Radiology

Can Preoperative Mapping with Functional MRI Reduce Morbidity in Brain Tumor Resection? A Systematic Review and Meta-Analysis of 68 Observational Studies

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Conflicts of interest are listed at the end of this article.

Radiology 2021; 300:338–349 • https://doi.org/10.1148/radiol.2021204723 • Content codes: NR MR

Background: Preoperative functional MRI (fMRI) is one of several techniques developed to localize critical brain structures and brain tumors. However, the usefulness of fMRI for preoperative surgical planning and its potential effect on neurologic outcomes remain unclear.

Purpose: To assess the overall postoperative morbidity among patients with brain tumors by using preoperative fMRI versus surgery without this tool or with use of standard (nonfunctional) neuronavigation.

Materials and Methods: A systematic review and meta-analysis of studies across major databases from 1946 to June 20, 2020, were conducted. Inclusion criteria were original studies that *(a)* included patients with brain tumors, *(b)* performed preoperative neuroimaging workup with fMRI, *(c)* investigated the usefulness of a preoperative or intraoperative functional neuroimaging technique and used that technique to resect cerebral tumors, and *(d)* reported postoperative clinical measures. Pooled estimates for adverse event rate (ER) effect size (log ER, log odds ratio, or Hedges *g*) with 95% CIs were computed by using a random-effects model.

Results: Sixty-eight studies met eligibility criteria (3280 participants; 58.9% men [1555 of 2641]; mean age, 46 years ± 8 [standard deviation]). Functional deterioration after surgical procedure was less likely to occur when fMRI mapping was performed before the operation (odds ratio, 0.25; 95% CI: 0.12, 0.53; $P < .001$]), and postsurgical Karnofsky performance status scores were higher in patients who underwent fMRI mapping (Hedges *g*, 0.66; 95% CI: 0.21, 1.11; $P = .004$]). Craniotomies for tumor resection performed with preoperative fMRI were associated with a pooled adverse ER of 11% (95% CI: 8.4, 13.1), compared with a 21.0% ER (95% CI: 12.2, 33.5) in patients who did not undergo fMRI mapping.

Conclusion: From the currently available data, the benefit of preoperative functional MRI planning for the resection of brain tumors appears to reduce postsurgical morbidity, especially when used with other advanced imaging techniques, such as diffusion-tensor imaging, intraoperative MRI, or cortical stimulation.

Online supplemental material is available for this article.

Functional MRI (fMRI) is increasingly implemented as a practical preoperative planning tool for brain tumor resection, but a considerable discrepancy between its current use and presumed utility remains. A recent survey among neurosurgeons found variability in the present use and assumed utility of fMRI for preoperative surgical planning in patients with brain tumors. This variation includes clinical and radiographic indications for ordering fMRI, functional paradigms to test in specific case studies, and clinical purposes of using fMRI (1).

Surgical resection of brain tumors aims to maximize tumor removal while avoiding the onset of permanent postoperative deficits. The extent of tumor resection independently correlates with patient survival (2,3). However, when resective surgery extends too far into infiltrated critical structures, the condition of the patient permanently worsens; this, in turn, compromises both quality of life and survival. Several neurosurgical advances aim to improve patient outcomes. To localize critical brain structures and the tumor, techniques such as preoperative functional neuroimaging, neuronavigation, fluorescent dyes, MRI in the surgical field, and intraoperative stimulation mapping have been used (4). Although meta-analyses have assessed the use of intraoperative stimulation mapping, awake craniotomy, and intraoperative MRI (4–6), the usefulness of these techniques and their effect on neurologic outcomes have not been sufficiently addressed in randomized trials or meta-analyses. These studies suggest that glioma resections that use intraoperative stimulation mapping and awake craniotomy are associated with better surgical outcomes, fewer late severe neurologic deficits, and a higher percentage of gross total resections (4,6). However, a recent meta-analysis of five studies comparing the use of the intraoperative fMRI with standard neuronavigation (5) showed attenuated incidence of postsurgical permanent neurologic deficits, although this finding was not statistically significant.

The primary objective of our study was to assess the overall postoperative morbidity within at least a 2-month

Abbreviations

fMRI = functional MRI, ER = event rate

Summary

The benefit of preoperative functional MRI planning for the resection of brain tumors appears to reduce postsurgical morbidity, especially when used with other advanced imaging techniques.

Key Results

- In a systematic review and meta-analysis of 68 observational studies, postsurgical functional deterioration was less likely to occur when presurgical functional MRI (fMRI) mapping was performed (odds ratio, 0.25; $P < .001$).
- Patients with fMRI mapping had higher postsurgical Karnofsky performance status scores (Hedges *g*, 0.66; $P = .004$).
- Preoperative fMRI mapping for the resection of brain tumors resulted in a pooled adverse event rate (ER) of 11%, compared with an ER of 21% in patients who did not undergo fMRI mapping.

follow-up period among patients with brain tumors who underwent preoperative functional MRI compared with those who did not. We performed a meta-analysis of published observational studies to assess the event rates (ERs) of new, worsened, and persistent neurologic deficits after resective brain surgery in patients with supratentorial tumors. In particular, we addressed the effect of presurgical functional MRI mapping and other determinants on neurologic outcomes.

Materials and Methods

Search Strategy and Eligibility Criteria

This systematic review and meta-analysis complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (known as PRISMA) statement (7) and followed a protocol defined a priori (available on request to the authors). The PubMed/MEDLINE, Scopus, and EMBASE electronic databases were searched from 1946 to June 20, 2020 (detailed search strings are provided in Figure E1 [online]). The search strategy was augmented by hand searching the reference lists of eligible articles. Two investigators (F.G.S., a medical graduate research fellow with 2 years of experience; I.B.O., a 3rd-year radiology resident) independently screened the titles and abstracts of retrieved references, assessed full texts for eligibility, extracted data, and rated the methodologic quality of eligible studies. Disagreements were resolved through consensus or consultation with a third investigator (L.P.L., a fellowship-trained neuroradiologist with 12 years of experience).

