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Postoperative fluid-attenuated inversion recovery MR imaging of cerebral gliomas: initial results

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Abstract Fluid-attenuated inversion-recovery (FLAIR) imaging has shown to be a valuable imaging modality in the assessment of intra-axial brain tumors; however, no data are available about the role of this technique in the clinically important postoperative stage. The purpose of this study was to evaluate the diagnostic potential of FLAIR MR imaging in residual tumor after surgical resection of cerebral gliomas. Fifteen patients with residual cerebral gliomas were examined within the first 18 days after partial surgical resection of cerebral gliomas. The imaging protocol included T1-weighted spin echo, T2- and proton-density-weighted fast spin echo, and FLAIR imaging with identical slice parameters. T1 and FLAIR were repeated after contrast media application. Detection and delineation of residual tumor were the primary parameters of the image analysis. Additionally, the influence of image artifacts on the image interpretation was assessed. On FLAIR images residual signal abnormalities at the border of the resection cavities were observed in all patients, whereas T2- and T1-weighted images present residual abnormalities in 13 of 15 and 10 of 15 patients, respectively. The FLAIR imaging was found to be superior to conventional imaging sequences in the delineation of these changes and comparable to contrast enhanced T1-weighted imaging in the delineation of residual enhancing lesions. Because of protein cell components and blood byproducts within the resection cavity, FLAIR imaging was unable to suppress the cerebrospinal fluid (CSF) in 4 patients. After the decomposition of proteins and blood, CSF could again be completely suppressed and residual or recurrent tumors were clearly identified. Our preliminary study has shown that FLAIR may be a valuable diagnostic modality in the early postoperative MR imaging after resection of cerebral gliomas due to its better delineation of residual pathologic signal at the border of the resection cavity. It should therefore be integrated into the early and/or intraoperative MR imaging protocol.

Keywords Fluid-attenuated inversion recovery · Cerebral gliomas · Early post-operative MR imaging

Introduction

A fluid-attenuated inversion-recovery sequence (FLAIR) has been described which produces heavily T2-weighted and cerebrospinal fluid (CSF)-nulled MR images [1] allowing a better delineation of lesions located adjacent to CSF-filled structures. The value of the FLAIR technique has been established for the imaging

of several pathologies of the brain and spine [2, 3, 4, 5, 6], with only preliminary evaluations available in patients with cerebral gliomas [7, 8, 9, 10]. In patients with cerebral gliomas FLAIR was found to be superior to conventional imaging in delineation of tumors close to CSF and the differentiation between tumor and edema [8].

After surgery residual macroscopic low-grade tumors present as a region of pathologic signal at the border of the resection cavity, which is most obvious on T2-weighted sequences [11]. Heavily T2-weighted images, however, have inherent limitations in the assessment of tumors after surgical resection. Specifically, lesion conspicuity close to the CSF-filled resection cavity is decreased because of partial-volume effects and fluid motion at brain – CSF interfaces [12, 13].

In patients with malignant gliomas previous studies have shown that early postoperative, enhanced T1-weighted MR is the imaging modality of choice to determine the extent of residual enhancing tumor, which correlates with the time of survival. Because of a mild T1-weighting, which is induced by the long inversion time, a marked contrast enhancement could also be observed on FLAIR images [9]. This effect has been shown to be very helpful in the diagnostic work-up of enhancing cerebral tumors [9]; however, no studies are available about the role of contrast-enhanced FLAIR imaging in the early postoperative stage.

The aim of our study was therefore to evaluate the diagnostic potential of FLAIR imaging in the assessment of residual tumor after incomplete resection of cerebral gliomas.

Materials and methods

Patient studies

Fifteen patients (6 women and 9 men; age range 18–70 years, mean age 33.7 years) underwent MR imaging within 18 days after partial surgical resection of a cerebral glioma. In all patients the surgeon reported residual, non-resectable tumor tissue. For the present study only patients with known residual tumors underwent further evaluation.

