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Early imaging radioresponsiveness of melanoma brain metastases as a predictor of patient prognosis

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OBJECTIVE The aim of this study was to analyze the early radiological response of melanoma brain metastases to single high-dose irradiation and to reveal possible correlations between tumor radioresponsiveness and patient clinical outcomes.

METHODS The authors performed a retrospective analysis of the medical data for all patients with melanoma brain metastases who had undergone Gamma Knife radiosurgery (GKRS) and follow-up MRI examinations with standard protocols at regular 2- to 3-month intervals. Volumetric measurements of the metastases on pretreatment and initial post-treatment images were performed to assess the rate of early radiological response. Patients were divided into 2 groups according to the rate of response, and overall survival, local control, and the appearance of new metastases in the brain were compared in these groups using the long-rank test. Univariate and multivariate analyses were performed to identify predictors of clinical outcomes.

RESULTS After retrospective analysis of 298 melanoma brain metastases in 78 patients, the authors determined that early radiological responses of these metastases to GKRS differ considerably and can be divided into 2 distinct groups. One group of tumors underwent rapid shrinkage after radiosurgery, whereas the other showed minor fluctuations in size (rapid- and slow-response groups, respectively). Median survival for patients with a slow response was 15.2 months compared with 6.3 months for those with a rapid response ($p < 0.0001$). In the multivariate analysis, improved overall survival was associated with a slow response to radiosurgery ($p < 0.0001$), stable systemic disease ($p = 0.001$), and a higher Karnofsky Performance Scale score ($p = 0.001$). Stratification by Recursive Partitioning Analysis, score index for radiosurgery, and diagnosis-specific Graded Prognostic Assessment classes further confirmed the difference in overall survival for patients with a slow versus rapid radiation response. Local recurrence was observed in 11% of patients with a rapid response and in 6% of patients with a slow response, at a median of more than 8 months after radiosurgery. New brain metastases were diagnosed in 67% of patients with a slow response at a median of 8.6 months after radiosurgery and in 82% of patients with a rapid response at a considerably earlier median time of 2.7 months. In the multivariate analysis, a longer time to the development of new brain metastases was associated with a slow response ($p = 0.012$), stable systemic disease ($p = 0.034$), and a single brain metastasis ($p = 0.030$).

CONCLUSIONS Melanoma brain metastases show different early radioresponsiveness to radiosurgery. Rapid shrinkage of brain metastases is associated with poor patient prognosis, which may indicate more aggressive biological behavior of this tumor phenotype.

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KEY WORDS melanoma; brain metastases; radiosurgery; imaging response; prognosis; oncology; stereotactic radiosurgery

ABBREVIATIONS DS-GPA = diagnosis-specific Graded Prognostic Assessment; GKRS = Gamma Knife radiosurgery; KPS = Karnofsky Performance Scale; RANO-BM = Response Assessment in Neuro-Oncology Brain Metastases; RPA = Recursive Partitioning Analysis; SIR = score index for radiosurgery; TDI = tumor dynamic index; TV = tumor volume; WBRT = whole brain radiation therapy.

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In advanced cutaneous melanoma, the brain is one of the dominant sites for tumor progression.[5,27] Nearly half of patients with late-stage melanoma reveal metastatic brain tumors, in multiples at initial presentation in the majority of cases.[29,32] Nowadays, radiosurgery has become a primary treatment option for melanoma brain metastases because of its high effectiveness combined with minimal toxicity as well as the possibility of irradiating multiple brain tumors in one procedure.[6,17] Local control of brain metastases and advantages for overall survival have been described in previous studies, which have also tried to identify prognostic factors that may predict treatment effectiveness and the extent to which treatment will benefit the patient in terms of improved neurological condition and better quality of life.[13,21,28,38]

To the best of our knowledge, however, no studies have systematically examined the imaging response of melanoma brain metastases to radiosurgery in a large series of patients. Today, relatively little is known about the radiological response of melanoma brain metastases to single high-dose irradiation, namely the dynamics of early tumor changes on MRI follow-ups (the time course and magnitude of volumetric response after radiosurgery).[16,34] Another question to address is whether there are any identifiable response patterns and how these may be correlated with clinical outcomes, including local tumor control, new brain metastases, and overall survival. Information on the dynamics of tumor radiological response to high-dose radiation may deepen our understanding of tumor biology in general and may also be considered by the physician while making a decision about the optimal scheduling of MRI follow-ups or the modification of systemic therapy intensity.

Therefore, the aim of this study was to assess the early radiological response of melanoma metastases in the brain following radiosurgery and to reveal its correlation with clinical outcomes.

Methods

Patient Selection

We conducted a retrospective review of all patients who had undergone Gamma Knife radiosurgery (GKRS) for melanoma brain metastases between 2009 and 2014 in the radiosurgical department at our medical center. The diagnosis of melanoma brain metastases was based on MRI studies and the histopathological type of primary cancer. Patients were eligible for the study if they had at least 1 radiological follow-up after GKRS performed according to the standard protocol (see below) and a Karnofsky Performance Scale (KPS) score of at least 60. We stopped recruiting patients for the study in 2014, because at this time targeted therapy became available for nationwide use, but our study aimed to estimate the radiation response to radiosurgery in the absence of targeted therapy–induced tumor modulation.[19] For this reason, we excluded 6 patients receiving mitogen-activated protein kinase pathway inhibitor therapy or monoclonal antibody immunotherapy (ipilimumab) at the time of GKRS and within the time interval to the first MRI follow-up. Further, 14 patients included in the study were checked for mutational status during the follow-up period. *BRAF* mutations were found in 11 patients, 5 of whom were receiving either *BRAF* inhibitor therapy (4 patients) or immunotherapy (1 patient), but at a later time (mean 6.07 months, median 4.97 months) than the first imaging follow-up assessment relevant for the present study. The other 6 patients with *BRAF* mutations were receiving chemotherapy according to the recommendations of their primary oncologists. Twenty-seven patients included in the study had undergone prior brain surgery and were further treated with GKRS for new or surgically untreated metastases. Finally, patients who had been subjected to whole brain radiation therapy (WBRT) or focal radiation therapy within 3 months before GKRS were excluded. The characteristics of the final patient cohort are summarized in Table 1.

