

Imaging

# Image fusion of fluid-attenuated inversion recovery magnetic resonance imaging sequences for surgical image guidance

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## Abstract

**Background:** Nonenhancing brain lesions can be relatively poorly defined on volumetric data sets routinely used for surgical guidance. Fluid-attenuated inversion recovery MRI sequences can provide better margin visualization of nonenhancing or poorly enhancing lesions.

**Methods:** Using image fusion programs, we combined data sets of SPGR imaging pulse sequence or volumetric CT with volumetrically acquired FLAIR sequences and subsequently used the fused data set for image-guided surgery. This technique was used in 50 surgical cases. Of these, 9 were nonenhancing intrinsic brain tumors, 13 were partially enhancing tumors, and 11 were enhancing tumors. In addition, FLAIR fusion was selectively used for 6 nontumoral lesions and in 11 nonlesional epilepsy surgery cases.

**Results:** Image guidance using the fused data set was accurate in all 50 cases. Despite the lack of enhancement, 3 of the 9 nonenhancing tumors were found to be high grade. One of the low-grade tumors was associated with considerable areas of gliotic change not considered to represent tumor on permanent histology. In all other cases, the FLAIR-bright resected margins were consistent with tumor, not gliosis. Radical resection (>95% volume) was achieved in 21 of 23 tumor cases in which this had been the preoperative intent.

**Conclusions:** Nonenhancing lesions are often poorly demarcated not only on imaging studies, but also during surgery. Fluid-attenuated inversion recovery fusion allows resection of such lesions using intraoperative computer image guidance. Complementary FLAIR information can also occasionally be useful during surgical approaches to enhancing lesions or in nontumor cases. It must be kept in mind that FLAIR has high sensitivity but low specificity. Fluid-attenuated inversion recovery abnormalities do not obviate the need for mapping in potentially functional areas.

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**Keywords:** Brain tumor; Epilepsy; FLAIR; Image fusion; Image guidance

*Abbreviations:* AVM, arterio-venous malformation; CA, carcinoma; CSF, cerebrospinal fluid; CT, computed tomography; DNET, dysembryoplastic neuroepithelial tumor; ECoG, electrocorticography; EEG, electroencephalography; FLAIR, fluid-attenuated inversion recovery; GBM, glioblastoma multiforme; GFAP, glial fibrillary acidic protein immunocytochemistry; IV, intravenous; MCA, middle cerebral artery; MR, magnetic resonance; MRI, magnetic resonance imaging; NeuN, neuron-specific nuclear protein immunocytochemistry; PE, pulmonary embolus; PET, positron emission tomography; SE, spin-echo; SPECT, single-photon emission computed tomography; SPGR, radiofrequency-spoiled gradient-recalled.

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## 1. Introduction

Widespread availability of frameless stereotactic systems has brought image-guided surgery into the operating theaters of many neurosurgeons. With regard to brain tumors, for those of us who were biased toward radical resection before volumetric image guidance, this technology has provided an intraoperative second anatomical opinion. It must be stressed that, at the present time, the bias for radical resection in this and many other studies is empirical and retrospective because there is no class I evidence yet to support this approach [3,18,23,35]. Most

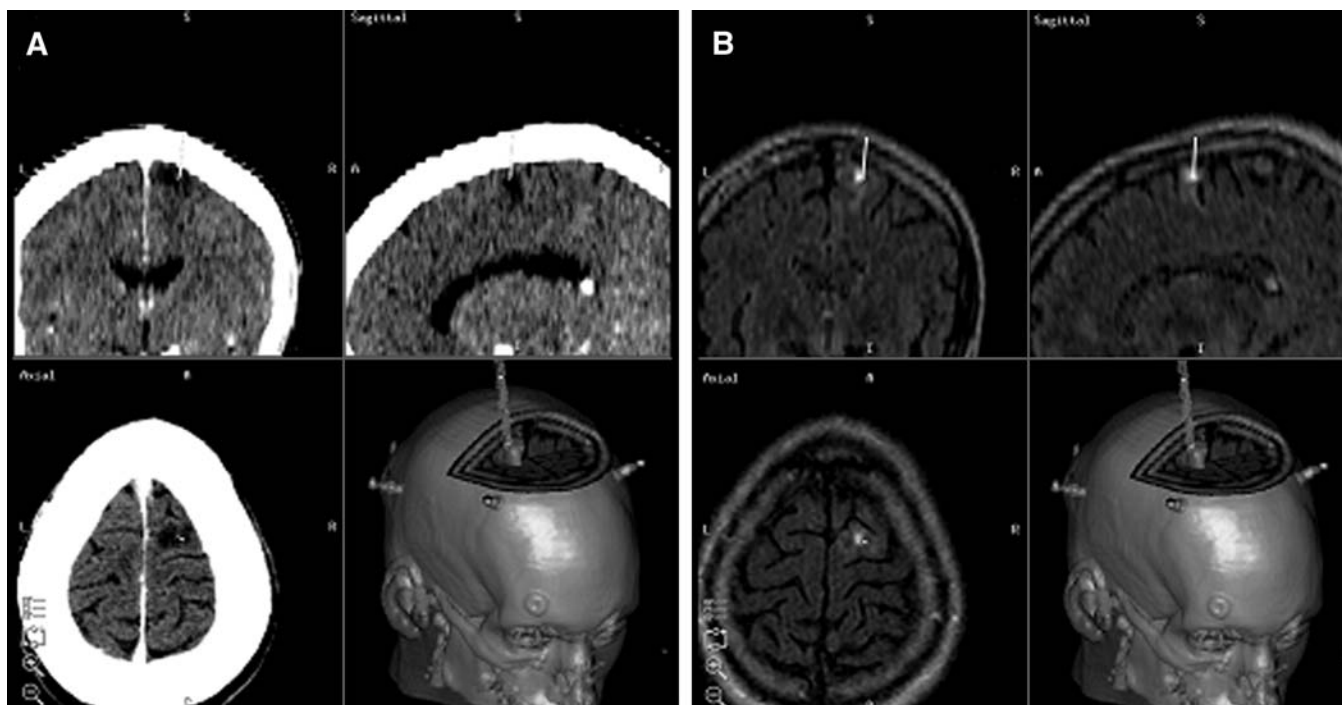


Fig. 1. A tiny frontal ganglioglioma illustrating fusion of CT (A) and MR FLAIR (B) data sets (ImMerge, StealthStation; Medtronic).

intrinsic malignant brain tumors have somewhat defined delineations at the time of surgery. As a result, immediate postoperative imaging studies often confirm a gross total resection of the enhancing component of these tumors even

without the benefit of volumetric image guidance. The situation can be somewhat different for nonenhancing intrinsic lesions, however. The transition between brain, gliotic brain, and nonenhancing glial tumor may be difficult

