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ORIGINAL ARTICLE

Defining treatment for brain metastases patients: nihilism versus optimism

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Abstract
Aims Treatment of brain metastases patients has included whole brain radiotherapy (WBRT) for over 50 years, and there is much data showing this to be associated with short-term gains. The integration of resection and radiosurgery to these patients allows some better prognostic groups to experience long-term local control and improvement in quality of life. The recursive partitioning analysis of the Radiation Therapy Oncology Group (RTOG) has been used as a predictive model for over a decade to identify three classes of patients. Number of lesions has been used to define treatment for a good prognostic subgroup that is eligible for surgery or radiosurgery, but there are few prospective studies of poorer prognosis brain metastases patients to evaluate the influence of number of lesions on the prediction of outcome. We examined patient, treatment and outcome parameters of all brain metastases patients in a 5-year period so that we could measure outcome and evaluate various factors on survival.
Methods and results This was a population-based study of all brain metastases patients in Southern Alberta between 2000 and 2005. It used an Excel spreadsheet database and STATA 8 software to analyze outcomes. The study included 568 patients representing 4.4% of our radiotherapy population. Median age, performance status and distribution of primary disease sites were comparable with other large series. Overall survival for the whole group was 3.05 months. Independent factors predicting for improved overall survival included younger age, KPS <70, less than four lesions and the use of stereotactic radiosurgery. Presence of extracranial disease or persistence of primary disease did not adversely impact survival outcome.
Conclusions This series shows that the number of lesions is a strong predictor of outcome. Integration of this factor into a decision-making model allows for identification of not only good prognosis patients who will benefit from aggressive treatment but it also facilitates decision making for poorer prognosis patients who are less likely to benefit from WBRT. Recursive partitioning RTOG class 2 and 3 patients with more than three lesions did particularly poor and had an overall survival of 3 months with WBRT. We question the value of WBRT in this subgroup and wonder if best supportive care would be more justifiable given the low survival figures achieved.

Keywords Brain metastases · Whole brain radiotherapy · Lesions

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Introduction

Several population-based series previously have shown the poor prognosis of brain metastases patients [1–4]. Median survival after pathologic or radiologic diagnosis is quoted as being between 2 and 4 months for such patients [1, 2]. This has led to a generally nihilistic approach to treating such patients, with whole brain hypofractionated radiotherapy (WBRT) and/or steroids being the mainstay of treatment [3–5]. With the evolution of radiosurgery and improved surgical techniques that control local disease relatively effectively, there is now interest in classifying

these patients a priori into those that should be treated aggressively because they have the potential for longer survival, and those who should be treated with simple whole brain radiation treatment because their survival is poor irrespective of management [6, 7].

There are now four main prognostic indices for brain metastases patients that assist decision making on what to offer these patients [7, 12–14] (Table 1). The two most rigorously developed are from the Radiation Therapy Oncology Group (RTOG) database of clinical trials, with the recursive partitioning analysis (RPA) model having been the gold standard for more than a decade and the graded prognostic assessment (GPA) a recent refinement from this [12]. There are two other less used models, namely the score index for radiosurgery and the basic score for brain metastases that have limited applicability to the general population of brain metastases patients [7, 14].

Sperduto recently demonstrated the influence of number of lesions on the outcome of brain metastases patients, but most of the work done in looking at this has been performed in subgroups who are only eligible for aggressive treatment, or who were on a randomized trial [11, 14]. Sperduto also has demonstrated that outcome can be stratified according to primary disease site [11].

Several groups have tried to assist decision making by publishing guidelines for the management of patients with brain metastases [8–10]:

1. Patients with solitary metastases in areas not considered vital are offered tumour resection or radiosurgery, followed by whole head radiotherapy. Median survival time for patients with solitary metastasis is greater than 6 months. In a small single-centre randomized controlled trial, Chang recently demonstrated that SRS patients are disadvantaged by WBRT [12]. A larger trial is being performed.
2. Patients with good performance status and one to three lesions. Most guidelines recommend whole brain radiotherapy (WBRT) with stereotactic radiosurgery (SRS) boost to these lesions. Median survival time for patients with one to three lesions and good performance is 4.5 months.
3. All other patients are recommended hypofractionated whole head radiotherapy (WBRT). This group makes up the bulk of the patients and has a median survival of approximately 3 months. No firm recommendation is provided for when best supportive care should be considered as an option.

