Brain metastasis prognostic nomograms and brain metastasis velocity: a narrative review

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Objective: To provide a review of the current status of predictive nomograms and brain metastasis velocity (BMV) in the prognostication of brain metastasis outcomes.

Background: Statistical analyses have been used for many years in an attempt to predict clinical outcomes of brain metastasis patients. Such models have attempted to predict such endpoints as survival and which patients would most benefit from stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT).

Methods: This narrative review includes documents the history of statistical models and nomograms through the stage migration of the brain metastasis population from a population with large symptomatic brain metastases to the modern population with small asymptomatic metastases found on surveillance imaging. It also tells the history of the derivation and validation of BMV, a recently identified biomarker for survival and neurologic death in the brain metastasis population treated with SRS.

Conclusions: Statistical models predicting brain metastasis behavior continue to evolve with the changing landscape of systemic therapy and the more aggressive use of SRS. Previous models with ultimately need to integrate biologic data and will continue to be updated.

Keywords: Brain metastasis velocity (BMV); brain metastasis nomograms; stereotactic radiosurgery (SRS); whole brain radiation

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Introduction

Recent randomized trials have demonstrated that stereotactic radiosurgery (SRS) has superior cognitive function over whole brain radiotherapy (WBRT) for patients with 4 or fewer brain metastases (1-3). Technology has also advanced such that treatment of more numerous lesions is technically feasible. Such advances as flattening filter free (FFF) linear accelerators, single isocenter multitarget (SIMT) radiosurgery, and stereotactic platforms that do not require rigid frame fixation have brought SRS into the community setting and made it more universally available and widely practiced (4).

As the ability to perform SRS has become ubiquitous, several issues have arisen in order to properly triage this resource. SRS is more technologically challenging to deliver, and therefore is more costly than a course of standard WBRT (5-7). Moreover, some patients will experience rapid development of numerous new brain metastases and therefore require WBRT soon after SRS - effectively wasting the efforts to spare cognition. In addition, there is a population of patients for which serial SRS is done in which cancer involves such a high volume of the brain that the likelihood of dying of neurologic death greatly rises (8).

It is unclear as of yet whether upfront WBRT may be able to mitigate such risk, but current trials are investigating this possibility (9).

Because of the higher cost of SRS as a resource and because there are populations for which either upfront SRS or upfront WBRT may be a more optimal treatment option, there is an incentive to distinguish the patients who are most likely to benefit from upfront SRS from those most likely to benefit from upfront WBRT. Several attempts have been made to use statistical modeling to predict clinical outcomes for these patients in order to determine which upfront treatment strategy may be more optimal (SRS *vs.* WBRT). The goal of the present narrative review is to discuss the previous attempts to statistically model brain metastasis behavior and to assess their clinical utility. We present the following article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-21-102/rc).

Methods

Electronic search was conducted using the PubMed database. Search terms included brain metastasis nomograms and brain metastasis velocity (BMV). The search was restricted to studies published in the English language. The search included studies spanning the dates of January 1, 1997 to December 31, 2020.

The heterogeneity of the brain metastasis population

It has been known for some time now that clinical outcomes for the brain metastasis population are heterogeneous and often depend on the histology of the primary cancer from which the brain metastases originated. Such cytogenetic abnormalities as Her2 overexpression (10) and ALK (11) or EGFR mutations (12) can significantly improve the responsiveness of cancers to targeted therapy. Presence of these biomarkers can lead to longer survival and decreased likelihood of re-seeding the brain (13,14); (12,15,16). In fact, even histological differences between subtypes of lung cancer can lead to differences in how commonly patients develop new brain metastases after SRS (7,17).

A critical theme that appears to tie together the variation in brain metastasis clinical outcomes is the control of extracranial disease. If patients have a large burden of extracranial disease (18) or disease that is less responsive to therapy (19), they are more likely to have a poor prognosis. As such, statistical models that would attempt to predict brain metastasis outcomes would be best derived by accounting for these factors.

There are also factors independent of control of extracranial disease that still affect brain metastasis outcomes. These factors include radioresistance, size and location of lesions within the brain, volume of brain metastases in the brain, as well as the propensity for hemorrhage. Radioresistance has been shown to worsen the likelihood of control of brain metastases and yield high rates of neurologic death when treated with conventionally fractionated whole brain radiation (20). SRS has been shown to have an improved local control in the radioresistant population (21).