Magnetic Resonance Imaging

On the day of GKRS, initial MRI was performed using a 1.0-T or 1.5-T scanner (Magnetom Harmony or Magnetom Symphony, Siemens). The scanners were configured to meet radiosurgical requirements. Axial T2-weighted images and axial 3D T1-weighted images of the entire brain first without and then with gadolinium contrast (0.2 mmol/kg) were obtained. Imaging parameters (repetition time, echo time, inversion time, flip angle, and acquisition time) varied slightly between the scanners, but the common settings for both machines were as follows: FOV 240 × 240 mm, matrix size 256 × 256, slice thickness 2 mm for the T2 sequence and 1 mm for the T1 sequences with a 0-mm interslice gap, and averaging number 1.

Radiosurgical Procedure

Radiosurgery was performed with the Leksell Gamma Knife model 4C until July 2014, and with the Perfexion model from September 2014 onward (temporary suspension of Gamma Knife in August 2014). On the day of treatment, the Leksell stereotactic frame type G (Elekta Instruments AB) was attached to the patient's head after applying a local anesthetic. After frame fixation, the patient underwent stereotactic MRI, which was used for treatment planning with the GammaPlan software (Elekta Instruments AB).

A mean number of 5 brain metastases per patient were treated at each Gamma Knife procedure. The median prescription dose delivered to the tumor margin was 22 Gy (range 15–25 Gy), and the median maximal dose was 36 Gy (range 23–55 Gy). Radiation doses were selected based on tumor volume and location in the brain in accordance with general practice in GKRS.[23] Therefore, prescription doses of 18–25 Gy were applied to 99% of the irradiated tumors and were reduced for tumors located close to critical brain structures or for deep-seated tumors of large volume (1%). More detailed information about radiosurgical doses in relation to tumor volume can be found in Table 2. Individual tumor volume varied from 0.01 to 24.3 cm^3 (median 0.35 cm^3, mean 1.73 cm^3), total tumor volume (sum of the volumes of all tumors in the case of multiple brain metastases) varied from 0.03 to 25.6 cm^3 (median 4.9 cm^3, mean 7.1 cm^3). The mean dose delivered to the

TABLE 1. Summary of patient and tumor characteristics at the time of GKRS

Parameter	Value
No. of patients	78
Median age in yrs (range)	51 (24–80)
Sex (no. [%])	
Male	39 (50.0)
Female	39 (50.0)
Median KPS score (range)	80 (60–90)
Neurological deficit (no. [%])	
Yes	13 (16.7)
No	65 (83.3)
Primary tumor status (no. [%])	
Controlled	53 (67.9)
Active	25 (32.0)
Anatomical site of primary melanoma (no. [%])	
Axial	35 (44.9)
Head/neck	9 (11.5)
Extremity	23 (29.5)
Unknown	11 (14.1)
Median thickness of primary melanoma in mm (range)	2.5 (1.0–17.0)
Thickness of primary melanoma (no. [%])*	
≤2 mm	25 (37.3)
>2 mm	42 (62.7)
Ulceration of primary melanoma (no. [%])*	
Present	35 (52.2)
Absent	32 (47.8)
Tissue samples for histology (no. [%])	
Primary melanoma	67 (85.9)
Lymph node metastases	5 (6.4)
Distant extracranial metastases	2 (2.6)
Brain metastases only	4 (5.1)
Brain metastases and extracranial tumor	24 (30.8)
AJCC stage at initial melanoma diagnosis (no. [%])	
I	11 (14.1)
II	34 (43.6)
III	22 (28.2)
IV	11 (14.1)
Presence of extracranial metastases (no. [%])	
Yes	57 (73.1)
No	21 (26.9)
Systemic disease status (no. [%])	
Stable	35 (44.9)
Active	43 (55.1)
Median time from initial melanoma diagnosis to brain metastases in yrs (range)	2.3 (0.0–11.9)
Median no. of brain metastases (range)	3 (1–15)
Brain metastases (no. [%])	
1	17 (21.8)
2–3	24 (30.8)
4–10	31 (39.7)
>10	6 (7.7)
Previous surgery for brain metastases (no. [%])	27 (34.6)
Median time from previous surgery to radiosurgery in mos (range)	2.7 (0.3–36.5)
Previous WBRT >3 mos before GKRS (no. [%])	5 (6.4)
Median time from WBRT to radiosurgery in mos (range)	14.3 (5.5–47.9)

AJCC = American Joint Committee on Cancer.
* Calculation includes only the 67 patients with primary melanoma treated with resection.

whole brain in one radiosurgical procedure ranged from 0.1 to 2.9 Gy (median 1.1 Gy, mean 1.2 Gy).

Follow-Up Assessment

After radiosurgery, all patients underwent radiological follow-up examinations locally, at one of the diagnostic MRI centers run by our medical center all over the country. Follow-up imaging studies were sent via the telecommunications network to the Department of Radiosurgery for comprehensive analysis. Radiological follow-up was usually scheduled initially for 2 months after GKRS and then every 3 months thereafter or more frequently if considered necessary. The median time to the first post-treatment MRI examination was 2.0 months (mean 1.96 months, range 0.8–3.3 months).

A standard MRI protocol was developed and applied to correlate follow-up images with stereotactic images taken at the time of GKRS. Follow-up studies were performed on 1.0-T, 1.5-T, or 3-T scanners, and the imaging protocol included the following sequences: axial 2-mm T2-weighted images, axial 1-mm 3D T1-weighted images, both naïve and with contrast enhancement, obtained with a square FOV and a square matrix (256 × 256 and higher). High-resolution square pixel images were required to make accurate assessments of tumor changes using the GammaPlan software.