The following inclusion criteria were applied: original studies that *(a)* included patients with brain tumors, *(b)* performed preoperative neuroimaging workup with task fMRI, *(c)* investigated the usefulness of a preoperative or intraoperative functional neuroimaging technique and used that technique to resect cerebral tumors, and *(d)* reported postoperative clinical measure. Postoperative outcome measures were considered if neurologic deficits were new, worsened, and persistent during at least a 2-month follow-up period, as reported by the attending physician assessments and patients' medical records. Preoperative planning with fMRI was considered when authors used the information from fMRI studies to guide surgical decision making, not necessarily using images intraoperatively.

We excluded the following: *(a)* studies reporting only postoperative deficits within a 2-month follow-up interval (transient deficits); *(b)* studies that used imaging methods other than fMRI (eg, diffusion-tensor imaging or conventional MRI only); *(c)* case reports or small series (three cases or fewer); and *(d)* literature reviews, conference papers, meeting abstracts, or meta-analyses. No language restrictions were applied.

Data Extraction

Two authors (F.G.S. and I.B.O.) independently extracted the data of selected papers by using a standardized spreadsheet. Discrepancies were resolved through consensus and, if necessary, by consulting with a third author (L.P.L.). Corresponding authors were electronically contacted on at least two occasions when extractable data were not provided in the original report. Recorded variables are provided in Appendix E1 (online). Outcome data were the number of patients experiencing neurologic or cognitive deficits that persisted after 2 months from surgery. We assessed patient performance scores and/or quality of life with the following methods: Karnofsky performance status (an 11-point patient functioning scale ranging from 0% [death] to 100% [no symptoms] that assesses patient functionality in the postoperative setting) (8,9), the modified Rankin scale (a 6-point disability scale that ranges from 0 [no symptoms] to 6 [death]) (8,9), or British Medical Research Council scale (a muscle scale that grades muscle power on a scale of 0 to 5 in relation to the maximum expected for that muscle) (8). Gross total resection was defined as less than 10% of residual tumor depicted at postoperative imaging (9).

Assessment of Methodologic Quality

Two reviewers (L.P.L. and F.G.S.) independently rated the methodologic quality of each included study. The Newcastle-Ottawa scale for nonrandomized studies is used to appraise quality of case-control studies (10), with scores ranging from 0 (worst quality) to 9 (best quality); studies with scores of 5 or more were graded as good quality. Case series were assessed by using a tool developed by Moga et al (11,12), which consists of 18 entries; studies achieving a score of 13 or greater are considered of high quality, 7–12 of moderate quality, and 0–6 of low quality (Appendix E1 [online]).

Statistical Analysis

The primary outcome was the proportion of patients with postsurgical functional deterioration (number of unfavorable events), reported as an ER. The events were defined by using the Karnofsky performance status, modified Rankin scale, or British Medical Research Council scale or general neurologic deficits (motor, language, and cognitive). If the outcome was reported as the mean and standard deviation of the scores and not the ER, then they were considered unfavorable events when the presurgical neurologic status worsened or a new postsurgical deficit persisted after 2 months of follow-up. Therefore, we obtained a standardized outcome measure for unfavorable outcomes following brain tumor resection that included all possible measures. Whenever the ERs were

reported in sufficient number, we considered events defined with only a single instrument. For the studies with a comparison group (surgical procedure without presurgical fMRI), the odds ratio was computed. For numeric variables, differences between the fMRI and the no-fMRI groups were estimated by using a standardized mean difference (Hedges *g*). For pooling, the logits of the ERs were computed as {logER = log [ER/(1 ± ER)]}, and odds ratios were log transformed. Pooled estimates for any effect size (log ER, log odds ratio, or Hedges *g*) with 95% CIs were computed by using a random-effects model according to the DerSimonian and Laird method (13). For reporting, pooled measures and 95% CIs of log ERs and log odds ratios were converted back to the original scale. See Appendix E1 (online) for details on statistical analyses of heterogeneity, publication bias, and small-study effects.

