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The Impact of MRI-Based Advanced Neuroimaging on Neurooncologists' Clinical Decision-Making in Patients With Posttreatment High-Grade Glioma: A Prospective Survey-Based Study

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Abstract

Background: Advanced MRI-based neuroimaging techniques, such as perfusion and spectroscopy, have been increasingly incorporated into routine follow-up protocols in patients treated for high-grade glioma (HGG), to help differentiate tumor progression from treatment effect. However, these techniques' influence on clinical management remains poorly understood.

Objective: To evaluate the impact of MRI-based advanced neuroimaging on clinical decision-making in patients with HGG in the posttreatment setting.

Methods: This prospective study, performed at a comprehensive cancer center from March 1, 2017, to October 31, 2020, included adult patients treated by chemoradiation for WHO grade 4 diffuse glioma who underwent MRI-based advanced neuroimaging (comprising multiple perfusion imaging sequences and spectroscopy) to further evaluate findings on conventional MRI equivocal for tumor progression versus treatment effect. The ordering neuro-oncologists completed surveys before and after each advanced neuroimaging session. The percent of care episodes with a change between the intended and actual management plan on the surveys conducted before

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and after advanced neuroimaging, respectively, was computed and compared with a previously published percent using the Wald test for independent samples proportions.

Results: The study included 63 patients (mean age, 55±13 years; 36 women, 27 men) who underwent 70 advanced neuroimaging sessions. Ordering neuro-oncologists' intended and actual management plans on the surveys completed before and after advanced neuroimaging, respectively, differed in 44% (31/70, [95% CI: 33–56%]) of episodes, which differed from the previously published frequency of 8.5% (5/59) ($p<.001$). These management plan changes included selection of a different plan for 6/8 episodes with an intended plan to enroll patients in a clinical trial, 12/19 episodes with an intended plan to change chemotherapeutic agents, 4/8 episodes with an intended plan of surgical intervention, and 1/2 episodes with an intended plan of re-irradiation. The ordering neuro-oncologists found advanced neuroimaging to be helpful in 93% (95% CI: 87%–99%) (65/70) of episodes.

Conclusion: Neuro-oncologists' management plans changed in a substantial fraction of adult patients with HGG who underwent advanced neuroimaging to further evaluate conventional MRI findings equivocal for tumor progression versus treatment effect.

Clinical Impact: The findings support incorporation of advanced neuroimaging into HGG posttreatment monitoring protocols.

Highlights

Key Finding: Neuro-oncologists' intended and actual management plans before and after advanced neuroimaging, respectively, differed in 44% (31/70, [95% CI: 33–56%]) of care episodes for patients with HGG and equivocal posttreatment findings on conventional MRI. Neuro-oncologists found advanced neuroimaging to be helpful in 93% (95% CI: 87%–99%) (65/70) of episodes.

Importance: The impact of advanced neuroimaging techniques on management decisions supports their incorporation into imaging protocols for treatment monitoring in adult patients with HGG.

Introduction

High-grade gliomas (HGGs) are the most common primary malignant brain tumors in adults. Despite advances in cancer precision therapy, the prognosis for HGG remains poor, with a 1-year relative survival of 42.9% and 5-year relative survival of 6.9% [1]. Neuroimaging is used to noninvasively monitor treatment response in patients with HGG in the absence of a validated molecular biomarker for this purpose. For example, NCCN guidelines from 2023 recommend follow-up of patients undergoing HGG treatment with serial conventional MRI examinations [2]. Recognizing the limited ability of conventional MRI to distinguish progression from treatment effects [3], working groups have refined different sets of imaging criteria to boost the modality's reliability for tumor assessment, such as the Response Assessment in Neuro-Oncology 2.0 criteria [4] and the Brain Tumor Reporting And Data Systems [5].

Advanced MRI-based neuroimaging techniques have also been used to aid the differentiation of tumor progression from treatment effects [6]. For example, MR perfusion imaging may aid identification of the structurally aberrant blood vessels that develop in association with tumor progression through visualization of hyperperfused foci having increased cerebral blood volume, flow, and capillary permeability. Similarly, MR spectroscopy (MRS) has been used to help distinguish progression from treatment change by detecting local metabolic signatures.

These advanced neuroimaging techniques' diagnostic accuracy for posttreatment brain tumor evaluation is well-established [7–12]. Nonetheless, their impact on clinical decision-making in real-world neuro-oncology practice remains poorly investigated. To our knowledge, the only study to address this issue was by Geer et al. in 2012 [13]. In that study, the addition of two MR perfusion imaging techniques, dynamic susceptibility contrast MRI (DSC) and arterial spin labeling MRI (ASL), to conventional MRI altered decision-making in 8.5% of care episodes. However, that study's retrospective nature and small sample size decreases its generalizability to the current neuro-oncology practice.

Advanced neuroimaging has been increasingly integrated into routine follow-up protocols for HGG. This clinical integration benefits from knowledge of which patients with HGG would most benefit from these techniques. Appropriate patient selection would not only influence clinical practice guidelines, but

also help ensure cost-effective resource utilization. Indeed, advanced neuroimaging is costly, increases acquisition time, and requires specialized expertise by technologists and neuroradiologists [14,15].

The purpose of this study was to evaluate the impact of MRI-based advanced neuroimaging on clinical decision-making in patients with HGG in the posttreatment setting.

Methods

Patient Selection

This survey-based, HIPAA-compliant, institutional review board-approved prospective study was conducted at the brain and spine institute of a comprehensive cancer center. Seven practicing neuro-oncologists at the study institution provided written informed consent to participate before the study's initiation date. The requirement to obtain written informed consent from patients was waived. The study was part of a larger initiative studying advanced neuroimaging in patients with HGG. At the study institution, approximately half of patients with HGG who undergo conventional MRI are also ordered to undergo advanced neuroimaging.

All patients treated at the study institution between March 1, 2017, and October 31, 2020, by one of the seven neuro-oncologists were screened for potential eligibility. Patients were eligible if they were at least 18 years old and had a diagnosis, based on histomolecular confirmation, of a WHO grade 4 diffuse HGG, defined as either glioblastoma isocitrate dehydrogenase (IDH)-wildtype or astrocytoma IDH-mutant WHO grade 4 (hereafter also described as IDH-wildtype and IDH-mutant tumors, respectively). These diagnoses were rendered based on the 2016 WHO classification of CNS tumors but were concordant with the subsequent 2021 classification given that all tumors had a grade of 4 and had been tested for IDH mutations by immunohistochemistry and/or next generation sequencing [16]. Additionally, to be eligible, patients were required at the time of selection to have completed a standard 6-week course of chemoradiation [17]. Finally, the patient's neuro-oncologist was required to have recommended that the patient undergo advanced neuroimaging for further evaluation of findings on

conventional MRI that were equivocal for the differentiation of tumor progression from treatment effect (defined as increased T2-weighted or T2-weighted FLAIR signal abnormality and/or mass-like enhancement on postcontrast T1-weighted images within or near the radiation field).

Given the institution's high clinical volume of advanced neuroimaging, a systematic sampling approach was used whereby every fourth patient meeting the eligibility criteria was selected for inclusion. For selected patients, the ordering neuro-oncologist received both a pre-survey at the time of the visit before advanced neuroimaging (after placing the advanced neuroimaging order), and a post-survey at the time of the patient's next visit after advanced neuroimaging. Selected patients could be included multiple times if, after selection, they were recommended to undergo multiple advanced neuroimaging sessions for further evaluation of equivocal findings on multiple conventional MRI examinations occurring during the study period; in such instances, a separate pre-survey and post-survey were completed for each such advanced neuroimaging session. The study's unit of analysis was an episode of care (EOC), defined as the advanced neuroimaging session and its associated pre-survey and post-survey. The final study sample comprised all EOCs for which the pre-survey and post-survey were completed, with no further exclusion criteria applied. The time from conventional MRI to advanced neuroimaging was recorded for all EOCs.

