# The value of two-dimensional gradient echo imaging (2D-GRE) and susceptibility weighted imaging (SWI) in the assessment of hemorrhagic lesions in diffuse brainstem gliomas treated with radiation and antiangiogenic therapy

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Purpose: Two-dimensional gradient echo (2D-GRE) imaging and susceptibility-weighted imaging (SWI) [1] are robust magnetic resonance imaging (MRI) techniques that enhance visualization of magnetically susceptible substances in biological specimens, e.g. hemorrhage (paramagnetic) or calcification (diamagnetic) in the brain parenchyma [2]. The recent introduction of angiogenesis inhibitors into treatment for children with brain tumors has raised concerns about the potentially increased risk of intratumoral hemorrhagic complications, a major exclusionary condition for antiangiogenic treatment [3,4]. Therefore, the aim of our study was to estimate incidence rate and temporal evolution of intralesional hemorrhages in children with diffuse pontine glioma who received combined conformal radiation and antiangiogenic treatment. Furthermore, we compared 2D-GRE and SWI for their diagnostic accuracy in detecting hemorrhages and differentiating them from calcifications.

Patient/Methods: Seventeen children (9 females, 8 males; age 3–17 years) were recruited from an ongoing IRB-approved phase I study of the angiogenesis inhibitor vandetanib administered concurrently with six weeks of conformal radiation therapy. Patients had baseline MRI scans and up to 8 follow-ups over a maximum of 10 months, making 92 scans available for analysis. MRI studies were performed under general anesthesia on 1.5/3T (Avanto/Trio, Siemens) platforms and included 2D-GRE and 3D-SWI in addition to anatomical and advanced imaging (**Table 1**). 2D-GRE and SWI images were randomized and scored independently by 2 reviewers. Lesions were presumed to be hemorrhagic if they presented with a hyposignal on magnitude 2D-GRE and SWI and a hyperintense center with hypointense rim on corresponding phase images [5] (**Fig. 1**). Lesion size and image quality were also systematically evaluated [6]. Both reviewers then reanalyzed the presumed hemorrhagic lesions, using 2D-GRE and SWI simultaneously to identify intra-observer discrepancies and resolve misinterpretations. Resulting data were analyzed using descriptive statistics and graphical tools. Both MRI methods and the evaluations from each reviewer were analyzed with Poisson Regression Mixed Effects Models.

2D-GRE magnitude / phase — SWI magnitude — SWI phase — SWI image — SWI minIP
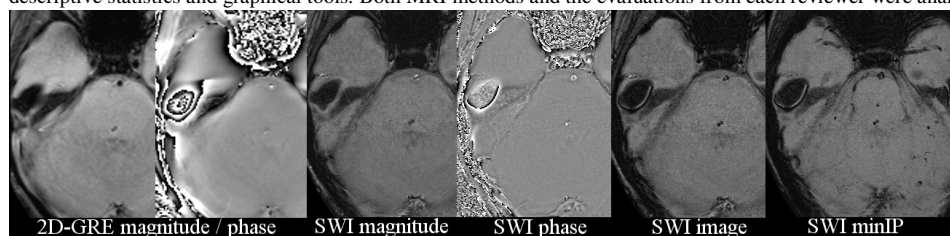
Sequence	1.5T		3.0T	
Parameter	T2*	SWI	T2*	SWI
TR/TE [ms]	1500/33.3	54/40	565/25	56/25
Matrix	256×192	338×384	256×192	338×384
FOV	210×157	138×158	210×157	138×158
Gap [mm]	4	n/a	4.8	n/a

Table 1: MRI imaging parameters

Fig.1: 2D-GRE and SWI images used for data analysis.

