

Factors affecting survival in patients with brain metastasis



**ASSIGN
BUSTER**

Prognostic factors affecting the survival in patients with brain metastasis: A Retrospective study

Abstract

Aims: To determine long term survival and prognostic factors in patients with brain metastases who underwent whole brain radiotherapy.

Introduction: Multiple brain metastases are unfortunate consequence, frequently found in patients of advanced cancer. The prognosis, even after treatment with Whole-Brain Radiation Therapy (WBRT) is poor with an average expected survival time of <6 months by all possible efforts.

Materials & methods: From January 2005 to August 2010, medical records of 186 patients with diagnosis of brain metastasis were analyzed. Out of these, 140 patients who received WBRT ± chemotherapy were included and 26 patients who did not take any treatment for brain metastasis were excluded from the study. The prognostic factors evaluated for overall survival were ECOG performance status, gender, age, number of lesions, primary tumor site, primary tumor status, extracranial metastases and chemotherapy & radiotherapy.

Results: The overall median survival was three months and one & two year survival was 8. 57% and 3. 57%, respectively. The most common primary tumor site was lung 82 (44. 08%) followed by breast 46 (24. 73%), renal cell carcinoma 11 (5. 91%) and unknown primary 11 (5. 91%). The overall median survival was 3 months, maximum being 4. 5 months in patients with breast cancer. and at one year survival 6/33(18. 2%) in breast cancer

patients ($p= 0. 10$). In this series, the patients with higher perform status ($p= 0. 21$), cancer breast ($p= 0. 10$) and solitary brain metastasis ($p= 0. 0003$) with primary tumor controlled ($p= 0. 14$) had better survival.

Conclusion: This study suggests that patients with some prognostic factors have good survival. So the overall assessment of the patient is always best done at the bedside and must be individualized. The above mentioned clinical features should be considered and hopefully will aid in the decision regarding treatment of brain metastases.

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 or hospice placement. Metastasis to the brain occurs in approximately 20% of the patients with limited survival and worse quality of life. ^[1] Glucocorticoids and whole brain radiotherapy (WBRT) has been the mainstay of treatment while craniotomy for tumor resection has been the standard local treatment for solitary lesion. The median survival of untreated patients is approximately one 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. [2, 3] Some of the strong prognostic factors for survival are: performance status, response to steroids and status of systemic disease. The main goal of WBRT is to improve neurologic deficits caused by the metastases and surrounding edema and to prevent any further deterioration of the 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. [4, 5]

The overall response rate to WBRT ranges from 50-85% in various studies. Traditionally, surgical resection has been offered rarely to patients with multiple metastases because of resection related excessive morbidity. The majority of patients who achieved control of cranial metastasis died from progressive extracranial disease whereas the cause of death in most of the cases is due to CNS disease in patients with recurrent brain metastases. [4,

6] In this study, the prognostic factors were evaluated for survival in patients with diagnosis of brain metastasis who receive WBRT.

Materials & Methods

The records of 186 patients with brain metastases in between January 2005 to August 2010 were analyzed retrospectively. Out of these, 46 patients not willing for radiotherapy and who chose only best supportive care were not included in the study. All the remaining 140 patients were planned WBRT after starting dexamethasone, mannitol and other supportive treatment. With diagnosis of brain metastasis, the following variables were analyzed for

survival: ECOG performance status, gender, age, number of brain lesions, primary tumor site (Table 2), extra cranial metastases, treatment of primary disease and radiotherapy (Table-1). The survival time was considered as time between diagnosis of brain metastasis and last follow up or recorded death.

Brain metastases were detected by computed tomography (CT) or magnetic resonance image (MRI) scan. All patients were treated with WBRT on telecobalt units Theratron 780 C and 780 E. The WBRT was given by bilateral fields. The total dose was 30-36 Gy with a median of 30 Gy delivered in two weeks, five fractions per week 3 Gy per fraction. The supportive care (dexamethasone & mannitol) was started at the beginning of treatment and continued during radiotherapy. Chemotherapy was administered to the patients with good performance status and progressive systemic disease after WBRT. All statistical analyses were performed using SPSS for windows, version 20. 0.

Results

One hundred forty patients were 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 overall median survival was 3 months, and the one & two year survival was 12 (8. 57%) and 5 (3. 57%).

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 ($p= 0. 0003$), high ECOG performance status ($p= 0. 21$), controlled extracranial disease ($p= 0.$

14) and breast carcinoma ($p= 0.10$) had better survival (Table 2 & 3). The single most significant prognostic factor associated with better survival was solitary brain metastasis ($p= 0.0003$).