Advanced Neuroimaging Acquisition and Processing

Conventional MRI examinations were routinely performed at the study institution on a clinical 1.5-T or 3-T scanner and included pre- and post-contrast T1-weighted sequences; T2-weighted, T2-weighted FLAIR, and T2*-weighted sequences; and DWI with ADC map reconstruction. Advanced neuroimaging was performed as a separate imaging session on a clinical 3-T scanner (Prisma, Siemens Medical Solutions, Erlangen, Germany; MR750, GE Healthcare, Waukesha, WI, USA) with acquisition of the following four techniques, in order: ASL, multi-voxel or single-voxel MRS, dynamic contrast-enhanced MRI (DCE), and gradient-echo DSC. An additional T1 mapping sequence was performed before DCE, to aid DCE analysis. **Table S1** lists parameters for each technique. ASL was acquired only for advanced neuroimaging sessions performed on a GE scanner.

For each advanced neuroimaging session, the patient received two separate injections (one each for DCE and DSC) of a full dose (0.1 mmol/kg, Gadavist, Bayer HealthCare, NJ) of gadolinium-based contrast agent, each administered at a rate of 3-5 mL/s followed by a 30-mL saline flush. ASL, DCE, and DSC images were post-processed to obtain parametric maps of relative cerebral blood flow, forward volumetric transfer constant, and relative cerebral blood volume, respectively. ASL images were processed on the scanner console using vendor software. DCE and DSC datasets were processed with nICE (Nordic ICE, NordicNeuroLab, Bergen, Norway). The transfer constant map was obtained by pharmacokinetic modeling of the DCE data using the extended Toft's model [18], after signal conversion using the pre-contrast T1 map. The relative cerebral blood volume map was obtained by calculating the area under the concentration-time curve of the DSC images, after correcting for contrast agent extravasation [19]. Additional T1-weighted and T2-weighted sequences were obtained during the advanced neuroimaging sessions for purposes of anatomic localization.

Advanced Neuroimaging Interpretation

Advanced neuroimaging sessions were interpreted clinically by one of 10 fellowship-trained, board-certified neuroradiologists (V.A.K., M.K.G., J.M.J., N.N.C., D.K., D.F.S., D.S., K.O.L., S.C. and K.B.S.; with 4 to 28 years [median, 9 years [IQR, 6.5-14.8 years]] of post-training experience in neuroradiology). Results were immediately available to clinicians via the EMR. Parametric maps derived from ASL, DCE, and DSC were evaluated qualitatively without specific cutoffs for determining the presence of tumor progression. This approach was used to mirror real-world practice whereby neuroradiologists apply varying thresholds when evaluating perfusion or permeability maps [20]. MRS spectra were similarly assessed qualitatively based on relative choline concentration (compared to contralateral normal white matter), choline-to-creatine ratio, and presence of a lipid/lactate peak. The interpreting radiologist classified the session as showing progression or treatment effect if all four techniques were concordant in this distinction. If the four techniques were discordant, or if individual

techniques showed heterogeneous findings, then the radiologist classified the session as showing mixed findings.

To facilitate subsequent data analysis for the present investigation, a neuroradiologist (M.M.C., 9 years of neuroradiology post-training experience) in consultation with a neuro-oncologist (J.Y.N., 9 years of neuro-oncology post-training experience) re-reviewed advanced neuroimaging sessions that had been interpreted as showing mixed findings. The two investigators categorized such sessions as showing progression if at least two techniques sequences showed progression in more than 50% of the tumor volume, and as showing treatment effect otherwise.

Survey Administration

Survey data were collected and managed using REDCap electronic data capture tools hosted at the study institution [21,22]. As soon as a participating neuro-oncologist placed an order for advanced neuroimaging in an eligible patient, the tool performed the previously described systematic sampling to determine if the patient was selected for further inclusion. If the patient was selected, then, immediately after order placement, the ordering neuro-oncologist automatically received an email with a hyperlink to the pre-survey. This survey contained questions relating to the patient's date of birth, legal sex, histomolecular diagnosis, treatment stage, adjuvant chemotherapy cycle number, suspected likely result of the ordered advanced neuroimaging, next likely step if the ordered advanced neuroimaging were to show progression, and next likely step if the ordered advanced neuroimaging were to show treatment effect. For included patients, at the time of the patient's next visit after advanced neuroimaging (occurring 4-6 weeks after the prior visit), the neuro-oncologist also automatically received an email with a hyperlink to the post-survey. This survey contained questions relating to the date of advanced neuroimaging, the advanced neuroimaging result, the setting in which the neuro-oncologist interpreted the advanced neuroimaging result, whether the neuro-oncologist agreed with the radiologist's interpretation, whether the neuro-oncologist found the advanced neuroimaging result helpful, whether there was a need to repeat advanced neuroimaging, the next step in management, and the next follow-up imaging procedure. All questions

regarding next treatment steps on the pre-survey and post-survey presented the same six options, as well as an option of "other." Survey questions included a combination of binary, multi-level categorical, and free-text responses. **Appendix 1** and **Appendix 2** show the pre-survey and post-survey, respectively.

Statistical Analysis

Survey results were summarized descriptively. Continuous variables were summarized in terms of their mean and SD or median and IQR; categorical variables were summarized via their count and percent. Agreement between neuro-oncologists' suspected advanced neuroimaging result reported on the pre-survey and the actual advanced neuroimaging result reported on the post-survey was assessed by a Cohen's kappa coefficient, characterized as [23]: <0.00, poor; 0.00-0.20, slight; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80, substantial; >0.80, almost perfect.

The study's primary endpoint was the percent of EOCs in which the neuro-oncologist's intended next management step on the pre-survey was different from the neuro-oncologist's actual next step on the post-survey. The intended next management step on the pre-survey was defined as the likely next management step for the suspected likely advanced neuroimaging result (progression vs treatment effect). The percent of EOCs with a management change was compared between the present study and the study by Geer et al.[13] using the Wald test for comparison of independent samples proportions. Fisher's exact test was used to assess for an association between a management change and IDH status.

In terms of the primary endpoint, the study investigators (comprising neuroradiologists and neuro-oncologists) hypothesized based on clinical experience that the intended and actual management plans would be different in at least one-third of EOCs. Based on this hypothesized frequency, at least 71 EOCs were required to estimate the proportion of EOCs with a management change with a confidence of 95% and an absolute margin of error of 11%, as well as to detect a significant difference in this percent between the present study and the study by Geer et al [13].

Several secondary analyses were performed. First, the distributions of intended and actual management plans were compared using a paired-sample McNemar-Bowker test of symmetry. This

comparison was followed by a post hoc power analysis with a target power of 80%. The frequency of a management change was also compared across HGG treatment stages as reported on the pre-survey (post-chemoradiation, adjuvant chemotherapy, surveillance) and, in patients on adjuvant chemotherapy, compared across ranges of prior numbers of cycles completed (<3, 3-6, >6), using Fisher's exact tests. The frequency of a management change was also separately compared among these groups for EOCs for IDH-wildtype tumors and EOCs for IDH-mutant tumors.

