

# Susceptibility-Weighted Imaging in Grading of Infiltrative Glial Tumors

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## ABSTRACT

**Purpose:** Histopathological and radiological examination is necessary for the evaluation of tumor types and staging. Histopathologic examination is considered as the gold standard, while the radiological examination is used for preoperative evaluation. The purpose of the present study was to evaluate susceptibility-weighted imaging (SWI) in the grading of infiltrative glial tumors.

**Materials and Methods:** The SWI sequences in pre-operative magnetic resonance imaging (MRI) images were retrospectively assessed in a total of 67 patients (mean age, 36.7 years; age range, 4–79 years; 29 female, 38 male) who were diagnosed with a glial tumor based on histopathological examination. The numbers of punctate intratumoral susceptibility sign (ITSS) in the SWI sequence in the tumors were determined by two radiologists on a consensus-based approach. Lesions with no ITSS were graded as Grade 0, while those having 1–5, 6–15, >15 ITSS were categorized as Grade 1, Grade 2, and Grade 3, respectively. No susceptibility was classified as ITSS, “non-punctate with blurred margins” and diffuse susceptibility were categorized as >15. ITSS grades were compared to the results of histopathological grading and diagnosis.

**Results:** The sensitivity, specificity, negative predictive value, and positive predictive value of the presence of ITSS regarding differentiating high and low-grade glial tumors were 97.6%, 88%, 95.65%, and 93.18%, respectively.

**Conclusion:** In diffuse glial tumors, while the presence of ITSS is indicative of high-grade tumors, its absence is associated with low-grade tumors. These data suggest that the presence rather than the number of ITSS yields more information on the grade of this type of tumor.

**Keywords:** Glial tumor, susceptibility-weighted imaging (SWI)

## İNFİLTRATİF GLİAL TÜMÖR EVRELEMESİNDE SUSCEPTİBİLY AĞIRLIKLI GÖRÜNTÜLEME

### ÖZET

**Amaç:** Tümör tipleri ve evrelendirme için histopatolojik ve radyolojik inceleme gereklidir. Histopatolojik inceleme altın standart olarak kabul edilirken, preoperatif değerlendirme için radyolojik inceleme kullanılır. Bu çalışmanın amacı infiltratif glial tümörlerin evrelemesinde susceptibility ağırlıklı görüntülemenin (SWI) değerlendirilmesidir.

**Materyal ve Metot:** Patolojik olarak glial tümör tanısı konmuş 67 hastanın (4–79 yaş, yaş ortalaması 36,7; 29 kadın ve 38 erkek) retrospektif olarak preoperatif MRG görüntülemelerindeki SWI sekansları değerlendirilmiştir. Tüm tümörlerin SWI sekansında izlenen punctat ITSS (intratumoral susceptibility sign) sayıları iki radyolog tarafından konsensusla patolojik tanıları bilinmeden kör olarak hesaplanmıştır. Hiç ITSS içermeyen lezyonlar ITSS Evre 0, 1–5 ITSS içeren lezyonlar ITSS Evre 1, 6–15 ITSS içeren lezyonlar ITSS Evre 2, 15<ITSS içeren lezyonlar ITSS Evre 3 olarak sınıflandırılmıştır. ITSS olarak izlenmeyen, “punctat olmayan sınırları belirsiz” ve yoğun olarak izlenen ‘susceptibility’lerin sayısı ‘15<’ olarak kabul edilmiştir. ITSS evreleri ile histopatolojik evreler ve tanıları karşılaştırılmıştır.

**Bulgular:** ITSS varlığının yüksek ve düşük glial tümörleri ayırt etmesinin duyarlılığı %97,6, özgüllüğü %88, negatif prediktif değeri %95,65, pozitif prediktif değeri ise %93,18 olarak hesaplanmıştır.

**Sonuç:** Glial tümörlerde ITSS varlığı yüksek evreli tümörlere, ITSS yokluğu ise düşük evreli tümörlere işaret etmektedir. Mevcut veriler doğrultusunda ITSS derecesinden ziyade ITSS mevcudiyetinin daha etkili olduğu görülmüştür.

