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Original research

Effect of high-field iMRI guided resection in cerebral glioma surgery: A randomized clinical trial☆

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ABSTRACT

Background: Extent of resection (EOR) in glioma contributes to longer survival. The purpose of NCT01479686 was to prove whether intraoperative magnetic resonance imaging (iMRI) increases EOR in glioma surgery and benefit survival.

Methods: Patients were randomized (1:1) to receive the iMRI (n = 161) or the conventional neuronavigation (n = 160). The primary endpoint was gross total resection (GTR); secondary outcomes reported were progression-free survival (PFS), overall survival (OS), and safety.

Results: 188 high-grade gliomas (HGGs) and 133 low-grade gliomas (LGGs) were enrolled. GTR was 83.85% in the iMRI group vs. 50.00% in the control group (P < 0.0001). In 321 patients, the median PFS (mPFS) was 65.12 months in the iMRI group and 61.01 months in the control group (P = 0.0202). For HGGs, mPFS was improved in the iMRI group (19.32 vs. 13.34 months, P = 0.0015), and a trend of superior OS compared with control was observed (29.73 vs. 25.33 months, P = 0.1233). In the predefined eloquent area HGG subgroup, mPFS, and mOS were 20.47 months and 33.58 months in the iMRI vs. 12.21 months and 21.16 months in the control group (P = 0.0098; P = 0.0375, respectively). From the exploratory analyses of HGGs, residual tumor volume (TV) < 1.0 cm^3 decreased the risk of survival (mPFS: 18.99 vs. 9.43 months, P = 0.0055; mOS: 29.77 vs. 18.10 months, P = 0.0042). LGGs with preoperative (pre-OP) TV > 43.1 cm^3 and postoperative (post-OP) TV > 4.6 cm^3 showed worse OS (P= 0.0117)

Conclusions: It showed that iMRI significantly increased EOR and indicated survival benefits for HGGs, particularly eloquent HGGs. Residual TV in either HGGs or LGGs is a prognostic factor for survival.

☆ Trial Registration: NCT01479686 at ClinicalTrials.gov.

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1. Introduction

Nowadays, multimodal image-guided resection has developed rapidly. Notably, over 200 neurosurgical centers have installed high-field (1.5 T or above) iMRI facilities to maximize tumor resection (Fig. S1). The extent of resection (EOR) is one of the most critical factors associated with prolonged progression-free survival (PFS) and overall survival (OS) in gliomas [1–3]. Additionally, multiple observational studies have shown the effectiveness of glioma surgery [4–6]. However, high-level evidence on the efficacy of high-field (1.5 Tesle or above) intraoperative magnetic resonance imaging (iMRI) in optimizing EOR and achieving higher gross total resection (GTR) and prolonging survival for gliomas is lacking. Previous evidence was provided by Senft et al. and Kubben et al.[7,8] The former study was unmasked to surgeons, while the latter reported negative results with an insufficient sample size. Recently, prospective non-randomized and several retrospective observational studies have shown that GTR and maximized EOR were prognostic survival factors compared with subtotal resection (STR) [4–6,9–12]. Although these investigations suggested that iMRI could improve survival [9,13], there is no high-level evidence [14].

iMRI is used in the surgical treatment of gliomas, with uncertain effects on outcomes. Thus, additional supporting evidence is needed to determine the clinical benefit of iMRI in managing gliomas. This randomized controlled trial (RCT) was designed to verify the hypothesis that high-field iMRI achieves higher GTR, leading to prolonged PFS and OS in malignant cerebral gliomas and the safety of iMRI application.

2. Methods

2.1. Study design and participants

The study was an investigator-initiated single center involving three surgical teams conducted by the Neurologic Surgery Department of Huashan Hospital, Fudan University, in February 2012. All participants or their attorneys gave written informed consent. The trial review was performed by an independent expert committee (IEC) at prespecified intervals. Three interim analyses were performed according to a monitoring and evaluation plan. Once a statistical result corrected of the primary GTR endpoint was given for interim analyses, it would be presented to the IEC for recommendation.

The study population included patients aged 18–70 years and a Karnofsky performance scale (KPS) of 70 or above with radiologically suspected, newly diagnosed, supratentorial WHO grade 2–4 gliomas for which GTR was intended were eligible. Since no clear pathological diagnosis can be obtained before the operation, tumor grade (HGG or LGG) was diagnosed by the preoperative MRI. Namely, HGG was defined as a tumor showing T1-weighted contrast-enhanced MRI, while LGG was described as a tumor showing T1-weighted contrast-non-enhanced MRI before surgery. Critical exclusion criteria included the previous medical history of treatments and diffuse midline tumors (diencephalon and below). (Details in ***Supplementary Inclusion and Exclusion criteria***).

2.2. Randomisation and masking

Randomization was carried out after the surgeons completed the standard resection procedure. Patients were randomly assigned (1:1) to receive the iMRI or the conventional neuronavigation via a

