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Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials

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See the editorial by Sul and Krainak, on pages 1179–1180.

A recent joint meeting was held on January 30, 2014, with the US Food and Drug Administration (FDA), National Cancer Institute (NCI), clinical scientists, imaging experts, pharmaceutical and biotech companies, clinical trials cooperative groups, and patient advocate groups to discuss imaging endpoints for clinical trials in glioblastoma. This workshop developed a set of priorities and action items including the creation of a standardized MRI protocol for multicenter studies. The current document outlines consensus recommendations for a standardized Brain Tumor Imaging Protocol (BTIP), along with the scientific and practical justifications for these recommendations, resulting from a series of discussions between various experts involved in aspects of neuro-oncology neuroimaging for clinical trials. The minimum recommended sequences include: (i) parameter-matched precontrast and postcontrast

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inversion recovery-prepared, isotropic 3D T1-weighted gradient-recalled echo; (ii) axial 2D T2-weighted turbo spin-echo acquired after contrast injection and before postcontrast 3D T1-weighted images to control timing of images after contrast administration; (iii) precontrast, axial 2D T2-weighted fluid-attenuated inversion recovery; and (iv) precontrast, axial 2D, 3-directional diffusion-weighted images. Recommended ranges of sequence parameters are provided for both 1.5 T and 3 T MR systems.

Keywords: Brain Tumor Imaging Protocol, clinical trials, glioblastoma, MRI.

Need for Increased Development of Therapeutics for Treating Brain Tumors

Approximately 67 900 new primary CNS tumors are diagnosed each year in the United States (21 per 100 000 persons), of which 44 910 are malignant.[1] Of these newly diagnosed tumors, approximately 28% are gliomas, which constitute 80% of all malignant primary brain tumors.[1] Glioblastoma, the most common and aggressive type of glioma, is the focus of this document for 2 reasons. First, it is the most common form of high-grade glioma, accounting for 54% of all gliomas and 45% of all malignant primary CNS tumors;[1] thus, it is a high priority area for therapeutic development. Second, glioblastoma is one of the most complex and treatment-resistant brain tumors; therefore, improvements in drug development and measurement of tumor response to therapy in glioblastoma may allow advancement of these efforts for other types of brain tumors.

The current standard of care for newly diagnosed glioblastoma patients involves maximum safe surgical resection, followed by radiotherapy plus concomitant and adjuvant temozolomide,[2] but this treatment affords only a median survival of 14–16 months,[3–6] and fewer than 10% of patients survive 5 years beyond diagnosis.[7] Furthermore, very few therapeutic options exist for recurrent disease since patients with prior temozolomide exposure have progression-free survival (PFS) rates at 6 months of 20%–40% regardless of chemotherapeutic intervention (eg, nitrosoureas, temozolomide rechallenge, or bevacizumab).[5,6,8] Thus, there is an urgent need for drug development in recurrent glioblastoma.

Role of Imaging in Brain Tumor Clinical Trials

Although overall survival (OS) is considered the gold standard for determining whether a cancer treatment is effective, OS may not directly reflect the specific impact of particular treatment regimens because of the confounding effects of known prognostic factors (eg, age, tumor size, neurological status), use of additional therapies prior to or after the therapy of interest, and other health-related factors.[9,10] Hence, PFS and *durable* objective response rate (ORR) are considered valuable end points for determining the relative value of a given treatment.[11] (Note that PFS also suffers from the impact of prognostic factors.) Identifying response and progression has traditionally been based on neuroimaging supported by clinical observation[12] with limited utility of serum or cerebrospinal fluid markers of disease for gliomas. However, surrogate measures of tumor burden (eg, area with contrast uptake) can suffer from issues associated with nonspecificity of the surrogate, measurement variability, false positives, and discordance in radiographic interpretation between observers.[13] Therefore, Response Assessment In Neuro-Oncology (RANO) needs refinement to minimize intrinsic errors and to improve the accuracy of determining true response to a particular therapy.

A joint meeting was held on January 30, 2014, among the Food and Drug Administration (FDA), National Cancer Institute (NCI), clinical scientists, imaging experts, clinical trials cooperative groups, representatives from pharmaceutical and biotechnology companies, and patient advocate groups to discuss endpoints for clinical trials in glioblastoma.[9,10,14,15] With only 4 drugs for glioblastoma having been approved by the FDA over the past 30 years (ie, nitrosoureas, carmustine, temozolomide, and bevacizumab), the significant costs associated with large studies, and few survival-extending breakthroughs, there is a need to quickly identify effective experimental therapies with a minimum of invested time and cost. For example, 3 large phase 3 trials were completed, based on promising phase 3 data, which failed to significantly extend OS.[5,6,16] These failures highlight the need to optimize the use of imaging as a surrogate tool to better understand the response to novel therapeutics. To address these needs, a key recommendation arising from this workshop, with the encouragement of the FDA, was the development of a set of priorities and action items including: (i) standardization of the MRI protocol for multicenter studies; (ii) validating the use of volumetric analysis of T1 subtraction maps for defining treatment response and failure for use in drug approval studies; and (iii) subsequent re-evaluation of the current RANO criteria with an effort to integrate standardized imaging and quantitative evaluations. These priorities set forth by the thought leaders in the neuro-oncology community, the *Jumpstarting Brain Tumor Drug Development Coalition* (consisting of the National Brain Tumor Society [NBTS], Society for Neuro-Oncology [SNO], Musella Foundation for Brain Tumor Research, Accelerate Brain Cancer Cure [ABC2]), the FDA, and NCI represent the procedures necessary for validating and building confidence in order to use quantitative imaging surrogates as endpoints in glioblastoma clinical trials for drugs. Indeed, Dr. Richard Pazdur, Director of the FDA Office of Hematology and Oncology Products, shared, "During our participation in the Brain Tumor Endpoints Workshop, we identified standardization of imaging data acquisition and analysis as a step towards increasing the reliability of radiographic endpoints in brain tumor clinical trials, and improving the ability to assess the impact of therapies in neuro-oncology."

