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ORIGINAL ARTICLE - BRAIN TUMORS

Cerebral metastases: do size, peritumoral edema, or multiplicity predict infiltration into brain parenchyma?

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Abstract

Background Brain metastases (BMs) are the most frequent malignancy of the central nervous system. Previous research suggested that some metastases show infiltrative behavior rather than sharp demarcation. We hypothesized that three magnetic resonance (MR) imaging parameters—(a) tumor size, (b) extent of peritumoral edema, and (c) presence of multiple BMs—are predictors of cellular invasion beyond the surgically identifiable tumor margins.

Methods We performed a post hoc analysis on prospectively collected data of patients with BMs. Biopsies beyond the resection margin and immunohistochemistry were performed to assess infiltration status. The three MR imaging parameters were dichotomized into diameters ≤ 30 mm ("small") and > 30 mm ("large"), amount of peritumoral edema "extended" and "limited," and "multiple BMs" and "single BMs," respectively. The association between infiltration status and imaging parameters was calculated using chi-square test.

Results Biopsy beyond the resection margin was performed in 77 patients; 49 (63.6%) had supramarginal infiltration and 28 patients (36.4%) showed no infiltration. Histological evidence of tumor infiltration was found in 25/41 patients with smaller lesions (61%) and in 24/36 with larger lesions (66.7%, $p = 0.64$), in 28/44 patients with limited (63.6%) and in 21/33 patients with extended edema (63.6%, $p = 1.0$), in 28/45 patients (62.2%) with single BM and in 21/32 patients (65.6%) with multiple BMs ($p = 0.81$).

Conclusions Based on the post hoc analysis of our prospective trial data, we could not confirm the hypothesis that infiltration of brain parenchyma beyond the glial pseudocapsule is associated with the MR imaging parameters tumor size, extent of edema, or multiplicity of metastases.

Keywords Brain metastases · Peritumoral edema · Multiple brain metastases · Supramarginal infiltration

Introduction

Brain metastases (BMs) are a frequent complication of solid tumors and will develop in as many as 30% of cancer patients [10, 38]. Surgery for metastases provides certain advantages over other treatments under certain conditions [31]. The excision of a BM can effectively control neurological symptoms and improve both overall survival (OS) and functional status [30]. Despite the intuitive neurosurgical assumption that metastases are encapsulated and have a clear cleavage plane within brain tissue, these tumors may show histological evidence of infiltrative growth beyond the border of the solid metastasis [3, 4, 38, 41]. Reports on any association of infiltrative growth pattern of BMs with prognosis have until today remained inconclusive [3, 38]. However, residual tumor beyond the

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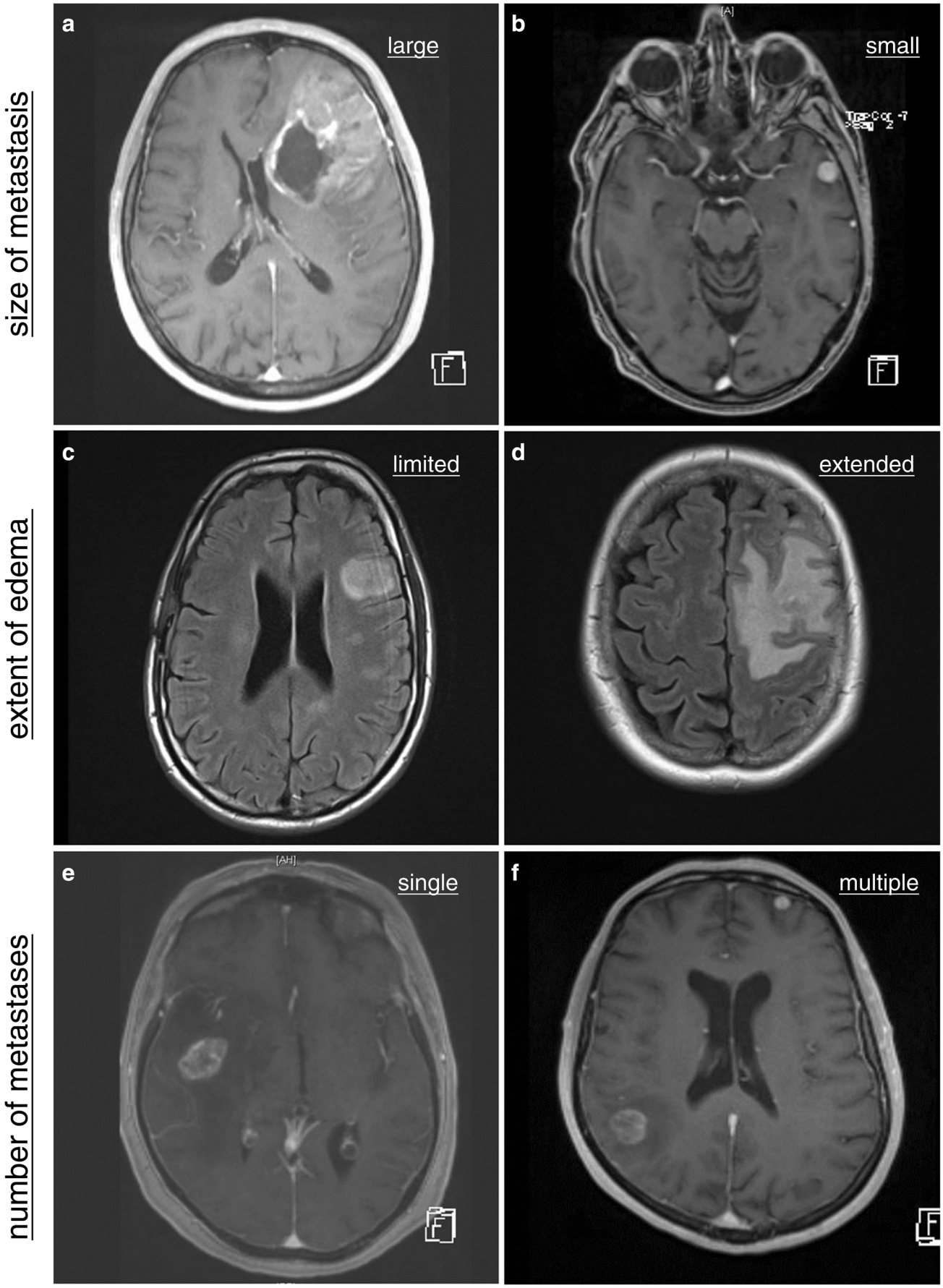
size of metastasis
extent of edema
number of metastases
a
large
b
small
c
limited
d
extended
e
single
f
multiple

