Outcomes of Patients Undergoing Surgical Resection of a Brain Metastasis: A Cancer Care Nova Scotia Project

Jonathan Gaudet, B.Sc (Hons)[1,], Liam Mulroy, M.D.,[2] and Derek Wilke, M.D.,[2]*
[1]Faculty of Medicine, Dalhousie University, [2]Cancer Care Nova Scotia.

Brain metastases pose a formidable and increasingly common challenge in contemporary cancer care. Current evidence suggests that surgical resection of single brain metastases affords a survival advantage over mainstay treatment of brain metastases with radiotherapy and corticosteroids. Despite advances attained by surgical resection, median survival times remain short, however, and most patients succumb to systemic progression of their cancer within a year following resection.

Patients with a single or solitary, tissue-proven brain metastasis obtained by surgical resection were retrospectively reviewed. Of eligible patients that met inclusion criteria, the mean age at diagnosis of the brain metastasis was 57. Lung cancer was the most common type of cancer producing metastasis to the brain. The most common histologies were adenocarcinoma (17/41; 41.5%) and unspecified carcinoma (12/41; 29.3%). Following resection, the overall median survival was 33.3 weeks. Good performance status and small brain metastasis size were favourable prognostic factors for prolonged survival in this series. The median survival times of patients in this series were slightly inferior, yet comparable to more stringently selected patients in randomized control trials of surgical resection of brain metastases. These comparable results add further support for the use of surgical resection in the treatment of a brain metastasis.

Corresponding Author: J. Gaudet, Box 325, Sir Charles Tupper Building, Halifax, NS, B3H 4H7, Canada, jgaudet@tupmcms1.med.dal.ca

Introduction

Cerebral metastases represent one of the most serious and challenging complications of cancer management. In the 15-30% of cancer patients anticipated to develop brain metastases, approximately half are single, and the vast majority of these behave symptomatically[1,2]. Metastatic brain deposits develop through dissemination via the arterial circulation. Carcinomas of the lung, breast, G.I. tract, kidney and malignant melanoma are the most common primary tumor sources. Although cerebral metastases are most frequently encountered in the context of advanced disease, they can sometimes be the first indication of malignancy. When untreated, patients with brain metastases have median survivals of approximately one to two months and usually die as a direct consequence of their brain involvement[3]. Mainstays in the management of cerebral metastases (corticosteroids and whole-brain radiation therapy) typically extend median survival to 3-6 months[4].

The poor prognosis anticipated with brain metastases has led to a certain degree of nihilism associated with patient management. There are relatively few studies assessing outcomes in patients with a brain metastasis. However, two randomized trials have shown that surgical resection of single brain metastases in addition to whole-brain radiation improves median survival to approximately 10 months[2,5]. In contrast, a Canadian randomized trial, failed to demonstrate the advantage of such an approach[6]. Despite these improved management strategies that can increase survival and decrease morbidity related to neurologic progression of disease, the survival of patients with single brain metastases remains short. The vast majority of patients continue to die from extracranial progression of their cancer with median survival still less than one year.

This retrospective analysis reviewed Cancer Care Nova Scotia (CCNS) patients whose single brain metastases were resected in order to compare their outcomes with those reported in the literature, and to document any unusual patterns of recurrence or complications. Reviewing the community experience of these patients may provide useful feedback on the applicability of randomized clinical trial results. Furthermore, previously determined prognostic factors can influence patient outcomes and help identify favourable subgroups of patients who may benefit from more intense therapy.