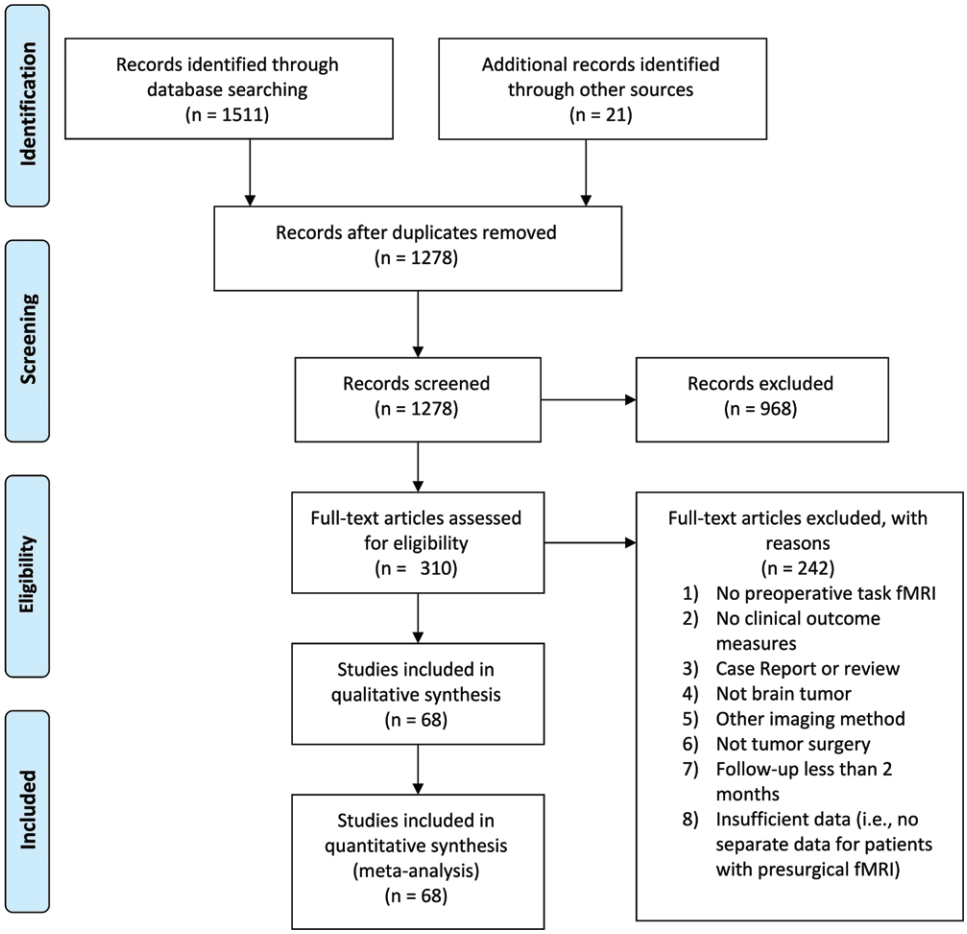

Figure 1: Flowchart of the search process. fMRI = functional MRI.

We explored potential sources of heterogeneity across studies for each effect size estimate by using either subgroup (if there were at least two studies in each subgroup) or random-effects meta-regression analyses. Meta-regression analyses were conducted when at least six studies provided data on potential moderators (14). For statistically significant effect size estimates, we performed sensitivity analyses in which we excluded one study at a time from analyses to verify whether a single study turned results nonsignificant or otherwise changed the direction of the effect size. All analyses were conducted with Stata MP software (version 14.0; StataCorp) by using the metan package or Comprehensive Meta-analysis software (Biostat). *P* values were considered to indicate statistically significant differences at the .05 level.

Results

Study Selection

The literature search retrieved 1511 records, and 21 additional references were found after review of the reference lists of included articles. After the removal of duplicates, 1278 unique references were screened. We excluded 968 references after title and abstract screening. Of the 310 full texts assessed, 242 were excluded (Table E1 [online]). Therefore, 68 studies (15–81) fulfilled the inclusion criteria for quantitative meta-analyses, which provided data from 3280 participants. Figure 1 depicts the flowchart of study selection.

Overall Characteristics and Methodologic Quality of Included Studies

The characteristics of the 68 studies included in the quantitative synthesis are shown in Table E2 (online). Nine (15,18,20,36,43,57,61,80,82) of the 68 studies (n = 946) compared a group that underwent presurgical fMRI assessment (fMRI group; n = 422) with a cohort that underwent standard volumetric imaging only (no-fMRI group; n = 524). The remaining 59 studies did not include a comparison group and reported only prognostic factors associated with undergoing brain tumor resection with presurgical fMRI assessment (Table E2 [online]). Across the included studies, most participants were men (59% [1555 of 2641] in the fMRI group and 53% [277 of 524] in the no-fMRI group). Mean age was 46 years ± 8 (standard deviation) in the fMRI group and 48 years ± 7 in the no-fMRI group.

Overall, study quality was good for case-control studies (median Newcastle-Ottawa Scale score, 7 [range, 6–9]) and moderate for case series (median Moga score, 12 [range, 7–16]) (Tables E3, E4 [online]). See Appendix E1 (online)

Table 1: Primary Random-Effects Meta-Analyses of Neurologic Outcomes and Gross Total Resection in Patients Undergoing Brain Tumor Surgery with or without Presurgical Functional MRI Assessment

Outcome in fMRI Groups Only (ER; with and without Comparison Group)	No. of Studies	fMRI Group (*n*)	Pooled ER	I^2	*P* Value for I^2	*P* Value (Egger)*	Small-Study Effects†
All outcomes‡	68	2756	0.11 (0.08, 0.13)	66.4	<.001	<.001	Yes
KPS/modified Rankin scale	10	256	0.07 (0.04, 0.13)	15.6	.30	<.001	Yes
Neurologic status	24	1248	0.10 (0.07, 0.15)	69.0	<.001	.07	Yes
Language deficits	8	374	0.14 (0.06, 0.28)	85.5	<.001	.004	No
Motor deficits	13	333	0.14 (0.11, 0.19)	0	.63	.03	Yes
Motor and language deficits	10	386	0.09 (0.05, 0.13)	33.0	.14	.05	No
Neuropsychological tests	3	135	0.14 (0.07, 0.24)	31.9	.23	.31	No

Note.—Data in parentheses are 95% CIs. ER = event rate, ES = effect size, fMRI = functional MRI, KPS = Karnofsky performance scale.

* In Egger test of publication bias.

† $P < .1$ in Egger test of publication bias and effect size of the largest study more conservative than the overall effect size or in the opposite direction.

‡ All standardized unfavorable outcome measures. The primary unfavorable outcome was the proportion of patients with postsurgical functional deterioration and/or new postsurgical deficit that persisted after 2 months of follow-up. Outcomes could be directly reported as rates in the paper or derived from several of the scales used to assess neurologic deficits.

for overall characteristics of participants, reported outcomes, imaging methods, techniques, and brain tumors investigated.

Overall Effect of Brain Tumor Resection Using Presurgical fMRI Mapping

The standardized unfavorable score (ie, functional deterioration compared with presurgical status) could be computed by considering the data reported in 68 studies that included 2756 patients undergoing brain tumor resection with presurgical fMRI mapping, with a median time for the last follow-up of 6 months (range, 2–122 months) (Table E5 [online]). The pooled ER for standardized unfavorable outcomes across all studies was 11% (95% CI: 8.4, 13.1) (Fig E2 [online]). The result of the Egger test for publication bias was significant ($P < .001$) (Table 1). A funnel plot shows that published studies with small sample sizes had smaller ERs than the pooled ER, whereas the studies with large samples were distributed symmetrically around the pooled ER (Fig E3 [online]).