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 WBRT followed by chemotherapy were evaluated.

Studies of ultra rapid fractionated WBRT (10 Gy in 1 fraction, 12 Gy in 2 fractions, 15 Gy in 2 fractions over 3 days) as carried out by Radiation Therapy Oncology Group (RTOG) and other investigators showed a possible increased risk of herniation and death within a few days after treatment and are generally avoided. Likewise, no advantage was seen with extended fractionation (50Gy in 20 fractions or 54.4Gy at 1.6Gy twice daily) compared to the more commonly prescribed 30Gy in 10 fractions. [6, 7, 8, 9] Regimens using 10 or fewer fractions are used in patients with poor prognosis, since such patients are not expected to live long enough to experience serious side effects. The institutional protocol followed in our patients is 30 Gy in 10 fractions, 3 Gy per fraction but in patients with good general condition and primary disease under control having solitary brain metastasis, the dose was escalated by 6 Gy to give total tumor dose of 36 Gy.

The end point of this study was to evaluate the different prognostic factors related with overall survival in patients with brain metastasis. The prognostic factors associated with better survival were solitary metastasis ($p= 0. 0003$), breast carcinoma ($p= 0. 10$), female sex ($p= 0. 12$), primary under control ($p= 0. 14$), higher ECOG performance status ($p= 0. 21$). These prognostic factors have also showed better survival in other studies. [7, 10, 11, 12, 13] Out of above mentioned prognostic factors only solitary brain metastasis was statistically significant ($p= 0. 0003$); 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, two year and three years survival were 5. 6% ($n= 48$) and 2. 9% ($n= 25$), respectively.

[14] Survival of two years or more was observed in RTOG recursive partitioning analysis (RPA) class 1 & 2 patients. 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 one & two year survival was 8. 57% ($n= 12$) and 3. 57% ($n= 5$), respectively and solitary brain metastases survival was significantly better than multiple metastasis ($p= 0. 0003$). There is small difference in two years survival in both studies because in our study, no patient received Stereotactic radiosurgery (SRS); however, a larger recently 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. [15]

In other recent studies, the role of WBRT following definitive treatment (surgery or SRS) of one to three metastases was most extensively evaluated in a trial conducted by the European Organization for Research and Treatment of Cancer (EORTC 22952-26001) which was presented at the American Society of Clinical Oncology (ASCO) meeting in 2009 . In that 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). Despite the better control of the brain metastases, overall survival was virtually the same following WBRT (median 10. 7 and 10. 9 months). ^[16]

Pease NJ et al showed that patient's survival with WBRT was increased by an additional three to seven months from unselected group (three to six months) if they are in the high performance status group. ^[17] For those in poor performance status groups, there was no overall survival benefit. In our study, ECOG performance status 1 & 2 had better overall median survival (3. 4 months) and one year survival (7. 85%) as compared to ECOG status 3 and 4 (p= 0. 21).

Lagerwaaed FJ et al reported that lesser systemic tumor activity was showed better median survival ranges 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 & other systemic metastasis).

^[18] In our study, overall survival was 2. 2 months & 4 months in active primary disease and controlled primary with or without systemic metastases respectively.

In our study, female showed better survival than male patients ($p= 0.12$). This may be due to all breast cancer cases were females and breast cases showed better survival than others. Other studies did not show gender related survival difference.

Conclusion

WBRT continues to be an efficacious treatment in the management of brain metastasis. 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 mainly in patients with single metastasis, good performance status and extra cranial disease controlled.

References:

1. Posner JB, Chernik NL. Intracranial metastases from systemic cancer. *Adv Neurol* 1978; 19: 579-92.
2. Coia LR. The role of radiation therapy in the treatment of brain metastases. *Int J Radiat Oncol Biol Phys* 1992; 23: 229-38.
3. Lagerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: A review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999; 43: 795-803.
4. Lassman AB, DeAngelis LM. Brain metastases. *Neurol Clin* 2003; 21: 1-23.

5. 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: 111-5.
6. Borgelt B, Gelber R, Larson M, Hendrickson F, Griffin T, Roth R. Ultra-rapid high dose irradiation schedules for the palliation of brain metastases: final results of the first two studies by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; 7: 1633-8.
7. 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: 1-9.
8. Kurtz JM, Gelber R, Brady LW, Carella RJ, Cooper JS. The palliation of brain metastases in a favorable patient population: A randomized clinical trial by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1981; 7: 891-5.
9. Berk L. An overview of radiotherapy trials for the treatment of brain metastases. *Oncology (Huntingt)* 1995; 9: 1205-12.
10. Lang FF, Sawaya R. Surgical treatment of metastatic brain tumors. *Semin Surg Oncol* 1998; 14: 53-63
11. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single brain metastases to the brain. *JAMA* 1998; 280: 1485-9.
12. Schellinger PD, Meinck HM, Thron A. Diagnostic accuracy of MRI compared to CT in patients with brain metastases. *J Neurooncol* 1999; 44: 275-81.