Methods

Patients with single or solitary, tissue-proven brain metastasis obtained by surgical resection performed between 1995 and 2002 were identified from a neurosurgery database and the treatment records of radiation oncologists working at CCNS centers. The term "single" brain metastasis denotes a situation in which only one metastasis exists in the brain- the phrase implies nothing about the extent of the cancer present elsewhere in the body, whereas "solitary" indicates an uncommon situation in which a single brain metastasis is the only detectable cancer in the body[1]. Eligible patients were at least 18 years old with radiographic evidence (CT, MRI) of a single brain lesion prior to craniotomy. Radiographic evidence or histopathologic diagnosis of the primary cancer was not necessary (i.e. some patients had no known primary tumor site prior to undergoing surgical resection of their brain metastasis), nor were minimum performance status criteria used to select eligible patients. The RTOG RPA classification scheme, a well-validated classification system for patients with brain metastases, was applied retrospectively based on baseline patient characteristics[7]. This analysis of 1200 patients found age = 65, Karnofsky score = 70, controlled primary tumor and brain as the only site of metastasis to be favourable prognostic factors. From this, a recursive partitioning analysis identified three separate patient groups with different median survivals[7].

Individual patient charts were retrospectively reviewed to collect information regarding primary malignancy, extent of disease, brain metastasis, performance status and corticosteroid use (when available), and survival outcome (including cause of death when available). Any early deaths or unusual patterns of recurrence were documented. Log-rank survival analyses were performed using SAS version 8.1 software and P-values of <0.05 were considered statistically significant.

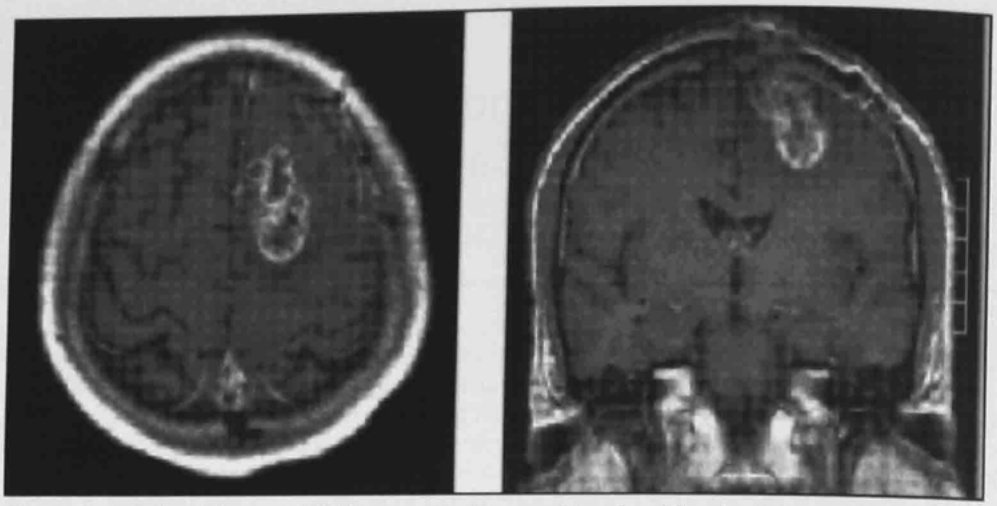

Figure 1. Axial and Coronal MRI images of a 43 year old male with a frontal metastasis.

