | 27 (50%) | 15 (39%) | |
| **KPS** | | | |
| 90-100 | 18 (33%) | 13 (33 %) | 1.0 |
| 70-80 | 36 (67%) | 26 (67 %) | |
| **Primary site control** | | | |
| Controlled | 33 (61%) | 25 (64%) | 0.77 |
| Uncontrolled | 21 (39 %) | 14 (36 %) | |
| **Metastases site** | | | |
| Brain alone | 28 (52 %) | 18 (46 %) | 0.88 |
| Brain and 1 extracranial site | 14 (26 %) | 11 (28 %) | |
| Brain and 2 or more extracranial sites | 12 (22 %) | 10 (26 %) | |

40% of cancer patients; multiple metastases are seen in more than 70% of cases.[10] Addition of stereotactic radiotherapy as treatment for multiple brain metastases has not proven to be of benefit for survival.[8,11] Palliative WBRT is still the pillar of treatment for these patients however fractionation schedules remain judgmental.[6] In this study, we have prospectively examined two of the most commonly used schedules, 20 Gy over 5 fractions and 30 Gy over 10 fractions, for differences in OS and response. We sought to identify patients most suitable for each schedule according to RPA classification for brain metastases.

In this trial we assessed response according to the previously discussed RTOG criteria.[8] Partial response was achieved in 30 (55%) patients from group 1 and in 19 (49%) from group 2. Stable disease was observed in 16 (30%) patients in group 1 and in 15 (38%) from group 2, while progression was documented in 8 (15%) in group 1 and in 5 (13%) patients from group 2. There was no statistically significant difference between the two groups ($P$= 0.67). These results were similar to those achieved by patients who received WBRT in 2.5 Gy fractions for a total dose of 37.5 Gy in

**Table 3.** Response assessed by MRI at three months.

| Radiographic response | Group 1 (n=54) | Group 2 (n=39) | *P*-value |
|---|---|---|---|
| Partial response (PR) | 30 (55%) | 19 (49%) | 0.67 |
| Stable | 16 (30%) | 15 (38%) | |
| Progression | 8 (15%) | 5 (13%) | |

the RTOG 9508 trial, 8 where at the three-month assessment, 6 (5%) patients had CR, 42 (31%) had PR, and 17 (13%) had SD whereas 13 (10%) patients had progression. Response after the two fractionation schemes assessed in this study and the more intense scheme used in the RTOG trial were comparable.

In the current study there was no statistically significant difference between OS in the two groups when the survival curves were compared ($P$=0.55), with a median survival of 9 months in group 1 and 10 months in group 2. One study by Chatani et al.[12] compared the same two fractionation schemes and similarly found no significant difference in median survival among the two groups, which was 3.4 months for the group that received 30 Gy in 10 fractions versus 2.4 months for the group that received 20 Gy in 5 fractions. The OS was noticeably lower than the present study which was probably due to the fact that the trial included only metastatic lung cancer patients, whereas we included all cases with breast cancer being the most common diagnosis. In addition, the introduction of many chemotherapeutic agents since that study was conducted might have improved survival. A comparison of these two schedules was also reported as a part of several schedules compared with a control of 3000 Gy in 10 fractions in an RTOG study,[4] which concluded that there was no statistically significant OS among the groups.

A review of literature by Tsao et al.,[13] which was published in 2006 and updated in 2012 assessed altered fractionation WBRT in 1420 metastatic brain cancer patients who participated in eight trials. Overall survival was reported in six of these trials. The authors considered both 30 Gy over 10 fractions and 20 Gy over 5 fractions "standard fractionation". The metaanalysis included trials that compared these two fractionation schemes with each other and with other schedules, considered "altered fractionation". The researchers concluded that no benefit existed in terms of OS or neurologic function with altered WBRT dose-fractionation schedules compared to standard fractionation.

In an attempt to better define patient groups most suited for each standard schedule, RPA classes for brain metastases were used to as classification for the patients in the present study. There were 27 patients with OS who were class 1 (50%) and 27 patients who were class 2 (50%) in group 1. A significant survival difference was found ($P$=0.02) between the classes with a median survival of 11 months for class 1 and 8 months for class 2. In group 2, there were 24 (61%) OS patients classified as class 1 and 15 (39%) who were class 2, which was significant ($P$=0.0014). Median survival was 15 months for class 1 versus 8 months for class 2. This is in agreement with findings of the randomized multicenter RTOG trial 9508,[8] in which upon multivariate analysis, RPA class predicted survival of brain metastases patients ($P \leq 0.0001$).

