Original Article

Prognostic factors affecting the survival of patients with brain metastasis treated by whole brain radiotherapy: A regional cancer center experience from North West India

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ABSTRACT

Background: Brain metastases are unfortunate consequences frequently found in patients with advanced cancer. The prognosis is poor with an average expected survival time of <6 months by all possible efforts (including radiotherapy). This retrospective study aims to determine survival and prognostic factors in patients with brain metastases who underwent whole brain radiotherapy (WBRT). **Materials and Methods:** From January 2005 to August 2010, a total of 186 patients with brain metastasis was analyzed with the help of available medical records. Of these, 140 patients who received WBRT ± chemotherapy were included in this study. The prognostic factors evaluated for overall survival were age, gender, Eastern Cooperative Oncology Group performance status, number of lesions, primary tumor site, extracranial metastases, chemotherapy, and radiotherapy. **Results:** The median overall survival was 4 months (95% confidence interval: 3.56-4.43), while 1- and 2-year survival rates were 8.57% and 3.57%, respectively. The most common primary tumor sites were the lung (n = 82; 44.08%) followed by the breast (n = 46; 24.73%), kidney (n = 11; 5.91%), and unknown primary (n = 11; 5.91%). The median overall survival was maximum (4 months) in patients with breast cancer. The 1-year overall survival rate was 8.57% (n = 12) for the whole group and 18.2% (6/33) in breast cancer patients (P = 0.058). In this study, the patients with higher performance status (P = 0.199), solitary brain metastasis (P < 0.0001), female (P = 0.201), and primary tumor under control (P = 0.223) had better survival. **Conclusion:** This study suggests that overall prognosis of patients with brain metastasis remains to be poor, 1-year survival being <10%. Patients with solitary metastasis and carcinoma breast have comparatively better prognosis.

Key words: Brain metastasis, prognostic factors, solitary metastasis, whole brain radiotherapy

INTRODUCTION

Brain metastasis is one of the most feared consequences of cancer. It is devastating both to patients and their families. Progression of brain metastases may cause headache, nausea, vomiting, neurological deficits, cognitive decline, delirium, and eventually death. Patients with brain metastases present dilemma for palliative health care professionals in terms of whether to proceed with whole brain radiotherapy (WBRT) or hospice placement. Metastasis to the brain occurs in approximately 20% of the patients with limited survival and worse quality-of-life.[1] The metastatic process is a complex phenomenon, and involves several genes. Recent studies recognize cell adhesion proteins especially E-cadherin and matrix metalloproteinases, growth factor receptors such as epidermal growth factor receptor (EGFR), ErbB-2, vascular endothelial growth factor, and contributions from signal transduction pathways in addition to the activation of specific chemokines/cytokines, as major regulators of the metastatic process.[2] ErbB-2 amplification/over-expression is a prognostic and predictive factor for the development of central nervous system (CNS) metastases.[3] Genes involved in apoptosis, such as caspase 2, transforming

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growth factor-β inducible early gene, and neuroprotective heat shock protein 70 are underexpressed in metastatic brain tumors.[4]

Glucocorticoids and WBRT have been the mainstay of treatment in multiple lesions while for solitary lesions, craniotomy for tumor resection (if feasible) has been the standard local treatment. The median survival of untreated patients is about a month, 1.6 months in patients treated with steroids only, 3.6 months in patients treated with radiotherapy and 8.9 months in patients treated with neurosurgery followed by radiotherapy.[5,6] Some of the strong prognostic factors for survival are: Performance status, response to steroids, and status of systemic disease. WBRT can improve the neurologic deficits caused by the metastases and surrounding edema and may prevent further deterioration in the neurologic functions. The response to WBRT is directly related to the time from diagnosis to radiation therapy and the earlier management is generally associated with a better outcome.[7,8]

The overall improvement in symptoms with WBRT ranges from 50% to 85% in various series. Traditionally, surgical resection has been offered rarely to patients with multiple metastases because of resection related excessive morbidity. In most of the cases, the cause of death is the recurrent/residual brain metastases; while the patients who achieve control of cranial metastasis usually die from progressive extracranial disease.[7,9] In this study, the prognostic factors for survival were evaluated in patients with brain metastasis who received WBRT.