Volumetric Analysis

Volumetric analysis was done using the GammaPlan software. The volume of the tumor was measured on stereotactic MR images at the time of radiosurgery and on the first available follow-up MR images at 1–3 months after treatment. All metastatic tumors in each patient were included in the volumetric analysis; however, for patients with more than 10 treated brain metastases, only the largest 10 metastases were incorporated into the statistical analysis as fully representative of the tumor dynamics for each patient (established as a result of a preliminary analysis involving all treated metastases). The tumor was identified as the enhancing lesion on gadolinium-enhanced T1-weighted MR images and was contoured manually in the axial planes slice by slice. Tumor volume was automatically calculated by the GammaPlan software. Our

TABLE 2. Radiosurgical doses in relation to tumor volume

Parameter	TV >0.5 cm^3	TV 0.5–0.065 cm^3	TV <0.065 cm^3	p Value*
No. of tumors	136	105	57	
Corresponding diameter†	>1 cm	1–0.5 cm	<0.5 cm	
Prescription dose in Gy				
Median	20.0	22.0	24.0	<0.0001
IQR	2.0	2.0	2.0	
Prescription isodose in %				
Median	50.0	60.0	90.0	<0.0001
IQR	10.0	25.0	10.0	
Maximal dose in Gy				
Median	40.0	36.7	26.7	<0.0001
IQR	10.5	12.6	2.5	
Mean dose in Gy				
Median	29.3	32.4	26.3	<0.0001
IQR	5.8	8.5	2.7	

* Kruskal-Wallis test.
† Calculated as a mathematical expression of spherical volume.

study was consistent with the recommendations of the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) working group given that all metastases included in the analysis were more than the minimal suggested size (2 mm for our MRI settings) and that 241 tumors (81%) were more than 5 mm in size.[22]

Mathematical Analysis

To assess the rate of tumor volume change within the 1st months after radiosurgery, we proposed a parameter called the "tumor dynamic index" (TDI), which was calculated with the following formula: $\{[(TV_{treatment} - TV_{follow\text{-}up})/TV_{treatment}] \times 100\%\}$/time from treatment to first follow-up in months, where TV refers to tumor volume. The TDI expresses relative changes in tumor volume per month after treatment. We introduced the TDI as a quantitative measure of tumor radioresponsiveness to radiosurgery, which is correlated with tumor sensitivity to ionizing radiation.

Statistical Analysis

Statistical analysis was performed using SPSS software version 17 (SPSS Inc.). The frequency distribution and Shapiro-Wilk test were used to verify normality. Statistical comparisons of data were performed using a chi-square test. The Pearson correlation test was applied to search for correlations between normally distributed parameters, while Spearman's rank correlation test was applied for other variables. Overall survival, local tumor control, and the appearance of new metastases in the brain after radiosurgery were estimated according to the Kaplan-Meier method, and group comparisons were made with the log-rank significance test. The Cox proportional-hazards model was used for univariate and multivariate analyses to assess the prognostic value of different variables of interest. A probability value < 0.05 was considered statistically significant.

Results

Results of Volumetric Analysis

The radiological response to GKRS of 298 melanoma brain metastases in 78 patients was analyzed. Tumor dynamic index was calculated for each tumor, based on volumetric measurements on pretreatment and initial posttreatment MRI. For patients with multiple metastases (78.2%), the mean TDI was found and used for further analysis. All patients in the study cohort were divided into 2 groups based on the TDI. The first group incorporated patients with a TDI > 25, that is, those who showed a rapid response to radiosurgery (Fig. 1A and B). Brain metastases in these patients promptly shrank at least twice from the initial volume within the first 2 months after radiosurgical treatment. The median TDI for this group was 40 with a range from 29 to 60. The second group comprised patients with a TDI ≤ 25, that is, those who had slow-responding metastatic brain tumors (Fig. 1C and D). For these patients, brain metastases remained stable, slightly decreasing (less than 2 times) or even slightly increasing within the first follow-up period after GKRS. The median TDI for the second group was 10 with a range from –21 to 23. The minus sign reflects the fact that tumor volume at the time of the first follow-up imaging exceeded that at the time of radiosurgery. This slight increment in tumor volume was transient and considered as a possible reaction to radiosurgery within the normal response.

Correlations Between TDI and Tumor-Related and Radiosurgery-Related Parameters

Correlation analysis did not reveal any strong or moderate associations between TDI and radiosurgical treatment parameters. In addition, only negligible correlations were found between TDI and tumor volume, tumor location in the brain, or presence of peritumoral edema (Table 3). The absence of a correlation between radiological tu-

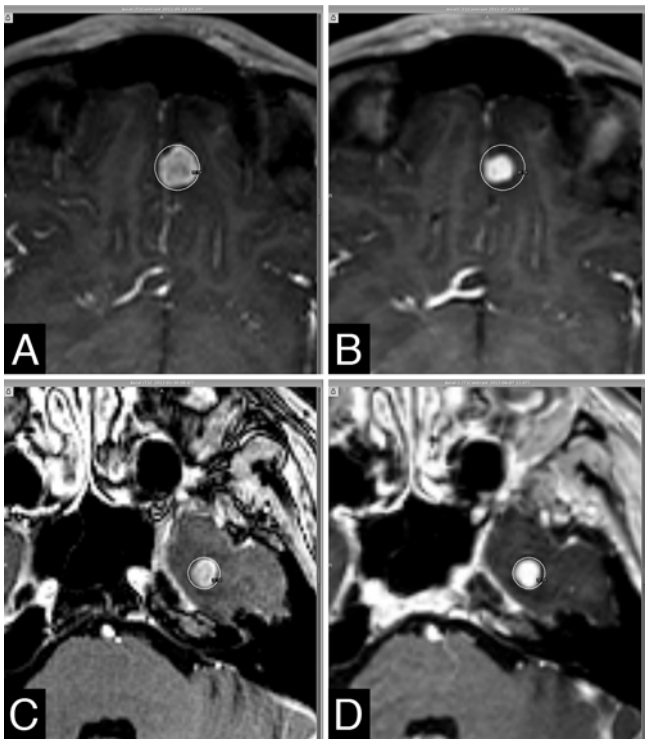

FIG. 1. Magnetic resonance images obtained at the time of GKRS (**A and C**) and at the first radiological follow-up (**B and D**), illustrating definitions of patient groups with a rapid (TDI > 25, A and B) and slow (TDI ≤ 25, C and D) response to radiosurgery. *Circular lines* indicate the prescribed dose of 22 Gy.

mor characteristics and radiosurgical parameters, and TDI allows us to assume that the rate of early tumor response to radiosurgery is determined by the molecular phenotype of the tumor, that is, its internal biological sensitivity to high-dose irradiation.