Magnetic resonance imaging was performed on a clinical 1.5-T MR system (Magnetom Vision, Siemens, Erlangen, Germany) using the standard circular polarized head coil. The imaging protocol included T1-weighted spin echo (SE), T2- and proton-density (PD)-weighted fast spin echo (FSE) and FLAIR imaging using identical slice parameters. T1- and FLAIR sequences were repeated after contrast media application. For T1-weighted SE (TR/TE = 600/15 ms) and T2-weighted fast SE (TR/TE = 4200/93 ms) the following slice parameters were used: 23 slices with a matrix size of 168 × 256; a rectangular field of view of 180 × 240 mm; and a slice thickness of 5 mm with an interslice gap of 1 mm. The FLAIR sequence was used with TR/TE = 9000/123 ms, an echo-train length of 7, and an inversion time (TI) of 2340 ms leading to a high lesion-to-white-matter contrast and allowing the acquisition of 23 sections in 3 h 36 min. For contrast-enhanced images 0.1 mmol/kg b.w. of gadodiamide (Omniscan, Nycomed Arzneimittel, Ismaning, Germany) was administered intravenously.

Evaluation of patient studies

All images were evaluated independently by two experienced MR readers blinded to the preoperative findings. Images were classified as in no residual, suspicious, or present residual pathologic signal, suspicious of residual tumor. If residual pathologic signal was stated as present, the volume of the enhancing and non-enhancing residual tissues were assessed. The volume was approximated as the product of the three measured dimensions of the enhancing tumor part in the MR images divided by two (ellipsoid formula).

For the delineation of the residual pathologic tissue from the surgical defect and the surrounding normal-appearing tissue the following three-point scale was used: 0 = poor delineation; 1 = fair delineation; and 2 = good delineation. In patients with enhancing residual tissue the contrast-enhanced T1-weighted images served as a reference.

Image artifacts were also evaluated regarding their influence on image interpretation. The artifact scales were: 0 = no artifacts; 1 = artifacts without influence on image interpretation; and 2 = artifacts with influence on image interpretation.

The statistical significance of the delineation was determined with a one-tailed sign test [18], the interobserver variability was determined with Cohen's Kappa test.

Results

Diagnostic image quality was achieved in 14 of 15 patients. One patient was excluded from further evaluation because of motion artifacts. Ten patients presented with an enhancing intra-axial tumor prior to surgery. Histology confirmed four tumors as anaplastic astrocytoma or anaplastic oligoastrocytoma and in 11 patients as glioblastoma multiforme. In all patients the neurosurgeon reported of residual tumor after surgery. Detailed patient information is summarized in Table 1.

On FLAIR images residual pathologic signal was observed in all patients, whereas T2- and T1-weighted images present residual pathologic tissue in 13 and 10 patients, respectively.

Mean volumes of the residual pathologic tissue were $0.7 \pm 0.3\ cm^3$ on T1-weighted images, $1.3 \pm 0.8\ cm^3$ on T2-weighted images, and $2.1 \pm 0.8\ cm^3$ on FLAIR images. In all patients FLAIR imaging presented the largest volumes; however, the difference between the modalities was not significant due to the small number of patients.

In the qualitative evaluation both readers found the FLAIR sequence superior to conventional imaging sequences in the delineation of residual pathologic signal (Table 2). Because of the suppression of CSF within the resection cavity, these changes, if present, could be better detected and more clearly delineated on the FLAIR images (Fig. 1).

In patients with previous enhancing tumors residual enhancement was observed in 3 of 7 patients. In all of these cases FLAIR images clearly detected and delineated the enhancing tissue (Fig. 2).

Table 1 Examined patients with age, time interval between MRI and surgery, and underlying tumor histology. Clinical patient data

Patient no.	Gender	Age (years)	Day after surgery	Histology
1	F	19	3	Anaplastic astrocytoma
2	M	18	2	Glioblastoma multiforme
3	M	31	3	Anaplastic astrocytoma
4	F	22	18	Glioblastoma multiforme
5	M	40	2	Glioblastoma multiforme
6	M	32	14	Glioblastoma multiforme
7	F	28	1	Glioblastoma multiforme
8	F	21	10	Glioblastoma multiforme
9	M	28	2	Glioblastoma multiforme
10	F	48	2	Anaplastic astrocytoma
11	M	39	14	Anaplastic oligoastrocytoma
12	F	32	2	Glioblastoma multiforme
13	F	70	3	Glioblastoma multiforme
14	F	44	3	Glioblastoma multiforme
15	F	35	2	Anaplastic astrocytoma

Cerebrospinal fluid within the resection cavity could not be suppressed in 4 patients examined at the end of the first postoperative week (patients 4, 6, 8, 11 examined at 18, 14, 10, and 14 days after surgical resection; Fig. 3). In these patients protein cell components and/or blood byproducts within the resection cavity significantly changed the relaxation time of the CSF, so that FLAIR was not able to suppress this fluid. On follow-up, which was available in 2 patients at 3 months after surgery, the CSF signal could again be suppressed after decomposition of the blood byproducts and decreased CSF protein content (Fig. 3c).