The current document outlines the consensus recommendations for a standardized *Brain Tumor Imaging Protocol* (BTIP), along with the scientific and practical justifications for these recommendations, resulting from a series of discussions between various experts in neuro-oncology neuroimaging for clinical trials. The recommendations in the current document

are in direct response to the priorities that resulted from the workshop in January 2014, and are supported by the RANO working group.

Need for Imaging Standardization for Better Response Measures

In multicenter MRI studies, the heterogeneity of MR scanners and parameters (eg, field strength, gradient system, manufacturer, sequences) must be considered. It is well known that even minor differences in hardware or sequence timing may result in significant changes in image contrast. Lesion contrast is also dependent on the magnetic field strength of the scanner,[17,18] with higher field strengths showing higher contrast-to-noise compared with lower field strength scanners (eg, 3 T vs 1.5 T). Moreover, a variety of MR protocols are commonly used for the same purpose, further hindering interpretation of imaging results from different treatment centers in the absence of tight control and standardization of image acquisition parameters.

Leveraging Lessons From the Alzheimer's Disease Neuroimaging Initiative (ADNI) Effort to Standardize Structural MRI Acquisition

Neuroimaging remains at the forefront of medical imaging technology and research; however, a lack of benchmarked standard acquisition protocols combined with rapidly evolving technologies can limit the ability to combine data in a multicenter fashion. This became readily apparent when attempting to study subtle structural changes in the brain related to degenerative diseases such as Alzheimer's disease. The subtle differences in acquisition parameters and sequences, along with variations in MR system technologies and hardware, resulted in significant measurement discordance across centers, masking the effects of the disease. To standardize image acquisition to better understand Alzheimer's disease, the Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched in October 2004.[19,20] This was a landmark effort to standardize brain imaging across clinical centers in the United States and Canada. ADNI was funded as a large public-private partnership between the National Institutes of Aging (NIA) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) of the National Institutes of Health (NIH), MR system manufacturers, several pharmaceutical companies (Pfizer, Wyeth, Eli Lilly, Merck, GlaxoSmithKline, AstraZeneca, Novartis, Eisai, Elan, Forest Laboratories, Bristol Meyers Squibb), and foundations (Alzheimer's Association, Institute for the Study of Aging).

One of the primary, tangible deliverables from ADNI was a standardized anatomic MRI protocol for accurate and reproducible brain imaging that is uniform across the major MR system manufacturers.[21] The ADNI initiative produced a vendor-neutral, standardized, inversion-recovery (IR) prepped volumetric T1-weighted gradient echo sequence for quantification of volumetric changes in brain structures, and a dual echo, proton-density T2-weighted turbo spin-echo sequence for quantifying pathologic changes via estimates of tissue T2.[22] The use of T1-weighted and T2-weighted images are critically important for brain tumor response assessment, as outlined in the RANO recommendations and discussed further in the current document. Since the imaging biomarkers and MRI pulse sequences of interest in ADNI are very similar to those required for measurement of brain tumor response to therapy, many of the ADNI recommendations were focused on the goal of expediting the process of developing a standardized anatomic MRI protocol for brain tumors and avoiding many of the pitfalls and expenses encountered by ADNI.

Development of MR Image Acquisition Standardization in the European Organization of Research and Treatment of Cancer Brain Tumor Group

The European Organization of Research and Treatment of Cancer (EORTC) Brain Tumor Group (BTG) acknowledged the need for standardization of MR image acquisition in the context of clinical trials in 2010. A core group of BTG members including neuroradiologists, neuro-oncologists and, MR physicists, with support from EORTC headquarters, developed both a basic and an advanced MR protocol. The basic protocol consisted of the core imaging sequences required to assess treatment response according to the RANO criteria, (ie, T1- and T2-weighted sequences). The basic protocol was deemed mandatory for all participating sites, while the advanced protocol was to be adopted by selected sites only. For both protocols, a balance was sought between feasibility and image quality. Since the protocol was required to be implemented in all participating sites throughout Europe, it needed to be feasible both in terms of available equipment and scan time. The main issue encountered when trying to implement this protocol was that sites were traditionally not selected on the basis of imaging facilities but rather on their ability to recruit and enroll patients in clinical trials. Radiologists are not commonly involved in the impeding EORTC trials, and generally no funding for any additional scan time is available in investigator-initiated trials. The protocol therefore needed to fit seamlessly into the clinical routine, while ensuring sufficient image quality. The development phase was concluded in 2012, after which the protocols were implemented in 2 newly opened trials: EORTC-26101 and EORTC-26091 (TAVAREC). General acceptance of the protocol was high, and only one site indicated that they would be unable to adhere to the protocol. After the initial rollout phase, major protocol violations were reduced markedly to less than 10%. The excellent adherence indicates that the protocol could be implemented into the clinical routine without losing sites for recruitment, with a pragmatic but rigorous quality assurance mechanism in place (which is crucial in this setting). The BTIP described in the current document has drawn from the EORTC-BTG experience, and care has been taken to maintain the same level of feasibility.

