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REVIEW ARTICLE

The Impact of Intra-Operative Magnetic Resonance Imaging and 5-ALA in the Achievement of Gross Total Resection of Gliomas: A Systematic Literature Review and Meta-Analysis.

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ABSTRACT

In an effort to maximize extent of resection (EOR) regarding gliomas, intraoperative MRI (i-MRI) and 5-aminolevulinic acid (5-ALA) have been developed. Our study aimed to investigate the comparative contribution of 5-aminolevulinic acid and i-MRI in maximizing EOR in gliomas.

We searched the PubMed and ScienceDirect services for randomized controlled trials, controlled trials and interrupted time series studies evaluating the effect of i-MRI on gross total resection (GTR) rates and on overall survival in glioma patients. Our primary study endpoint was the definition of the percentage of patients who were offered GTR. Other relevant points of interest included the determination of overall and progression-free survival and subgroup analyses for level of evidence.

I-MRI aids in achieving GTR (odds ratio 2.71, $p<0.0001$). Magnet field strength does not affect significantly either GTR rates ($p=0.08$). The cost of the procedure is dependent on the workload of the i-MRI system. These data suggest that i-MRI or 5-ALA improves progression-free and overall survival, although there are several restrictions related to their effectiveness and reliability.

I-MRI and 5-ALA are considered to be effective adjuncts in the achievement of GTR of gliomas. When these methods are compared, there is no definite conclusion regarding which method is more effective.

Introduction

Gliomas account to as much as 81% of the total case load of primary malignant brain tumors with an incidence of 4.2-5.2 persons per 100.000[1]. Amongst gliomas, glioblastomas are considered to be the most aggressive histologic subtype and also the most common one, with an incidence of about 3.16-3.21 cases per 100.000[1]. Surgical removal plays a central role in their treatment and maximizing the extent of resection clearly confers a benefit in overall survival of both low-and high-grade gliomas[2,3]. Glioblastomas invariably recur, but gross total resection improves progression free and overall survival time[4,5,6,7,8]. Concerning our plan for maximal tumor resection, neuronavigation has been shown to aid in the selection of the optimum surgical approach, the site and dimensions of craniotomy and provides an estimate of the location of tumor margins[9], all of which are crucial to achieve maximal tumor resection. However, intraoperative events such as cerebrospinal fluid loss, brain tissue retraction and resection, result in alteration of the preoperative anatomy and diminish the accuracy of any neuronavigation[10].

This limitation has led to the development of intraoperative imaging modalities such as intraoperative ultrasound, fluorescence-guided resection and i-MRI, which can be employed to monitor differentiations in operative anatomy due to brain shift and can help in tracking the translocation of the tumor margins and their relationship with eloquent brain loci.

Regarding the adult population, gliomas constitute the vast majority of primary tumors of the central nervous system (CNS), constituting up to nearly 80% of malignant CNS tumors[11,12]. Albeit a lot of efforts have been performed, the ultimate prognosis for high grade gliomas (HGG) remains poor and ultimately fatal[13]. The most important factor that determines outcome in this subgroup of patients continues to be considered the EOR, which has been repeatedly correlated with overall survival, quality of life, delay in malignant transformation, seizure-free rate, and duration of functional independence[14,15,16]. Despite recent advancements in neuro-oncology, it is common concept that high-grade gliomas, especially glioblastomas, have not changed substantially regarding their expected survival rate. More precisely, the EOR continues to be the main contributing factor that determines the outcome of these patients, which carry poor prognoses and patient survival is heavily dependent upon that. In order to overcome this situation, a helpful aid has proved to be the use of conventional image-guided surgery, using frame based and more recently, frameless systems. However, its usefulness is under consideration because of intraoperative brain shift, due to cerebrospinal fluid (CSF) loss. More precisely, its accuracy is limited by the fact that the acquisition data and, in accordance, the provided neurovavigation, is based on preoperative imaging alone. Intraoperatively, brain shift is an unavoidable circumstance, due to gravitational forces (related to patient position), edema, fluid shifts and CSF loss, and other physiological alterations associated with intraoperative manipulations and physiological alterations. The net effect of all these factors, in combination, renders preoperative image guidance relatively unreliable during the evolution of the surgical procedure, a fact that eliminates the safety of performing more extensive resection of invasive lesions[17].

Relatively recently, a concentrated effort has been performed in order to overcome these restrictions. In an effort to overcome these restrictions, more evolving techniques have been developed, in order to maximize EOR, including i-MRI and the use of fluorescent dyes, namely 5 ALA. Several innovations have been proposed in order to surmount the practical constraints of neuronavigation, such as fluorescent tumor markers[18]. This stands for 5-ALA— a naturally occurring heme precursor capable of producing fluorescent porphyrins in malignant tissue· this is the marker that is most commonly utilized and accompanied with the greater bulk of data which support its efficacy for offering an expansion of the EOR, along with a statistically significant prolongation of progression-free survival in glioma patients[19,20]. Apart from that, another useful modality that was introduced to neurosurgery in 1997 consists of intraoperative imaging modalities, namely, i-MRI. This technique can update source images and improve spatial information for the acquisition of neuronavigation[21]. Nevertheless, there are several drawbacks associated with the widespread use of this technique. Although i-MRI is more efficacious than frameless stereotactic navigation based on preoperative imaging in achieving a better degree of tumor resection, it is more expensive, is associated with prolongation of the operating time, and it adds significantly to the complexity of the operating room[22,23].

The first i-MRI device specifically designated for neurosurgery was a 0.5 Tesla double donut design installed by Dr. P. Black at Brigham and Women's Hospital in Boston MA[24]. Virtually simultaneously, an equivalent system was established by Siemens at the University Hospital in Erlangen under Dr. R. Fahlbusch[24,25]. Subsequent i-MRI designs either used smaller and more OR-adapted magnets with field strength less than 0.5 Tesla or bulkier high-field units, usually employing 'off the shelf' MRI units with (>1.5 Tesla)[26].

Despite the relatively widespread utilization of these two techniques, the ultimate outcome associated with their adoption remains to be verified with systemic statistical analysis. Based on that, the authors performed a detailed literature review, mainly based on published systematic research, in conjunction with quantitative network meta-analyses. The ultimate goal of our study was to investigate the comparative contribution of 5-ALA and IMRI in maximizing EOR in HGG.

I-MRI scans provide images of high quality and afford valuable information about the differentiated intraoperative anatomy in real time. However, glioblastoma tumor margins are not often clearly demarcated[27] and the prognosis remains bleak despite gross total resection. Moreover, MRI technology remains expensive and its installation requires costly structural modifications of the operating theatre. The aim of the current meta-analysis is to appraise the benefit of intraoperative MRI scanning in achieving gross total resection in patients with high (III and IV grade gliomas) and provide an estimate of the costs incurred in order to provide these benefits.

Fluorescence-guided section (FGS) is extensively used in current neuro-oncology practice. It is based on the utilization of various fluorophores in order to differentially label tumor tissue relative to the surrounding normal tissue, thus facilitating maximal tumor resection. FGS based on 5-ALA allows for real-time identification of the tumor tissue with particularly increased sensitivity and specificity and facilitates the identification of the brain- tumor interface in newly diagnosed HGG. 5-ALA FGS has proved to be an invaluable adjunct in terms of improving the EOR in contrast-enhancing and non-enhancing HGG, accompanied with an associated improvements in the clinical outcomes[28,29].

Based on that data, several studies have been published, aimed at comparing the effectiveness of either 5-ALA or i-MRI with stereotactic navigation, whereas a limited number of efforts have been performed, in order to obtain a quantitative comparison of 5-ALA with i-MRI for maximizing EOR[11]. According to a very recently published meta-analysis, it is confirmed that i-MRI as well as 5-ALA individually improve the rate of GTR over conventional stereotactic navigation and, consequently, extend the progression-free and overall survival rate. This search attempted to compare i-MRI and 5-ALA, but it failed to reveal any difference among them· that means that neither method was statistically superior in order to achieve GTR. Another important consideration that needs to be elucidated is related to the potential complementary relationship that potentially exists between these two modalities and if the extracted benefit of the combined use of them is additive. An extended literature search is based on this enquiry[30,31,32,33,34,35,36,37,38,39]. Although there is no universal agreement among these studies, and there a relative heterogeneity based on their conclusions, we can assume that there are some concepts that these reports share in common:

1) 5-ALA was more sensitive than IMRI for the identification of tumor remnants at the infiltrating edge, and

2) a high GTR rate and/or EOR were obtained with statistically significant accuracy using the combination approach. These notifications, as well as the potential for synergistic action between i-MRI and 5-ALA could have significance and important application regarding patient care decisions, program development, and healthcare spending in neurosurgery[11]. In conclusion, our bibliographic research showed that i-MRI increases the rate of GTR over conventional neuronavigation[23,40,41,42,43,44,45]. Apart from that, we should mention that IMRI is not devoid of limitations and restrictions. It is an "off-line" method which necessitates that the surgeon should temporarily pause the procedure in order image acquisition to be performed, something that is often accompanied with movement of the patient to a separate room[32,46]. Another drawback of this modality is that the cost of installing an IMRI suite cannot be ignored[46].