Finally, the frequency of a management change was computed for a hypothetical scenario whereby the intended management plan corresponded with a suspected advanced neuroimaging result that matched the actual advanced neuroimaging result for all EOCs. In this hypothetical scenario, because the intended management plan was adjusted post hoc to reflect the actual advanced neuroimaging results, the intended and actual management plans would theoretically be expected to match for all EOCs. As in the primary analysis, the distributions of intended and actual management plans were compared using a paired-sample McNemar-Bowker test of symmetry, followed by a post hoc power analysis.

A statistically significant difference was defined at a p value threshold of less than .05. Clopper-Pearson exact 95% CIs were calculated for select results on the post-survey and for select comparisons between the pre-survey and post-survey. Data were analyzed using version 28.0 (IBM SPSS, inc., Chicago, IL). Post hoc power analyses were performed using PASS version 23.0.2 (NCSS, LLC., Kaysville, UT). Charts were generated using Prism version 10.0 (GraphPad Software, Boston, MA). Statistical analysis was performed in consultation with a biostatistician (J.S.).

Results

Patients and Care Episodes

A total of 448 patients were treated by one of the seven neuro-oncologists at the study institution during the study period. Of these patients, 252 fulfilled the eligibility criteria. After systematic sampling, 63 of these patients were selected for inclusion. Seven of these patients underwent two advanced

neuroimaging sessions. For all of these sessions, the pre-survey, advanced neuroimaging session, and post-survey were successfully completed. Thus, the final study sample included 70 EOCs in 63 patients. **Figure 1** shows the flow of patient selection. A total of 28/70 advanced neuroimaging sessions included ASL; all sessions included DCE, DSC, and MRS.

Pre-Survey Results

Table 1 summarizes pre-survey results. A total of 27 patients (who underwent 30 EOCs) were male; 36 patients (who underwent 40 EOCs) were female. Patients had a mean age of 54.6±12.9 years at the time of the 70 advanced neuroimaging sessions. A total of 54/63 patients (who underwent 60 EOCs) had IDH-wildtype glioblastoma, and 9/63 patients (who underwent 10 EOCs) had IDH-mutant astrocytoma WHO grade 4. In the 70 EOCs, the median time from the equivocal conventional MRI to the subsequent advanced neuroimaging session was 3 weeks (IQR, 2-4 weeks). At the time of advanced neuroimaging, the patient was receiving adjuvant chemotherapy in 45/70 (64%) EOCs [median, 4 cycles completed (IQR, 2–7 cycles completed)]; the patient was on surveillance (i.e., off treatment) in 17/70 (24%) EOCs; and the patient was post-chemoradiation (i.e., had just completed such therapy) in 8/70 (11%) EOCs.

The neuro-oncologist suspected the ordered advanced neuroimaging would show progression in 32/70 (46%) EOCs and treatment effect in 38/70 (54%) EOCs. The frequency of suspected progression was not significantly different between EOCs with IDH-wildtype tumors [28/60 (47%)] and EOCs with IDH-mutant tumors [4/10 (40%)] (p=.75). The neuro-oncologist reported that, if advanced neuroimaging showed progression, their likely next step would most commonly be to change the chemotherapeutic agents (30/70, 43%), enroll the patient in a clinical trial (19/70, 27%), or pursue surgical intervention (i.e., resection, biopsy, or laser interstitial thermal therapy) (11/70, 16%). In comparison, if advanced neuroimaging showed treatment effect, their next likely step would most commonly be to continue the current treatment with or without short-term follow-up evaluation (59/70, 84%) or change chemotherapeutic agents (7/70, 10%). Based on the neuro-oncologists' suspected advanced neuroimaging

result and the likely next step for that result, the intended management plan was most commonly to continue current treatment with or without short-term follow-up evaluation (32/70, 46%) or change chemotherapeutic agents (19/70, 27%).

Post-Survey Results

Table 2 summarizes post-survey results. Based on the post-survey, advanced neuroimaging showed progression in 37% (26/70), treatment effect in 46% (32/70), and mixed findings in 17% (12/70). The subsequent retrospective review of the 12 EOCs with mixed findings re-classified nine as showing progression and three as showing treatment effect. Following this reclassification, advanced neuroimaging showed progression in 50% (35/70), and treatment effect in 50% (35/70) of EOCs. The frequency of progression was not significantly different between EOCs for IDH-wildtype tumors [34/60 (57%)] and EOCs for IDH-mutant tumors [4/10 (40%)] (p=.50). The neuro-oncologist found the advanced neuroimaging results helpful in 93% (95% CI: 87-99%) (65/70) of EOCs and indicated that there was no need to repeat advanced neuroimaging in 91% (95% CI: 83–96%) (64/70) of EOCs. The frequency with which advanced neuroimaging results were helpful was not significantly different between EOCs for IDH-wildtype tumors [93% (95% CI: 84–98%] (56/60)] and EOCs for IDH-mutant tumors [90% (95% CI: 56–100%) (9/10)] (p=.55). After advanced neuroimaging, neuro-oncologists' next step in management was most commonly to continue current management with or without short-term follow-up evaluation [53% (37/70)] or change chemotherapeutic agents [27% (19/70)].

Changes in Diagnoses and Management Plans Between Pre-Survey and Post-Survey

Table S2 shows the cross-tabulation between the neuro-oncologists' suspected advanced neuroimaging result reported in the pre-survey and the actual advanced neuroimaging result reported in the post-survey. The suspected and actual advanced neuroimaging results were discordant in 44% (31/70) of EOCs [kappa, 0.11 [95% CI: -0.12, 0.35]; slight agreement].

Table 3 shows the cross-tabulation between intended and actual management plans from the pre-surveys and post-surveys, respectively. Neuro-oncologists' intended and actual management plans differed in 44% (95% CI: 33–56%) (31/70) of EOCs. This frequency was significantly greater than the frequency of 8.5% (5/59) reported by Geer et al. [13] (p<.001). The frequency of a management change was not significantly different between EOCs for IDH-wildtype tumors [45% (95% CI: 32–58%) (27/60)] and EOCs for IDH-mutant tumors [40% (95% CI: 12–74%) (4/10)] (p>.99).

For 6/8 (75%) EOCs in which the intended management plan was to enroll the patient in a clinical trial, the actual management plan entailed a different option. Of these six EOCs, the suspected and actual advanced neuroimaging results differed in three EOCs and matched in three EOCs. For 12/19 (63%) EOCs in which the intended management plan was to change chemotherapeutic agents, the actual management plan entailed a different option. Of these 12 EOCs, the suspected and actual advanced neuroimaging results differed in seven EOCs and matched in five EOCs. Additionally, for 4/8 and 1/2 EOCs for which the intended management plan was surgical intervention or re-irradiation, respectively, the actual management plan entailed a different option; in all of those EOCs, the suspected and actual advanced neuroimaging results differed. Of 8/32 (25%) EOCs for which the intended management plan was to continue current management with or without short-term follow-up evaluation, the actual management plan entailed a different option (change chemotherapy agents, enroll in a clinical trial, surgical intervention, or re-irradiation); in all of those EOCs, the suspected and actual advanced neuroimaging results differed. **Figure 2** illustrates the management plan changes among the EOCs.

Secondary Analyses

The distribution of management plans was not significantly different between the intended and actual plans (p=.71). In the post hoc power analysis, 242 EOCs would have been required to detect a significant difference in this distribution, reflecting a discordant proportions ratio sum of 0.078. Furthermore, this distribution was not significantly different between intended and actual management plans among IDH-wildtype tumors (p=.69) (**Table S3**) or IDH-mutant tumors (p=.57) (**Table S4**). **Figure 3** and **Figure 4**

present conventional MRI examinations and subsequent advanced neuroimaging in patients with tumor progression and treatment effect, respectively.