Few studies have been performed outside the RTOG database to examine the impact of number of lesions on survival in the *general population* of brain metastases patients, and it could be argued that even the RTOG RPA results are not generalisable since they were derived from patients participating in clinical trials. An important question that cannot be easily answered from such series is whether or not some patients are likely to benefit from palliative radiotherapy at all [14, 15]. We attempted to answer this question in a population-based series of brain metastases patients.

Methods

All radiotherapy referrals for brain metastases between 2000 and 2005 in Southern Alberta were assessed for inclusion in this study. Booking sheets/charts for brain metastases patients referred for radiotherapy were assessed and entered into an electronic database. Charts were audited for information on primary cancer, metastatic disease and the extent of brain involvement. Patients excluded from this analysis included patients with brain metastases from leukaemia or lymphoma where there is a risk of leptomeningeal spread, patients with presumed brain metastases without a confirmed primary cancer diagnosis and patients who were registered but not seen at the centre. Outcome of patients was measured as of June 30, 2006. All patients had to have undergone computerized tomography (CT) and/ or magnetic resonance (MR) scanning of the brain.

Table 1 Predictive models for brain metastases patients

Model (year of manuscript)	Factors included	Issues with model
Recursive partitioning analysis (1997)	Age, KPS, presence of extracranial or primary disease	Strong statistical support uses decision tree software. Validated in multiple studies
Graded prognostic assessment (2008)	Age, KPS, number of lesions, extracranial disease	Scored for each factor. May not assist decision making for poorer prognostic groups
Score index for radiosurgery (2000)	Age, KPS, number of lesions, volume of lesion, systemic disease or not	Arbitrary scores allocated, validated by several retrospective studies
Basic score for brain metastases (2004)	KPS, persistent primary disease, extracranial disease	Least known of models. Does not consider age or number of lesions

The primary hypothesis was that number of lesions will improve our ability to define the subgroup of patients less likely to benefit from WHRT. We defined benefit as median survival of more than 3 months. It is important to note that because of the retrospective nature of this study, quality of life, cause of death and brain control fields could not be collected. It is therefore difficult to use our results to address the value of improvement in quality of life with WBRT. Statistical analysis was performed using Stata version 8.0. Descriptive factors were evaluated using Student's *t* and Chi-squared tests. Survival outcomes were created using Kaplan–Meier estimates and tested for differences using log rank testing. Multivariate analysis was performed using the proportional hazards model.

Results

There were 13,057 patients treated with radiotherapy in the department of Radiation Oncology between 2000 and 2005. Of these, 568 brain metastases patients met the criteria for inclusion in this study, comprising 4.4% of the radiotherapy treatment population. In 31 cases, despite them having had imaging, there was insufficient information on number of lesions or lesion size to include them in evaluation of all fields. This meant that comprehensive data was available for all fields in only 537 cases. The 31 cases whose radiographic images were not available for re-evaluation were categorized as having an unknown number of lesions and not included in the descriptive analysis of number of lesions or lesion size. They were censored from the multivariate analysis but included in the survival estimates where appropriate. When this group was included in the multivariate analysis as an "unknown number of lesions" category, this did not change the predictive model.

Patient characteristics (568 patients)

The median age of patients was 61 years, the median number of lesions detected was 3 (537 patients) and the average size of the biggest lesion was 2.7 cm (537 patients; see Table 2). Of the primary sites, 75 patients (13.2%) had breast cancer, 346 (60.7%) had lung cancer, 26 (4.6%) had melanoma and 123 (21.6%) comprised other primary sites.

Analysis showed 369 patients (65%) had persistent or recurrent disease at the primary site, and 274 patients (48%) had extracranial metastases at the time of brain metastases diagnosis. Ninety-nine patients (17.4%) had neither persistent/recurrent primary disease nor extracranial metastases at the time of brain metastases. Three hundred and seventy-eight patients (66%) had Karnofsky performance status of ≤70.