On the other hand, 5-ALA, is a natural intermediate in the heme synthesis pathway that is converted intratumorally to fluorescent protoporphyrin IX, which is visible intraoperatively under blue light (wavelength range 375–440 nm)[47]. It was referred as an adjunct for HGG visualization by Stummer et al. in 1998 and since then the sensitivity and specificity of 5-ALA for HGG tissue has been in the order of 95% to 100%, respectively[11,33,39]. There are a lot of reports which have established the usefulness of 5-ALA in order to improve the EOR, when compared with conventional stereotactic navigation alone[19,42,47,48,49,50].

Methods

The study was conducted in accordance with the PRISMA guidelines. We performed a literature search on the PubMed and ScienceDirect services using the terms "(glioblastoma) OR (high grade glioma) OR (glioma) AND (intraoperative mri) OR (i-MRI) OR (intraoperative Magnetic resonance imaging) OR (intraoperative imaging)" for dates up to February 2022.

We included randomized controlled trials, non-randomized controlled trials and interrupted time series studies. Eligible studies ought to have intervention and control groups both consisting of high- grade glioma patients (grade III or IV gliomas; HGG). The intervention group ought to have undergone intraoperative magnetic resonance while the control group ought to have been operated without the assistance of i-MRI by the same group of surgeons. The eligible studies had to report outcomes as a) the primary outcome of the study was the contribution of i-MRI on improving gross total Review Manager v5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Random effects models were used for the analyses and statistical heterogeneity was evaluated by x2 and the inconsistency I2 statistics.

Despite the relatively widespread utilization of these two techniques, the ultimate outcome associated with their adoption remains to be verified with systemic statistical analysis. Based on that, the authors performed a detailed literature review, mainly based on published systematic research, in conjunction with quantitative network meta-analyses. The ultimate goal of our study was to investigate the comparative contribution of 5-ALA and i-MRI in maximizing EOR in HGG.

We performed a detailed search, based on data that were extracted from studies published at PubMed, Embase, Cochrane Central, and Web of Science. Our main aim was to collect and analyze studies which were dedicated on the evaluation of the efficacy of conventional neuronavigation, i-MRI, and 5-ALA in HGG resection. Our primary study endpoint was the definition of the percentage of patients who were offered GTR, defined as 100% elimination of contrast-enhancing lesion on postoperative MRI. Other relevant points of interest included the determination of overall and progression-free survival and subgroup analyses for level of evidence.

Our analysis included the data of relevant studies, which included single institutions experience and metanalyses. The collection of all these data converge to the suggestion that the use of IMRI or 5-ALA improves progression-free and overall survival, although there are several restrictions related to the effectiveness and reliability of these adjuncts.

Results

The search yielded 1309 results in the PubMed database and 4634 results in the ScienceDirect database. We screened 185 results out of which 66 articles were deemed appropriate for full text assessment. Twenty studies provided appropriate data, but 12 studies met our inclusion criteria for the gross total resection part of our meta-analysis and seven studies met our inclusion criteria for the overall survival part (Figure 1). Table 1 provides an overview of the included literature[23,37,40,42,43,44,45,51,52,53,54,55].

Figure 1. Flow chart of the study selection process according to the PRISMA guidelines.

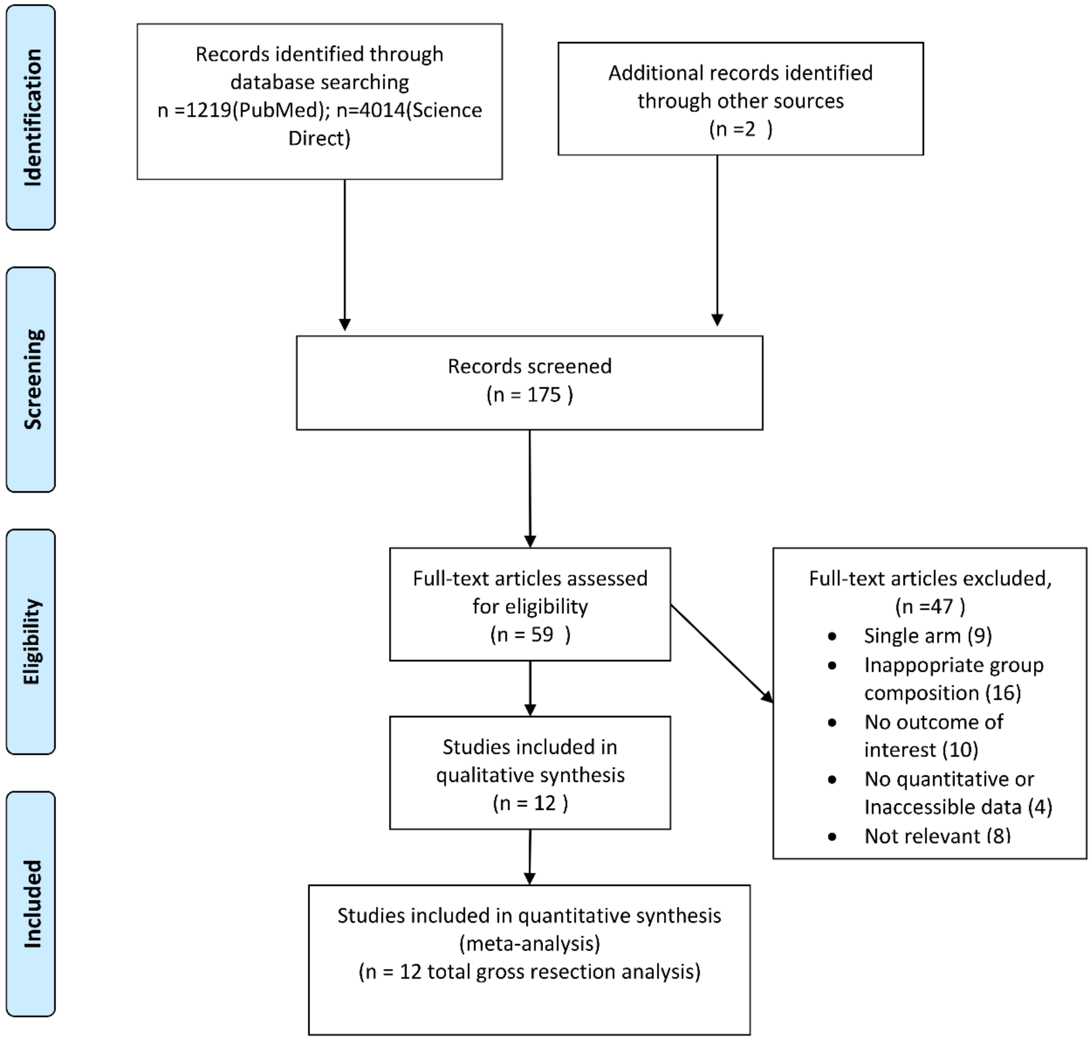


Table 1. Summary of the included literature in the meta-analysis. N/A: not applicable, GTR: gross total resection OS: overall survival, GBM: glioblastoma multiforme, KPS: Karnofsky performance score, WHO PS: World Health Organization performance status, ASA class: American society of Anaesthesiologists classification, 5-ALA: 5-aminolevulinic acid fluorescence.