Table 4 compares the frequency of a management plan change among treatment stages and, for patients on adjuvant chemotherapy, among ranges of number of completed cycles. **Table 4** also shows these comparisons separately among EOCs for IDH-wildtype tumors and EOCs for IDH-mutant tumors. None of these comparisons of the frequency of a management change was statistically significant (all $p>.05$), although p values were not computed for the comparisons among ranges of number of completed cycles among EOCs for IDH-mutant tumors given very small sample sizes.

Table 5 shows management changes in a hypothetical scenario whereby the intended management plan corresponded with a suspected advanced neuroimaging result that matched the actual advanced neuroimaging result for all EOCs. In this hypothetical scenario, the intended and actual management plans differed in 33% (95% CI: 21-44%) (23/70) of EOCs. For 7/10 (70%) EOCs for which the actual management plan was surgical intervention, 6/14 (43%) EOCs for which the actual management plan was to change chemotherapy agents, and 8/37 (22%) EOCs for which the actual management plan was to continue current treatment with or without short-term follow-up evaluation, the intended and actual management plans differed. In the hypothetical scenario, the distribution of management plans was not significantly different between the intended and actual management plans ($p=.20$). However, in a post hoc power analysis, 120 EOCs would have been required to detect a significant difference in this distribution, reflecting a discordant proportions ratio sum of 0.158.

Discussion

This prospective survey-based study assessed the clinical utility of advanced neuroimaging for posttreatment follow-up of adult patients with HGG. All patients had equivocal findings on conventional MRI before advanced neuroimaging, which comprised four techniques (ASL, MRS, DCE, and DSC). The intended and actual management plans, based on surveys performed before and after advanced neuroimaging, differed in 44% (31/70) of EOCs, confirming the hypothesis that there would be a

management change in at least one-third of cases. This focus on management changes is distinct from prior literature that has primarily addressed the diagnostic accuracy of various advanced neuroimaging techniques.

The observed frequency of a management change was higher than the frequency previously reported by Geer et al [13]. This greater frequency may relate to differences in the compositions of the two studies' patient samples. The study by Geer et al. included gliomas spanning all histologic grades, whereas the present sample included only WHO grade 4 tumors, which are more aggressive and associated with poor survival outcomes [1,16,24]. A neuro-oncologist may more promptly change management in a patient with HGG and evidence of progression on advanced neuroimaging, yet continue to consider short-term follow-up evaluation for such scenario in a patient with low-grade glioma. Additionally, the study by Geer et al. included consecutive patients with glioma, some of whom may not require advanced neuroimaging to evaluate tumor progression; in comparison, the present sample included only patients in whom findings on conventional MRI were equivocal for progression. As conventional MRI findings poorly correlate with tumor status [3], the present study would be expected to contain a higher proportion of patients with discordant suspected and actual diagnoses before and after advanced neuroimaging, respectively, and thus also yield a greater frequency of management plan changes.

The ordering neuro-oncologists deemed advanced neuroimaging to be helpful in 93% of EOCs. These results are concordant with the study by Geer et al., in which neuro-oncologists reported that perfusion sequences were useful in 87% of EOCs, and that their confidence in tumor status determination increased after advanced neuroimaging for 58% of EOCs [13]. Additional recent studies show that DSC-derived metrics, such as fractional tumor burden, inform clinical decision-making and increase neuroradiologists' confidence in their clinical assessment [25,26].

The high frequency of management changes observed in the present study supports a role for advanced neuroimaging in the evaluation of patients with treated HGGs and equivocal findings on conventional MRI. However, we are unable to suggest more narrow indications for advanced neuroimaging among such patients, as the frequency of management changes was not significantly

associated with type of HGG (IDH-wildtype vs IDH-mutant), stage of glioma therapy, or number of completed chemotherapy cycles. Future work could focus on further refining the subpopulation of patients who would most strongly benefit from advanced neuroimaging, determining the timing and frequency of advanced neuroimaging examinations, as well as understanding the contexts in which the various advanced neuroimaging techniques should be performed. Such insight would help to craft more efficient imaging protocols, minimizing information redundancy. Clinical trials are also needed to assess whether changes in management plan secondary to advanced neuroimaging in patients with HGG confer downstream survival advantages.

The secondary analysis showed that, even if the suspected and actual advanced neuroimaging results were concordant in all EOCs, the neuro-oncologist would have deviated from their intended management plan in 33% of EOCs. As HGGs evolve rapidly, patients may have exhibited clinical deterioration between the time of advanced neuroimaging ordering and subsequent follow-up, prompting a management change despite the concordant advanced neuroimaging result. The neuro-oncologist may have also deviated from the intended management plan based on an intervening multidisciplinary tumor board discussion, reflecting the complexity of HGG therapy. In addition, the neuro-oncologist may have deviated from their intended management plan to fulfill a subsequent patient request for a different strategy, such as for less aggressive treatment, for reasons unrelated to imaging findings. The nature of the data collected through the surveys did not allow further detailed evaluation of these possible confounding effects.

A consideration of potential incorporation of advanced neuroimaging into routine HGG monitoring protocols requires a consideration of advanced neuroimaging's overall value. Although the frequency of management changes identified in the present study supports the benefit of advanced neuroimaging, advanced neuroimaging increases health systems' resource utilization and costs. For example, the addition of these four sequences increases examinations' scan time and gadolinium contrast media dose, as well as technologists' post-processing time and neuroradiologists' interpretation time. In the United States, these additional techniques do not lead to additional reimbursement for the examination. Thus,

further thorough cost-benefit analysis, including of individual advanced neuroimaging techniques and of advanced neuroimaging overall, remains warranted.

This study had limitations. First, the sample size was small, and certain comparisons were underpowered in post hoc power analyses. Second, the study was performed at a single comprehensive cancer center. The results may not be generalizable to non-tertiary settings, where it is not standard to concurrently perform the four advanced neuroimaging techniques. Third, no reference standard was available for the diagnostic accuracy of the advanced neuroimaging results. Fourth, the analysis included a retrospective re-classification of advanced neuroimaging results when the advanced neuroimaging was initially interpreted as showing mixed findings. Fifth, patients lacked longitudinal follow-up; such follow-up could help determine the frequency at which advanced neuroimaging should be performed throughout patients' disease course. Sixth, the analysis did not account for possible clustering effects among instances of multiple advanced neuroimaging sessions in individual patients. Seventh, the study did not evaluate the relative utility of the different advanced neuroimaging techniques. Finally, the management plan commonly changed even when the suspected and actual advanced neuroimaging results were concordant; even when these results were discordant, it was not possible to confirm that management changes were directly attributable to the change in imaging diagnosis.

In conclusion, neuro-oncologists' management plan changed after completion of advanced neuroimaging in a substantial fraction (44%) of care episodes for adult patients with HGG who had findings on conventional MRI that were equivocal for tumor progression versus treatment effect. These results highlight the clinical utility of advanced neuroimaging and support their incorporation into monitoring protocols for these patients.

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Tables

Table 1. Results of pre-surveys, completed by ordering neuro-oncologists before advanced neuroimaging, for 70 episodes of care.