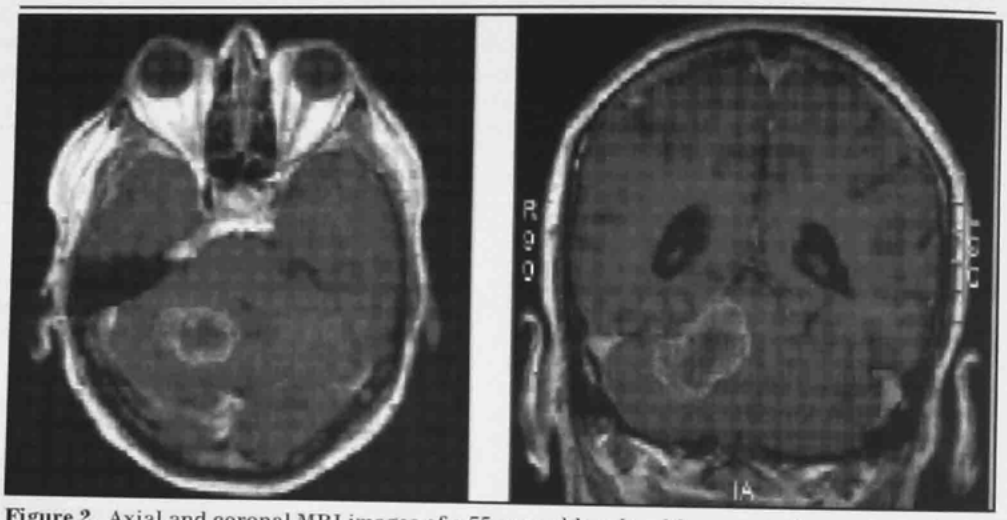

Figure 2. Axial and coronal MRI images of a 55 year old male with a cerebellar metastasis.

Results

Forty-one eligible patients treated by CCNS between 1995 and 2002 were reviewed (for all review criteria in which no data could be obtained for a given patient, results are reported herein as the proportion of patients experiencing an event compared to the overall number of patients who experienced the same event for which data existed out of the set of 41). Accurate data on patient steroid requirements and Karnofsky performance status was lacking from the charts for a significant number of patients enrolled in this study.

The mean age at diagnosis of the brain metastasis was 57; frontal and cerebellar metastases were most common (Table 1; Figs. 1-2). The primary cancer was considered to be controlled in 31 of 37 patients and the mean time interval until diagnosis of the brain metastasis was 54.1 weeks. For 31 of 39 patients the first site of metastasis was the brain, although metastasis to the brain was not in isolation- 19 of those 39 patients developed both extracranial and brain metastases following diagnosis and treatment of their primary cancer. Lung cancer (21/41; 51.2%) was the most common type of cancer producing metastasis to the brain. The most common histologies of metastases to the brain were adenocarcinoma (17/41; 41.5%) and unspecified carcinoma (12/41; 29.3%; Table 1). Seven percent of patients (3/41) developed leptomeningeal metastases. This is an uncommon pattern of recurrence at sites within the CNS distant to the resection site (Table 1; Fig. 3).

The overall median survival following resection of the brain metastasis was 33.3 weeks (SE: 6.1; Fig. 4). A large proportion of patients died within a year of their treatment (Fig. 4). The impact of sex, age, brain metastasis histology, grade or differentiation, whole brain radiation post-operatively and timing of presentation (brain metastasis on presentation vs. brain metastasis following diagnosis of primary tumor) on survival were not statistically significant. Performance status, reflected by RTOG RPA classification, did have a significant impact upon survival. There were statistically significant differences in median survival based on RPA classification (Class 1 median survival 29.9; SE: 2.7; Class 2 median survival 76.7 weeks; SE: 11.2; Class 3 median survival 7.3 weeks; SE: 8.6; $p = 0.007$; Fig 5). RPA Class 1 and 2 (median survival = 29.9 and 76.7 weeks respectively) patients lived significantly longer than Class 3 patients ($p = 0.0017$; Fig.6). Patients with smaller (<3 cm) brain metastases had median survivals that were significantly longer than patients with larger (> 3cm) metastases ($p = 0.03$; Fig. 7). A strong, statistically significant trend existed with regard to disease distribution (Fig. 8). Patients with a brain metastasis and an extracranial metastasis had shorter median survival (19 weeks) than patients with a brain metastasis only ($p = 0.0005$). Median survivals of patients with solitary metastases (51.7 weeks; SE: 6.7) exceeded those of patients with single metastases (33.2 weeks; SE: 15.2). Although patients with solitary metastases had substantially longer median survivals, the survival difference compared to patients with single metastases was not statistically significant ($p = 0.89$; Fig. 9).