Patient Survival

Among the patients included in the study, 61 were deceased and 17 were still alive at the time of our analysis. Thirty-four patients (55.7%) were thought to have died of systemic disease progression, 10 patients (16.4%) of causes related to CNS disease, 11 patients (18.0%) of general progression (disease progressed both extracranially and intracranially to a comparable extent), and 6 patients (9.9%) of unknown causes. Median survival for the cohort after radiosurgery was 10.9 months (95% CI 8.5–13.4 months). Actuarial survival rates were 82.9% ± 4.4% at 6 months, 45.0% ± 5.8% at 12 months, and 19.3% ± 4.9% at 24 months after radiosurgery. Median survival for patients with a slow response (TDI ≤ 25) was 15.2 months (95% CI 10.4–20.0 months) compared with 6.3 months (95% CI 5.9–6.7 months) for patients with a rapid response (TDI > 25; Fig. 2A). The difference in overall survival between these 2 groups was statistically significant. In terms of causes of death, there was little difference between the 2 groups: Systemic disease progression was thought to have caused death in 17 patients (63.0%) with a TDI > 25 and in 17 patients (50.0%) with a TDI ≤ 25; CNS-related mortality was established for 4 patients (14.8%; 2 patients' deaths were probably related to intratumoral hemorrhage, and 2 other patients most likely died of leptomeningeal dissemination) and for 6 patients (17.6%; all of whom developed leptomeningeal carcinomatosis), respectively; general progression triggered death in 5 patients (18.5%) and in 6 patients (17.6%), respectively; and cause of death could not be identified for 1 patient (3.7%) and 5 patients (14.7%), respectively.

TABLE 3. Correlation coefficients between TDI and radiosurgical parameters

Parameter	Correlation Coefficient	p Value*
Tumor vol	0.027	0.654
Tumor location in brain	−0.026†	0.664
Presence of peritumoral edema	−0.064†	0.293
Prescription dose	0.187‡	0.002
Maximum dose	−0.184‡	0.002
Mean dose to tumor	−0.143‡	0.019

* Two-tailed test.
† Spearman's rank correlation coefficient; for other variables, Pearson's correlation coefficient is given.
‡ Partial correlation coefficient controlling for tumor volume.

In the univariate analysis, a higher KPS score ($p < 0.0001$), stable systemic disease ($p < 0.0001$), single metastasis in the brain ($p = 0.025$), lower total tumor volume ($p = 0.002$), and lower TDI ($p < 0.0001$) predicted longer overall survival after GKRS. Other variables such as age, sex, primary tumor status, extracranial metastases, and neurological deficit did not have significant predictive value for patient survival. In the multivariate analysis conducted with a model including the 5 variables significant in the univariate analysis, a higher KPS score ($p = 0.001$), stable systemic disease ($p = 0.001$), and TDI ≤ 25 ($p < 0.0001$) continued to be positive predictors of an improved survival outcome (Table 4).

Among the 35 patients with controlled systemic disease, 25 with a TDI ≤ 25 had a median overall survival of 20.1 months compared to 7.0 months for the other 10 patients with a TDI > 25. In contrast, among the 43 patients with active systemic disease, 26 patients with a TDI ≤ 25 had a median survival of 12.0 months compared to 5.6 months for the 17 patients with a TDI > 25. Thus, regardless of the status of systemic disease, TDI remains an important factor in patient survival.

Stratification of the patients according to commonly applied prognostic scoring systems—Recursive Partitioning Analysis (RPA), score index for radiosurgery (SIR), and diagnosis-specific Graded Prognostic Assessment (DS-GPA)[9,35,37]—further confirmed that there is a difference in survival between patients with a TDI ≤ 25 and TDI > 25 (Table 5). However, the distribution of patients into the RPA, SIR, and DS-GPA classes within the analyzed groups was not identical: patients with a TDI ≤ 25 belonged to the classes with a more favorable prognosis, whereas patients with a TDI > 25 possessed less favorable prognostic scores. Nevertheless, median survival for patients with a slow response was 2 or more times greater than that in patients with a rapid response in the corre-