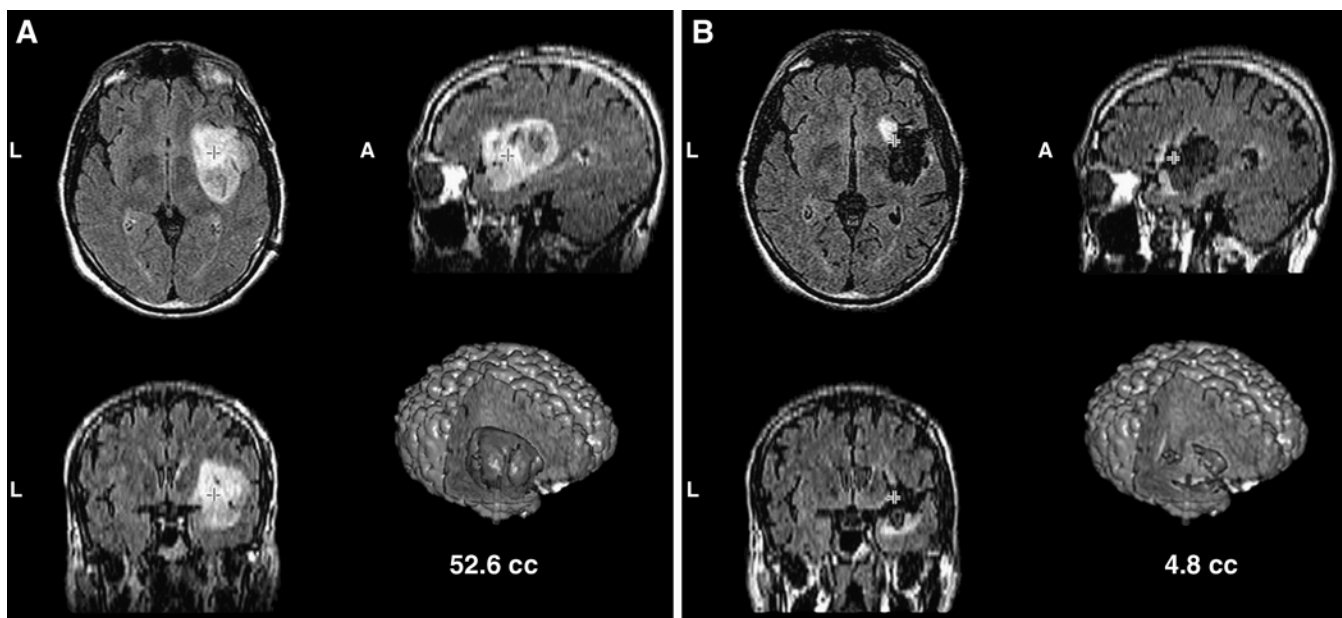


Fig. 2. FLAIR sequences of a nonenhancing grade A oligodendroglioma of the insula. As part of functional risk assessment, this left-handed patient underwent preoperative sodium amobarbital testing, which demonstrated left-sided speech. Panel A shows the FLAIR sequences used at surgery, which were correlated to an SPGR sequence (not shown). Panel B shows FLAIR sequences at 6-month follow-up, which have been fused to the preoperative volume (A) for this illustration (Compass Image-correlation, 3-dimensional model done on StealthStation). The immediate postoperative FLAIR-bright edema changes have disappeared. The residual FLAIR-bright areas most likely represent residual tumor. The patient who had very poorly controlled seizures preoperatively has been seizure-free and deficit-free postoperatively. He refused additional surgery for residual tumor. Residual tumor has been stable on sequential volumetric imaging studies over 2 years without adjuvant therapy.

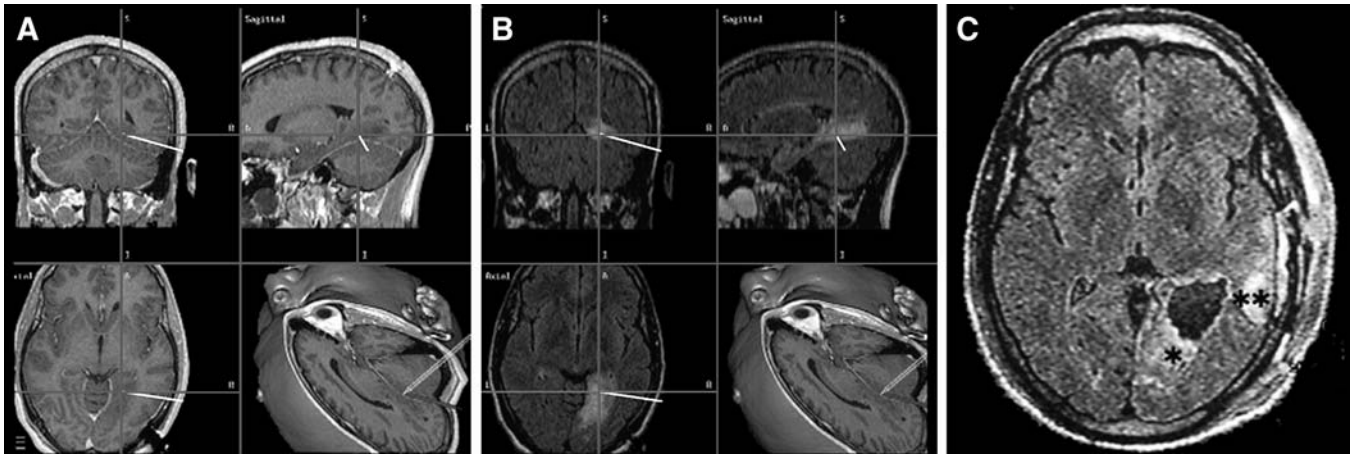


Fig. 3. Image fusion of SPGR sequence volume shown under A and FLAIR volume shown under B (ImMerge, StealthStation; Medtronic). This was a nonenhancing posterior parahippocampal grade II astrocytoma. C shows a nonfused postoperative day 1 FLAIR image. Serial biopsies were performed along the posterior resection margin (\*) and showed only gliosis on both frozen section and permanent sections (GFAP, vimentin, NeuN). We had suspected this before surgery because the patient had had a stereotactic biopsy elsewhere before referral, which had only shown gliosis. Resection of the entire FLAIR abnormality was not planned in view of the encroachment on primary visual cortex. There was transient worsening of a preexistent visual field deficit after the resection. On the immediate postoperative FLAIR sequence (C), edema is seen in the lateral cortex (\*\*) despite the avoidance of retractors (Merocel® patties only for subtemporal approach). This is an illustration of the exquisite sensitivity but lack of specificity of FLAIR imaging. The bright signal subsided on subsequent follow-up imaging.

to distinguish. Furthermore, preoperative imaging studies do not necessarily provide a clearer delineation of operative pathology. Other nontumor pathologies such as gliosis or cortical dysplasia can be the target of resective surgery for control of epilepsy, in particular. Although gliotic areas of brain can be identified at the time of surgery, the change in consistency of these is usually more gradual than what is visualized on the more sensitive of imaging studies. The concept of planning resections of gliotic brain with image guidance in combination with electrophysiology becomes appealing in this context. In nonlesional epilepsy surgery cases, sulcal anatomy is sometimes better seen on FLAIR sequences, thus, facilitating the planning of transsulcal

approaches, especially if a minimal craniotomy is planned over a sulcus.

## 2. Clinical material and methods

### 2.1. Patient population

Over a 3-year period, FLAIR image-guided resections were performed in 50 cases involving 46 patients. Twenty-seven of the 46 patients presented with seizures (59%). The other patients presented with headaches, raised intracranial pressure, or focal neurologic deficits. The patients' median age was  $39 \pm 17$  years (range, 6 to 69 years).

Table 1  
Nonenhancing tumors (9 cases in 8 patients)

Patient	Age (y)	Sex	Lesion location	Seizures	Lesion FLAIR	Perilesion FLAIR	ECoG	Pathology	Comments
CB (X 2)	33	M	Left limbic	None	Bright	Unremarkable	No	Mixed oligoastro grade 3	
JC	36	M	Right parahippocampal	Multiple	Bright	Bright/gliosis	Yes	Astrocytoma, grade 2	Most of FLAIR-bright area was gliosis
PB	31	F	Right insula	Multiple	Bright	Unremarkable	Yes	Mixed oligoastro grade 3	
AF	40	F	Right parahippocampal	Multiple	Bright	Unremarkable	Yes	Mixed oligoastro grade 2	
CN	42	M	Right insula	Multiple	Bright	Unremarkable	Yes	Oligo grade 2	
SC	18	M	Right parahippocampal	Multiple	Bright	Unremarkable	Yes	Ganglioglioma	
ES	28	M	Right premotor cortex	Single	Bright	Some increase (Fig. 1)	No	Ganglioglioma	Motor mapping
DF	31	M	Left motor cortex	Single	Bright	Unremarkable	No	Mixed oligoastro grade 3	Motor mapping

Table 2

Partially enhancing tumors (13 cases in 11 patients)

Patient	Age (y)	Sex	Lesion location	Seizures	Lesion FLAIR	Perilesion FLAIR	ECoG	Pathology	Comments
RN	11	F	Left motor cortex	Many	Bright	unremarkable	Yes	DNET	Motor mapping
DS	39	M	Cerebellum	None	Bright	Some increase	No	Medulloblastoma	
SI (X 2)	9	F	Brainstem and cerebellum	None	Bright	unremarkable	No	Pilocytic Astrocytoma	
AB	6	M	Brainstem	None	Bright	unremarkable	No	Pilocytic Astrocytoma	
CH	22	F	Thalamus, hypothalamus, brainstem	None	Patchy	*	No	Astrocytoma, grade 3	Third ventriculostomy and biopsy
PG	51	F	Left orbitofrontal	Many	Bright	Bright	Yes	Astrocytoma, grade 2	
NE	13	F	Right optic nerve	None	Bright	unremarkable	No	Pilocytic astrocytoma	Excellent definition of tumor margin in optic nerve on FLAIR
JS	49	F	Right temporal	Multiple	Bright	Bright	No	GBM	Upgrade from previously known grade 3 gliomatosis cerebri
JA (X 2)	14	M	Right ventricular, thalamic, and callosal	None	Bright	Patchy*	No	Oligoastrocytoma, grade 3	Intentional subtotal resection
JD	47	F	Bifrontal	Many	Bright	Some increase*	No	Malignant oligodendroglioma	Low-grade glioma previously known $\times$ 6 y. Intentional subtotal resection
WR	49	M	Bifrontal	Many	Bright	Some increase*	No	Malignant oligodendroglioma	Low-grade glioma previously known $\times$ 10 y. intentional subtotal resection

\* When FLAIR abnormality was patchy and if only a biopsy or sub-total resection was performed, it is difficult to define what is "lesional" versus "peri-lesional" on imaging alone.

