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Differentiation of cerebral tumors using multi-section echo planar MR perfusion imaging

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Abstract

Objective: We have investigated the performance of magnetic resonance (MR) perfusion imaging to differentiate between astrocytomas grade II, grade III and glioblastomas in a prospective study. *Materials and methods:* In 33 patients with suspected supratentorial primary cerebral tumors we performed multi-section Echo Planar MR perfusion imaging. Regional cerebral blood volume (rCBV) maps were calculated and the maximum rCBV was determined from the entire lesion. This value was divided by the mean rCBV value from the contralateral side, which provided the rCBV index used in this study. The rCBV index was correlated with the histological tumor classification after stereotactic biopsy ($n = 7$) or open resection ($n = 26$). *Results:* The maximum rCBV index was 1.2 ± 0.8 for grade II astrocytomas ($n = 3$), 4.0 ± 1.2 for grade III astrocytomas ($n = 13$), and 10.3 ± 3.3 for glioblastomas ($n = 17$). The difference between grade III astrocytomas and glioblastomas was highly significant ($P < 0.001$). *Discussion and conclusion:* The rCBV index measured with multi-section Echo Planar MR perfusion is capable of differentiating grade III astrocytomas from glioblastomas. It serves as an additional parameter to establish a diagnosis in cases where it is not possible to clearly differentiate between these types of tumors on the basis of conventional MR imaging. MR perfusion imaging also provides information about spatial heterogeneities within a tumor which might improve diagnostic performance. This technology may also be of interest for follow-up examinations after histological diagnosis and further treatment.

Keywords: Malignant glioma; Perfusion measurement; Echo planar imaging; Cerebral blood volume

1. Introduction

Neovascularization of tumor tissue is an important criteria for malignancy assessment in astrocytomas and glioblastomas, and most histological grading systems use tumor vascularity as a decisive characteristic of tumor dignity. Other criteria include cytologic atypia, mitoses, endothelial proliferation, and necrosis. Since therapy and prognosis strongly depend on tumor malignancy, reliable information about the malignancy is of great interest for the neuroradiologic assessment of brain tumors.

Positron emission tomography [1–3] and magnetic resonance (MR) perfusion imaging [4–7] can provide preoperative information on tumor vascularity but only biopsy or surgical resection provides details. Both imaging modalities also provide information for differentiating between vital tumor tissue and necrosis [4,5]. MR perfusion imaging is of special interest because it can easily be combined with conventional MR examinations due to its high spatial resolution of typically 2–3 mm in-plane [8–10]. The latter is important to identify small regions of high malignancy in heterogeneous tumors. Additionally, fast imaging techniques such as echo planar imaging (EPI) allow the assessment of multiple intratumoral sections.

To assess the potential of MR perfusion imaging to differentiate between grade II and III astrocytomas and glioblastomas we have conducted a prospective study.

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2. Materials and methods

2.1. Patients

Thirty-three patients (23 male, 10 female) with suspected supratentorial, primary cerebral tumors underwent conventional MR and MR perfusion measurements before surgery. The tumors were classified on the basis of biopsy or surgical resection which was done after the MR examination. The pathologist and the radiologist were blinded to each other's reports. The stereotactic target point was determined as an enhancing part of the lesion suspected to be of highest malignancy according to conventional and perfusion MRI.

The histologic grading was based on the most malignant component obtained from a series of histologic samples because astrocytomas often show heterogeneity with components of different cell types as well as necrotic regions. For two patients with a suspected grade II astrocytoma (patients 8 and 30 of Table 1) a confirmatory report was obtained from a second reference center. Tumors were graded according to the World Health Organisation (WHO) tumor grading system. MR examination, surgery and tumor classification was completed within 7 days.

All patients had a transcranial Doppler ultrasound examination to exclude hemodynamically relevant stenoses of the major cerebral arteries, which could flaw our MR perfusion measurements.

This study was performed according to a protocol that was approved by the local ethics committee. Written and informed consent was obtained from all patients who participated in this study.