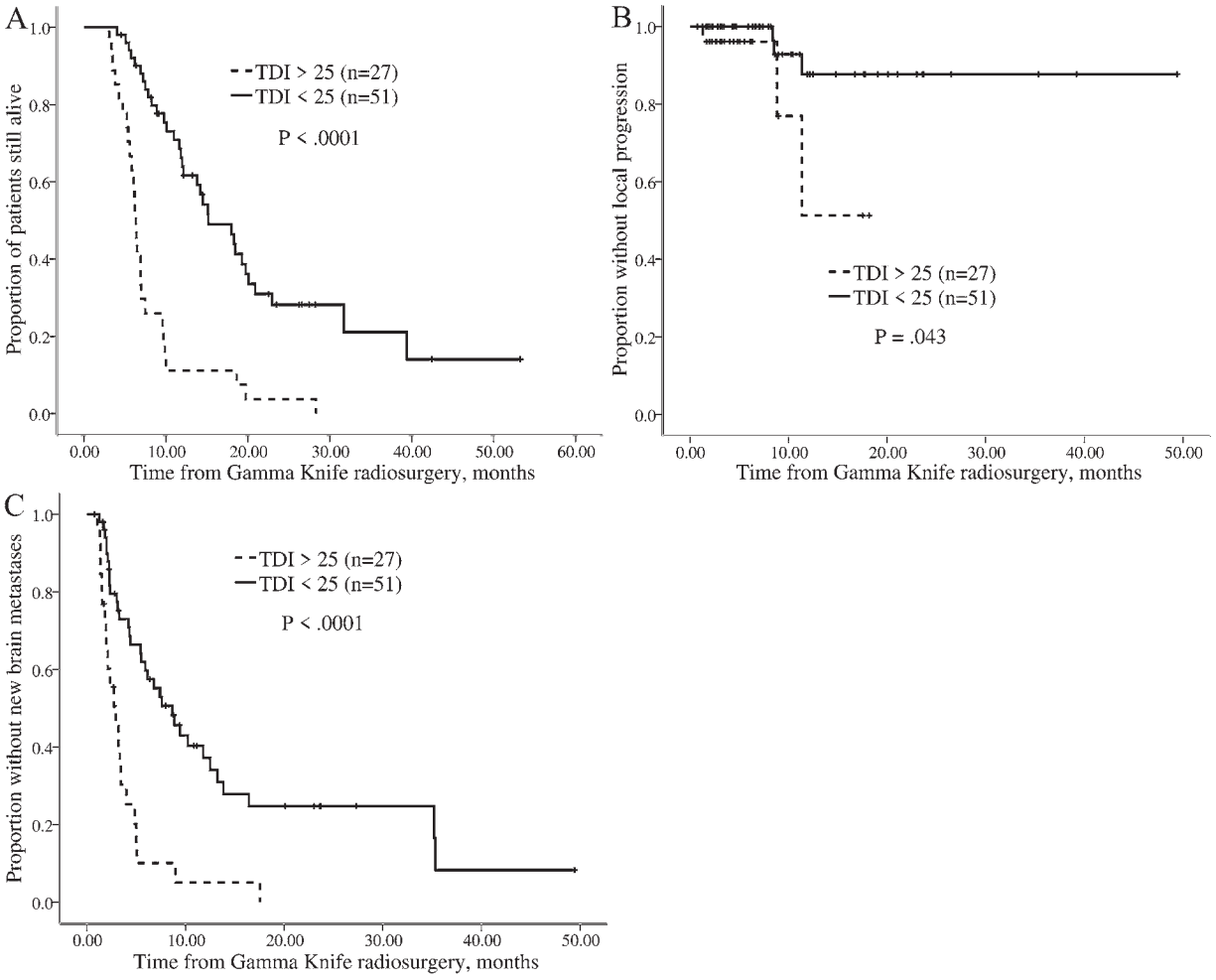

FIG. 2. Kaplan-Meier estimate of overall survival (**A**), local control (**B**), and appearance of new brain metastases (**C**) for patients showing rapid (TDI > 25) and slow (TDI ≤ 25) responses to GKRS.

TABLE 4. Univariate and multivariate Cox regression analysis of overall survival after GKRS

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Age	1.01 (0.99–1.03)	0.269		
Sex	1.25 (0.75–2.09)	0.383		
KPS (higher vs lower)	0.92 (0.89–0.95)	**<0.0001**	0.94 (0.90–0.97)	**0.001**
Primary tumor status (active vs controlled)	0.75 (0.43–1.31)	0.317		
Extracranial metastases (presence vs absence)	1.82 (0.99–3.33)	0.053		
Systemic disease status (active vs stable)	2.90 (1.67–5.04)	**<0.0001**	2.75 (1.49–5.09)	**0.001**
Neurological deficit (presence vs absence)	1.64 (0.87–3.11)	0.129		
No. of brain metastases				
Continuous	1.05 (0.99–1.12)	0.100		
Multiple vs single	2.19 (1.11–4.34)	**0.025**	1.35 (0.63–2.92)	0.443
Total tumor vol (higher vs lower)	1.06 (1.02–1.09)	**0.002**	1.01 (0.96–1.05)	0.736
TDI continuous	1.03 (1.02–1.05)	**<0.0001**		
TDI >25 vs ≤25	4.11 (2.41–7.02)	**<0.0001**	4.76 (2.61–8.68)	**<0.0001**

Boldface type indicates significance ($p < 0.05$).

TABLE 5. Survival after GKRS in patients with melanoma brain metastases showing rapid and slow responses, stratified by RPA, SIR, and DS-GPA prognostic scoring systems

Scoring System	Patients w/ TDI <25/>25	Median Survival in Mos (95% CI)		p Value*
		TDI ≤25	TDI >25	
RPA				
RPA I	9/5	19.7 (18.4–21.1)	7.0 (6.9–7.2)	0.029
RPA II	41/20	14.2 (10.2–18.1)	6.1 (5.3–6.8)	<0.0001
RPA III	1/2	6.9 (NA)	4.3 (NA)	0.808
SIR				
1–3	1/3	20.9 (NA)	5.6 (1.6–9.6)	0.182
4–6	23/17	11.6 (8.7–14.5)	6.1 (5.0–7.2)	0.001
7–9	27/7	19.7 (17.2–22.2)	7.0 (6.8–7.2)	0.004
DS-GPA				
0–2	30/23	13.8 (9.8–17.8)	6.2 (5.4–7.0)	<0.0001
3–4	21/4	31.7 (19.0–44.5)	7.0 (5.3–8.7)	0.011

NA = not applicable.
* Log rank test.

sponding prognostic classes. Thus, to summarize, patients harboring slow-responding brain metastases have a more favorable prognosis for life expectancy than those showing rapid tumor shrinkage in response to single high-dose irradiation.

Local Control

For the entire cohort, the median follow-up was 6.7 months. Actuarial freedom from local progression was 98.7% ± 1.3% at 6 months and 80.9% ± 7.4% at 12 months after GKRS (Fig. 2B). At the time of the last available MRI examination, complete disappearance was noted in 69 tumors, regression (tumor volume decrease > 50% of the initial value) in 130 tumors, stabilization in 74 tumors, and increase (tumor volume increase of more than 20% of the initial value) in 25 tumors. Enlargement of tumor volume was associated with recurrence in 7 tumors and with the consequences of intratumoral hemorrhage or radiation necrosis in all others.

A detailed comparison of radiological control rates between patients with a rapid response and those with a slow response to radiosurgery is presented in Table 6. It is worth emphasizing that complete disappearance of tumor after radiosurgery is less common for patients with a slow response than for the patients with a rapid response. In the slow-responding group, brain metastases gradually shrank to small lesions, which remained stable thereafter on all subsequent MRI follow-ups.

A second important point to note is that radiation necrosis occurred only in tumors demonstrating a slow early radiological response to radiosurgery. In total, 23 tumors (12 patients) passed through the stage of radiation-induced necrosis at a median time of 6.76 months after GKRS (range 3.5–12.2 months). The development of radiation necrosis was confirmed using PET with ^{11}C-methionine and further MRI follow-ups.

