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Research Article

# Common Prognostic Scoring Systems for Patients Presenting with Brain Metastases

***Erkan Topkan[1*], Ahmet Kucuk[2], Duygu Sezen[3], Sukran Senyurek[3], Eyub Yasar Aydemir[3], Nulifer Kılıc Durankus[3], Esma Didem Ikiz[4], Yasemin Bolukbasi[3], Berrin Pehlivan[5] and Ugur Selek[3]***

[1]*Baskent University Medical Faculty, Department of Radiation Oncology, Adana, Turkey*
[2]*Mersin City Education and Research Hospital, Radiation Oncology Clinics, Mersin, Turkey*
[3]*Koc University, School of Medicine, Department of Radiation Oncology, Istanbul, Turkey*
[4]*Ege University, School of Medicine, Radiation Oncology Department, Izmir, Turkey*
[5]*Department of Radiation Oncology, Bahcesehir University, Istanbul, Turkey*

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ABSTRACT

Brain metastases (BM) of various primaries merely remain the most prevalent type of intracranial tumors, and approximately 25% of all cancer patients are diagnosed with this poor prognostic disease condition somewhere during their treatment course. Contingent upon the general wellbeing status of the potential patient, currently available major treatment options typically include palliative radiotherapy, chemotherapy, and best supportive care. Various published studies have convincingly shown the likelihood to stratify BM patients into particular prognostic gatherings according to the conceivable combinations of multiple patients- and tumor-related characteristics; namely the prognostic scoring systems, which might be useful in the accurate prediction of survival, and thusly, the appropriate choice of the best-fit treatment alternative. In this present article, we meant to review the pros and cons of the as of now accessible and broadly acknowledged prognostic scoring systems for BMs and their clinical values.



## Introduction

Approximately 25% of all cancer patients are diagnosed with brain metastases (BM), which tragically increases up to 64% throughout their treatment course [1-4]. The exact incidence of the newly diagnosed BM is unknown, but it is estimated to be 3 to 10 times the incidence of newly diagnosed primary brain tumors [5, 6]. The BM incidence assuredly appears to further rise in the foreseeable future as a tangible result of longer survival expectations following the successful implementation of more sophisticated diagnostic imaging modalities and earlier commencement of effective local/regional and systemic anticancer interventions.

Hypothetically, all aggressive cancers may metastasize to the brain, however, the majority of BMs stem from the lung cancers (36-64%), breast cancers (15-25%), malignant melanoma (15-25%), and gastrointestinal cancers (5-10%), with an unknown primary in further 10-15%, respectively [7-9]. Malignant melanomas have the highest penchant for BM amongst all primary malignant tumors [10]. The distribution patterns of BMs usually follow the natural brain bloodstream pathways: 80%, 15%, and 5% in the cerebral hemispheres, cerebellum, and brainstem, individually [11]. Moreover, most BMs typically emerge at the intersection zones between the gray and white matters of the brain, presumably as the desired result of the natural localization of the capillary beds at these regions [12]. Currently, essentially 50% of all BMs are multiple at diagnosis possibly owing to the frequent utilization of highly sensitive and specific magnetic resonance imaging (MRI).

Presentation with BM indicates an adverse prognostic condition with expected survival duration of usually less than a year, yet the prognosis of BM patients may differ broadly due to multiple factors; including the age, performance status, total number and volume of the metastatic lesion(s), treatment modality utilized against the BM, extracranial disease status, and histology of the primary malignancy. Various tumor-

[*]*Correspondence to: Erkan Topkan, M.D., Baskent University Medical Faculty, Department of Radiation Oncology, 01120, Adana, Turkey; Tel: 905337381069; Fax: 903223444452; ORCID ID: 0000-0001-8120-7123; E-mail: docdretopkan@gmail.com*


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specific molecular factors, pathologic biomarkers, and driver mutations have also demonstrated significant prognostic utility in BM of lung-, breast-, hepatocellular carcinomas, and malignant melanomas [13-17]. In past investigations, numerous researchers have blended these identified factors in various manners and created prognostic scoring systems to accurately anticipate the survival of BM patients and to properly guide their treatments in an ideal way. Considering the fundamental significance of the stratification of BM patients according to the widely accepted prognostic factors which may guide for the selection of the best-fit treatment modality and its intensity, the present article aimed to succinctly summarize the pros and cons of accessible prognostic systems developed for BM patients.