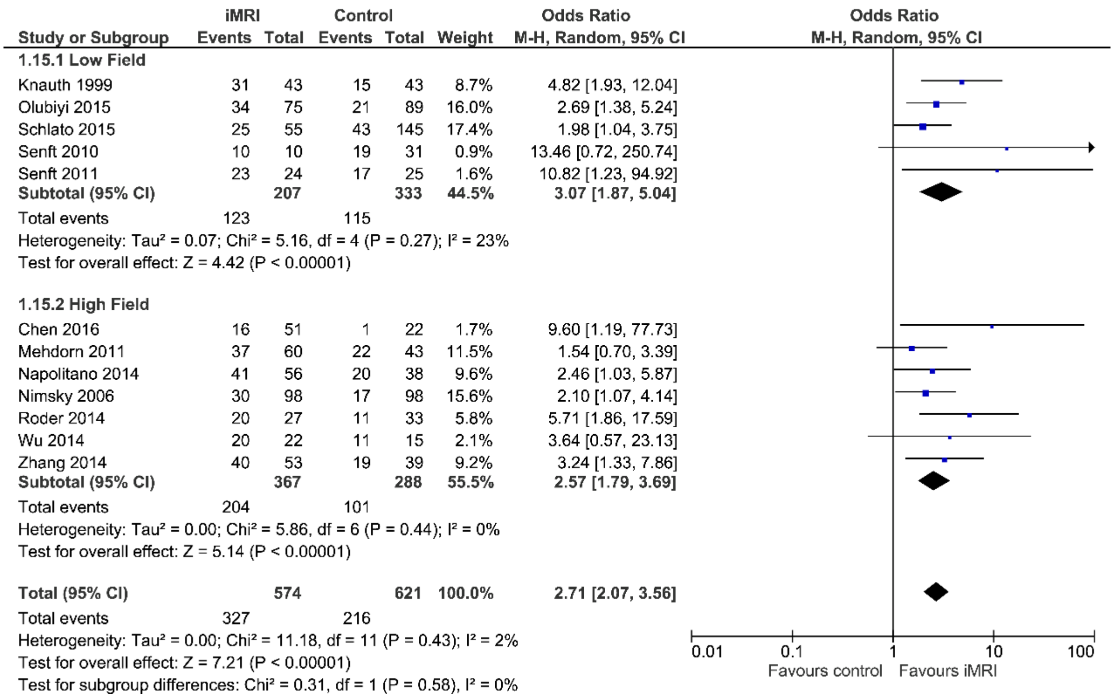
Studies	Study Types	Primary Outcomes	Outcomes Used	Magnet Field (Tesla)	Sequences Used	Grades	Gross Total Resection Definition	Overall Survival Follow Up (Months)	Confounders Addressed
KNAUTH 99[14]	interrupted time series	Impact of ioMRI on EOR	GTR	0.2	T1+c	high grade gliomas	no visible tumor in MRI	N/A	
NIMSKY 06[30]	interrupted time series	Impact of ioMRI on EOR	GTR	1.5	T1+c ,T2-TSE, , FLAIR, MPRAGE, MRS,	III & IV	no visible tumor in MRI	N/A	

					DTI, fMRI				
CHEN 16[3]	controlled trial	Impact of ioMRI on EOR,PFS OS	GTR&OS	1.5	T1+c, FLAIR, MPRAGE, DTI	III & IV	100% volume	50	age, sex, location, grade, KPS, surgical approach
MEHDRON 11[26]	controlled trial	Impact of ioMRI on EOR, OS, KPS	GTR	1.5	T2 T1, T1+C, DWI	mainly III and IV	no visible tumor in MRI	N/A	grade, age, sex, carmustine implants, KPS
NAPOLITANO 14[28]	controlled trial	Impact of ioMRI on EOR, OS, KPS	GTR	3	T1+c	GBM	100% volume (ntr 95%)	N/A	age, sex, location, eloquent location, KPS, adjuvant treatment
OLUBIYI 15[31]	controlled trial	Impact of ioMRI on EOR (volumetry)	GTR	0.5	T2/FLAIR, T1+c	III and IV	100% volume	N/A	age, initial volume, adjuvant treatment, grade, eloquent location
RODER 14[36]	controlled trial	Impact of ioMRI on EOR (volumetry	GTR	1.5	T1+c	IV	100% volume	N/A	age, sex, location, primary or relapse, KPS, preoperative volume
SCHLATO 15[39]	controlled trial	Impact of ioMRI on EOR, PFS, OS	GTR	0.15	T1+C	III & IV	no visible tumor in MRI		age, sex, grade, KPS, eloquence, adjuvant therapy, 5ALA
SENFT 10[42]	controlled trial	Impact of ioMRI on EOR, OS	GTR&OS	0.15	T1+c	high grade gliomas	no visible tumor in MRI	62	balanced assignment according to gender, age. Adjuvant treatments not significantly different
SENFT 11[41]	randomized controlled trial	Impact of ioMRI on EOR, 6mo-PFS	GTR	0.15	T1+c	most IV	no visible tumor in MRI	N/A	grade, age, sex, KPS, primary vs recurrence, tumor volume
ZHANG 14[46]	controlled trial	Impact of ioMRI on EOR (volumetry), Aphasia quotient, PFS, OS	GTR&OS	1.5	T2,FLAIR, T1+C	High grade gliomas	no visible tumor in MRI	28	grade, location, age, gender, tumor volume, aphasia quotient
WU 14[45]	randomized controlled trial	Impact of ioMRI on EOR (volumetry),	GTR	3	FLAIR, T1+c	III & IV	no visible tumor in MRI	N/A	age, sex location, KPS, eloquent location, grade, neurophysiological monitoring, adjuvant treatment

Meta-analysis on the benefit of i-MRI on Gross Total Resection

Twelve studies provided data on 574 operations of high-grade gliomas under i-MRI assistance in 327 of which gross total resection was achieved. This pooled cohort compares to 621 operations in which no intraoperative MRI assistance was employed and which resulted in 216 total gross resections. The pooled odds ratio from all 12 studies is 2.71 (0.95 confidence intervals 2.07-3.56, $p<0.0001$ and heterogeneity $I2= 2\%$, $Chi2(11)=11.18$, $p=0.43$; Figure 2). The risk difference was estimated at 0.23 (95% CI 0.18-0.29, $p<0.00001$).

Figure 2. Forest plot demonstrating the meta-analysis comparing gross total resection odds ratio of low field (<0.5T) i-MRI systems and high field strength (>1T) i-MRI systems compared to conventional surgery.

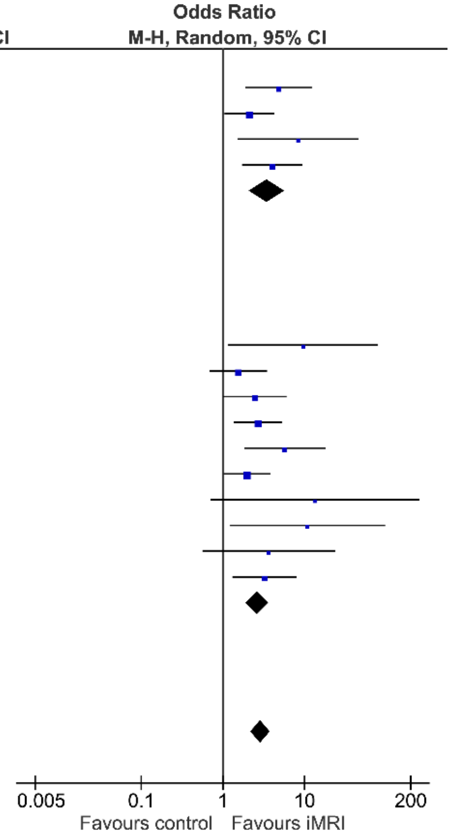


These pooled estimates lump together controlled studies, where a distinct control group was used for comparison with the intervention group, and interrupted time series studies, where the extent of resection at the first intraoperative scan was compared with the extent of resection at the first postoperative scan. However, concerns have been risen that the latter comparison might exaggerate the effectiveness of the i-MRI. The reason is that a surgeon having access to i-MRI will defer decisions for more aggressive resection until after the intraoperative scan[22]. On the other hand, the interrupted time series study design avoids allocation issues, where differences in age, gender, comorbidities, preoperative KPS, tumor location, tumor grade may act as confounders.

Indeed, the pooled odds ratio of the studies employing this comparison scheme was somehow higher (3.48, with 0.95 confidence intervals 2.1-5.78, $p<0.00001$; heterogeneity $chi2(3)=3.75$ and $I2=20\%$; Figure 3).