Philosophical Considerations and Compromises

During the course of discussions with panel experts, many philosophical concepts and approaches were considered, resulting in specific notable compromises. The concept of an "ideal" or "optimized" protocol is elusive and ill-defined in terms of the required performance measures used for optimization. Instead, a pragmatic approach was considered, striving for a balance between an ideal protocol, which may be available only on select high-performance systems or at state-of-the-art academic

centers, and a protocol that could reach large-scale compliance and acceptance from the community, including international participants. The goal of the initiative was not only to define a protocol for trials with reimbursement for imaging by the sponsor but also for use in investigator-initiated trials without funding or even in daily practice. Thus the suggested protocol needs to approach that used in clinical practice in terms of examination time and types of sequences. The concept of tightly controlling acquisition parameters to limit variability was felt to be desirable; however, this clearly must be balanced against the practicality of employing such regulations at the large numbers of centers with variable imaging capabilities. With MR systems currently in use at large institutions dating back more than 20 years, a degree of flexibility was desired in order to allow these centers to still be involved in future clinical trials without significantly affecting image quality or performance. In short, *perfect* can be the enemy of *good enough*, and what is required here is an MRI protocol that is both adequate in terms of quality and feasibility at the majority of institutions. Additionally, we attempted to think progressively and consider aspects related to the future of imaging response assessment, namely the potential use of volumetry (compared with current bidirectional assessments) for determining response, duration of response, and the potential for quantifying subclinical measures of tumor response including growth kinetics, use of T1 subtraction maps (compared with current evaluations on postcontrast T1-weighted images) to increase lesion conspicuity and more accurately quantify enhancing tumor burden, and the use of dual echo proton-density/T2-weighted images for estimating tissue T2 (instead of relying solely on T2-weightedimages (which are relatively nonspecific for delineating nonenhancing tumor from vasogenic edema). Because many new and promising pulse sequences may be more widely available in the future, the panel recommends that the current protocol serve as a well-needed *benchmark* for comparison of future sequences and imaging systems. Any new addition to the protocol should be evaluated for its potential to improve treatment evaluation with OS as the key endpoint. Lastly, the current recommended protocol was designed to obtain necessary content while minimizing total scan time to ideally 30 minutes of actual image acquisition because patient tolerance in this population can be a challenge, and patient throughput is a primary concern for most imaging centers.

Recommended MRI Acquisition Protocols

The recommended minimum requirements for MR image acquisition for use in brain tumor clinical trials are outlined in Table 1. This protocol is applicable to both 1.5 T and 3 T scanners, although some modifications to scan parameters may be needed to ensure similar signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) in the resulting images. Additional examples of compliant MR acquisition protocols specific to 3 T and 1.5 T scanners are found in Tables 2 and 3. The total amount of actual scan time (image acquisition only) was benchmarked at approximately 21 minutes and 30 seconds on a 3 T Siemens Skyra with parallel imaging, suggesting that the entire acquisition including setup and teardown can be performed in approximately 30 minutes using current 3 T systems. Key elements of this protocol include: (i) a precontrast, 3-dimensional, isotropic, IR-prepped T1-weighted gradient echo (IR-GRE) sequence; (ii) an axial, 2-dimensional T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence obtained using a turbo-spin-echo (TSE) readout; (iii) an axial, 2-dimensional, 3-directional (isotropic) diffusion-weighted imaging (DWI) sequence obtained using echoplanar (EPI) or radial acquisition; (iv) an axial, 2-dimensional T2-weighted TSE sequence (dual echo preferred, but not required); and (v) a postcontrast, 3-dimensional, isotropic, T1-weighted IR-GRE sequence with matching acquisition parameters to precontrast T1-weighted images.

Precontrast and Postcontrast Volumetric, IR-Prepared T1-Weighted Gradient Echo MRI

The use of precontrast and postcontrast images (CT or MRI) has been the standard for detection, delineation, and response assessment of malignant brain tumors for more than 60 years. The most aggressive brain tumors are characterized by angiogenesis, and studies have demonstrated a clear association between neovascularization and increased malignancy.[23,24] This new vasculature is structurally abnormal, resulting in contrast agent leakage from the vascular to the extravascular, extracellular space and increased conspicuity of lesions on imaging in the general vicinity of active tumor. T1-weighted MRI sequences, used after administration of a contrast agent that shortens T1 relaxation time, are the standard for response assessment due to better soft tissue contrast and lack of ionizing radiation with MRI as opposed to contrast-enhanced CT.