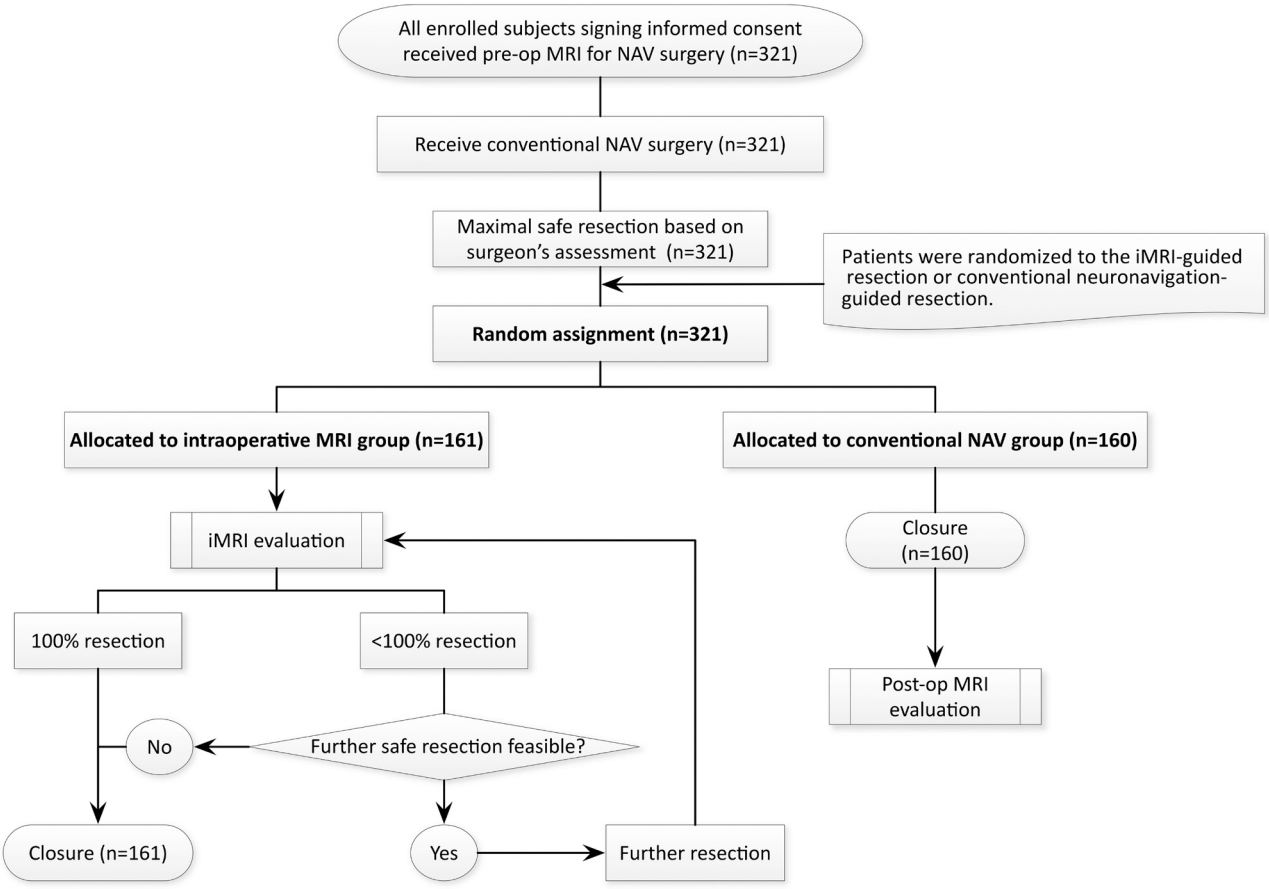


Fig. 1. Maximal safe resection was based on the surgeon's assessment in accordance with conventional neuronavigation and intraoperative neurophysiological monitoring.

randomization system. The randomization sequence was generated via the Pocock-Simon range method [15], and stratified by tumor grade (HGG vs. LGG), pre-op KPS (70–90 vs. 100), age ([17.5, 45], (45, 65), [65,72]), tumor location (frontal, temporal, parietal, occipital, and insular lobe), hemisphere (non-dominant vs. dominant) and function (non-eloquent vs. eloquent). Patients, assessment staff, investigators, and the statisticians responsible for final data analyses were masked (Fig. 1) until the final statistical analysis [15].

2.3. Procedures

Initially, patients underwent the first maximal safe resection, determined by the unblinded neurosurgeons and guided by preoperative MRI, within the same 3 T iMRI integrated IMRIS Surgical Theatre (formerly IMRIS, Inc., Canada, now Deerfield Imaging, Inc., US). Subsequently, patients were randomized into either iMRI-guided resection or conventional neuronavigation-guided surgery groups. Patients allocated to the iMRI group would receive multiple iMRI evaluations until 100% resection was performed or if it was unfeasible to conduct further resections safely. Conversely, patients assigned to the control group would receive closure directly (Fig. 1). All patients received a postoperative MRI to assess the EOR within 72 h after surgery. All other surgical interventions were identical between the groups. Fig. 2 presents the CONSORT flow diagram.

Two blinded, independent board-certified neuro-radiologists calculated the EOR to assess whether GTR was achieved, using T2-weighted fluid attenuated inversion recovery (FLAIR) images for LGGs and T1-weighted contrast-enhanced MR images for HGGs based on the Response Assessment in Neuro-Oncology (RANO) criteria [16–18].

Tumor tissue and blood samples were stored for pathological review (Supplementary Methods *for Molecular Evaluation*) and re-assessed based on the 2021 WHO classification of Tumors of the CNS (WHO CNS5) following molecular marker testing.

Postoperative follow-ups and treatment for HGGs and LGGs adhered to the guidelines established by the National Comprehensive Cancer Network (NCCN) and the guidelines for diagnosing and treating central nervous system gliomas in China [19–21].

2.4. Outcomes

The primary endpoint was GTR, defined as 100% elimination of contrast-enhancing lesions on T1-weighted MR images for HGGs and hypersignal intensity lesions on T2-weighted FLAIR images for LGGs. Secondary outcomes included PFS (time from initial surgery to the demonstration of an increase in tumor volume by 25% or more, or death), OS (time between initial surgery and death), KPS, and safety.