MATERIALS AND METHODS

Between January 2005 and August 2010, the medical records of 186 patients with brain metastases were analyzed retrospectively. Of these, 46 patients not willing for radiotherapy and who chose only best supportive care were excluded from the study. All the remaining 140 patients were treated with WBRT along with dexamethasone, mannitol, and other supportive treatment. Patient characteristics are described in Table 1. The prognostic factors for overall survival considered were age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, number of brain lesions, primary tumor site, extracranial metastases, treatment of primary disease, and radiotherapy. Table 2 shows the primary site wise survival. The survival times were considered as the time between diagnoses of brain metastasis and the last follow-up or recorded death.

Brain metastases were detected by computed tomography or magnetic resonance image scan. All patients were treated with WBRT on telecobalt units Therateron 780 C and 780 E. The WBRT was given by bilateral portals. The total dose delivery was 30-36 Gy with a median of 30 Gy delivered in 2 weeks, five fractions/week 3 Gy/fraction. The supportive care (dexamethasone and mannitol) was started at the beginning of treatment and continued during radiotherapy. Chemotherapy for primary tumor was administered to the patients with good performance status and progressive systemic disease. All statistical analyses were performed using SPSS for windows, version 20.0 (IBM Corp., Armonk, New York, USA).

RESULTS

A total of 140 patients was analyzed who completed WBRT and came for follow-up. The survival results were computed by recorded deaths (97 cases) or last follow-up (43 cases). The median overall survival was 4 months (95% confidence interval [CI]: 3.561-4.439), and the 1- and 2-year survival rates were 8.57% and 3.57%, respectively. One patient of carcinoma breast (primary under control) with brain metastasis was alive at the time of this analysis with survival time of 4.2 years. Those patients who had solitary brain metastasis ($P < 0.0001$), high ECOG performance status ($P = 0.199$), controlled extracranial disease ($P = 0.223$), and breast carcinoma ($P = 0.058$) had better survival [Tables 2 and 3]. The single most significant prognostic factor associated with better survival was solitary brain metastasis ($P < 0.0001$). One patient of head and neck cancer with brain metastasis survived till 1 year ($P = 0.03$). Three patients of breast cancer and two patients of lung cancer survived till 2 years of follow-up. Figure 1 shows Kaplan–Meier survival curve plotted against site of primary. The median overall survival for

Table 1: Characteristics of patients and treatment

Variables	Number	Percentage
Total patients	140	100
Sex		
Male	81	57.85
Female	59	42.15
Age		
<65 years	109	77.85
>65 years	31	22.15
ECOG performance status		
1–2	101	72.14
3-4	39	27.85
Number of lesion		
Single	25	17.86
Multiple	115	82.14
Primary tumor		
Controlled	55	39.29
Uncontrolled	85	60.71
Extracranial metastases		
Yes	41	29.29
No	99	70.71
Brain metastases and primary		
Synchronous	48	34.29
Metachronous	92	65.71
Treatment of secondary brain		
RT alone	89	63.57
RT+CT	16	11.43
No treatment	35	25.00

RT: Radiotherapy, CT: Chemotherapy, ECOG: Eastern Cooperative Oncology Group

Table 2: Distribution of patients and 1-year survival with primary tumor site

Primary tumor site	Number of cases	Percentage	Number of treated cases (%)	Survival at 1 year
Lung	82	44.08	62 (44.28)	2
Breast	46	24.73	33 (23.57)	6
Renal cell carcinoma	11	5.91	9 (6.4)	1
Head and neck	7	3.76	5 (3.50)	1
GIT	6	3.22	5 (3.50)	0
GUT	6	3.22	4 (2.85)	0
Testicular tumor	5	2.68	4 (2.85)	0
Sarcomas	4	2.15	3 (2.14)	0
Other	8	4.30	7 (5.00)	1
Unknown	11	5.91	8 (5.71)	1
Total	186	100	140	12