The acquisition of 3-dimensional, isotropic T1-weighted images allows for potential improvements in response assessment, including detection of smaller lesions, use of volumetric measurements of enhancing tumor burden, and better alignment of tumor regions on subsequent follow-up examinations. Data from the literature clearly indicate that volumetric measurements of tumor burden and response are equal to—or better than—1D/2D measurements of tumor extent, especially with tumors that are irregular in shape such as glioblastoma.[13,25–32] A higher interobserver variability has been noted when assessments are made using bidirectional or unidirectional measurements compared with volumetric quantitation.[33–37] Volumetric changes observed during therapy may be useful for quantifying trends in tumor growth or response that provide insight into whether a treatment is having an effect on the tumor despite lack of clear radiographic response according to the RANO criteria.[38] Additionally, a significant limitation of comparisons in tumor size performed on relatively thick (~3–5 mm) 2-dimensional T1-weighted images includes the effects of slightly different slice prescriptions (eg, different head tilt) on the ability to properly align similar slices for side-by-side comparison.[39] Acquisition of 3-dimensional isotropic T1-weighted images will provide the ability to easily register or align images from subsequent follow–up time points to the baseline scans for more accurate comparison of tumor size. Also, acquisition of 3-dimensional isotropic T1-weighted images allows for resampling image data along different orientations without the need for additional MR acquisitions (eg, in the sagittal or coronal planes, which are often desired for surgical and radiation therapy planning).

Table 1. Minimum standard 1.5 T & 3 T MRI protocol

	3D T1w Pre[b]	Ax 2D FLAIR[j]	Ax 2D DWI		Ax 2D T2w[h,i]	3D T1w Post[b]
Sequence	IR-GRE[e,f]	TSE[c]	SS-EPI[g]		TSE[c]	IR-GRE[e,f]
Plane	Sagittal/axial	Axial	Axial		Axial	Sagittal/axial
Mode	3D	2D	2D		2D	3D
TR [ms]	2100[m]	>6000	>5000		>2500	2100[m]
TE [ms]	Min	100–140	Min		80–120	Min
TI [ms]	1100[n]	2000–2500[k]				1100[n]
Flip angle	10°–15°	90°/≥160°	90°/180°	Contrast Injection[a]	90°/≥160°	10°–15°
Frequency	≥172	≥256	≥128		≥256	≥172
Phase	≥172	≥256	≥128		≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1
FOV	256 mm	240 mm	240 mm		240 mm	256 mm
Slice thickness	≤1.5 mm	≤4 mm[l]	≤4 mm[l]		≤4 mm[l]	≤1.5 mm
Gap/spacing	0	0	0		0	0
Diffusion options[p]			$b = 0$, 500, 1000 s/mm^2 ≥3 directions			
Parallel imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan time (approx) [benchmarked on 3 T Skyra]	5–10 min [5:49 for 1 mm isotropic]	4–8 min [3:22 for 2D FLAIR]	2–4 min [1:22 for 3 direction DWI and 3 b-values]		4–8 min [5:10 for dual echo]	5–10 min [5:49 for 1 mm isotropic]

Abbreviations: 2DFL, 2-dimensional FLASH (fast low angle shot) gradient recalled echo; 3D, 2-dimensional; A/P, anterior to posterior; ADC, apparent diffusion coefficient; Ax, Axial; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; EPI, echo-planar imaging; FLAIR, fluid-attenuated inversion recovery; FOV, field of view; GE-EPI, gradient-echo echo-planar imaging; IR-GRE, inversion-recovery gradient-recalled echo. MPRAGE, magnetization prepared rapid gradient-echo; NEX, number of excitations or averages; PD, proton density; R/L, right to left; SS-EPI, single-shot echo-planar imaging; TE, echo time; TI, inversion time; TR, repetition time; TSE, turbo spin-echo.

[a]0.1 mmol/kg dose injection with a gadolinium-chelated contrast agent. Use of a power injector is desirable at an injection rate of 3–5 cc/s.

[b]Postcontrast 3D T1-weighted images should be collected with equivalent parameters to precontrast 3D T1-weighted images.

[c]TSE = turbo spin-echo (Siemens & Philips) is equivalent to FSE (fast spin-echo; GE, Hitachi, Toshiba).

[d]FL2D = 2-dimensional fast low angle shot (FLASH; Siemens) is equivalent to the spoil gradient recalled echo (SPGR; GE) or T1-fast field echo (FFE; Philips), fast field echo (FastFE; Toshiba), or the radiofrequency spoiled steady state acquisition rewound gradient echo (RSSG; Hitachi). A fast gradient echo sequence without inversion preparation is desired.

[e]IR-GRE = inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).

[f]A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.

[g]In the event of significant patient motion, a radial acquisition scheme may be used (eg, BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Further, this type of acquisition takes considerably more time.

[h]Dual echo PD/T2 TSE is optional for possible quantification of tissue T2. For this sequence, the PD echo is recommended to have a TE < 25 ms.

[i]Advanced sequences can be substituted into this time slot, so long as 3D postcontrast T1-weighted images are collected between 4 and 8 minutes after contrast injection.