## Prognostic Factors

Brain metastases diagnosed at any phase of cancer treatment or follow-up is typically perceived as an incredibly poor prognostic factor for almost all cancers with an expected median survival of 2 to 7 months from the diagnosis [18]. Most patients die because of widespread systemic disease rather than the BM, but still, a particular group may survive for longer durations or even may cure if appropriately managed. For the treatment of BM, such patients are potentially suitable candidates for more aggressive and potentially less neurotoxic treatment strategies like neurosurgery or stereotactic radiosurgery (SRS) rather than the more toxic long-course whole-brain radiotherapy (WBRT) [4]. In this patients' group, comprehensive assessment of independent prognostic factors and their unique blends may undoubtedly guide the proper selection of best-fit treatment strategies which may result in the excellent preservation of neurologic functions with likely protraction of survival times.

Besides the individual usage of the previously mentioned clinical variables, a comprehensive combination of prognostic factors for BM patients may thoroughly stratify them into specific groups with significantly distinct brain control and survival outcomes. To date, many demographic and clinical variables have been extensively examined for their predictive and prognostic roles in BM patients (Table 1).

**Table 1:** Prognostic factors for patients presenting with brain metastases.

| Factor | Tumor site |
|---|---|
| Age | Common |
| **Gender** | Common |
| **Performance status** | Common |
| **Location of BM** | Common |
| **Number of BM** | Common |
| **Size of BM** | Common |
| **BM velocity** | Common |
| **Volume of BM** | Common |
| **Neurologic deficit status** | Common |
| **Extracranial disease status** | Common |
| **Histology of BM** | Radioresistant vs. radiosensitive |
| **ER/PR status** | Breast |
| **HER-2 status** | Breast |
| **EGFR status** | Non-small cell lung |
| **EML4-ALK status** | Non-small cell lung |
| **BRAF status** | Malignant melanoma |
| **Caveolin-1** | Non-small cell lung |
| **Peritumoral edema status** | Common |
| **Radiologic features** | Common |
| **Interval from primary diagnosis** | Common |
| **Radiotherapy technique (SRS vs. others)** | Common |
| **Type of systemic therapy** | Non-small cell lung, breast, malignant melanoma |

BM: Brain metastasis; ER: Estrogen receptor; PR: Progesteron receptor; HER-2: Human epidermal growth factor receptor 2; EML4-ALK: Echinoderm microtubule associated protein-like 4 and anaplastic lymphoma kinase; BRAF: v-Raf murine sarcoma viral oncogene homolog B.

Among them, the performance status, age at presentation, neurologic function status, tumor histology, the primary tumor control status, the presence/absence of extracranial metastases (ECM), and the number and size of BM were distinguished to be clinically meaningful [4, 19-21]. Moreover, independent investigators proposed various prognostic scoring frameworks for patients with BM by utilizing different combinations of these prime factors with variable approaches (Table 2), as discussed below:

### I Recursive Partitioning Analysis Scoring System

In 1997, Gaspar *et al.* proposed the first prognostic scoring system for BM patients by utilizing the recursive partitioning analysis (RPA) methodology in 1,200 patients enrolled on three RTOG studies and treated with WBRT [22-25]. This scoring system discovered the KPS, age, primary tumor control status, and the status of ECM as the significant correlates of survival among the 21 influential factors analyzed. Accordingly, the RPA class I patients had the best prognosis with a median OS of 7.1 months, while the RPA II and RPA III patients

