Whole brain radiotherapy for poor prognosis patients with brain metastases: predictably poor results

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Background Patients with brain metastases from solid tumors can be subdivided by characteristics into separate prognostic groups, such as the Radiation Therapy Oncology Group's Recursive Partitioning Analysis (RPA) or the Graded Prognostic Assessment (GPA). At our institution, patients falling into the poorest prognostic groups are often treated with whole brain radiotherapy (WBRT).

Objective To determine if observed survival of poor prognosis patients treated with WBRT for brain metastases at our institution matches the survival predicted by RPA and GPA prognostic indices.

Methods The charts of 101 consecutive patients with newly diagnosed brain metastases from solid tumors who received WBRT were retrospectively reviewed. We calculated each patient's RPA and GPA and compiled treatment and survival data. Observed median survival was compared to that predicted by the RPA and GPA prognostic indices.

Results RPA III patients (n = 25) had a median survival of 2.4 months in our study. GPA 0.0-1.0 patients (n = 35) had a median survival of 2.4 months in our study. These values did not vary significantly from those predicted by the respective indices.

Limitations This is a retrospective analysis and subject to selection bias.

Conclusion Given the delivery time for WBRT and the potential side effects associated with the treatment, the predictably short overall survival in poor prognosis patients calls into question the value of WBRT in this patient subgroup.

Over 170,000 cases of metastatic brain tumors are diagnosed in the United States each year; and the length of survival for patients with brain metastases is often quite limited, ranging from a few weeks to several months.[1] The Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) and the Graded Prognostic Assessment (GPA) are 2 prognostic indices that have been validated to predict survival and guide the treatment of these patients.[2-5] The RPA and GPA indices were formulated by comparing survival to patient and tumor characteristics compiled from RTOG brain metastasis treatment protocols spanning greater than 3 decades.

The RPA has 3 classes of patients enumerated as "I", "II", and "III," with class I patients having the longest predicted survival and class III patients having the worst prognosis. The RPA classes are based upon factors that include patient age and Karnofsky Performance Status (KPS) as well as control of the primary tumor and evidence of extra-cranial metastases (Table 1).[2] The GPA has 4 classes of patients with a score that may be considered analogous to a grade point average achieved by students in school. The classes are arranged into 4 groupings, which are divided from best to worst prognosis as follows: 3.5 to 4.0, 3.0, 1.5 to 2.5, and 0.0 to 1.0. The GPA employs criteria similar to but slightly different from those used in the RPA, estimating survival by patient age and performance status as well as the number of brain metastases and evidence of extracranial metastases (Table 2).[4]

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TABLE 1 Recursive Partitioning Analysis (RPA)

RPA Class	Characteristics	Predicted median survival (months)
I	KPS ≥ 70, Controlled Primary, Age < 65, no extracranial metastases	7.1
II	All others	4.2
III	KPS < 70	2.3

Abbreviation: KPS, Karnosky Performance Status.

Treatment options for patients with brain metastases include surgery, stereotactic radiosurgery (SRS), whole brain radiation therapy (WBRT), supportive measures such as corticosteroids, or a combination of these modalities. The survival of the worst prognosis brain metastases patients treated with WBRT and steroids is estimated by the RPA and GPA tools to be 2.3 months and 2.6 months, respectively.[2,4] As noted above, the patient data from which the RPA and GPA indices were created included patients treated on clinical trials. This could have resulted in the selection of patients more fit than average patients and lead to an overestimation of survival when applied to all patients. The clinical trial data used were drawn from over 3 decades, during which supportive care and chemotherapy treatments improved. This could result in an underestimation of survival when applied to patients treated with current systemic therapies and supportive care. It is important for physicians to have an accurate method to predict survival in patients to ensure that appropriate treatments can be recommended.

Our goal was to determine if the RPA and GPA indices correctly predict survival in the population of general cancer patients that fall into the lowest categories on each index. We retrospectively analyzed patients with brain metastases treated with whole brain radiation in our practice using current systemic therapies and supportive care to determine if our observed survival for patients in the lowest prognostic groups by the RPA and GPA scales differs from the survival predicted by those indices.