## 2.2. Tumors (n = 33)

Location of the 9 nonenhancing tumors was as follows: motor or premotor cortex (n = 2) (Fig. 1), right insula (n = 2) (Fig. 2), right posterior hippocampus/parahippocampal gyrus (n = 3) (Fig. 3), left limbic system including; amygdala, hippocampus, parahippocampal gyrus, retrosplenial cortex, and cingulate gyrus (n = 2) (Table 1). Partially enhancing lesions (n = 13) (Table 2) were found in the motor cortex (n = 1), the posterior fossa (n = 4) (Fig. 4), frontal or bifrontal cortex (n = 3) (Fig. 5), temporal lobe (n = 1), thalamus/hypothalamus (n = 3), and the orbit (n = 1) (Fig. 6). The 11 enhancing tumors were in motor cortex (n = 1), frontal or bifrontal (n = 3), temporal/parietal (n = 5), and skull base (n = 2) (Table 3). Using FLAIR sequence image guidance for enhancing tumors was not routine but for specific information on these sequences pertaining to each individual case.

## 2.3. Other lesions (n = 6)

Fluid-attenuated inversion recovery fusion image guidance was used for 6 nontumoral lesions (Table 4). In

these cases, 4 lesions were vascular (Fig. 7). One case was for biopsy of multifocal infection (abscess). In one case, the lesion was a congenital cyst with surrounding gliosis. Fused FLAIR sequences were used for image guidance in these cases selectively because they highlighted abnormalities that were not clear on routine SPGR (T1 type) sequences.

## 2.4. Nonlesional epilepsy cases (n = 11)

Posttraumatic gliotic scar was found on FLAIR sequences in the right frontal lobe in one patient with a 10-year history of intractable epilepsy. An area of FLAIR hyperintensity (pathology: ischemia) was seen in the occipital lobe of a patient presenting with visual seizures progressing to status epilepticus. The remaining cases included 7 temporal lobe surgeries, 1 frontotemporal resection, and 1 functional hemispherectomy (Table 5). Although FLAIR hyperintensity was seen in mesiotemporal structures in a proportion of the temporal lobe epilepsy cases, the FLAIR sequences were sometimes used intraoperatively because the definition of sulcal anatomy on coronally acquired sequences was easier to see on the monitor at a distance



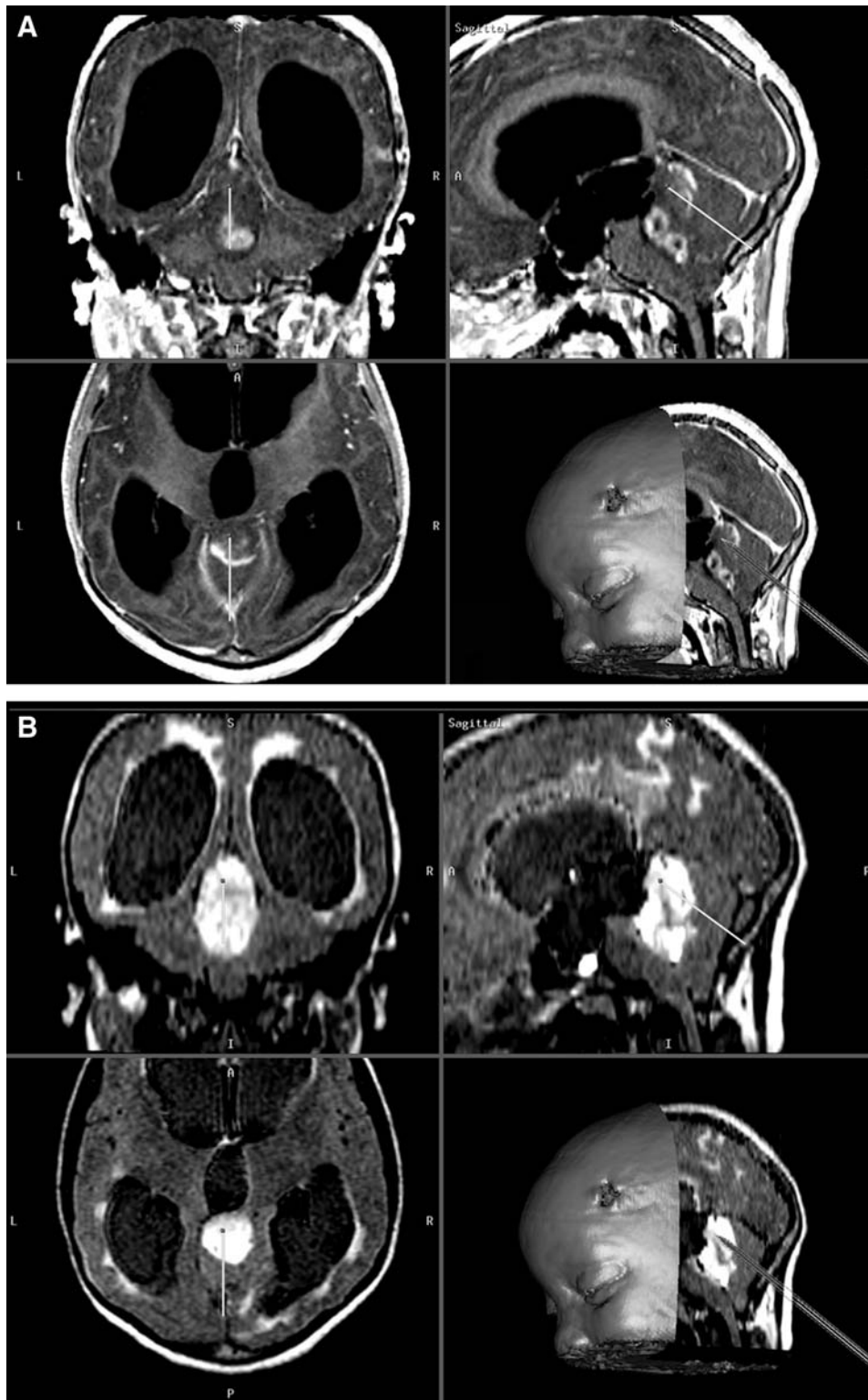


Fig. 4. Illustration of partially enhancing tumor. Radiofrequency-spoiled gradient-recalled sequence is shown in panel A. A more complete view of the entire tumor is seen on the fused FLAIR sequence (B) shown at the identical level. The target for resection was the entire tumor as seen on FLAIR (ImMerge, StealthStation; Medtronic). Resection was limited in this case by invasion of the brainstem. Despite pilocytic histology, the tumor had a malignant course with rapid regrowth and subsequent ventricular seeding and death.

during surgery rather than for targeting abnormal FLAIR signals. The latter could be highlighted for better discussion at epilepsy conference preoperatively. Conversely, cortical

dysplasia is seen particularly well on FLAIR sequences, and not using FLAIR for image guidance can lead to suboptimal targeting of these areas (Fig. 8).

