Clinical Neurology and Neurosurgery 180 (2019) 7–17

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

The role of navigated transcranial magnetic stimulation for surgery of motor-eloquent brain tumors: a systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Brain tumors
Glioma
Metastasis
Motor cortex
Navigated transcranial magnetic stimulation
Rolandic area

ABSTRACT

Navigated transcranial magnetic stimulation (nTMS) is an emerging tool for surgery of motor-eloquent intrinsic brain tumors, but a critical reappraisal of the literature evidence has never been performed, so far. A systematic review and meta-analysis was performed searching on PubMed/MEDLINE, and the Cochrane Central Register of Controlled Trials for studies that analyzed the impact of nTMS-based motor mapping on surgery of patients affected by motor-eloquent intrinsic brain tumors, in comparison with series of patients operated without using nTMS. The impact of nTMS mapping was assessed analyzing the occurrence of postoperative new permanent motor deficits, the gross total resection rate (GTR), the size of craniotomy and the length of surgery. Only eight studies were considered eligible and were included in the quantitative review and meta-analysis. The pooled analysis showed that nTMS motor mapping significantly reduced the risk of postoperative new permanent motor deficits (OR = 0.54, p = 0.001, data available from eight studies) and increased the GTR rate (OR = 2.32, p < 0.001, data from seven studies). Moreover, data from four studies documented the craniotomy size was reduced in the nTMS group (-6.24 cm^2, p < 0.001), whereas a trend towards a reduction, even if non significant, was observed for the length of surgery (-10.30 min, p = 0.38) in three studies. Collectively, currently available literature provides data in favor of the use of nTMS motor mapping: its use seems to be associated with a reduced occurrence of postoperative permanent motor deficits, an increased GTR rate, and a tailored surgical approach compared to standard surgery without using preoperative nTMS mapping. Nonetheless, a growing need of high-level evidence about the use of nTMS motor mapping in brain tumor surgery is perceived. Well-designed randomized controlled studies from multiple Institutions are clearly advocated to continue to shed a light on this emerging topic.

1. Introduction

The goal of the modern surgical treatment of intrinsic brain tumors located in eloquent areas is to obtain the maximal safe resection of the lesion [1,2]. This means the achievement of the gross total resection (GTR) and the preservation of the surrounding eloquent brain, which are nowadays the challenges to face for positively impacting patients' survival. Several modern pre- and intraoperative techniques has been introduced in the clinical practice to help neurosurgeons to achieve such a goal [2].

Among these, navigated transcranial magnetic stimulation (nTMS) is emerging as a new helpful tool for preoperative cortical mapping and planning before surgery of intrinsic brain tumors located within or in proximity of the motor and language areas [3–16]. Preoperative nTMS motor mapping has been reported to reliably provide a non-invasive preoperative identification of the primary motor cortex (M1), with an accuracy that is similar to that of intraoperative neurophysiological mapping (IONM) [8,9,17,18]. It can be used prior to surgery to plan a tailored strategy aiming to the goal of maximal safe resection. Moreover, it can be also used during surgery, eventually associated with nTMS-based tractography, as a further guide to IONM and tumor resection [6,19–22]. Several studies have attempted to evaluate the impact of nTMS motor mapping and planning on surgery of motor-eloquent brain tumors, performing also a specific comparison with standard surgical resection performed without the support of nTMS. Nevertheless, a critical analysis and reappraisal of the literature evidence has never been performed, so far.

The objective of the present systematic review and meta-analysis is

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https://doi.org/10.1016/j.clineuro.2019.03.003
Received 16 January 2019; Received in revised form 1 March 2019; Accepted 3 March 2019
Available online 05 March 2019
0303-8467/

to analyze the current literature on the use of nTMS mapping and planning for surgery of motor-eloquent intrinsic brain tumors and to objectively evaluate and summarize the impact of the nTMS-based approach (occurrence of postoperative new permanent motor deficits, GTR rate, size of craniotomy, length of surgery) as compared to standard surgery performed without using nTMS.