Methods

Following study approval by the Indiana University Purdue University Indianapolis (IUPUI) Institutional Review Board, the charts of all consecutive brain metastasis patients treated with WBRT at the Indiana University School of Medicine between August 2008 and September 2010 were reviewed. Reasons for exclusion from the study included primary brain tumors, pediatric cases (< 19 years old), diagnosis of multiple myeloma/leukemia/lymphoma, patients who were being re-treated with WBRT, and patients who received WBRT but were without evidence of parenchymal brain disease (ie, with cranial bone or leptomeningeal metastases only or receiving prophylactic treatment before any metastasis had been identified).

A total of 101 patients met the inclusion criteria for our study. A retrospective chart review collected the required data for calculating each patient's RPA and GPA (Tables 1 and 2) as well as their initial WBRT consult date and prescribed/delivered treatment. For 18 of the identified patients, KPS had to be retrospectively assigned based on the history and physical from the radiation oncologist's consult note (n = 13) or converted from the Eastern Cooperative Oncology Group (ECOG) performance status scale (n = 5). Other recorded data included primary diagnosis and treatment modalities employed in addition to WBRT, including stereotactic radiosurgery, surgical resection, and corticosteroid use. To calculate survival time from their consultation date, the social security death index (SSDI) was used to ascertain date of death or ongoing survival of each patient.

Statistical methods

Each patient was categorized by RPA (I, II, III) and GPA (3.5-4.0; 3.0; 1.5-2.5; and 0.0-1.0) classifications. Survival was calculated from the time of the WBRT consult date. Median survival was calculated using the Kaplan-Meier method. Overall survival between RPA (I, II, and III) and GPA (1.5-2.5 vs 0.0-1.0) groups was compared using log-rank tests. The median survival for each group was compared descriptively to the median survival predicted by the RPA and GPA indices. Due to the small size of most groups, no statistical comparison of survival was made between patients with different tumor histologies.

Results

Of the 101 cases reviewed, the number that fit the RPA I, II, and III classes were 8, 68, and 25 patients, respectively. The 25 RPA class III patients in this study showed a median survival of 2.4 months versus a predicted survival of 2.3 months (Figure 1).

All 101 patients were also grouped according to the GPA prognostic index. This analysis showed that 2, 3, 61, and 35 patients resided in the 4 GPA classes, which are divided by GPA scores of 3.5 to 4.0; 3.0; 1.5 to 2.5; and 0.0 to 1.0, respectively. For the 35 patients in the GPA 0.0-1.0 group, the median survival was 2.4 months (Figure 2). Given that the predicted median survival of 2.6 months falls within the 95% CI of the actual median survival, it is unlikely that these groups are significantly different (Table 3). It should also be noted that in both

TABLE 2 Graded prognostic assessment

GPA characteristics	0	0.5	1.0	Grade	Predicted median survival (months)
Age	≥ 60	50-59	< 50	3.5-4.0	11.0
KPS	< 70	70-80	90-100	3.0	6.9
#CNS mets	> 3	2-3	1	1.5-2.5	3.8
Extracranial mets	Present	-	Absent	0.0-1.0	2.6

Abbreviations: GPA, graded prognostic assessment; KPS, Karnofsky Performance Status; mets, metastases.
#CNS mets, number of central nervous system metastasis.

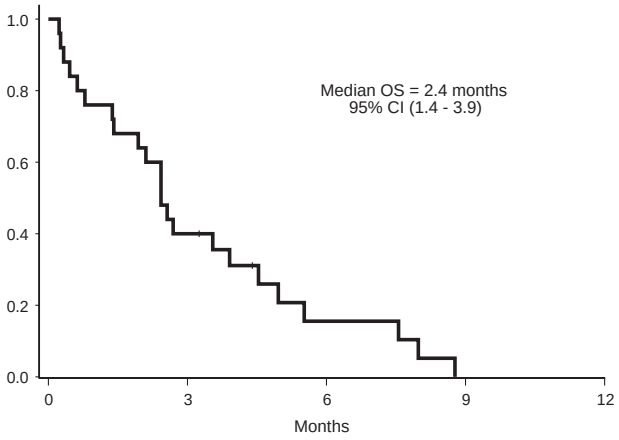

FIGURE 1 Kaplan-Meier curve depicting survival for patients in the Recursive Partitioning Analysis (RPA) Group III.