2.5. Statistical analysis

The initial sample size was 320 based on a 15% difference between two arms with a one-sided alpha level of 0.025 and a power of 90% for GTR in a 1:1 ratio [15]. The Lan–DeMets alpha-spending function with O'Brien-Fleming-type boundaries was used to preserve type I error of false positive effectiveness with a one-sided alpha level of 0.025 (Details in ***Supplementary Sample Size and Interim Analyses***). In 2014, during the first interim analysis conducted with one-third of the information (relative to the initially calculated sample size), the sample sizes for HGG and LGG were adjusted to 228 and 75, respectively, based on the GTR results [16]. The second and third interim analyses were scheduled at 1/3 and 4/5 information fraction (relative to the recalculated sample

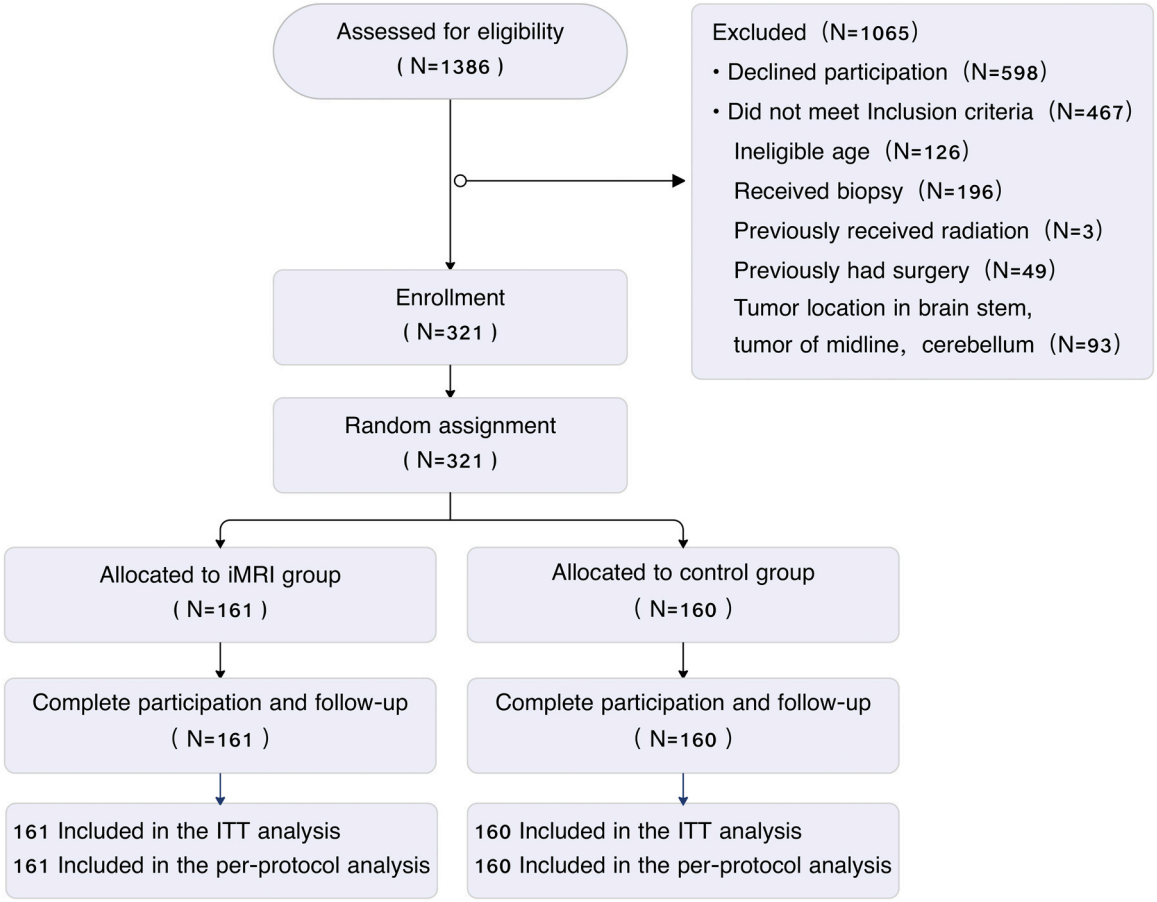


Fig. 2. Consort Flowchart.

size). Based on the results of the third interim analysis involving approximately four-fifths of the recalculated intended sample size, no more HGG patients were recommended to be enrolled. The final total sample sizes for HGG and LGG groups were 188 and 133, respectively, as of September 2018.

Analyses were performed in the intention-to-treat principle. The Wald Z-Test was used to test the difference between risk differences and relative risks with 95% confidence intervals (CIs) for GTR. A multivariate logistic model with adjusted randomization factors was also fitted to estimate ORs. Prespecified subgroup analyses for GTR were conducted using the Cochran-Mantel-Haenszel test, including terms for intervention type, subgroup, and intervention type x subgroup to assess the consistency of the iMRI effect. The Kaplan-Meier method was used for PFS and OS to describe survival experiences and estimate medians and 95% CIs. Differences between groups were compared using the stratified Log-rank test with randomization factors as stratification factors. Hazard ratios and 95% CIs were estimated using the multivariate COX model adjusted for randomization factors. Exploratory analyses using the Kaplan-Meier method and log-rank test to determine the effect of GTR and residual tumor volume on survival benefit in different glioma populations. Details were provided in the supplementary analysis.

A two-sided alpha level of 0.05 was set for indicators except for primary endpoints. All data analyses reported here were conducted using SAS9.4 (SAS Institute Inc., Cary, NC, USA), R4.0, and stata12.0 (StataCorp, TX, USA).

2.6. Role of the funding source

The sponsor had no role in the study design, data collection, analysis, interpretation, or report writing. The corresponding authors had full access to all the data in the study and were ultimately responsible for deciding to submit it for publication.

3. Results

3.1. Participants

From March 2012 to August 2018, 161 and 160 patients were randomly assigned to the iMRI group (95 radiologically diagnosed with HGGs and 66 with LGGs) and the control group (93 radiologically diagnosed with HGGs and 67 with LGGs). Pathological findings of 7 patients (1 with HGG and 6 with LGGs) suggested non-gliomas, and no molecular evaluation was carried out. All patients accepted complete imaging evaluation, with up to a 108-month (median, 43.17 months) follow-up period. The baseline characteristics of the patients between groups were similar in all patients and all HGGs and LGGs. (Table 1, Tables S1 & S2).