Image artifacts occurred more frequently on FLAIR (4 of 15 patients, 27 %) than on conventional images (1 of 15 patients, 6 %), but the image interpretation was not influenced in any of the examined patients. Most image artifacts occurred close to large intracranial vessels as pulsation artifacts. Hyperintensities at the border of the ventricles are also common findings in FLAIR imaging.

Discussion

T2-weighted sequences are widely accepted to be the most sensitive imaging modality for detecting primary intra-axial brain tumors [11]. Studies using FLAIR [14] techniques in the assessment of brain tumors have shown that the method is a valuable adjunct to conventional sequences [7, 8, 9, 10]. Due to the suppression of

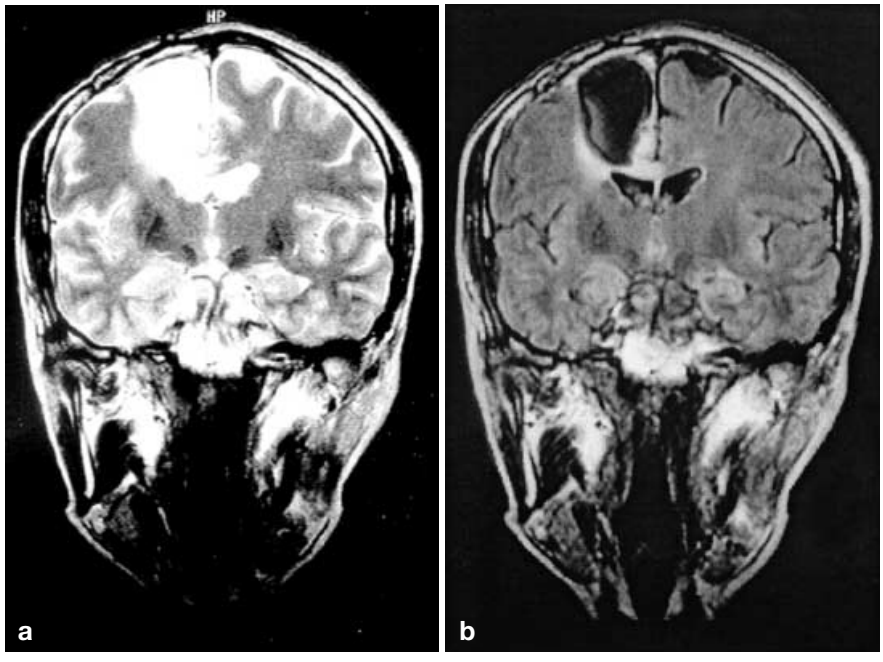

Fig. 1 **a** T2-weighted fast spin echo (FSE) and **b** fluid-attenuated inversion recovery (FLAIR) imaging in a 48-year-old female patient 2 days after resection of a right frontal anaplastic astrocytoma. The T2-weighted images present residual T2 hyperintensities at the caudal and medial border of the resection cavity and a suspicious infiltration of the corpus callosum. On FLAIR images these residual tumor masses could be better delineated, especially the hyperintensities at the medial portion of the resection cavity are clearly demonstrated. The infiltration of the corpus callosum is obvious on FLAIR

Table 2 Delineation of enhancing and non-enhancing tumor tissue from surrounding brain parenchyma. Displayed are the score points for lesion delineation in each patient. Tumor delineation. *n.a.* Not applicable. *CM* contrast medium

Delineation of non-enhancing tumor				
Patient	Reader 1		Reader 2	
	T2	FLAIR	T2	FLAIR
1	1	2	2	2
2	1	2	1	2
3	2	2	2	2
4	2	2	2	2
5	1	2	1	2
6	2	2	2	1
7	1	2	1	2
8	1	2	1	2
9	1	2	2	2
10	0	2	1	2
11	2	2	2	2
12	2	2	2	2
13	0	1	0	1
14	2	2	2	1
Mean	1.29[a]	1.93[a]	1.5[a]	1.79[a]
Delineation of enhancing tumor				
Patient	Reader 1		Reader 2	
	T1+CM	FLAIR+CM	T1+CM	FLAIR+CM
1	0	0	0	0
2	0	0	0	0
3	1	1	2	1
4	1	1	1	1
5	0	0	0	0
6	2	2	2	2
7	1	1	0	0
8	0	0	0	0
9	1	0	1	1
10	2	2	1	1
11	0	0	0	0
12	1	n.a.	1	n.a.
13	0	0	0	0
14	2	2	2	2
Mean	0.79[b]	0.69[b]	0.71[b]	0.62[b]