Item	Result
Age at time of advanced neuroimaging (y)[a]	54.6 ± 12.9
"Legal sex"[b]	
Male	30 (43)
Female	40 (57)
"Diagnosis?"[c]	
Glioblastoma, IDH-wild type	60 (86)
Astrocytoma, IDH-mutant, WHO grade 4	10 (14)
"Patient's current treatment stage?"[d]	
Post-chemoradiation	8 (11)
Adjuvant chemotherapy	45 (65)
Surveillance	17 (24)
"Adjuvant chemotherapy cycle number?"[e]	4 (2-7)
"I think advanced neuroimaging is more likely to show:"	
Progression	32 (46)
Treatment effect	38 (54)
"Next likely step if advanced neuroimaging shows progression?"	
Continue treatment with or without short-term follow-up[f]	8 (11)
Change chemotherapeutic agents	30 (43)
Enroll in a clinical trial	19 (27)
Surgical intervention (resection, biopsy or LITT)	11 (16)
Re-irradiation	2 (2.9)
Stop further anti-cancer treatment	0 (0)
Other	0 (0)
"Next likely step if advanced neuroimaging shows treatment effect?"	
Continue treatment with or without short-term follow-up[f]	59 (84)
Change chemotherapeutic agents	7 (10)
Enroll in a clinical trial	1 (1)
Surgical intervention (resection, biopsy, or LITT)	2 (3)
Re-irradiation	0 (0)
Stop further anti-cancer treatment	1 (1)
Other	0 (0)
Intended management plan[g]	
Continue treatment with or without short-term follow-up[f]	32 (46)
Change chemotherapeutic agents	19 (27)
Enroll in a clinical trial	8 (11)
Surgical intervention (resection, biopsy, or LITT)	8 (11)
Re-irradiation	2 (3)
Stop further anti-cancer treatment	1 (1)
Other	0 (0)

Unless otherwise indicated, data expressed as count with percentage in parentheses.

[a]Mean ± SD.
[b]Male in 27/63 patients, female in 36/63 patients.
[c]Glioblastoma, IDH-wild type in 54/63 patients, astrocytoma IDH-mutant WHO grade 4 in 9/63 patients.
[d]Response of post-chemoradiation indicated that the patient had just completed such therapy. A response of surveillance indicated that the patient was off therapy.
[e]Median (IQR).
[f]Indicates continuation of current management with or without short-term follow-up within 4 weeks.
[g]Derived based on neuro-oncologist's selected response for suspected advanced neuroimaging result and next likely management step for that result; used to represent plan before advanced neuroimaging in primary analysis comparing plans before and after advanced neuroimaging.
IDH = isocitrate dehydrogenase; LITT = laser interstitial thermal therapy.

Table 2. Results of post-surveys, completed by neuro-oncologists at time of follow-up visit 4-6 weeks after advanced neuroimaging, for 70 episodes of care (EOCs).

Item	Result
"What did the advanced neuroimaging show?"	
Progression	26 (37)
Treatment-effect	32 (46)
Mixed[a]	12 (17)
"In which setting did the neuro-oncologist interpret the results?"	
Independently	4 (6)
In collaboration with the neuroradiologist	62 (89)
In collaboration with their colleagues	4 (6)
"Did the neuro-oncologist agree with the radiologist's interpretation?"	
Yes	62 (89)
No	4 (6)
Other	4 (6)
"Did the neuro-oncologist find the advanced neuroimaging results helpful?"	
Yes	65 (93)
No	2 (3)
Other	3 (4)
"Is there a need to repeat the advanced neuroimaging?"	
Yes	6 (9)
No	64 (91)
"What is your next step in management?"	
Continue current management with or without short-term follow-up[b]	37 (53)
Change chemotherapeutic agents	14 (20)
Enroll in a clinical trial	6 (0)
Surgical intervention (resection, biopsy, or LITT)	10 (14)
Re-irradiation	1 (1)
Stop further anti-cancer treatment	2 (3)
Other	0 (0)
"Next follow-up imaging procedure?"[c]	
Short-term conventional MRI (in approximately 4 weeks or less)	14 (38)
Regularly scheduled conventional MRI (in approximately 8 weeks or more)	15 (41)
Repeat advanced neuroimaging	5 (14)
Other advanced imaging, such as dual time-point PET	0 (0)
Other	0 (0)
No response	3 (8)

Data expressed as count with percentage in parentheses.

[a]Based on re-review of 12 cases with mixed findings, nine were recategorized as showing progression, and 3 were recategorized as showing treatment effect. Following this reclassification, advanced neuroimaging showed progression in 50% (35/70) of EOCs and showed treatment effect in 50% (35/70) of EOCs.

[b]Indicates continuation of current management with or without short-term follow-up within 4 weeks.

[c]Only completed if next management step was to continue current management with short-term follow-up.

LITT = laser interstitial thermal therapy.

Table 3. 6x6 contingency table comparing intended and actual management plans from pre-surveys and post-surveys, respectively, for 70 episodes of care (EOCs).

Intended Management	**Actual Management**					
	Continue treatment with or without short-term follow-up	**Change chemo-therapeutic agents**	**Enroll in a clinical trial**	**Surgical intervention[a]**	**Re-irradiation**	**Stop further anti-cancer therapy**
Continue treatment with or without short-term follow-up	**24**	3	3	2	0	0
Change chemo-therapeutic agents	8	**7**	1	3	0	0
Enroll in a clinical trial	3	1	**2**	1	0	1
Surgical intervention[a]	2	2	0	**4**	0	0
Re-irradiation	0	1	0	0	**1**	0
Stop further anti-cancer therapy	0	0	0	0	0	**1**

Terms along table's main diagonal (indicated in bold) correspond to EOCs for which intended and actual management plan were concordant.

[a]Surgery, biopsy, or laser interstitial thermal therapy.

Table 4. Frequency of management changes between intended and actual management plans for varying subsets of episodes of care (EOCs).

EOCs	Frequency	P
All		
By treatment stage		.67
Post-chemoradiation	50 (4/8)	
Adjuvant chemotherapy	40 (18/45)	
Surveillance	53 (9/17)	
Number of chemotherapy cycles completed		.80
<3	46 (6/13)	
3-6	35 (7/20)	
>6	42 (5/12)	
IDH-wildtype tumors		
By treatment stage		>.99
Post-chemoradiation	50 (4/8)	
Adjuvant chemotherapy	44 (18/41)	
Surveillance	46 (5/11)	
Number of chemotherapy cycles completed		.78
<3	50 (6/12)	
3-6	37 (7/19)	
>6	50 (5/10)	
IDH-mutant tumors		
By treatment stage		.08
Post-chemoradiation	NR[a]	
Adjuvant chemotherapy	0 (0/4)	
Surveillance	67 (4/6)	
Number of chemotherapy cycles completed		NR[b]
<3	0 (0/1)	
3-6	0 (0/1)	
>6	0 (0/2)	

Data expressed as percentage with numerator and denominator in parentheses.
[a]No IDH-mutant tumor in the post-chemoradiation stage.
[b]No EOC with a management change in any subset.
NR = not reported

Table 5. 6x6 contingency table comparing intended and actual management plans from pre-surveys and post-surveys, respectively, for 70 episodes of care (EOCs), based on hypothetical scenario whereby the intended management plan corresponded with a suspected advanced neuroimaging result that matched the actual advanced neuroimaging result for all EOCs.

	Actual Management					
Hypothesized Intended Management	**Continue treatment with or without short-term follow-up**	**Change chemo-therapeutic agents**	**Enroll in a clinical trial**	**Surgical intervention[a]**	**Re-irradiation**	**Stop further anti-cancer therapy**
Continue treatment with or without short-term follow-up	**29**	2	1	1	0	1
Change chemo-therapeutic agents	5	**8**	0	4	0	0
Enroll in a clinical trial	3	2	**5**	2	0	0
Surgical intervention[a]	0	1	0	**3**	0	0
Re-irradiation	0	1	0	0	**1**	0
Stop further anti-cancer therapy	0	0	0	0	0	**1**

Terms along table's main diagonal (indicated in bold) correspond to EOCs for which hypothesized intended and actual management plans were concordant.