Local recurrence was observed in 11% of patients with a rapid response at a median 8.8 months (range 2.3–11.4 months) and in 6% of patients with a delayed response at a median 8.5 months after radiosurgical treatment (range 8.4–11.4 months). The presence of active tumors was confirmed using PET with ^{11}C-methionine and short-interval MRI examination.

Thus, patients with a rapid response to radiosurgery (TDI > 25) are characterized by the complete disappearance of brain metastases after treatment and a higher rate of local recurrence, which may be associated with the high proliferative potential of tumor cells due to severe dysregulation of the cell cycle and its components. By contrast, patients with a slow response to radiosurgery (TDI ≤ 25) are more likely to exhibit a gradual decrease in tumor volume after treatment, postradiation necrosis, and a lower rate of local progression, which could be associated with a less aggressive biological behavior of this melanoma phenotype.

TABLE 6. Radiological response of melanoma brain metastases to GKRS at the final MRI follow-up in patients with slow and rapid radiation response

Parameter	TDI ≤25	TDI >25	p Value*
No. of patients	51	27	
No. of tumors	186	112	
FU interval in mos			
Median (mean)	8.9 (12.3)	4.6 (5.9)	
Range	1.27–49.4	0.8–23.2	
Radiological response at last FU			
Complete disappearance			
No. of tumors (%)	20 (10.8)	49 (43.8)	
Median time in mos	20.2	6.1	<0.0001
Regression			
No. of tumors (%)	79 (42.5)	51 (45.5)	
Median time in mos	7.1	2.9	<0.0001
Stabilization			
No. of tumors (%)	73 (39.2)	1 (0.9)	
Median time in mos	4.7	6.1	—
Enlargement of tumor vol			
No. of tumors (%)	14 (7.5)	11 (9.8)	
Median time in mos	6.0	3.5	0.048
Radiation-induced necrosis			
No. of tumors (%)	23 (12.4)	0	
No. of patients (%)	12 (23.5)	0	
Median time in mos	6.76		
Local recurrence			
No. of tumors (%)	4 (2.2)	3 (2.7)	
No. of patients (%)	3 (5.9)	3 (11.1)	
Median time in mos	8.5	8.8	1.000
Intratumoral hemorrhage after GKRS			
No. of tumors (%)	24 (12.9)	11 (9.8)	
No. of patients (%)	12 (23.5)	9 (33.3)	
Median time in mos	3.3	2.1	0.102

FU = follow-up.
* Mann-Whitney test.

TABLE 7. Univariate and multivariate analysis of the appearance of new metastases in the brain after GKRS

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Neurological deficit (presence vs absence)	1.32 (0.62–2.80)	0.470		
KPS (higher vs lower)	0.94 (0.91–0.98)	**0.001**	0.97 (0.93–1.00)	0.073
Primary tumor status (active vs controlled)	1.24 (0.69–2.23)	0.478		
Extracranial metastases (presence vs absence)	1.65 (0.89–3.16)	0.129		
Systemic disease status (active vs stable)	2.55 (1.43–4.52)	**0.001**	1.96 (1.05–3.66)	**0.034**
No. of brain metastases				
Continuous	1.07 (1.01–1.14)	**0.024**		
Multiple vs single	3.31 (1.49–7.39)	**0.003**	2.67 (1.10–6.49)	**0.030**
Total tumor vol (larger vs smaller)	1.04 (1.00–1.08)	**0.028**	1.00 (0.95–1.04)	0.832
TDI continuous	1.03 (1.01–1.04)	**<0.0001**		
TDI >25 vs TDI <25	3.40 (1.92–6.02)	**<0.0001**	2.17 (1.18–3.97)	**0.012**
Prior WBRT	1.78 (0.61–5.17)	0.290		

Boldface type indicates significance ($p < 0.05$).

Appearance of New Metastases in the Brain

New brain metastases were found in 56 patients on subsequent MRI studies. The median time to new metastases for the entire cohort was 8.6 months after radiosurgery (95% CI 5.6–11.6 months). Actuarial freedom from new brain metastases was 68.6% ± 5.5% at 3 months, 44.3% ± 6.0% at 6 months, and 27.1% ± 5.7% at 12 months after radiosurgery. Patients with TDI ≤ 25 were found to have new brain lesions at a median of 8.6 months after treatment, whereas patients with TDI > 25 developed new brain lesions much earlier, at a median of 2.7 months (Fig. 2C).

Univariate analysis revealed that a lower KPS score ($p = 0.001$), active systemic disease ($p = 0.001$), higher number of brain metastases ($p = 0.003$), larger total tumor volume ($p = 0.028$), and higher TDI ($p < 0.0001$) were predictive for the development of new metastases in the brain. Multivariate analysis further confirmed that active systemic disease ($p = 0.034$), multiple brain metastases ($p = 0.030$), and a TDI > 25 ($p = 0.012$) continued to be significant predictors for the appearance of new brain metastases (Table 7).

Intratumoral Hemorrhages

One characteristic feature of melanoma brain metastases is their predisposition to hemorrhage spontaneously. In this study, intratumoral hemorrhage was found in 37 (12.4%) of 298 brain metastases at the time of radiosurgery and in 35 lesions (11.7%) after treatment. A similar incidence of intratumoral hemorrhage before and after radiosurgery supports the view that intratumoral bleeding is more related to internal biological tumor features rather than the external influence of high-dose radiation exposure.[25]

About half of the patients who experienced intracranial hemorrhage after radiosurgery had already developed metastatic lesions with hemorrhage before treatment (11 of 21 patients). In comparing patients with a slow versus a rapid radiological response to radiosurgery, it must be noted that intratumoral hemorrhage occurs more frequently in the latter group.