Figure 3. Forest plot demonstrating the meta-analysis of odds ratio of GTR v control. The two subgroups display the difference in odds ratio estimation in interrupted time series studies and in controlled studies.

	iMRI		Control			Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI
1.16.1 interrupted time series studies						
Knauth 1999	31	43	15	43	7.7%	4.82 [1.93, 12.04]
Nimsky 2006	30	98	17	98	13.6%	2.10 [1.07, 4.14]
Wu 2014	20	22	12	22	2.4%	8.33 [1.56, 44.64]
Zhang 2014	40	53	23	53	9.3%	4.01 [1.75, 9.19]
Subtotal (95% CI)		**216**		**216**	**33.1%**	**3.48 [2.10, 5.78]**
Total events	121		67			
Heterogeneity: Tau² = 0.05; Chi² = 3.75, df = 3 (P = 0.29); I² = 20%						
Test for overall effect: Z = 4.83 (P < 0.00001)						
1.16.2 controlled trials						
Chen 2016	16	51	1	22	1.5%	9.60 [1.19, 77.73]
Mehdorn 2011	37	60	22	43	10.2%	1.54 [0.70, 3.39]
Napolitano 2014	41	56	20	38	8.5%	2.46 [1.03, 5.87]
Olubiyi 2015	34	75	21	89	14.0%	2.69 [1.38, 5.24]
Roder 2014	20	27	11	33	5.2%	5.71 [1.86, 17.59]
Schlato 2015	25	55	43	145	15.1%	1.98 [1.04, 3.75]
Senft 2010	10	10	19	31	0.8%	13.46 [0.72, 250.74]
Senft 2011	23	24	17	25	1.4%	10.82 [1.23, 94.92]
Wu 2014	20	22	11	15	2.0%	3.64 [0.57, 23.13]
Zhang 2014	40	53	19	39	8.2%	3.24 [1.33, 7.86]
Subtotal (95% CI)		**433**		**480**	**66.9%**	**2.68 [1.96, 3.66]**
Total events	266		184			
Heterogeneity: Tau² = 0.00; Chi² = 9.14, df = 9 (P = 0.42); I² = 2%						
Test for overall effect: Z = 6.19 (P < 0.00001)						
Total (95% CI)		**649**		**696**	**100.0%**	**2.90 [2.24, 3.77]**
Total events	387		251			
Heterogeneity: Tau² = 0.01; Chi² = 13.54, df = 13 (P = 0.41); I² = 4%						
Test for overall effect: Z = 8.03 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0%						



If one omits the interrupted time series studies from the analysis, the remaining 10 studies provide 266 gross total resections from 433 patients that underwent i-MRI assisted surgery which are compared to 184 gross total resections from 480 operated with no intraoperative aid. The pooled odds ratio is more modest (2.68) but still strongly significant ($p<0.00001$) and the heterogeneity of the studies remains low ($chi2(9)=17.93$, $p=0.42$; $I2=2\%$). Nevertheless, the difference in the estimation of the odds ratio for GTR between the two study groups did not reach statistical significance ($chi2=0.74$, $p=0.39$).

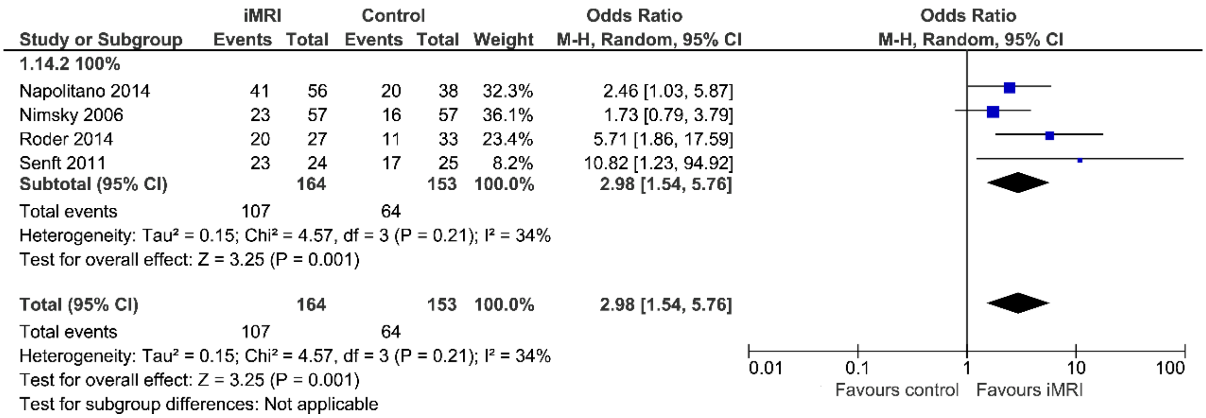
Currently, only two studies used a randomized controlled design to evaluate the benefit of intraoperative MRI on GTR. One employing a low field i-MRI system[23] and a second using a high field i-MRI system[44]. Based on their results, 43 gross total resections were achieved in 46 operations using i-MRI and 28 gross total resections were attained in the 40 patients of the control group. The pooled odds ratio for GTR from the high quality randomized controlled studies is 5.75 (0.95 confidence intervals 1.41-23.52, $p=0.01$; Heterogeneity $chi2=0.58$, $p=0.58$, $I2=0\%$) and is close to the estimates of the other studies.

MRI machines that employ higher magnet strengths, while more cumbersome in their operation, provide images of superior quality. We performed subgroup analysis to evaluate if machines with field strengths over 1.5 Tesla can provide better outcomes (Figure 2). Five of the included studies used machines of magnet strength less than 0.5 Tesla. 123 total gross resections were achieved in 207 operations with low field i-MRI assistance, which contrasted to 115 total gross resections in 333 conventional control operations. The pooled odds ratio for GTR in the low field i-MRI studies is 3.07 (95% CI 1.87-5.04, $p<0.00001$; Figure 3). The studies were homogenous ($Chi2(4)=5.16$, $p=0.27$ $I2=23$). The risk difference was 0.26 (95% CI 0.18-0.35, $p<0.00001$). In the 7 high-field i-MRI studies (>1T) 204 gross total resections were attained in 367 operations using intraoperative imaging, contrasting to 101 gross total resections in 288 conventional operations. The pooled odds ratio for GTR in the 7 high field studies is 2.57 (95% CI 2.12-4.78, $p<0.00001$) with heterogeneity of $I2=0\%$ ($Chi2(6)=5.86$, p=0.44).The risk difference was 0.21 (95% CI 0.14-0.28, p<0.00001). The odds ratio for the gross total resection achieved with high field i-MRI systems is not statistically different from the odds ratio for GTR with low field i-MRI (chi2=0.31, p=0.58).

Four studies focused on glioblastomas. They achieved 107 gross total resections in 164 i-MRI guided operations compared to 64 gross total resections in 153 conventional operations. The pooled odds ratio is 2.98 (CI 1.54-5.76; heterogeneity I2=34%, Chi2(3)=4.57, p=0.21).

The funnel plot of Figure 4 provides a visual overview of the bias risk of the included studies. Generally, all the studies are distributed symmetrically, perhaps with the exception of the Senft 2010[43] study which appears to provide a more favorable estimate of gross total resection for the i-MRI group compared to the rest of the studies.

Figure 4. Forest plot of the subgroup of the studies evaluating the performance (odds ratio) of i-MRI in achieving gross total resection in exclusively glioblastoma patients.



Discussion

Independently of our results regarding the usefulness of i-MRI to improve the GTR and overall survival (OS) in patients harboring brain tumors, and especially gliomas, there is a considerable discrepancy between different studies that are published. Recently, a systematic review and meta-analysis was published, focused on the utility and impact of intra-operative imaging for glioma resection on patient outcome and extent of resection[56]. This meta-analysis was not able to statistically confirm the existence of a difference in GTR rates between individual i-MRI and standard neuronavigation cohorts. According to that study, the existing bulk of evidence is inadequate in order to definitely conclude whether or not any difference exists in GTR when our intraoperative decisions are based on novel imaging techniques, compared to conventional neuronavigation. They declare that the main reason for that ambiguity emanates from the limited database in the literature, which render us unable to definitively justify, or, on the other hand, exclude, the utility of intraoperative imaging.

Apart from that, according to that meta-analysis, the existing literature is adequate to establish the superiority of i-MRI compared with neuronavigation, in terms of increased GTR, decreased post-operative neurological deficits, or reduced complications.

Another recently published survey that deserves special mention refers to a multi-institutional analysis of factors influencing surgical outcomes for patients with newly diagnosed grade I gliomas[57]. Even though this study failed to demonstrate a statistically sufficient correlation between the utilization of i-MRI (when used independently) and improved OS or progression-free survival (PFS), this could be attributed to the existence of variables that confound the overall outcome (e.g., age, American Society of Anesthesiologists (ASA) score, or tumor location). Consistent with that, these researchers underlie the fact that a lot of studies exist which favor the ability of i-MRI to increase with safety the EOR in low-grade gliomas (LGG) resection[54,58,59,60,61]. Moreover, this study, in accordance with other similar papers, demonstrated that EOR has been correlated with improved OS, as well as PFS, in grade I gliomas[62,63,64].