demonstrated stepwise OS decrements with respective 4.2- and 2.3-months duration. Nonetheless, the RPA classification has some critical drawbacks including the ignorance of patients with KPS≤ 60 by fixing its utility for patients presenting with pre-WBRT KPS of≥70, significantly large variations between WBRT doses of the trials and prohibition of the number of BM from RPA analysis. Further constraining its broad and convenient routine usage, this system amasses most patients mainly in the RPA class II, as the dominant class. One further basic impediment of the RPA classification system is the fact that it incorporates all KPS <70 patients into a single class, namely the RPA class III regardless of the accompanying clinicopathological factors. However, these additional factors may alter the survival times hugely either negatively or positively. Landing support on these adverse remarks, Nieder *et al.* in a later study incorporating 113 BM patients underlined that there were no meaningful survival differences between the patients in classes II and III (3.6 versus 4.2 months; P>0.05) after a total dose of 30 Gy WBRT in 3 Gy daily fraction doses [26].

**Table 2:** Comparison of frequently utilized prognostic scoring systems for brain metastases.

| | **RPA (n=1200)** | **SIR (n=65)** | **Rotterdam (n=1292)** | **BSBM (n=110)** | **Rades (n=1797)** | **GGS (n=479)** | **GPA (n=1960)** | **DS-GPA (n=4259)** |
|---|---|---|---|---|---|---|---|---|
| **Age** | Yes | Yes | | | Yes | Yes | Yes | Yes |
| **Performance status** | KPS | KPS | ECOG | KPS | KPS | KPS | KPS | KPS |
| **Primary control** | Yes | Yes | | Yes | | | | |
| **ECM** | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| **Number of BM** | | Yes | | | Yes | Yes | Yes | Yes |
| **Volume of BM** | | Yes | | | | | | |
| **Steroid response** | | | Yes | | | | | |
| **Tumor histology** | | | | | | Yes | Yes | Yes |
| **Interval from diagnosis to RT** | | | | | Yes | | | |
| **ER/PR status** | | | | | | | | Yes |
| **HER-2 status** | | | | | | | | Yes |
| **EGFR status** | | | | | | | | Yes |
| **EML4-ALK status** | | | | | | | | Yes |
| **BRAF status** | | | | | | | | Yes |
| **AFP** | | | | | | | | Yes |
| **Child-Pugh-Score** | | | | | | | | Yes |

Note: Empty spaces represents for 'No'.

RPA: Recursive Partitioning Analysis Scoring System; SIR: Score index for radiosurgery; BSBM: Basic score for brain metastases; GGS: Golden grading system; GPA: Graded prognostic assessment; DS-GPA: Disease specific graded prognostic assessment; ECM: Extracellular matrix; BM: Brain metastasis; RT: Radiotherapy; ER: Estrogen receptor; PR: Progesteron receptor; HER-2: Human epidermal growth factor receptor 2; EGFR: Epidermal growth factor receptor; EML4-ALK: Echinoderm microtubule associated protein-like 4 and anaplastic lymphoma kinase; BRAF: v-Raf murine sarcoma viral oncogene homolog B; AFP: Alpha fetoprotein.

### II Score Index for Radiosurgery

The score index for radiosurgery (SIR) system created by Weltman *et al.* involved the number of BM, the volume of the largest BM, the location of BM, and post-SRS WBRT in addition to the essential components of RPA [27]. The authors proposed the SIR as a comparably more reliable post-SRS survival predictor than the RPA system. Even though the SIR was later approved by further research which incorporated patients treated with neurosurgery alone or with additional WBRT, yet couldn't gain a wide arena for its daily usage in the oncology communities mainly due to the small population size of the seminal study (N=65) and probably for a more considerable extent due to the need for clinically impractical and time-consuming comprehensive workup for evaluation of the systemic disease in this classification method.

### III Rotterdam Score

Lagerwaard *et al*. identified prognostic factors in 1292 patients with BM to accurately determine proper subgroups of patients suitable for wise selection in future trials [28]. Besides the well-recognized KPS, age, control of primary tumor, and the status of ECM the authors further demonstrated that the response to steroids, serum lactate dehydrogenase, sex in lung primary, number of brain metastases, and site of the primary tumor comprised the factors to be associated with outcomes. The most powerful three factors, namely the performance status, response to steroids, and evidence of ECM were used for the simpler lamination of BM patients. However, because most cancer centers do not retain adequate records for the response to steroids, the Rotterdam scoring system could never attain a broad application arena in routine oncology practice.