2.2. Imaging protocol

MR imaging was carried out on 1.5 T Magnetom Vision MR scanner (Siemens, Medical Engineering, Erlangen, Germany) equipped with a gradient booster capable of switching 25 mT/m within 300 μs. A quadrature head coil was used for signal excitation and reception. The head coil has two cushions that can

Table 1
Survey of patient data, pathologic diagnosis (WHO), and rCBV index

Patient No./Age/Sex	Pathologic diagnosis	Surgery [No. of Samples]	rCBV index
1/57/f	Oligoastrocytoma WHO III	r	3.5
2/46/m	Astrocytoma WHO III	r	5.5
3/57/f	Glioblastoma	r	10.5
4/65/m	Glioblastoma	r	9.1
5/47/f	Glioblastoma	r	11.8
6/53/m	Glioblastoma	r	7.0
7/57/f	Astrocytoma WHO III	r	2.1
8/36/m	Suspected Astrocytoma WHO II	r	1.1
9/59/m	Oligoastrocytoma WHO III	sb [8]	4.4
10/56/m	Glioblastoma	sb [8]	10.3
11/77/f	Glioblastoma	r	9.6
12/62/m	Astrocytoma WHO III	sb [3]	4.2
13/63/m	Glioblastoma	r	10.6
14/42/m	Astrocytoma WHO III	r	3.9
15/36/m	Glioblastoma	r	11.6
16/35/m	Astrocytoma WHO III	r	3.5
17/49/m	Glioblastoma	r	5.0
18/47/m	Glioblastoma	r	7.0
19/66/f	Glioblastoma	r	16.8
20/70/f	Glioblastoma	r	9.7
21/44/m	Astrocytoma WHO III	sb [5]	6.0
22/60/m	Glioblastoma	r	17.3
23/36/m	Astrocytoma WHO III	sb [6]	2.5
24/33/f	Astrocytoma WHO III	r	2.3
25/45/m	Astrocytoma WHO III	r	4.1
26/63/f	Glioblastoma	r	10.3
27/38/m	Astrocytoma WHO II	r	2.1
28/67/f	Glioblastoma	r	13.1
29/46/m	Astrocytoma WHO III	r	5.6
30/39/m	Suspected Astrocytoma WHO II	sb [6]	0.6
31/30/m	Astrocytoma WHO III	r	4.0
32/72/m	Glioblastoma	sb [2]	6.0
33/51/m	Glioblastoma	r	8.6

Histological diagnosis was made on gross tumor resection (r) or stereotactic biopsy (sb). For the latter the number of samples are given in brackets.

be adjusted in its position to minimize lateral movement of the head.

Prior to the MR perfusion measurement conventional unenhanced MR images were acquired for each patient. T1-weighted spin-echo images (echo time (TE) = 17 ms, repetition time (TR) = 550 ms, field-of-view (FOV) = 210 mm, matrix size = 192 × 256) were obtained in coronal sections with 5 mm thickness and 1 mm gaps between adjacent sections. T2-weighted images were acquired in transverse sections using a turbo spin-echo sequence (TE = 98 ms, TR = 4000 ms, FOV 220 mm, matrix size = 190 × 256, turbo factor = 5). The section thickness was 6 mm with a gap of 1.8 mm in case of the first seven patients and 5 mm with a gap of 1 mm in the case of all the following patients. Position and extent of the tumors were determined on the basis of the T2-weighted images.

A gradient echo sequence which was sensitive to time-of-flight (TOF) effects [11] (TE = 9 ms, TR = 30 ms, flip angle = 50°) was used to identify larger vessels inside the tumor, which might otherwise be misinterpreted as highly perfused tissue. Orientation, thickness and gap of these transverse sections were identical to those used for T2-weighted imaging.

Multi-section perfusion measurements were carried out during the first pass of a gadopentetate dimeglumine (Gd-DTPA, Schering GmbH, Berlin, Germany) bolus. A gradient-echo EPI sequence was used to acquire 128 echoes with an effective echo time of 54 ms and a TR of 1500 ms. Again, orientation, thickness and gap of the transverse sections were the same used for T2-weighted imaging. This allowed direct comparison between rCBV maps and anatomical images. The number of sections varied between five and nine, depending on the extent of the tumor. The entire tumor volume identified in the T2-weighted images was covered in all patients. The FOV was 220 ms, equivalent to a nominal spatial in-plane resolution of 1.7 mm.