GIT: Gastrointestinal tract, GUT: Genitourinary tract

Table 3: Univariate analysis of characteristic of patients

Variables	Number	Percentage	Number of patients with survival ≥1 year (%)	*P*
Total patients	140	100	12 (8.57)	
Sex				
Male	80	57.14	5 (6.25)	0.201
Female	60	42.86	7 (11.66)	
Age				
<65 years	109	77.85	10 (9.17)	0.491
>65 year	31	22.15	2 (6.45)	
ECOG performance status				
1-2	118	84.28	11 (9.32)	0.199
3-4	22	15.72	1 (4.54)	
Number of lesions				
Single	22	15.71	6 (27.27)	<0.0001
Multiple	118	84.29	6 (5.08)	
Primary tumor				
Controlled	61	43.57	7 (11.47)	0.223
Uncontrolled	79	56.43	5 (6.33)	
Extracranial metastases				
Yes	49	35.00	3 (6.12)	0.346
No	91	65.00	9 (9.89)	
Brain metastases and primary				
Synchronous	53	37.85	5 (9.43)	0.739
Metachronous	87	62.14	7 (8.04)	
Treatment of secondary brain				
RT alone	119	85.00	10 (8.40)	0.788
RT+CT	21	15.00	2 (9.52)	

RT: Radiotherapy, CT: Chemotherapy, ECOG: Eastern Cooperative Oncology Group

patients with primary of breast was 4 months (95% CI: 2.131-5.869) while that for patients with other primary sites was 3 months (95% CI: 2.506-3.494; $P = 0.058$ by Log rank test). The addition of chemotherapy like carboplatin did not result into a significant survival advantage ($P = 0.788$).

DISCUSSION

With gradual improvements in the care of cancer patients, longer survival is expected even in patients with metastatic disease. In this study, patients with brain metastases who received WBRT alone or with chemotherapy were evaluated.

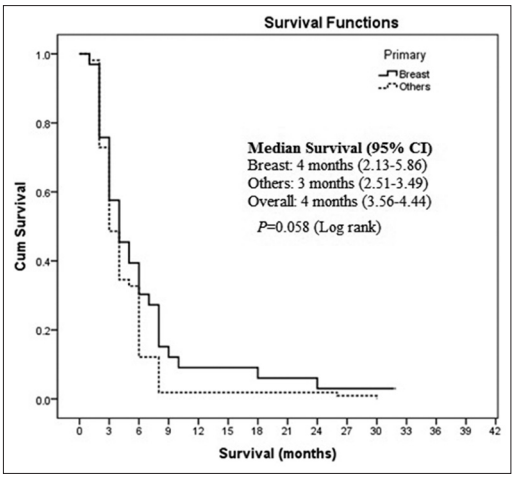

Figure 1: Kaplan–Meier survival curve for the patients with brain metastasis undergoing whole brain radiotherapy plotted against the primary of the disease (breast vs. others)

Radiation Therapy Oncology Group (RTOG) trial for studies of ultrarapid fractionated WBRT (10 Gy in one fraction, 12 Gy in two fractions, 15 Gy in two fractions over 3 days) showed a possible increased risk of herniation and death occurring within a few days of treatment and thus are generally avoided.[9] No advantage was observed with dose escalation (50 Gy in 20 fractions or 54.4 Gy at 1.6 Gy twice daily) compared to the commonly prescribed dose 30 Gy in ten fractions.[10-13] Hypofractionated radiotherapy, using 10 or fewer fractions is used in patients with poor prognosis, since such patients have life expectancy short enough to experience late adverse effect of radiotherapy. The institutional protocol followed in our patients is 30 Gy in 10 fractions, 3 Gy/fraction, 5 fractions/week.

