

Brain metastases: “How much longer do I have, doctor? “- Prognostic factors and treatment considerations

Vincent Thai, MD
Director, Palliative Care , University of Alberta Hospital

Introduction

Brain metastases is often one of the most feared consequences of cancer. It is devastating both to patients and their families. Progression of brain metastases may cause headaches, nausea and vomiting, neurological deficits and cognitive decline, delirium and eventually death.

Patients with brain metastases may present dilemmas for palliative health care professionals in terms of whether to proceed with whole brain radiotherapy and hospice placement. It is often difficult to prognosticate survival in these patients and organizing whole brain radiation can be fraught with practical difficulties. The following discussion is meant to look at some prognostic factors and treatment issues that might make it easier to resolve some of the dilemma that palliative health care professionals face.

Discussion

A recent review in 2003 of published randomized controlled trials concluded that ‘the best treatment strategy remains unknown for a large group of patients affected by brain metastases’¹.

Patients can be categorized into the following groups:

- 1) Best Supportive care: The overall survival from historical data is about 1 month in patients who are receiving only best supportive care².
- 2) Best Supportive care with steroids: The survival may be extended up to 2-3 months with steroid use. ^{3,4}. The prognosis is also dependent on steroid responsiveness. It is interesting to note that radiological response cannot be translated into clinical response.
- 3) Whole brain Radiotherapy (WBRT) : WBRT seems to offer a modest survival benefit (up to approximately 3 months)⁵ in treating ‘unselected patients’. This is in addition to the median survival of 2-3 months in patients managed with ‘best supportive care’ and steroids. However, this is modified by the patients’ performance status where patients’ survival can increase by an additional 3-7 months⁵ if they are in the high performance status group. For those in poor performance status groups, there was no overall survival benefit. Another way of looking at this is that for ‘unselected’ patients, the median survival is approximately 3-6 months after WBRT.⁵.

However, in another study by Frank J et al⁶, the overall median survival is about 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. Some of the strong prognostic factors for survival are: performance status, response to steroids and evidence of systemic disease.

So, what can we do to help recommend which patients for radiotherapy? Some suggested clinical features to look at for the time being are:

- 1) Preferably patients with good performance status – a patient with a Karnofsky performance scale (KPS) of ≥ 70 has an estimated median survival of 3.75 months

- to 7.5 months when treated with whole brain RT versus a median survival of 1.7 to 2 months for patients with a KPS of less than 70^{7,8}.
- 2) For the relief of symptoms – Studies seem to suggest that the WBRT does help with the relief of symptoms and motor loss. However, the relief of symptoms (e.g seizures, headaches, nausea and vomiting) is achieved to a greater degree than relief of motor loss. (56-96% vs 46-77% respectively)^{9,10,11}
 - 3) Good steroid responsiveness - It is noted that patients with a poor response to steroids also had a poorer response to subsequent WBRT. ¹²Moreover, in the study by Frank J et al, patients with good response to steroids alone had a median survival of 4.3 months vs 1.6 months with poor responders⁶. Hence, it seems to be acceptable to withhold further treatment in patients who are in a poor condition and not responding to steroids as their prognosis is very short.
 - 4) Lesser systemic tumor activity the better – Patient's systemic tumor activity can be classified as
 - i) none (brain metastases only + no other sites of metastases + primary tumor absent)
 - ii) limited (brain metastases + other metastases + primary tumor absent/ controlled or brain metastases + primary tumor progressing + no other known metastases)
 - iii) extensive (progressive tumor growth + brain metastases + systemic metastases).

The median survival ¹² ranges from 6.6 months for the 'none' group to 3.4 months in the 'limited' group and 2.4 months in the 'extensive group'. Hence, the more extensive the cancer, the more likely a conservative approach is going to be appropriate.

CONCLUSION

The basis of selecting patients for whole brain radiation remains a difficult area as the current evidence is rather heterogeneous and of variable methodical quality. More robust randomized trials of WBRT in patients with brain metastases would need to be done. These trials will need to look at stratifying patients by the various prognostic factors (e.g functional status, response to steroids) and include relevant outcome measures such as survival, function, symptom relief, quality of life and cost effectiveness.

The overall assessment of the patient is always best done at the bedside and must be individualized. The above mentioned suggested clinical features should be considered and hopefully will aid in the decision regarding radiotherapy. However, these prognostic factors are not cast in stone. The patient's and family's goals of care are always the guiding light of the decision making process.

REFERENCES

1. Tsao MN, Sultanem K, Chiu D, et al. Supportive care management of brain metastases: What is known and what we need to know. Conference proceedings of the national cancer institute of Canada (NCIC) workshop on symptom control in radiation oncology. *Clin Oncol (R Coll Radiol)*. 2003;15:429-434.
2. DiStefano A, Yong Yap Y, Hortobagyi GN, Blumenschein GR. The natural history of breast cancer patients with brain metastases. *Cancer*. 1979;44:1913-1918.
3. KOFMAN S, GARVIN JS, NAGAMANI D, TAYLOR SG,3rd. Treatment of cerebral metastases from breast carcinoma with prednisolone. *J Am Med Assoc*. 1957;163:1473-1476.
4. RUDERMAN NB, HALL TC. Use of glucocorticoids in the palliative treatment of Metastatic brain tumors. *Cancer*. 1965;18:298-306.
5. Pease NJ, Edwards A, Moss LJ. Effectiveness of whole brain radiotherapy in the treatment of brain metastases: A systematic review. *Palliat Med*. 2005;19:288-299.

6. 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.
7. Murray KJ, Scott C, Greenberg HM, et al. A randomized phase III study of accelerated hyperfractionation versus standard in patients with unresected brain metastases: A report of the radiation therapy oncology group (RTOG) 9104. *Int J Radiat Oncol Biol Phys*. 1997;39:571-574.
8. 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;45:427-434.
9. Borgelt B, Gelber R, Kramer S, 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.
10. 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;7:1633-1638.
11. Priestman TJ, Dunn J, Brada M, Rampling R, Baker PG. Final results of the royal college of radiologists' trial comparing two different radiotherapy schedules in the treatment of cerebral metastases. *Clin Oncol (R Coll Radiol)*. 1996;8:308-315.
12. Lagerwaard FJ, Levendag PC. Prognostic factors in patients with brain metastases. *Forum (Genova)*. 2001;11:27-46