Discussion

Radiosurgery is a technique of delivering a high dose of radiation to a precisely defined target while minimizing the dose to normal surrounding brain tissues. Equally efficient for the treatment of single and multiple brain metastases from radiosensitive as well as radioresistant tumor histologies, radiosurgery has been widely applied as a predominant therapeutic strategy for melanoma metastases in the brain. Reported local control rates vary from 73% to 97%, while median survival after radiosurgery ranges from 6 to 11 months.[2,14,21,24,25,28,33] Among the prognostic factors that influence patient survival, the most frequently identified ones are KPS score, number of brain metastases, extracranial disease control, and patient sex and age;[4,10,12,21,38] however, none of these factors adequately characterize the tumor itself, that is, its internal biological behavior, although tumor aggressiveness, as we would like to suggest below, is likely to be one of the most important determinants of clinical outcome.

In the present study, we aimed to investigate the early radiological response of melanoma brain metastases to single high-dose irradiation and reveal its correlation with patient clinical outcomes. The methodology of the study involved precise measurements of tumor volume across all imaging time points (in accordance with the institutional protocol, as specified in *Methods*). Accurate volumetric measurements were performed using high-resolution, thin-slice MR images available for all patients included in the study. We specifically analyzed the early changes in tumor volume after high-dose irradiation (corresponding to the time of the first MRI follow-up, usually scheduled at 2 months after treatment) because we realized that the pattern of early volumetric response quite likely reflected tumor internal biological sensitivity to radiosurgery and might prove to be an important factor when considering

patient outcome. We found that there is significant heterogeneity in the early radiological response of melanoma brain metastases to GKRS—shrinkage, stabilization, or transient increase—all of which can be regarded as falling within the normal response to radiosurgery. To account for the observed variation, which to the best of our knowledge has not been identified in any previous studies, we introduced a parameter called the "tumor dynamic index" (TDI) as a quantitative measure of early tumor radioresponsiveness. The TDI for melanoma brain metastases varied widely, from –21 to 60, reflecting a slight increment in or significant shrinkage of the tumor after high-dose irradiation, respectively. The main reason to introduce this new TDI-based approach is to overcome the limitations of more standard assessment techniques, which are not sufficiently sensitive to reflect variations in early tumor response (Fig. 3) and thus provide clinically important implications (when we divided the patients in accordance with RANO-BM at the time of the first imaging follow-up, we did not find any statistically significant differences in survival curves, $p = 0.327$).

As the TDI was independent of tumor-related and dosimetry-related parameters, it seems probable that the rate of early tumor response to radiosurgery is determined by the molecular phenotype of melanoma brain metastases and their intrinsic biological sensitivity to ionizing radiation. The observed differences in melanoma brain metastases' radioresponsiveness to single high-dose irradiation accord with results of previous clinical investigations as well as melanoma xenograft and cell survival studies, which have demonstrated that melanoma is a highly heterogeneous tumor with respect to radiation response and sensitivity.[18,30]

The present study clarifies the question regarding the rate of tumor response and survival prognosis. Previous studies addressing this issue investigated the imaging response of brain metastases to radiosurgery on a long-term scale, analyzing changes in tumor volume within a follow-up period of up to 24 months, and found no correlation between long-term volumetric response and overall patient survival.[16,34] It is worth noting, however, that patients with melanoma in those studies constituted only a small part of the total cohort and were even analyzed as a separate group (as in the study by Iyer et al.[16]).

In contrast, the present study was focused on a short-term imaging assessment, which reflects the early response to radiosurgery. Our work with a group of 78 melanoma patients showed that the rate of early tumor response to radiosurgery correlates with clinical prognosis: patients with rapidly shrinking tumors had a poor survival outcome at a median of more than 6 months and a shorter time to disease progression in the brain at a median of under 3 months, whereas patients with slowly responding tumors had a much higher life expectancy at a median of more than 15 months and a much longer period of distant brain control at a median of more than 8 months. On the assumption that a tumor's early response to radiosurgical treatment is a reliable indicator of its internal biological characteristics, it is possible to speculate that such response patterns can be used effectively in the formulation of patient prognosis.

However, the status of extracranial disease should also be taken into consideration as an important determinant of clinical outcome. It appears to be especially valuable for the patients with a slow response to radiosurgery, who demonstrated a median overall survival of 20.1 months (95% CI 17.6–22.6 months) for stable systemic disease and 12.0 months (95% CI 8.6–15.3 months) for active systemic disease ($p = 0.002$). On the other hand, survival outcome for the patients with a rapid response to radiosurgery dif-

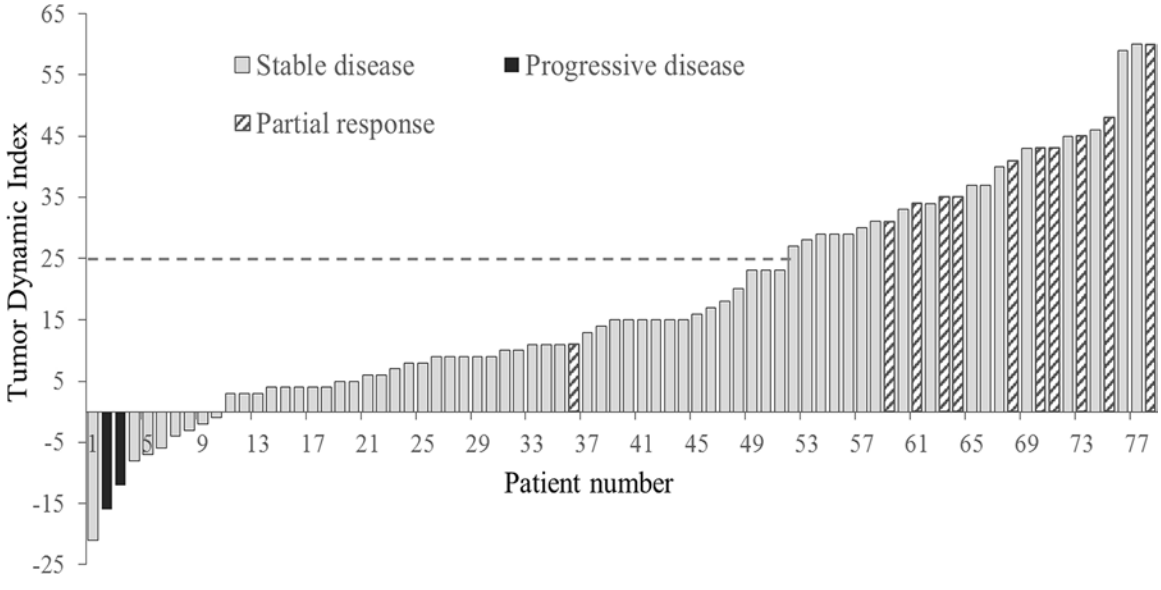

FIG. 3. Response of melanoma brain metastases by patient at the time of the first MRI follow-up after GKRS. *Bars* indicate the TDI. Sixty-five patients had stable disease according to the RANO-BM, 11 patients experienced a partial response, and 2 patients were classified as having disease progression (although further MRI indicated that it was, in fact, pseudoprogression associated with treatment-related effects). *Dashed line* indicates a TDI of 25, the threshold for dividing patients into 2 groups with a rapid (TDI > 25) and slow response (TDI ≤ 25) to radiosurgery.