**Anahtar sözcükler:** Glial tümör, SWI

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Cerebral gliomas represent the most frequent type of primary brain tumors, comprising 40–67% of all primary brain neoplasia with an incidence of 5–10/100,000 (1). The World Health Organization (WHO) first published the classification of central nervous system tumors in 1979 and revised in 1993, 2000 and 2007. In the WHO 2007 classification, major neuroepithelial tumors were defined as astrocytes, oligodendroglial tumors and oligoastrocytomas (2). Classification of tumors is crucial in establishing a treatment plan, and imaging-assisted diagnosis provides a complete differential diagnosis, staging, and distinction of glial tumors from non-neoplastic lesions and metastases (3). In this respect, standard x-rays and computed tomography can be used in the diagnostic process. Furthermore, magnetic resonance imaging (MRI) is usually more useful than detailed information about tumor type, stage, position, and size (1). However, none of these imaging systems can provide sufficient information for an accurate diagnosis.

Histological staging is the indicator of the biological behavior of the tumor which helps to determine the treatment and prognosis of the tumors to be staged (4). Although pathologists determine the tumor type and stage precisely, determination of the tumor type before surgery might be beneficial in the treatment process (5, 6). Morphologic criteria such as heterogeneity, size, post-contrast signal behavior, edema, mass effect, and cystic and necrotic degeneration contents are used in the cloning of glial tumors in conventional MRI. Also, advanced imaging techniques such as MR perfusion, MR spectroscopy, dynamic contrast T1, DTI, and susceptibility weighted imaging (SWI) can be used for staging (3, 4).

As a relatively novel method, SWI is a tissue contrast developed by Haacke et al. (7). SWI is a 3D high-resolution gradient echo sequence that uses both phase images and magnitude images which also contains a reconstruction of the minIP and MPR techniques with 3–10 mm images with high sensitivity to the blood, iron, and calcification in the tissue which builds-up susceptibility. Signal intensity in SWI is influenced by factors such as hematocrit, a deoxyhemoglobin concentration, erythrocyte integration, clot structure, molecular diffusion, pH, heat, voxel size, contrast material, blood flow, and vessel orientation (8). High-grade gliomas are associated with an increase in relative deoxyhemoglobin due to angiogenesis and increased tumor blood supply causing a signal loss due to susceptibility effect. As a relatively new imaging system, 3D SWI is very sensitive to blood oxygen binding capacity and local magnetic susceptibility showing microvascular structures as well as extravascular blood products. As another factor

might compromise the differential tumor grade and stage diagnosis, calcification might be difficult to be detected by conventional MRI. The phase component of the SWI sequence can be used for recognizing calcification, which cannot be separated from the hemorrhage by GRE (9).

High-grade gliomas are characterized by a relative increase in deoxyhemoglobin concentrations due to angiogenesis and increased vascularization of the tumor leading to a signal loss due to a susceptibility effect in SWI (10). Conventional pre-operative imaging of the tumors might not provide enough information regarding cellularity, nuclear atypia, mitotic activity, vascularity, and necrosis which are all considered to be important factors in tumor diagnosis (2, 5, 6). Furthermore, grading is the most important factor in the treatment option and the prognosis of the patient (6). However, previous studies and existing MR imaging systems may not be useful in treatment and tumor staging before surgery (3, 4). Therefore, SWI might be used for grading of brain tumors (9). Based on these facts, the purpose of the present study was to compare SWI as a novel imaging system to the conventional imaging technique in the grading of infiltrative glial tumors.

## Methods

### *Patient selection*

The study population consisted of 67 patients (age range 4–79, mean age 36.7, 29 male and 38 female) admitted to our hospital between the years 2012–2014. The study protocol was approved by the Local Medical Ethics Committee (with approval number: Atadek-2016/8). Patients undergoing conventional MRI and SWI sequence imaging between 1st January 2012 and 1st May 2014 were retrospectively screened. Informed consent from all participants was obtained. Patients with glial tumors were included if they had no medical or surgical interventions performed for the tumor before MRI.