The purpose of this study was to evaluate the different prognostic factors in patients with brain metastasis related to overall survival. The prognostic factors associated with better survival were solitary metastasis ($P < 0.0001$), breast carcinoma ($P = 0.063$), female sex ($P = 0.201$), primary under control ($P = 0.223$), good ECOG performance status ($P = 0.199$). These prognostic factors have also showed better survival in other studies.[10,13-16] Out of above mentioned prognostic factors, only solitary brain metastasis was statistically significant ($P < 0.0001$); other factors could not show statistical significance which may be due to small number of study sample.

Lutterbach *et al*. reported overall median survival of 3.4 months, 2, and 3 years survival were 5.6% ($n = 48$) and 2.9% ($n = 25$), respectively.[17] Survival of 2 years or more was observed in RTOG recursive partitioning analysis class 1 and

2 patients.[16] Within both classes, survival was significantly better for patients with a single brain metastasis compared with those having multiple brain metastases. In our study, the overall median survival was 3 months, and the 1 and 2 year survival was 8.57% (n = 12) and 3.57% (n = 5), respectively, and solitary brain metastases survival was significantly better than multiple metastasis (P < 0.0001). There is small difference in 2 years survival in both the studies because in our study, no patient received stereotactic radiosurgery (SRS); however, a larger published trial (RTOG 95-08) provides compelling evidence for the use of SRS boost following WBRT in patients with newly diagnosed one to three brain metastases.[18]

In a trial conducted by the European Organization for Research and Treatment of Cancer (EORTC 22952-26001), 359 patients with one to three brain metastases were randomly assigned to observation or WBRT following definitive treatment of their metastases with either surgery (n = 160) or SRS (n = 199). Although the local control of the brain metastases was better following WBRT but overall survival was virtually the same (median 10.7 and 10.9 months).[19]

Pease *et al.* showed that patient's survival with WBRT was increased by an additional 3-7 months from unselected group (3-6 months) if they are in the high-performance status group.[20] For those in poor performance status groups, there was no overall survival benefit. In our study, ECOG performance status 1 and 2 had better median overall survival (3.4 months) and 1-year survival (7.85%) as compared to ECOG status 3 and 4 (P = 0.199).

Lagerwaard and Levendag reported that lower systemic tumor activity showed better median survival ranging from 6.6 months for the "none" group (no extracranial disease) to 3.4 months in the "limited" group and 2.4 months in the "extensive" group (primary uncontrolled and other systemic metastasis).[21] In our study, females showed better survival (P = 0.201). This may be due to breast cancer cases which showed better survival than others. Other studies have not shown gender-related survival difference.

Over the past decade, the role of systemic therapies and in particular, targeted therapies has been increasingly explored in patients with brain metastases from solid tumors. For example, lapatinib has been studied as monotherapy, and in combination with capecitabine, in patients with HER2-positive breast cancer, and activity has been observed in both the upfront and refractory settings.[22] In patients with nonsmall cell lung cancer, CNS activity has been reported with gefitinib and erlotinib. In a single arm phase II trial, 40 patients unselected for mutation status received erlotinib 150 mg daily for 1 week, then concurrently with WBRT followed by maintenance.[23] The overall response rate was 86%. As expected, median survival time was longer among patients with a known EGFR mutation. Finally, in melanoma, the B-raf inhibitors vemurafenib and dabrafenib, and the immunomodulator, ipilimumab, have reported CNS activity.[24] Ipilimumab has also been studied in an open-label phase II trial in patients with melanoma brain metastases.[25] Among 51 patients with asymptomatic brain metastases on study entry, nine patients (18%) exhibited disease control in both brain and body. Among 21 patients, who were symptomatic and on corticosteroids, one patient (5%) exhibited disease control in all sites.

CONCLUSION

Whole brain radiotherapy is the mainstay modality of treatment in the management of brain metastasis. Despite the use of WBRT, outcomes are not so hopeful and efforts should be made to incorporate multimodality approaches including radiotherapy, radiosurgery, surgery, and chemotherapy and sensitizers to improve survival mainly in patients with single metastasis, good performance status, and extracranial disease controlled.

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