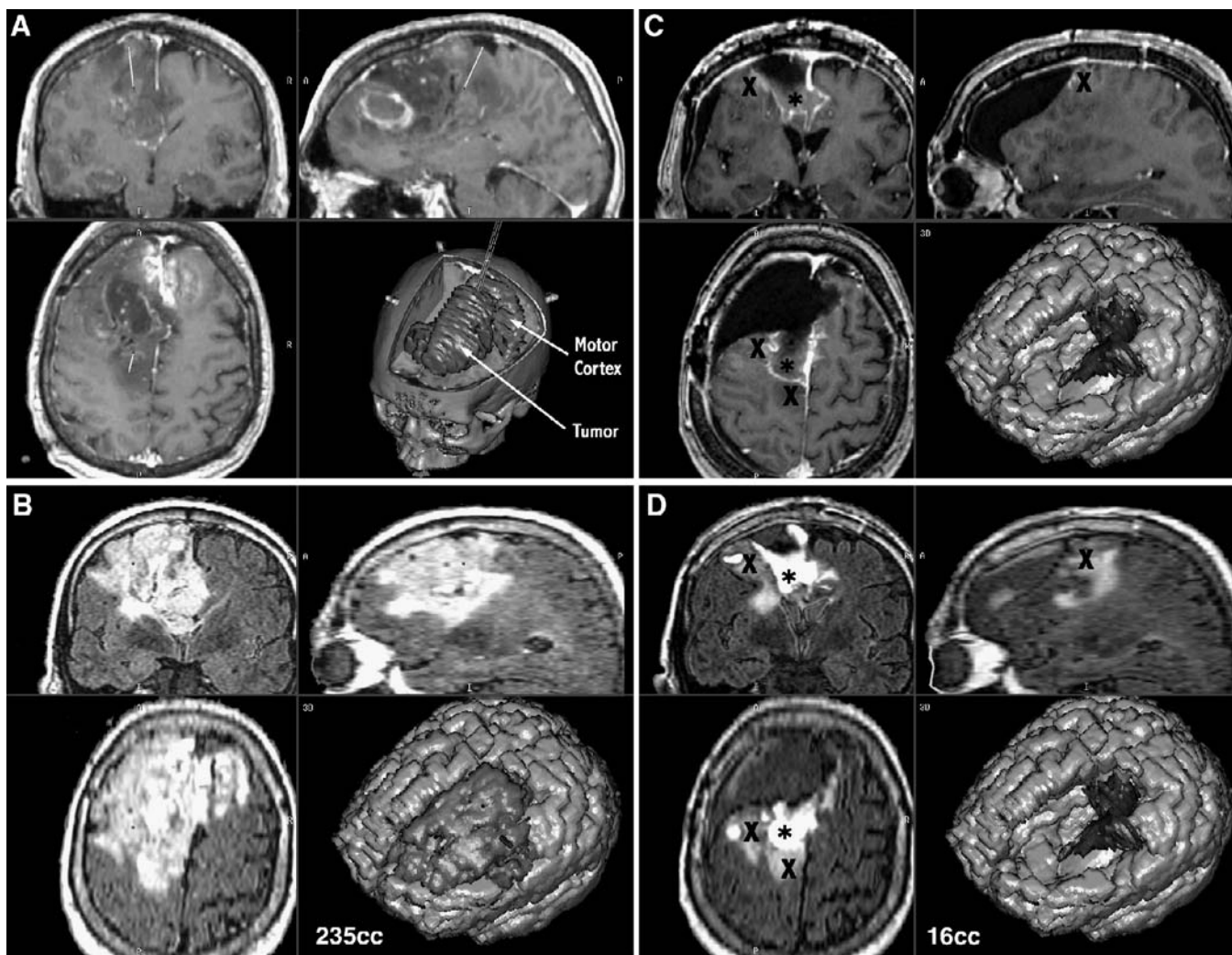


Fig. 5. Patient with partially enhancing anaplastic oligodendroglioma (oligodendroglioma B). Panel A illustrates an SPGR sequence with contrast. Behind the reconstructed tumor volume, a model of motor cortex and pathways has been built on an anatomical basis. Location of motor cortex was confirmed intraoperatively with stimulation mapping. The trajectory shown in A represents the planned posterior resection margin, leaving an area of tumor deep to motor cortex. Anterolateral resection was also planned to be submaximal in order not to undercut Broca's area. The patient had no postoperative speech or motor deficit. Panel B shows the extent of abnormalities on preoperative FLAIR, some of which probably represent tumor and some of which probably represent edema. Panels C and D are postoperative data sets 3 weeks after surgery. Panel C is an SPGR sequence volume with contrast. Panel D is a FLAIR sequence. Panels B, C, and D are fused data sets shown at the same levels for postoperative assessment and discussion (not for surgical guidance). Panel A is not correlated with B, C, or D. There is postoperative enhancement of resection margin on C, which does not represent tumor enhancement. Images C and D illustrate some of the complexities in interpreting postsurgical FAIR sequences. We believe that areas labeled X represent residual tumor. At 3 weeks postsurgery, there are still some areas of edema, some related to tumor, and some related to surgery, but these are decreasing overall. The central FLAIR-bright area in D (\*) represents methemoglobin as confirmed by the location of the resection margin in panel C.

### 2.5. Imaging data and surgical planning

For frameless stereotactic surgical image guidance, we routinely acquired axial volumetric SPGR imaging pulse sequence data sets (1.5-mm slices, GE Signa; General Electric Medical Systems, Waukesha, WI) after administration of IV gadolinium contrast as well as a postcontrast FLAIR sequence acquired in 3-mm slices with no gap in either coronal or axial planes. In some patients, volumetric CT studies (1- or 3-mm slices) were also obtained. Stick-on fiducial markers were placed on the scalp of all patients before data acquisition. In most patients (32 of 50 cases),

these noninvasive fiducials were supplemented by 4 implanted titanium screw fiducials and markers (Leibinger-Stryker, Freiburg, Germany). Data sets were downloaded onto a StealthStation (Medtronic SNT, Louisville, CO), the Cygnus-PFS system (Compass Intl, Rochester, MN), or onto both systems. On the StealthStation, data sets were loaded into "ImMerge" an image fusion program. The SPGR sequence is usually loaded as the "reference set" and the FLAIR as the "working set," although this order can be inverted without any untoward consequences. Within the "ImMerge" program, common landmarks are selected in each of the data sets. Good correlation can be readily

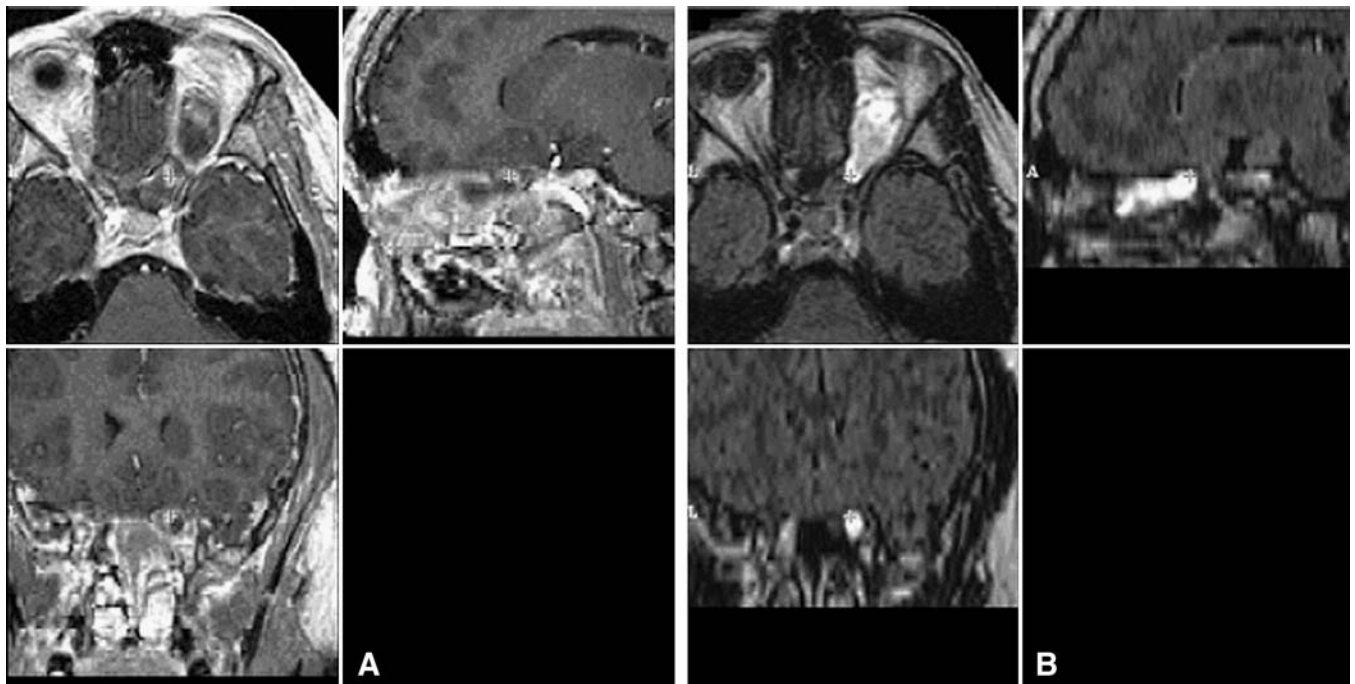


Fig. 6. Right orbital pilocytic astrocytoma (Image Correlation, Cygnus-PFS, Compass Intl). Note that the limit of the tumor is much easier to distinguish on the FLAIR sequence (B) than the SPGR sequence (A). Panels A and B represent illustrations of fused imaging sets at the same levels. The key factor in image guidance was to section the optic nerve at the level of the tumor interface to avoid interfering with optic tract fibers from the other eye.

observed in the fused data sets, and the calculated accuracy of fusion usually ranges between 0.5 and 1.5 mm. When using the Cygnus-PFS, data sets were matched in a similar manner under the Image Correlation program also with

calculated fusion accuracy between 0.5 and 1.5 mm. Preoperative planning and selection of fiducial markers in image space were performed in the usual manner on both systems.