There are a lot of reports that are derived from relevant monocentric studies which state that i-MRI neuronavigated surgery was capable of providing maximal EOR, regardless of the histologic subtype of glioma and their location. According to them, its usefulness was superior when surgeons were confronted with non- or minimally enhancing tumors[65,66]. Another recent monocentric study focused on the potential benefits of the utilization of i-MRI concomitant with awake surgery[67]. According to them, this combination was associated with low morbidity, increased total resections rates, along with longer patient survival. Based on that, they suggested their use when we have to manage gliomas associated with inherent risks due to their intrinsic features or locations, irrespective of their grade.

Another interesting study has been published[68], centered on the application of i-MRI to tumor cases that are in the vicinity of the motor cortex and corticospinal tracts. Under these circumstances, deformation and displacement of these tracts can occur, which are in intimate relationship with the tumor margins. Via the aid of i-MRI, the operating team is allowed to be better prepared in order to optimize the identification of the corticospinal tracks and maximize the EOR.

Another study[69] was focused on the dual-use of i-MRI in cases of glioblastoma resection, and more precisely on the results of surgical site infections. According to the authors, the main reason for that review was the fact that there is an ongoing discussion about the possible increase of the risk of surgical site infections when i-MRI is utilized. According to their monocentric study, this rate proved to be within the normal range of neurosurgical procedures, so, regarding the risk of infection, i-MRI could be considered a safe concept.

As a general rule that applies to all neurosurgical oncology procedures, it is common concept that in case of LGG and HGG, our basic aim is the achievement of safe, along with maximal tumor resection. This combination affords an improvement in the patient's quality of life, PFS, and OS[70,71,72]. It is common concept that the combination of advancement in neuroimaging, along with the refinement of microsurgical techniques, the improvement in our ability to achieve better tumor visualization intraoperatively, as well as the utilization of advanced adjuvant therapy has helped us in order to achieve a more extensive tumor resection and improve the ultimate survival of our patients[73,74,75,76,77]. 5-ALA has proved to be a reliable and valuable ally in our effort to improve the EOR in contrast-enhancing and non-enhancing HGG, a fact that is accompanied with a remarkable improvement in the clinical outcome[29].

Apart from the aforementioned information supporting the utility of 5-ALA, there is an increasing bulk of evidence which undermine the potential limitations associated with the limitations of the usefulness of this substance. Actually, the vast majority of previous studies have been concentrated on the critical role of 5-ALA and a limited number of papers referred to its limitations and tried to enhance a new concept regarding ongoing research aimed on augmenting the 5-ALA FGS.

More precisely, it seems that 5-ALA FGS has proved to be a valuable adjunct which is able to enhance our ability to recognize the tumor mass intraoperatively, and this aid is not related with the intraoperative use of neuronavigation and is not impaired by the presence of brain shift in cases of HGG[17,18]. Its use offers about 26% higher rates of GTR, which is associated with a statistically significant improvement in OS, compared with a sample of patients in whom the only intraoperative aid was the surgical microscope[79,80,81]. Its usefulness seems to be related with the ability offered to the surgeon to extend the area of tumor resection well beyond the margins of the tumor, as they are recognized based on the findings of the preoperative MRI, after the administration of gadolinium enhancement[82]. This is in concordance with the concept that this substance is able to label tumor tissue that is not enhancing in a subgroup of patients[83]. An inherent limitation is associated with the decline of the intraoperative visualization that is in accordance with the reduced cellular density which is evident at the infiltrative tumor edges. In these areas, the signal related with 5-ALA exhibits a gradual decline, a fact that adds another obstacle in our effort to discriminate these tissues from the nonfluorescent normal tissues. In order to overcome this restriction, it is imperative to develop more efficient visualization techniques, capable of augmenting our capacity to discriminate active tumor embedded within the infiltrative, non-enhancing tumor margins[84].

Another subgroup of patients in whom the clinical utility of 5-ALA has been extensively studied refers to those harboring LGGs. Existing data suggest that the relative benefit from its use is limited, as this substance is visible in a small minority of these patients, namely 10%-20%[85.86]. Despite that, it has been suggested that it is able to differentiate foci harboring anaplastic features in cases of diffuse gliomas, as they have proved to be reliable markers for the determination of OS in patients harboring LGGs[86].

As a general rule, 5-ALA offers the ability to the neurosurgeon to visually differentiate, with reliability, the malignant tumor cells from nearby brain parenchyma during surgical resection. A lot of studies have conceptually established the effectiveness of 5-ALA FGS in the achievement of maximum resection, with associated safety, in cases of malignant gliomas. A consistent result in a lot of relevant studies stands for the increased diagnostic ability to distinguish HGG, a parameter that is in conjunction with an associated increase regarding the resection rates and OS in selected patients. Regarding patients harboring recurrent HGG, 5-ALA appears to be related with different visualization patterns, as well as is not associated with very promising outcome in cases of LGG. Our conclusions are constituent with that of a very recently published meta-analysis, centered on an effort to investigate the possibility to consider 5-AA as an acceptable fluorescent agent in the resection of high- grade gliomas. In this research, the authors analyzed and compared the rates of GTR with fluorescein reported in the literature[87]. According to their results, they were able to establish a statistically significant increase regarding GTR rates in patients harboring fluorescein-guided HGG resections, when they were compared with another subgroup of patients who were operated without the aid of fluorescein. Consequently, they stated that there were enough data available in order to provide adequate evidence to establish supporting the utility of 5- AA in order to aid in HGG resection.

Based on our attempt to deepen our knowledge about the role of 5-AA, we should mention a recent report, which states that a strong 5-ALA uptake is anticipated in cases of radionecrosis, and/or delayed effects of chemo or radiotherapy treatment[88]. Apart from that, a recent review of the existing literature points out that 5 -AA has additionally been identified in a divergent and inhomogeneous group of patients, which cannot be categorized under the neuro-oncology group. Examples include patients suffering from multiple sclerosis[89], neurodegenerative diseases[90], as well as infectious conditions[91,92,93,94]. An important notification is that all these pathological processes share in common a protuberant number of immune cells. These share in common the ability to exhibit significant degrees of 5-AA positivity, attributable to 5-ALA uptake and metabolism. Attempting a widespread literature review, we found out a lot of relevant reports centered on 5-AA. More precisely, extended reports, published reviews, overviews and neurosurgical society recommendations, have been encountered[95,96,97,98,99].

Attempting to compare i-MRI with 5-ALA, this failed to reclaim anyone of them as definitely more effective. More detailed studies are necessitated in order to better elucidate the comparative cost and extension of the duration of the operation associated with IMRI and 5-ALA. This could provide us with the information needed in order to contemplate a more complete cost-benefit analysis.

Independently of our results regarding the usefulness of i-MRI to improve the GTR and OS in patients harboring brain tumors, and especially gliomas, there is a considerable discrepancy between different studies that are published. Recently, a systematic review and meta-analysis was published, focused on the utility and impact of intra-operative imaging for glioma resection on patient outcome and extent of resection[56]. This meta-analysis was not able to statistically confirm the existence of a difference in GTR rates between individual i-MRI and standard neuronavigation cohorts. According to that study, the existing bulk of evidence is inadequate in order to definitely conclude whether or not any difference exists in GTR when our intraoperative decisions are based on novel imaging techniques, compared to conventional neuronavigation. They declare that the main reason for that ambiguity emanates from the limited database in the literature, which render us unable to definitively justify, or, on the other hand, exclude, the utility of intraoperative imaging.

Apart from that, according to that meta-analysis, the existing literature is adequate to establish the superiority of i-MRI compared with neuronavigation, in terms of increased GTR, decreased post-operative neurological deficits, or reduced complications.

Another recently published survey that deserves special mention refers to a multi-institutional analysis of factors influencing surgical outcomes for patients with newly diagnosed grade I gliomas[57]. Even though this study failed to demonstrate a statistically sufficient correlation between the utilization of i-MRI (when used independently) and improved OS or PFS, this could be attributed to the existence of variables that confound the overall outcome (e.g., age, ASA score, or tumor location). Consistent with that, these researchers underlie the fact that a lot of studies exist which favor the ability of i-MRI to increase with safety the EOR in LGG resection[58,59,60,61,100]. Moreover, this study, in accordance with other similar papers, demonstrated that EOR has been correlated with improved OS, as well as PFS, in grade I gliomas[62,63,64].