3.2. Primary endpoints

GTR was achieved more in the iMRI group than in the control group (83.85% vs. 50.00%, rate difference (RD) was 33.85% (24.24%, 43.46%), $P < 0.0001$. In the iMRI group, GTR was achieved in 89 patients (55.28%) when the first iMRI scan was conducted, and 46 of 72 patients (63.89%) with non-totally resection received further resections. The rate of GTR was also higher in the iMRI group for both 188 HGG patients and 133 LGG patients (HGG: 87.37% vs. 56.99%, RD: 30.38% [18.30%, 42.46%], $P = 0.0005$; LGG: 78.79% vs 40.30%, RD: 38.49% [23.15%, 53.83%], $P = 0.0001$) (Fig. 4). A comparison of post-OP TV between the two groups in box plots is shown in Fig. 3.

Predefined subgroup analyses are presented in Fig. 4. The interactions didn't reach statistical significance. The GTR of the iMRI group was higher than the control in any predefined subgroup. In contrast, eloquent areas exhibited a numerically higher rate of GTR in the iMRI group compared to the control group (38.76% vs. 26.15%, $P = 0.3789$) because the small sample size led to insufficient statistical

Table 1
Baseline Characteristics (all eligible patients).

Characteristics	iMRI Group (n = 161)	Control Group (n = 160)
Sex		
Male	97 (60.25%)	96 (60.00%)
Female	64 (39.75)	64 (40.00)
Age*		
[17.5, 45]	81 (50.31)	78 (48.75)
(45, 65)	69 (42.86)	67 (41.88)
[65,72]	11 (6.83)	15 (9.38)
Tumor Grade		
LGG	66 (40.99)	67 (41.88)
HGG	95 (59.01)	93 (58.13)
Pre-op KPS		
[70,90]	15 (9.32)	18 (11.25)
100	146 (90.68)	142 (88.75)
Function Area		
Non-eloquent	57 (35.40)	62 (38.75)
Eloquent	104 (64.60)	98 (61.25)
Tumor Location		
Frontal lobe	92 (57.14)	89 (55.63)
Parietal lobe	16 (9.94)	14 (8.75)
Temporal lobe	5 (3.11)	9 (5.63)
Insular lobe	18 (11.18)	22 (13.75)
Occipital lobe	30 (18.63)	26 (16.25)
Hemisphere		
Nondominant	78 (48.45)	79 (49.38)
Dominant	83 (51.55)	81 (50.63)
Pre-surgical epilepsy		
No	102 (63.35)	99 (61.88)
Yes	59 (36.65)	61 (38.13)
Adjuvant therapy	155	157
None	32 (20.65)	34 (21.66)
RT alone	21 (13.55)	26 (16.56)
Chemotherapy alone	17 (10.97)	19 (12.10)
RT + Chemotherapy	85 (54.84)	78 (49.68)
Post-op KPS		
< 100	54 (33.54)	50 (31.25)
100	107 (66.46)	110 (68.75)
Pre-op tumor volume (cm^3) Median (IQR)	38.03 (23.50, 65.55)	40.17 (17.51, 72.68)
1st EOR (%) (Median, IQR)		
HGG	100.00 (97.33, 100.00)	100.00 (97.08, 100.00)
LGG	98.45 (91.78, 100.00)	95.63 (84.45, 100.00)
Molecular characteristics	156	158
IDH		
Mutant	71 (45.51)	65 (41.14)
Wildtype	85 (54.49)	93 (58.86)
Undetected	0	0
MGMT		
Methylation	93 (59.62)	94 (59.49)
Unmethylation	55 (35.26)	57 (36.08)
Undetected	8 (5.13)	7 (4.43)
TERT		
Mutant	77 (49.36)	80 (50.63)
Wildtype	71 (45.51)	68 (43.04)
Undetected	8 (5.13)	10 (6.33)
1p19q		
Codeletion	34 (21.79)	24 (15.19)
Retain	78 (50.00)	85 (53.80)
Undetected	44 (28.21)	49 (31.01)

N (%) unless otherwise stated
KPS, Karnofsky performance scale; RT, Radiotherapy; IDH, Isocitrate dehydrogenase gene; MGMT, Methyl-guanine methyl transferase gene; TERT, Telomerase reverse transcriptase
*Patients 101 and 206 were 72 and 17.5 years old, respectively, at enrollment, which marginally falls outside the inclusion age range. Being minor protocol violations, these two cases can be safely included in all data analysis sets without creating bias.
Molecular characteristics: We conducted molecular marker testing on all 314 samples except 7 non-gliomas (5 non-gliomas in the HGG group and 3 non-gliomas in the LGG group)
Undetected: We conducted molecular marker testing for some tumor samples, but its indicator could not be determined.

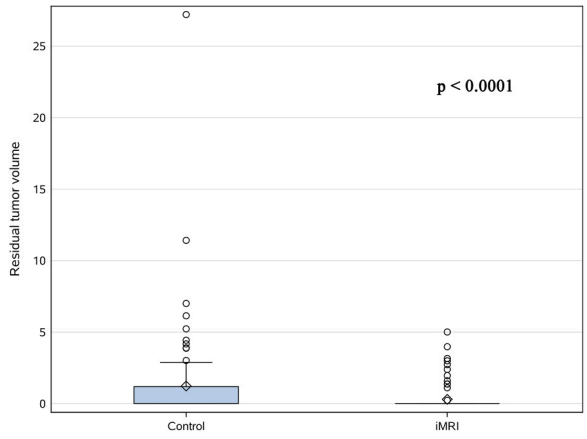


Fig. 3. Comparison of post-OP TV between the control and iMRI groups.

power for the interaction test.

3.3. Secondary endpoints

Survival analysis included 166 disease progressions and 142 deaths. The mPFS was 65.12 months in the iMRI group and 61.01 months in the control group (P = 0.0202). (Fig. 5A) The OS didn't demonstrate statistical significance (mOS: 9.82 months vs. unreached, P = 0.3722).