Table 3  
Enhancing tumors (11 cases in 10 patients)

Patient	Age (y)	Sex	Lesion location	Seizures	Lesion FLAIR	Perilesion FLAIR	ECoG	Pathology	Comments
FS	47	F	Left postcentral	Single	Bright	Bright (hemorrhage)	No	Metastatic breast CA	
JK (X 2)	68	F	Left parietal	Single	Bright	Bright (edema)	No	GBM	
HC	71	M	Left parietal	None	Bright	Bright (edema)	No	GBM	Biopsy only
TN	25	F	Right middle fossa	Many	Bright	Bright (gliosis)	Yes	Schwannoma (nerve VII)	Presented with epilepsy related to gliotic changes in temporobasal cortex
JA	56	M	Left frontal	Many	Bright	Bright (gliosis and edema)	Yes	Meningioma	Intractable seizures with recurrent tumor. gliosis addressed for seizure control
EE	70	F	Callosal	Single	Bright	Bright (edema and falx)	No	Gliosarcoma	Intentional subtotal resection. Died from PE
TP	71	F	Right amygdala	Single	Bright	Bright (edema)	No	GBM	
SL	26	F	Left cavernous sinus	None	Bright	Bright in dura	No	Nondiagnostic	Biopsy only
AF	48	M	Left motor cortex	Occasional	Bright	Bright over hemisphere. Prior surgery $\times 3$ . Radiation. Brachytherapy	No	Radiation necrosis. (previous mixed oligoastro grade 3)	
WR	44	M	Callosal. Right frontal	None	Bright	Some increase. (prior surgery and radiation)	No	GBM	



Table 4  
Nontumor lesions (6 cases in 6 patients)

Patient	Age (y)	Sex	Lesion location	Seizures	Lesion FLAIR	Perilesion FLAIR	ECoG	Pathology	Comments
MA	41	F	Right amygdala	Many	Bright	Unremarkable	Yes	Cavernoma	Selective polymorph sclerosis in hippocampus
JM	49	M	Basal ganglia, splenium	None	Bright	*(biopsy only)	No	Toxoplasmosis	Biopsy of multiple nonenhancing lesions in AIDS patient.
AD	27	F	Left parietal	None	Mixed	Unremarkable	No	AVM (predominantly thrombosed)	
TH	18	M	Left parietal	Single	Mixed	Bright (hemorrhage)	No	AVM	
CT	31	F	Septum pellucidum	No	Unremarkable	Bright near cyst	No	Arachnoid cyst	The patient had had a failed shunt placement due to deviation by the very gliotic cyst. We used FLAIR to define the least gliotic area for image-guided fenestration and endoscopic shunt placement
DM	34	F	Left frontoopercular	Yes	Bright. Lesion thought to be cavernoma preoperative.	Bright along dura	No	Partially thrombosed MCA aneurysm	Operative evidence of prior hemorrhage. Lesion only visible on preoperative FLAIR

\* When FLAIR abnormality was patchy and if only a biopsy or sub-total resection was performed, it is difficult to define what is “lesional” versus “peri-lesional” on imaging alone.

## 2.6. Surgery

Patients were taken to surgery 1 to 5 days after image acquisition. After skull immobilization in a Mayfield head holder (OMI, Cincinnati, OH), registration was performed using the StealthStation, Cygnus-PFS, or both. Median calculated accuracy was  $1.2 \pm 0.7$  mm (range, 0.3–2.9 mm). These numbers are a reflexion of the higher calculated and application accuracies obtained with implanted skull fiducials. Intraoperative accuracy as verified by intracranial anatomical landmarks was good in all cases. From a practical standpoint, we preferred to switch completely between the primary imaging set and the FLAIR volume during surgery rather than use a “blended” set of images. In tumor cases, intraoperative frozen section histology was used to help confirm tumor margins. In the 2 nonlesional frontal and occipital lobe epilepsy cases, electrocorticography was used for additional guidance of cortical resection. Electrocorticography was also performed in 5 of the tumor cases presenting with seizures, but recordings did not modify the surgical plan, which was restricted to lesionectomy. All temporal lobe epilepsy cases, whether for selective amygdalohippocampectomy or with varying degrees of neocortical resection or subpial transection, were routinely investigated with electrocorticography, and surgery was tailored accordingly. The FLAIR sequences played no role in the surgical strategy other than to highlight sulcal anatomy.

Electrocorticography was also used for the frontotemporal and the hemispherectomy cases.

## 3. Results

### 3.1. Extent of tumor resection

Gross total tumor resection was defined, for enhancing tumors, as no residual enhancement on volumetric MRI (SPGR sequence without and with contrast, 1.5-mm slice) within 3 days of surgery. Imaging assessment of partially enhancing or nonenhancing tumors was more complicated but referred to postoperative assessment of resection of the preoperatively defined tumor volume. Gross total tumor resection was achieved in 20 of 23 tumor cases where total resection had been the preoperative goal. In the other 3 cases, 80%, 91% (Fig. 2), and 97% resections were obtained.

Of these, the 80% resection was achieved in a posterior fossa tumor, which was invasive of brainstem with poorly defined margins (Fig. 4). In this case, we were aware of the residual tumor, which was intentionally not resected for fear of undue neurologic risk. Postoperative imaging assessment of extent of resection in partially enhancing or nonenhancing tumors was a complex task beyond the scope of this article. In summary, imaging studies on postoperative days 0 to 2 were performed per protocol using SPGR sequence without and with contrast and FLAIR sequences similar to preoperative acquisition.



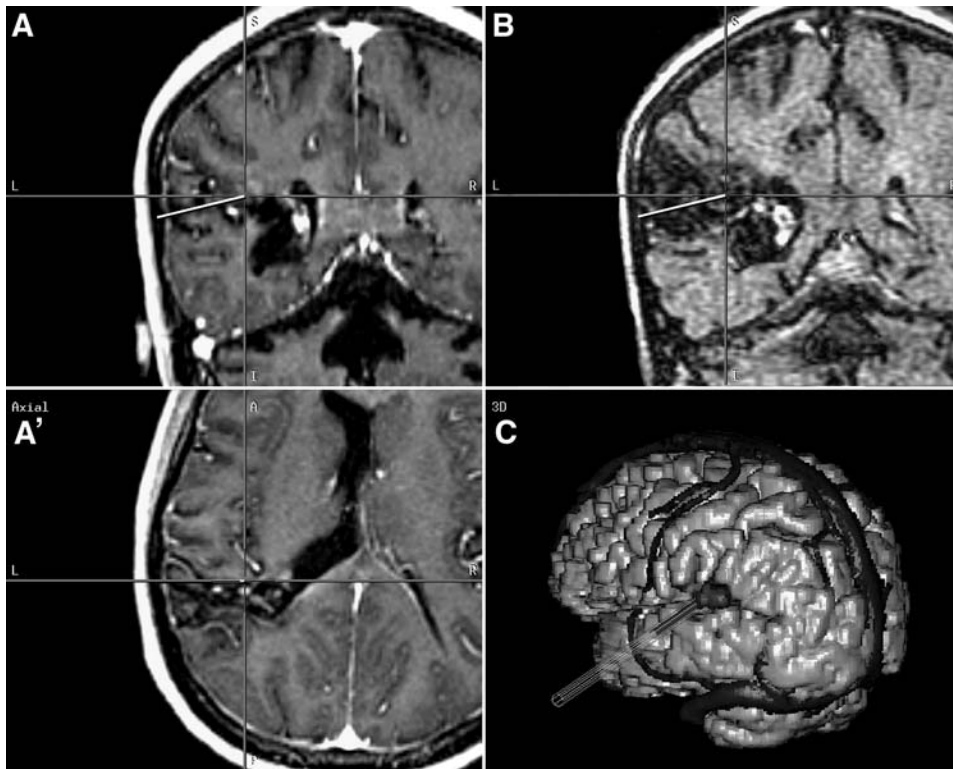


Fig. 7. A partially thrombosed parietal AVM. Panels A and A' are SPGR sequences; panel B is the fused coronal FLAIR image (ImMerge, TM, StealthStation) with much better delineation of both the vascular anomaly and surrounding abnormal cortical areas, both of which were FLAIR hypointense. Speech deficit was a concern in this patient who would not have psychologically tolerated awake mapping. Functional MRI has been unreliable for receptive speech mapping in our experience. If the patient had presented with seizures, we would have considered a grid for mapping and recording seizures. The patient presented with multiple recurrent hemorrhages, however. We elected to strictly resect the vascular lesion after the path of maximal cortical abnormality (C). There was no permanent postoperative speech deficit.