A bolus of 0.1 mmol/kg Gd-DTPA immediately followed by a saline flush was injected using a Spectris MR injector (Medrad, Pittsburgh, PA, USA). The injection was applied to an antecubital vein with a standard iv. cannula at a flow rate of 6 ml/s. A series of 60 data sets was acquired at 1.5 s intervals. Ten data sets were acquired prior to the bolus injection to obtain a steady-state precontrast baseline. The other data sets were acquired during and after the injection.

Besides local heat and pressure sensations at the injection side, we experienced one patient who complained of a mild headache without any neurological deficit, which spontaneously resolved after 8 h.

2.3. Data analysis

Image analysis was performed on a Sun SparcStation 20 (Sun Microsystems, Mountain View, USA) using home-developed software. Evaluation of the rCBV was carried out on a voxel-by-voxel basis. A linear relationship between relaxation rate change ΔR_2 and the regional concentration of contrast medium c_{KM}

$$\Delta R_2 = k_2 \cdot c_{KM}, \quad (1)$$

was used [12,13], where k_2 is a tissue, field strength and pulse sequence specific constant. Assuming a monoexponential relationship between the contrast agent induced relaxation rate changes and signal intensity $S(t)$

$$S(t) = S_0 \cdot \exp(-\mathrm{TE} \cdot \Delta R_2(t)), \quad (2)$$

concentration–time curves can be calculated from Eqs. (1) and (2):

$$c_{KM}(t) = -\ln(S(t)/S_0)/k_2\ \mathrm{TE}. \quad (3)$$

S_0 is the steady-state signal intensity before injection of the contrast agent. Since k_2 was not known in this study, all calculated values of c_{KM} are relative values. Relative rCBV maps were determined by gamma variate analysis of the first passage of the contrast agent bolus. Calculations were based on the principles of indicator solution theory [14–16]. No filtering of the data in the spatial or in the temporal domain was applied. No postprocessing was carried out to correct for patient movement.

Perfusion data was evaluated without knowing the histologic findings. To assess the hemodynamic status of the tumor the maximum rCBV value was determined from the entire lesion. Regions of interest (ROI) which covered the entire tumor tissue was selected in each slice intersecting the neoplasm. The extent of the tumor was determined on the basis of the T2-weighted images. Care was taken to avoid larger vessels identified with the TOF images. The maximum rCBV value obtained by this procedure was referenced to an internal standard to facilitate the comparison of the data between different patients. Therefore, a ROI in the contralateral hemisphere was selected due to the following criteria: The ROI should solely contain white matter, it should include at least 100 pixel to be representative and it should avoid larger vessels. The maximum rCBV value obtained from the tumor was divided by the mean rCBV value from the contralateral ROI, which provided the rCBV index used in this study.

2.4. Statistical analysis

Statistical significance of differences in the maximum rCBV index between the various tumor species was assessed using Mann–Whitney's U-test. This statistical test when compared with the Student's t-test, has the advantage of not depending on a normal distribution of the samples.

3. Results

Our population consisted of three patients with grade II astrocytomas, 13 with grade III astrocytomas and 17 with glioblastomas. Twenty-six patients underwent conventional gross tumor resection, in seven cases stereotactic biopsy was performed prior to resection or further non-surgical therapy (Table 1).

The maximum rCBV index was 1.2 ± 0.8 for grade II astrocytomas, 4.0 ± 1.2 for grade III astrocytomas, and 10.3 ± 3.3 for glioblastomas. Grade II astrocytomas did not show distinct hyperperfusion and because of their small sample size we could not perform meaningful comparisons with other tumor groups. The difference between grade III astrocytomas and glioblastomas was highly significant ($P < 0.001$).

Transcranial Doppler ultrasound examinations did not show hemodynamically relevant stenoses of large cerebral arteries in any case. Therefore, all tissue perfusion abnormalities were felt to be tumor related. Patient movement during the perfusion measurement occurred in four cases; however, none of the data sets had to be excluded from the study because movements occurred after the first contrast agent pass.