### IV Basic Score for Brain Metastases

The basic score for BM **(**BSBM) was generated as a novel classification by Lorenzoni *et al.* in 2004 and incorporated only three factors to simplify the scoring system: KPS, primary tumor control status, and the presence of ECM [29]. Analysis of 110 BM patients undergoing SRS showed excellent agreement between the BSBM and SIR for accurate prognostic stratification of the study population. Lorenzoni's published findings were later confirmed by further evaluation of BSBM in patients receiving WBRT plus neurosurgery and WBRT with/without SRS,

However, alike the SIR system, the BSBM framework was also handicapped by the initial work's limited cohort size (N=110), which may render the assessment of more compact groups formidable because of the large confidence intervals [13, 26, 30].

**V Graded Prognostic Assessment**

Outcomes of the randomized RTOG 95-08 trial exhibited that the number of BM was a significant prognostic factor in patients with 1 to 3 BM who received WBRT alone or WBRT plus SRS boost [31]. However, the number of BM was not included in either of the published RPA, BSBM, and Rotterdam scoring systems [21]. On this account, the graded prognostic assessment (GPA) which incorporated age, KPS, ECM, and the number of BM in the scoring framework by analyzing the outcomes of 1960 patients treated with WBRT alone, WBRT plus radiosensitizers, or WBRT plus SRS in five RTOG trials (RTOG 7916, 8528, 8905, 9104, and 9508) was proposed as a novel prognostic scoring system in 2007 [32]. This novel system scored each factor as 0, 0.5, or 1.0 and stratified patients into four prognostic groups according to the resultant sum score of all 4 factors. Patients with the best prognosis were signed to GPA 4. The median OS was 2.6, 3.8, 6.9, and 11 months in GPA 0-1, GPA 1.5-2.5, GPA 3.0, and GPA 3.5-4 score groups, respectively. Considering these outcomes, the creators of GPA inferred that the GPA was the least subjective, most quantitative, and easiest to use scoring system compared to the preceding RPA, SIR, and BSBM systems. Following its publication, the GPA scoring system became a commonly preferred tool for prognostic stratification of BM patients as further studies confirmed the validity of the GPA system shortly after its announcement [33-35].

**VI Disease-Specific Graded Prognostic Assessment**

In 2008, Golden *et al.* analyzed the outcomes of 479 newly diagnosed BM patients of various primaries treated with SRS and demonstrated that the primary tumor type provided significant prognostic impact on the survival results [36]. Principally based on this challenging finding Sperduto *et al.* assessed the outcomes of 4,259 patients from 11 institutions to define disease-specific GPA (DS-GPA), and the authors exhibited that different variables had significantly distinct influences on the survival of patients in specific tumor types [37]. In 2012, Sperduto and colleagues in a large database of women presenting with BM of a breast primary refined their previous GPA scoring system for this particular patient's group [16]. In this multi-institutional study, significant prognostic factors by multivariate Cox regression and RPA were determined to be the KPS, HER-2, ER/PR status, and the interaction between ER/PR and HER2. RPA showed age was significant only for patients with KPS 60 to 80. The median OS for GPA scores of 0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0 were 3.4, 7.7, 15.1, and 25.3 months, respectively ($p<0.0001$). Additionally, being ER (+)/PR (+) improved median OS from 6.4 to 9.7 months among HER-2(-) patients, while being ER (+)/PR (+) improved median OS from 17.9 to 20.7 months in HER-2(+) patients.

For BM of the malignant melanoma, the first and original Melanoma-GPA was based on data from 483 patients diagnosed between 1985 and 2005 [37]. The initial investigation identified the KPS and the number of BM as the unique factors with significant influence on the survival outcomes. Its recently published multi-institutional update involved 823 malignant melanoma patients with BM [15]. In this refined index, namely the 'melanoma molecular-GPA (Melanoma mol-GPA)', the molecular markers were also investigated for their impact on results. In multivariable analyses; age, KPS, ECM status, number of BM, and BRAF status were identified to comprise the five significant prognostic factors for survival. The median OS times for patients with Melanoma mol-GPA of 0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0 were 4.9, 8.3, 15.8, and 34.1 months ($P<.0001$ between each adjacent group), respectively.