◀**Fig. 1** Possible MR-morphologic surrogate parameters. **a**, **b** Metastasis with a diameter > 3 cm (large, **a**) or ≤ 3 cm (small, **b**). **c**, **d** Extent of peritumoral edema with an edema ratio ≤ 1 (limited, **c**) or > 1 (extended, **d**). **e**, **f** Number of brain metastases, single (**e**) or multiple (i.e., number of metastases ≥ 2, **f**). An edema ratio of > 1 is reached when the size of the edema exceeds that of the metastasis

margin of the glial pseudocapsule might be a major cause for local recurrence of metastases [19, 26, 39, 44]. Ideally, the information on infiltration status would be available to the surgeon ahead of time for surgical planning. However, up to now, it is unclear whether or not tumor infiltration correlates with magnetic resonance (MR) imaging parameters. As central hypoxic necrosis (which starts when the metastasis has reached a certain size) is associated with invasion, an interrelation of metastasis size and infiltrative behavior is deemed possible [33]. Furthermore, peritumoral edema was shown to be associated with increased β-catenin and E-cadherin expression in brain metastatic squamous cell carcinoma [43], which also raises the question of a relation between edema extension and infiltrative behavior. Lastly, the advanced oncological treatments of cancer in an aging population lead to longer survival and an increasing possibility of patients living long enough to develop multiple BMs. Selection pressures such as already administered or ongoing chemotherapy as well as targeted therapies can provoke the development of subclones within these BMs which might then dominate the tumor mass and drive tumor progression [18, 22, 25]. Moreover, as the presence of multiple lesions is not a significant predictor of shorter survival on its own, resection of multiple metastases may potentially be considered a useful concept in carefully selected cases [6, 17]. On the basis of these considerations, we hypothesized that (a) the tumor size, (b) the extent of peritumoral edema, and (c) the presence of multiple cerebral metastases, which are easily visible on preoperative MRI, all constitute predictors of increased cellular invasion beyond the surgically identifiable tumor margins.

Patients and methods

Patient population

Between 2013 and 2016, 175 patients were treated surgically for BMs within the scope of the prospective BMBF-funded MetastaSys trial (grant no. 0316173C) [38]. In this study, we performed post hoc analysis on data from a cohort of 77 patients (44%) in which supramarginal biopsies were taken to determine the presence of tumor cells beyond the resection margins of GTR. Briefly summarized, we resected the BM including the gliotic pseudocapsule with the aid of an operating microscope. After GTR, biopsies were taken from the margins beyond the resected gliotic pseudocapsule with a biopsy forceps to a depth of at least 5 mm, which was determined by an intraoperative navigation system (Brainlab AG, Munich, Germany). These biopsies were studied histologically for the detection of tumor cells. Demographic parameters and histopathological diagnoses were retrieved from electronic records.

Study design

The study was performed as a prospective surgical monocentric analysis. Inclusion criteria were histopathologically confirmed BMs in patients over 18 years of age. Furthermore, informed consent was signed by every patient and the study was approved by the local ethics committee (study number 21/3/11).

Imaging parameters

In analogy to a previous study [20], the largest size of the operated metastasis was calculated on contrast-enhanced T1 magnetic resonance imaging (MRI) sequence using Centricity Enterprise Web V3.0 software (GE Healthcare, Barrington, IL, USA) by manually measuring the maximum diameter of the contrast-enhanced area of the BM. For binary evaluation, the BM diameter was dichotomized according to the median into the diameters ≤ 30 mm ("small") and > 30 mm ("large"; Fig. 1).

