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# Overall Survival and Related Prognostic Factors in Metastatic Brain Tumors Treated with Whole Brain Radiation Therapy

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**Abstract:** Multiple brain metastases are a common health problem, frequently found in patients with cancer. The prognosis, even after treatment with Whole-Brain Radiation Therapy (WBRT) is poor with an average expected survival time of >6 months. To evaluate the prognostic factors associated with overall survival in patients with brain metastasis treated with Whole Brain Radio Therapy (WBRT) and estimate the potential improvement in survival for patients with brain metastases, stratified by Karnofsky Performance Status (KPS), gender, age, number of lesions, primary tumor site, surgery, chemotherapy and radiation doses and fractionation. From January 2007 to May 2010, 54 medical records of patients with diagnosis of brain metastasis, who received WBRT in the shohadaye tajrish in Tehran Iran were analyzed. The most common primary tumor type was breast (22.2%) followed by lung (21.9%), unknown primary (16.6%) and solitary brain metastasis was present in 29.6% of patients. The surgery followed by WBRT was used in 11.1% of patients and 88.9% of others patients were submitted at WBRT alone. About 36 patients (66.7%) received the fractionation schedule of 30 Gy in 10 fractions. The prognostic factors evaluated for overall survival were Karnofsky Performance Status (KPS), gender, age, number of lesions, primary tumor site, surgery, chemotherapy and radiation doses and fractionation. The OS in 1 and 2 years was 15, 3, 5 and 4%, respectively and the median survival time was 3.5 months. In the analysis, the significant prognostic factors associated with better survival were: KPS>70 ($p<0.001$), neurosurgery ($p<0.001$), primary tumor site breast ($p<0.001$) and solitary brain metastasis ($p = 0.01$). In this series, the patients with higher perform status or primary tumor site breast or treated with surgery followed by whole brain radiotherapy had better survival. This data suggest that patients with cancer and a single metastasis to the brain may be treated effectively with surgical resection plus radiotherapy. The different gender, age, radiotherapy doses and fractionation schedules did not altered survival.

**Key words:** Overall survival, prognostic factors, whole brain radiation, therapy, brain metastases, Iran

## INTRODUCTION

Metastatic disease to the brain occurs in approximately 10-30% of patients with cancer and can limit survival and worsen quality of life. Glucocorticoids and Whole-Brain Radiation Therapy (WBRT) have been the mainstay of intracranial treatments while craniotomy for tumor resection has been the standard local therapy Wen *et al.* (2008). The risk of developing brain metastases varies according to primary tumor type with lung cancer accounting for approximately one half of all brain metastases (Johnson and Young, 1996). The prognosis of patients with brain metastases is poor, the median survival time of untreated patients is approximately 1 month (Coia, 1992) with treatment, the overall median survival time after diagnosis is approximately 4 months (Harwood and Simson, 1977; Gaspar *et al.*, 1997). The most widely used treatment for patients with multiple brain metastases is WBRT. The main goal of WBRT is to improve neurologic deficits caused by the metastases and surrounding edema and to prevent any further deterioration of neurologic function. The extent of improvement after WBRT is directly related to the time from diagnosis to radiation therapy and early treatment is generally associated with a better outcome (Patchell and Regine, 2003; Lassman and DeAngelis, 2003). 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 (Borgelt *et al.*, 1981).

In most series, the use of fractionated WBRT extends a patient's survival by 3-5 months. Although, more patients harbor multiple rather than solitary brain metastases at presentation, few gains have been made in the treatment of this disease. Most physicians expect a poor outcome in a patient with multiple brain metastases. Treatment regimens are often palliative in nature. The overall response rate to WBRT ranges from 50-85% in

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various studies. Traditionally, surgical resection has been offered rarely to patients with multiple metastases because the resection-related morbidity in multiple brain locations was believed to be excessive and the risk for developing additional tumors was perceived to be high. The majority of patients who achieve local tumor control die from progression of extracranial disease whereas the cause of death is most often due to CNS disease in patients with recurrent brain metastases (Lassman and DeAngelis, 2003; Borgelt *et al*., 1981). In this study, the prognostic factors were evaluated for survival in patients with diagnosis of brain metastasis who receive WBRT alone or postoperative (Borgelt *et al*., 1981).

## MATERIALS AND METHODS

The records of 54 patients with brain metastases, who were treated with WBRT at the institution between January 2007and May 2010 were analyzed retrospectively. At diagnosis of brain metastasis the following variables were analyzed for survival: Karnofsky Performance Status (KPS), gender, age, number of lesions, primary tumor site, surgery, chemotherapy and radiation doses and fractionation showed in Table 1. The supportive care (Dexamethasone IM) and neurological status was not evaluated. Chemotherapy was administered to the patients with systemic disease in activity after WBRT.

