Increase in FLAIR Signal of the Fluid Within the Resection Cavity as Early Recurrence Marker: Also Valid for Brain Metastases?

FLAIR-Signalanstieg der Flüssigkeit in der Resektionshöhle als früher Rezidivparameter: auch gültig für Hirnmetastasen?

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ZUSAMMENFASSUNG

Ergebnisse 3 von 6 Fällen mit einem lokalen Tumorrezidiv zeigten einen FLAIR-Signalanstieg (Sensitivität 50.0 %, Spezifität 100.0 %). In einem Fall wurde dieses Zeichen sogar ca. 3 Monate vor Diagnose des Tumorrezidivs beobachtet. Die Spezifität für ein Tumorrezidiv (lokal und distant) lag ebenfalls bei 100,0 % mit einer jedoch niedrigeren Sensitivität (13,0 %). Die quantitativ Analyse zeigte signifikante Unterschiede der Signalintensität in der Resektionshöhle bei Patienten mit und ohne lokales Tumorrezidiv, ebenso für die Änderung der Signalintensität.
Schlussfolgerung Ein FLAIR-Signalanstieg der Flüssigkeit in der Resektionshöhle könnte auch bei zuvor operierten Hirnmetastasen ein spezifisches und frühes Zeichen für einen Tumorprogress / ein Tumorrezidiv sein.

Kernaussagen
- Ein FLAIR-Signalanstieg der Flüssigkeit in der Resektionshöhle wird nicht nur bei Gliomen, sondern auch bei Hirnmetastasen beobachtet
- Die Pathophysiologie dieses Zeichens könnte auf einen proliferativen Prozess zurückzuführen sein

ABSTRACT
Purpose Increase in FLAIR signal of the fluid within the resection cavity is described as a highly specific and early sign for tumor recurrence in gliomas. The aim of this study was to assess the prognostic value of FLAIR signal increase in partially or completely resected brain metastases.

Materials and Methods 209 cases of surgery for brain metastases were assessed. 41 cases with at least two follow-up MRIs were retrospectively included in this study. Quantitative and qualitative assessment of the FLAIR signal intensity of the fluid within the resection cavity was performed in the MRI examination at recurrent disease/ last contact and in the previous MRI examination.

Results 3 of 6 cases with local tumor recurrence showed a FLAIR signal increase (sensitivity 50.0 %, specificity 100.0 %). In one case, this sign was observed even about 3 months before tumor recurrence. The specificity of FLAIR signal increase for overall tumor recurrence (local and distant) was also 100.0 %, but with a lower sensitivity of 13.0 %. Quantitative analysis showed significant differences for signal intensity of the resection cavity as well as for the change of signal intensity of the resection cavity in cases with or without local tumor recurrence.

Conclusion An increase in FLAIR signal of the fluid within the resection cavity might be a highly specific and early sign of local tumor recurrence/tumor progression also for brain metastases.
**Introduction**

Brain metastases are the most common malignant brain tumors in adults. Especially breast cancer, lung cancer, melanoma and renal cell cancer are known to develop brain metastases [1, 2]. According to current guidelines, surgery is recommended for symptomatic and accessible brain metastases followed by whole-brain irradiation or stereotactic irradiation [3–6]. As surgery is a safe treatment according to a recent study, some risk factors such as location in an eloquent region or preoperative radiotherapy that may increase the risk of postoperative neurological deficits have to be considered preoperatively [7].

Magnetic resonance imaging (MRI) is used for surveillance of therapy and detection of tumor progression or tumor recurrence. Early detection of tumor recurrence/progression is important to adapt therapy regimes in a timely manner. Recent studies showed a signal increase in T2-weighted fluid attenuated inversion recovery (FLAIR) sequences of the fluid within the resection cavity as a specific and early sign for tumor recurrence/tumor progression in glioma patients [8–10]. To our knowledge, this has not yet been assessed for brain metastases.

Analogously to a previous study [8], the aim of this study was to analyze the prognostic value of a FLAIR signal increase in fluid within the resection cavity for tumor recurrence/tumor progression in patients with previously resected brain metastases.

**Methods**

**Patient population**

The local ethics committee (5626/12) approved this non-interventional single-center study. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki and its later amendments [11].