Figs. 1–3 show examples of precontrast T2-weighted images (a), postcontrast T1-weighted images (b), and rCBV maps (c). Grade II astrocytomas appeared homogeneous without edema in the precontrast T2-weighted images. There was also no distinct contrast enhancement in the T1-weighted images, and there was no clear rCBV enhancement in particular (Fig. 1c). In one grade II astrocytoma rCBV was even reduced when compared to the contralateral normal tissue. rCBV was increased in all grade III astrocytomas (Fig. 2). Glioblastomas typically presented with a heterogeneous structure of vital tumor tissue, enclosed necrotic regions and extensive edema in the T2-weighted images. In the postcontrast T1-weighted images vital tumor tissue became visible because of contrast enhancement.

Different structures were easily recognized in the rCBV maps according to their hemodynamic properties: necrotic areas showed hardly any perfusion, whereas rCBV in vital tumor tissue was significantly increased in comparison with contralateral tissue. Vital tumor tissue rCBV in glioblastomas was typically higher than in grade III astrocytomas. These qualitative findings are in good agreement with the quantitative results of the rCBV maps of the various tumor entities. Fig. 4 shows the mean values for the maximum rCBV index of the different tumor entities.

4. Discussion

Accurate determination of tumor grade is essential for optimal treatment strategy [17]. Among the histologic criteria for tumor grading, vascularity is a decisive one and there is sound evidence that increasing malignancy is associated with the degree of vascular proliferation and neovascularization [18–20]. We have used MR perfusion imaging in this study and our data indicates that MR based rCBV measurements using single shot EPI, which largely reflects neovascularity, is capable of differentiating grade III astrocytomas from glioblastomas. Lee et al. reported a 100% sensitivity and 75% specificity for differentiation between high- and low-grade astrocytoma using their technique, which is comparable to ours, and stated hat perfusion MR imaging is a reliable technique for estimation of tumor dignity [17]. The microvascular architecture and environment of gliomas is very complex [19], and at present our imaging modalities cannot depict all relevant details. It is likely that neovascularization involves both the arterial supply as well as the venous drainage and further studies are needed to investigate such details.

rCBV in grade II astrocytomas evaluated in this study showed that rCBV was lower or only slightly increased compared with normal brain tissue of the contralateral hemisphere. In addition, the rCBV index in grade II astrocytomas was lower than in grade III astrocytomas and there was no overlap between both groups. Similar findings of an increased rCBV in grade III astrocytomas in comparison with grade II astrocytomas was reported by Aronen et al. [4,21] and Knopp et al. [5]. Unfortunately as stated above we could not perform meaningful comparisons with other tumor groups because of the small number of grade II astrocytomas. Nevertheless, in combination with previously published data by Aronen and Knopp, our results indicate that it may be possible to differentiate between astrocytomas grade II and III on the basis of their neovascularization assessed with MR perfusion imaging.

The rCBV index of 1.2 ± 0.8 in grade II astrocytomas determined in this study compare well to results published by Aronen et al., who report 1.11 ± 0.08 [21]. There are, however, rCBV differences for grade III astrocytomas and glioblastomas with our values exceeding theirs [21]. This difference can be explained by the EPI sequence used. Contrary to their spin-echo EPI we employed a gradient-echo sequence. Numerical simulations have shown that these sequences differ in their sensitivity to blood vessel size. Gradient-echo sequences show a higher sensitivity to larger vessels in contrast to spin-echo sequences which have a higher sensitivity to capillaries [12,17,22]. Consequently differences between healthy brain tissue and highly neovascularized tissue may be better depicted using gradient-echo sequences.

The data for grade II astrocytomas reported by Knopp et al. [5] with an rCBV index between 0.92 and 2.19 correspond to our values of 1.2 ± 0.8, but this similarity does not hold up for glioblastomas. Their