Patients with no preoperative medical records, SWI images or a histopathological diagnosis based on WHO 2007 classification, patients having medical records of the period before biopsy or radiotherapy, patients with previous surgery or therapy, patients with major bleeding in conventional imaging or patients who were diagnosed in another medical center were excluded.

### *The devices and technical parameters*

Siemens Espree 1.5 T and Siemens Trio 3T devices were used for screening. In 3T MRI a 32-canal and 1.5 MRI an 8-canal head coil is utilized. The following parameters have been utilized for SWI:

For 1.5 T; TR: 49 ms, TE: 40 ms, Voxel size: 1.1×0.9×2 mm, SNR: 1, cross-sections: 2 mm, Base resolution: 256, flip angle: 15°, FOV phase: 230 mm, image matrix: 177×256, time: 3.59'min.

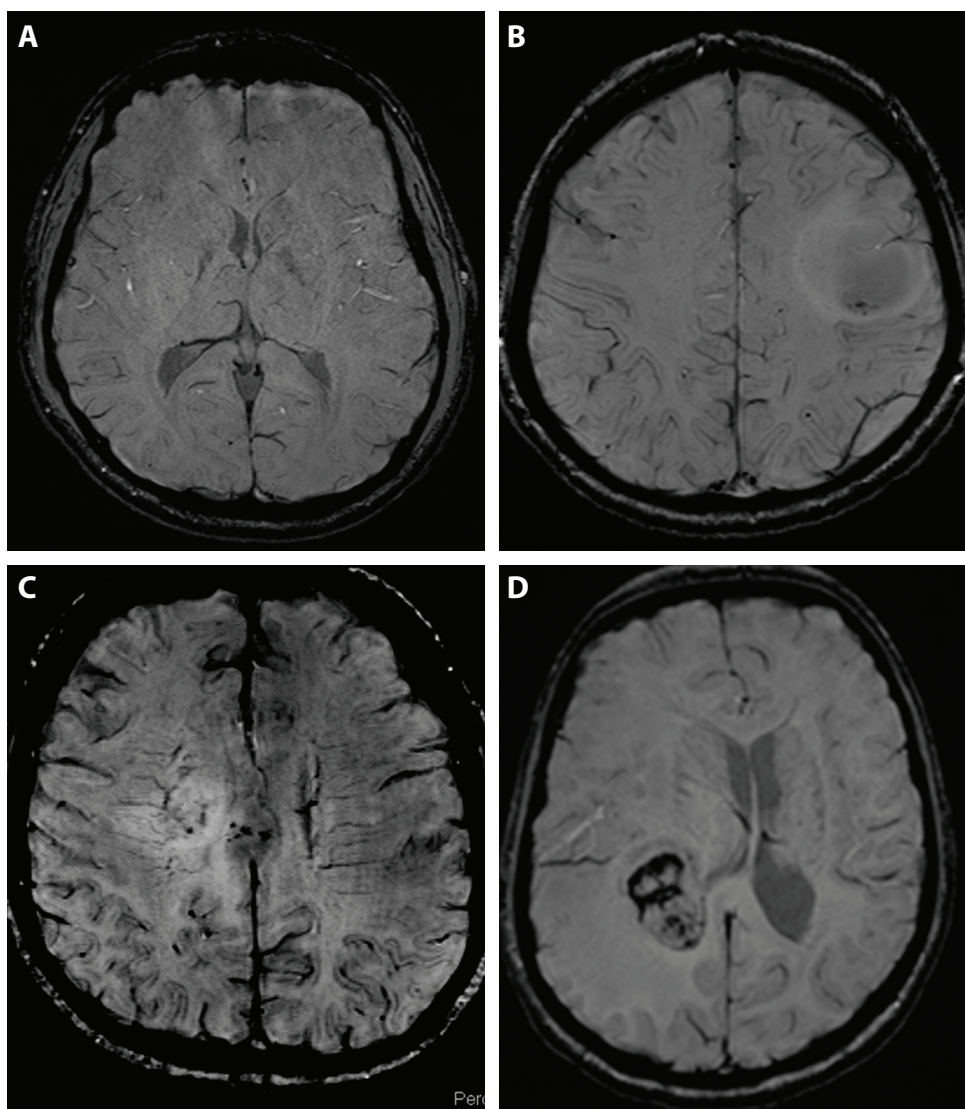
For 3 T; TR: 28 ms, TE: 20 ms, Voxel size: 0.8×0.7×1.6 mm, SNR: 1, cross-sections: 1.6 mm, Base resolution: 320, flip angle: 15°, FOV phase: 186.9 mm, image matrix: 247×320, time: 3.01'min.

