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Effect of Magnetic Field Intensity on Tumor Resection: A Systematic Review and Meta-analysis

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Abstract [**Objectives**] The paper was to comprehensively assess the available evidence on the diagnostic value of high-field intraoperative MRI (iMRI) for residual tumor in high-grade glioma (HGG) and its prognostic impact on HGG. [**Methods**] We conducted a systematic literature search of electronic databases including PubMed, Embase and Cochrane Library to identify eligible studies. Study quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). The primary outcome was the gross total resection rate, with secondary outcomes including overall survival and 6-month progression-free survival. [**Results**] From a review of 132 candidate articles, we identified six articles with a total of 573 patients. The pooled risk ratio (RR) was 1.583 (95% *CI*: 1.235 – 2.029), indicating that high-field intraoperative MRI guided resection was associated with a reduced risk of 6-month progression-free survival, with a HR of 0.53 (95% *CI*: 0.348 – 0.806). The pooled HR of overall survival was 0.796 (95% *CI*: 0.581 – 1.089) between the two groups. [**Conclusions**] High-field iMRI appears to enable achievement of an ideal resection, although no strong evidence indicates that its application is associated with patient survival. Our study innovatively considered the effect of magnetic field intensity on tumor resection, and we found that 3 Tesla did not show a more favorable impact on improving the tumor resection rate compared with 1.5 Tesla.

Key words High-grade glioma, Intraoperative MRI, Meta-analysis

1 Introduction

Glioma is one of the most commonly diagnosed and treated primary tumors of the brain. It is typically classified into high and low grades based on the type of glial cell involved in the tumor, and originates in the brain parenchyma. This type of tumor is responsible for approximately 18 000 new cases and 13 000 deaths in the United States each year[1]. The diagnosis and treatment of glioma can be challenging due to the complex nature of the disease. Accurate diagnosis typically involves imaging studies, such as magnetic resonance imaging (MRI) and computed tomography (CT), as well as biopsy for pathological analysis. Treatment options can range from observation and monitoring of low-grade tumors, to surgical resection, radiation therapy, chemotherapy or a combination of these therapies for higher grade tumors. The prognosis for glioma patients is highly variable, and depends on factors such as tumor grade, location, age, and overall health status. Despite advances in diagnostic and treatment modalities, glioma remains a challenging disease to manage and further research is needed to improve patient outcomes and quality of life. The 5-year survival rate of glioma improves significantly once resected thoroughly[2–4]. Therefore, it is crucial to completely identify any residual tumor tissue during surgery to improve prognosis and prevent potential neurological disorders. The main reasons for using imaging technology to assist in resection of gliomas are intraoperative resection evaluation and control of brain metastases.

High-field iMRI, first applied to knee scanning for better imaging, was performed using a scanner ≥1.5 Tesla[5]. It was initially used in neurosurgery in 2000, for seeking safe and necessarily radical resection[6]. To date, most MRI therapy suites have been designed for low-field MRI (<0.5T) scanners, the most advantage of which is greater patient access during surgical procedures. However, low-field MRI system is associated with decreased resection, extending scan times, increased image distortion, diminished signal-to-noise rations, and limited or absent functionality[7]. The main goal of resection is to achieve surgical radicality, and the primary goal of any intraoperative imaging technology is to detect tumor location, control residual volume, and prevent postoperative functional impairment. The overall objective of this study was to externally revalidate the diagnostic and prognostic performances of intraoperative MR imaging techniques for achieving total resection and to analyze the impacts of different imaging fields on patients with high-grade glioma, thereby providing insights for future studies.

2 Materials and methods

2.1 Search strategy and selection criteria The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta–Analysis (PRISMA) guidelines[8]. We conducted a comprehensive literature search online using the following keywords and their various combinations: "intraoperative magnetic resonance imaging", "intraoperative ultrasound", "glioma", "glioblastoma", "predict", "gross total resection", and "survival". The search was performed in PubMed, Cochrane Library and Embase, with the final search executed on August 12, 2019.