Table 1: Characteristic of treatment and patients

| Characteristic | Number | Percentage |
|---|---|---|
| **Sex** | | |
| Male | 28 | 51.9 |
| Female | 26 | 48.1 |
| **KPS** | | |
| <70 | 30 | 55.6 |
| > = 70 | 24 | 44.4 |
| **Neurosurgery** | | |
| Yes | 6 | 11.1 |
| No | 48 | 88.9 |
| **Dose (gy) Fractionation (Fr)** | | |
| 40 Gy/20 fr | 18 | 33.3 |
| 30 Gy/10 fr | 36 | 66.7 |
| **Number lesions** | | |
| Single | 16 | 29.6 |
| Multiple | 38 | 70.4 |
| **Chemotherapy** | | |
| Yes | 10 | 18.5 |
| No | 44 | 81.5 |
| **Primary disease control** | | |
| Yes | 28 | 51.9 |
| No | 26 | 48.1 |
| **Extra cranial metastasis** | | |
| Yes | 37 | 68.6 |
| No | 17 | 31.4 |
| **Ptimery tumor site breast** | | |
| Yes | 12 | 46.1 |
| No | 14 | 53.9 |
| | Median | Range |
| Patients | 51 | 18-85 |

Brain metastasis were measurable by CT or MRI scan. WBRT was performed in all patients with cobalt 60 γ rays. The whole brain was irradiated by usual bilateral fields. The total dose was 30-40 Gy with a median of 35 Gy in daily fractions of 2.0-3.0 Gy.

During the study period 2 fractionation schemes were used conventional fractionation with daily fractions of 2 Gray (Gy), 5 days per week to a planned total dose of 40 Gy (n = 18) and hypofractionation with daily fractions of 3 Gy, 5 days week$^{-1}$ to a planned total dose of 30 Gy (n = 36).

The surgical resection was indicated in single brain metastases with favorable localization and control systemic disease. The supportive care (Dexamethasone IM) was introduced in begin of treatment or during radiotherapy.

## RESULTS AND DISCUSSION

The OS in 1 and 2 years was 15, 3, 5 and 4%, respectively and the median survival time was 3.5 months. About 2 patients were alive in moment of this analysis with a median survival time of 2.3 years. All these patients had single brain metastasis, high KPS, cranial extra disease controlled and were submitted to neurosurgery before WBRT. The median survival time for all the studied patients was 3.5 months (CI 95% 2.3-6, 4). The significant prognostic factors associated with better survival were: higher KPS ($p<0.001$), neurosurgery ($p<0.001$), single metastases ($p = 0.01$)and primary tumor site breast ($p<0.001$) showed in Table 2.

As improvements in the care of cancer patients are achieved, longer survival times will be expected. The diagnosis of a patient with multiple brain metastases will become even more common. Because of advances in the diagnoses and management of this condition, most patients receive palliative treatment and majorities don't die from metastases. In this study, patients were evaluated with brain metastasis, multiples or solitaries lesions who receive WBRT alone or WBRT after surgical resection of lesion.

Studies of ultrarapid fractionated WBRT (10 Gy in 1 fraction, 12 Gy in 2 fractions, 15 Gy in 2 fractions over 3 days) as carried out by RTOG and other investigators showed a possible increased risk of herniation and death within a few days of treatment and are generally avoided. Likewise, no advantage was seen with extended fractionation (50 Gy in 20 fractions or 54.4 Gy at 1.6 Gy twice daily) compared to the more commonly prescribed 30 Gy in 10 fractions (Borgelt *et al*.,

Table 2: Univariate analysis of significant factors for survival (Log rank test)

| Variables | Number | Percentage | Percentage of OS 12 months | p-value |
|---|---|---|---|---|
| **Age** | | | | |
| <65 years | 39 | 72.3 | 29 | 0.84 |
| > = 65 years | 15 | 27.7 | 22 | |
| **Sex** | | | | |
| Male | 28 | 51.9 | 24.4 | 0.17 |
| Female | 26 | 48.1 | 26.6 | |
| **Kps** | | | | |
| <70 | 30 | 55.6 | 11.4 | <0.001 |
| > = 70 | 24 | 44.4 | 31.2 | |
| **Neurosurgery** | | | | |
| Yes | 6 | 11.1 | 39.2 | <0.001 |
| No | 48 | 88.9 | 11.2 | |
| **Dose (gy) Fractionation (Fr)** | | | | |
| 40 Gy/20 Fr | 18 | 33.3 | 25.3 | 0.12 |
| 30 Gy/10 Fr | 36 | 66.7 | 22.7 | |
| **Number lesions** | | | | |
| Single | 16 | 29.6 | 31.7 | 0.01 |
| Multiple | 38 | 70.4 | 16.8 | |
| **Chemotherapy** | | | | |
| Yes | 10 | 18.5 | 26.8 | 0.1 |
| No | 44 | 81.5 | 20.7 | |
| **Primary disease Control** | | | | |
| Yes | 28 | 51.9 | 30.1 | 0.11 |
| No | 26 | 48.1 | 20.2 | |
| **Extra cranial metastasis** | | | | |
| Yes | 37 | 68.6 | 21.1 | 0.09 |
| No | 12 | 31.4 | 22.9 | |
| **Ptimery tumor site breast** | | | | |
| Yes | 12 | 46.1 | 25.7 | <0.001 |
| No | 14 | 53.9 | 7.8 | |