In the predefined HGG subgroup, improvement in PFS was observed, with mPFS of 19.32 months in the iMRI group (n = 95) compared with 13.34 months in the control group (n = 93) (P = 0.0015) (Fig. 5B). There was also a trend of superior OS compared with control (mOS in iMRI vs. control: 29.73 vs. 25.33 months; P = 0.1233). In the predefined LGG subgroup, there was no statistically significant effect on survival between groups (PFS: P = 0.4136; OS: P = 0.1753).

In the predefined subgroup of HGG within eloquent area, mPFS and mOS were 20.47 months (95%CI, 13.90–43.89 months) and 33.58 months (95%CI, 22.11–59.50 months) in the iMRI group vs. 12.21 months (95%CI, 8.51–18.69 months) and 21.16 months (95%CI, 13.01–29.77 months) in the control group (PFS: P = 0.0098; OS: P = 0.0375) (Fig. 5C, D). In HGGs aged > 45 and < 65 years and KPS 100 subgroups, mPFS was 18.04 months (95%CI, 13.80–22.11 months) and 20.47 months (95%CI, 13.86–33.54 months) for iMRI vs 11.47 months (95%CI, 8.51–13.34 months) and 13.17 months (95%CI, 9.92–18.69) for control (aged >45 and <65 years: P = 0.0115; KPS=100: P = 0.0384). Other randomization factors, including tumor location and hemisphere, were not associated with survival (***Supplementary Survival Post-hoc Analysis***).

The proportional hazards assumptions were not rejected for all survival analyses. However, Schoenfeld Residual Plots indicated a non-PH pattern and early effect might exist, so non-PH methods for post-hoc analysis were performed. Notably, the results were similar to the PH methods (***Supplementary Survival Post-hoc Analysis***).

3.4. Exploratory analysis

Exploratory analysis with multiple regression was conducted to evaluate GTR on survival. From stepwise Cox regression analysis in all patients revealed that GTR significantly decreased the risk of progression and death compared with STR (PFS: HR, 0.504; 95%CI, 0.362–0.702; P < 0.0001; OS: HR, 0.606; 95%CI, 0.422–0.869; P = 0.0065 (Table S3). Additionally, HGG patients showed GTR was associated with a significantly 51.4% lower risk of tumor progression (Median 20.37 vs. 10.94 months; P = 0.0009) (Fig. 5E). Moreover, GTR resulted in a significantly lower risk of death by 40.5% (mOS, 29.73 vs. 19.84 months; P = 0.0108) (Fig. 5F and Table S3). In IDH-wildtype gliomas (n = 178), GTR was associated with improved survival (mPFS: 18.99 months [95%CI, 14.65–24.61 months] vs. 12.65 months [95%CI, 8.41–18.43 months]; P = 0.0210; mOS: 29.70 months [95%CI, 25.17–42.64 months] vs. 22.08 months [95%CI, 13.83–30.42 months]; P = 0.0461) (Fig. 5G and H). In IDH mutant gliomas (n = 136), there was no significant difference in survival improvement in GTR compared with STR (mPFS: unreached; P = 0.6988; mOS: unreached; P = 0.7879) (Fig. S2).

Post-OP residual TV has been shown to have a significant impact on survival as suggested by recent multi-institutional studies [18,22]. Therefore, we conducted the further exploratory analyses and categorized HGGs according to residual TV 1.0 cm^3 and LGGs according to pre-OP TV > 43.1 cm^3 and post-OP TV > 4.6 cm^3 based on the previous studies [18,22]. In HGGs, residual TV < 1.0 cm^3 significantly decreased the risk of progression and death compared with residual TV ≥ 1.0 cm^3 (mPFS: 18.99 vs. 9.43 months, P = 0.0055; mOS: 29.77 vs. 18.10 months, P = 0.0042). Furthermore, we classified LGGs with pre-OP TV > 43.1 cm^3 and post-OP TV > 4.6 cm^3 as one category, and this group had worse OS (p = 0.0117) (Fig. 6).

3.5. Adverse effect

No significant difference was observed in KPS scores between groups at 1-month and 6-month follow-ups (median=100; IQR [90,100]; median=100; IQR [100,100] for iMRI vs. median=100; IQR [90,100]; median=100; IQR [90,100] for control; P = 0.5175; 0.9595). Additionally, the postoperative intracranial infection rate in the iMRI group was higher. All central nervous system infections were classified as Grade 3 and were cured after intravenous antibiotics. There was no significant difference in postoperative early language disorder, early motor deficit, late language disorder, chronic dyskinesia, and the total number of postoperative inpatient days between the two groups. Furthermore, the operation time of iMRI (IQR [5.00 h, 7.75 h]) was longer than the control (IQR [5.00 h, 7.00 h]) (Table 2).

4. Discussion

This clinical trial was the first carefully designed, well-executed, and sizeable prospective RCT evaluating the efficacy of iMRI in cerebral glioma resection compared to previous studies [7, 8, 14].

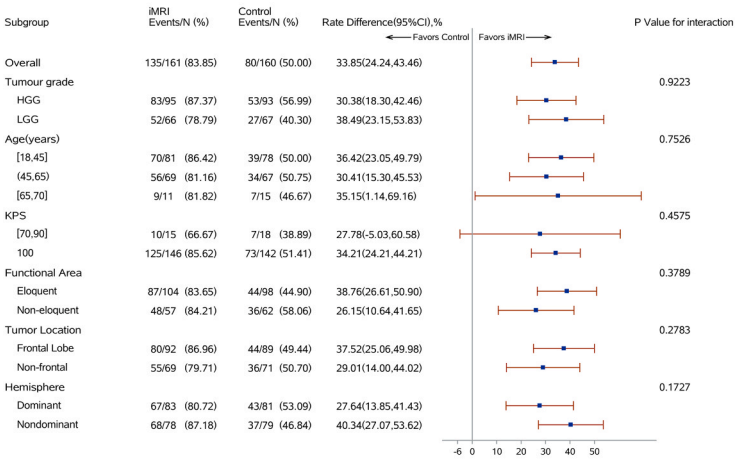
This study demonstrated that using iMRI resulted in a higher chance of attaining GTR (>30%), a significant improvement in PFS, and a trend towards prolonged OS observed in HGGs. However, using iMRI might not improve survival for LGGs because of its lower malignant and better prognostic characteristics when 90% resection is achieved [3]. However, Wijnenga's work found that even minimal residual tumor volume negatively affected OS in IDH-mutated astrocytoma but not in oligodendroglioma patients, proposing the iMRI value [23]. In our study, LGGs include oligodendroglioma and some WHO grade 1 gliomas, affecting the value evaluation of iMRI in LGGs.