Surgical FLAIR hyperintensity changes were seen around resection cavities within hours of surgery. To distinguish residual FLAIR signal from postoperative changes, we again made use of the ImMerge(R) and Image Correlation image fusion programs. Preoperative FLAIR volumes were fused with postoperative FLAIR volumes (Figs. 2 and 5). We found that the FLAIR hyperintensity was greater in tumor preoperatively than that seen in surrounding postsurgically reactive brain. This became particularly evident when blending between the fused pre- and postoperative data sets. Often, follow-up imaging data

after weeks, months (Fig. 2), or years were necessary to confirm our original impression of extent of resection. In a patient with an extensive left limbic tumor, 2 surgeries were performed via different approaches. The initial approach was posterior interhemispheric. Because of the firm nature of the tumor, only a limited initial resection was possible (33%). A much more radical resection (97%) was accomplished via a subsequent anterior approach (simultaneous interhemispheric and transsylvian). Tumors that were intended for subtotal resection showed the expected postoperative imaging.

Table 5  
Nonlesional epilepsy cases (11 cases in 10 patients)

Patient	Age (y)	Sex	Surgery location	Seizures	FLAIR	ECoG	Pathology
DH	41	F	Right frontal	Many	Bright (posttraumatic gliosis)	Yes	Gliosis
SK	43	M	Left temporal	Many	unremarkable	Yes	Hippocampal sclerosis
TM (X 2)	32	M	Right temporal and frontal	Many	Unremarkable	Yes	Hippocampal sclerosis
YL	20	F	Right hemispherectomy	Many	Patchy	Yes	Cortical dysplasia
HB	68	M	Right occipital	Many	Occipital lesion	Yes	Stroke
MR	31	M	Left temporal	Many	Unremarkable	Yes	Hippocampal sclerosis
EH	28	F	Right temporal	Many	Brighter right hippocampus	Yes	Hippocampal sclerosis
EP	57	F	Right temporal	Many	Unremarkable	Yes	Some hippocampal cell loss
EG	41	M	Right temporal	Many	Unremarkable	Yes	Some hippocampal cell loss
NR	43	M	Left temporal	Many	Bright	Yes	Gliosis. Some hippocampal cell loss

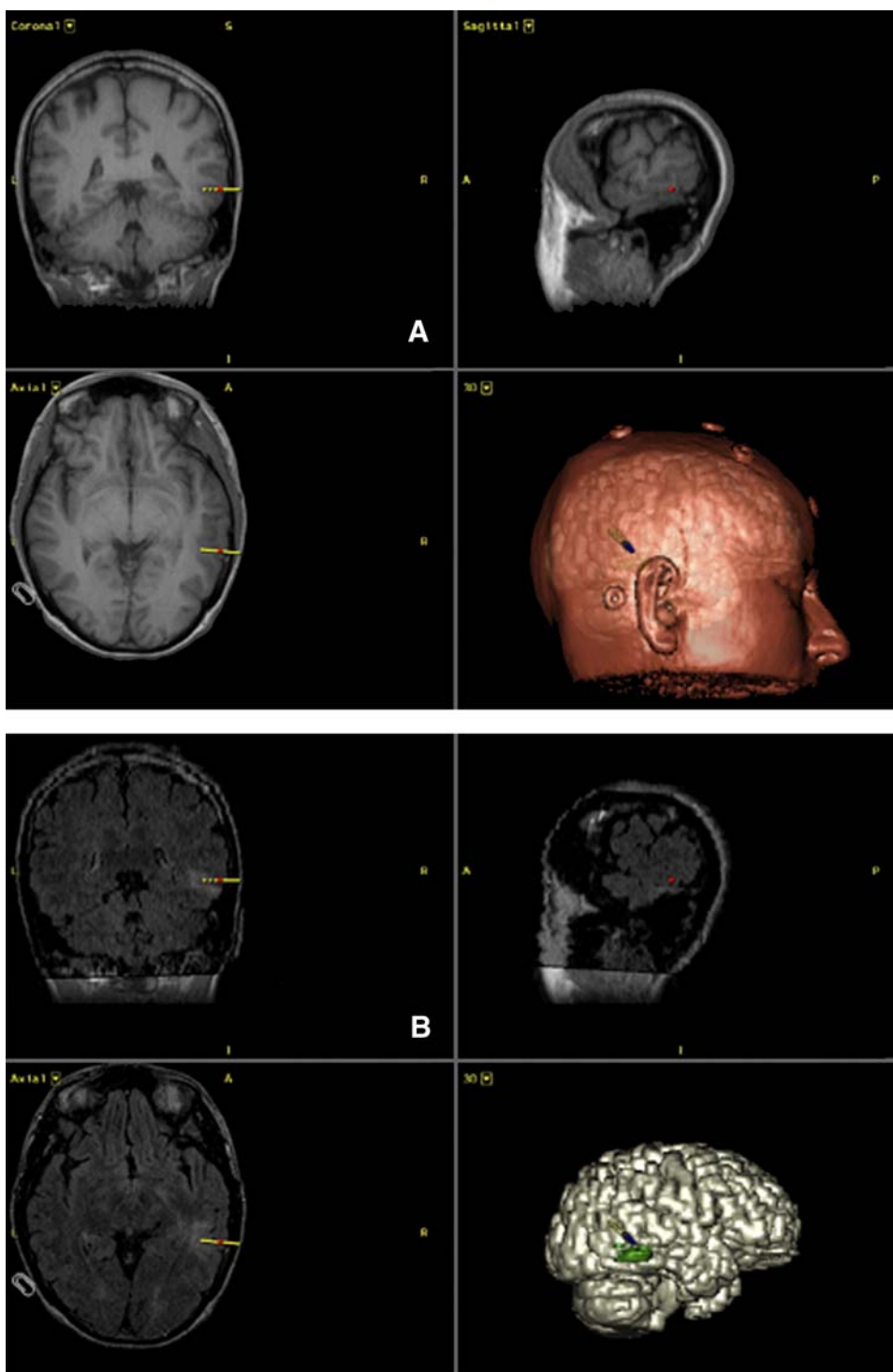


Fig. 8. This is an illustration of an epilepsy surgery case from another institution. A triple fusion of preoperative SPGR sequence (A), preoperative FLAIR (B) and postoperative SPGR sequence (C) has been performed by the authors. The patient had EEG evidence of right temporal seizure onset. Imaging was remarkable for high signal on the FLAIR sequences preoperatively, suggestive of cortical dysplasia (B). Surgery was intended to remove this area of abnormality. Image guidance was used with an SPGR sequence where this abnormality was minimally visible (A). For the initial surgery, the FLAIR sequence (B) was not fused to the SPGR sequence (A). The fusion in this figure was performed postoperatively for retrospective analysis. The area of surgical resection is seen in C. Although in the correct overall location, the resection is shown to be too superficial and not extensive enough. On histologic examination, the resected specimen showed no abnormality. Postoperatively, the patient's seizures were not improved. Using fused FLAIR sequences at surgery would have improved the intended extent of resection. It should be stressed that outcome of epilepsy surgery does not depend on resection of visible lesions alone, however.