The largest extent of peritumoral edema was determined by manually measuring the maximum diameter of the edema including the metastasis surrounded by the edema on the FLAIR MRI sequence. The actual extent of the edema was then calculated by subtracting the diameter of the metastasis from the diameter of the edema. A coefficient (ratio = size$_{edema}$ size$_{tumor}$) was then calculated to dichotomize the cohort into cases with a ratio > 1, in which the extent of the edema exceeded the tumor size ("extended"), and into cases with a ratio ≤ 1, in which the extent of the edema was smaller than or equal to the tumor ("limited").

To determine the existence of multiple metastases, the contrast-enhanced T1 MR images were carefully evaluated for the number of BMs. Accordingly, the cohort was dichotomized into "multiple BMs" (including patients presenting ≥ 2 metastases) and "single BMs" (including patients suffering from a single BM only).

Histological workup

To determine the presence of infiltrating tumor cells in the adjacent brain parenchyma, the brain biopsy specimens were immunohistochemically assessed with appropriate labeling for pan-cytokeratin CK-AE1/3 (NSCLC, breast carcinoma, kidney carcinoma, and colorectal carcinoma), melan-A (melanoma), or chromogranin A (SCLC), based on the

immunoreactivity of the tumor bulk. According to the presence or absence of metastatic tumor cells beyond the glial pseudocapsule, the cohort of 77 patients was dichotomized into two groups referred to as (a) "infiltration-positive" and (b) "infiltration-negative."

Statistical analysis

We tested whether the MR imaging parameters—(a) size of the operated BM (i.e., small vs large), (b) extent of edema (i.e., limited vs extended), and (c) presence of multiple filiae (i.e., single vs multiple)—were correlated with the binary invasion status ("infiltration-positive" vs "infiltration-negative"). For comparison, chi-square test, Fisher's exact test, and *t* test were applied. p values < 0.05 were considered significant. Statistical workup was performed using SPSS 21.0 (IBM Corp., Armonk, NY, USA).

Results

We included $n = 77$ patients in this study, aged between 44 and 85 years (mean 63.5 ± 9.5 years). The female-to-male ratio was 42:35 = 1.2:1 (54.5% female). Clinical data are summarized in Table 1. A total of 270 biopsies were obtained from the resection cavity wall with a median of three biopsies per patient. Of the 77 patients, 49 (63.6%) had supramarginal infiltration ("infiltration-positive"), whereas 28 patients (36.4%) showed no infiltration ("infiltration-negative").

In the infiltration-positive cohort, 197 biopsies from 49 patients (median of 3.5 biopsies per patient) were taken and at least one sample per patient revealed metastatic tumor infiltration. In the infiltration-negative cohort, 73 biopsies from 28 patients were taken (median of 2.5 biopsies per patient) and merely displacing, non-infiltrating growth patterns were observed (Fig. 2). There was no specific association of an infiltration status to be seen for the primary tumor type ($p = 0.48$).

Tumor size

The average tumor size was 32.6 ± 13.8 mm. In 36 patients (46.8%), tumor size exceeded 30 mm ("large") while in 41 patients (53.2%), tumor size was equal to or smaller than 30 mm ("small"). Histological evidence of tumor infiltration was found in 25 out of the 41 smaller lesions (61%) and in 24 out of the 36 larger lesions (66.7%, $p = 0.64$). In the infiltration-positive cohort, small metastases were present in 25/49 patients (51.0%) while in the "infiltration-negative" cohort, small metastases were present in 16/28 patients (57.1%).

Peritumoral edema

The average extent of peritumoral edema was 29.5 ± 18.6 mm. In 33 patients (42.9%), edema extent exceeded tumor size ("edema ratio > 1") while in 44 patients (57.1%), the edema

Table 1 Baseline and demographic parameters of the study population. Significance was assumed for values ≤ 0.05

		Status of margin infiltration						
		Infiltration negative ($n = 28$)		Infiltration ($n = 49$)		Total ($n = 77$)		
		n	Percentage of "infiltration positive"	*n*	Percentage of "infiltration positive"	*n*	Percentage of "total"	*p* value
Age (mean ± SD)		63.7 ± 9.1		63.7 ± 9.8		63.5 ± 9.5		$p = 0.82$
Sex	Female	15	53.6	27	55.1	42	54.5	$p = 0.90$
	Male	13	46.4	22	44.9	35	45.5	
Multiple metastases	No	17	60.7	28	57.1	45	58.4	$p = 0.81$
	Yes	11	39.3	21	42.9	32	41.6	
Metastasis size > 30 mm	No	16	57.1	25	51.0	41	53.2	$p = 0.64$
	Yes	12	42.9	24	49.0	36	46.8	
Histology of NSCLC	No	19	67.9	30	61.2	49	63.6	$p = 0.56$
	Yes	9	32.1	19	38.8	28	36.4	
Edema ratio	Ratio ≤ 1	16	57.7	28	55.3	41	56.2	$p = 1.00$
	Ratio > 1	12	42.3	21	44.7	32	43.8	
Histology of primary	NSCLC/SCLC	11	39.3	27	55.1	38	49.4	$p = 0.23$
	Gastrointestinal	1	3.6	5	10.2	6	7.8	
	Breast	5	17.9	10	20.4	15	19.5	
	Mal. melanoma	7	25.0	5	10.2	12	15.6	
	Kidney	2	7.1	1	2.0	3	3.9	
	Unknown	2	7.1	1	2.0	3	3.9	