[a] FLAIR significantly better than T2-weighted fast spin echo: $p < 0.01$ for reader I; $p < 0.05$ for reader II (one-tailed sign test). There was no difference between the two readers ($\kappa = 0.67$, Cohen's Kappa test)

[b] There was no difference between contrast-enhanced FLAIR and T1-weighted spin echo ($p > 0.1$, one-tailed sign test). There was no difference between the two readers ($\kappa = 0.71$, Cohen's Kappa test)

the CSF, lesion-to-CSF contrast and contrast-to-noise ratio could be significantly increased leading to a much better delineation of tumors that abut the border of the CSF. Therefore, the radiologically defined tumor margins can be clearly delineated from the ventricles and subtle lesions near the cortex stand out against a background of attenuated CSF [9].

Previous studies [8] have suggested that the advantage of FLAIR imaging in the delineation of tumors is also obvious in patients with recurrent tumors after previous surgery. Most recurrent tumors are located at the border of the surgical defect and frequently present identical signal intensities to CSF on conventional imaging. By suppressing the CSF using the FLAIR technique, recurrent tumors may therefore be better detected and delineated. To our knowledge, no studies have been performed to examine the diagnostic potential of FLAIR imaging of residual tumor after partial surgical resection.

In the presented preliminary study on patients with high-grade gliomas, FLAIR imaging performed in the early postoperative stage was found to be more sensitive than conventional MR imaging sequences in the detection of residual pathologic signal at the border of the resection cavities. By nulling the signal from the CSF, residual tissue with pathologic high signal, suspicious of residual non-enhancing tumor, stands out against the suppressed fluid within the resection cavity (Figs. 1, 2; Table 2). Although the signal intensity of these areas are lower than on T2-weighted SE images, both readers found the delineation significantly better on FLAIR images (Table 2). This could be explained by a reduction of the gray-to-white-matter contrast, which is induced by the long inversion time used for suppression of the CSF signal.

In patients with previous enhancing tumors, residual enhancing tissue could be assessed on contrast-enhanced FLAIR images as well. Due to a mild T1 effect induced by the long inversion time, FLAIR images present with a marked enhancement if performed after contrast media application [9]. As to the treatment of gliomas, the main goal of surgery is the gross total resection of the tumor along its enhancing margins. The enhancing tumor boundaries have to be defined before surgery. Resection along these margins makes the tumor more sensitive to additional therapies and increases the survival time [6]. After surgery, the exact definition of residual pathologic tissue and the possible delineation of residual enhancing tumor is essential for further treatment planning and follow-up. Previous reports [15] have also shown that most of the recurrent tumors in high-grade gliomas originate from solid remnants of the tumor bulk or microscopic infiltrating tumor cells in the adjacent brain. The microscopic parts extend at least as far as the abnormal signal on T2-weighted images, the enhancing areas represent the macroscopic parts. The detection and delineation of the macroscopic residual tumor is essential for the decision and planning of further therapies and the survival time of the patient.

For contrast-enhanced MR imaging T1-weighted SE or FSE imaging is still the gold standard. However, contrast-enhanced FLAIR, which allows a parallel depiction of the signal changes on T2-weighted imaging and the enhancing tissue representing the macroscopic