The original DS-GPA for BMs from NSCLC was depended on four factors identified in 1833 patients and incorporated the age, KPS, ECM, and number of BMs [37]. In the more recent updated version, 2186 NSCLC patients (1521 adenocarcinoma and 665 non-adenocarcinoma) with a newly diagnosed BM were included and patients were furthermore examined for their molecular marker status: Lung molecular GPA (Lung molGPA) [14]. Noteworthy prognostic variables included the original four factors of the DS-GPA and added two new factors: EGFR and ALK alterations in patients with adenocarcinoma with no respect to the mutation status for non-adenocarcinoma cases. The median OS for the updated investigation accomplice was 12 months, and those with NSCLC-adenocarcinoma and Lung-molGPA scores of 3.5-4.0 had a median survival of almost 4 years.

For renal cell carcinoma (RCC) patients presenting with BM, the first DS-GPA distinguished the KPS and the number of BMs as the unique factors to significantly altering the OS outcomes in a group of 286 patients [37]. Recently, the same group identified additional prognostic factors in a larger cohort of 711 patients and updated the original Renal GPA [38]. In the revised Renal GPA; KPS, number of BM, ECM, and hemoglobin were discovered as the four most powerful variables. The median OS for Renal GPA groups 0-1.0, 1.5-2.0, 2.5-3.0, and 3.5-4.0 were 4, 12, 17, and 35 months ($p<0.05$, for each intergroup comparison), individually.

For gastrointestinal cancers, Sperduto *et al.* observed that the KPS was the key determinant of survival in the initial DS-GPA, with median OS times of 3.1, 4.4, 6.9, and 13.5 months for GPA groups 0-1.0, 2.0, 3.0, and 4.0, respectively [37]. Later the unique gastrointestinal system site specific GPA investigation was reported by Lim *et al.* in 2014 for BM of hepatocellular carcinomas [39]. In this study, the authors retrospectively reviewed the data from 118 hepatocellular carcinoma patients with newly diagnosed BM between 1985 and 2011, and created hepatocellular carcinoma GPA index by including the number of BM (single: 0.5, multiple: 0 points), alpha-fetoprotein (<400 ng/mL: 0.5, ≥400 ng/mL: 0 points), and Child-Pugh-Score (A: 3, B: 2, C: 0 points). The investigators could not demonstrate any values for age, sex, performance status, and time interval from initial diagnosis to development of BM, but reported that the median OS durations were significantly different when the hepatocellular carcinoma GPA was implemented: 1.7, 3.2, 7.9, and 27.0 weeks for hepatocellular carcinoma GPA scores of 0-1.0, 1.5-2.5, 3.0-.5, and 4.0, respectively ($P<0.001$).

**VII Rades Prognostic Score**

This comprehensive framework was generated by Rades *et al.* in 2011 [40]. In their investigation, 1,797 patients were randomly assigned to

either of the test (n= 1,198) or the validation gatherings (n= 599). Two scoring frameworks were developed; one for intracranial control (IC) and another for OS. In multivariate analyses; age, performance status, ECM, the interval from the tumor diagnosis to RT, and the number of BM were found to be significantly connected with OS. Tumor type, performance status, interval, and number of BM were associated with IC. In the test group, 6-month IC rates were 17% for 14-18 points, 49% for 19-23 points, and 77% for 24-27 points ($p<0.0001$). IC rates in the validation group were 19%, 52%, and 77%, respectively ($p<0.0001$). In the test group, 6-month OS rates were 9% for 15-19 points, 41% for 20-25 points, and 78% for 26-30 points ($p<0.0001$). Corresponding OS rates in the validation group were 7%, 39%, and 79%, respectively ($p<0.0001$).

