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Prognostic scoring of brain metastases

The clinical utility of prognostic scoring systems in patients with brain metastases treated with radiosurgery

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ABSTRACT

Purpose: The RTOG recursive partitioning analysis (RPA) classification is the gold standard for assessing the prognosis of patients with brain metastases (BM). Newer prognostic scoring systems for BM patients have been proposed, but their superiority over RPA needs to be established for patients treated with radiosurgery.

Methods: 380 patients with 1–3 BM were treated at the VUmc with radiosurgery (RS) from 2002 to 2011. Using baseline characteristics, patient scores were calculated for RPA, the Rotterdam-system, the score index for radiosurgery (SIR), the basic score for BM (BSBM), the graded prognostic assessment (GPA), the diagnosis-specific GPA, the Rades score, and the Golden grading system (GGS) for comparison with survival time and survival classification ($\leqslant$3 months or $\geqslant$12 months).

Results: Median survival after RS was 7.7 months, with 3-month and 1-year overall survival (OS) of 76% and 39%, respectively. Multivariate analysis confirmed the prognostic value of performance status, age, absence of extracranial metastases, primary tumor site, gender, and steroid response for OS. The percentage of patients included within the intermediate prognostic classes ranged from 48% to 77%, and was 64% for the RPA. All scoring systems highly correlated with OS ($p < 0.001$). The specificity for predicting early death ranged from 85% to 98% (RPA 88%), with the unfavorable classes of Rades, GGS, BSBM and SIR performing best. The sensitivity for predicting long-term survival ranged from 10% to 69% (RPA 29%), and was highest for the favorable classes of Rades and GGS.

Conclusions: All prognostic scoring systems correlated very well with OS. All scores shared the limitation of unbalanced proportions of patients within the prognostic classes. As the clinical superiority of more recently developed prognostic scoring systems was only modest in predicting early death and long term survival, the well-known and easy to use RPA system currently remains the standard.

Stereotactic radiosurgery (RS) is an established treatment modality for patients with a limited number of brain metastases (BM) from solid tumors [1]. In patients treated with RS with or without upfront whole brain radiotherapy (WBRT) [2], median survival duration ranges from 6 to 12 months [3,4]. The increasing availability of RS facilities and the introduction of frameless RS techniques has considerably lowered the threshold for the application of RS in terms of patient condition, tumor status and number of BMs. Although modern frameless RS is generally considered to be a well tolerated patient-friendly technique, it remains a time-consuming and relatively costly treatment modality for palliation, underscoring the need for appropriate patient selection.

Many prognostic factors for the survival of patients with BM have been identified in the medical literature including performance status, presence or absence of extracranial metastases, primary tumor control, and age. In order to facilitate the use of these prognostic factors in clinical practice, Gaspar et al. published the recursive partitioning analysis (RPA) prognostic classification system, which was derived from patient groups treated with WBRT in several RTOG studies [5]. The RPA classification which is still the most commonly used prognostic classification system was subsequently validated for patients treated with RS [6,7] and surgery [8]. However, the unbalanced distribution of patients within the three RPA classes with the majority of patients included in the intermediate group remains the major limitation of this classification system [9].

In an attempt to improve the clinical utility of prognostic classification systems, several alternatives to the RPA have been published; i.e. the Rotterdam score [10], the scoring index for radiosurgery (SIR) [11], the basic score for BM (BSBM) [12], the

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graded prognostic assessment (GPA) [13], disease-specific GPA (DS-GPA) [14], Rades score [15], and the Golden grading system (GGS) [16]. All classification systems share two common factors performance status and absence or presence of extracranial metastases, but differ by the addition of other prognostic factors such as age, primary tumor control, site of primary tumor, volume and number of BM, time interval between the diagnosis of the primary tumor and BM, and clinical response to steroid treatment (Table 1). The different classification systems also vary with respect to the patient population that these were derived from; the SIR, BSBM, and GGS were developed in RS patients, the RPA was based on WBRT patients, whereas the Rotterdam, Rades, GPA, and DS-GPA were derived from patient populations treated with WBRT, surgery, RS or a combination of treatment modalities.

It remains unclear whether newer proposed classification systems perform better than the current standard of RPA in BM patients treated with RS. An optimal prognostic classification system with a high clinical utility should not only be correlated with overall survival, but should also be able to identify patients who are likely to have short survival (e.g. $\leqslant$3 months) despite adequate treatment or alternatively identify patients who are likely to have long-term (e.g. $\geqslant$12 months) survival. In addition, these should result in a balanced distribution of patients in clinical practice and be as simple as possible for use in clinical practice. Such an optimal classification system would allow for a better selection of patients suitable and less suitable for RS. In a cohort of RS patients, we studied the clinical utility of the eight reported prognostic classification systems for BM by assessing the aforementioned characteristics for clinical utility.