Table 2 Patient and treatment characteristics (568 patients)

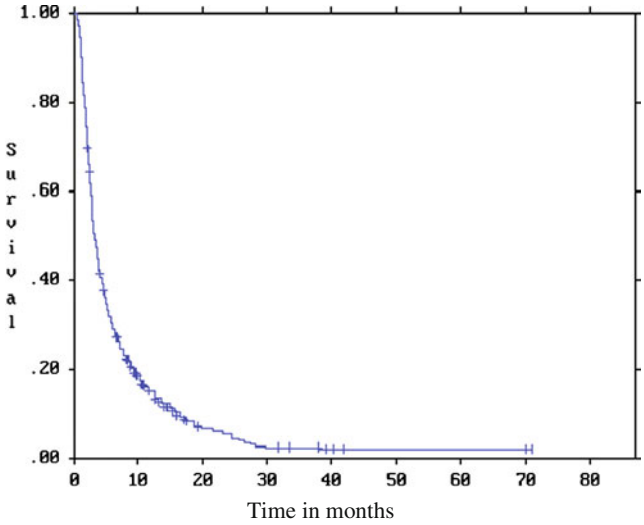
Median age	61 years
Median size of lesions (537)	2.7 cm
Median number of lesions (537 cases)	3
Unknown number or size of lesion	31 cases
Persistent primary disease	369 (65%)
Extracranial metastases	247 (48%)
Neither primary disease nor extracranial metastases	99 (17.4%)
KPS ≤70	378 (66%)
Primary cancer	
Lung	346 (60.7%)
Breast	75 (13.3%)
Melanoma	26 (7.4%)
Other primaries	123 (21.6%)
RPA class 1	23 (4%)
RPA class 2	154 (21%)
RPA class 3	391 (75%)
Whole head RT (2,000 cGy in 5 fractions)	400 (70%)
Whole head RT (3,000 cGy in 10 fractions)	134 (25%)
Other regimens	20 (3%)
Post-resection planned therapy	7 (1%)
Did not complete RT	7 (1%)
SRS boost post-WBRT	47 (7.4%)

Treatment-related factors (568 patients)

Four hundred patients (70%) received 2,000 cGy in five fractions, 134 patients (25%) received 3,000 cGy in ten daily fractions, 20 patients had another WBRT regimen (3%), 7 patients (1%) had higher planned radiotherapy after cranial resection and 7 patients (1%) did not complete radiotherapy. Forty-seven patients (8.3%) underwent SRS after WBRT. The median time between diagnosis and treatment was 12 days, with 95% of patients having started radiation within 15 days.

Survival outcomes (568 patients)

Figures 1, 2, and 3 show the Kaplan–Meier estimates of overall survival for the whole group and for various subgroups. Median survival from diagnosis for all patients was 3.05 months. There was a significant improvement in the survival of patients with good performance status (KPS ≥70; 4.4 versus 2.8 months; $p=0.00007$). Patients younger than 70 years of age had significantly better survival than older patients (3.5 versus 2.4 months; $p=0.0003$). There was a significantly better survival for patients with one to three compared with four or more lesions ($p=0.000001$). Survival was markedly better for patients undergoing radiosurgery (10 versus 2.9 months; $p=0.000001$). Neither the presence of persistent primary disease ($p=0.56$) nor the

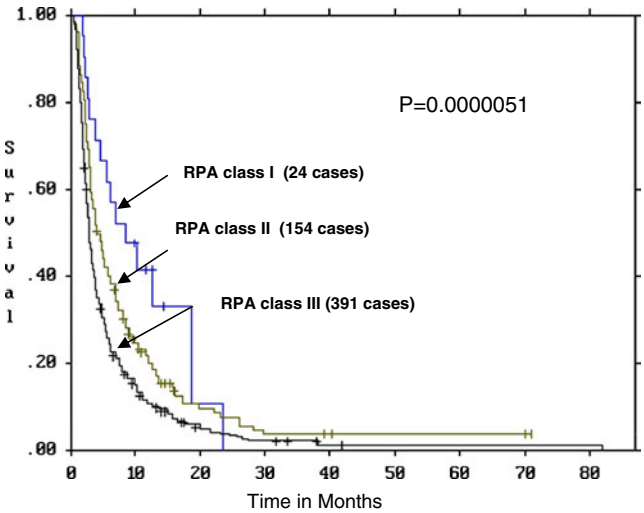


Median Survival = 3.05 months

Fig. 1 TBCC outcomes for brain metastases: Kaplan–Meier estimates of overall survival (568 patients), 2000–2005

absence of extracranial metastases (p=0.12) significantly altered the survival outcome. Proportional hazards modelling showed that good PS, younger age, less than four lesions and treatment with SRS were all independent predictive factors for better survival.