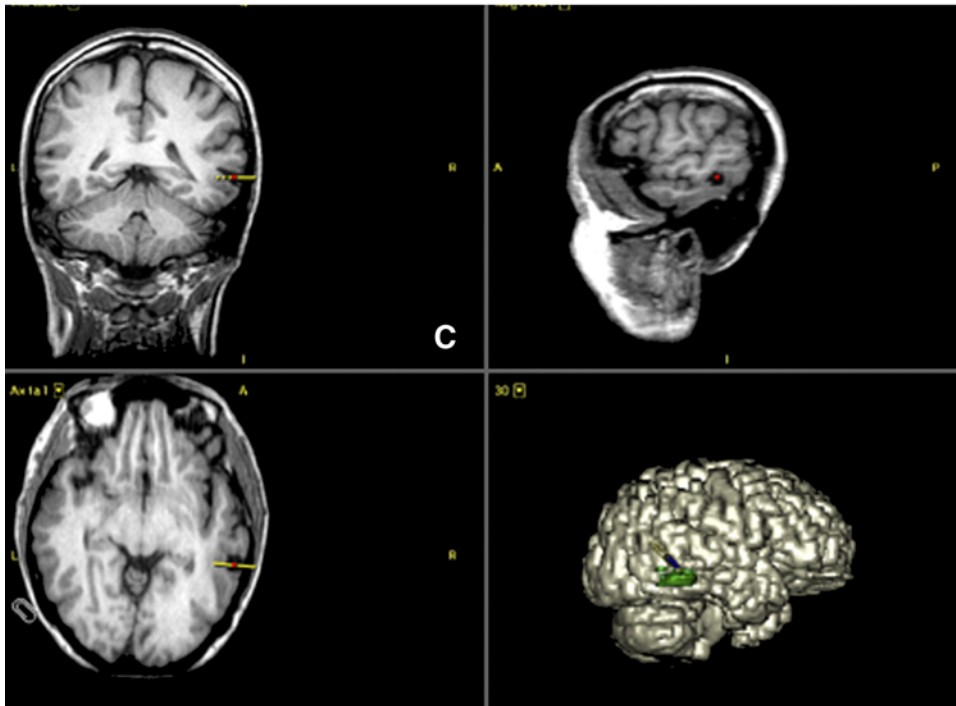


Fig. 8. (continued).

### 3.2. Complications

All complications were seen among tumor patients. No complication was related to failure of image guidance. There was one death due to a pulmonary embolus 2 weeks after surgery. Permanent new or worsening neurologic deficit was seen in 5 patients. Transient worsening or new neurologic deficits were seen in 8 patients. There was one wound

infection requiring bone flap removal in a patient who had chronic drainage from an old craniotomy site preoperatively.

### 3.3. Seizure control

All 5 tumor patients presenting with seizures have been seizure-free for at least 2 years since surgery (minimum follow-up, 2 years; maximum follow-up, 3.5 years). In all

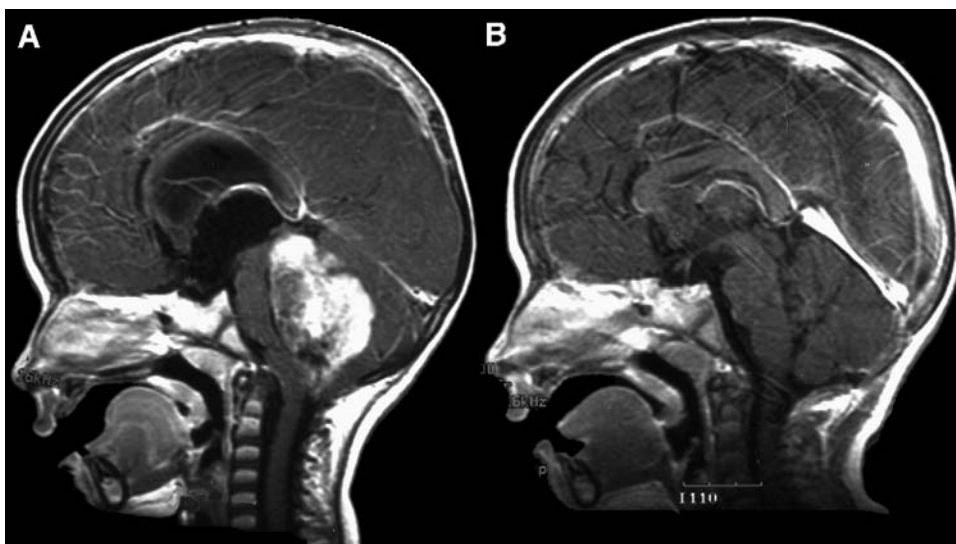


Fig. 9. This 3 year-old boy had surgery for a pilocytic astrocytoma before FLAIR sequences were available. Preoperative contrast-enhanced T1 mid-sagittal view (A) and early postoperative view (B) are shown. The resection of contrast-enhancing tumor was radiologically complete.

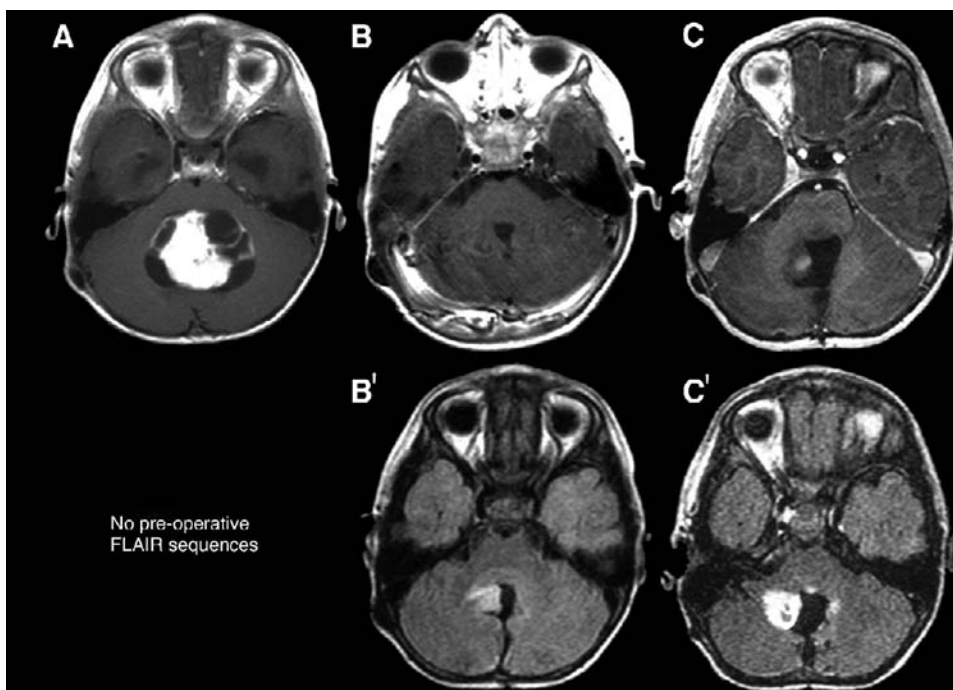


Fig. 10. A preoperative axial view in A. Images B and B' represent a follow-up at 9 months with SPGR sequence with contrast shown in panel B and a corresponding fused FLAIR image in panel B' (the first FLAIR sequence obtained in this patient). A follow-up of 3 years after initial surgery is shown in panel C and C', illustrating that tumor recurrence is seen at the exact location of the early FLAIR abnormality. Had a FLAIR sequence been available at the time of initial surgery, the FLAIR-bright nonenhancing tumor could have been targeted for resection along with the enhancing tumor.

5 tumor cases presenting with seizures, electrocorticography was not used to modify surgical strategy; thus, these cases were strictly lesionectomies. Electrocorticography was performed to document possible epileptiform activity in surrounding neocortex for future reference in case of persistent seizures. The patient with posttraumatic frontal lobe seizures was seizure-free for 2 years, with the exception of 2 drug withdrawal seizures at 18 months. Status epilepticus was broken in the patient with a stroke but subsequently recurred because of additional pathology leading to death. The patient with the large left limbic tumor who did not present with seizures developed controllable seizures 6 months after second surgery and radiation. Six of 7 temporal lobe epilepsy cases are seizure-free at 2 years. The remaining patient has a >90% seizure reduction at 2 years.

## 4. Discussion

### 4.1. FLAIR sequences

Fluid-attenuated inversion recovery MRI has become state-of-the-art in viewing a variety of lesions as well as normal areas of the brain. It was first introduced by Hajnal et al [11] in 1992. Fluid-attenuated inversion recovery imaging is based on the premise that suppression or reduction of the CSF signal occurs with the use of an inversion recovery pulse sequence with a long T1 (inversion time). This, coupled with a long TE (echo time), provides

improved visualization of the brain and enables distinction of brain parenchyma from lesions [7,11,30,31]. Increased sensitivity to disease processes results from decreased partial volume or artifact effects from CSF, in contrast to conventional T2-weighted SE MRI [7,11]. Using qualitative criteria such as lesion conspicuity and lesion detectability, we found FLAIR to be superior to T2-weighted imaging. Fluid-attenuated inversion recovery thus gives a strong T2 weighting, nulls the CSF signal, and minimizes the contrast between gray matter and white matter [14].