[a]Surgery, biopsy, or laser interstitial thermal therapy

Appendix 1-Pre-survey sent to neuro-oncologists immediately after order for advanced neuroimaging was placed for a patient meeting the eligibility criteria and selected for inclusion in study. In survey item relating to current treatment stage, post-chemoradiation indicated that patient had just completed such therapy, and surveillance indicated that patient was off therapy. Survey item on adjuvant chemotherapy survey item was only completed if for patients with a current treatment stage of advanced chemotherapy. In survey items on next likely steps, first option entailed continuation of current treatment with or without short-term follow-up within 4 weeks.

Value of Advanced MRI: Initial Survey

This is a prospective, observational study on how advanced neuroimaging affects physicians' medical decision-making processes for adult high-grade glioma patients with conventional MRI findings concerning for progression or treatment-related changes.

Please complete the survey below:

Patient MRN	_____
Patient date of birth	_____
Legal sex	o Male o Female
Diagnosis?	o Glioblastoma, IDH-wildtype o Astrocytoma, IDH-mutant, WHO Grade 4 o Other _____
Patient's current treatment stage?	o Post-chemoradiation o Adjuvant chemotherapy o Surveillance
Adjuvant chemotherapy cycle number?	_____
I think advanced neuroimaging is more likely to show:	o Progression o Treatment effect
Kindly justify your answer to the previous question:	_____
Next likely step if advanced neuroimaging shows progression?	o Continue treatment with or without short-term follow-up o Change chemotherapeutic agents o Enroll in a clinical trial o Surgical intervention (resection, biopsy or LITT) o Re-irradiation o Stop further anti-cancer treatment

	○ Other _____
Next likely step if advanced neuroimaging shows treatment effect?	○ Continue treatment with or without short-term follow-up ○ Change chemotherapeutic agents ○ Enroll in a clinical trial ○ Surgical intervention (resection, biopsy or LITT) ○ Re-irradiation ○ Stop further anti-cancer treatment ○ Other _____

Appendix 2-Post-survey sent to neuro-oncologists at time of patient's next visit after advanced neuroimaging. In survey item on next likely steps, first option entailed continuation of current treatment with or without short-term follow-up within 4 weeks. Survey item on next follow-up imaging procedure only completed if the selected next management step was continuation of current treatment with or without short-term follow-up.

Value of Advanced MRI: Follow-Up Survey

Please complete the survey below:

Patient MRN	_____
Advanced neuroimaging date	_____
What did the advanced neuroimaging show?	o Progression o Treatment effect o Mixed
In which setting did the neuro-oncologist interpret the results?	o Independently o In collaboration with the neuroradiologist o In collaboration with their colleagues o Other
Did the neuro-oncologist agree with the radiologist's interpretation?	o Yes o No o Other _____
Did the neuro-oncologist find the advanced neuroimaging results helpful?	o Yes o No o Other _____
Is there a need to repeat the advanced neuroimaging?	o Yes o No
What is your next step in management?	o Continue treatment with or without short-term follow-up o Change chemotherapeutic agents o Enroll in a clinical trial o Surgical intervention (resection, biopsy or LITT) o Re-irradiation o Stop further anti-cancer treatment o Other _____
Next follow-up imaging procedure?	o Short term conventional MRI (in approximately 4 weeks or less) o Regularly scheduled conventional MRI (in approximately 8 weeks or more) o Repeat advanced neuroimaging o Other advanced imaging, such as dual time-point PET
	o Other _____

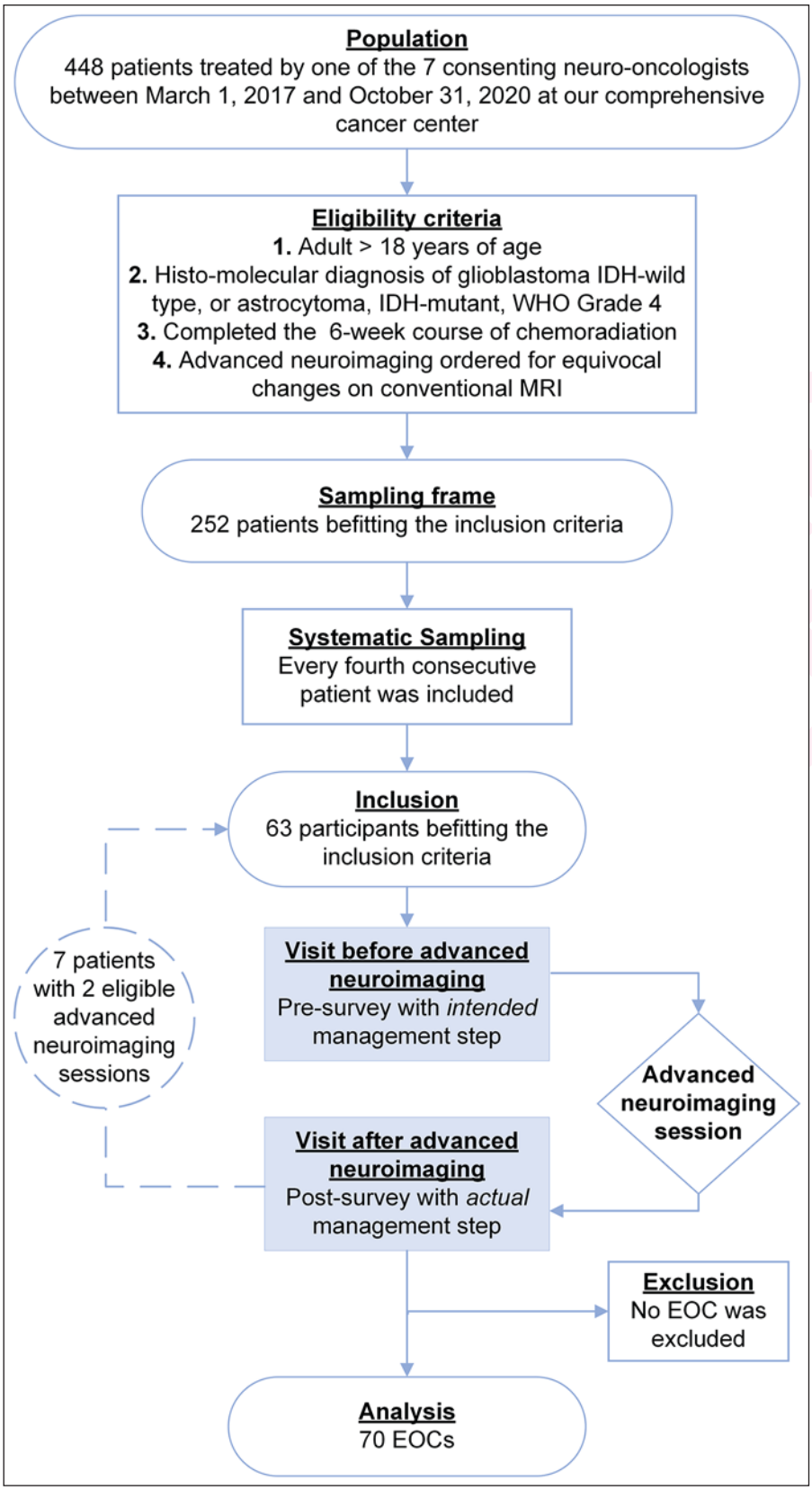

Fig. 1 – Flow diagram of study. EOC: episode of care.