#### *Histopathological assessment*

The histopathologic diagnosis and grading of the tumors were established by an experienced neuropathologist using immunochemical analyses.

#### *Radiological assessment*

The number of punctate ITSS observed in SWI sequences of all tumors was calculated in consensus by two radiologists who were blinded to the pathological diagnoses. The classification was performed based on the number of ITSS that was not considered the hypo-intensities produced by linear vascular structure continuity of which could be observed. Lesions with no ITSS were classified as grade 0 lesions (Figure 1a), while those with 1 to 5, 6 to 15, and 15<ITSS were classified as grade 1 (Figure 1b), grade 2 (Figure 1 c), and grade 3 (Figure 1 d), respectively. For susceptibilities with no ITSS, "poorly defined non-punctate" susceptibilities, and intense susceptibilities, an ITSS number of 15< was adopted. The ITSS grading was compared to histopathological grades.



**Figure 1. A–D.** Representative images of the ITSS grades 0, 1, 2, and 3. Lesions with no ITSS were classified as grade 0 lesions (A), while those with 1 to 5, 6 to 15, and 15<ITSS were classified as grade 1 (B), grade 2 (C), and grade 3 (D).

## Results

Among the 67 participants in the present study, 30 (44.7%) had grade 4 diseases, 12 (17.9%) had grade 3 diseases, and 25 (37.3%) had grade 2 diseases. Grade 1 tumors were not included as these were non-infiltrative.

ITSS was present in all histopathological Grade 4 tumors. Among the histopathologically diagnosed grade 4 tumors, 73.3% had ITSS Grade 3, 23.3% had ITSS Grade 2, and 3.3% had ITSS grade 1.

There was only one patient who had histopathological grade 3 and ITSS grade 0 (Table 1, Figure 2).

In 88% of histopathological grade 2 tumors, the ITSS Grade was 0. In the remaining cases, 4% had ITSS Grade 1, 8% had ITSS grade 2.

Of the 23 lesions with no ITSS (i. e., ITSS Grade 0), 95.6% had Grade 2 gliomas, histopathologically, while the remaining one patient had Grade 3 glioma.

Of the 26 patients with ITSS Grade 3 lesions, 84.6% had Grade 4 disease histopathologically, while 15.4% had Grade 3 disease histopathologically (Table 2, Figure 3).

The average number of ITSS among 25 low-grade tumors was 1.2. There was a high number of patients with ITSSs precluding estimation. Therefore, the average number of ITSS in high-grade tumors could not be determined (Table 3).

The sensitivity, specificity, negative predictive value, and positive predictive value of the presence of ITSS between high and low-grade glial tumors were 97.6%, 88%, 95.65%, and 93.18%, respectively.

The majority of the tumors with a histopathological grade 4 had ITSS grade 3, and these lesions had varying numbers of ITSS.

Although varying numbers of ITSS were detected in tumors with a histopathological grade of 3, one patient had no ITSS.