Data analysis was performed by a neuroradiologist (SB, 6 years of experience) analogously to the previous study [8]. Retrospective analysis of 204 patients with 209 consecutive surgeries for brain metastases (recurrent or primary disease) between December 2008 and December 2015 was performed. Patients with an early postoperative MRI examination and at least two follow-up MRI examinations were included. Patients with a shrunken resection cavity (smaller than the intended size for measurement of regions of interest (ROIs)) (n = 46), missing follow-up MRI scan (n = 111), infection in the resection cavity (n = 6), missing FLAIR images (n = 3), solid tumor in the resection cavity (n = 1) or blurred images (n = 1) were excluded. Therefore, 35 patients with 41 surgeries were included in the analysis. In two patients two different resection cavities (right and left hemisphere) and in one patient three different resection cavities (both hemispheres) were analyzed and assessed as two/three different cases. Surgery of brain metastases was performed with the aim of the maximum resection of the contrast-enhancing part of the tumor while sparing motor and language function. The extent of resection was assessed in the early postoperative MRI examination and defined as: complete resection (total resection of the contrast-enhancing part of the tumor), incomplete resection (residual contrast-enhancing tumor at the resection cavity) or complete resection in the resection cavity but residual distant metastases. The date of FLAIR signal intensity change, date of MRI examination at recurrent disease/follow-up, date of previous MRI, and date of surgery and previous radiotherapy were recorded. Tumor progression/tumor recurrence was defined according to the RANO criteria for brain metastases and in an interdisciplinary consensus (neuroradiology, neurosurgery, radiation oncology, nuclear medicine) [12]. The date of change in further treatment (e.g., surgery, radiotherapy) was defined as the date of tumor recurrence/tumor progression. Advanced imaging methods such as perfusion or (O-[2(18-F]-Fluorethyl)-L-Tyrosin-Positron Emission Tomography (PET-PET)) were used for the diagnosis of tumor progression or tumor recurrence in unclear cases. Tumor recurrence/tumor progression was classified as local (at the site of previous surgery) or distant (distant to the site of previous surgery) tumor recurrence/progression.

**Magnetic resonance imaging**

MRI scans were performed similarly to the previous study [8] either on a Philips Achieva (n = 12), Ingenia (n = 4) or Gyroscan (n = 3) (Philips Medical Systems, The Netherlands B.V.) or on a Siemens Verio (n = 12), Avanto (n = 6), Skyra (n = 1) or Symphony (n = 1), (Siemens Healthcare, Erlangen, Germany). On the Philips Achieva the following sequences were acquired: axial T2-weighted (w) FLAIR images (acquisition time 3:00 min, TR/TE of 12 000/140 ms, 0.45×0.45×4 mm spatial resolution) or T2w 3D FLAIR images (acquisition time 4:52 min, TR/TE of 4800/278 ms, 1.04×1.04×1.12 mm spatial resolution) as well as axial T1w fast field echo (FFE) images pre and post gadolinium T1w images (acquisition time: 2:53 min, TR/TE of 530/10 ms, 0.45×0.45×4 mm spatial resolution) or pre and post gadolinium MPRage images (acquisition time 5:55 min, TR/TE of 9/4 ms, 1mm³ isotropic spatial resolution). On the Siemens Verio axial T2w FLAIR images (acquisition time 3:44 min, TR/TE of 8560/136 ms, 0.8×0.7×4 mm spatial resolution) or T2w 3D FLAIR (acquisition time 5:52 min, TR/TE of 5000/395 ms, 1mm³ isotropic spatial resolution) and axial T1w images pre and post gadolinium (T1 inversion recovery, time of inversion 860 ms, acquisition time 4:02 min, TR/TE of 2000/9 ms, 0.9×0.7×4 mm spatial resolution) or MPRage (acquisition time 4:18 min, TR/TE of 1900/2.45 ms, 1.1×1.1×1 mm spatial resolution) were acquired. The contrast agent Magnograf® or Magne-
was administered intravenously (0.2 ml/kg, 0.5 – 1 ml/sec) using an MR-compatible contrast medium injection system (Spec-
tris Solaris EP, Siemens Medical, Erlangen, Germany). Axial or cor-
oral T2w FLAIR images were acquired in 26 cases, and 3Dw FLAIR
images in 15 cases.

Image analysis
Image analysis was also performed by a neuroradiologist (SB, 6
years of experience) as previously described, who was not blinded
to the patient data [8, 10]. A second rater (TBB, 10 years of experi-
ence) also assessed the MR images while blinded to the clinical
data. Interrater reliability for qualitative analysis was assessed
using Cohen’s kappa. The signal intensity in FLAIR images (classi-
fied as: normal signal intensity compared to cerebrospinal fluid
(CSF) or elevated signal intensity) was assessed at the date of rec-
current disease/last MRI. For qualitative analysis the signal intensi-
ty was compared to the previous MRI scan and classified as in-
crease/decrease or no change. Analysis was not performed in the
early postoperative MRI examination (< 72 hours after surgery) to
avoid bias due to postoperative hemorrhage. The connection of
the resection cavity to CSF was classified as visible open connec-
tion/no visible open connection. The date of signal intensity
change (increase or decrease) was recorded.