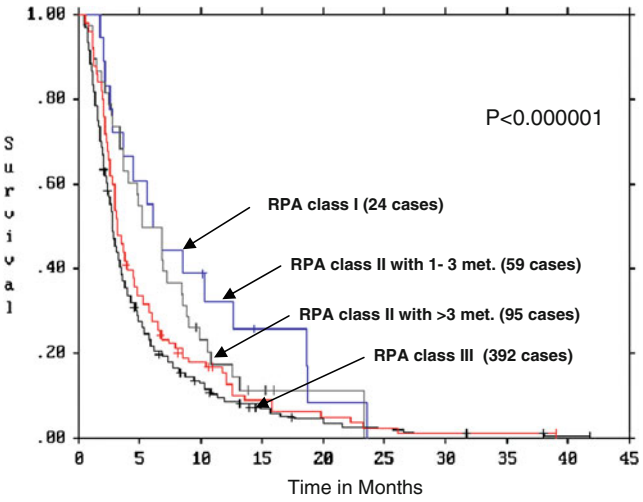
When we examined survival outcome by classifying patients according to the RPA model, there was a significant difference between classes (see Fig. 2). The median survival in classes 1, 2 and 3 was 7.5, 3.9 and



Median Survival:

RPA class I – 7.5 month,
RPA Class II – 3.9 months,
RPA class III – 2.7 months

Fig. 2 TBCC outcomes: overall survival according to recursive partitioning analysis (568 patients), 2000–2005



Median Survival:

RPA class I – 7.5 mo, RPA Class IIA – 6.1 mo,
RPA Class IIB – 3.0 mo, RPA class III – 2.7 months
RPA class IIA = class II with ≤ 3 lesions;
RPA class IIB = class II with 4 or more lesions

Fig. 3 TBCC outcomes: overall survival according to RPA and number of lesions (568 patients), 2000–2005

2.8 months, respectively (p=0.000005). By integrating number of lesions into the RPA model, we demonstrated further stratification of RPA class 2 and 3 patients. Patients within either class 2 and 3 who had fewer than four lesions could be shown to have done better than similar class patients with four or more lesions (5.1 versus 3.0 months, p=0.0002; see Fig. 3 and Table 3 for detailed analysis). When we examined patients from these classes separately, we found that patients with the lower number of lesion did significantly better in each class. To ensure that influence of number of lesions was not due to a treatment effect, where patients with less than four lesions were more likely to receive SRS boost, we ran an analysis without SRS patients. Number of lesions was still an independent predictive factor in class 2 and 3 patients after SRS patients were censored from analysis.

Discussion

This large, contemporary population-based experience with brain metastases has shown that a high proportion (66%) of patients had poor performance status, reflected by the low median survival of 3.05 months for the total population of patients. This is consistent with the findings of other retrospective studies from other centres [1–5]. This low median survival emphasizes the need to refine selection of treatment for patients with brain metastases.

Our data confirms the importance of aggressive treatment for solitary metastases patients, with median survival of such

Table 3 Proportional hazards model: overall survival

Covariate	Coefficient	Hazard	*P* value	95% confidence intervals
KPS	0.3352	1.3982	0.00050	1.1576, 1.6889
Age	0.4233	1.5270	0.0000411	1.2473, 1.8693
SRS	−0.7582	0.4685	0.0000443	0.3256, 0.6742
1 versus 2 lesions	0.2728	1.3137	0.0270	1.0315, 1.6729
2 versus 4 lesions	0.5040	1.6533	0.0000054	1.3322, 2.0568
4 versus ≥5 lesions	1.0737	2.9263	<0.000001	2.0254, 4.2279
Uncontrolled primary	−0.0411	0.9597	0.6469	0.8049, 1.1443

patients in this study treated by resection or SRS boost being 10 months. This is consistent with the results of one large prospective trial and several retrospective studies [16–18]. Controversy remains as to whether or not WBRT should be added to locally aggressive treatment in better prognosis patients who undergo surgical resection or radiosurgery [19, 20, 22]. In a small randomized trial, Kondziolka demonstrated that SRS alone patients did better than SRS plus WBRT [24]. Chang demonstrated that WBRT reduced neurocognition with no overall survival benefit [12].

However, a Japanese randomized trial by Aoyama demonstrated that whole head radiotherapy reduced neurological relapse in patients receiving SRS boost [23]. All these trials have been criticized for their small size and suboptimal methodology. Several other non-randomized trials also have demonstrated that WBRT significantly reduces neurologic relapse in post-resection patients [21, 25, 26]. We could not address this question in our study and continue to offer such patients WBRT. Randomized trials are underway to substantiate the value of WBRT in better prognostic subgroups [9].