As performance status has been demonstrated to be a critical determinant of survival for patients with brain metastases (22,23), lesions located within eloquent portions of the brain may have an influence on patient outcomes such as survival. In addition, the cumulative volume of brain metastases can also affect patient outcomes by affecting patient neurocognitive status as well as the ability to successfully eradicate disease with radiotherapy (24).

Patient subgroups that may benefit from upfront SRS

The main reason patients benefit from SRS upfront is to avoid the cognitive sequelae of WBRT. The degree to which traditional WBRT can affect cognition can be quite dramatic as it is not unusual to have patient performance decline by a standard deviation or greater on cognitive testing within several months after WBRT completion (1,25). The cognitive toxicity of WBRT may ultimately be mitigated by recent strategies of using a neuroprotective agent (memantine) (26) and using hippocampal avoidance techniques (26,27). However, trials are presently being conducted comparing these strategies, and it may be several years before trials can determine whether these new strategies may preserve cognition as well as SRS does. The presently accruing CE7 study is randomizing patients with 5–15 brain metastases to SRS *vs.* hippocampal avoidance WBRT with memantine (28).

As WBRT is most commonly limited to a single application during the natural history of a patient's cancer, choosing the optimal time to deliver WBRT can be an important decision. While repeat WBRT has been reported, it by and large treats cancer to a lower dose than what is considered sufficient for long term control (29).

It has been associated with poor survival outcomes (30). As such, postponing WBRT as long as possible with upfront SRS (with the intention of using WBRT only once during a patient's treatment) can be a strategic decision for many patients who do not have rapid multifocal brain failure.

Patient subgroups that may benefit from upfront WBRT

Patients that may benefit from upfront WBRT generally do so because either SRS has a high likelihood of missing subclinical disease or because the risk of SRS outweighs the toxicity of WBRT. Patients with numerous metastases may be more likely to benefit from WBRT as opposed to SRS. This is because with a greater number of metastases at time of diagnosis, there is a greater likelihood of there being radiographically occult disease that is not seen at time of SRS (31), and because as the cumulative volume irradiated with SRS rises, so does the risk of toxicity (32,33). While the maximum number of metastases that are treatable is controversial, volume constraints can likely better elucidate the limitations of SRS. A contiguous V12 of greater than 8.5 cc yields a greater risk of radiation necrosis (32). If an SRS plan has a contiguous V12 that is significantly greater than this value or multiple individual volumes within the brain greater than this value, then the patient is likely at a high risk of significant toxicity from SRS. At present, there are several prospective trials being conducted assessing the role of SRS in patients with patients with maximum allowed brain metastases between 10 and 20 (4).

Patients with large and symptomatic brain metastases for which surgery is not feasible or appropriate may benefit from WBRT. The clinical response rate for patients with symptomatic brain metastases after WBRT is between 50% and 75% (34). Patients with symptomatic brain metastases that are left untreated have a median survival of 1–2 months (35,36). Patients receiving WBRT for symptomatic brain metastases will be less likely to die of brain metastases than if they had gone untreated (37). The recently published QUARTZ study was a randomized trial comparing WBRT to supportive care for patients with brain metastases from non-small cell lung cancer that were unsuitable for surgery or SRS (38). While the trial showed no difference in survival, there was concern that many patients with poor performance status on this trial were enrolled, and that these patients would do poorly regardless of whether they had treatment for brain disease or not. While the trial was designed to include poor performance status patients, it would be more difficult to determine any benefit from WBRT in this population.

Small cell lung cancer has traditionally been a population thought to benefit from upfront WBRT (39), and even prophylactic cranial irradiation in patients who have not yet developed clear metastases (40-42). However, more recent data with upfront SRS alone suggests that some populations with small cell lung cancer (particularly if they have single or few lesions) may have equivalent outcomes to those treated with upfront WBRT (43). The NRG CC009 study is a presently open phase III trial comparing hippocampal avoidant WBRT with memantine to SRS for brain metastases from small cell lung cancer (44). This trial will likely determine the future upfront standard of care for patients with brain metastases from small cell lung cancer.

Patients with leptomeningeal dissemination represent a population that probably do not benefit from upfront SRS. This is due to the diffuse nature of the cancer spread along with meninges, the inability of imaging to predict the full extent of the disease, and the poor prognosis (45,46). WBRT on the other hand has been shown to have a demonstrable benefit with regards to symptoms, though the ability to affect life expectancy is more controversial (47).