Previous studies also reported observational findings supporting this conclusion [11,24,25]. Nimsky et al. reported that iMRI use effectively decreased tumor residual [24]. Another study showed that using iMRI resulted in 28.6% of cases with an enhanced tumor undergoing further resection, increasing the GTR rate by nearly 20% [25]. This finding is consistent with our results that iMRI use could improve the GTR rate in high-grade and low-grade gliomas.

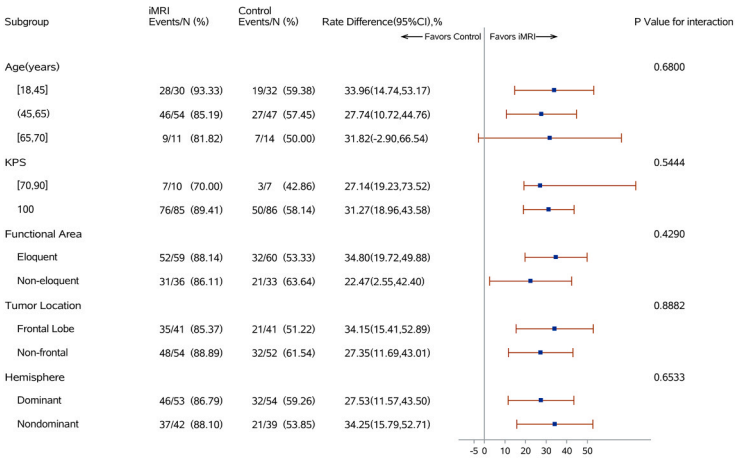
GTR is significant to glioma, and improving GTR is associated with more prolonged survival in HGGs and IDH-wildtype gliomas [7,8]. Thus, we hypothesized that the improvement in GTR could reflect the effectiveness of iMRI, especially for HGGs and IDH-wildtype gliomas, translating into significant survival benefits. Moreover, Karschnia's work reviewed the meaning of supra-maximal resection in glioblastoma and IDH-wildtype glioma [26].

Recently, Hervey-Jumper and Karschnia's work explored the relationship between residual TV and glioma prognosis [18,22]. From our study, 1.0 cm^3 as the threshold for residual TV could bring significant

A Subgroup Analysis for GTR in HGG + LGG patients



B Subgroup Analysis for GTR in HGG patients



C Subgroup Analysis for GTR in LGG patients

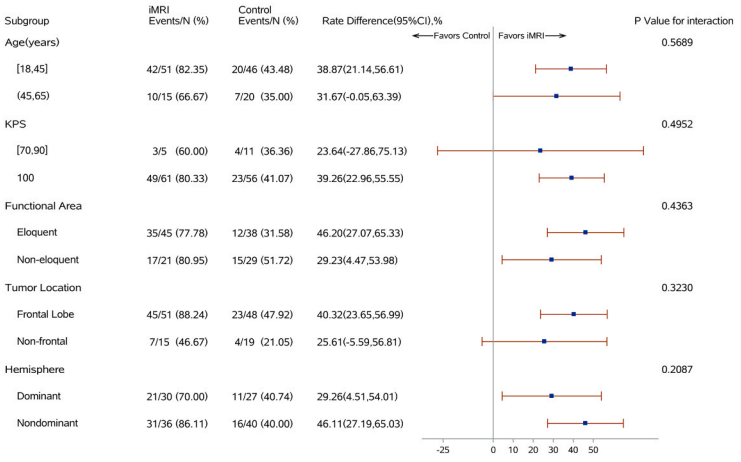


Fig. 4. Subgroup analysis for GTR between the iMRI and the control groups.