### VIII Golden Grading System

The Golden Grading System (GGS) was developed by Golden *et al.* in 2008 [36]. In this system, the creators assessed the information acquired in 479 patients who experienced SRS with or without WBRT from 1991 to 2005 for newly diagnosed BM. Four groups were analyzed: 1) all locales consolidated, 2) breast, 3) lung, and 4) malignant melanoma primary sites. A multivariate examination of every essential site joined exhibited that the age <65 years, KPS ≥70, no ECM, and ≤3 BM were linked with longer OS, while primary tumor control was most certainly not. In the subgroup analysis of patients with breast, lung, or malignant melanoma primaries, favorable factors included only primary tumor control for breast-; age <65 years, no extracranial metastases, and ≤3 BM for lung-; and KPS ≥70, primary tumor control, and ≤3 BM for malignant melanoma primaries, respectively. The median OS for ≤3 versus > 3 BM was 15.6 and 16.9 months for breast, 16.5 and 11.3 months for lung, and 9.0 and 5.7 months for malignant melanoma gatherings.

### Discussion

Survival of patients with BM has significantly prolonged with the valuable addition of novel targeted agents, immunotherapeutic, and locally ablative SRS to the conventional systemic chemotherapy and palliative RT. Since it is arduous for most agents to penetrate the blood-brain-barrier and achieve efficient concentrations in the cerebrospinal fluid the incidence of BM is ascending in parallel with the enhanced survival times. Enthusiastically supporting this critical observation, approximately 1/4 to 1/3 of all recurrences manifest in the form of the brain only relapses in radically treated stage III non-small cell lung cancer patients, the so-called oligometastatic state, if not all. As newer therapeutic agents are continuously added to the arsenal of oncologic treatment, it is pivotal to stratify BM patients into significantly distinct prognostic groups to handle them with the accessible best-fit option or spare some others from the futile toxicities of various aggressive treatment maneuvers.

The prognostic scoring systems for patients presenting with BM are useful tools in the accurate prediction of their survival outcomes and comforting assurance of the best treatment decision. Thusly, patients with the expected good prognoses can be treated with aggressive multimodality strategies, while those with poor prognostic guess can be offered supportive care. The phase III randomized QUARTZ trial represents an excellent example in this setting, which exhibited no viable advantage of WBRT over dexamethasone plus best supportive care in poor prognostic patients [41]. Therefore, the BM scoring systems may likewise serve as beneficial by the provision of realistic desires to the patients and their caregivers and in properly adjusting the treatment costs [42]. Furthermore, the prognostic scoring frameworks might be of principal significance by stratifying the BM patients with the comparative prognoses in the similar arms of the randomized trials, and in this way, might minimize the confounding factors and meaningfully improve the academic legitimacy of the published results of such investigations in an increasingly trustable manner.

Besides their practical usefulness, all attainable BM scoring systems, unfortunately, have some inherent limitations. One essential common hindrance of every unique prognostic system is the incorporation of relatively more favorable patients' groups, rendering it troublesome to decide the ideal treatment for patients with comparable unfavorable prognosticators. Additionally, relatively higher accumulation of BM patients in the better score groups brings the question of whether there is a general inclination for the intentional omission of some potentially effective treatment measures in more inferior prognostic groups. This is justifiable somewhat since the best supportive care remains the more frequently chosen management strategy for such patients, but still, this undoubtedly creates unavoidable statistical power bias in head to head comparisons.

Another common drawback is the utility of remarkably diverse prognostic factors in different scoring systems. For instance, the frequently referred RPA and BSBM do not esteem the number of BM as a significant prognostic factor. In the same way, the volume of BM, steroid response and primary tumor site are included merely in the SIR, Rotterdam, and DS-GPA systems, respectively. Moreover, the respective prerequisites for the BM volume for SIR and tedious clinical workup for steroid response evaluation for Rotterdam scores may severely limit their routine usage only for SRS and low-volume radiation oncology clinics.