What about WBRT or SRS in patients not recommended for aggressive treatment? The RTOG 9508 trial randomly compared WBRT against WBRT and SRS boost in good performance brain metastases patients and demonstrated that although stereotactic boost did not alter overall survival in the overall trial population, it did improve neurologic quality of life. Furthermore, SRS boost translated into a significant survival benefit when subgroup analysis for patients with solitary metastases was performed [17].

It is less clear from previous reports as to which patients fail to benefit from whole head radiotherapy [11]. Our results suggest that RPA class 2 and 3 patients with more than three lesions both do poorly, with a median survival of less than 3 months, consistent with other studies [1, 2]. Furthermore, this is unlikely to improve even with more aggressive radiotherapy, given that a recent Cochrane review could not demonstrate improvement in survival or quality of life with higher whole brain doses [8]. The recent flurry of activity relative to our technical ability to deliver targeted radiotherapy should be counterbalanced with a dose of reality [7, 25].

The desire and ability to use aggressive approaches need to be justified with data showing which patients will benefit from this approach. Although this is a single-centre study, its population-based nature and reasonable study size allow for hypothesis generation around future treatment options. These include the following:

1. Until the GPA has been validated for a general population of brain metastases patients, the RPA classification system is a useful predictive model, as long as number of lesions is used to further select poor prognosis patients. We did not attempt to validate the GPA model with our data.
2. Our data suggests that patients in all RPA classes with one to three lesions do better. We recommend resection or SRS for younger, good performance status patients who have single lesions and SRS in other patients with one to three lesions. All of these patients, other than those in a trial, are also offered WBRT. The only group of patients not considered for locally aggressive treatment with one to three lesions would be those who have significant extracranial disease and poor performance status. These patients are considered for WBRT alone. Whether or not the SRS patients benefit from WBRT is the focus of much discussion, including attempts to complete a randomized trial in North America.
3. Patients who fall into the poorer prognosis subgroup (more than three lesions, and features of the previous RPA class 2 and 3 categories) should be considered for best supportive care rather than WBRT. Their median survival is 2.8 months, making the real value of RT questionable. This is especially relevant for elderly patients with rapidly progressive primary or uncontrolled extracranial disease. This group does particularly poor, and the adverse short-term impacts of radiotherapy do not justify its use here.

There may be concern about our suggestion that radiotherapy may be obsolete for the poorer prognostic group because clinicians often justify the use of radiotherapy in this subgroup by arguing that it allows patients to be weaned from steroids or that there may be quality of life

benefits with treatment [4, 11]. Although speculative, we suggest that the short median survival in certain subgroups implies that neurocognitive benefits for WBRT in that subgroup will be minimal. However, our study did not look at this endpoint. A further weakness of this study is the relatively small size, with the result that further categorization according to outcome of poor prognostic patients per tumour group is not possible. Furthermore, it is important to note that physicians tend to overestimate the benefit of WBRT in brain metastases patients [4]. Ultimately, the question of offering these poor prognosis patients WBRT will come down to the physician's perspective of what they view as a threshold level of benefit.

The fact that the presence of progressive primary or extracranial disease did not adversely impact survival outcome within our proportional hazards model raises questions of whether or not the new era of systemic therapy was allowing better control of other disease elements in current brain metastases patients. A criticism of this perspective would be the failure on our part to show that these patients did not die from causes such as extracranial disease. Although deaths due to extracranial disease could have impacted the survival outcomes of these patients, it would not reduce the importance of our finding that at diagnosis, the presence of EC disease does not seem to affect the outcome. Furthermore, from a pragmatic standpoint, whether or not patients died from brain metastases or EC disease does not minimize the important finding that certain groups seem to benefit more from WBRT than others. Consequently, we are less likely to view controlled extracranial disease as a filter preventing consideration of aggressive or WBRT approaches [13–16].

It is important to recognize that without a prospective study, many of the hypotheses generated in this paper should be considered as speculation. With the limitations as described, it is important that we focus how this study has demonstrated that number of lesions is an important factor to integrate into decision making for these patients. It is important that we consider strategies of how exactly to treat poorer prognostic patients, since it appears that they may not benefit significantly from WBRT.

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