Between-study heterogeneity was large ($I^2 = 66.4\%$; $P < .001$). Possible sources of heterogeneity were explored by using meta-regression and subgroup analyses (Tables 2, 3). In meta-regression analysis, the mean preoperative tumor volume, the extent of resection, and higher frequency of insular and frontotemporal tumor locations emerged as significant moderators ($P < .05$). Lower mean preoperative tumor volume (54.0 $cm^3 \pm 23.0$; $P = .049$) and mean extent of resection (56.10% ± 28.4; $P = .02$) were associated with an increased rate of postsurgical deficits. A higher frequency of insular tumors (13.4% ± 10.0; $P = .03$) was associated with a lower rate of postsurgical deficits. However, a higher proportion of tumors located in the frontotemporal regions (7.50% ± 3.8; $P = .01$) was associated with a higher rate of unfavorable delayed postsurgical outcomes. Subgroup analysis showed that heterogeneity was small for studies that assessed functional deterioration by using the Karnofsky performance status or modified Rankin scale scores, motor deficits, or neuropsychologic tests (Table 1) and was the highest for studies that reported neurologic status and language deficits ($I^2 = 69.0\%$ and 85.5%, respectively). The summary ER was decreased when intraoperative MRI (ER, 0.08; 95% CI: 0.03, 0.20) or cortical stimulation (ER, 0.09; 95% CI: 0.06, 0.11) was performed compared with the ER estimates of studies that did not report the use of these procedures (ER, 0.11 [95% CI: 0.09, 0.13] and 0.14 [95% CI: 0.10, 0.19], respectively). However, significant heterogeneity was detected for these studies (I^2 range, 58.3%–84.6%; $P < .001$). In addition, the magnitude of the ER was lower in studies that used the 3.0-T magnetic field strength (ER, 0.08; 95% CI: 0.06, 0.10), that used both fMRI and diffusion-tensor imaging in presurgical assessment, and that included younger patients (ER for age <50 years, 0.10; 95% CI: 0.07, 0.13) (Table 3). An example of a study that used presurgical fMRI mapping at 3.0 T and direct cortical stimulation technique is shown in Figure 2.

Meta-Analysis of Studies with a Comparison Group

Nine studies with a no-fMRI group were included in the quantitative synthesis. The random-effects meta-analysis showed that postsurgical functional deterioration was less likely when presurgical functional fMRI mapping was performed (odds ratio, 0.25; 95% CI: 0.12, 0.53; $P < .001$) (Table 4; Fig 3, *A*). The heterogeneity was large ($I^2 = 53.2\%$; $P = .03$). The random-effects meta-analysis of three studies that reported presurgical and postsurgical Karnofsky performance status scores (Table 4; Fig 3, *B*) for both the fMRI and no-fMRI groups showed a difference favoring the presurgical fMRI group (Hedges $g = 0.66$; 95% CI: 0.21, 1.11; $P = .004$). The random-effects meta-analysis of four studies that reported gross total resection (Table 4; Fig 3, *C*) suggested no difference between the two groups (odds ratio, 1.45; 95% CI: 0.49, 4.31; $P = .50$]. The degree of heterogeneity was high ($I^2 = 80.4\%$; $P = .002$). We found no evidence of small-study effects for studies that compared presurgical fMRI with no

Table 2: Metaregressions of Standardized Unfavorable Neurologic Outcomes in Patients Undergoing Presurgical Functional MRI Mapping for Brain Tumor Resection

Variable	No. of Studies	No. of Participants*	Mean	Slope	Slope *P* Value	Intercept	Intercept *P* Value
fMRI groups general characteristics							
Publication year	68	2756	2011 (1999–2020)†	−0.022 (−0.071, 0.026)	.36	42.995	.38
Sample size	68	2756	40.5 ± 36.7	−0.003 (−0.009, 0.003)	.30	−1.966	<.001
Age (y)	64	2403	46 ± 8	0.014 (−0.021, 0.049)	.43	−2.807	.001
Male sex (% of patients)	66	2641	59.0 ± 14.6	0.013 (−0.008, 0.034)	.21	−2.959	<.001
Left-handed (%)	20	979	8.7 ± 8.2	0.007 (−0.059 , 0.073)	.82	−2.076	<.001
Awake surgery (% of patients)	49	1785	24.0 ± 39.7	−0.003 (−0.01, 0.003)	.31	−2.026	<.001
Quality score	68	2756	0.74 ± 0.1	−0.627 (−3.148, 1.894)	.62	−1.679	.08
Tumor characteristics							
Mean preoperative tumor volume (cm^3)	25	1238	54.0 ± 23.0	−0.019 (−0.037, 0)	.049	−1.406	.01
Gross tumor resection (%) (>90%)	44	1721	66.8 ± 23.5	0.003 (−0.012, 0.019)	.65	−2.373	<.001
Mean postoperative tumor volume (cm^3)	6	361	18.5 ± 20.2	−0.012 (−0.104, 0.079)	.73	−2.510	.03
High-grade glioma (%)	65	2575	41.0 ± 31.6	0.004 (−0.005, 0.013)	.38	−2.295	<.001
Low-grade glioma (%)	64	2451	42.6 ± 34.6	−0.003 (−0.012, 0.005)	.40	−2.011	<.001
Metastasis (%)	18	871	20.7 ± 23.8	0.002 (−0.02, 0.023)	.88	−2.083	<.001
Extent of resection (%)	6	361	56.10 ± 28.4	−0.032 (−0.055, −0.008)	.02	−0.679	.32
Tumor location (any side) (%)							
Frontal lobe	6	222	42.0 ± 14.8	0.016 (−0.022, 0.055)	.31	−2.863	.02
Parietal lobe	22	1045	14.6 ± 11.3	0.007 (−0.041, 0.054)	.78	−2.183	<.001
Occipital lobe	24	1071	1.15 ± 3.2	−0.038 (−0.238, 0.162)	.70	−2.082	<.001
Insula‡	26	1088	13.4 ± 10.0	−0.051 (−0.096, −0.005)	.03	−1.724	<.001
Frontotemporal	26	1088	7.50 ± 3.8	0.126 (0.029, 0.222)	.01	−2.278	<.001
Parietal temporal	26	1088	6.43 ± 4.2	0.017 (−0.148, 0.181)	.84	−2.033	<.001
Multiple lobes (>2)	20	713	35.8 ± 31.9	−0.007 (−0.025, 0.012)	.46	−1.811	<.001
Tumor location (left) (%)							
Left cerebral hemisphere	48	1692	67.4 ± 20.0	0.006 (−0.010, 0.021)	.47	−2.501	<.001
Left frontal	16	399	30.15 ± 20.4	−0.004 (−0.026, 0.019)	.74	−2.682	<.001
Left temporal	10	256	22.9 ± 16.1	0.036 (−0.027, 0.100)	.23	−3.758	.002
Tumor location (right) (%)							
Right frontal	8	208	23.6 ± 9.3	−0.038 (−0.144, 0.068)	.41	−2.003	.11
Right parietal	6	141	23.9 ± 24.8	0.021 (−0.050, 0.093)	.45	−3.289	.02
Presenting symptoms (%)							
Seizures	38	1214	67.2 ± 26.9	−0.004 (−0.015, 0.007)	.47	−1.967	<.001
Headaches	18	643	20.9 ± 15.2	0.023 (−0.012, 0.058)	.18	−2.868	<.001
Neurologic deficits	35	1163	30.2 ± 21.0	−0.002 (−0.019, 0.016)	.85	−2.098	<.001
Incidental finding	11	427	7.9 ± 6.9	0.021 (−0.111, 0.153)	.72	−2.535	.001