Quantitative analysis was also performed as previously de-
scribed [8, 10]. Signal intensity was assessed in the MRI examina-
tion with recurrent disease/last contact and in the previous MRI
examination via regions of interest (ROIs) with a size of 5 –
10 mm that were drawn in the resection cavity (1), extracranially
(2) to avoid background noise and in the CSF to avoid bias due to
measurement on different scanners (3) (Fig. 1). ROI ratios of 1/
2 and 1/3 were calculated. Differences in signal intensity were cal-
culated for ROIs measured in the resection cavity (ROI 1) as well as
for ROI ratios 1/2 and 1/3 and then again classified as increase/de-
crease or no change.

Statistical analysis
Statistical analysis including descriptive data analysis was per-
formed using IBM SPSS Statistics version 23.0 (SPSS Inc., IBM
Corp., Armonk, NY, USA). Normally distributed data are shown
as mean (+/− standard deviation). Non-normally distributed data
are shown as median (interquartile range (IR)). For comparison
between two independent groups, the Mann-Whitney U Test
was performed. Specificity and sensitivity were calculated. A p-
value <.05 was defined as significant.

Results
Patient and tumor characteristics (Table 1)
41 cases (20 male, 21 female, mean age at date of surgery 57y)
with the diagnosis of a brain metastasis and neurosurgical resec-
tion were retrospectively included in this study. Complete tumor
resection was achieved in 24/41 cases. In 8/41 cases local com-
plete tumor resection was achieved, but other metastases were
present. 36/41 patients received radiotherapy after surgery dur-
ing follow-up. Histopathological analysis revealed brain metasta-
ses of lung cancer (n = 5), breast cancer (n = 13), melanoma
(n = 2), gastrointestinal cancer (n = 6), renal cell/urothelial cancer
(n = 6), sarcoma (n = 2), germ cell cancer (n = 3) and other cancers
(n = 4). Table 1 lists the histological entities of the brain meta-
tases.
23/41 cases presented with recurrent disease during follow-
up. 6 cases showed local tumor recurrence. 17 cases showed dis-
tant tumor recurrence only. The median time of the observation
period was 462 days (IR 259 – 994 days). Recurrent disease was
proven by MR imaging according to the RANO criteria in 16 cases
or by additional advanced imaging methods (including FET-PET)
in 1 case. 5 patients received further surgery for recurrent disease,
and tumor cells were found in the CSF in 1 patient. Local recurrent
disease was proven histopathologically in 2/6 cases by another
surgery, in one case by proof of tumor cells in the CSF, in one
case by advanced imaging methods (FET-PET) and in two cases
by progression of the residual tumor.

Qualitative analysis (Table 2, 3, Fig. 2, 3)
Interrater reliability revealed excellent agreement between the
two raters (Cohen’s kappa = 1). A change of FLAIR signal intensity
of the fluid within the resection cavity was observed in 10/41
(24.4 %) cases. An increase in FLAIR signal intensity was recorded
in 3/41 (7.3 %) cases, while a decrease was recorded in 7/41
(17.1 %) cases. 3/23 (13.0 %) cases with recurrent (local and dis-
tant) disease showed a signal increase, whereas 3/6 (50.0 %) cases
with local recurrent disease showed a signal increase (gastrointestinal cancer (n = 1), germ cell cancer (n = 1), sarcoma (n = 1)). All patients with an increase in signal intensity of the resection cavity showed local tumor recurrence resulting in a specificity of 100.0 % (95 % confidence interval (CI) 90.0 – 100.0 %) and a sensitivity of 13.0 % (95 % CI 2.8 – 33.6 %) of FLAIR signal increase for tumor recurrence and a specificity of 100.0 % (95 % CI 90.0 – 100.0 %) and a sensitivity of 50.0 % (95 % CI 11.8 – 88.2 %) for local tumor recurrence. None of the patients with distant tumor recurrence only showed a signal increase in the resection cavity. 2 cases showed a change in signal intensity at the date of recurrent disease. In one case a signal intensity increase was observed 122 days before the date of recurrent disease. All three cases with an increase in signal intensity of the fluid within the resection cavity showed no connection to the cerebrospinal fluid and had undergone previous radiotherapy. 2 of the 3 cases with a signal intensity increase had previous incomplete tumor resection, and 1 case had complete tumor resection.