Though the primary tumor characteristics and the driver mutations were comprehensively addressed in the initial GPA and DS-GPA, yet they didn't include the highly active targeted agents or novel immunotherapies in the scoring systems. However, these novel therapeutic agents may subtly alter the bleak prognosis of patients in a significant manner in their ways. Amply supporting this real-world experience, lapatinib and alectinib have exhibited remarkable clinical activities on BMs from HER-2 positive breast cancer patients and anaplastic lymphoma kinase (ALK) rearranged non-small cell lung cancer patients, separately [43, 44]. Likewise, dabrafenib and vemurafenib demonstrated considerable activity against the BRAF mutated malignant melanoma BMs [42, 45]. Establishing these rational anticipations, Johung *et al*. assessed the role of driver mutation genotype in predicting recurrence among 496 NSCLC BM patients treated with SRS and revealed that none of the patients with EGFR mutation and EML4-ALK translocation experienced in SRS field relapses [46]. Conversely, 18% of patients with KRAS mutation and 19% without these mutations had in SRS field relapses. Survival analysis was unperformed in this critical investigation; however yet, announced discoveries are significant for the way that they provided valuable insights into the profound influence of driver mutations on radiation

efficacy by powerfully suggesting higher radiosensitivity for EGFR and EML4-ALK mutant tumors and relative radioresistance for KRAS mutation-positive BMs.

An impressive study reported by Spanberger *et al.* assessed the prognostic value of the Ki-67 index, hypoxia-induced factor 1α expression, peritumoral edema, and micro vascularization patterns in 219 patients who underwent neurosurgical resection for BMs [47]. This comprehensive examination is notable for the direct assessment of extra factors for their prognostic worth notwithstanding the entrenched GPA. Other than asserting the legitimacy of GPA, peritumoral edema seemed, by all accounts, to be the unique variable related to prognostic worth. The MRI characteristics were further studied in 65 patients with single BM for their predictive power on survival outcomes, and the preoperative diffusion-weighted imaging signal intensities were found to be significantly correlated with survival results [48]. In another study of 69 BM patients from non-small-cell lung cancer caveolin-1 was surveyed for its predictive role on survival and radiotherapy responsiveness as a pathologic marker [49]. The study outcomes convincingly demonstrated that caveolin-1 expressing BMs were linked with notable more dismal prognoses and an increased risk of death ($p=0.015$). Moreover, in patients <54 years caveolin-1 expression was shown to neutralize the favorable effect of young age on survival. Unequivocally certifying the presence of a caveolin-1 related radioresistant strain, an increased risk of death was detected in the group with caveolin-1 expressing BMs among the RT receivers (HR=6.839; $P=0.004$) contrasted with their non-expressing counterparts. Though further corroborative investigations are required, accessible proof humbly proposes that peritumoral edema, diffusion-weighted imaging signal intensities, and caveolin-1 deserve to be investigated for their prognostic worth in future prognostic scoring systems.

Finally, another common impediment of all BM scoring systems is that all variables are merely inferred to foresee OS outcomes and with none focusing on other endpoints, such as time to neurologic progression/decline or BM-specific survival. In affirmation, even the two externally validated famous nomograms reported by Ahn *et al.* for breast cancer patients and Zindler *et al.* for non-small-cell lung cancer patients presenting with BMs likewise chose the OS as the essential endpoint [50, 51]. Given that the more frequent use of targeted agents and immunotherapies may positively enhance the intra- and extracranial tumor control rates and the WBRT results in different local control than SRS, it is imperative to control for the confounding effect of a particular treatment strategy to optimally predict outcomes. In this peculiar manner, subsequent investigations ought to be explicitly designed with the ultimate objective of developing novel prognostic models or nomograms which adequately address these particular issues in patients presenting with BMs.

## Conclusions

Although too much work is needed to be done to improve the currently available prognostic scoring systems for patients presenting with BMs, yet, they are however worthwhile for true prognostic laddering and most fit treatment arrangements of such patients. However, the results of statistically well-powered further studies addressing the potential prognostic worth of novel molecular, genetic, pathological, radiological, and treatment-related factors are eagerly awaited. Such extra and profoundly explicit markers may hopefully further enhance the prognostic and predictive strength of the entrenched prognostic scoring systems, particularly in the era of targeted and immune-therapies and progressively favored SRS.

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## Author Contributions

All authors contributed equally.

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