Prognostic models for survival

Life expectancy can be an important factor that may help to dictate the optimal treatment for a patient with brain metastases. For example, patients with short life expectancy and small asymptomatic lesions may not benefit from any CNS-directed therapy (38). Conversely, those with greater life expectancy may benefit more from aggressive use of SRS in order to postpone WBRT for as long as possible (48). Prognostic models for brain metastasis survival have been used for more than two decades. The brain metastasis population has evolved over that interval from being a population with predominantly larger symptomatic brain metastases to now being a population with smaller asymptomatic brain metastases diagnosed due to screening MRI's done at staging. As such, prognostic models have also evolved and have required updating to account for improved therapies and outcomes.

The first major prognostic index gaining widespread acceptance was the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA). The RPA represented an analysis of multiple RTOG prospective trials performed between 1979 and 1993, identifying

performance status, age, and presence of extracranial disease as the dominant factors affecting survival (22). Over the next decade after the RPA was published, several additional prognostic indices were developed which also attempted to correlate predictive factors with survival. Each of these analyses found age, KPS and extracranial disease status to be important prognostic factors (23,49,50). The score index for radiosurgery (SIR) also took into account the number and volume of largest metastases to indicate appropriateness for SRS (49). While these factors remain important in the modern setting, the predicted survival from these early prognostic indices has become obsolete given improving cancer treatments and the stage migration towards a modern population of small asymptomatic metastases.

The next major evolution for brain metastasis prognostic indices was the classification of metastases based on the primary cancer from which the metastases originated. Sperduto *et al.* performed a multi-institutional analysis of survival of 3,940 patients with newly diagnosed brain metastases, grouping them by the primary cancer (51). This analysis produced the diagnosis-specific graded prognostic assessment (ds-GPA). This ds-GPA has since been updated to include molecular markers in lung cancer such as EGFR and ALK (52), as well as estrogen/progesterone and HER2 status for breast cancer (53).

Nomograms for distant brain failure and salvage WBRT

A recent cost analysis of brain metastasis management in the USA found that the determination of management strategy between upfront SRS and upfront WBRT was the single most significant factor that affects the cost of brain metastasis management over a patient's lifetime (7). This is clearly a difficult issue as cost effectiveness of treatments will depend on the insurance system from each country. However, identifying the population who require early WBRT salvage would be meaningful not only clinically, but also with regards to resource utilization. In general, these patients represent the population who experience rapid development of numerous new brain metastases (54). Several attempts have been made to predict distant brain failure. Ayala-Peacock published a nomogram predicting the incidence of distant brain failure after upfront SRS and found that systemic disease status, number of metastases and histology were dominant factors that affected the rate of distant brain failure (18). Press *et al.* created a nomogram that was predictive of distant brain failure and salvage WBRT and found that number of metastases, smaller lesion volume and melanoma or breast histology to be important risk factors (55). Gorovets *et al.* created a nomogram that was predictive of survival without salvage WBRT finding extracranial disease burden, symptom burden and number of metastases to be significant predictive factors (56).

While the aforementioned nomograms have potential for impacting clinical management, several issues with nomogram application in the brain metastasis population have been identified. These concerns include the heterogeneity of the brain metastasis population and the fact that systemic cancer treatment continues to evolve and improve. As such, predictive models need validation with independent datasets. A validation study of two nomograms that predicted distant brain failure showed that attempts with independent validation from a mixed academic and community population demonstrated limited predictive ability from either nomogram with the independent dataset (57). Ayala-Peacock *et al.* recently updated a nomogram for distant brain failure that was validated by data from 9 academic centers (58). A summary of brain metastasis predictive nomograms is seen in *Table 1*. The presently accruing CCTG CE7 study will be attempting to prospectively validate this nomogram in the patients randomized to the SRS arm (28).

Even with validation, however, models that predict clinical outcomes can quickly become obsolete with the advent of a novel systemic therapy that significantly changes control of extracranial disease. This phenomenon was seen first with the advent of targeted agents (13,21), and then also with the wide adoption of immunotherapy (59). A likely future direction will be to have a continually updated repository for brain metastasis outcomes, as well as predictive models based on genomic biomarkers.

BMV

Farris *et al.* recently identified BMV as a biomarker that predicted overall survival and likelihood of dying from neurologic death (60). BMV is defined as the number of new brain metastases diagnosed since upfront SRS (not including those treated at the first SRS) divided by the time since SRS. The resulting value represents the rate at which new cancer is seeding the brain, and is representative of the degree of control of systemic cancer. BMV has been validated by multiple subsequent studies including from North America, Japan and Europe (61-63). A summary of available series that have validated BMV is shown in *Table 2*.