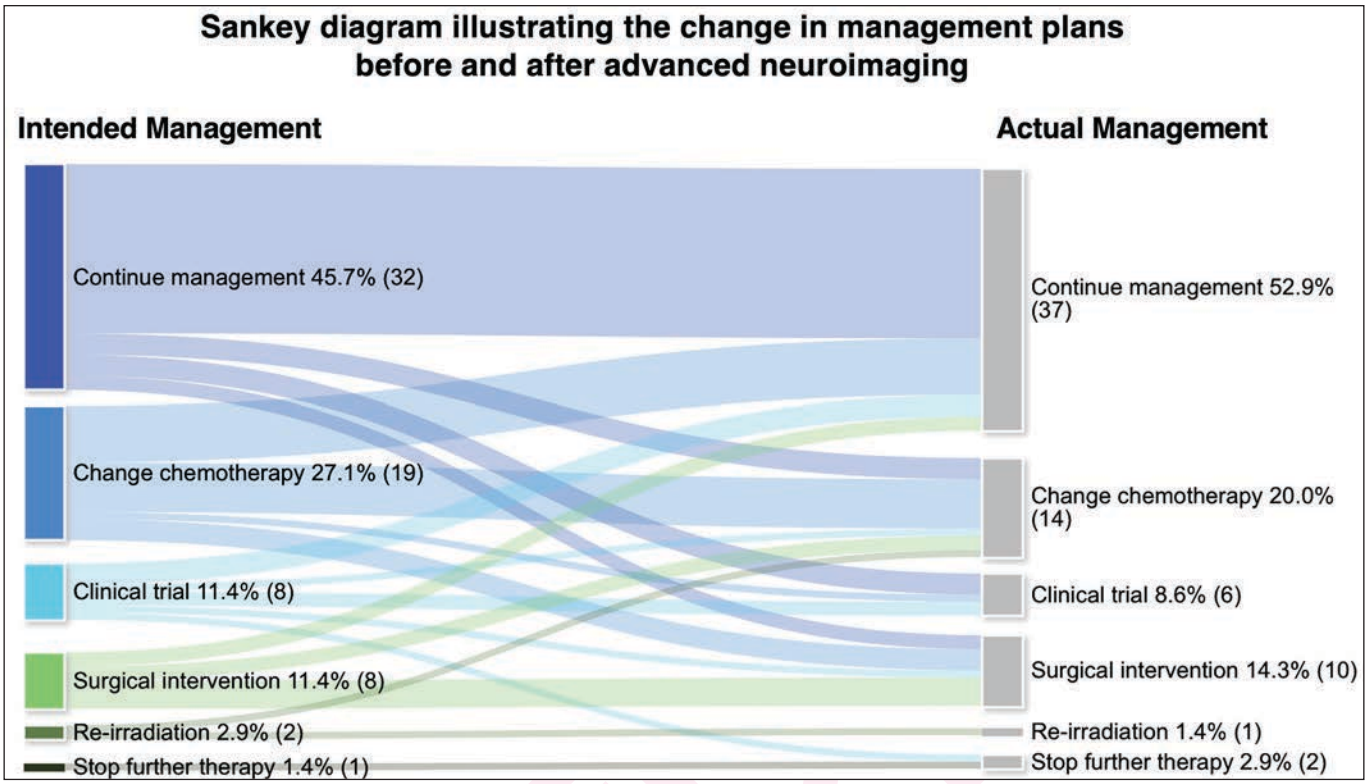

Fig. 2 – Sankey diagram shows change in management plans between intended management plan from pre-survey performed before advanced neuroimaging and actual management plan from post-survey performed after advanced neuroimaging. Surgical intervention includes surgery, biopsy, or laser interstitial thermal therapy.