Note.—Unless otherwise mentioned, data in parentheses are 95% CIs. Mean data are ± standard deviation. fMRI = functional MRI.

* fMRI groups.

† Data are medians, with ranges in parentheses.

‡ Insular, frontal and insular, or temporoinsular.

fMRI (Table 4, Fig E4 [online]). Meta-regression and subgroup analyses are shown in Tables E6 and E7 (online), respectively. In sensitivity analysis, the exclusion of one individual study at a time from the analysis did not alter the significance of the pooled odds ratio estimate (Fig E5 [online]).

Discussion

To our knowledge, this systematic review with meta-analysis provides the largest evidence synthesis of studies reporting the functional outcomes in patients undergoing preoperative functional MRI (fMRI) mapping for brain tumor resection.

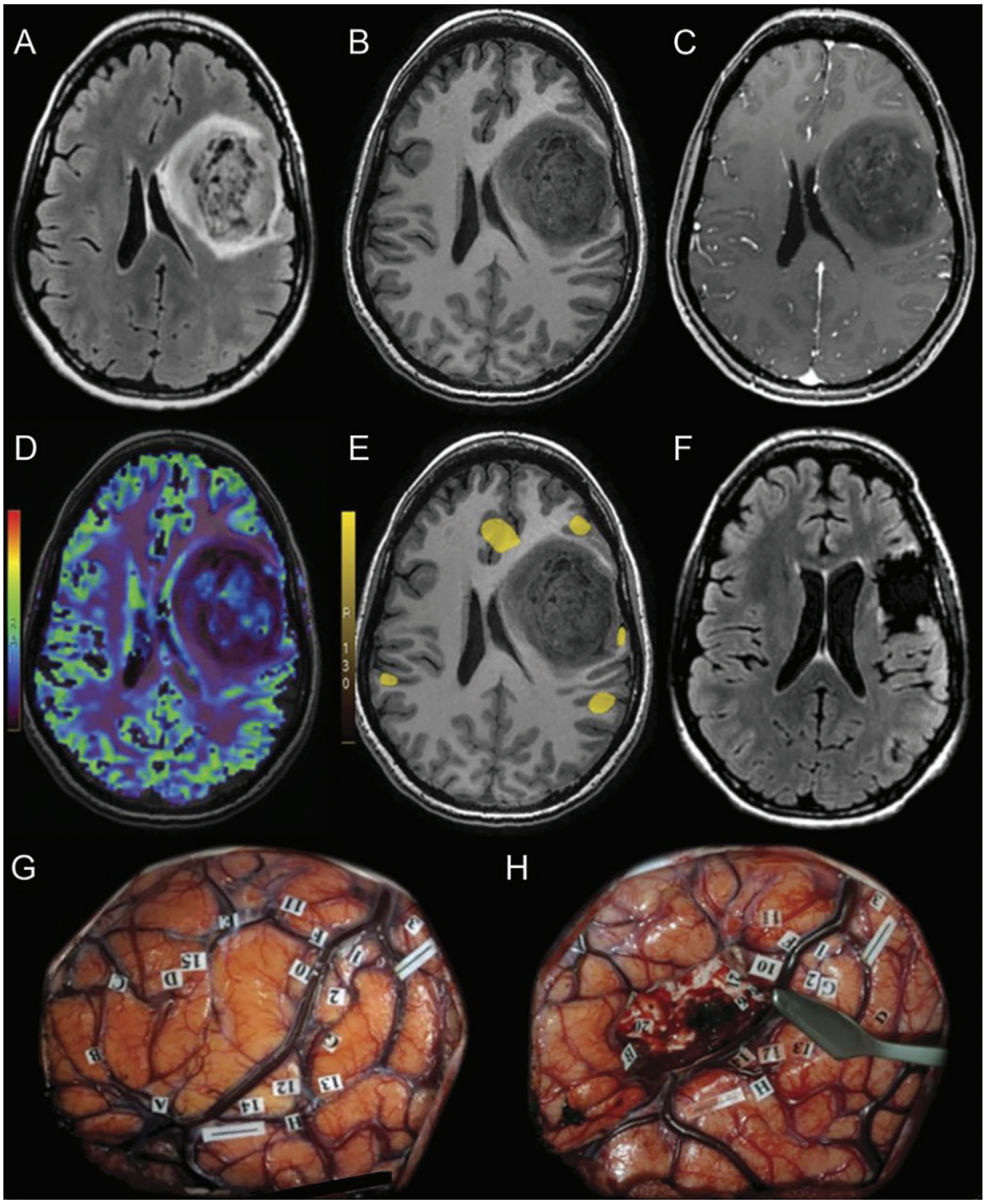

Figure 2: MRI scans and direct cortical stimulation technique in a 32-year-old woman with a grade II astrocytoma. Preoperative MRI shows a well-delineated mass within the left frontal lobe on, *A*, three-dimensional fluid-attenuated inversion recovery and, *B*, precontrast three-dimensional T1-weighted scan. *C*, Patchy and faint contrast enhancement is observed on postcontrast three-dimensional T1-weighted MRI scan. *D*, Cerebral blood volume map shows a globally hypoperfused tumor with hyperperfused foci. *E*, Preoperative functional MRI indicates language responses surrounding the lesion. *F*, Three-month postoperative fluid-attenuated inversion recovery image shows complete resection of the tumor. *G*, Intraoperative direct cortical stimulation helped confirm the presence of language areas (labels 10–15) in the vicinity of the tumor (demarcated by letters A–H). *H*, Resection was performed according to the functional landmarks. After the surgical procedure, the patient presented with mild aphasia that completely regressed 3 months later. (Reprinted, with permission, from reference 21.)

Our results suggested that postsurgical functional deterioration was less likely when presurgical fMRI mapping was performed (odds ratio, 0.25; 95% CI: 0.12, 0.53; $P < .001$) and postsurgical Karnofsky performance status scores were higher in patients who underwent fMRI mapping (Hedges *g*, 0.66; 95% CI: 0.21, 1.11; $P = .004$). We also found that surgical procedures performed with preoperative fMRI planning were associated with a pooled adverse event rate of 11%, compared with 21%