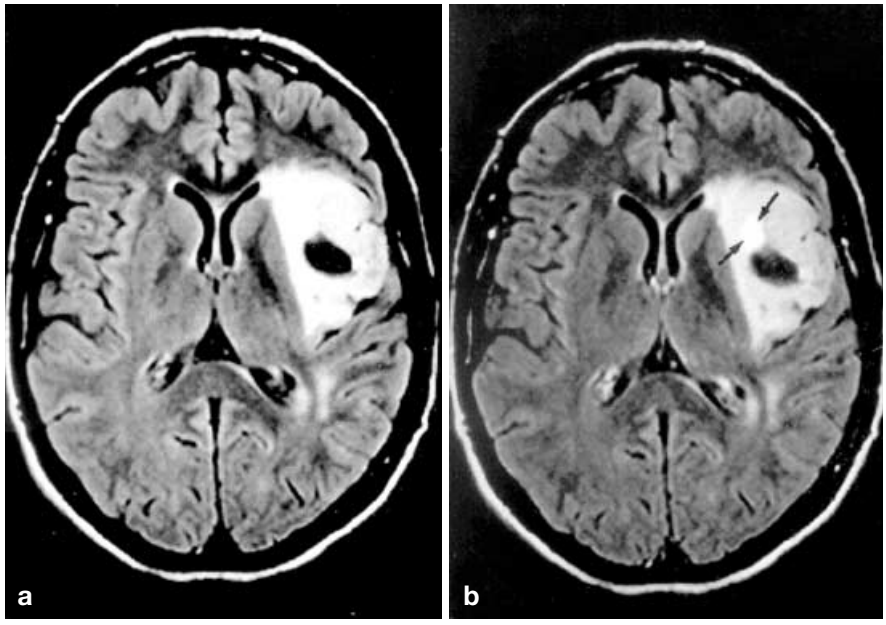

Fig. 2 **a** The FLAIR imaging and **b** contrast-enhanced FLAIR imaging in a 31-year-old male 5 days after surgical resection of a left insular glioblastoma multiforme. The FLAIR imaging clearly presents residual tumor at the border of the resection cavity. On contrast-enhanced FLAIR imaging an enhancing tumor nodule is seen at the anterior border of the resection cavity *(arrows)*. The enhancing residual tumor mass is clearly identified on the contrast enhanced FLAIR images due to a parallel depiction of enhancing and non-enhancing tumor margins

tumor in one imaging sequence, may a valuable diagnostic technique which can be used as an adjunct to the existing sequences. In the planning protocol of further treatments, e.g., radiotherapy, where only a limited number of images can be assessed, contrast-enhanced FLAIR techniques may by of some advantage.

In both conventional contrast-enhanced T1 and FLAIR imaging, problems may occur from surgically induced signal abnormalities at the border of the resection cavity. As previously described by Knauth and coworkers [19] different types of surgically induced contrast enhancement are observed. Meningeal enhancement, increased enhancement of the choroid plexus, delayed enhancement of the resection, margins and immediate intraoperative parenchymal enhancement are observed. They differ regarding their location, configuration, and time course, and they have to be analyzed carefully to avoid misinterpretation of early postoperative MR imaging.

The mechanisms of these postoperative changes are not fully understood but can include local blood-brain barrier disruption, formation of neovascularity, and luxury perfusion. The delayed enhancement at the resection margins does not appear before the fifth day after surgery [15, 16]. Therefore, postoperative imaging should be performed prior to the formation of postoperative enhancement to avoid misinterpretation of the imaging findings. In our selected series of patients with incomplete resection, residual tumor was present in each case. Therefore, we defined pathologic signal at the border of the resection cavity present within the first five postoperative days as residual tumor. In patients examined thereafter the residual tissue was defined as residual tumor if congruent with the preoperative tumor localization and the report of the localization by the neurosurgeon.

Additional problems occur from increasing protein content and the formation of methemoglobin which results in marked T1 shortening within the CSF-filled resection cavity [13, 14].

Methemoglobin derives from clots of fresh blood or hemorrhagic CSF within the area of extirpation. The early appearance of methemoglobin differs from the typical time course of hemoglobin degradation which may be related to the use of hydrogen peroxide (H_2O_2) for local hemostasis by the neurosurgeons.

Because the FLAIR technique is based on inversion recovery, the fluid within the resection cavity could only be completely suppressed if the relaxation time equals the chosen inversion time. With the presence of protein cell components and/or blood byproducts, the relaxation time of the CSF within the resection cavity is changed and FLAIR is unable to suppress this kind of fluid at the optimized inversion time. Therefore, the diagnostic utility of FLAIR imaging in the assessment of residual cerebral gliomas is significantly reduced. In theory, the suppression of the fluid within the resection cavities would be possible again if the inversion time is adapted to the changes in relaxation time. But since the combination of repetition time, echo time, and inversion time are such that a high sensitivity to T2 differences is obtained for non-CSF materials, the adaptation of the inversion time leads to a substantially reduced pathology-to-brain contrast [12]. Additionally, the detection and delineation of lesions at the border of unaffected CSF is worsened.