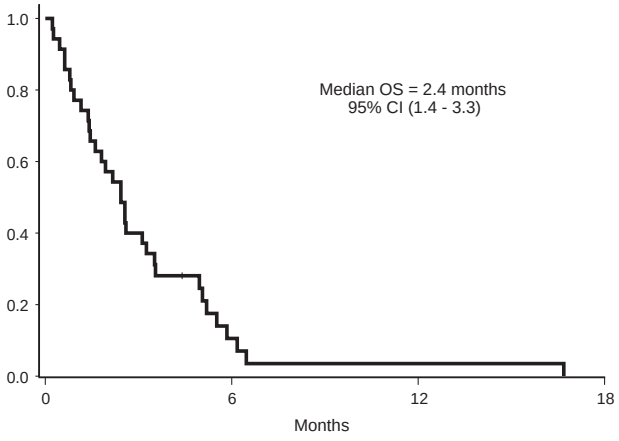

FIGURE 2 Kaplan-Meier curve depicting survival for patients with a Graded Prognostic Assessment (GPA) score of 0.0-1.0.

the RPA III group and the GPA 0.0-1.0 group, 3 patients had received previous SRS for brain metastases before going on to WBRT. In both groups, 88% of the patients were on corticosteroids at the time of WBRT.

TABLE 3 Predicted and actual median survival for poor prognostic group patients

	Predicted median survival	Sample median survival	Sample 95% C.I.	Sample n
RPA III	2.3	2.4	1.4, 3.9	25
GPA 0.0-1.0	2.6	2.4	1.4, 3.3	35

Abbreviations: GPA, graded prognostic assessment; RPA, recursive partitioning analysis.

The survival of our patients varied significantly according to prognostic class. The survivals of patients in RPA class I vs II vs III was significantly different (log-rank test $P = .0016$, data not shown). The patients in GPA 0.0-1.0 vs GPA 1.5-2.5 also varied significantly (log-rank $P < .0001$, data not shown). There were not enough patients in the higher GPA categories to allow comparison between groups. As in the RPA and GPA datasets, our dataset consisted predominantly of patients with non-small cell lung cancer, breast cancer and other cancer being the second most prevalent histologies in the RPA III and GPA 0.0-1.0 groups, respectively (Tables 4 and 5). Survival appeared similar across groups, with the exception of small cell lung cancer patients who had a slightly longer survival than others in the RPA III group.

Discussion

Only a limited amount of survival data for patients with metastatic brain cancer in a nonprotocol setting has been published. Our results show that both the RPA and GPA indices accurately predict the median survival of patients in the lowest prognosis categories in a general cancer patient population. The use of the RPA and GPA indices should allow for a frank discussion with patients about their prognosis and help clinicians recommend appropriate treatments based upon easily obtained patient- and tumor-related factors. Like many publications evaluating patients with brain metastases, our dataset included a

TABLE 4 Survival by histology in RPA III patients

	n	%	n died	Median survival	95% C.I.
Breast cancer	5	20	5	1.4 mo	0.5 mo-8.8 mo
NSCLC	14	56	13	2.4 mo	0.3 mo-3.9 mo
SCLC	3	12	3	5.0 mo	4.5 mo-7.6 mo
Other	3	12	2	2.4 mo	1.9 mo-NE†

Abbreviations: NE, not estimable; mo, months; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

TABLE 5 Survival by histology in GPA 0.0-1.0 patients

	n	%	n died	Median survival	95% C.I.
Breast cancer	6	17	6	2.3 mo	0.5 mo-6.5 mo
NSCLC	16	46	15	1.8 mo	0.8 mo-2.6 mo
Melanoma	4	11	4	3.8 mo	1.8 mo-5.2 mo
Other	9	26	8	3.5 mo	1.4 mo-5.8 mo

Abbreviations: mo, months; NSCLC, non-small cell lung cancer.

plurality of patients with non-small cell lung cancer. However, it appears that survival was similarly poor across groups, with the exception of patients with small cell lung cancer in the RPA III group. However, this finding should be viewed with caution as there were only 3 patients in that group.