Table 3: Subgroup Analysis of Standardized Unfavorable Outcomes in Patients Undergoing Presurgical Functional MRI Mapping for Brain Tumor Resection

	Meta-Analysis		Heterogeneity		
Variable	df	ER (95% CI)*	I^2	Q	*P* Value
fMRI group					
Neuronavigation†					
Yes	33	0.11 (0.08, 0.14)	61.5	0.64	<.001
No	33	0.10 (0.07, 0.14)	70.2	0.68	<.001
Intraoperative MRI					
No	58	0.11 (0.09, 0.14)	58.3	0.13	<.001
Yes	8	0.08 (0.03, 0.20)	84.6	0.80	<.001
Cortical stimulation					
No	28	0.14 (0.10, 0.19)	65.6	0.33	<.001
Yes	38	0.09 (0.06, 0.11)	60.7	0.81	<.001
Awake surgery					
No	53	0.11 (0.08, 0.13)	69.7	0.8	<.001
Yes	13	0.10 (0.07, 0.15)	41.4	0.17	.05
Magnetic field strength					
1.5 T	31	0.11 (0.08, 0.16)	55.2	0.27	<.001
1.5 T or 3.0 T	7	0.18 (0.11, 0.28)	85.8	0.39	<.001
3.0 T	16	0.08 (0.06, 0.10)	0	0.50	.96
Presurgical imaging					
fMRI	35	0.12 (0.09, 0.16)	61.1	0.89	<.001
fMRI and DTI	28	0.10 (0.07, 0.14)	71.2	0.36	<.001
Study type					
Prospective	30	0.11 (0.08, 0.15)	45.4	0.95	.004
Retrospective	30	0.10 (0.07, 0.15)	77	0.46	<.001
Mean age (y)					
≥50	18	0.12 (0.09, 0.16)	34.3	0.39	.07
<50	47	0.10 (0.07, 0.13)	72.1	0.76	<.001
Men (% of sample)					
<70	53	0.09 (0.07, 0.12)	64.7	0.10	<.001
≥70	11	0.19 (0.12, 0.27)	50.6	0.29	.02
Total or gross total tumor resection (% of sample)					
≥50	31	0.14 (0.11, 0.19)	0	0.86	.63
<50	11	0.10 (0.07, 0.15)	69	0.26	<.001
Outcome score					
Motor deficits	12	0.14 (0.11, 0.19)	0	0.86	.63
Neurologic status	23	0.10 (0.07, 0.15)	69	0.26	<.001
KPS/modified Rankin scale score	9	0.07 (0.04, 0.13)	15.6	0.67	.30
Language deficits	7	0.14 (0.06, 0.28)	85.5	0.13	<.001
Motor and language deficits	9	0.09 (0.05, 0.13)	33	0.43	.14
Neuropsychological tests	2	0.14 (0.07, 0.24)	31.9	0.94	.23

Note.—df = degrees of freedom, DTI = diffusion-tensor imaging, ER = pooled event rate, fMRI = functional MRI, KPS = Karnofsky performance scale, Q = Cochran *Q* value.

* Pooled event rate of postsurgical permanent neurologic deficits in fMRI groups. The unfavorable outcome was the proportion of patients with postsurgical functional deterioration and/or new postsurgical deficit that persisted after 2 months of follow-up.

† Reported use of surgical neuronavigation, any imaging modality.

in patients who did not undergo preoperative fMRI mapping. Several factors associated with lower rates of unfavorable outcomes were identified, including the use of intraoperative MRI and cortical and subcortical stimulation; however, these results were not statistically robust because of large between-study heterogeneity.