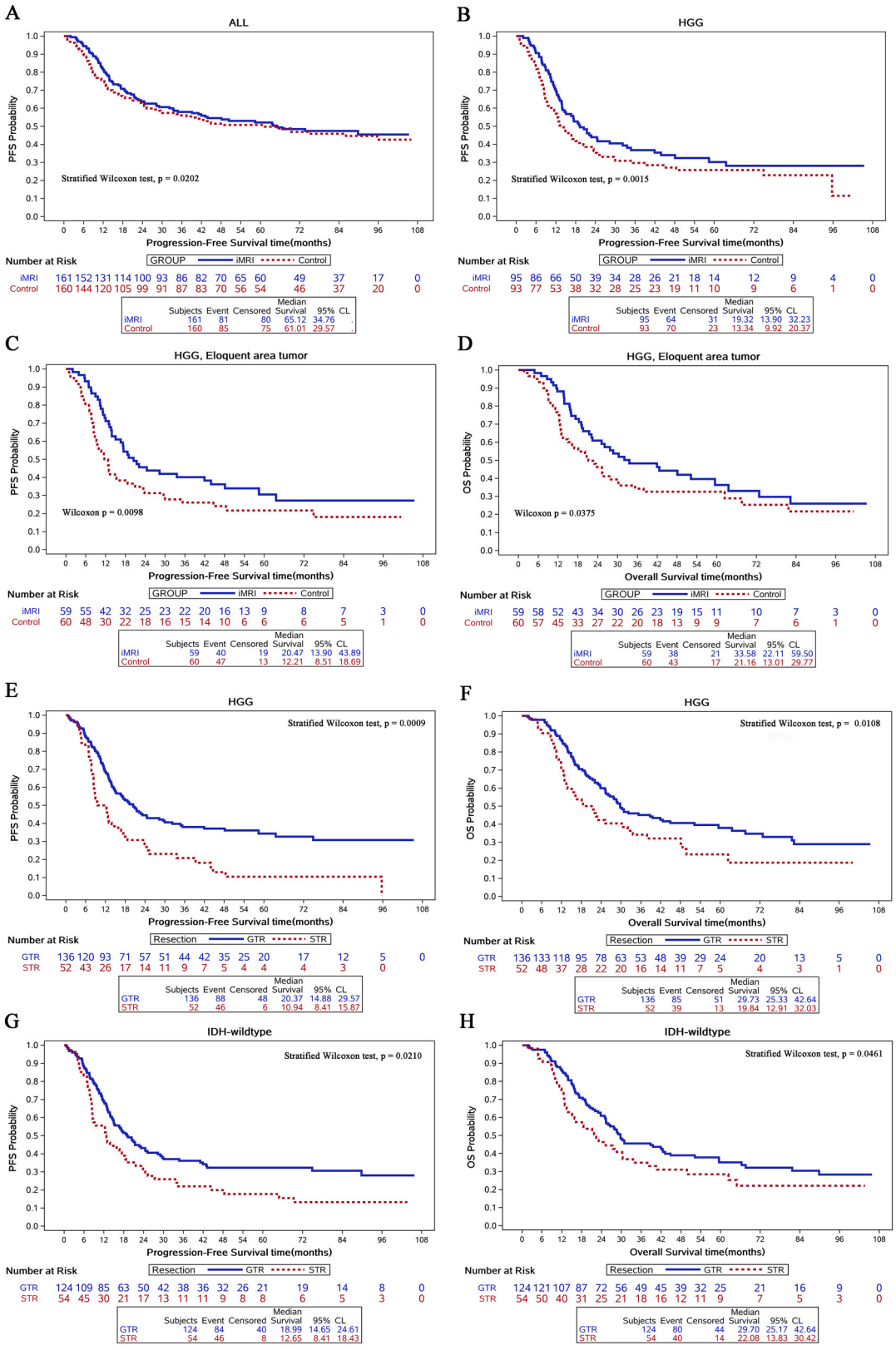


Fig. 5. Survival analysis between the iMRI group and the control group. **A**, All patients, iMRI group vs. control group (Median PFS: 65.12 vs. 61.01 months, p = 0.0202); **B**, HGGs, iMRI group vs. control group (Median PFS: 19.32 vs. 13.34 months, p = 0.0015); **C**, Eloquent area HGGs, iMRI group vs. control group (Median PFS: 20.47 vs. 12.21 months, p = 0.0098); **D**, Eloquent area HGGs, iMRI group vs. control group (Median OS: 33.58 vs. 21.16 months, p = 0.0375). Survival analysis between the GTR and STR groups. **E**, HGG patients, GTR vs. Sub-total resection (Median PFS: 20.37 vs. 10.94 months, p = 0.0009); **F**, HGG patients, GTR vs. Sub-total resection (Median OS: 29.73 vs. 19.84 months, p = 0.0108); **G**, IDH-wildtype gliomas, GTR vs. STR (Median PFS: 18.99 vs. 12.65 months, p = 0.0210); **H**, IDH-wildtype gliomas, GTR vs. STR (Median OS: 29.70 vs 22.08 months, p = 0.0461).