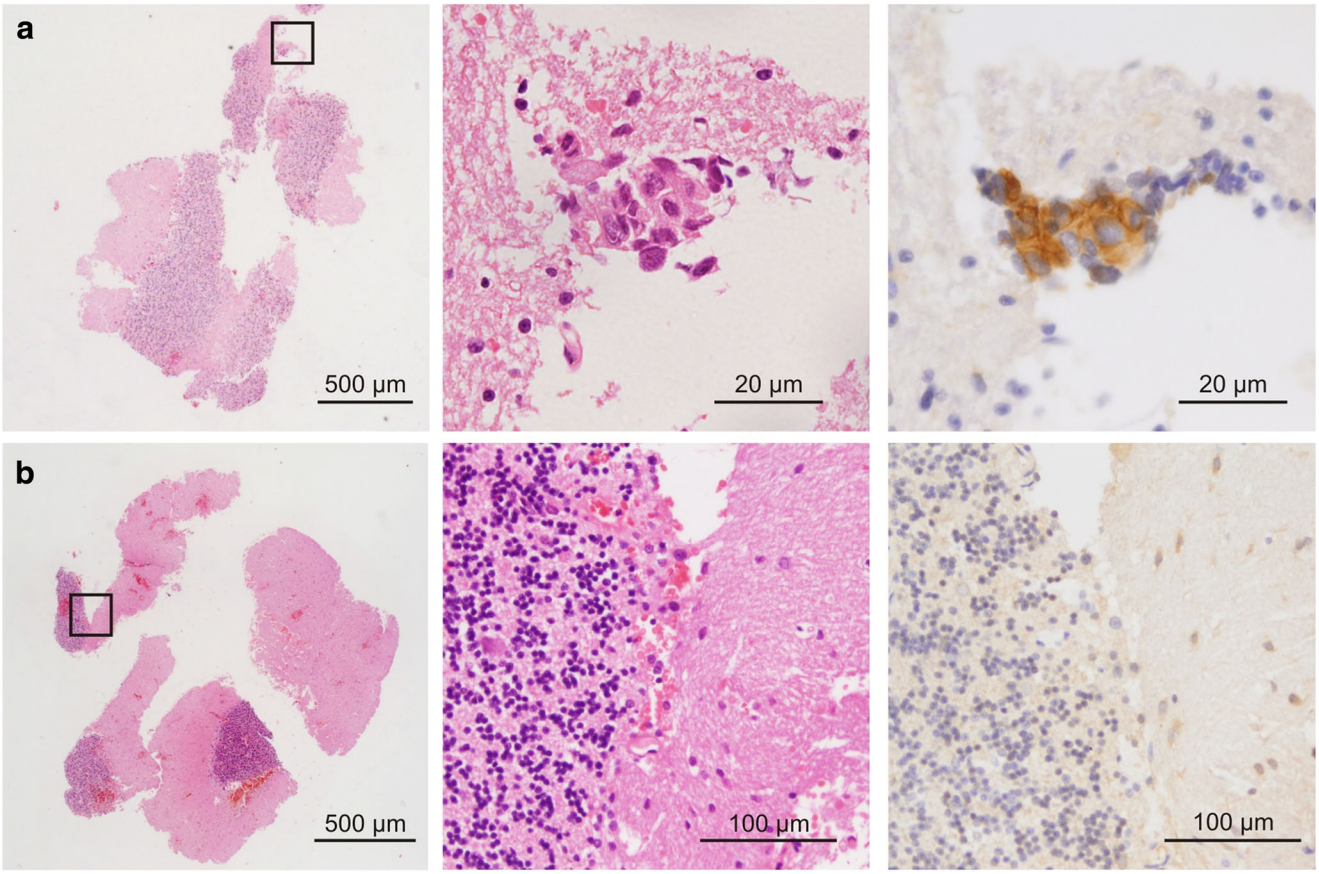

Fig. 2 Metastatic infiltration in supramarginal biopsies. Representative microphotographs of biopsy specimens from two different regions beyond the resected gliotic pseudocapsule (**a**, **b**) of a cerebellar metastasis of a colon adenocarcinoma. **a** H&E stainings of border biopsy with positive tumor infiltration showing a small group of cells adjacent to the parenchyma (left and middle columns). Tumor cells are immunoreactive for the epithelial marker pan-cytokeratin (right column). **b** In the negative sample of the same case, tumor cells could not be demonstrated morphologically with H&E (left and middle column) nor with pan-cytokeratin (right column)

extent was equal to or smaller than tumor size ("edema ratio ≤ 1"). Histological evidence of tumor infiltration was found in 28/44 in patients with limited edema (63.6%) and 21/33 in patients with extended edema (63.6%, $p = 1.0$). Limited edemas were observed to be present in 28/49 (57.1%) of the infiltration-positive 28/49 patients, and in 16/28 (57.1%) of the infiltration-negative cohort.