Table 1. Patient Characteristics

Characteristic	N = 41	Stats
Gender		
Men	22	53.7%
Women	19	46.3%
Age at D_x of Primary		56.1 (12.3)
Mean (SD)		
Primary Tumor Site		
Lung	21	51.2%
GI	7	17.1%
Breast	3	7.3%
No Known	6	14.6%
Other	4	9.8%
Primary Status		
Controlled	31	75.6%
Uncontrolled	6	14.6%
Missing	4	9.8%
Age at D_x of Brain Metastasis		57 (11.7)
Mean (SD)		
Time between D_x of Primary Tumor and Dx of Brain Metastasis		
On Presentation Preceding Primary D_x	24	58.5%
< 1 Yr	6	14.6%
1-2 Yrs	9	22.0%
> 2 yrs	2	4.9%
Brain Metastasis Symptoms		
Headache	29/41	70.7%
Focal Neurologic Deficit(s)	26/41	63.4%
Behavioral Change	14/41	34.1%
Ataxia	14/41	34.1%
Nausea	13/41	31.7%
Vomiting	11/41	26.8%
Seizure	10/41	24.4%
Visual Deficit	9/41	22.0%
Neuroendocrine	0/41	0%
Brain Metastasis Size		
> 3 cm	17/33	51.5%
≤ 3 cm	16/33	48.5%
Brain Metastasis Side		
Left	20	48.8%
Right	19	46.3%
Midline	2	4.9%
Brain Metastasis Location		
Frontal	15	36.6%
Cerebellum	11	26.8%
Parietal	6	14.6%
Occipital	6	14.6%

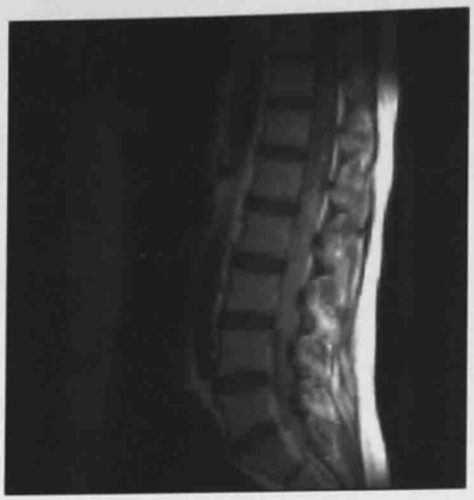

Figure 3. MRI image of leptomeningeal recurrence.

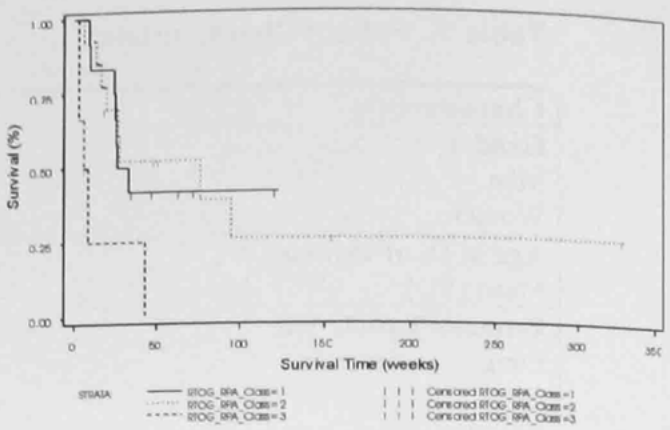

Figure 5. Overall survival by RTOG RPA Classification.

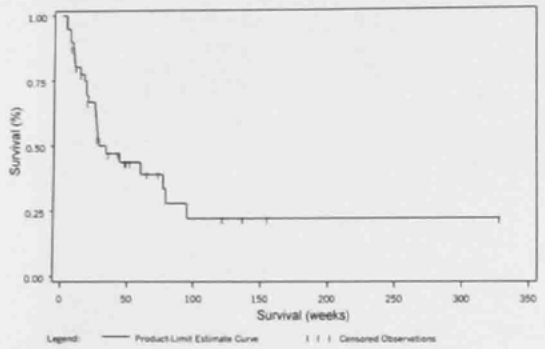

Figure 4. Overall patient survival.