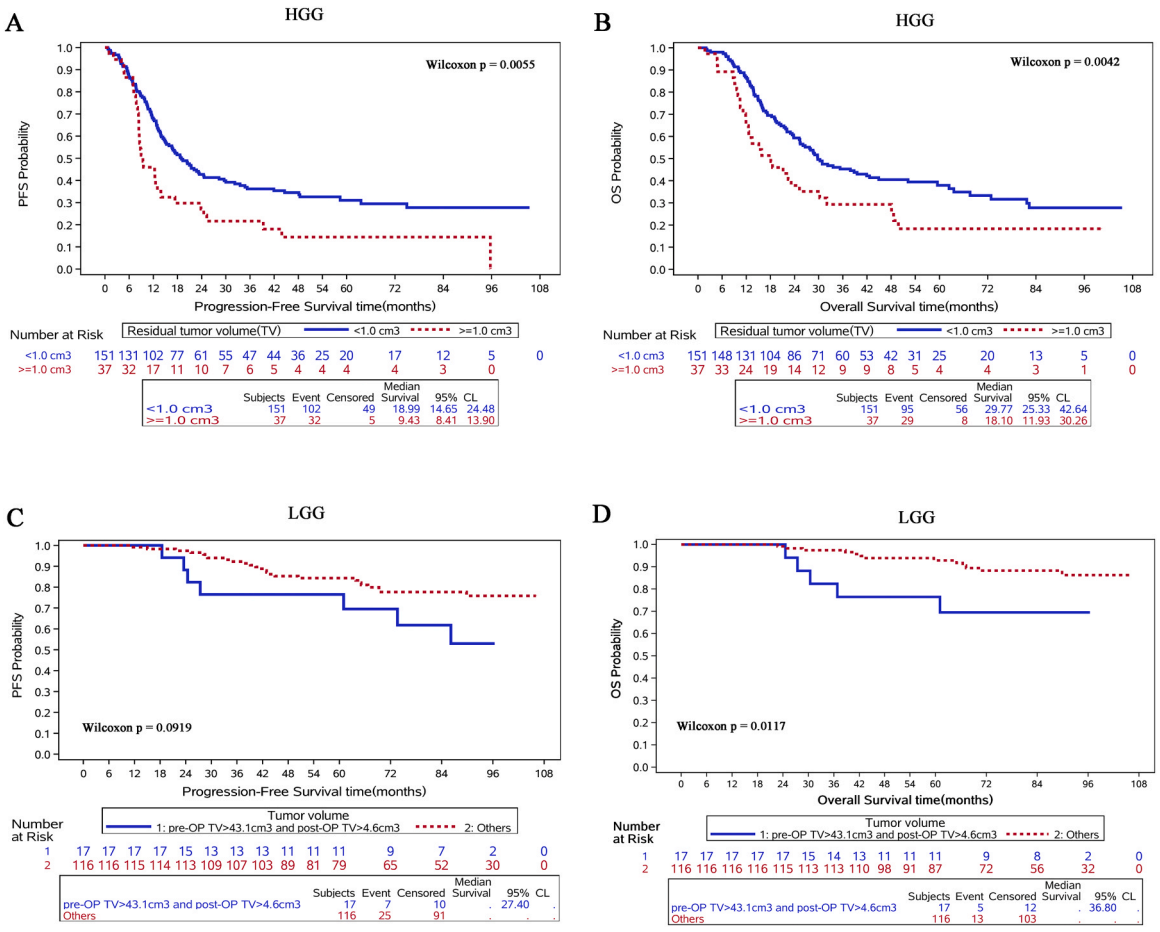


Fig. 6. Survival analysis for TV. **A**, HGGs, residual TV < 1.0 cm^3 vs. residual TV ≥ 1.0 cm^3 (Median PFS: 18.99 vs. 9.43 months, p = 0.0055); **B**, HGGs, residual TV < 1.0 cm^3 vs. residual TV ≥ 1.0 cm^3 (Median OS: 29.77 vs. 18.10 months, p = 0.0042); **C**, LGGs, pre-OP TV > 43.1 cm^3 and post-OP TV > 4.6 cm^3 vs. Other (Median PFS: unreached, p = 0.0919); **D**, LGGs, pre-OP TV > 43.1 cm^3 and post-OP TV > 4.6 cm^3 vs. Other (MedianOS: unreached, p = 0.0117);.

Table 2
Safety Analysis.

	No. (%)		P value
	iMRI group	Control group	
Intracranial infection (any Grade)	29 (18.01%)	15 (9.38%)	0.0245
Grade 3	29 (18.01%)	15 (9.38%)	0.0245
Grade 4	0	0	
Post-surgical epilepsy (any Grade)	18 (11.18%)	15 (9.38%)	0.5944
Grade 1-2	18 (11.18%)	15 (9.38%)	0.5944
Grade 3	0	0	
Grade 4	0	0	
Early language disorder	12 (7.45%)	14 (8.75%)	0.6703
Early motor disorder	24 (14.91%)	22 (13.75%)	0.7674
Late language disorder	5 (3.16%)	8 (5.19%)	0.3696
Late motor disorder	8 (5.06%)	11 (7.14%)	0.4425
Surgical time (h)	6.70 ± 2.15	6.26 ± 1.72	0.0441
Postoperative inpatient days (d), median (IQR)	11.00 (9.00, 15.00)	11.00 (9.00, 14.00)	0.4908

survival benefits to HGGs. Besides, LGGs with pre-OP TV > 43.1 cm^3 and post-OP TV > 4.6 cm^3 were classified as one category with the worst prognosis. Notably, our results were consistent with theirs. Shah AS figured that iMRI increased EOR and GTR, accordingly, and that GTR increased OS for patients with newly diagnosed glioblastoma [27]. Thus, we confirmed that iMRI was just a surgical guidance technique to reduce residual TV, contributing to survival benefits.

In eloquent area tumors, surgeons face the challenge of preserving neurologic function, often leading to STR compared to non-eloquent tumors [28,29]. The pre-planned subgroup analysis indicated that using iMRI resulted in a greater chance of attaining safe GTR in eloquent HGGs related to longer PFS and OS. Still, this sign was not observed in non-eloquent area HGGs.

Advanced techniques, such as intraoperative multimodal image-guided neuronavigation, are becoming crucial to achieving maximal glioma resection [7,8]. Using 5-aminolevulinic acid (5-ALA) fluorescence has also increased in recent years [30]. However, the absence of fluorescence as an indicator of no tumor is controversial, decreasing the chance of GTR [31]. Furthermore, it is currently not approved by the National Medical Products Administration (NMPA) for clinical use in China. Recently, an important work by Roder figured out that the 5-ALA could achieve the same result as iMRI for glioblastoma [32]. Although 5-ALA may be more economically advantageous, the choice between iMRI and 5-ALA will depend on the availability of drugs and equipment and surgeons' personal preference.

We observed that iMRI use resulted in relatively higher post-operative intracranial infection. We assume this was due to the re-draping steps required and longer operation times. However, this did not affect KPS scores. Furthermore, no difference in either early or late language and motor deficits was recorded between groups.

Limitations include a single-center study with a limited sample size, insufficient data on OS for iMRI, a small number of patients in the subgroup analysis, and non-PH suspected. For the latter, non-PH methods as post-hoc were performed, and results were consistent with PH methods. Based on molecular biomarkers, signs of survival benefits appeared in IDH-wildtype gliomas. It suggests the value of iMRI in IDH-wildtype gliomas. In the future, iMRI-guided surgery would focus on the

WHO CNS5 integrated diagnosed HGGs.

In conclusion, this trial confirms that iMRI can significantly increase the EOR in cerebral gliomas. Residual TV in either HGGs or LGGs is a prognostic factor for survival. Patients with eloquent area HGGs could benefit from using iMRI. Additionally, HGGs and IDH-wildtype gliomas do benefit from iMRI-assisted radical resection.

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CRediT authorship contribution statement

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Declaration of Competing Interest

All authors have declared no conflicts of interest.

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Data sharing statement

Requests for data should be directed to the corresponding author. The data supporting the findings of this study are available within the article. Requests will be assessed for scientific rigor before being granted. A data-sharing agreement should be signed. Data will be anonymized and securely transferred.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113528.

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