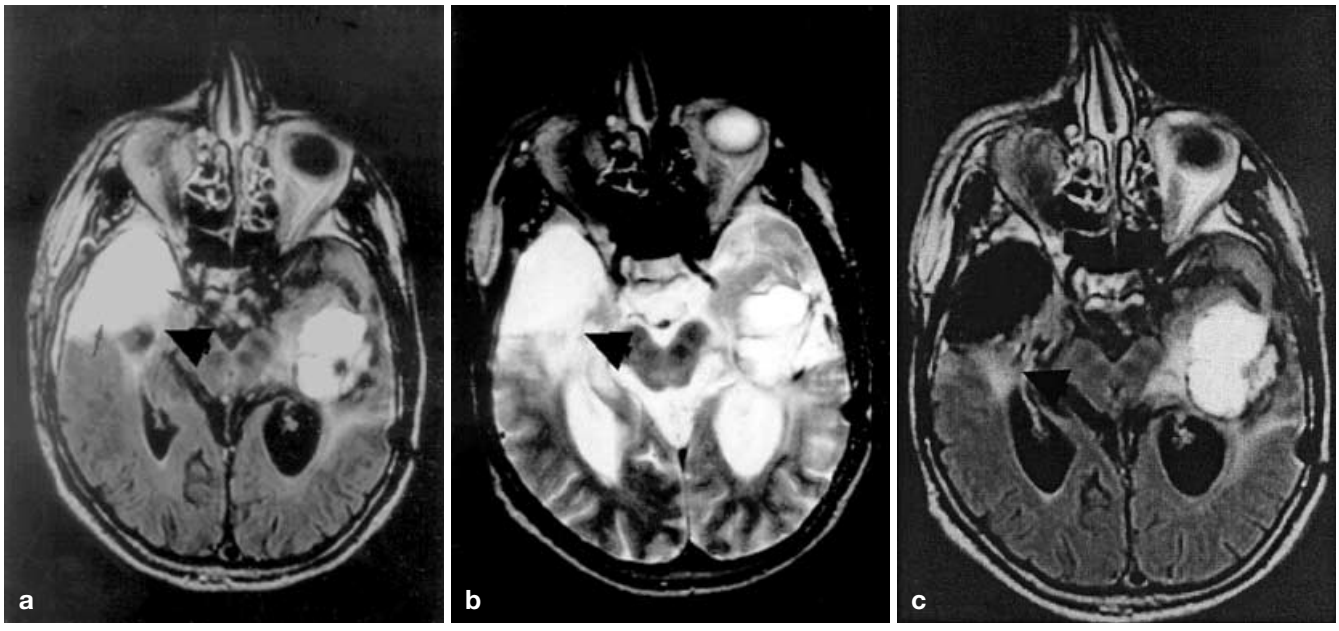

Fig. 3 **a** The FLAIR imaging and **b** T2-weighted SE imaging of a 38-year-old male patient 20 days after partial surgical resection of a low-grade oligoastrocytoma of the right temporal lobe and **c** FLAIR imaging in the same patient 12 months after the initial examination. On the FLAIR image (**a**) the fluid in the resection cavity *(arrows)* could not be completely suppressed at the chosen inversion time. The residual tumor could be better delineated than on the FSE images *(curved arrows)*, but could not be exactly differentiated from the border of the fluid-containing defect. On T2-weighted fast SE (**b**) the fluid revealed a higher signal than CSF indicating the presence of blood-degradation products or proteins within the surgical defect. A radiotherapeutically treated low-grade oligoastrocytoma is seen in the contralateral temporal lobe. Twelve months after the initial exam (**c**), the fluid in the surgical defect could now be completely suppressed and therefore the residual tumor *(curved arrow)* could clearly be differentiated from the surgical defect

Due to the presence of methemoglobin even in the first postoperative days [13], FLAIR might also have problems with the detection of residual tumor in early postoperative MR imaging. With the availability of intraoperative MR imaging the usefulness of FLAIR imaging in the intraoperative or very early postoperative stage has to be evaluated.

If the CSF within the resection cavity is cleared from proteins or blood-degradation products, FLAIR is again able to clearly delineate residual or recurrent tumor as seen in Fig. 3c.

As described in previous studies [8], image artifacts occurred more frequently on FLAIR than on conventional images, but the image interpretation was not influenced in any of the examined patients in our study. In artifact-sensitive regions, such as close to large vessels or at the skull base, we recommend use of an ECG-triggering to reduce artifacts from vessel pulsation.

Based on our preliminary findings in the reported cases, we conclude that FLAIR imaging may be a valuable adjunct in the diagnostic work-up of patients with residual pathologic tissue at the border of the resection cavity. However, in the early postoperative stage the method may be limited due to surgically induced signal changes and different protein or blood byproduct components within the CSF-filled surgical defect.

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