Multiplicity of cerebral metastases

Most patients ($n = 45$, 58.4%) presented with a single BM ("multiplicity-negative"), while 32 patients (41.6%) presented with multiple BMs ("multiplicity-positive"). The multiplicity-positive cohort consisted of eight patients having two, nine patients having three, and 15 patients having more than three metastases. Histological evidence of tumor infiltration was found in 28/45 patients (62.2%) with a single metastasis and in 21/32 patients (65.6%) with a multiple metastasis ($p = 0.81$). In the infiltration-positive cohort, 28/49 patients (57.1%) presented with a single BM, whereas in the infiltration-negative cohort, this was 17/28 patients (60.7%).

Discussion

Our aim was to assess whether standard MR imaging parameters correlate with infiltration status of BMs. In our large cohort, we found that neither size, amount of edema, nor multiplicity of BM was predictive of infiltration behavior. We were also able to shed light on the impact of infiltrative behavior of BMs on size, peritumoral edema, and multiplicity of BMs. To our knowledge, this is the first study addressing the potential usefulness of MRI parameters to assess the infiltration status of BMs.

In spite of the strengths of our study such as (1) large patient number, (2) prospective design, and (3) histological workup, we could not show a significant correlation of infiltration status (positive vs negative) and the MRI parameters "size of metastasis," "extent of peritumoral edema," and "multiplicity of metastases" (Table 2). To achieve a better

OS, some authors suggest performing supramarginal resection in BM surgery [15, 44]. However, our results suggest that established, readily available and easy to interpret radiological parameters are not decisive for the preoperative planning of a surgical strategy with regard to supramarginal resection.

Role of supramarginal resection

Although Yoo et al. [44] and Kamp et al. [19] were able to significantly minimize local recurrences by resecting 2–5 mm beyond the glial pseudocapsule, they failed to detect vital tumor cells during histopathological investigation of the supramarginal resected tissue. In contrast to previous studies [19, 34, 44], we were able to detect vital tumor cells within biopsy samples taken beyond the resection margins of GTR in 63.6% of the cases in our study; this observation corresponds to the results of Siam et al. [38]. It contradicts earlier studies which could not substantiate any direct infiltration of the brain parenchyma beyond the glial pseudocapsule due to the lack of evidence of vital tumor cells [24, 44]. This finding of supramarginal infiltration may lead to the interpretation that the infiltrative process beyond the tumor margin is not a detached process on its own (apart from the bulk growth of the whole metastasis) but it is closely related to the ongoing growth of the metastasis itself. As such, it seems to only precede the growth of the metastasis in a defined relation, before the bulk mass of the metastasis grows into the upfront infiltrated brain parenchyma. This would explain that the infiltration zone typically does not seem to extend more than 5 mm beyond the tumor pseudocapsule [41]. A previous study [34] provided contradictory results when the researchers found no evidence of tumor cells but only a reactive astrocytosis beyond the pseudocapsule when analyzing 36 samples that were taken up to 10 mm beyond the resection margin of 12 patients

Table 2 Correlation between the infiltration-positive and the infiltration-negative cohorts in respect to the dichotomized MRI parameters: (a) size of metastasis with a diameter ≤ 3 cm or > 3 cm (p = 0.64), (b) extent of peritumoral edema with an edema ratio ≤ 1 or > 1 (p = 1.0), and (c) number of metastases where multiple metastases indicate multiplicity (p = 0.81). An edema ratio of > 1 is reached when the size of the edema exceeds the size of the metastasis. For example, 57.1% of the infiltration-negative cohort and 51.0% of the infiltration-positive cohort show a metastasis size of ≤ 30 mm

imaging parameter	classification		p-value (infiltration positive vs infiltration negative)
size of BM	diameter ≤ 30mm (small) infiltration negative 57.1%, 16 of 28 pats. infiltration positive 51.0%, 25 of 49 pats.	diameter > 30 mm (large) infiltration negative 42.9%, 12 of 28 pats. infiltration positive 49%, 24 of 49 pats.	0.64
edema ratio	edema ratio ≤ 1 (limited) infiltration negative 57.1%, 16 of 28 pats. infiltration positive 57.1%, 28 of 49 pats.	edema ratio >1 (extended) infiltration negative 42.9%, 12 of 28 pats. infiltration positive 42.9%, 21 of 49 pats.	1.0
multiplicity	multiplicity negative number of BM = 1 infiltration negative 60.7%, 17 of 28 pats. infiltration positive 57.1%, 28 of 49 pats.	multiplicity positive number of BM ≥ 2 infiltration negative 39.3%, 11 of 28 pats. infiltration positive 42.9%, 21 of 49 pats.	0.81

operated on a BM. As infiltration beyond the tumor margin was already shown in autopsy studies at that time point [3, 27], the authors argued that at the time of death, patients with a BM will have increased local metastatic infiltration of adjacent brain tissue, leading to positive autopsy specimens. Along with the proven existence of supramarginal infiltration in living individuals, further studies within the realms of bioimaging and its recently added capabilities to monitor and characterize cellularity and metabolite concentrations among other parameters [32] are necessary to effectively detect and diagnose supramarginal infiltration in BMs to aid in developing an adequate treatment strategy.