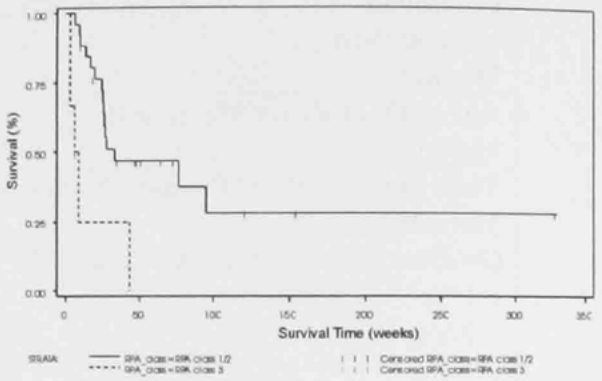

Figure 6. Overall survival of RTOG RPA Class I and II vs. III.

Discussion

Brain metastases continue to pose an onerous challenge to oncologists because of the limited survival of patients and the limited number of effective therapeutic strategies. In this study, overall survival was comparable, but somewhat inferior (33 weeks vs. 40 weeks) to that reported in two positive randomized control trials favouring resection of brain metastases[2,5]. The observed inferior median survival times in this study may be explained by our less rigorous selection criteria, particularly with regard to minimum performance status requirements. Our results demonstrate that patients with poorer performance status (RPA Class 3) had significantly shorter median survivals. The finding that RPA Class 2 patients exhibited much longer median survival times than their Class 1 counterparts was surprising, however, and may be a spurious finding due to the limited number of patients enrolled in this study (Fig. 4). One would normally expect RPA Class 1 patients to live longer than their RPA class 2 counterparts; class 1 survival was 7.1 months while class 2 survival was 4.2 months in patients receiving whole brain radiotherapy alone[7]. For undetermined reasons, a handful of patients in this group also lived remarkably long periods after their resection (e.g. upwards of 325 weeks in one patient). Large standard errors (SE: 11.2) were also noted within the RPA Class 2 subgroup, further contributing to this unexpected finding.

Smaller sized brain metastases predicted for more favourable median survival times (Fig. 5). A larger brain metastasis may be an indication of a more aggressive and rapidly proliferating metastasis, or one that has been present for an extended period of time. It may also be that survival is diminished in patients with larger brain metastases because of greater morbidity associated with surgical resection and subsequent post-operative care.

Although statistical significance did not exist when comparing median survivals between patients with solitary and single brain metastases, a clinically significant (i.e. substantially longer) survival differential existed (51.7 weeks for solitary metastasis vs. 33.2 weeks for single metastases; p= 0.89; Fig. 9). This is not surprising- most patients who undergo successful resection of their brain metastasis ultimately die because of the progression of their extracranial disease. In the small subset of patients with undetectable disease elsewhere in the body and only one brain metastasis ("solitary"), extracranial cancer progression may be much delayed. If extracranial metastases eventually develop, it may be some time until the burden of disease leads to death, and, in rare instances extracranial metastases may never materialize at all. This may explain the prolonged survival in this subgroup. The small numbers within the subgroups and the high standard error (single metastasis SE: 6.7 vs. solitary metastasis SE: 15.2) limited the likelihood of reaching statistical significance when comparing patients with solitary vs. those with single metastases.