2.2 Inclusion and exclusion criteria In order to be eligible for analysis, the following criteria had to be met: (i) cohort studies of more than 10 patients; (ii) adult patients (age ≥18 years old) diagnosed with high-grade glioma and undergoing surgery;

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(iii) comparison of high-field iMRI with classic neuronavigation-guided surgery as intraoperative techniques for tumor resection; and (iv) primary endpoint of gross total resection rate, defined as more than 95% absence of any residual enhancement on postoperative volumetric-enhanced MRI performed within 48 – 72 h of surgical resection. The gross total resection rate could be explicitly compared between the two groups or calculated from the data presented in the articles. Studies were excluded if they (i) only referred to animal studies, low-grade glioma, or other types of neurogenic tumors such as medulloblastoma, ganglioglioma, optic nerve glioma, gliosarcoma, or biopsy; or (ii) did not provide relevant information on the data items mentioned above.

2.3 Assessment of risk of bias and quality of evidence The quality of the included studies was scored independently by two authors according to the criteria of the Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2)[9]. All included studies underwent an evaluation of bias and applicability using 10 signaling questions and three correlative questions, respectively, and were answered as "yes", "no", or "unclear" as recommended. Risk of bias and concerns about applicability were then analyzed and graded as low risk, high risk, or unclear risk. Data were extracted from each study, including author information, country, assay methods, demographic data, and survival data. For the primary outcome, a 2 × 2 contingency table was constructed to evaluate the gross total resection rate in high-grade glioma between the iMRI guided group and the classic neuronavigation guided group for each individual study.

2.4 Data extraction and statistical analysis Data were completed in Excel 2019, then transferred to STATA12[10] (Stata, College Station, TX, USA) for statistical analysis. Images data were processed by GetData Graph Digitizer 2.25[11]. The gross total resection rate compared between high-field iMRI guided group and no iMRI guided group (control) was estimated by the overall pooled RR. To extrapolate the results to the population, random-effect model was used. Statistical heterogeneity was explored with χ^2 and inconsistency statistics; an I^2 value of 50% or more represented substantial heterogeneity[12]. Potential publication bias was evaluated by the funnel plot. We assessed funnel plot asymmetry by using Egger's regression test and Begg's adjusted rank correlation test. Significant publication bias was defined as $P < 0.1$.

3 Results and analysis

3.1 Basic information about the included studies A total of 132 publications were initially identified from PubMed, Cochrane library and Embase, 42 of which were excluded for duplication. For the remaining 90 articles, 59 were excluded for reviews ($n = 3$), case reports and case series ($n = 2$), letters and communications ($n = 1$) or other publication types that did not focus on HGG ($n = 53$). A total of 31 articles were included for full-text reading, 25 of which were lack of clinical data ($n = 10$) and nonstandard comparison ($n = 15$). In the end, only 6 studies fulfilled our inclusion criteria[13-18]. Fig. 1 shows the study selection process.

The eligible studies were conducted in 4 countries (Germany, Belgium, Italy and China) and articles were published from 2011 to 2018. All of the 6 studies were retrospective studies. The number of patients included in each study ranged from 60 to 129, and mean age ranged from 57 to 62 years old. The demographic characteristics of the 6 eligible studies are summarized in Table 1.