Quantitative analysis (▶ Table 3)
Significantly higher values of signal intensity in the resection cavity were observed in cases with local recurrent disease than in cases without recurrent disease (292.0 [112.3 – 646.5] vs. 38.0 [24.0 – 135.0], P = 0.004) and for the change in signal intensity in
the resection cavity (76.5 [−12.5 – 428.0] vs. −12.0 [−87.0 – 16.0], P = 0.031) (Fig. 4). No differences were observed for signal intensity values in the resection cavity in cases with or without overall tumor recurrence (41.0 [24.0 – 224.0] vs. 53.5 [29.8 – 171.8], P = 0.958). Similar results are shown for the ratios ROI1/2 and ROI1/3, ▶Table 4 (online).

Quantitative assessment of FLAIR signal increase showed a sensitivity and specificity of 56.5 % (95 % CI 34.5 – 76.8 %) and 61.1 % (95 % CI 35.8 – 82.7 %), respectively, for tumor recurrence and a sensitivity and specificity of 83.3 % (95 % CI 35.9 – 99.6 %) and 57.1 % (95 % CI 39.4 – 73.7 %), respectively, for local tumor recurrence.

Discussion
An increase in FLAIR signal intensity of the fluid within the resection cavity might be an early and highly specific sign of local tumor recurrence for patients with brain metastases. Accordingly, this sign is not glioma-specific, but specific for cell-proliferative processes revealing more information about the pathophysiology of FLAIR signal increase.

Previous studies showed that an increase in FLAIR signal of the fluid within the resection cavity occurs in partially and completely resected glioma and is a specific sign for tumor recurrence and tumor progression [8 – 10]. However, the pathophysiology of this sign still remains unclear. The previous studies postulated that FLAIR signal increase might occur due to an encapsulation of the resection cavity by tumor cells leading to higher protein concentration. This hypothesis is also confirmed by the fact that this sign
mainly occurs in cases without an open connection of the resection cavity to the CSF. In these cases exchange of CSF is not possible, leading to higher protein concentration and hindering wash-out of the protein [8, 10]. Also in this study a FLAIR signal increase was only observed in cases without an open connection to the CSF, thus supporting this hypothesis.

A FLAIR signal increase is observed as a specific sign for local tumor recurrence, but not for distant tumor recurrence in brain metastases as was expected according to the potential pathophysiology. Moreover, this strengthens the hypothesis of the potential described pathomechanism. As a FLAIR signal increase is also observed in brain metastases and not only in gliomas, the conclusion can be drawn that this sign is not glioma-specific, but also occurs in other cell-proliferative diseases. This fact also supports the hypothesis that encapsulation of the resection cavity by tumor cells is the possible pathophysiology of the signal increase. However, this is still a theory and studies with analysis of the fluid composition will have to be performed to investigate the exact pathomechanisms of the signal increase.

The previous study showed that a FLAIR signal increase can occur in partially and completely resected and in irradiated and only rarely in non-irradiated gliomas [8]. In this study a signal increase was observed in both completely and partially resected brain metastases, but only in irradiated metastases. However, as a FLAIR signal increase was only observed in two completely and one partially resected as well as in three irradiated brain metastases in this study, the validity of this sign for subgroups is too low. Further studies with larger patient cohorts will have to be performed. Furthermore, the delineation between complete and partial tumor resection remains challenging in malignant brain tumors – both in gliomas and in brain metastases – as the exact borders of the tumor are hard to define [13, 14].

Hemorrhage as well as infarction with a subsequently disrupted blood barrier are described as showing a FLAIR signal increase and may represent a pitfall in the application of this sign for tumor recurrence/tumor progression [15, 16]. Hemorrhage as a confounding factor of FLAIR hyperintensity was discussed in the previous studies [8, 10]. As bleeding is a rare complication in glioma [17, 18], it is observed more often in brain metastases, especially in brain metastases of melanoma or renal cancer [1]. In our study bleeding was mainly observed in the early postoperative MRI examination (<72 hours after surgery) and not during follow-up. Therefore, only cases with at least two follow-up MRI scans after the early postoperative MRI scan were included in order to avoid this bias. To avoid misinterpretation due to bleeding in the resection cavity, T1-weighted images without contrast agent are important for differentiation and are also routinely used in brain tumor imaging [19]. Moreover, postoperative infarction is observed after surgery of brain metastases and may cause a bias of the FLAIR signal increase [20]. However, vasogenic edema due to infarction is observed mainly in the first days after surgery and these images were excluded from analysis.

In addition to hemorrhage and infarction, infection might present another pitfall in the evaluation of the FLAIR signal intensity of the resection cavity as discussed previously [8]. Intracranial infection is known to show a higher protein concentration and subsequently a higher FLAIR signal intensity [21]. In our study patients with infection in the resection cavity were excluded from analysis.