We acknowledge the limitations of this study- its retrospective nature and the relatively small cohort of patients reviewed, as well as the paucity of data documenting patient steroid requirements and Karnofsky performance status. In-

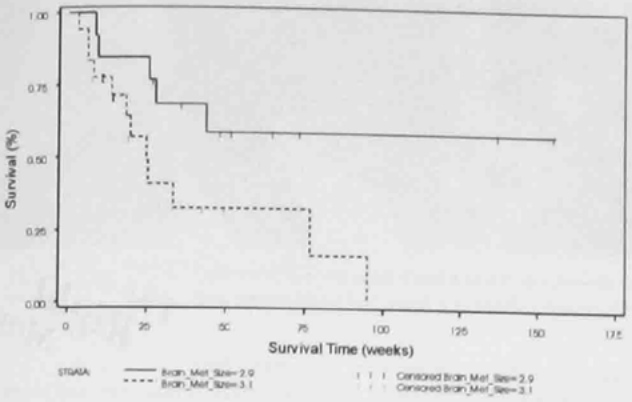

Figure 7. Overall survival by brain metastasis size.

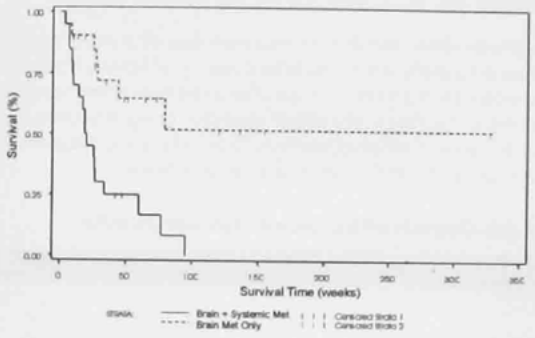

Figure 8. Overall survival by disease distribution.

formation on the cause of death for some patients was also lacking, despite our best efforts to retrieve it from the provincial registry and hospital records. These inherent challenges of retrospective reviews highlight the importance of prospective data collection.

Future studies exploring outcomes of patients with brain metastases need to prospectively collect salient outcome measures reflected by patient performance status and steroid requirements as well as quality of life measures. Quality of life instruments would provide an opportunity to record and quantify important outcomes such as patient physical function, emotional well-being and symptoms[8].

Future randomized control trials should also seek to evaluate the efficacy and potential benefit of stereotactic radiosurgery as compared to that of surgical resection in the management of brain metastases. Stereotactic radiosurgery is considered by many to be a reasonable alternative to surgical excision of brain metastases. It may be particularly useful in patients with surgically inaccessible lesions or medical contra-indications to surgery. Non-randomized studies suggest patients live longer and have much lower rates of progressive neurologic disease when radiosurgery is added to whole brain radiation[9]. Hopefully future studies will clarify the relative benefits of radiosurgery and surgical excision.

Despite the therapeutic nihilism often associated with brain metastases, the potential for dramatically longer survival exists in certain favourable patient subgroups. Prolonged survival was noted in several patients in this series, particularly those presenting with small brain metastases, good performance status and no other sites of extracranial or metastatic disease. These factors should be considered

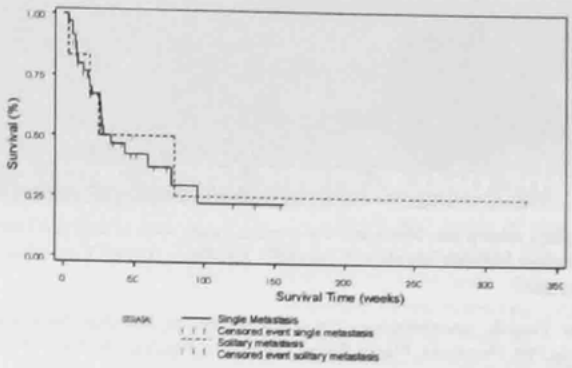

Figure 9. Overall survival of single vs. solitary metastasis.

when evaluating and selecting patients for surgical resection, because they help to identify subgroups of patients who may particularly benefit from craniotomy. For many, however, life expectancy with a brain metastasis remains unduly short. Future management of single brain metastases requires a search for therapies that will both prolong the duration and improve quality of life.

Acknowledegement

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