fered to a much lesser extent between stable and active extracranial disease status: 7.0 months (95% CI 2.9–11.1 months) vs 5.6 months (95% CI 4.3–6.9 months), respectively ($p = 0.012$).

Returning to the question of the biological aggressiveness of a tumor, it should be noted that its molecular nature is still unknown and that the highly aggressive melanoma behavior is probably triggered by simultaneous alterations in several molecular pathways.[11,19,36] These molecular pathways are engaged in the regulation of cell cycle progression, cell death initiation, and the development of the tumor vascular network in particular, all of which are extremely important in the realization of high-dose radiation effects as well as in melanoma progression.[18]

Since melanoma is known to be a highly angiogenic tumor, given that its progression strongly depends on the initiation of neoangiogenesis, tumor vascularity would appear to be the most crucial consideration.[1] The aggressiveness of melanoma behavior is directly correlated with the development of new vessels: the more aggressive a tumor is, the higher potential for angiogenesis it exhibits.[31] As reported by Rofstad and Mathiesen, the metastatic propensity of melanoma xenografts is determined by the tumor microvascular density, which is governed by the angiogenic potential of tumor cells. In this way, the propensity to develop new vessels may promote malignant progression, invasive growth, and metastatic dissemination of malignant melanoma in humans.

On the other hand, tumor vascularity is also immediately involved in the realization of the biological effects of high-dose radiation. It is probable that microvascular damage is especially relevant for tumors whose growth is mediated by their angiogenic potential. Thus, it has been shown that high-dose radiation affects tumor vessels, causing endothelial apoptosis and microvascular dysfunction, which trigger tumor cell death.[8,20] This has been established to be true for mouse MCA/129 fibrosarcoma and B16 melanoma models. Exposure of these tumors to single doses of 15–20 Gy in vivo resulted in a rapid wave of endothelial cell apoptosis mediated via the acid sphingomyelinase pathway.[7,8,20]

Moreover, the rate of tumor shrinkage and tumor susceptibility to radiosurgery may be correlated with the presence of abnormal microvasculature, so that the faster a tumor develops new vessels, the more these vessels will be susceptible to radiation, as they consist predominantly of immature endothelial cells, which are programmed more to divide than to differentiate.[3,15] It has recently been shown that tumor vessels are heterogeneous among tumors with different biological behavior: blood vessels formed in highly metastatic tumors are more immature than those in low metastatic tumors. Furthermore, endothelial tumor cells isolated from highly metastatic tumors have a higher proliferative index and demonstrate increased motility, sensitivity to vascular endothelial growth factor, and invasiveness of the extracellular matrix compared with those isolated from low metastatic tumors.[15,26]

Therefore, we are confronted with the following 2 facts, which may be related to each other. On the one hand, if quicker volume reduction after irradiation is observed, patient prognosis is less favorable; on the other hand, faster melanoma growth and a higher propensity to metastasize are dependent on the tumor's vascular density.

In our study, we have demonstrated that patients who showed a slow response to radiosurgery had much better clinical outcomes. Moreover, the research summarized above indicates that tumor vascularity may underlie melanoma aggressiveness and radiosensitivity. Thus, further studies intended to clarify the link between tumor angiogenesis and early radiation response are warranted to confirm our observations.

However, there are several important limitations to this study. First, it should be noted that its retrospective character made some clinically important information inaccessible for all the patients, for example, certain molecular tumor characteristics such as *BRAF*, *NRAS,* and *C-KIT* mutational status. Treatment with *BRAF* inhibitors became available for nationwide use in 2014, whereas most patients from our study had undergone GKRS prior to that time, which is why we have these data for only 18% of the patients. It would be interesting to assess the prognostic value of melanoma mutational status; however, recent studies conflict quite considerably with regard to the impact of, at least, *BRAF* mutational status on disease progression and overall survival. This suggests to us that the results of our study would not have been invalidated by the inclusion of such data. Nevertheless, to establish with certainty whether *BRAF* mutational status is relevant for the identified patterns of radiation response, further studies are advisable. Secondly, a lack of available data precluded the possibility of estimating extracranial disease progression with the same degree of systematicity that we were able to apply to the study of intracranial disease progression. For this reason, the predictive value of TDI must be strengthened by further studies to substantiate its potential importance as a reliable indicator of disease progression in the body, given that it has been fully validated only for disease progression in the brain. Finally, although we consider the molecular phenotype of the tumor to be the primary determinant of patient outcome, more extensive research into those molecular parameters that can be said to have prognostic value for melanoma progression and radiation response will have to be performed.

Conclusions

In our study, which focused on the assessment of the early radiological response of melanoma brain metastases to high-dose irradiation, we established its potential prognostic value for patient clinical outcome. We observed that rapid tumor shrinkage after radiosurgery is associated with a poor clinical prognosis, whereas gradual tumor regression indicates a more favorable outcome. To formalize the observed heterogeneity in tumor response patterns, we introduced a novel volume-based parameter, which we called the "tumor dynamic index." We also hypothesized that TDI is determined by the same molecular characteristics that underlie different causes of disease progression. To the best of our knowledge, this is the first time anyone has tried to raise this issue, and we hope that this may be the beginning of a potentially promising avenue of research.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Statistical analysis: Zubatkina. Study supervision: Ivanov.

Supplemental Information

Previous Presentations

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