There are a lot of reports that are derived from relevant monocentric studies which state that i-MRI neuronavigated surgery was capable of providing maximal EOR, regardless of the histologic subtype of glioma and their location. According to them, its usefulness was superior when surgeons were confronted with non- or minimally enhancing tumors[65,66]. Another recent monocentric study focused on the potential benefits of the utilization of i-MRI concomitant with awake surgery[67]. According to them, this combination was associated with low morbidity, increased total resections rates, along with longer patient survival. Based on that, they suggested their use when we have to manage gliomas associated with inherent risks due to their intrinsic features or locations, irrespective of their grade.

Another interesting study has been published[68], centered on the application of i-MRI to tumor cases that are in the vicinity of the motor cortex and corticospinal tracts. Under these circumstances, deformation and displacement of these tracts can occur, which are in intimate relationship with the tumor margins. Via the aid of i-MRI, the operating team is allowed to be better prepared in order to optimize the identification of the corticospinal tracks and maximize the EOR.

Another study[69] was focused on the dual-use of i-MRI in cases of glioblastoma resection, and more precisely on the results of surgical site infections. According to the authors, the main reason for that review was the fact that there is an ongoing discussion about the possible increase of the risk of surgical site infections when i-MRI is utilized. According to their monocentric study, this rate proved to be within the normal range of neurosurgical procedures, so, regarding the risk of infection, i-MRI could be considered a safe concept.

It is well established that high-field i-MRI systems provide excellent imaging quality and are used for resection control and intraoperative update of image guidance systems. Because of that, high-field i-MRI is part of the neurosurgical armamentarium to improve the extent of glioma resection. This could afford a potentially positive impact, as it enhances our effort of achieving a GTR which, in turn, has a positive impact on the survival of patients with malignant brain tumors. Although there are different available intraoperative imaging modalities, nowadays i-MRI is considered to offer the best image quality[66].

Our meta-analysis shows that Intraoperative MRI scans when utilized for resection of high-grade gliomas significantly increase the odds of gross total resection. To the best of our knowledge, two other meta-analyses exist that have studied the impact of i-MRI in glioma resection. The Eljamel[9] study focuses on high grade gliomas and provides an excellent overview of the effectiveness and cost of three major intraoperative modalities, i-MRI, intraoperative ultrasound and fluorescence guided surgery. However, their meta-analysis provides an estimate of the raw gross total resection rate achieved and not the improvement in gross total resection compared to conventional surgery. Because of the apparently different setup and patient makeup of the studies included in their meta-analysis, there is extreme variation in the estimates of the GTR in the individual studies. Especially in the i-MRI part of their analysis, the GTR rates range between 20.8% and 98.8%. In their table 3, a figure for GTR from conventional surgery and estimates for progression free survival are given, but it is not clear how they were calculated.

The Li et al[101] meta-analysis focuses on the i-MRI intervention and provides estimates for improvements on gross total resection, extent of resection, tumor size reduction, six months progression free rate and 12 months overall survival rate. Their meta-analysis of GTR rates included studies of low-grade gliomas[38,45]. Low grade gliomas have a slower course and maximizing extent of resection offers very different benefits on survival[2,26]. For this reason, we restricted our meta-analysis to high grade glioma studies. Another recent study[65] has emerged which enhances the statistical significance of our conclusions. It considers that surgery enhanced via High-field i-MRI neuronavigation significantly enhanced the EOR of gliomas, even though they state that the benefit is greater when we are dealing with non- or minimal enhancing tumors, that is mainly LGG.

Besides that, some recent meta-analyses are published, centered on the relative utility and efficacy of i-MRI in achieving gross total resection of brain gliomas. One of them[102] is a meta-analysis, dedicated to the usefulness and impact of intraoperative imaging for glioma resection on patient outcome and extent of resection. The main conclusion extracted from this research is that, according to their data, we are unable to certify, definitively and irrevocably, the notion that advanced imaging techniques (i-MRI is one of them) are superior, either as a combined cohort or individually, in the achievement of GTR, or survival, compared with traditional neuronavigation. A major difference of this study from our report is based on the fact that our results are extracted after consideration of high-grade gliomas alone, and not after incorporation of all subtypes of gliomas. Additionally, there are inherent limitations of the study that are extensively analyzed, although, to the best of our knowledge, they are practically impossible to be completely eliminated. Among them, we would like to mention their report that the goal of the study was not to compare individual modalities (as i-MRI), but to examine their impact on the field as a whole.

Another recent publication which, according to our opinion, deserves special mention, is a multi-institutional analysis of factors that influence surgical outcome for patients suffering from grade I glioma[103]. They postulated that i MRI aids in the achievement of more complete resection of these types of tumors, even though it was not independently associated with increased overall survival and progression free survival. The results of these two meta-analyses, although their aim and materials are not identical, underscore the inconsistency of our conclusions and that our results could be conflicting.

Limitations

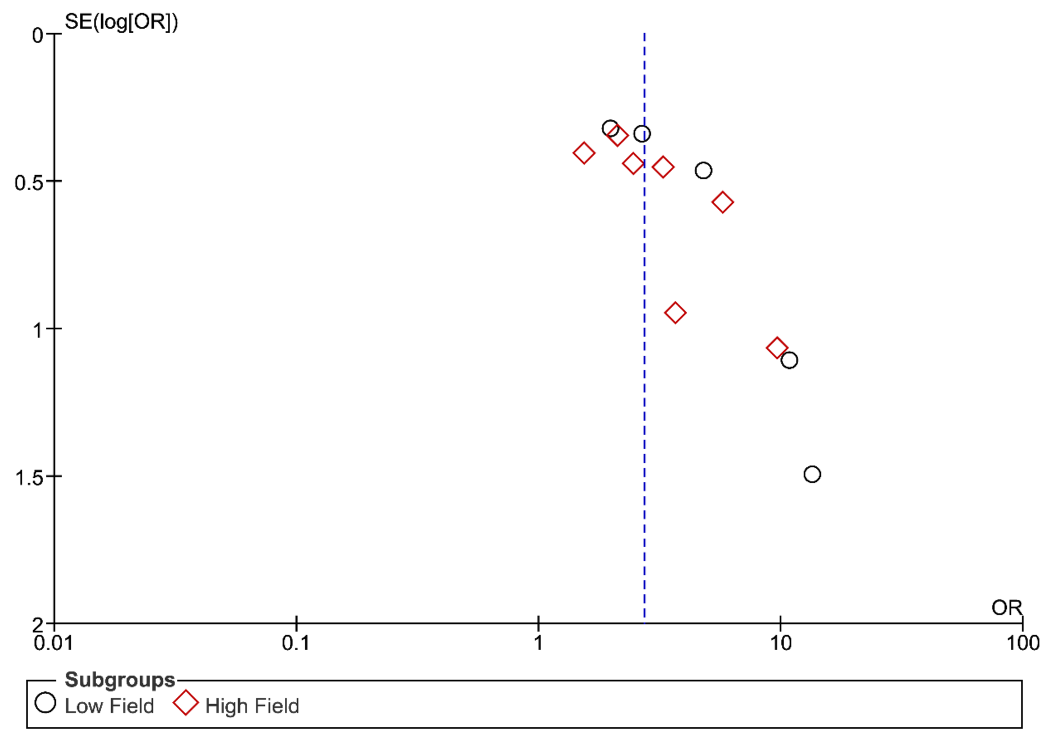
Unfortunately, only two randomized controlled trials have been performed evaluating the benefit of i-MRI in gross total resection of high-grade gliomas. Pooling the two randomized trials together yields an odds ratio of 5.75 (p=0.01), despite the fact that this difference did not reach statistical significance in one of them. We included 9 studies with interrupted time series design, where the extent of resection before and following the i-MRI scan was compared. These studies provide an estimate for gross total resection that is not statistically different compared to the controlled trials, but, as discussed previously, there is concern that they might overestimate the benefits of the i-MRI. In the rest of the studies the allocation was not random. In some studies[10,42,102] the allocation was dependent on the availability of the i-MRI machine. Others[37,40,55] acknowledged potential confounders and took into consideration their effect. Despite these limitations, the estimates of the interrupted time series studies and the non-randomized controlled studies were close to the results that the randomized controlled studies provided for the improvement on gross total resection rates and overall survival.