[j]3D FLAIR is an optional alternative to 2D FLAIR, with sequence parameters as follows per EORTC guidelines: 3D TSE/FSE acquisition; TE = 90–140 ms; TR = 6000–10 000 ms; TI = 2000–2500 ms (chosen based on vendor recommendations for optimized protocol and field strength); GRAPPA ≤ 2; fat saturation; slice thickness ≤1.5 mm; orientation sagittal or axial; FOV ≤ 250 mm × 250 mm; matrix ≥244 × 244.

[k]Choice of TI should be chosen based on the magnetic field strength of the system (eg, TI ≈ 2000 milliseconds for 1.5 T and TI ≈ 2500 milliseconds for 3 T).

[l]In order to ensure comparable SNR, older 1.5 T MR systems can use contiguous (no interslice gap) images with 5 mm slice thickness or increase NEX for slice thickness ≤4 mm.

[n]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400–450 milliseconds for similar contrast.

[m]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5–15 milliseconds for similar contrast.

[p]Older model MR scanners that are not capable of >2 *b* values should use $b = 0$ and 1000 s/mm^2.

Table 2. Recommended 3T protocol

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI	Contrast Injection[a]	Ax 2D T2w	3D T1w Post[b]
Sequence	IR-GRE[d,e]	TSE[c]	EPI[f]		TSE[c]	IR-GRE[d,e]
Plane	Sagittal/axial	Axial	Axial		Axial	Axial/sagittal
Mode	3D	2D	2D		2D	3D
TR [ms]	2100[g]	>6000	>5000		>2500	2100[g]
TE [ms]	Min	100–140	Min		80–120	Min
TI [ms]	1100[h]	2500				1100[h]
Flip angle	10°–15°	90°/≥160°	90°/180°		90°/≥160°	10°–15°
Frequency	256	≥256	128		≥256	256
Phase	256	≥256	128		≥256	256
NEX	≥1	≥1	≥1		≥1	≥1
FOV	256 mm	240 mm	240 mm		240 mm	256 mm
Slice thickness	1 mm	3 mm	3 mm		3 mm	1 mm
Gap/apacing	0	0	0		0	0
Diffusion options			$b = 0$, 500, and 1000 s/mm^2 ≥3 directions			
Parallel imaging	Up to 2x	Up to 2x	Up to 2x		Up to 2x	Up to 2x
Scan time (approx)	5–8 min	4–5 min	3–5 min		3–5 min	5–8 min

Abbreviations: 3D, 3-dimensional; ADC, apparent diffusion coefficient; A/P, anterior to posterior; Ax, Axial; DWI, diffusion-weighted imaging; EPI, echo-planar imaging; FLAIR, fluid-attenuated inversion recovery; FOV, field of view; IR-GRE, inversion-recovery gradient-recalled echo. MPRAGE, magnetization-prepared rapid gradient-echo; NEX, number of excitations or averages; R/L, right to left; TSE, turbo spin-echo.
[a]0.1 mmol/kg or up to 20 cc (single, full dose) of MR contrast.
[b]Postcontrast 3D axial T1-weighted images should be collected with identical parameters to precontrast 3D axial T1-weighted images.
[c]TSE = turbo spin-echo (Siemens & Philips) is equivalent to FSE (fast spin-echo; GE, Hitachi, Toshiba).
[d]IR-GRE = inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens & Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[e]A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[f]In the event of significant patient motion, a radial acquisition scheme may be used (eg, BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme is can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
[g]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5–15 milliseconds for similar contrast.
[h]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400–450 milliseconds for similar contrast.

Three-dimensional IR-GRE, including MPRAGE or IR-SPGR, is the most commonly used sequence for fast, 3-dimensional evaluation of tumor burden and has been studied extensively as a clinical tool in neuro-oncology for nearly 20 years.[40–44] The use of inversion preparation provides superior gray matter-to-white matter image contrast as well as significant enhancement of vascular structures; however, there is concern that inversion preparation may reduce the amount of lesion conspicuity. We considered potential use of 3-dimensional sequences without inversion preparation but felt the use of IR-GRE sequences was warranted given their current widespread use and extensive literature substantiating their clinical utility. Thus, we recommend 3-dimensional isotropic T1-weighted IR-GRE acquisition, which is available on almost all MR systems as part of the standardized ADNI protocol, and agreement with previous ACRIN, Alliance, and EORTC imaging guidelines for brain tumor clinical trials.

We also considered the potential use of a 3-dimensional turbo spin-echo (TSE) acquisition (eg, SPACE [Siemens] or CUBE [General Electric]) instead of GRE, which studies have suggested may provide a higher CNR between enhancing tumor and background tissues.[45] An inherent drawback of 3-dimensional GRE acquisition is the hyperintensity of blood vessels after contrast agent injection, which may make tumor segmentation more difficult due to increased signal from normal vasculature. The use of 3-dimensional TSE with motion-sensitized driven-equilibrium preparation has been shown to overcome this limitation by suppressing signal from blood.[46] Despite the potential advantages of 3-dimensional TSE over GRE, this sequence is not available on all MR systems, may require additional costs to purchase these sequences, and the specific pulse sequences are not necessarily standardized across vendors. Thus, we recommend 3-dimensional isotropic T1-weighted images using a GRE acquisition, available on almost all MR systems as part of the standardized ADNI protocol and in agreement with previous ACRIN, Alliance, and EORTC imaging guidelines for brain tumor clinical trials.