Fig. 3 Case of a patient with previous incomplete resection of ovarian cancer brain metastasis. FLAIR images during follow-up B show an increase in signal intensity in the resection cavity. Progressive contrast enhancement was observed surrounding the resection cavity D.

Fig. 4 Box plots for signal intensity values in the resection cavity A and for the change of signal intensity in the resection cavity C in cases with and without recurrent disease and in cases with or without local tumor recurrence B, D respectively. *P<0.05.
to avoid this bias. However, in the clinical routine diffusion-weighted imaging, which is routinely used in brain tumor imaging, can help to differentiate a FLAIR signal increase due to infection from a FLAIR signal increase due to tumor progression/tumor recurrence [22, 23].

Comparing this method to other advanced imaging methods such as perfusion-weighted imaging and PET imaging, the sensitivity of 50.0% is low, thus making this sign unsuitable for screening [24–29]. However, the high specificity is of significant importance in the clinical routine. FLAIR images are included in the standard imaging protocol of brain tumors. No other imaging methods have to be used.

The main limitations of this study are its retrospective design and the low patient number, especially the low number of patients with a FLAIR signal increase and local tumor recurrence. However, in this study we assessed 204 patients. Due to missing follow-up or shrinking of the resection cavity, many cases could not be included for further analysis. This might be explained by the poor prognosis of patients with brain metastases as well as by early tumor recurrence/tumor progression despite therapy in many cases (depending on the histopathological subtype) [5]. Also the number of cases of local tumor recurrence especially after local radiotherapy to the resection bed is low compared to the risk of distant tumor recurrence/progression [30]. Furthermore, a separate analysis for different histopathological subtypes of brain metastases might be useful to estimate the value of this sign for each primary tumor. However, due to the low number of patients developing this sign (n = 3), this calculation is not possible and might be a subject for further studies.

Another limitation is the analysis of data from different MR scanners and different sequences which might introduce an unavoidable bias. To reduce this bias, the ratio of the FLAIR signal intensity in the resection cavity compared to the CSF was calculated as previously described and showed similar results [10]. However, to solve this problem, further studies with images from a single MR scanner with the same FLAIR sequence should be performed.

Another limitation might arise due to the sometimes quite difficult differentiation between tumor progression and pseudoprogression in brain metastases [28, 31, 32]. For gliomas, PET and perfusion imaging are important for differentiation. For brain metastases, the data are limited, and progression is defined according to the RANO criteria for brain metastases [12, 24, 26, 27, 33, 34]. In this study, recurrent tumor was proven histopathologically in 3 of 6 cases with local recurrence. The other 3 cases were either proven by advanced imaging methods (PET) or progressive residual tumor.

**Clinical Relevance of This Study**
- An increase in FLAIR signal intensity of the fluid within the resection cavity might be a highly specific and early sign for local tumor recurrence/progression also for brain metastases, suggesting that this sign is not glioma-specific, but specific for cell-proliferative processes.
- As FLAIR images are included in the standard imaging protocol in brain tumor imaging, this sign might help in the diagnosis of tumor recurrence or tumor progression in completely or partially resected brain metastases.
- Studies with larger patient cohorts should be performed to confirm the results of this study.

**Abbreviations**
- FLAIR fluid attenuated inversion recovery
- MPRage magnetization prepared rapid gradient echo
- MRI magnetic resonance imaging
- IR interquartile range
- SI signal intensity
- NPV negative predictive value
- PPV positive predictive value
- CSF cerebrospinal fluid
- CI confidence interval

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**Conflict of interest**

SB, JG, TH and BM work as consultants for Brainlab AG (Feldkirchen, Germany). CZ has served on scientific advisory boards for Philips and Bayer Schering; serves as co-editor on the Advisory Board of Clinical Neuroradiology; has received speaker honoraria from Bayer-Schering and Philips and has received research support and investigator fees for clinical studies from Biogen Idec, Quintiles, MSD Sharp & Dome, Boehringer Ingelheim, Inventive Health Clinical UK Ltd., Advance Cor, Brainsgate, Pfizer, Bayer-Schering, Novartis, Roche, Servier, Penumbra, WCT GmbH, Syn-gis, SSS International Clinical Research, PPD Germany GmbH, Worldwide Clinical Trials Ltd., Pheno, Covi-dien, Actelion, Medivation, Medtronic, Harrison Clinical Research, Concentric, Penumbra, Phar-trace, Reverse Medical Corp., Premier Research Germany Ltd., Surpass Medical Ltd. and GlaxoSmithKline. All named potential conflicts of interest are unrelated to this study.
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