## Conclusion

RPA classes for brain metastases can aid in the

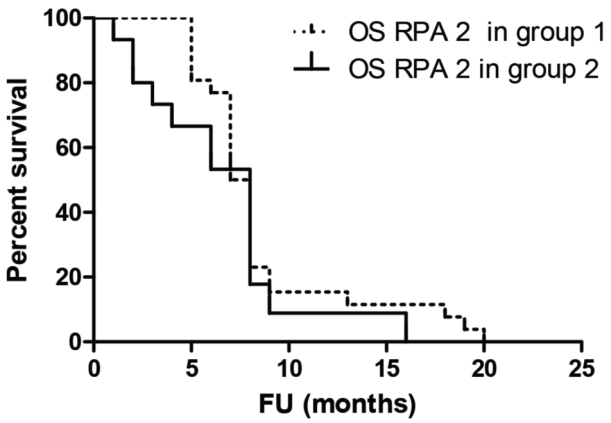


**Figure 5.** OS of RPA 2 patients in each group.

standardization of the choice between commonly used palliative WBRT schedules. In this study we observed no statistically significant difference in response or survival after WBRT for multiple brain metastases given in 20 Gy over 5 fractions or in 30 Gy over 10 fractions. Both schedules had acceptable toxicity. When the patients were classified according to RPA classification for brain metastases, RPA 1 patients had significantly better survival than RPA 2, regardless of the fractionation they received. Therefore, 20 Gy over 5 fractions should be routinely considered for multiple metastases for RPA 2 class patients who are less likely to experience neurocognitive deficit or other late toxicities. This treatment can save precious time for the patient, in addition to the department economics and logistic load of the 30 Gy over 10 fraction schedule. It can also be considered for RPA 1 patients, but multicenter randomized trials are needed to confirm differences in late toxicity.

## Conflict of Interest

No conflict of interest is declared.

## References


1. Loeffler, JS; Patchell, RA; Sawaya R. Treatment of metastatic cancer. In: Devita, VT; Hellman, S; Rosenberg, SA, editors. Canc: principles and practice of oncology. 5th ed. Philedelphia: Lippincott-raven; 1997. p. 2523.
2. Weissman DE. Glucocorticoid treatment for brain metastases and epidural spinal cord compression: a review. *J Clin Oncol.* 1988;6(3):543-51.
3. Diener-West M, Dobbins TW, Phillips TL, Nelson DF. Identification of an optimal subgroup for treatment evaluation of patients with brain metastases using RTOG study 7916. *Int J Radiat Oncol Biol Phys.* 1989;16(3):669-73.
4. Borgelt B, Gelber R, Kramer S, Brady LW, Chang CH, Davis LW, et al. 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):1-9.
5. Chow E, Fung K, Panzarella T, Bezjak A, Danjoux C, Tannock I. A predictive model for survival in metastatic cancer patients attending an outpatient palliative radiotherapy clinic. *Int J Radiat Oncol Biol Phys.* 2002 ;53(5):1291-302.
6. Meyer A, Steinmann D, Malaimare L, Karstens JH, Bremer M. Prediction of prognosis regarding fractionation schedule and survival in patients with whole-brain radiotherapy for metastatic disease. *Anticancer Res.* 2008;28(6B):3965-9.
7. Gasper LE, Mehta MP, Patchell RA, Burri SH, Robinson PD, Morris RE, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol.* 2010; 96:17-32.
8. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, 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(9422):1665-72.
9. 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):1001-6.
10. Patchell RA. The management of brain metastases. *Cancer Treat Rev.* 2003;29(6):533-40.
11. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys.* 1999 ;45(2):427-34.
12. Chatani M, Matayoshi Y, Masaki N, Inoue T. Radiation therapy for brain metastases from lung carcinoma. Prospective randomized trial according to the level of lactate dehydrogenase. *Strahlenther Onkol.* 1994;170(3):155-61.
13. Tsao MN, Lloyd N, Wong RK, Chow E, Rakovitch E, Laperriere N, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev.* 2012; 4:CD003869.