The use of precontrast and postcontrast T1-weighted images with matched sequence parameters also allows for use of contrast-enhanced T1-weighted subtraction for tumor visualization and quantification of enhancing tumor. By subtracting the voxel intensities obtained on precontrast T1-weighted

Table 3. Recommended 1.5T protocol

	3D T1w Pre	Ax 2D FLAIR	Ax 2D DWI		Ax 2D T2w	3D T1w Post[b]
Sequence	IR-GRE[d,e]	TSE[c]	EPI[f]		TSE[c]	IR-GRE[d,e]
Plane	Sagittal/axial	Axial	Axial		Axial	Sagittal/axial
Mode	3D	2D	2D		2D	3D
TR [ms]	2100[g]	>6000	>5000		>3500	2100[g]
TE [ms]	Min	100–140	Min		100–120	Min
TI [ms]	1100[h]	2200		Contrast Injection[a]		1100[h]
Flip angle	10°–15°	90°/≥160°	90°/180°		90°/≥160°	10°–15°
Frequency	≥172	≥256	128		≥256	≥172
Phase	≥172	≥256	128		≥256	≥172
NEX	≥1	≥1	≥1		≥1	≥1
FOV	256 mm	240 mm	240 mm		240 mm	256 mm
Slice thickness	≤1.5 mm	≤4 mm	≤4 mm		≤4 mm	≤1.5 mm
Gap/spacing	0	0	0		0	0
Diffusion options[i]			$b = 0$, 500, and 1000 s/mm^2 ≥3 directions			
Parallel imaging	No	Up to 2x	Up to 2x		Up to 2x	No
Scan time (approximate)	5–10 min	4–5 min	3–5 min		3–5 min	5–10 min

Abbreviations: 3D, 3-dimensional; A/P, anterior to posterior; ADC, apparent diffusion coefficient; Ax, axial; DWI, diffusion-weighted imaging; EPI, echo-planar imaging; FLAIR, fluid-attenuated inversion recovery; FOV, field of view; IR-GRE, inversion-recovery gradient-recalled echo; MPRAGE, magnetization prepared rapid gradient-echo; NEX, number of excitations or averages; R/L, right to left; TSE, turbo spin-echo.
[a]0.1 mmol/kg or up to 20 cc (single, full dose) of MR contrast.
[b]Postcontrast 2D axial T1-weighted images should be collected with identical parameters to precontrast 2D axial T1-weighted images.
[c]TSE = turbo spin-echo (Siemens & Philips) is equivalent to FSE (fast spin-echo; GE, Hitachi, Toshiba).
[d]IR-GRE = inversion-recovery gradient-recalled echo sequence is equivalent to MPRAGE = magnetization prepared rapid gradient-echo (Siemens and Hitachi) and the inversion recovery spoiled gradient-echo (IR-SPGR or Fast SPGR with inversion activated or BRAVO; GE), 3D turbo field echo (TFE; Philips), or 3D fast field echo (3D Fast FE; Toshiba).
[e]A 3D acquisition without inversion preparation will result in different contrast compared with MPRAGE or another IR-prepped 3D T1-weighted sequences and therefore should be avoided.
[f]In the event of significant patient motion, a radial acquisition scheme may be used (eg, BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option.
[g]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TR = 5–15 milliseconds for similar contrast.
[h]For Siemens and Hitachi scanners. GE, Philips, and Toshiba scanners should use a TI = 400–450 milliseconds for similar contrast.
[i]Older model MR scanners that are not capable of >2 *b*-values should use $b = 0$ and 1000 s/mm^2.

images from postcontrast T1-weighted images, contrast agent accumulation can be more easily identified and quantified. This technique has been used in conjunction with MRI for brain tumors starting in the early 1990s, when Suto et al[47] and Lloyd et al[48] demonstrated the ability to identify enhancing tumors in the presence of blood products. Subsequent studies over the next few decades have further established the added value of T1-weighted subtraction maps for lesion evaluation during standard therapies, and a recent study clearly demonstrated that enhancing tumor could be better identified on T1-weighted subtraction maps during antiangiogenic therapy,[49] where vascular permeability is markedly reduced. Additionally, T1-weighted subtraction maps have been shown to reduce the interobserver variability in lesion volume quantification, even in the presence of antiangiogenic therapies,[14] suggesting that evaluation of tumor response may be significantly improved through the use of T1-weighted subtraction techniques.

Ranges of sequence parameters were chosen for volumetric T1-weighted images based on known scanner and time limitations. An isotropic resolution of 1 mm × 1 mm × 1 mm is recommended with full brain coverage (field-of-view of 25.6 cm), but this may not be possible with older MR systems or with adequate SNR at 1.5 T. Therefore, we recommend acquiring volumetric T1-weighted images with a *maximum* resolution of 1.5 mm × 1.5 mm × 1.5 mm, particularly for scanners at 1.5 T. Additionally, sagittal image acquisition is recommended over axial acquisition because sagittal acquisition is faster due to fewer required slices moving from left-to-right, although postcontrast flow artifacts have occasionally been observed. Although standard 3-dimensional T1-weighted GRE sequences are preferred (eg, MPRAGE [Siemens & Hitachi] or IR-SPGR [GE]), faster volumetric T1-weighted GRE sequences with internal motion compensation may also be used under similar acquisition parameters to reduce artifacts (eg, BRAVO [GE] or VIBE [Siemens]). Additional scan parameters and details are documented in Table 1.