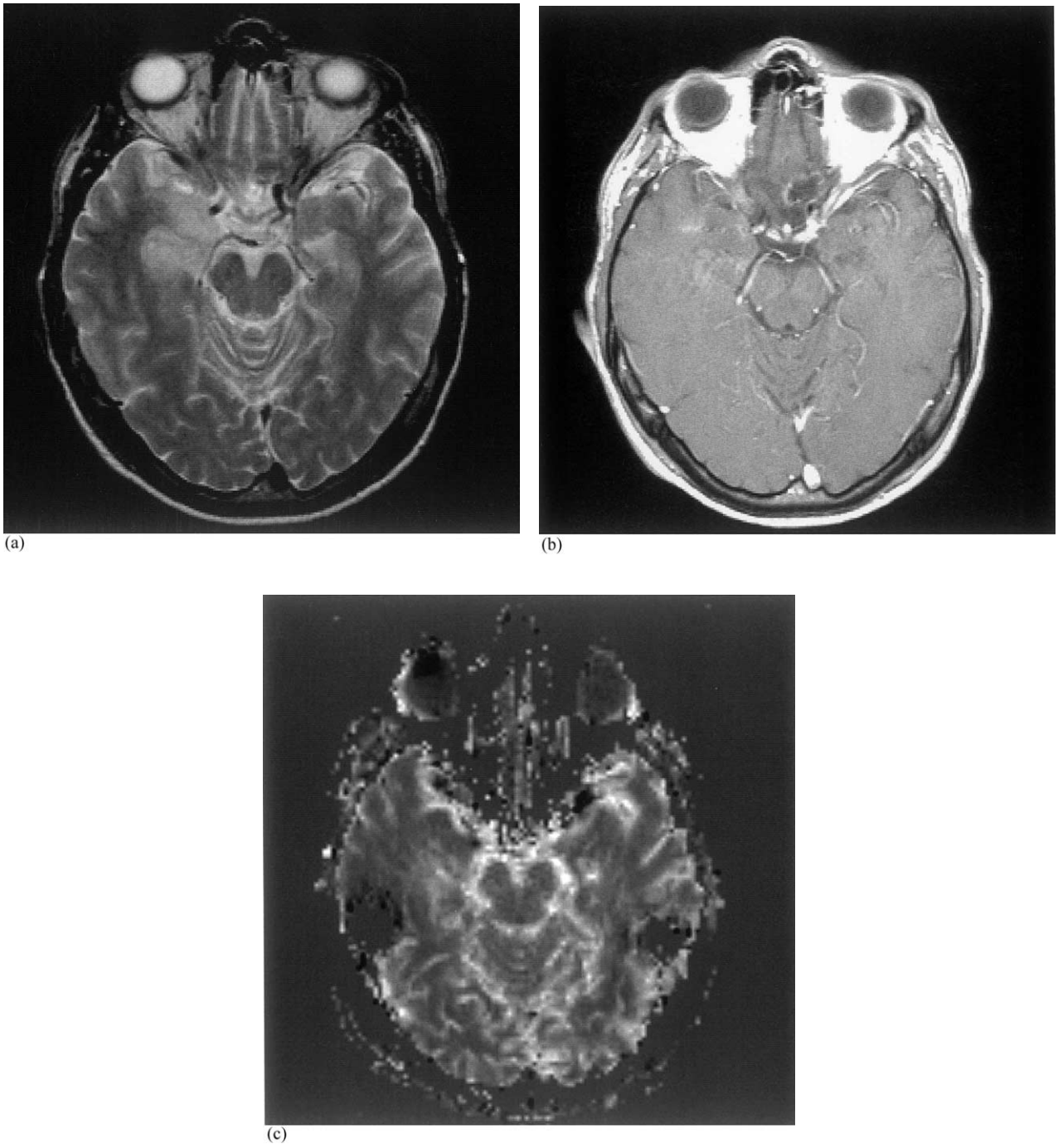

Fig. 1. Precontrast T2-weighted image (a), T1-weighted postcontrast image (b) and rCBV map (c) from a 39-year-old man suffering from an astrocytoma grade II with hyperintense signal alterations in T1 and EPI indicating contrast media enhancement. A dark grey shade corresponds to low and a light grey shade to high perfusion. The appearance of the tumor on these images is characteristic of astrocytomas grade II investigated in this study. Typically, they do not show edema in the precontrast T2-weighted images nor a distinct contrast agent enhancement in the T1-weighted images. There was no clear enhancement of rCBV in the tumor region in particular.