1981, 1980; Kurtz *et al*., 1981; Berk, 1995). As a result, the most common WBRT fractionation schemes include 30 Gy in 10 fractions, 37.5 Gy in 15 fractions and 40 Gy in 20 fractions. Regimens using 10 or fewer fractions which are thought to have increased toxicity are used in patients with poor prognosis, since such patients are not expected to live long enough to experience serious side effects. In this study, 40 Gy in 20 fractions or 30 Gy in 10 fractions were not associated with any benefit to survival (p = 0.12). The according with our data, patients with good prognosis such as those with single metastasis with controlled systemic disease should be treated with prolonged fractionation to decreased the likelihood of late CNS toxicity.

The goal of postoperative WBRT in patients with solitary brain metastasis is to destroy microscopic residual cancer cells at the site of resection and others localizations within the brain. Until recently, the value of this approach was derived exclusively from retrospective studies (Borgelt *et al*., 1981; Berk, 1995; Rades *et al*., 2004). Several studies found that adjuvant WBRT reduced the recurrence rate and two studies demonstrated prolong survival (Rades *et al*., 2004; Patchell *et al*., 1990). One randomized trial has examined the role of pos operative WBRT in patients with single metastasis (Patchell *et al*., 1990). In this study patients who received radiation were significantly less likely to fail in the brain (18 and 70%) and were significantly less likely to die of neurological causes. In the series, patients submitted at resection plus WBRT were significantly less likely to die (p = 0.01), mainly the patients with solitary metastasis and higher KPS.

The end point of this study was to evaluate the different prognostic factors related with overall survival in patients with brain metastasis. In the data, the prognostic factors associated with better survival were: higher KPS (p<0.001), solitary metastasis (p = 0.01), resection of lesion (p<0.001), primary tumor site breast (p<0 001) all these prognostic factors were showed for others researchers (Borgelt *et al*., 1981; Lang and Sawaya, 1998; Patchell *et al*., 1998; Schellinger *et al*., 1999; Gaspar *et al*., 2000). The others factors (age, gender, chemotherapy, dose and fractionation schedule) analyzed were not associated with any effect in survival.

In this study, patients with multiple brain metastases that received WBRT had poorer survival than patients with single brain metastases (p = 0.01). The supportive care did not evaluated (Dexamethasone IM) plus radiotherapy versus supportive care alone or WBRT alone versus supportive care. However, Hempen *et al*. (2002) compared WBRT plus supportive care (oral prednisone) versus supportive care alone. Median survival in the prednisone alone arm was 10 weeks compared with 14 weeks in the combined arm (p-value not stated). The proportion of patients with an improvement in performance status was similar in the prednisone-alone and the combined WBRT and prednisone arms (63 versus 61%, respectively). Data on tumor response, intracranial progression-free duration, quality of life and toxicity were not reported.

In the study no patients received Radiosurgery (SRS); however, a larger recently published trial (RTOG 95-08) (Breneman *et al*., 1997) provides compelling evidence for the use of SRS boost following WBRT in patients with newly diagnosed one to three brain metastases. In the RTOG 95-08, SRS after WBRT has been validated with level 1 evidence as a standard of care option in the management of patients with single brain metastases.

In other recent studies the role of WBRT following definitive treatment (surgery or SRS) of 1-3 metastases was most extensively evaluated in a trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC 22952-26001) which was presented at the American Society of Clinical Oncology (ASCO) meeting in 2009 . In this trial, 359 patients with one to three brain metastases were randomly assigned to WBRT or observation following definitive treatment of their metastases with either SRS (n = 199) or surgery (n = 160). Progression-free survival was significantly prolonged compared to observation (median 4.6 and 3.4 months, Hazard Ratio (HR) 0.71, 95% CI 0.58-0.88). At 24 months, significantly fewer patients had intracranial progression

after WBRT either at the original site or at new locations (31 and 54%). Despite the better control of the brain metastases, overall survival was virtually the same following WBRT (median 10.7 and 10.9 months) (Kondziolka *et al*., 1999).

## CONCLUSION

WBRT continues to be an efficacious treatment in the management of brain metastasis. mainly in those patients with single metastases, higher KPS and cranial extra disease controlled. Despite the use of WBRT, outcomes are poor and efforts should be made to incorporate multimodality approaches including surgery, radiosurgery, chemotherapy and radiotherapy sensitizers to improve survival.

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