Institutions may desire to collect postcontrast T1-weighted images according to their own protocols in addition to the recommended 3-dimensional isotropic T1-weighted images (eg,

2-dimensional, fat-saturated, T1-weighted TSE images). For compliance with the proposed protocol, we recommend that additional postcontrast sequences be acquired *after* 3-dimensional, postcontrast T1-weighted images in order to ensure consistency in terms of the timing of contrast agent injection and acquisition of postcontrast T1-weighted images.

Use of Contrast Agents and Consistency of MR Scanners

Consistency in MR scanning hardware, software, contrast agent dose, and contrast agent composition is absolutely imperative for maximizing accurate and reproducible serial measurements of tumor size. Patients involved in clinical trials should be scanned on the same physical MRI scanner during routine follow-up examinations to the extent that this is both economically and technically feasible. If this ideal recommendation is not achievable, patients should at the very least be scanned on MRI scanners with the same field strength. Although it may be difficult to control the specific contrast agent used for clinical trials, it is critical to use contrast agents with the same chemical composition at each follow-up evaluation as baseline to limit potential variability arising from differences in contrast agent relaxivity (the amount of MR relaxation effects for a given concentration of contrast agent). Additionally, the precise dose and agent should be explicitly documented on the MR system during acquisition or labeled in the DICOM header (eg, Contrast_BolusAgent (0018,0010) = 1.5 cc Gadovist).

Axial, 2-Dimensional, T2-Weighted Turbo Spin-echo (Optional Dual-Echo Proton-Density/T2-Weighted TSE) MRI

Damadian[50] documented distinct differences in proton relaxation rates between normal and cancerous tissues as early as 1971, which were subsequently confirmed by various groups.[51–53] Clinical diagnoses and monitoring of the nonenhancing tumor are often performed using T2-weighted images. Approximately 30%–40% of brain tumor patients exhibit nonenhancing tumor progression prior to changes in contrast enhancement,[32] and some studies have described nonenhancing tumor growth and infiltration prior to emergence of contrast-enhancing progressive disease during antiangiogenic therapy.[54] Further, T2 hyperintense lesions are currently used to assess tumor burden in nonenhancing, low-grade glioma clinical trials. Therefore, use of T2-weighted images in the proposed protocol is recommended for all clinical brain tumor trials.

The protocol recommended for T2-weighted imaging was based on the parameters from ADNI as well as ACRIN, Alliance, and EORTC guidelines in existing trials. The recommended slice thickness for 3 T scans is 3 mm with no interslice gap, and 1.5 T scanners should acquire images up to 4 mm slice thickness with no interslice gap. (Older scanners still in operation may be allowed to acquire data up to a maximum of 5 mm slice thickness [contiguous] or increase the number of averages with slice thicknesses $\leq$4 mm to ensure comparable SNR to other T2-weighted images acquired with newer systems; however, this should be avoided if possible.) The recommended echo train length (ETL) is between 8 and 16, since an increase in ETL both accelerates acquisition and increases inaccuracies[55] associated with T2 mapping when using dual echo TSE to estimate tissue T2.

Timing of Contrast Agent Injection and Postcontrast T1-weighted Images

A high CNR between tumor and surrounding tissue is critical for precise measurement of tumor size. In addition to differences in sequences and sequence parameters,[56] the timing of contrast injection and acquisition of subsequent postcontrast T1-weighted images can also lead to variability in tumor size estimation. Dynamic contrast-enhanced imaging has shown that the maximum contrast agent uptake typically occurs and stabilizes between 4 and 8 minutes after contrast agent application,[57] suggesting that this may be the most effective window for acquiring postcontrast T1-weighted images for minimal variability in lesion size estimation caused by the timing of contrast agent administration. It is important to note that one inherent limitation to implementing a *minimal* time delay constraint is the preferential sensitivity to regions of the tumor with higher vascular permeability and/or blood flow. To standardize the minimal time between contrast agent injection and acquisition of postcontrast T1-weighted images, we recommend acquiring T2-weighted images after injection and just prior to postcontrast T1-weighted images. Presumably, T2-weighted images utilizing spin-echo or TSE acquisitions should be relatively insensitive to the presence of contrast agent in the vasculature, assuming transient changes have already occurred (ie, assuming it is not during the first pass of the bolus injection), such that RANO interpretation and volumetric segmentation of T2-hyperintense regions should be minimally impacted.

Axial, 2-Dimensional, T2-Weighted Fluid-Attenuated Inversion Recovery) MRI

T2-weighted fluid-attenuated inversion recovery (FLAIR) MRI uses a combination of T1- and T2-weighting to suppress the signal originating from bulk fluid including cerebrospinal fluid. T2-weighted FLAIR techniques increase lesion conspicuity, allowing for better visualization of vasogenic edema, surgery-induced and radiation- induced gliosis and infiltrating tumor, particularly near the cortex and ventricles where cerebrospinal fluid can inhibit lesion detection. Additionally, T2-weighted FLAIR sequences (or T2-weighted images) are recommended for determination of nonenhancing tumor progression using RANO criteria.