Part of our meta-analysis includes studies where high-grade gliomas of grade III and IV were considered together[37,40,55]. These studies took measures to ensure that the distribution of grade III patients was equivalent among the two groups. Out meta-analysis of grade IV restricted studies[23,25,41,42] provided similar estimates of i-MRI efficacy in aiding gross total resections. Tumor location can also be a confounding factor; one study included in the meta-analysis explicitly assessed gliomas of language areas[45].

Low field magnets compared to high field ones.

Our meta-analysis examined the difference in performance in achieving gross total resections and extending overall survival between low field and high field magnets, each of which has distinct advantages (Figure 5).

Figure 5. Funnel plot of the studies evaluating the benefit from iMRI in rates of gross total resections. Studies employing MRI systems with high (>1 Tesla) field strength are represented with diamonds, while studies using low field magnets are illustrated with open circles.



Low field i-MRI units are better adapted for the surgical environment, offering faster mobilization into the scanner and less risk to compromise sterility. High field i-MRI systems offer superior image quality and can be used in a twin room setup that enables the utilization of the system for routine diagnostic procedures when it is not used intraoperatively[26]. Gross total resection rates improvement and overall survival extension was slightly better for the high field i-MRI systems but this difference was not statistically significant.

Quality of evidence for i-MRI

We used Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate the quality of evidence available for the intraoperative MRI. Our meta-analysis includes evidence from 2 randomized controlled trials. A large part of the meta-analysis data is derived from the 8 non-randomized controlled studies and 3 interrupted time series studies. While their results are in line with the results of the RCTs, their design makes the susceptible to bias. For this reason, we subtracted one point from the 'Bias' category. We analyzed the performance of i-MRI in achieving tumor gross total resection. This is an intermediate aim towards the end of increasing overall survival. Therefore, we subtracted another point for indirectness. The heterogeneity of all analyzed subgroups was low to low-moderate (I2 at worst 34%) exhibit. Table 2 summarizes our evaluation. The number of participants in the pooled subgroups was adequate to provide a precise estimate (n>400). Finally, the funnel plot of the included studies, save for the Senft '10 study, is symmetrical, so the publication bias was minimal.

Table 2. Summary of the level of evidence for the use of intraoperative MRI in high grade gliomas.

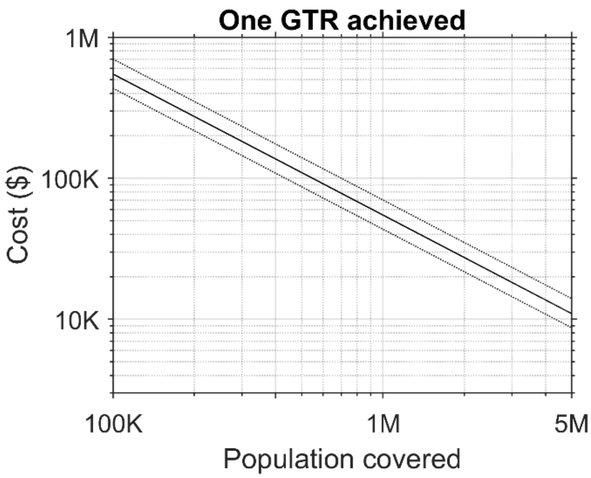
Grade Criteria	*Rating*	*Quality of evidence*
Study design	2 RCT	
Risk of Bias	Possible (-1)	⊕⊕○○ Low
Indirectedness	Yes (-1)	
Inconsistency	No	
Imprecision	No	
Publication Bias	No	

Our evaluation concludes that up to now the quality of evidence for i-MRI is relatively low (Table 2). The two primary reasons for this conclusion are the sparsity of randomized control trials and the use of gross total resection as an intermediate to evaluate benefits in survival. Numerous studies have attempted to evaluate directly the benefit on i-MRI in overall survival and in progression free survival (citations). However, evaluation of effect on overall survival requires careful accounting for the adjunct therapy received and, most importantly, for the different glioblastoma molecular subtypes, as they can confer dramatically different survival times. Up to now only MGMT status has already been considered in two studies[103,104].

Cost considerations

Installing an i-MRI system costs about 2,500,000$ to 3,000,000$ (cost of MRI system itself, plus structural modification of the building; estimated from quotes we obtained, which are consistent with prices reported by Makary et al[105]. Using the prices reported by Makary et al. and assuming a 5-year life span for the system, 10-year life span for the building structural modification and straight-line depreciation, we calculated the yearly cost of operation at about 588.319$. The cost per procedure is dependent on the number of procedures performed by the system within a year and, thus, dependent on the population that the hospital covers. The number-needed-to-treat to achieve one gross total resection is 1/risk difference i.e., 1/0.23=4.35[106]. The added cost to achieve one additional gross total resection by employing intraoperative MRI is the cost of the scan multiplied by the number-needed-to-treat. Given that the incidence of the gliomas per 100.000 per year is about 4.67[1,107] one can estimate the usage of the MRI and the cost of each scan. Figure 6 provides an evaluation of the cost for a gross total resection as a function of the population covered by the hospital.

Figure 6. Log-log plots illustrating the cost for one gross total resection as a function of the population covered by the hospital. Dashed lines represent 95% confidence intervals.



Treatment options for GBM are expensive. The cost of temozolomide chemotherapy is an illustrative example that puts the costs incurred by i-MRI into perspective. Temozolomide therapy has an estimated cost of about 40,000$ per QALY (42,912 Euros[108], 32,471 Euros[109],35,861 pounds[110] and between 8,875 and 102,364 $ per QALY[111]. A threshold of 50,000$ per QALY has been deemed as reasonable to judge acceptable costs for a medical intervention[112]; alternatively, a WHO report has suggested a threshold of three times the per capita income of a given country[113]. The costs of the emerging therapies with small molecular inhibitors can be even more expensive; bevacizumab, for instance has debatable efficacy[114] and consistently costs more that 305,000$ per QALY[115].

The cost of the i-MRI scan is dependent on the workload during its lifetime. A hospital caring for a population of 1,113,000 is expected to operate one glioblastoma patient per week. According to our estimate this workload corresponds to 49,210$ per gross total resection. These figures become financially more favorable as the workload increases. Therefore, the use of i-MRI for high grade gliomas is more cost effective when employed by large tertiary centers that cover a population sizable enough to secure a steady and considerable flow of such patients. Alternatively, intraoperative US and fluorescence guidance may be considered as more affordable intraoperative interventions[116].

Although still far from being perfect, various intraoperative aids and tools have made it possible to increase the GTR of glioma from a disappointing 40% in the 1990s to an encouraging 80% of the contemporary series[69]. I-MRI helps in the recognition of the residual tumor with an unparalleled spatial and contrast resolution and significantly minimizes the main limitation of the standard image-guided surgeries. That is the non-real time nature with brain shift and distortions that will eventually make the scans unusable toward the end of the resections, when they would actually be most needed[117]. Besides that, undoubtedly, it is an expensive tool only available in a limited number of hospitals. Its high costs are related to the initial installation (building the facilities, buying the machine, and the related accessories to be used in the operative room), as well as to its maintenance and its use (radiographers and radiologists). Two recently published series[65,69] indicated that the use of the i-MRI is efficacious in dealing with gliomas with inherent peculiar features (location, eloquence, shape, contrast enhancement features, cloudy T1/T2 appearance) and making them more safely resectable, enabling a safe greater EOR than the control group. In conclusion, while there are numerous studies evaluating the effectiveness of i-MRI, randomized controlled trials with ample sample populations are still lacking. Nevertheless, our meta-analysis demonstrates that intraoperative MRI can help the surgeons achieve more radical tumor resection in patients with high grade gliomas. Moreover, the costs involved, can be comparable with the cost of other more established treatment modalities, especially in centers with considerable high-grade glioma patient inflow. Figure 7 represents a risk of bias graph, explaining our judgement regarding the risk of bias per item represented as percentages across all included studies.

Figure 7. Risk of bias graph. Our judgement regarding the risk of bias per item represented as percentages across all included studies.