value of 5.07 ± 0.55 [5] is much lower than ours of 10.3 ± 3.3. Although somewhat contradictory at first sight this finding can be explained by differences in the repetition time of 1 s used by Knopp et al. [5] and 1.5 s used in our series. Grade II astrocytomas typically show an intact blood–brain barrier keeping contrast media within the capillaries. As a consequence of this spatially heterogeneous distribution of the contrast agent, temporal changes in the signal amplitude obtained during the first passage of the contrast agent bolus are dominated by T2* effects [10]. Difference in T1-weighting due to variations in TR can be neglected. In contrast to this,

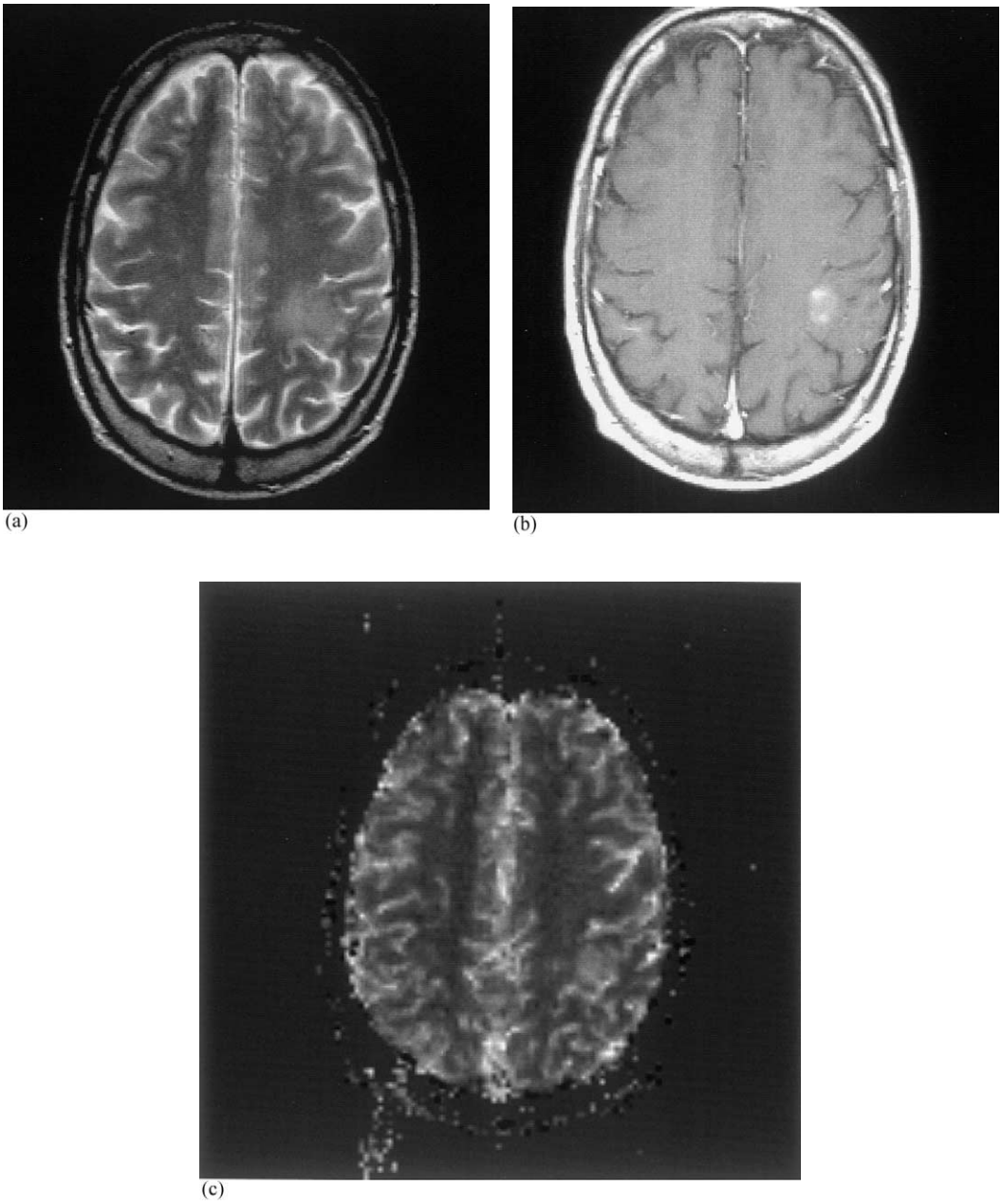

Fig. 2. Precontrast T2-weighted image (a), T1-weighted postcontrast image (b) and rCBV map (c) of a left parietal astrocytoma III (a dark grey shade corresponds to low and a light grey shade to high perfusion). The tumor shows a moderate hyperperfusion compared to the contralateral white matter.