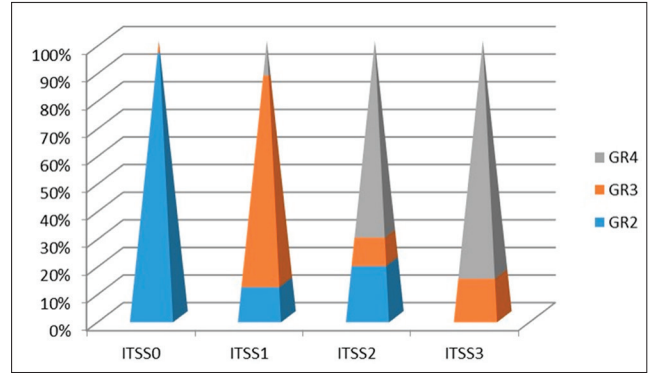
Regarding histopathological grade 2 tumors, 88% of the tumors had no ITSS and none of the lesions had ITSS grade 3, indicating that ITSS Grade 3 lesions are specific for tumors with a high grade.

Also, one patient had no ITSS despite the high grade of the lesion, and three patients had ITSS despite the low grade of the lesion.

**Table 1.** The distribution of histopathological and ITSS grades

	ITSS0	ITSS1	ITSS2	ITSS3
GR2	22	1	2	0
GR3	1	6	1	4
GR4	0	1	7	22

GR: Grade; ITSS: Intra-tumoral susceptibility sign

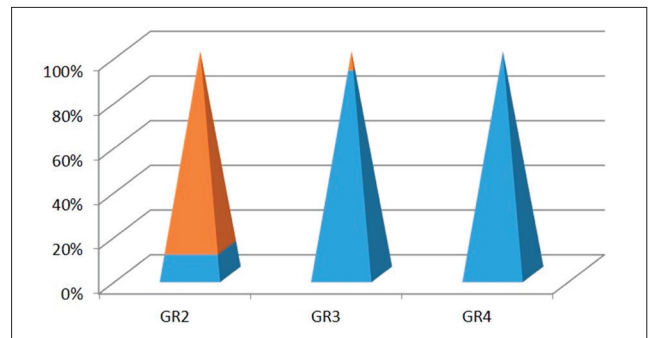


**Figure 2.** The graph showing the distribution of histopathological and ITSS grades (GR: Grade; ITSS: Intra-tumoral susceptibility sign).

**Table 2.** The association between the presence of ITSS and tumor grade

	ITSS present	ITSS absent
GR2	3 (12%)	22 (88%)
GR3	11 (91.6%)	1 (8.4%)
GR4	30 (100%)	0 (0%)

GR: Grade; ITSS: Intra-tumoral susceptibility sign



**Figure 3.** The graph showing the association between the presence of ITSS and tumor grade. Orange: absence of ITSS; Blue: presence of ITSS. (GR: Grade; ITSS: Intra-tumoral susceptibility sign).

**Table 3.** The distribution of high or low-grade tumors according to the presence of ITSS

	ITSS present	ITSS absent
HGG	41	1
LGG	3	22

HGG: High grade glioma; LGG: Low grade glioma; ITSS: Intra-tumoral susceptibility sign



## Discussion

The present study assessed whether the preliminary diagnosis of gliomas via pre-operative SWI matches with the definitive diagnosis via post-operative histopathology. As a result, ITSS presence in glial tumors was found to be associated with high-grade tumors, whereas the absence of ITSS refers to low-grade tumors. SWI evaluation revealed ITSS in all histopathologically diagnosed stage 4 tumors. This ratio is very high for glioblastoma multiforme (GBM). This finding is consistent with many studies in the literature such as Park et al. and Balaji et al. In the present study, the classification of diffuse gliomas was performed according to WHO classification (2007). Despite the change in classification in 2016, using WHO classification (2007) for grading diffuse gliomas is not a drawback for the study due to the usage of the same grading systems, basically depending on necrosis, angiogenesis and mitotic activity (11).