Despite the fact that systemic therapies and supportive care have both improved over the years, the patients in these lowest prognostic groups continue to have very limited survival from the time of radiotherapy consultation. The average time to schedule and deliver WBRT for our patient population was 11 days (excluding initial consultation, set-up time, or weekends). In this subset of patients with predictably short overall survival, both the length and overall value of WBRT are called into question.

The treatment approach for these poor prognosis brain metastases patients has historically included both WBRT and corticosteroids. Indeed, the RTOG protocols that were used first for the creation of the RPA and later for the creation of the GPA included a dosage of WBRT and number of fractions in all treatment arms of the studies. While radiotherapy has commonly been prescribed to 30 Gy in 10 fractions for this patient group, the appropriate dose fractionation for these patients has been debated for some time. Before the RPA and GPA were published, Berk et al published a 1995 meta-analysis of radiotherapy trials for metastatic brain disease that supported the use of 20 Gy in 5 fractions for palliative treatment of patients with the poorest performance status.[6] A later 2005 systematic review of 37 randomized controlled trials looking at the best treatment options for patients with brain metastases found that there is no overall survival benefit or change in neurological function when comparing WBRT regimens of 30 Gy in 10 fractions to 20 Gy in 5 fractions in poorly performing patients.[7] A Cochrane review of WBRT for the treatment of multiple brain metastases showed no proven advantage to delivering doses other than 30 Gy in 10 fractions or 20 Gy in 5 fractions for patients with multiple brain metastases.[8]

Furthermore, the authors of the Cochrane meta-analysis (who also authored a Canadian consensus guideline for the treatment of brain metastases) suggest that patients with a low performance status might fare better with supportive care/steroids alone rather than more aggressive treatment such as WBRT.[7,8]

Along this line of thought, there have been recent calls for trials examining the value of WBRT vs supportive care in the worst prognosis patients with metastatic brain cancer.[7,9,10] In addition, some researchers have expressed a concern that WBRT can lead to a decreased quality of life for the terminally ill patient. It remains uncertain whether patients with a short life expectancy to begin with have a chance to recover from the treatment before their deaths.[11] To date, there has only been one randomized controlled trial published that attempted to compare WBRT with steroids vs steroid treatment alone. That trial was completed in the pre-CT/MRI imaging era and lacked statistical analysis between treatment arms. Therefore, the results of this study have been equivocal as far as guiding therapy.[12] However, there is an ongoing NCI randomized controlled trial (NCT00403065) re-

"This is not how I wanted to spend my last two months. . . . . ."

The authors' primary aim was to determine if their very ill patients' clinical courses comported with predictions made by 2 prognostic indices—the so-called RPA and GPA.

Although limited by the potential for selection bias and a relatively small sample size, this retrospective study appears to validate the statistical predictions of the RPA and GPA systems. WBRT was associated with very short survival (2 to 2.4 months) and was indistinguishable from the "predictably poor" survival forecast by the RPA and GPA.

These provisional findings may be seen as vindication for prognostic models that have yet to be validated by prospective clinical trials. However, more important are the clinical questions raised, but not answered, by these results:

- Does WBRT, typically provided in conjunction with oral corticosteroids and general supportive care, provide clinical results meaningfully superior to those treatments alone?
- Is there any survival benefit associated with WBRT administered to "poor prognosis" patients?
- Is there any evidence of quality of life differences between groups of patients receiving vs not receiving WBRT?