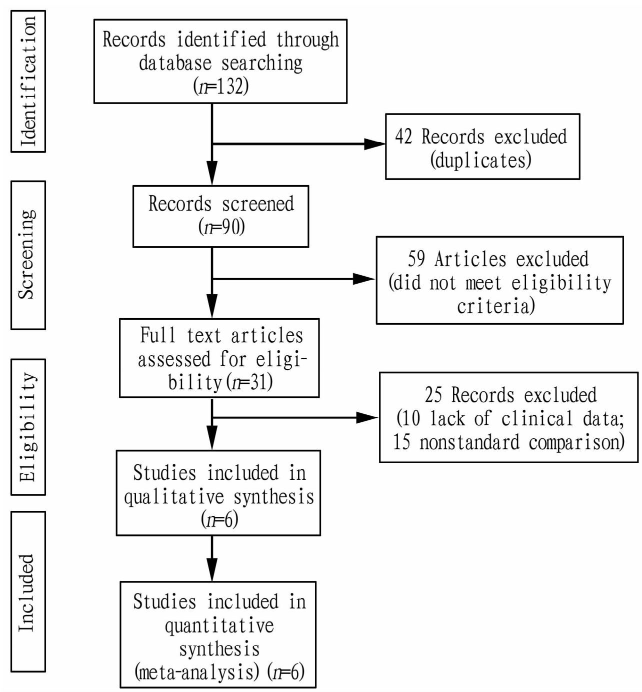

Fig. 1 Flowchart of the selection process

Table 1 Demographic characteristics of the included studies

Study	No. of patients cases	Country	Mean age years old	Sex ($M:F$)	Inclusion time		Tesla
					Start	End	
Familiari et al. [13]	129	Italy	57	68 : 61	March 2009	January 2017	1.5T
Marongiu et al. [14]	114	Italy	62	61 : 53	January 2009	January 2013	1.5T
Chen et al. [15]	73	China	48	46 : 27	July 2010	July 2014	1.5T
Roder et al. [16]	60	Germany	57	28 : 32	June 2010	November 2012	1.5T
Napolitano et al. [17]	94	Belgium	60	55 : 39	March 2006	November 2011	3.0T
Mehdorn et al. [18]	103	Germany	NA	NA	September 2005	May 2009	1.5T

3.2 Risk of bias and quality of evidence The applicability and potential sources of bias of individual study were assessed using the second edition of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2) tool. No study fulfilled all of the methodological criteria. Only one study had a low risk of bias, while the others were considered to have a high risk or unclear risk (Fig. 2).

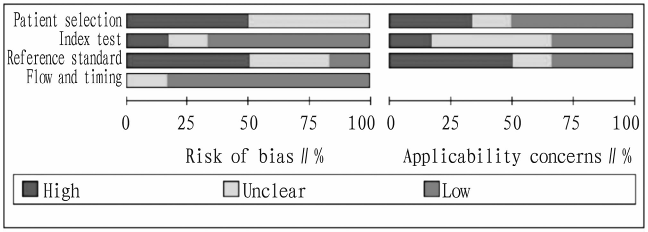

Fig. 2 Risk of bias summary

3.3 Primary outcome: gross total resection Overall, 573 patients were included in this study, 336 of which were treated with high-field iMRI guided resection and 237 did not receive high-field iMRI guided resection (control). The GTR rate in iMRI guided group ranged from 31.3% to 88.5%, and that in control group ranged from 4.5% to 52%. The pooled gross total resection rate was 37.8% (95% *CI*: 19.5% – 56.0%, $z = 4.05$, $P = 0.000$) in control group compared with 64.7% (95% *CI*: 47.9% – 81.5%, $z = 7.55$, $P = 0.000$) in high-field iMRI guided group. The total RR was 1.583 (95% *CI*: 1.235 – 2.209, $z = 3.63$, $P < 0.0001$) (Fig. 3). There was middle latent heterogeneity in 6 studies ($I^2 = 48.5\%$, $P = 0.084$). The Begg's test suggested there was no significant publication bias.

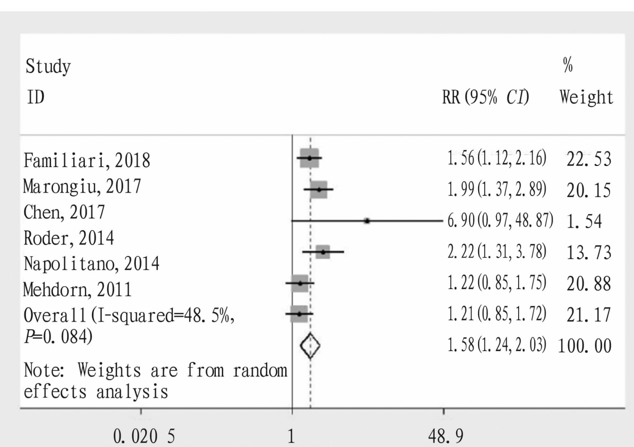

Fig. 3 The forest plots representing the meta-analysis of gross total resection between high-field iMRI guided group and control group