glioblastomas often demonstrate a disrupted blood–brain barrier which allows the contrast agent to homogeneously spread into the tissue. This compares well with the histological features of astrocytomas III and glioblastomas, the latter showing extensive neovascularization. The T2* related signal decrease will, therefore, be partly compensated by a T1 related signal increase. This T1 effect in the presence of a disrupted blood–brain barrier may lead to an underestimation of rCBV.

As discussed above rCBV is a valid measure to differentiate between grade III astrocytomas and glioblastomas and such measurements can serve as additional criteria to determine the dignity of a tumor, especially when conventional MR imaging fails to safely differentiate them. Differentiation between these tumors will only in exceptional cases influence the therapeutic strategy which consists of tumor resection and subsequent radiotherapy. Nevertheless, MR perfusion imaging may provide detailed knowledge of spatial tumor heterogeneity and thus has potential to improve diagnostic performance. The ability to safely differentiate between grade III astrocytomas and glioblastomas is of certain interest in follow-up examinations after resection of an astrocytoma grade III. Although this imaging

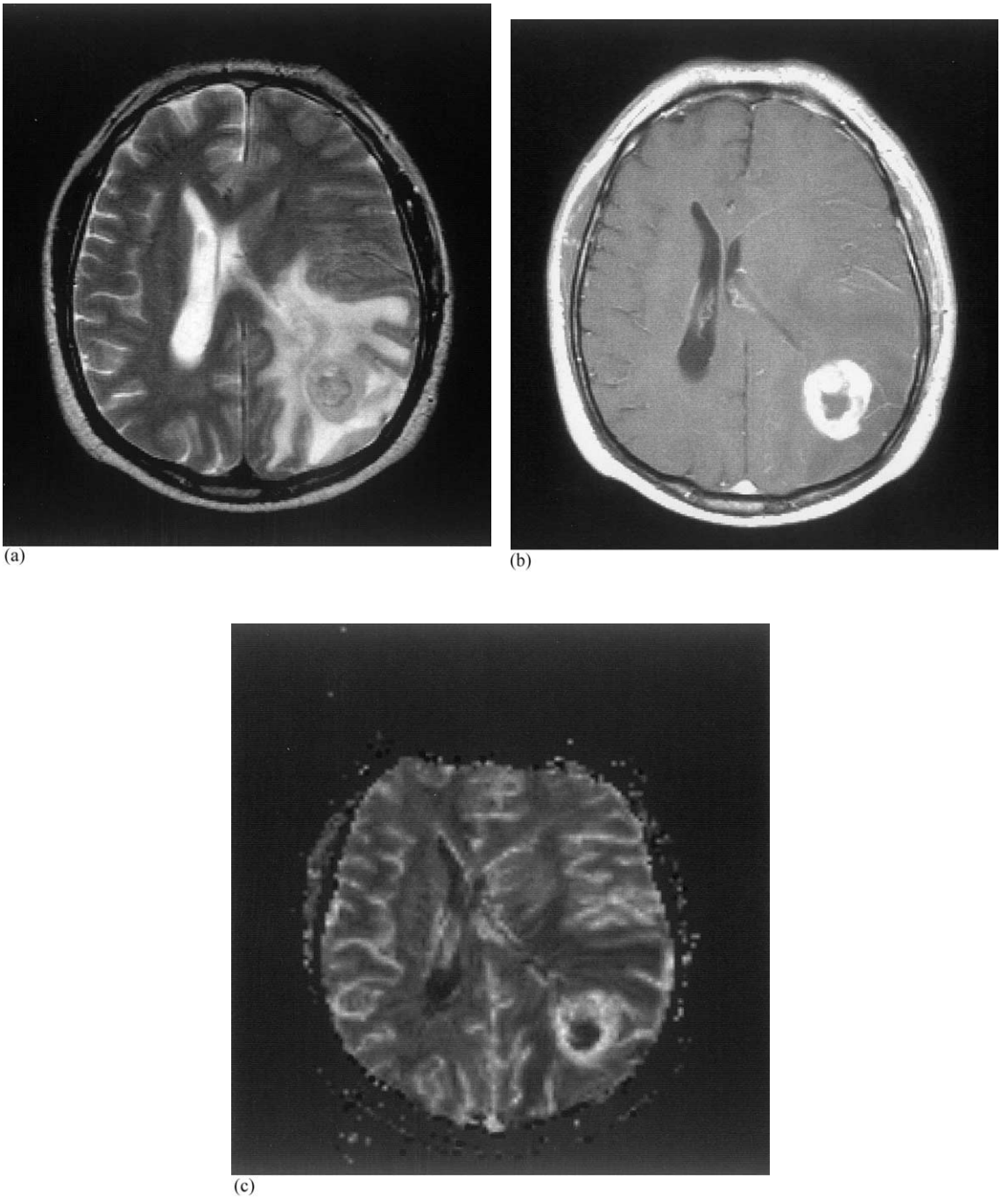

Fig. 3. Precontrast T2-weighted image (a), T1-weighted postcontrast image (b) and rCBV map (c) obtained from a 56-year-old man with a left parietal glioblastoma (a dark grey shade corresponds to low and a light grey shade to high perfusion). The circular region of the vital tumor tissue is clearly visible in the rCBV map due to its increased rCBV value. In contrast, the necrotic core of the tumor shows a distinctly decreased rCBV value.