Since its inception, FLAIR has been used to evaluate a wide range of central nervous system disease. Gliomas, multiple sclerosis, metastatic disease, subarachnoid hemorrhage, mesial temporal sclerosis, tuberous sclerosis, cerebrovascular disease, and intracranial infections have all been shown to have reliable conspicuity on FLAIR imaging [2,5,7,12,14-16,25-27,33]. The very heavy T2 weighting highlights certain white matter tracts and provides high sensitivity to disease [28]. Fluid-attenuated inversion recovery has obviously proven very useful in brain tumor imaging, especially in tumors with no or partial contrast enhancement. Fluid-attenuated inversion recovery imaging also provides superior delineation of cortically located small lesions [5,9,31]. In some cases, FLAIR images may provide better definition between tumor and surrounding edema than T2-weighted images [34], and we used this feature in our image-guided approach to higher-grade tumors. Our routine protocol always included postgadolinium FLAIR sequences, which frequently improved tumor margin definition. We



cannot comment on the contribution of contrast administration in a definitive manner, however, because we did not routinely perform non-contrast-enhanced FLAIR sequences preoperatively. In follow-up imaging, we have noted contrast enhancement on FLAIR sequences that was not seen on T1/SPGR sequences, a phenomenon that merits further study. In some of our cases, low-grade tumor and surrounding gliosis could not be distinguished on FLAIR images, and we had to rely on serial biopsies (Fig. 3C).

Mesial temporal sclerosis, the most common known substrate of symptomatic partial onset epilepsy, has been the topic of a number of studies using FLAIR imaging [13,21,36,37]. We routinely acquired coronal FLAIR sequences for epilepsy patients using a volumetric protocol. This facilitated preoperative determination of sclerosis, whereas intraoperatively, we used the FLAIR sequences for sulcal visualization.

Newer techniques for FLAIR have evolved recently. These include 3-dimensional fast FLAIR, which provides better estimation of tumor size and improved sensitivity in epilepsy imaging [13,30,37]. Future use of fast FLAIR for image guidance may further enhance the exact delineation of intraaxial brain tumors because fast FLAIR has been shown to have even better contrast and contrast-to-noise ratio than those of CSF. Fast FLAIR also provides more marked contrast enhancement in imaging cerebral gliomas and metastases, resulting in a higher background-to-background contrast ratio [8,10,22]. In the presence of reduced gray and white matter differentiation due to the mild T1 weighting of fast FLAIR [4,10,19], administration of contrast increases signal intensities of gliomas and metastases significantly, allowing better delineation of enhancing tumor boundaries [4,10].

#### 4.2. Image fusion

Image fusion combines complementary volumetric information from 2 or more imaging modalities [1,6,20]. These modalities may be identical or different, with one image being superimposed upon another. Image fusion can integrate functional information (such as PET, SPECT, EEG, magnetoencephalography, MR spectroscopy, or functional MRI) with anatomical information obtained from MRI or CT [32].

There are several image fusion, or coregistration, techniques in use today. The first one uses fiducial markers, in which the same markers are used in both imaging modalities and are subsequently matched to align the 2 images. A second technique is based on surface matching between volumes defined on each separate image [17,29]. Another image fusion technique recently described in radiosurgery uses the full volumetric information to rapidly fuse the image sets [1]. Chamfer matching involves automated matching of sets of points from the skull surface from both MR and stereotactic CT data, eliminating most of the anatomical spatial distortion of stereotactic MRI [1]. Fiducial accuracy of CT is combined with the high

resolution offered by MR, thus, yielding a spatially accurate image [1,20].

Image fusion has widespread applications in neurosurgery. Some of its uses include the ability to identify a tumor's boundaries in the face of surrounding edema, the distinction between pathology and its proximity to eloquent cortex, and the ability to aid in the distinction between radiation necrosis and recurrent tumor [6,24,32]. Computed tomography and MRI images may be fused to enhance surgical localization of lesions in relation to adjacent bony structures. Fusion of functional images (ie, PET) with structural images, such as MRI, can play an important role in epilepsy surgery.

#### 4.3. Surgical guidance

Image-guided surgery using the StealthStation and/or the Cygnus-PFS was accurate against well-defined intracranial anatomical landmarks in all cases reported here (calculated accuracy in all cases,  $1.2 \pm 0.7$  mm). To improve accuracy, we resorted to the use of implanted fiducial markers (Leibinger) in most of our recent cases (calculated accuracy in 32 cases with implanted fiducials,  $0.9 \pm 0.4$  mm; range, 0.2–1.7 mm). In addition, it is known that stereotactic accuracy is better on CT than on MRI because there are field distortions on MRI images, especially at the surface of the head [20]. For this reason, we have also performed image correlations between CT volumes and FLAIR volumes. This was done instead of, or in addition to, SPGR-FLAIR fusions to further increase stereotactic precision.

In some of the enhancing tumors, especially the malignant ones, peritumoral edema was responsible for most of the FLAIR hyperintensity. In this situation, we used the FLAIR sequence to highlight edema on the image guidance systems and sometimes modified the surgical approach accordingly. Occasionally, the FLAIR tumor enhancement went beyond the enhancement seen on SPGR sequences, thus, defining a more extensive target for resection. Determining tumor margins intraoperatively can be challenging in nonenhancing tumors because these tumors may be more difficult to distinguish from surrounding brain. The appearance and consistency of lower-grade tumors may be similar to the surrounding gliotic white matter, in particular, in the absence of the surrounding edema. This is where image guidance is particularly useful. On FLAIR sequences, gliotic changes may also be hyperintense but usually somewhat less so than pure tumor. We supplemented our guidance for radical resection with serial frozen section biopsies in a number of tumor cases. In nonenhancing tumors, we only found one case (Fig. 3) where FLAIR-bright signal did not define tumor margins, the posterior extent of the FLAIR abnormality representing reactive gliosis on frozen and permanent sections. Thus, in nonenhancing low-grade tumors without evidence of edema, we found a correlation between FLAIR signal abnormality and tumor margins in most cases. It is well known that cortex may retain function despite tumor infiltration.

Additional functional mapping was always considered when near mappable highly functional areas.

In biopsy, vascular, and miscellaneous other cases, FLAIR was used selectively for better contrast, visualization of surrounding gliosis, or anatomical reference.

In the context of epilepsy surgery, coronal FLAIR sequences often showed better anatomical definition of sulci than SPGR sequences, which was useful in the context of transsulcal selective amygdalohippocampectomies or in estimating sulcal depth when performing subpial transactions. For this application, however, we now have replaced FLAIR by high-resolution T1-weighted inversion recovery imaging as our data set of choice to highlight sulcal anatomy in epilepsy cases. On the other hand, FLAIR image guidance remains a technique of choice when addressing cortical dysplasia. Retrospective analysis of 2 cases where FLAIR sequence image-guidance was not used are illustrated in Figs. 8-10. Fig. 8 was a cortical dysplasia epilepsy case and 9 and 10 a tumor case.

## 5. Conclusions

Image fusion of FLAIR volumetric sequences with SPGR sequence or volumetric CT provides a relatively simple means for enhancing image guidance to subtle, nonenhancing, or poorly enhancing intrinsic brain lesions. Fluid-attenuated inversion recovery sequences were also found to be useful in selected cases to highlight sulcal anatomy or extent of gliosis or edema. We present a series of 50 cases where we believe that this additional technique was useful for image guidance during surgery. This technique, although extending the useful applications of intraoperative image guidance, should be used with caution because FLAIR abnormalities are nonspecific (tumor vs edema vs gliosis) and serial biopsy may be necessary. Functional mapping should be considered in addition for appropriate cases.

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## Commentary

The information in this manuscript may be very useful to the readership. I agree with the authors that FLAIR pulse sequence can provide better visualization of nonenhancing or poorly enhancing brain lesions. FLAIR allows for increased sensitivity in detecting pathologic brain and spinal cord lesions, more precise determination of extent of disease, and more accurate characterization of brain lesions. I also agree with the authors that FLAIR sequence highlights abnormalities better than the T1-weighted SPGR pulse sequence. FLAIR pulse sequence is a powerful technique to evaluate brain tumor, demyelinating process, gliosis, cortical dysplasia, subarachnoid hemorrhage, leptomeningeal process, and ischemic brain lesions. Hyperintensity in FLAIR, however, is nonspecific. In nonenhancing low-grade tumors without evidence of edema, the hyperintensity on FLAIR most often represents tumor rather than gliosis. In summary, I also agree with the authors that fusion of functional images with structural anatomical images using MRI can play an important role in neurosurgical operative procedures.

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