4 Discussion and conclusions

4.1 Discussion Our meta-analysis demonstrated a high pooled risk ratio of high-field iMR imaging for identifying tumor tissues from normal brain tissues. Subgroup analysis revealed that studies using a 3.0 Tesla device did not have a higher resection rate than those using a 1.5 Tesla device. However, while survival analysis did not show a significant association between iMRI employment and overall survival of HGG patients, the 95% confidence interval of the hazard ratio approached but did not exceed 1. Analysis of progression-free survival showed a favorable impact of high-field iMRI. These results indicate that the application of high-field iMRI, a type of functional neuronavigation, can significantly improve the total resection rate of HGG. With regard to the prognostic role of high-field iMRI, limited statistical power makes it difficult to draw a definitive conclusion.

Similar meta-analyses have confirmed the value of iMRI in discovering residual tumor in patients with glioma. Eljamel *et al.*[19] identified 12 eligible studies and found iMRI significantly improved GTR and PFS of HGG. However, their analysis, along with large heterogeneity ($I^2 = 97.33\%$), did not explore the substantial impacts of high-field iMRI on HGG resection, nor did they compare the imparity of GTR exposed under different fields separately. Michael *et al.*[20] published a Cochrane systematic review including 4 trials. Findings in this review showed high-field iMRI might be of benefit in maximizing extent of resection in participants with high grade glioma. But due to low-quality evidence, the conclusions were uncertain. To our knowledge, this is the first comprehensive review to date on the magnetic field intensity following tumor resections in combination with survival analysis. The search strategy involved multiple databases and captured most of the relevant published data. We believe this is a robust review to provide estimates on diagnostic values intraoperatively and prognostic value in patients with HGG.

In recent studies, the mortality of glioma is due primarily to late detection and uncomplete resection[21-23]. The extent of surgical resection has been shown to be an independent prognostic factor for progression-free survival and overall survival. Therefore, the aim of surgical treatment of HGG is to achieve safe maximum surgical resection whenever possible and to preserve normal function and good quality of life. While increasing EOR, it is important to monitor neurological deficits in cases of eloquently located tumors. Neurosurgeons pointed out what matters most for patients' quality of life and survival, were new permanent neurological deficits (nPNDs)[24], which could be caused by increased extent of resection. Nevertheless, Yordanova *et al.*[25] supported the idea that an acceptable deficit, with only a few consequences on daily life, might be the price to pay to live longer. Our analysis could not identify whether iMRI employment showed lower rates of new neurological deficits than surgery without additional imaging or not because of lacking of relevant data in most studies. Only Chen *et al.*[15] collected operative outcomes and indicated medium term of total neurological deficits in iMRI-assisted group was significantly lower than control group (3.9% *vs.* 27.3%, $P = 0.012$).

There are some limitations in this meta-analysis. First, among 6 included studies, none was randomized controlled trial. Because of low quality of included studies, the results were likely to bias. Second, there were 6 studies included in gross total resection comparison, and different definitions of GTR were used in different studies. Familiari *et al.*[13] and Napolitano *et al.*[17] used EOR > 95% as criterion. Marongiu *et al.*[14] defined GTR as 98% or higher resection. Chen *et al.*[15] and Roder *et al.*[16] characterized GTR as no residual tumor. Mehdorn *et al.*[18] did not make a clear illustration. Besides, incomplete or ambiguous descriptions in some studies led to a QUADAS-2 assessment of "unclear". These limitations need to be considered when evaluating the conclusions.

4.2 Conclusions The iMRI revealed a remnant that required further resection, which was deemed safe and feasible based on our findings. Our systematic review and meta-analysis suggested that iMR images have a favorable discriminative capacity in diagnosing residual tumors in high-grade glioma. Surgeons should exercise caution when considering the implications of iMRI and choosing between 1.5 Tesla and 3.0 Tesla devices for medically fit patients.

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