13. 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: 1001-6.
14. Lutterbach J, Bartelt S, Ostertag C. Long-term survival in patients with brain metastases. *J Cancer Res Clin Oncol* 2002; 128: 417-25.
15. Breneman JC, Warnick RE, Albright RE Jr, Kukiatinant N, Shaw J, Armin D, et al. Stereotactic radiosurgery for the treatment of brain metastases. Results of a single institution series. *Cancer* 1997; 79: 551-7.
16. 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: 427-34.
17. Pease NJ, Edwards A, Moss LJ. Effectiveness of whole brain radiotherapy in the treatment of brain metastases: A systematic review. *Palliat Med* 2005; 19: 288-99.
18. Lagerwaard FJ, Levendag PC. Prognostic factors in patients with brain metastases. *Forum (Genova)* 2001; 11: 27-46

Table 1: Characteristics of patients and treatment

Variables	Numbe Percenta	
	r	ge
Total patients	186	100
Sex		

Male	108	58.06
Female	78	41.94
Age		
<65 years	145	77.95
> 65 years	41	22.05
ECOG Performance Status		
1-2	135	72.58
3-4	51	27.42
Number of lesion		
Single	35	18.82
Multiple	151	81.18
Primary tumor		
Controlled	73	39.25
Uncontrolled	113	60.75

Extra cranial
metastases

Yes 67 29.56

No 119 70.44

Brain metastases &
primary

Synchronous 64 34.40

Metachronous 122 65.60

Treatment of secondary
brain

RT alone 119 63.98

RT+CT 21 11.29

No treatment 46 24.73

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

Primary Tumor site	No. of cases	Percentage	Treated Patients	Survival at	p-value
Extra cranial metastases	186	100%	67	29.56%	
Brain metastases & primary	186	100%	186		
Synchronous	64	34.40%	64	34.40%	
Metachronous	122	65.60%	122	65.60%	
Treatment of secondary brain	186	100%	186		
RT alone	119	63.98%	119	63.98%	
RT+CT	21	11.29%	21	11.29%	
No treatment	46	24.73%	46	24.73%	

ts			No. of		1 year	
	es		cases		cases	
			62			
			(%)			
Lung	82	44.08	(44.28)	2	0.10	
Breast	46	24.73	(23.57)	6		
Renal cell ca	11	5.91	9 (6.4)	1		
Head & 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		140	12

Table 3: Univariate analysis of characteristic of patients

Variables	number	percentage	Overall survival	
			≥1 year	p-value
			No of patient (%)	
Total patients	140	100	12(8.57)	

Sex

Male	80	57.14	5(3.57)	0.12
------	----	-------	---------	------

Female	60	42.86	7(5.0)	
--------	----	-------	--------	--

Age	0.31			
-----	------	--	--	--

<65 years	109	77.85	10(7.14)	
-----------	-----	-------	----------	--

> 65 year	31	22.15	2(1.43)	
-----------	----	-------	---------	--

ECOG

Performance	0.21			
-------------	------	--	--	--

Status

1-2	118	84.28	11(7.85)	
-----	-----	-------	----------	--

3-4	22	15.72	1(0.72)	
-----	----	-------	---------	--

Number of lesions	0.003			
-------------------	-------	--	--	--

Single	22	15.71	6(4.27)	
--------	----	-------	---------	--

Multiple	118	84.29	6(4.27)	
----------	-----	-------	---------	--

Primary tumor 0. 14

Controlled	61	43. 57	7(5. 0)
------------	----	--------	---------

Uncontrolled	79	56. 43	5(3. 57)
--------------	----	--------	----------

Extra cranial
metastases 0. 22

Yes	49	35. 00	3(2. 14)
-----	----	--------	----------

No	91	65. 00	9(6. 43)
----	----	--------	----------

Brain
metastases & 0. 38
primary

Synchronous	53	37. 85	5(3. 57)
-------------	----	--------	----------

Metachronous	87	62. 14	7(5. 0)
--------------	----	--------	---------

Treatment of
secondary 0. 43
brain

RT alone	119	85. 00	10(7. 14)
----------	-----	--------	-----------

RT+CT	21	15. 00	2(1. 43)
-------	----	--------	----------

1