modality may not have a direct therapeutic impact on these prognostically poor tumors it is conceivable that is may prove its role for early detection and monitoring of tumor progression. It may also serve in linking neoplasm-inherent vascular features with diagnostic and therapeutic clinical decisions enhancing our understanding of tumor biology.

5. Conclusions

The results of this study substantiate the correlation between rCBV obtained from MR perfusion imaging and tumor dignity. MR perfusion imaging enables the differentiation of grade III astrocytomas and glioblastomas, and the difference between grade III astrocyto-

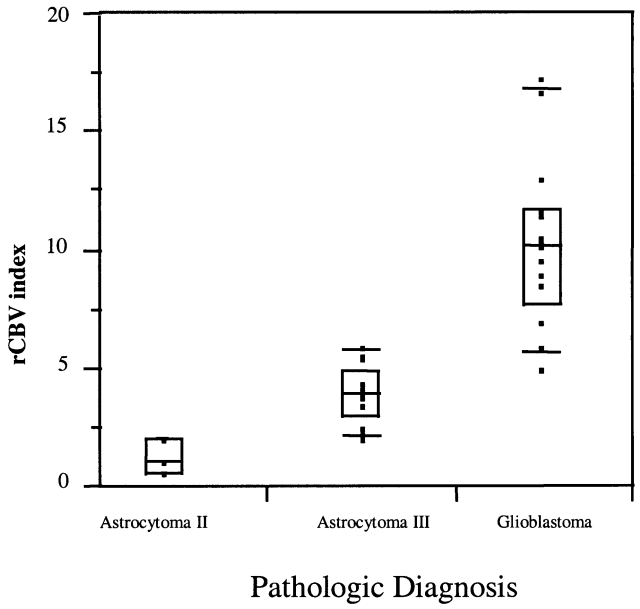

Fig. 4. Dependency of the maximum rCBV value on the tumor species. The quartile boxes show the median as a line across the middle and the quartiles (25th and 75th percentiles) as its ends. The 10th and 90th quartiles are shown as lines above and below the boxes.

mas and glioblastomas was highly significant. rCBV in Grade II astrocytomas was lower than in grade III astrocytomas. Due to the small number of grade II tumors further meaningful statistical analysis was not possible. Because such tumors are generally very rare, a multi-center study appears appropriate for further investigation.

Other than its utility for establishing a preoperative diagnosis MR perfusion imaging may be helpful as a method to monitor therapy. Further studies should address the question of whether MR perfusion imaging is capable of differentiating between radiation necrosis and tumor recurrence. Perfusion imaging can also provide important information about perfusion heterogeneity and provide a tumor map indicating malignant regions, which eventually has a potential to improve diagnostic safety in stereotactic biopsies.

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