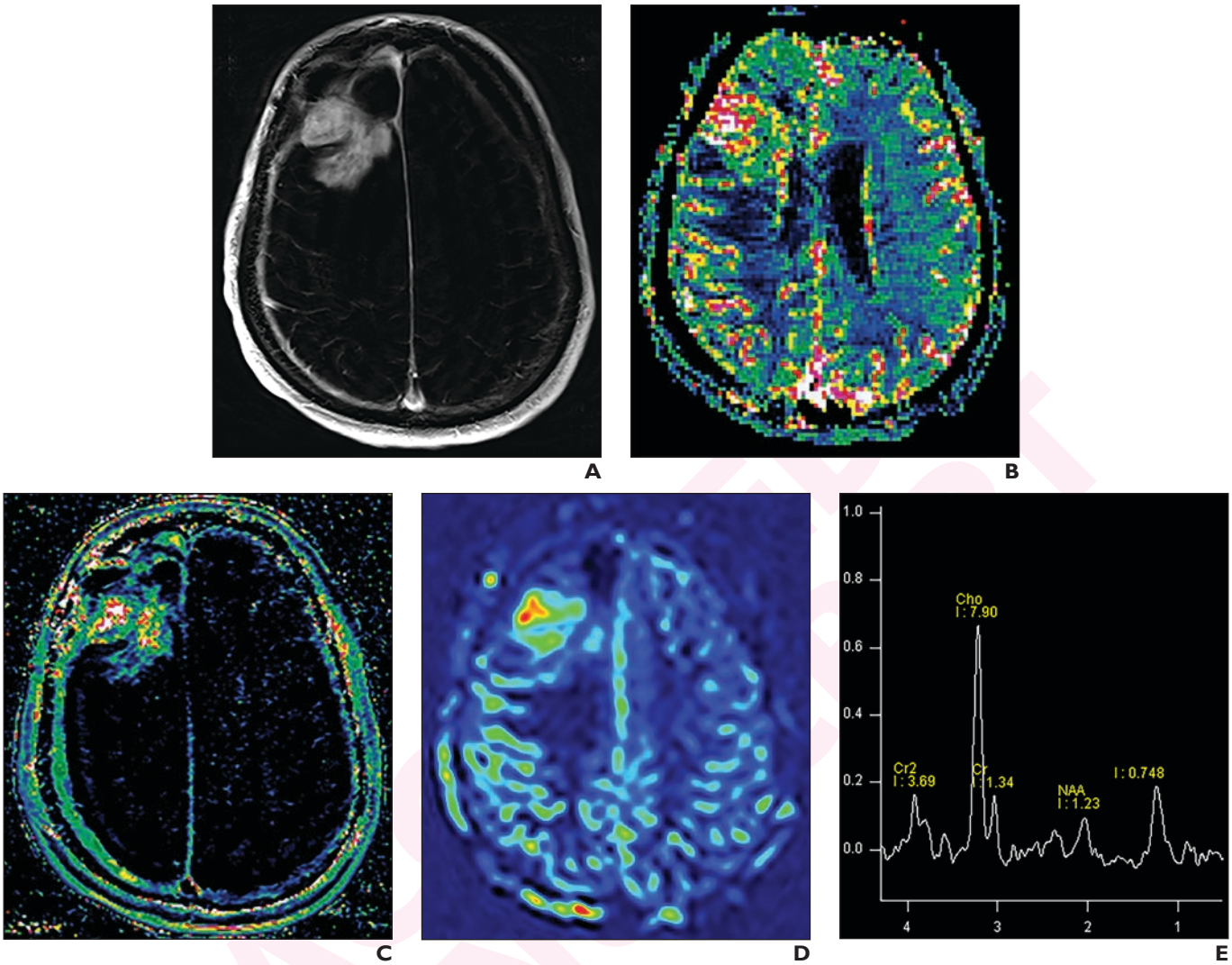

Fig. 3 – 66-year-old asymptomatic patient diagnosed 2 years earlier with right frontal glioblastoma, IDH-wildtype, MGMT indeterminate. Patient had undergone multiple surgical resections, chemotherapy, radiotherapy, and immunotherapy, and had been off treatment for 4 months. Conventional MRI performed 1 month earlier (not shown) showed nodular enhancement in posteroinferior aspect of resection cavity with increased surrounding T2/FLAIR hyperintensity, considered equivocal for tumor progression versus treatment effect. Neuro-oncologist ordered advanced neuroimaging for further evaluation of equivocal findings on conventional MRI. On pre-survey, neuro-oncologist indicated suspected advanced neuroimaging result of treatment effect, and that next likely management step (i.e., intended management plan) for such result was to continue management with or without short-term follow-up within 4 weeks. A – Subtraction image from axial contrast-enhanced T1-weighted image obtained during advanced neuroimaging again shows mass-like enhancement in resection cavity. B, C, and D – rCBV, Ktrans, and rCBF maps from DSC, DCE, and ASL, respectively, show significant increase in capillary permeability and perfusion in contrast-enhancing component of cavity. E – MRS at level of lesion shows markedly increased choline-to-creatine ratio (greater than 2:1) with depressed N-acetylaspartate peak and relatively elevated lipid/lactate peak. All advanced neuroimaging techniques were concordant with tumor progression. On post-survey, neuro-oncologist indicated next management step of surgical intervention. Patient subsequently underwent surgical resection at outside hospital and was then enrolled in clinical trial. IDH isocitrate dehydrogenase; MGMT: O6-methylguanine-DNA methyltransferase; rCBV: relative cerebral blood volume; Ktrans: volumetric transfer constant; rCBF: relative cerebral blood flow; DSC: dynamic susceptibility contrast; DCE: dynamic contrast-enhance; ASL: arterial spin labeling; MRS: MR spectroscopy.

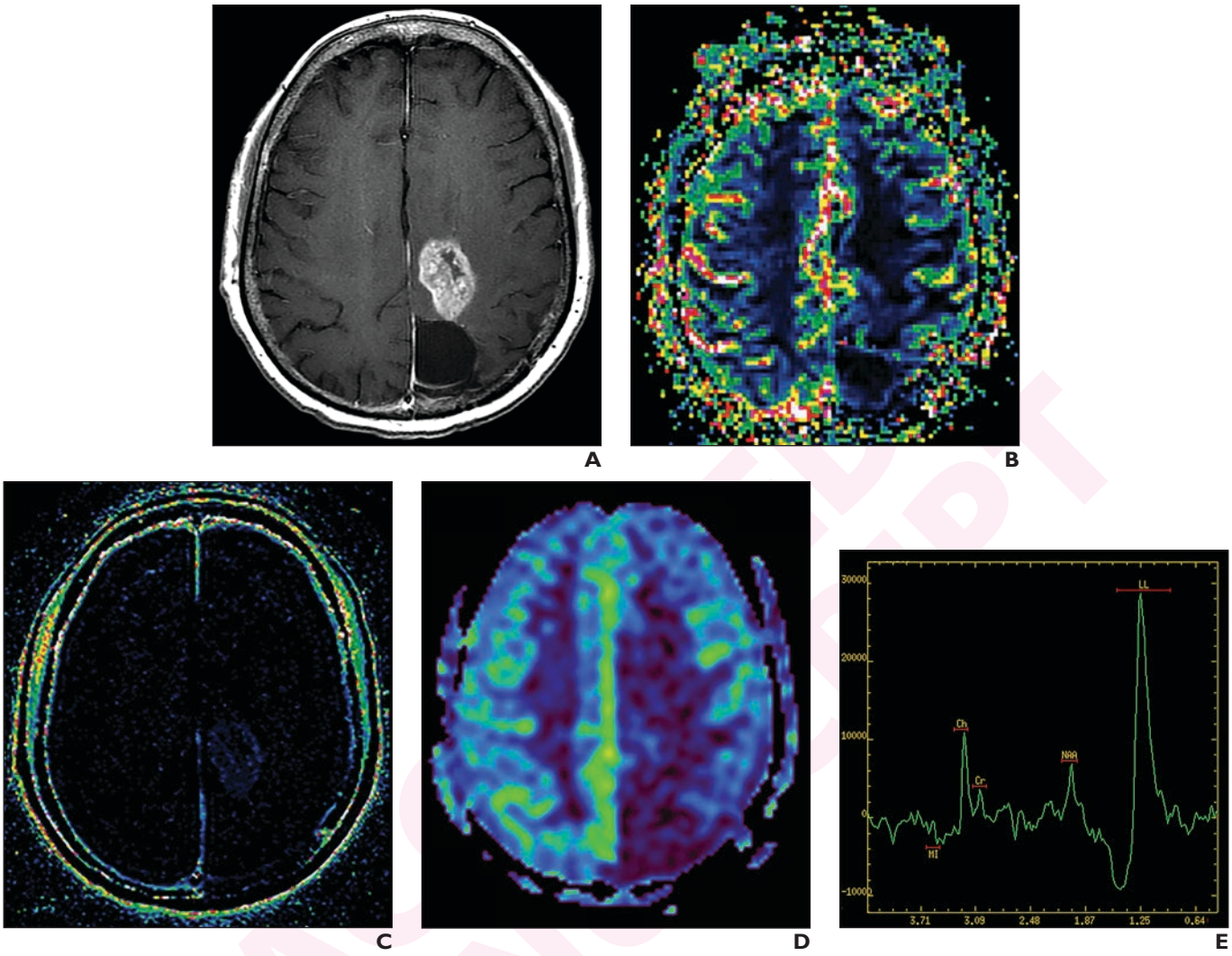

Fig. 4 – 64-year-old patient with recurrent left-sided glioblastoma, IDH-wildtype, MGMT indeterminate, who presented with right-sided sensorimotor impairment. Patients had undergone chemoradiation 9 months earlier and had just completed 12 cycles of temozolomide. Conventional MRI (not shown) showed enlarging left parietal lesion with "soap bubble" enhancement anterior to resection cavity. Although this enhancement pattern favored treatment-related effects, progression could not be ruled out, particularly in view of patient's clinical decline, and conventional MRI was considered equivocal for tumor progression versus treatment effect. Neuro-oncologist prescribed corticosteroids and ordered advanced neuroimaging for further evaluation of equivocal findings on conventional MRI. On pre-survey, neuro-oncologist indicated suspected advanced neuroimaging result of treatment effect, and that next likely management step (i.e., intended management plan) for such result was to continue management with or without short-term follow-up (within 4 weeks). A – Axial contrast-enhanced T1-weighted image shows enhancing left parietal lesion anterior to resection cavity. B, C, and D – rCBV, Ktrans and rCBF maps from DSC, DCE, and ASL, respectively, show no significant increase in capillary permeability and perfusion. E – MRS at level of enhancing lesion reveals mildly depressed N-acetylaspartate peak and reversed choline-to-creatine ratio. Given intermediate TE of 144 ms, large peak at 1.3 ppm could have resulted from poor phasing of lactate resonance or overlapping lactate and lipid resonances. All advanced neuroimaging sequences were consistent with treatment effect. On post-survey, neuro-oncologist indicated that next management step was to continue management with or without short-term follow-up within 4 weeks. Although not indicated by response to post-survey, bevacizumab was also initiated as steroid-sparing agent in setting of symptomatic treatment effect. IDH: isocitrate dehydrogenase; MGMT: O6-methylguanine-DNA methyltransferase; rCBV: relative cerebral blood volume; Ktrans: volumetric transfer constant; rCBF: relative cerebral blood flow; DSC: dynamic susceptibility contrast; DCE: dynamic contrast-enhanced; ASL: arterial spin labeling; MRS: MR spectroscopy.

AJR

Title

The Impact of MRI-Based Advanced Neuroimaging on Neurooncologists' Clinical Decision-Making in Patients With Posttreatment High-Grade Glioma: A Prospective Survey-Based Study

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