The preferred protocol for T2-weighted FLAIR imaging was based on guidelines from the EORTC, ACRIN, and Alliance. Similar to T2-weighted MRI, the recommended slice thickness for 3 T scans is 3 mm with no interslice gap, and 1.5 T scanners should acquire images up to 4 mm slice thickness with no interslice gap. Older scanners still in operation may be allowed to acquire data up to a maximum of 5 mm slice thickness (contiguous) or increase the number of averages with slice thicknesses $\leq$4 mm to ensure comparable SNR to other T2-weighted FLAIR images acquired with newer systems. Also note that T2-weighted FLAIR MR images have intrinsically less SNR compared with standard T2-weighted MR images. The recommended ETL for T2-weighted FLAIR images is between 8 and 16.

Three-dimensional T2-weighted FLAIR techniques are commonly used on newer MR systems but may not be available on all MR systems. A 3-dimensional acquisition allows for slice reorientation in all 3 anatomical planes, the potential for

quantification of T2-hyperintense lesion volumes, and less sensitivity to flow artifacts compared with 2D sequences. Given that 3-dimensional acquisition is not universally available, the use of this technique, while strongly endorsed, is optional. Protocols or studies considering the use of 3D FLAIR should use the EORTC-recommended parameters listed in the footnotes in Table 1.

Axial 2-Dimensional Diffusion-Weighted Imaging

Diffusion-sensitive MR techniques are routinely acquired as part of standard brain MRI protocols, primarily due to the high sensitivity to early ischemic injury as well as infection/abscess. DWI is sensitive to microscopic, subvoxel water motion, resulting in relatively restricted diffusion in areas of tumor due to tightly packed tumor cells. Measures of the apparent diffusion coefficient (ADC) can be estimated from the DWI data, reflecting the general magnitude of water motion. In brain tumors, ADC has been shown to be a surrogate for cellularity in certain circumstances, with ADC inversely correlated with tumor cell density,[58–61] suggesting that DWI measures of ADC may be a useful biomarker for quantifying treatment response.[62]

The recommended DWI protocol for routine evaluations is largely based on the EORTC, ACRIN, and Alliance-recommended protocols as well as the International Society for Magnetic Resonance in Medicine and NCI consensus recommendations from 2008.[62] Specifically, we recommend that 3 *b*-values be collected, one at $b = 0$ s/mm^2 (no diffusion weighting), one mid-range *b*-value of 500 s/mm^2, and one higher *b*-value at $b = 1000$ s/mm^2. These images should be collected in at least 3 directions (ie, *x, y,* and *z* orientations with respect to the MR system frame of reference). Older MR scanners that are not capable of obtaining 3 or more unique *b*-values should use $b = 0$ and $b = 1000$ s/mm^2. The high *b*-value for routine DWI in clinical trials should be limited to $b = 1000$ s/mm^2, resulting in a relative signal intensity of 37% of available MR signal if tissue has an ADC of 1 μm^2/millisecond, commonly associated with mean diffusivity of normal white matter. The recommended slice thickness for 3 T scans is 3 mm with no interslice gap, and 1.5 T scanners should acquire images up to 4 mm slice thickness with no interslice gap. Older scanners still in operation may be allowed to acquire data up to a maximum of 5 mm slice thickness (contiguous) or increase the number of averages with slice thicknesses $\leq$4 mm to ensure comparable SNR echo-planar imaging (EPI) should be used when available. In the event of significant patient motion, a radial acquisition scheme may be used (eg, BLADE [Siemens], PROPELLER [GE], MultiVane [Philips], RADAR [Hitachi], or JET [Toshiba]); however, this acquisition scheme can cause significant differences in ADC quantification and therefore should be used only if EPI is not an option. Additionally, radial acquisition techniques may require considerably more time.

Conclusion

The proposed recommendations for brain tumor MRI acquisition reflect a balance of state-of-the-art imaging technology with techniques that are practically employable across the majority of imaging centers involved in multicenter clinical trials. We specifically recommend this protocol for use in multicenter clinical trials to reduce variability associated with response assessment, but we also encourage the use of this protocol in routine clinical practice where it will allow intra-institutional comparisons. The protocol was designed to allow flexibility in terms of adding subsequent imaging techniques, such as the addition of perfusion MRI prior to acquisition of postcontrast 3D T1-weighted images, the addition of susceptibility-weighted or gradient-echo acquisition before contrast injection, or acquisition of postcontrast, 2D T1-weighted TSE images following postcontrast 3D T1-weighted image acquisition. The current recommendations were designed to serve as a benchmark for comparison to future improvements and evaluations.

The current recommendations solely involve acquisition of MR images and do not provide guidelines for the clinical interpretation or quantitation of tumor extent for the purposes of response evaluation. The current protocols were designed to be flexible and allow for both current RANO evaluations as well as the potential for future improvements including volumetric analyses.

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