SWI is a relatively novel MRI technique with a 3D high-resolution gradient-echo sequence (GRE) sensitive to structures producing susceptibilities such as blood, iron, and calcification in the tissues (4, 12). The information provided by SWI in tumor grading is associated with the differential magnetic susceptibility of oxygenized vs. deoxygenized hemoglobin (12, 13). On the other hand, SWI is well suited for the visualization of very small vessels such as the caput medusae of venous angiomas and telangiectasias as a result of a combination of slow flow with changes in deoxyhemoglobin concentration (14).

SWI sequence allows the acquisition of three different types of images: filtered phase SWI images, combined magnitude SWI images, and MIP SWI images produced by the minimum intensity projection of 8 to 10 SWI images (15). The actual image consists of the combined phase and magnitude images. Phase images alone are important for the differentiation of paramagnetic (iron-containing substances) vs. diamagnetic (calcium) substances since these substances are associated with a hypointense or hyperintense image in phase imaging, while all appear as hypointense lesions in SWI images (16). The main differences of SWI from T2\* GRE include the long TE, high resolution, flow compensation, and the filtered phase data in each voxel of 3D GRE images (4). While the SWI sequence is 3D, the GRE T2\* sequence is 2D. The cross-sectional thickness of SWI is much smaller as compared to those of GRE T2\* (17). Also, it is up to 6 times more sensitive to blood in comparison with GRE T2\* sequence (4, 15).

Besides, contrast enhancement is not required in SWI sequences. In patients with low tolerance to the contrast medium, and particularly in children, it offers the advantages of being a non-invasive method that does not

require preparation and that can be added to conventional MRI whenever needed (18). However, the shortcomings of SWI include the magnetic susceptibility artifacts seen in air and tissue inter-phase and the associated interpretation difficulty in paranasal sinuses and the adjacency of the temporal bone (4). Furthermore, the utility of SWI is limited due to time constraints in 1.5 T MRI. However, it has become a more feasible and practical imaging modality thanks to the advances in the field of parallel imaging methods allowing increased speed and SNR (10, 19).

Pinker et al. (20) examined the production and frequency of intra-tumoral susceptibility effect in SWI, while Park et al. (21) assessed the morphology and degree of intra-tumoral susceptibility signal intensity in SWI. As shown by Pinker et al. (20), the presence of ITSS in SWI sequences was correlated with PET and histopathological findings in tumor staging. Balaji et al. (22), in their study involving a total of 48 patients with glial tumors, assigned a grade of "0" to tumors with no ITSS, while those with 1 to 5, 5 to 10, and >11 ITSS were classified as grade 1, grade 2, and grade 3, respectively. They suggested that grade 3 ITSS was correlated to GBM, while low-grade astrocytomas had no ITSS. In the study of Wasif Mohammed et al. (23), the numbers of small vessels in SWI sequences of high grade and low-grade astrocytomas were  $17.7 \pm 12.71$  and  $7.94 \pm 7.6$ , respectively. Chuating Li et al. (24) estimated and compared the number of small vessels within the tumors as well as the intra-tumoral hemorrhage area in conventional images vs. SWI sequences. ITSS evaluation in SWI provided a higher specificity and sensitivity of SWI sequences compared to conventional images.

Nonetheless, the presence of ITSS might be considered as an indicator of tumor grading while the absence of ITSS was related to non-tumoral lesions (25). Therefore, the complete absence of ITSS in non-tumoral lesions such as lymphoma, granuloma, or demyelinating plaques may be useful for the differentiation of GBM and lymphoma, particularly (25, 26). Our results revealed that the presence of ITSS in glial tumors indicates high-grade tumors, while its absence is indicative of low-grade tumors. Therefore, it can be suggested that SWI can be used for grading glial tumors alongside the other advanced imaging methods and the presence/absence, rather than the grade of ITSS had more predictive value, as supported by the present results.

However, there are certain limitations to the present study. Firstly, the present study has a retrospective study design and secondly; there are no post-contrast SWI sequences. Further validation of our results with the assessment of post-contrast SWI sequences in a prospectively designed study is necessary.

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