In patients undergoing fMRI, the pooled ER of postsurgical permanent neurologic deficits (11%) was close to the reported incidence in a recent systematic review and meta-analysis by Caras et al (5). That study assessed the effect of intraoperative imaging for glioma resection by using morphologic and advanced imaging, including diffusion-tensor

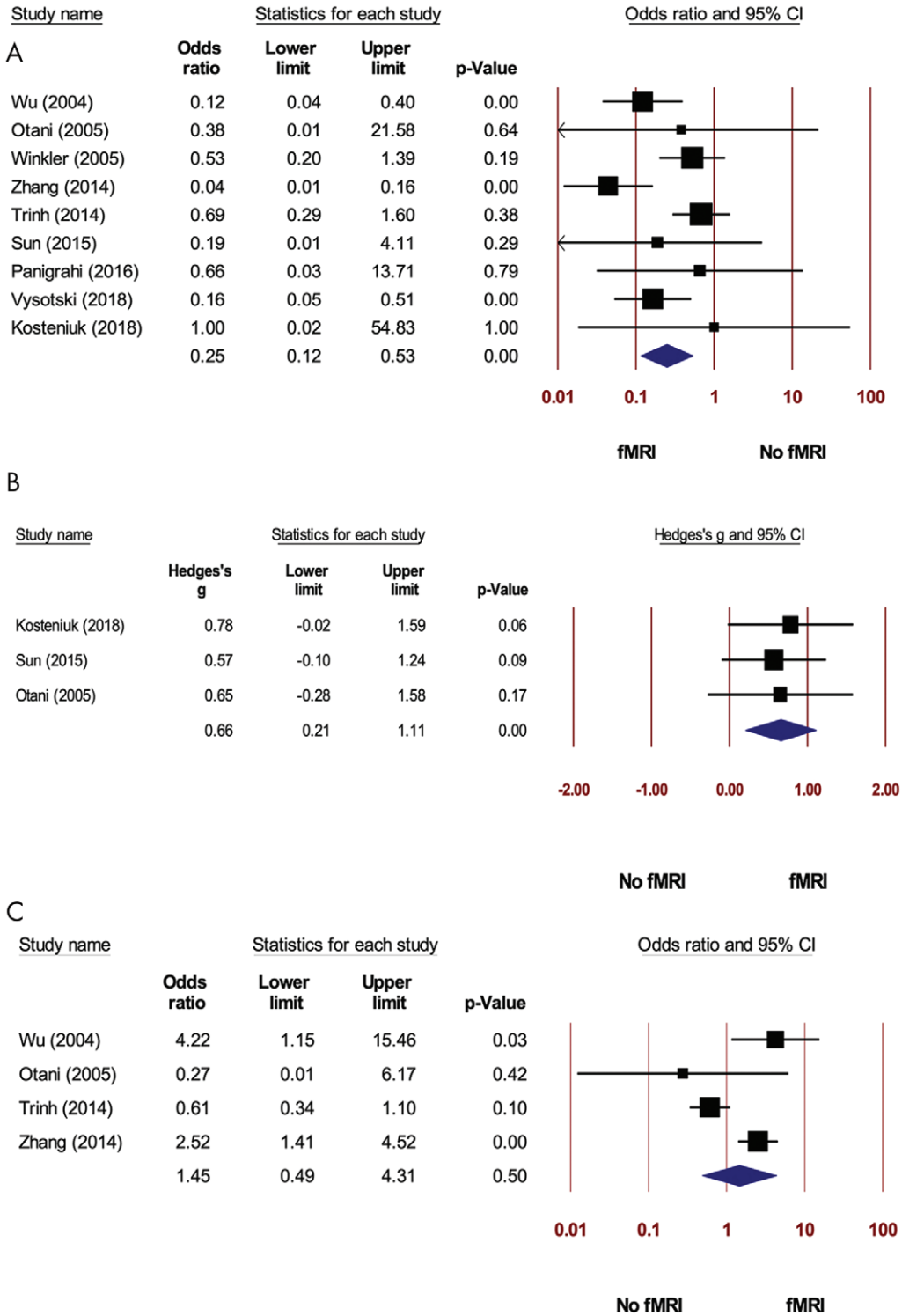

Figure 3: Forest plot for random-effects meta-analyses with 95% CIs in patients undergoing brain tumor surgery with and without presurgical functional MRI (fMRI) mapping by using, *A*, pooled odds ratios for standardized unfavorable outcomes, *B*, Hedges *g* for pre- and postsurgical mean Karnofsky performance status score, and, *C*, odds ratios for gross total resection.

imaging and fMRI, in 29 studies (11.3%). In contrast to our study, the study by Caras et al found no statistically significant difference in the incidence of neurologic deficits between patients undergoing preoperative advanced imaging and those who had standard neuronavigation. However, the authors included studies that used diffusion-tensor imaging and/or fMRI techniques, with fewer fMRI data sets (n = 5). Our data showed a rate of permanent postoperative neurologic deficits of 22.5% (118 of 524) (pooled incidence, 21.0%; median follow-up time, 6 months) in patients who did not undergo

Table 4: Primary Random-Effects Meta-Analyses of Neurologic Outcomes and Gross Total Resection in Patients Undergoing Brain Tumor Surgery with or without Presurgical Functional MRI Assessment

Outcome	No. of Studies	fMRI Group, No. of Patients	No-fMRI Group, No. of Patients	ES (95% CI)	*P* Value (Overall)*	I^2	*P* Value for I^2	*P* Value (Egger)†	Small-Study Effects‡
Studies with comparison group (odds ratio)									
All outcomes§	9	337	395	0.25 (0.12, 0.53)	<.001	53.2	.03	.79	No
Gross total resection‖	4	242	249	1.45 (0.49, 4.30)	.50	80.4	.002	.98	No
Studies with comparison group (Hedges *g*)									
KPS before and after surgery#	3	57	48¶**	0.66 (0.21, 1.11)	.004	0	.92	.64	No

Note.—Data in parentheses are 95% CIs. ES = effect size, fMRI = functional MRI, KPS = Karnofsky performance scale.