2. Methods

2.1. Study design

A specific Institutional protocol was developed to collect data from studies reporting the comparison between patients operated after nTMS motor mapping vs. patients operated without using nTMS. The following outcomes were analyzed: 1) the occurrence of postoperative new permanent motor deficits; 2) the GTR rate. Then, a further analysis was performed among selected papers to assess the impact of nTMS planning on surgical strategy by analyzing the reported length of surgery and size of craniotomies.

The meta-analysis was performed in accordance with PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [23].

2.2. Search strategy

A systematic literature search of PubMed/MEDLINE, and Cochrane Central Register of Controlled Trials (CENTRAL) was conducted using the following terms: “navigated transcranial magnetic stimulation” OR “nTMS” AND “brain tumors,” OR “gliomas”, OR “metastasis”, using different combinations (date last search: October 30th 2018). No limitations in language, publication type or period were applied. In addition, the reference lists of eligible studies were screened with the aim to identify further qualified studies.

2.3. Selection criteria

Duplicated studies and papers written in non-English language or using a non-useful format (e.g. case reports, editorials, etc.) were discarded. Then, title and abstract of the remaining studies were reviewed to identify papers dealing with the topic of the meta-analysis and presumably including all the necessary outcome information. After this step, the full-text version of the remaining studies was read to assess the eligibility to be included in the present meta-analysis. In particular, all studies including patients affected by motor-eloquent brain tumors 1) reporting a comparison between patients operated using the nTMS motor mapping and planning vs. patients operated without using nTMS, and 2) reporting data on the occurrence of postoperative new permanent motor deficits, and on the GTR rate were considered eligible, regardless of the study design (i.e. randomized or not). Studies without outcome data were excluded. In addition, among the remaining screened studies, two subgroups of papers were further created according to the possibility to extract the length of surgery and the size of craniotomy.

2.4. Data extraction

Data regarding the study settings, patient population demographics, occurrence of postoperative new permanent motor deficits, GTR rate, length of the surgical procedure, and size of craniotomies were collected in a specific database for the purpose of this meta-analysis.

2.5. Assessing the studies’ quality and risk of biases

The quality of the included studies was defined according to the “The Oxford Levels of Evidence 2” from the OCEBM Levels of Evidence Working Group (Oxford Centre for Evidence-Based Medicine. https://www.cebm.net/index.aspx?o=5653). The risk of bias at a study level was assessed using the Cochrane Collaboration’s tool for assessing risk of bias [24]. All the process of literature review, studies’ selection, data extraction, assessment of the risk of bias, and definition of the quality of studies was independently performed by two coauthors. In cases of disagreement, a third coauthor (the first author) mediated up to achieve a final agreement.

2.6. Statistical analysis

The individual and pooled odds ratio (OR) for the occurrence of postoperative new permanent motor deficits and for the GTR rate were calculated by using the Mantel-Haenszel ((M − H)) random effect model in the nTMS vs. non-nTMS populations. Then, a further analysis using the inverse variance model with random effect was performed to compare the craniotomy size and length of surgery in the two populations. For each outcome, 95% confidence intervals (CIs) and 2-sided p values were calculated. A $p < 0.05$ was considered statistically significant. Heterogeneity was evaluated using the I^2 statistic. An I^2 value > 50% was considered to be indicative of significant heterogeneity. Publication biases were defined through the visual inspection of funnel plot for each outcome, and no quantitative test (e.g the Egger’s test, etc.) were used because of the reduced number of analyzed studies (less than 10): in such a scenario it is commonly recommended to not perform any tests because their power is too low to distinguish chance from real asymmetry [25]. In case of asymmetry, a further subgroup analysis was performed removing studies responsible of this phenomenon. Statistics was performed using the software Cochrane Review Manager (RevMan, Version 5.3. The Nordic Cochrane Centre, The Cochrane Collaboration 2014, Copenhagen, Denmark).

3. Results

3.1. Search results

A total of 229 studies were retrieved during the literature search using the Pubmed/Medline and Cochrane Central Register of Controlled Trials databases. One hundred thirty-one duplicates were initially excluded. The remaining 98 studies were further screened and 71 were excluded because they were not dealing with the topic of the meta-analysis (57), written in different manuscript formats (4 case reports, 2 editorials, 2 reviews, 2 conference proceedings, 1 technical note) or in non-English language (2). We found also one randomized controlled clinical trial (RCT) that was still ongoing, but results were not available at the time of this manuscript preparation (ClinicalTrials.gov: NCT02879682). Twenty-seven remaining studies were reviewed in full-text to identify the eligibility to be included in the meta-analysis. Of these, 19 were excluded because they did not report any useful outcome data.