Role of imaging parameters

Although other imaging modalities such as computer tomography (CT) and ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) [13] are available to detect BMs, the MRI technique of passive contrast enhancement is considered to be the gold standard and has a clear superiority in sensitivity over both CT [16] and PET/CT [23, 42]. MR perfusion imaging [12] is another supplementary technique; however, it is not as widely available as the standard MRI procedure, due to the complexity of image acquisition, postprocessing, and interpretation. As such, standard passive contrast enhancement MRI is nowadays the diagnostic modality of choice for the detection and evaluation of the number, size, and location of BMs as well as secondary effects such as peritumoral edema of the lesions [2]. Peritumoral edema, demonstrated by hyperintense signal changes on T2 and FLAIR images, is due to tumor-induced blood-brain barrier disruption and release of fluid with high protein content into the interstitial space [9, 29]. Reports on the relationship of extent of peritumoral edema to the size of the causative BM [2, 7, 35, 36] as well as on the impact of peritumoral edema remain conflicting [5, 20]. Focusing on the early and sensitive detection of BMs, a recent study was able to detect very small BMs with a proposed tumor volume two to three orders of magnitude smaller ($0.3–3 \times 10^5$ cells) than those volumes already detectable with gadolinium-enhanced MRI ($10^7–10^8$ cells) by identifying VCAM-1 upregulation on the cerebral endothelium on tumor-associated vessels in the early stages of BM development using molecular MRI [37]. However, in our study, we could show that the biometric parameters of size, peritumoral edema, and multiplicity of BMs do not correlate with infiltration status. Therefore, intraoperative imaging—and its power to document specific features of a given disease like BMs which are essential for the safe and effective delivery of therapy—needs to be investigated further. Although hybrid PET/MRI scanners nowadays represent the new frontier for imaging complex pathophysiological processes, are useful for the differentiation between radiation injury and brain metastasis recurrence, and can aid in target selection for stereotactic biopsies, they cannot yet afford a clear delineation of hypermetabolism outside the tumor pseudocapsule because of the limited spatial resolution provided by PET [1, 8, 14].

Hence, additional efforts should be pursued to enhance intraoperative imaging to detect the presence of supramarginal infiltration and to optimize resection margins while limiting neurological morbidity, e.g., in the context of a hybrid operating room [11].

Role of primary tumor

Our study could not show a correlation of the primary tumor to the infiltration status ($p = 0.23$).

In the study of Siam et al. [38], the presence of metastatic cells in the adjacent brain parenchyma was observed in 64.1% of their cases and in the study of autopsy specimens by Baumert et al. in 63% [3]. This corresponds well with our results, where 63.6% (49 out of 77 patients) of the patients presented supramarginal infiltration. Our results, however, are not in line with the findings of Neves et al. [27] who reported a tumor infiltration of only 40.3% of their autopsy specimens.

However, when comparing the results of Siam et al. [38] to our own, infiltration rates depending on the primary tumor were similar in NSCLC: 75% (15/20) and 67.9% (19/28), respectively. Differences in the infiltration rate in malignant melanoma amounting to 41.7% (5/12) and 66.7% (4/6) might be of limited significance due to the relatively small value of total numbers recruited here. In regard to the other tumor types (GIT, breast, kidney), the total numbers seemed to be too low (≤ 4) in order to justify comparison.

In our study, we did not perform an analysis of the metastatic infiltration type at the M/BP-interface. Therefore, in our opinion, we cannot relate our results to any other studies which performed this analysis.

In both MRI and autopsy studies, multiple BMs are found in 50 to 80% of the cases [13, 21]. In our study, multiple metastases were present in only 41.6% of the cases. This discrepancy might be due to a selection bias because all patients in this report were not only diagnosed with multiple metastases in imaging or autopsy studies but actually operated on. Surgery in multiple BMs is generally limited to removal of the dominant, life-threatening lesion, and to obtain a histological diagnosis but not to achieve local disease control, as is the case in patients with a single metastasis. Although studies suggest that patients with a limited number of multiple BMs may benefit from resection of all lesions [6] or at least the dominant lesion [28, 40], performing surgical resection in the case of multiple metastases might thus have been indicated more conservatively.