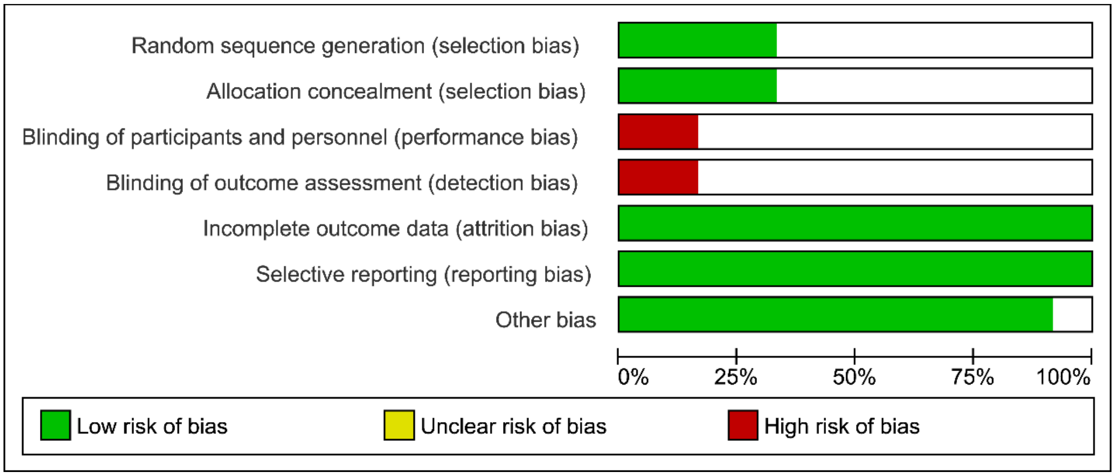


Figure 8a, b presents a summary of our judgements regarding the risk of biases of the included studies.

Figure 8a.

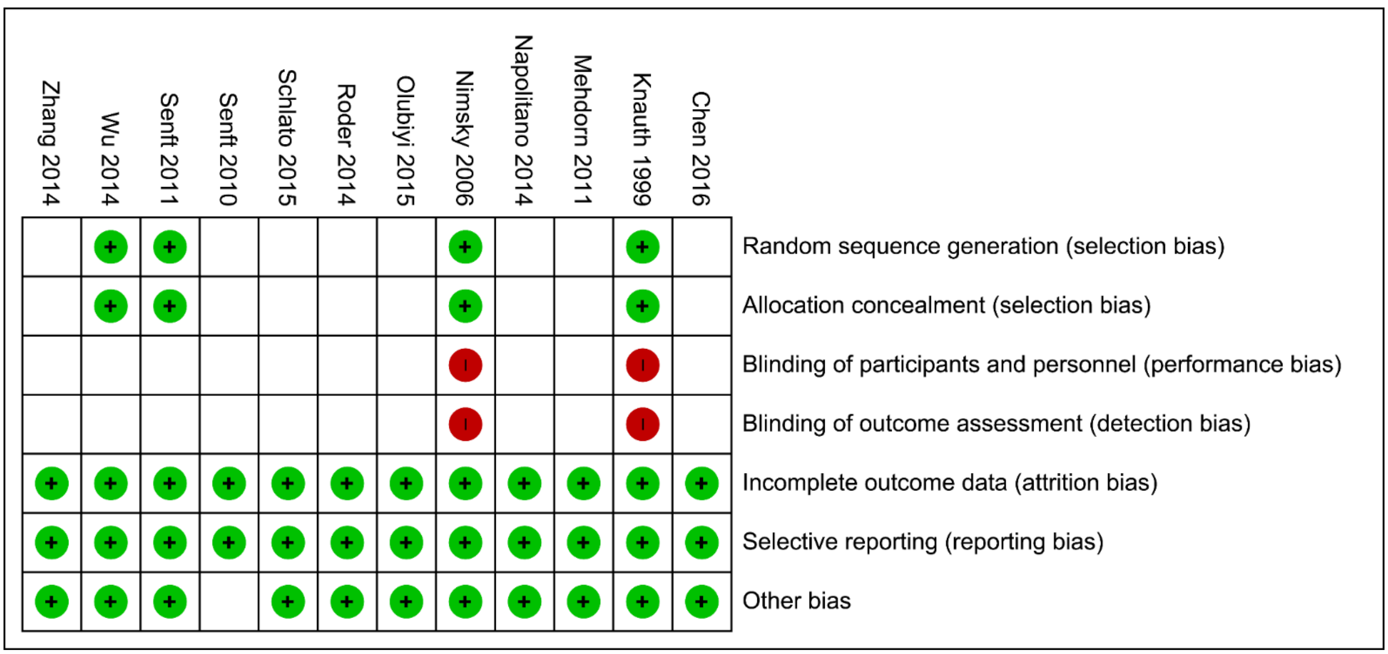
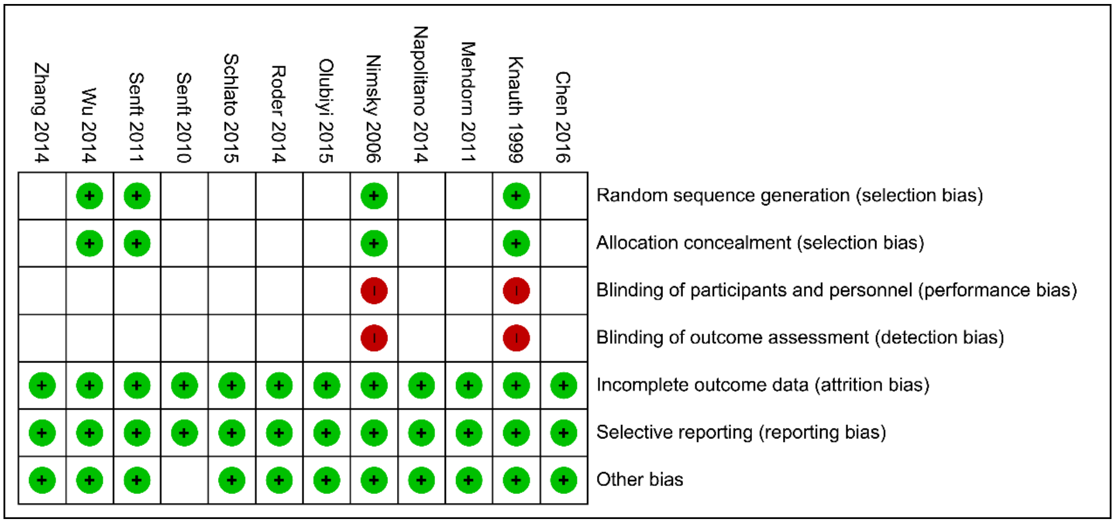


Figure 8b.



Conclusions

It is of paramount importance that the evolvement of our surgical intervention techniques regarding high grade, as well as low-grade gliomas is a prerequisite for the achievement of better patient outcomes. A lot of scientific reports exist that support the existence of a benefit, centered on clinical and quality of life parameters, when modern imaging modalities are used for resection. More precisely, i-MRI can lead to increased EOR by means of offering a more extensive surgical resection. However, when the use of i-MRI was evaluated as an independent variable, it was not shown to increase OS or PFS longer follow-up studies of larger cohorts of patients may be necessary in order to more clearly elucidate the impact of i-MRI.

On the other hand, 5-ALA gives us the opportunity for better intraoperative differential visualization of malignant tumor cells. The role of 5-ALA FGS in the achievement of safe maximal resection in cases of malignant gliomas seems to be well established. 5-ALA consistently shows superior diagnostic accuracy in HGG, with additional improvements in resection rates and OS. When individually compared with frameless neuronavigation, I-MRI and 5-ALA have proved to offer superior results, when our ultimate goal is the achievement of GTR of HGG and the overall survival benefit. Attempting to perform a comparison between IMRI and 5-ALA failed to distinguish which method is the most effective, regarding the achievement of GTR. There is ongoing evidence that support the concept of a relatively greater benefit of 5-ALA in HGG surgery when we are focusing on the histopathological verification of true tumor margins, along with the relevant cost. In order to further elucidate this point of interest, further studies centered on the evaluation of the comparative cost and surgical time associated with IMRI and 5-ALA could be sufficient to facilitate any cost-benefit analysis. There seems to be a relative lack of class I evidence, along with a relevant heterogeneity of the available data, a fact that limits the conclusiveness and generalizability of the published studies. Apart from that, it is common concept that both adjuncts are of ultimate importance to the field of HGG surgery. Based on that, we could state that every attempt should be performed in order to incorporate at least one of these intraoperative tools across operating theaters. IMRI, as well as 5-ALA, when are individually evaluated, are considered to be more effective adjuncts relative to conventional neuronavigation, in order to achieve GTR of HGG. If i-MRI and 5-ALA are compared, there is no definite conclusion regarding which is method effective. Further studies evaluating the comparative cost and surgical time associated with IMRI and 5-ALA will better support any cost-benefit analysis.

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