Therefore, at the end of the selection process, only 8 studies [19,26–32] met the inclusion criteria and were considered eligible for the evaluation of the outcome “occurrence of new postoperative permanent motor deficits”. Of these, 7 were considered eligible also for the analysis of the outcome “GTR rate” [19,26–31]. Four studies [19,28,30,31] were included for the assessment of the craniotomy size and 3 for the length of surgery [28,30,31] (Fig. 1).

3.2. Description of included studies

Three observational controlled studies reported a comparison between prospectively enrolled series of patients [26,29,31]. Four studies included prospectively enrolled series compared with a matched retrospective control group [27,28,30,32]. The remaining one was a retrospective study [19]. Collectively the level of evidence of the included studies was moderate-low, since two studies were classified as Level II [29,31], and the remaining 6 as Level III [19,26–28,30,32] according to

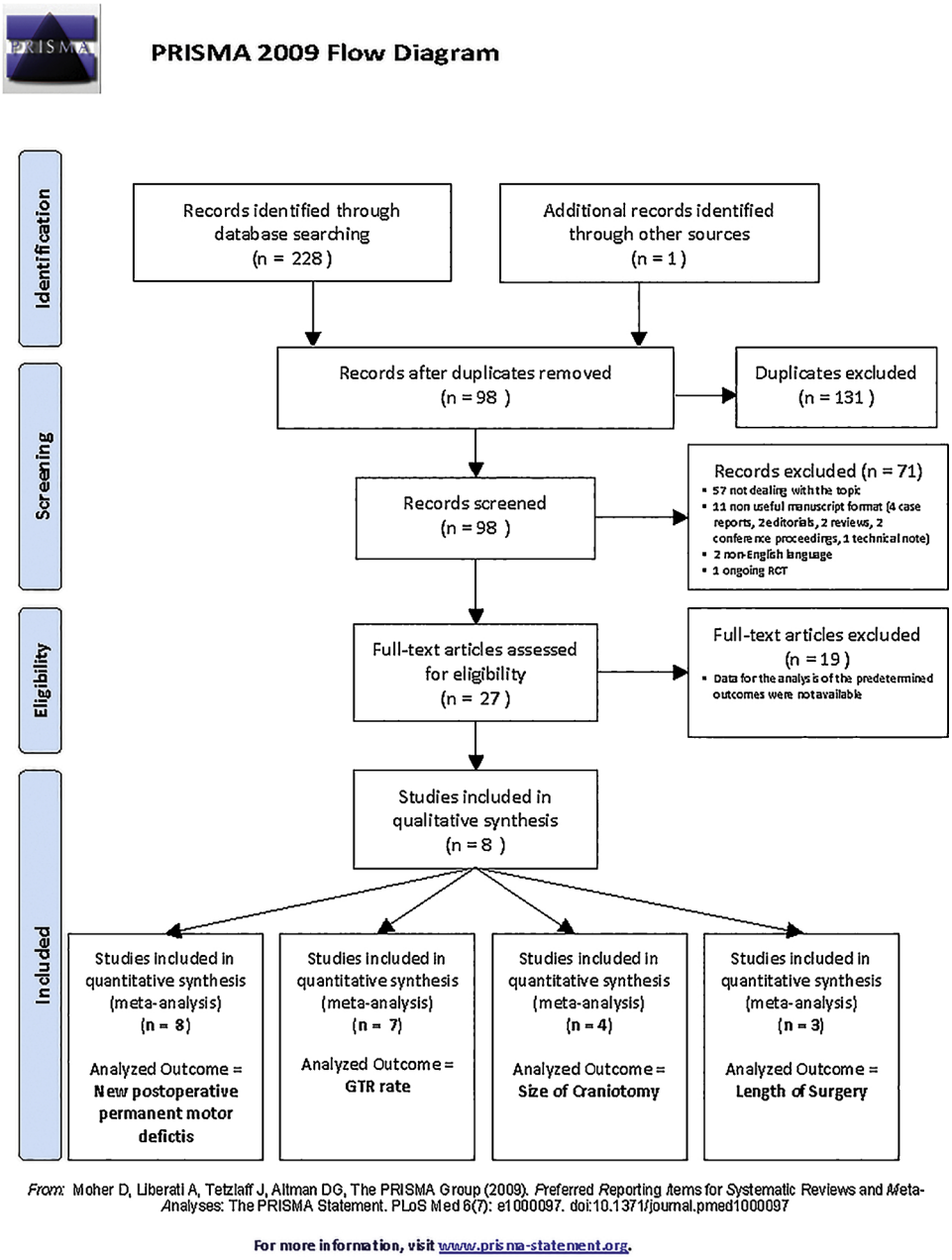

Fig. 1. PRISMA flow chart describing the process of literature review [23].

the OCEBM classification.

The studied population was mixed: two studies included only patients with low grade gliomas [26,32] (LGGs; one of these [26] disclosed the postoperative diagnosis of few cases of WHO grade III gliomas), one paper reported only patients with high grade gliomas (HGGs) [30], another one exclusively patients affected by glioblastomas (GBMs) [29], one manuscript patients with brain metastasis (METs) [31], while the remaining three studies included a mixed population of patients affected by HGGs, LGGs, metastasis and few cases of vascular malformations and other lesions (cavernous and artero-venous malformations, respectively CMs and AVMs) [19,27,28].

Patient characteristics were roughly equivalent in both arms (nTMS vs. non-nTMS) of each study. All studies reported that the two analyzed groups were well matched for main clinical characteristics.

Table 1 summarizes the characteristics of each study and patients' populations.

3.3. Assessment of study quality and risk of bias

All studies except two were at high risk of selection biases (random sequence generation bias). In these two studies the risk of allocation concealment biases was unclear because not described in details [29,31].

There was a high risk for performance biases in all studies because of the difficult blinding of personnel and patients to the type of treatment. The risk of detection bias was low in 4 studies [19,28,30,31], unclear in three [27,29,32], and high in the remaining one [26]. Only one study was at high risk for attrition and reporting biases due to the selective report of incomplete outcome data [32]. Nevertheless, this limitation was overpassed due to the possibility to have access to unpublished data regarding the outcome "occurrence of postoperative new permanent motor deficits".

Finally, two studies were considered at high risk for other bias: the first one reported a clearly different methodology for surgical

Table 1
Summary of the included studies, with the description of the populations and outcomes analyzed.