Conclusion

Based on the post hoc analysis of our prospective trial data, we could not confirm the hypothesis that infiltration of brain parenchyma beyond the glial pseudocapsule is associated with tumor size, extent of edema, or multiplicity of metastases in MR imaging. Our data suggest that these MRI parameters are not decisive for the preoperative planning of a surgical strategy with regard to supramarginal resection in larger or multiple lesions, or when an extended edema is present.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Aiello M, Cavaliere C, Fiorenza D, Duggento A, Passamonti L, Toschi N (2018) Neuroinflammation in neurodegenerative diseases: current multi-modal imaging studies and future opportunities for hybrid PET/MRI. Neuroscience S0306–4522(18):30508–30516
2. Aminoff A, Josephson A (2014) Aminoff's neurology and general medicine. Elsevier, Oxford
3. Baumert BG, Rutten I, Dehing-Oberije C, Twijnstra A, Dirx MJ, Debougnoux-Huppertz RM, Lambin P, Kubat B (2006) A pathology-based substrate for target definition in radiosurgery of brain metastases. Int J Radiat Oncol Biol Phys 66:187–194
4. Berghoff AS, Rajky O, Winkler F, Bartsch R, Furtner J, Hainfellner JA, Goodman SL, Weller M, Schittenhelm J, Preusser M (2013) Invasion patterns in brain metastases of solid cancers. Neuro-Oncology 15(12):1664–1672
5. Berghoff AS, Fuchs E, Ricken G, Mlecnik B (2015) Density of tumor-infiltrating lymphocytes correlates with extent of brain edema and overall survival time in patients with brain metastases. Oncoimmunology 5(1):e1057388 eCollection 2016
6. Bindal RK, Sawaya R, Leavens ME, Lee JJ (1993) Surgical treatment of multiple brain metastases. J Neurosurg 79:210–216
7. Bravo-Rodríguez F, Diaz-Aguilera R, Hygino da Cruz LC Jr (2012) Learning neuroimaging: 100 essential cases. Springer, Berlin
8. Ceccon G, Lohmann P, Stoffels G, Judov N, Filss CP, Rapp M, Bauer E, Hamisch C, Ruge MI, Kocher M, Kuchelmeister K, Sellhaus B, Sabel M, Fink GR, Shah NJ, Langen KJ, Galldiks N (2017) Dynamic O-(2-18F-fluoroethyl)-L-tyrosine positron emission tomography differentiates brain metastasis recurrence from radiation injury after radiotherapy. Neuro-Oncology 19(2):281–288
9. Criscuolo GR (1993) The genesis of peritumoral vasogenic brain edema and tumor cysts: a hypothetical role for tumor-derived vascular permeability factor. Yale J Biol Med 66(4):277–314
10. DeAngelis LM, Currie VE, Kim JH, Krol G, O'Hehir MA, Farag FM, Young CW, Posner JM (1989) The combined use of radiation therapy and lonidamine in the treatment of brain metastases. J Neurol 7:241–247
11. Dunne RM, O'Neill AC, Tempany CM (2017) Chapter 10 – Imaging tools in human research: focus on image-guided intervention. In: Robertson D, Williams GH (eds) Clinical and translational science. Elsevier, Oxford, pp 181–190
12. Essig M, Shiroishi MS, Nguyen TB et al (2013) Perfusion MRI: the five most frequently asked technical questions. AJR Am J Roentgenol 200(1):24–34
13. Fox BD, Cheung VJ, Patel AJ, Suki D (2011) Epidemiology of metastatic brain tumors. Neurosurg Clin N Am 22(1):1–6
14. Heiss WD (2016) Hybrid PET/MR imaging in neurology: present applications and prospects for the future. J Nucl Med 57(7):993–995
15. Hjorthaug K, Højbjerg JA, Knap MM, Tietze A, Haraldsen A, Zacho HD, Kramer SMJ, Borghammer P (2015) Accuracy of 18F-FDG PET-CT in triaging lung cancer patients with suspected brain metastases for MRI. Nucl Med Commun 36(11):1084–1090
16. Hochstenbag MM, Twijnstra A, Wilmink JT, Wouters EF, ten Velde GP (2000) Asymptomatic brain metastases (BM) in small cell lung cancer (SCLC): MR-imaging is useful at initial diagnosis. J Neuro-Oncol 48:243–248
17. Iwadate Y, Namba H, Yamaura A (2000) Significance of surgical resection for the treatment of multiple brain metastases. Anticancer Res 20:573–577
18. Johnson BE, Mazor T, Hong C, Barnes M, Aihara K, McLean CY et al (2014) Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science 343:189–193
19. Kamp MA, Dibue M, Niemann L, Reichelt DC, Felsberg J, Steiger HJ, Szelenyi A, Rapp M, Sabel M (2012) Proof of principle: supramarginal resection of cerebral metastases in eloquent brain areas. Acta Neurochir 154:1981–1986
20. Kerschbaumer J, Bauer M, Popovscaia M, Grams AE, Thomé C, Freyschlag CF (2017) Correlation of tumor and peritumoral edema volumes with survival in patients with cerebral metastases. Anticancer Res 37(2):871–876
21. Khuntia D, Brown P, Li J, Mehta MP (2006) Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol 24(8):1295–1304
22. Kreso A, O'Brien CA, van Galen P, Gan OI, Notta F, Brown AMK et al (2013) Variable clonal repopulation dynamics influence chemotherapy response in colorectal cancer. Science 339:543–548
23. Krüger S, Mottaghy FM, Buck AK et al (2011) Brain metastasis in lung cancer. Comparison of cerebral MRI and 18F-FDG-PET/CT for diagnosis in the initial staging. Nucl Med (Stuttg) 50:101–106
24. Li B, Yu J, Suntharalingam M, Kennedy AS, Amin PP, Chen Z, Yin R, Guo S, Han T, Wang Y, Yu N, Song G, Wang L (2000) Comparison of three treatment options for single brain metastasis from lung cancer. Int J Cancer 90:37–45
25. Linnert M, Iversen H, Gehl J (2012) Multiple brain metastases - current management and perspectives for treatment with electrochemotherapy. Radiol Oncol 46(4):271–278. https://doi.org/10.2478/v10019-012-0042-y
26. McPherson CM, Suki D, Feiz-Erfan I, Mahajan A, Chang E, Sawaya R, Lang FF (2010) Adjuvant whole-brain radiation therapy after surgical resection of single brain metastases. Neuro-Oncology 12(7):711–719
27. Neves S, Mazal PR, Wanschitz J, Rudnay AC, Drlicek M, Czech T, Wustinger C, Budka H (2001) Pseudogliomatous growth pattern of anaplastic small cell carcinomas metastatic to the brain. Clin Neuropathol 20(1):38–42