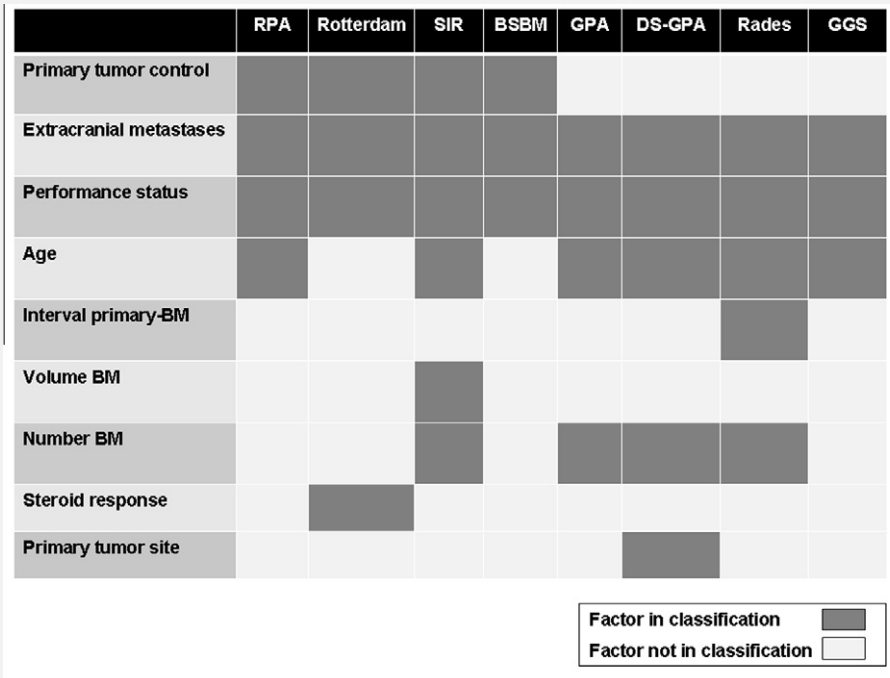
Materials and methods

The VUmc institutional database contains baseline characteristics, treatment details and follow-up data of newly diagnosed BM patients treated with Linac-based RS. At our center, patients with 1–3 BM diagnosed on high resolution contrast-enhanced MRI scans are eligible for RS as a single modality. RS has been delivered using 5 dynamic conformal arcs on a Novalis (2002–2008) or Novalis TX (2008 onwards) linear accelerator. Patient fixation was performed using the relocatable Gill–Thomas–Cosman frame, and as of 2008 using the BrainLAB's frameless mask system [BrainLAB, Feldkirchen, Germany]. RS was prescribed using a 'risk-adapted' fractionation, with lesions $\leqslant$7.5 cm^3 receiving 21 Gy prescribed at the encompassing 80% isodose line. The RS target volumes consisted of the gross target volume contoured on the planning MRI with a 1 mm margin to correct for potential setup-inaccuracies. For lesions measuring 7.5–25 cm^3 or BM that were adjacent to the brainstem, the prescription dose was lowered to 18 Gy at the 80% isodose. For the largest lesions with volumes exceeding 25 cm^3, a single fraction of 15 Gy or 3 fractions of 8 Gy, both prescribed at the 80% isodose was used.

Between December 2002 and July 2011, a total of 380 patients with 536 newly diagnosed BM were treated with Linac-based RS. The most relevant baseline characteristics are summarized in Table 2. Briefly, the median age of the patient group was 61 years, with the majority of patients (58%) having primary lung cancer. Sixty-four percent of patients underwent RS for a single BM, 30% for two lesions and only 6% of patients underwent RS for 3 lesions. Follow-up consisted of 3-monthly clinic visits with contrast-enhanced MRI during the first year, followed by 6-monthly MRI scans during the second year, and yearly thereafter. Survival was calculated from the date of RS. The median follow-up duration calculated using the reverse Kaplan–Meier method was 32 months.

Univariable Log-rank test and multivariable Cox regression analysis was used to determine risk factors for death for the baseline clinical variables. From the collected baseline characteristics, individual scores for all prognostic classification systems were calculated, i.e. the RPA, Rotterdam score, SIR, BSBM, GPA, DS-GPA, Rades score, and GGS. The distribution of patients within the

Table 1
Baseline characteristics included in various prognostic scoring systems for patients with brain metastases.



Recursive partitioning analysis (RPA), Rotterdam score (Rotterdam), the scoring index for radiosurgery (SIR), basic score for brain metastases (BSBM), graded prognostic assessment (GPA), disease-specific GPA (DS-GPA), Rades score, and Golden grading system (GGS).