Results: Intralesional hemorrhages seem common in patients with brainstem glioma, and in our series their incidence rate was 47% (±12.5). Interobserver variations for the number of lesions were not significant (p_{2D-GRE}=0.11,p_{SWI}=0.75). The number of hemorrhages increased under treatment during the course of the disease; cumulative incidences were 85.9±10.4% (at 4 months) and 92.9±8.8% (at 6–12 months). Lesion diameters ranged from 0.16 to 2.66 cm and 0.10 to 2.56 cm, with only 9.67% and 5.22% of lesions larger than 0.5 cm on 2D-GRE and SWI, respectively. More hemorrhagic lesions were visible on SWI in 40 cases for Reviewer 1 (p=0.02) and in 42 cases for Reviewer 2 (p=0.0006). Conjoint re-evaluation of cases of mismatch between 2D-GRE imaging and SWI findings revealed that on 35 (Reviewer 1) and 36 (Reviewer 2) scans the lesion was missed or a vessel, necrotic area, calcification, or imaging artifact was misinterpreted on 2D-GRE compared with only 7 (Reviewer 1) and 2 (Reviewer 2) on SWI. Image quality was generally poorer for 2D-GRE. Artifacts hampered correct interpretation in 65 cases for 2D-GRE and 21 for SWI, which might explain the more frequent misinterpretations on 2D-GRE, especially at the pontomedullary junction and within the substantia nigra (**Fig. 2a**). Another drawback in interpreting images by 2D-GRE was that calcification and necrotic areas could not be clearly differentiated from hemorrhage. As seen in **Fig. 2b**, 2D-GRE magnitude and phase images show signal characteristics suggesting intratumoral hemorrhage (see **Fig. 1**), whereas phase images from SWI reveal hypointensity consistent with calcification. In another example, a hypointensity could be mistaken for a hemorrhage on 2D-GRE, but SWI shows no hypersignal on the corresponding phase image (**Fig. 2c**), which is more consistent with conventional imaging findings of an area of intratumoral necrosis. No significant neurological event was recorded in our patients during the follow-up periods, regardless of the number and size of intratumoral hemorrhages.
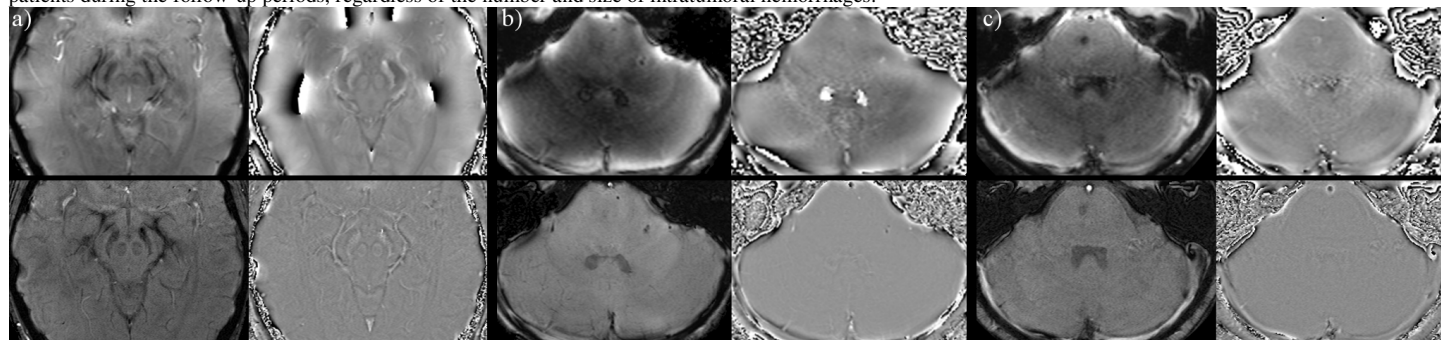

Fig. 2: Misinterpretations in 2D-GRE included a lesion missed within the left substantia nigra (a), a calcification (left middle cerebellar peduncle) (b), and a necrotic area with marginal hemorrhagic effusion misread as hemorrhage (c). 2D-GRE (top row) and corresponding SWI (bottom row) magnitude and phase images.

Conclusion: Punctate hemorrhagic lesions are common in patients with brainstem glioma and their number increases during treatment with conformal radiation and vandetanib. Conversely, large hematomas (>0.5 cm) are rare, explaining the lack of significant adverse clinical/neurological correlates. The effect that two or more small adjacent lesions appear as one large lesion seems more common with 2D-GRE than SWI because of the inherently higher spatial resolution of 3D-SWI [7]. Both techniques benefit from the availability of phase images, which facilitate the differentiation of hemorrhages from calcification. We found that SWI detects more hemorrhages and is more accurate in differentiating those from calcifications as well as other sources of misinterpretation such as intratumoral vessels, necrotic areas, or pulsation artifacts. Overall, image analysis and interpretation are more accurate with SWI as fewer lesions are missed or misinterpreted. We expect that SWI will most likely replace conventional 2D-GRE imaging as SWI becomes increasingly available in routine clinical practice. SWI will also become the new gold standard to image magnetically susceptible substances, including blood degradation products or calcification within brain tumors. Our work contributes to a better understanding of the strength and shortcomings of SWI. The more direct importance of our study relates to the ability of 3D-SWI to more confidently identify petechial hemorrhages and hence reduce the number of patients excluded from novel therapeutic protocols using antiangiogenic drugs for concerns of therapy-related hemorrhagic complications.

References: [1] Reichenbach J.R. and Haacke E.M. (2001) *NMR Biomed* 14:452-467; [2] Tong K.A. et al. (2008) *Am J Neuroradiol* 29: 9-17; [3] Pollack I.F. et al. (2007) *Neuro Oncol* 9:145-160; [4] Pope W. et al. (2006) *Neurology* 66:1258-1260; [5] Deistung A. et al. (2006) *Z Med Phys* 16:261-267; [6] Seghal V. et al. (2006) *J Magn Reson Imag* 24:41-51; [7] Tong K.A. et al. (2004) *Ann Neurol* 56, 36-50.