28. Paek SH, Audu PB, Sperling MR, Cho J, Andrews DW (2005) Reevaluation of surgery for the treatment of brain metastases: review of 208 patients with single or multiple brain metastases treated at one institution with modern neurosurgical techniques. Neurosurgery 56:1021–1034 discussion 1021–1034
29. Papadopoulos MC, Saadoun S, Binder DK, Manley GT, Krishna S, Verkman AS (2004) Molecular mechanisms of brain tumor edema. Neuroscience 129(4):1011–1020
30. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Markesbery WR, Macdonald JS, Young B (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500
31. Patel AJ, Lang FF, Suki D, Wildrick DM, Sawaya R (2017) Metastatic brain tumors. In: Youmans and Winn (ed) Neurologic surgery, 7th edn. Elsevier, Philadelphia, pp 1091–1106
32. Pope WB (2018) Brain metastases: neuroimaging. Handb Clin Neurol 149:89–112
33. Popper HH (2016) Progression and metastasis of lung cancer. Cancer Metastasis Rev 35(1):75–91
34. Raore B, Schniederjan M, Prabhu R, Brat DJ, Shu H-K, Olson JJ (2011) Metastasis infiltration: an investigation of the postoperative brain-tumor interface. Int J Radiat Oncol Biol Phys 81:1075–1080
35. Runge VM (1997) Contrast-enhanced clinical magnetic resonance imaging. The University Press of Kentucky, Lexington
36. Schneider T, Kuhne JF, Bittrich P, Schroeder J, Magnus T, Mohme M, Grosser M, Schoen G, Fiehler J, Siemonsen S (2017) Edema is not a reliable diagnostic sign to exclude small brain metastases. PLoS One 12(5):e0177217
37. Serres S, Soto MS, Hamilton A et al (2012) Molecular MRI enables early and sensitive detection of brain metastases. Proc Natl Acad Sci U S A 109(17):6674–6679
38. Siam L, Bleckmann A, Chaung H-N et al (2015) The metastatic infiltration at the metastasis/brain parenchyma-interface is very heterogeneous and has a significant impact on survival in a prospective study. Oncotarget 6(30):29254–29267
39. Spanberger T, Berghoff AS, Dinhof C, Ilhan-Mutlu A, Magerle M, Hutterer M, Pichler J, Wöhrer A, Hackl M, Widhalm G, Hainfellner JA, Dieckmann K, Marosi C, Birner P, Prayer D, Preusser M (2013) Extent of peritumoral brain edema correlates with prognosis, tumoral growth pattern, HIF1a expression and angiogenic activity in patients with single brain metastases. Clin Exp Metastasis 30(4):357–368
40. Stark AM, Tscheslog H, Buhl R, Held-Feindt J, Mehdorn HM (2005) Surgical treatment for brain metastases: prognostic factors and survival in 177 patients. Neurosurg Rev 28:115–119
41. Sundaresan N (2007) Surgical treatment of brain metastases. Proc 13th Eur Congr Neurosurg pp 63–71
42. Suzuki K, Yamamoto M, Hasegawa Y, Ando M, Shima K, Sako C, Ito G, Shimokata K (2004) Magnetic resonance imaging and computed tomography in the diagnoses of brain metastases of lung cancer. Lung Cancer 46:357–360
43. Wood SL, Pernemalm M, Crosbie PA, Whetton AD (2014) The role of the tumor-microenvironment in lung cancer-metastasis and its relationship to potential therapeutic targets. Cancer Treat Rev 40: 558–566. https://doi.org/10.1016/j.ctrv.2013.10.001
44. Yoo H, Kim YZ, Nam BH, Shin SH, Yang HS, Lee JS, Zo JI, Lee SH (2009) Reduced local recurrence of a single brain metastasis through microscopic total resection. J Neurosurg 110:730–736