Table 1 Predictive nomograms for brain metastasis outcomes

Author, year/predictive model	No. of patient	What the model predicted	Major predictive factors	Validation (internal/external)
Gaspar *et al.*, 1997: RPA (22)	1,200	OS	Performance status, age, presence of extracranial metastasis, primary tumor	External
Weltman *et al.*, 2000: SIR (49)	65	OS	Age, performance status, extracranial disease status, number and volume of brain lesions	Internal
Sperduto *et al.*, 2012: ds-GPA (51)	3,940	OS	Performance status, age, presence of extracranial metastases, number of brain metastases Primary tumor	External
Ayala-Peacock *et al.*, 2014: Wake Forest DBF Nomogram (18)	464	DBF	Primary diagnosis, number of brain metastasis, widespread/progression of systemic disease	Internal
Press *et al.*, 2015: Emory DBF Nomogram (55)	270	DBF/time to WBRT	Primary diagnosis, number of and volume of brain metastasis, previous WBRT	External
Gorovets *et al.*, 2017: Brown WBRT Nomogram (56)	895	time to WBRT	Age, primary tumor type, molecular markers, number of brain metastases, presence of neurologic symptoms, systemic disease burden	Internal
Ayala-Peacock, 2017: USA/Canada DBF Nomogram (58)	1,354	DBF/BMV	Age, sex, primary tumor type, largest tumor size, number of brain metastases	External

RPA, recursive partitioning analysis; SIR, score index for radiosurgery; ds-GPA, diagnosis-specific graded prognostic assessment; OS, overall survival; DBF, distant brain metastasis; WBRT, whole brain radiotherapy; BMV, brain metastasis velocity.

Table 2 Series on brain metastasis velocity

Author, year/Institution	Total number of patients with upfront SRS without WBRT	Number of patients with DBF after initial SRS	Low risk BMV mOS (months) (95% CI)	Intermediate risk BMV mOS (months) (95% CI)	High risk BMV mOS (months) (95% CI)
Farris *et al.* 2017/Wake Forest (60)	737	286	12.4 (10.4–16.9)	8.2 (5.9–9.7)	4.3 (2.6–6.7)
Yamamoto *et al.*, 2019/Tokyo Women's Medical University Center East, Japan (63)	3,424	833	12.9 (10.2–17.7)	7.5 (6.5–9)	5.1 (4.0–5.6)
McTyre *et al.*, 2020/USA/Canada (62)	2,092	786	12.5 (11.0–14.8)	7.0 (5.9–9.4)	4.6 (3.8–5.3)
Fritz *et al.*, 2018/University Hospital Zurich, Switzerland (61)	42	NA	23	19	10 (combined)

SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy; DBF, distant brain failure; BMV, brain metastasis velocity; mOS, median overall survival; CI, confidence interval; NA, not available.

The proposed utility of BMV has been to help to triage patients to the proper salvage regimen after distant brain failure from SRS. Those patients with low BMV (<4 metastases/year) likely benefit from further SRS at time of distant brain failure. Those with high BMV (>13 metastases/year) have a shorter life expectancy and are more likely to die from brain metastases. The ongoing NRG BN009 study is randomizing patients with intermediate or high BMV to repeat SRS *vs.* repeat SRS with adjuvant hippocampal avoidant WBRT in order to determine whether adding WBRT can treat subclinical disease sufficiently to decrease the likelihood of future death from brain metastases.

BMV's application as a potential biomarker continues to evolve. BMV has also been suggested as a marker for the efficacy of systemic therapy in preventing new brain metastases (9). Initial BMV (iBMV) has been recently described as a marker for how quickly brain metastases

develop from the time of initial cancer diagnosis (64). iBMV may represent the biological predilection that a cancer subtype or an individual cancer may have on seeding the brain. Several studies have since attempted to validate iBMV's utility (65-67). Presently, there are ongoing efforts to correlate genomic markers to both BMV and iBMV (68,69). One particularly important advancement in BMV will be to assess a disease-specific BMV to determine whether the histology of the brain metastasis affects the effect of BMV on survival.

Conclusions

Statistical models to predict brain metastasis outcomes have long contributed to clinical management decisions and have been integrated into modern prospective trials. As the brain metastasis population and systemic treatments evolve, these models will require continual updating. Future directions likely involve prospective gathering of multi-institutional data in order to better facilitate the evolution of these models, as well as integration of molecular biomarkers.

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Footnote

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