We do not have high quality clinical trials data to answer these very important questions specifically for the "poor prognosis" groups, although Henderson et al describe an ongoing NCI trial designed to address them. According to a 2012 Cochrane Collaborative review of WBRT, "The benefit of WBRT as compared to supportive care alone has not been studied in RCTs. It may be that supportive care alone, without WBRT, is appropriate for some participants, particularly those with advanced disease and poor performance status."[1]

Here is what we do know:

- WBRT treatment planning takes time: Preliminary data from an international (Australia and New Zealand) trial of WBRT plus steroids and optimal supportive care vs steroids and optimal supportive care alone yielded a median time of 13 days from study enrollment to first WBRT session (with a mean of 2-29 days).[2] Wait times are likely to be much shorter in US centers.
- WBRT takes time to work: Although some symptom relief can be attained within the first week, most experts suggest 3-4 weeks is required from WBRT initiation to maximal benefit. Early symptom relief from WBRT may make downward titration of corticosteroids possible; for patients experiencing high corticosteroid side-effect burden, this can be a very meaningful but impossible to predict benefit.
- WBRT can cause side effects of its own: These are well described and can include headache, fatigue, drowsiness, erythema and desquamation of the scalp, and hairloss. While it is likely that the typical "poor prognosis" WBRT patient will already be experiencing many of these symptoms, WBRT may amplify those that already exist and confer new burdens as well.
- WBRT requires patients and families to go to a radiation oncology center on 5 (20 Gy in 5 fractions) to 10 occasions for the actual treatments. For at least some patients and their families, the logistical burdens (travel, work absences, etc) and added symptom burden (expending precious energy reserves, pain associated with getting on/off treatment table) are significant.

In a "poor prognosis" patient of the type described in the Henderson trial, this could mean that a patient spends up to 6 of his/her last 10 weeks of life "doing" WBRT: getting started, waiting for the radiation to kick-in and bring relief from central nervous system symptoms, tolerating potentially new WBRT-specific side effects, and travelling multiple times to the treatment center.

Conversely, many patients and their families are more terrified by news of brain metastases than any other manifestation of illness. There is something truly horrifying about the idea that one's relentless disease has now breached the fortress of the blood-brain barrier and is systematically assaulting the organ of perception, sensation, motor function, thought, memory, mind (ie, the self, as most of us know it). Foregoing RT, a highly potent, modern machine-based effort to stave off the invader (even if the benefit were proved to be more symbolic than measurable) is a difficult notion. We are also regularly reminded of patients' cognitive biases in favor of over estimating the potential benefits of various cancer treatments.[3] If the NCI trial mentioned above fails to show either survival or quality of life benefits of WBRT over steroids and supportive care alone, we would probably be doing our poor-prognosis patients a favor by not bringing WBRT into the treatment-planning conversation at all.

Palliative care clinicians are increasingly called upon to help patients and families think carefully about the implications and consequences of treatment decisions they are facing. The title of this commentary comes directly from patients who had spent what they judged in hindsight to be too much of their precious last 8-12 weeks of life commuting daily to a cancer center for WBRT. On the other hand, it may be that it was precisely the benefits of WBRT that made it possible for my patient to be sentient enough to rue the way she spent her time. If we and our patients knew this a priori, they might make the same decision again in a hypothetical future, favoring consciousness over slow inanition. Thus we face off once again with one of the great challenges of clinical oncology and palliative care: though we speak as if clinical decision points were binary propositions, the road not taken is an unknown and the road taken is hardly predictable.

— By Thomas Strouse, MD

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investigating the same question in an effort to determine if WBRT imparts any survival benefit or improvements in quality of life for patients with metastatic brain cancer.

The limitations of this study include its retrospective nature and the lack of a comparison arm with similar patients treated with supportive care alone. Accrual to randomized trials, such as the one listed above, is the best way to further explore the optimal treatment for these poor prognosis patients.

Conclusion

The RPA and GPA indices are intended to estimate the prognosis of patients with metastatic brain cancer and can help guide clinicians in their choice of recommended treatment. Our data validate these indices for patients in the poorest prognostic groups when treated in a non-protocol setting. Patients in the poorest prognostic group by either the RPA or GPA have short median survivals that are very close to those predicted by the respective index. These data reinforce the need for additional trials, such as the on-going NCI trial, to determine the optimal treatment for these poor prognosis patients.

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