* In Z-test of overall effect.

† In Egger test of publication bias.

‡ $P < .1$ in Egger test of publication bias; effect size of the largest study more conservative than the overall effect size or in the opposite direction.

§ All standardized unfavorable outcome measures. The primary unfavorable outcome was the proportion of patients with postsurgical functional deterioration and/or new postsurgical deficit that persisted after 2 months of follow-up. Outcomes could be directly reported as rates in the report or derived from several of the scales used to assess neurologic deficits.

‖ Proportion of patients that underwent gross total resection (>90% of tumor volume) within each group.

Mean difference (after surgery minus before surgery) within each group.

** Proportion of patients that had worsening (decreased) postsurgical KPS scores compared with the presurgical values.

preoperative fMRI mapping (n = 9), which is higher than reported numbers (6%–20%) (83,84).

Our data showed a significant negative correlation between preoperative tumor volumes and the incidence of worsening postoperative deficits. Paiva et al (85) reported a significant positive correlation between preoperative tumor volume and postoperative neurologic deficits in the immediate postoperative period, but not at 3-month follow-up. They evaluated a sample of 47 patients with tumors in the precentral gyrus, including both metastatic and primary lesions, resected with standard neuronavigation and cortical mapping. Likewise, other studies that used standard neuronavigation showed nonsignificant associations between preoperative tumor volume and late postoperative neurologic or cognitive deficits (3–6 months) (83,86). These results suggest more surgical effort with larger lesions (eg, fMRI and concomitant use of other advanced imaging techniques, intraoperative MRI, cortical stimulation) compared with smaller lesions, which ultimately may lead to a greater incidence of late postoperative deficits with lesions that were assumed to be more easily removed. In addition, surgeons may have less room for error with smaller tumors. Smaller lesions may also be associated with attempts of greater resection, which may increase postoperative deficits. This is supported by a negative correlation with late postsurgical deficits in our meta-analysis (P = .02).

Studies reporting frontotemporal tumor locations were associated with significantly increased pooled permanent postsurgical deficits. Similar findings have been reported with the use of standard neuronavigation (83). Conversely, insular location was negatively correlated with increased late postoperative deficits in meta-regression analyses. It may be that surgical procedures were less aggressive with insular tumors (ie, biopsy over resection), thus reducing the insular tumor group's deficits, and more aggressive with resection in the broader frontotemporal regions.

The heterogeneity in the meta-analyses was high. This was observed for the ER of unfavorable outcomes in patients with presurgical fMRI assessment (68 studies; I^2 = 66.8%) and for the odds ratio when patients with or without presurgical assessment were compared (nine studies, I^2 = 53.2%). Although heterogeneity was low in some of the subgroup analyses, the I^2 values remained greater than 50% in most of the subgroups. Therefore, this must be considered when the pooled estimates are interpreted.

Our study had limitations. First, the high between-study heterogeneity was likely the result of differences in defining permanent postsurgical deficits, the heterogeneous or limited sizes of the small study samples, different types of tumors, retrospective design, and nonrandomized treatment assignment. Second, although one of the study goals was to assess how these factors influence heterogeneity (by using meta-regression analyses), the real effect of these factors for achieving gross total resections and influencing permanent postsurgical morbidity was difficult to determine because of the retrospective nature of the studies. Third, it is impossible to know whether the overall effects of fMRI depend on those other factors. This would require the investigation of interactions, which was impossible in this study because of the limited number of studies or lack of data (ie, inconsistent reports). Finally, details of the intraoperative technique and MRI parameters were infrequently specified, and we could not delineate subgroups among neuronavigation use, cortical stimulation, general anesthesia, and awake surgery

populations in all studies, or the possible use of other imaging techniques if these were not reported.

In conclusion, our results suggest that preoperative functional (fMRI) mapping results in a lower risk for delayed or permanent neurologic deficits that persists after a 2-month follow-up period when compared with surgery without preoperative fMRI. However, these results should be interpreted with caution because of the moderate quality of the available evidence. In addition, no consensus has been reached on the definition of permanent neurologic deficits. From the currently available data, however, the benefit of preoperative fMRI planning for the resection of brain tumors appears to reduce postsurgical morbidity, particularly when used with other advanced imaging techniques such as diffusion-tensor imaging, intraoperative MRI, or cortical stimulation. Thus, it should be considered as the standard of care for brain tumor surgery, even with small tumor volumes. Future studies should include clearly defined outcome measures by using objective measurements and scales and standardizing the definition of permanent neurologic deficits. Such a standardized definition would improve both the comparability among studies and the quality of evidence provided by studies investigating the effect of preoperative imaging in brain tumor surgery. A critical next step toward clinical acceptance of fMRI will be to develop a comprehensive set of guidelines that specifies where and when to implement fMRI in the preoperative planning of neurosurgical oncology.

Author contributions: Guarantors of integrity of entire study, L.P.L., F.G.S.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, L.P.L., F.G.S., H.I.S., C.A.K.; clinical studies, H.I.S.; statistical analysis, L.P.L., I.B.O., C.A.K.; and manuscript editing, L.P.L., H.I.S., D.M., C.A.K.

Disclosures of Conflicts of Interest: **L.P.L.** disclosed no relevant relationships. **F.G.S.** disclosed no relevant relationships. **H.I.S.** disclosed no relevant relationships. **D.M.** disclosed no relevant relationships. **I.B.O.** disclosed no relevant relationships. **C.A.K.** disclosed no relevant relationships.

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