Study	Study Design	Level of Evidence	N° of patients enrolled	Population Groups (Age, Gender)		Tumor Location		Preoperative Deficits	
				nTMS	*Controls*	*nTMS*	*Controls*	*nTMS*	*Controls*
Picht et al., 2013[26]	Prospective observational controlled	Level III	22 (8 were not operated)	11 (median 38 yo; 8 m, 3 f)	surgery in 3/11 (median 43 yo; 6 m, 5 f)	Left M1 = 3 Right M1 = 8	Left M1 = 6 Right M1 = 5	18.2%	18.2%
Frey et al., 2014[27]	Prospective series matched with retrospective controls	Level III	365	250 (median 54 yo; 139 m, 111 f)	115 (median 53 yo; 67 m, 48 f)	M1 = 88 CST = 35 M1 + CST = 127	M1 = 32 CST = 22 M1 + CST = 61	59%°	55%°
Krieg et al., 2014[28]	Prospective series matched with retrospective controls	Level III	200	100 (mean 53.1 yo; 59 m, 41 f)	100 (mean 55.5 yo; 66 m, 34 f)	n/a	n/a	34%°	27%°
Krieg et al., 2015[30]	Prospective series matched with retrospective controls	Level III	140	70 (mean 58.0 yo; 35 m, 25 f)	70 (mean 60.3 yo; 45 m, 15 f)	n/a	n/a	31.4%	28.6%
Krieg et al., 2016[31]	Multicenter prospective observational controlled	Level II	250	120 (mean 59.1 yo; 58 m, 62 f)	130 (mean 62.3 yo; 67 m, 63 f)	Frontal = 87 Parietal = 33	Frontal = 90 Parietal = 40	51.7%	39.2%
Picht et al., 2016[29]	Prospective observational controlled	Level II	127	93 (mean 53.9 yo; 50 m, 43 f)	34 (mean 53.2 yo; 19 m, 15 f)	M1 = 38 CST = 23 M1 + CST = 32 Left = 37 Right = 56	M1 = 13 CST = 9 M1 + CST = 12 Left = 11 Right = 23	Mean MRC score = 4.1	Mean MRC score = 3.9
Raffa et al., 2017[32]	Prospective series matched with retrospective controls	Level III	32	16 (mean 50.2 yo; 10 m, 6 f)	16 (mean 53.7 yo; 8 m, 8 f)	Frontal = 12 Parietal = 1 Insular = 5 Temporal = 5§ Right = 10 Left = 6	Frontal = 11 Parietal = 6 Insular = 4 Temporal = 8§ Right = 8 Left = 8	18.7%	62.5%
Raffa et al., 2018[19]	Retrospective series matched with retrospective controls	Level III	105	70 (mean 54.3 yo; 43 m, 27 f)	35 (mean 57.3 yo; 18 m, 17 f)	Frontal = 45 Parietal = 28 Insular = 8 Temporal = 21§ Right = 29 Left = 41	Frontal = 19 Parietal = 14 Insular = 5 Temporal = 14§ Right = 23 Left = 12	48.6%°	40%°

Study	Histology		New permanent motor deficits - 3 months		GTR rate		Craniotomy size		Length of surgery	
	nTMS	*Controls*	*nTMS* N° of patients (%)	*Controls* N° of patients (%)	*nTMS* N° of patients (%)	*Controls* N° of patients (%)	*nTMS*	*Controls*	*nTMS*	*Controls*
Picht et al., 2013[26]	LGGs (4 + 1 WHO III gliomas)		1 of 11 (9.1%)	1 of 3 (33.3%)	10 of 11 (90.9%)	0 of 3	/	/	/	/
Frey et al., 2014[27]	90 HGGs 38 LGGS 85 Mets 37 other	37 HGGs 18 LGGs 40 Mets 20 other	15 of 250 (6.1%)° 10 of 128 (7.5%) Gliomas only	10 of 115 (8.5%)° 5 of 55 (9.5%) Gliomas only	75 of 128 (58.6%) Gliomas only	23 of 55 (41.8%) Gliomas only	Smaller craniotomies in 17.5%	/	/	/
Krieg et al., 2014[28]			13 of 100 (13%)°	18 of 100 (18%)°	78 of 100 (78%)°	58 of 100 (68%)°	22.4 ± 8.3 cm^2	26.7 ± 11.3 cm^2	196.2 ± 57.5 min	189 ± 59.8 min

(*continued on next page*)

Table 1 (*continued*)

Study	Histology		New permanent motor deficits - 3 months		GTR rate		Craniotomy size		Length of surgery	
	nTMS	*Controls*	*nTMS* *N° of patients (%)*	*Controls* *N° of patients (%)*	*nTMS* *N° of patients (%)*	*Controls* *N° of patients (%)*	*nTMS*	*Controls*	*nTMS*	*Controls*
	17 LGGs 49 HGGs 24 METs 3 AVMs 3 CMs 4 other	15 LGGs 51 HGGs 24 METs 3 AVMs 3 CMs 4 other								
Krieg et al., 2015[30]	HGGs		9 of 70 (12.9%)	18 of 70 (25.7%)	46 of 70 (65.7%)	32 of 70 (45.7%)	25.3 ± 9.7 cm^2	30.8 ± 13.2 cm^2	201.0 ± 57.0 min	208.9 ± 65.5 min
Krieg et al., 2016[31]	METs		4 of 120 (3.3%)	17 of 130 (13.1%)	111 of 120 (92.5%)	103 of 130 (79.2%)	16.7 ± 8.6 cm^2	25.0 ± 17.1 cm^2	128.8 ± 49.4 min	158.0 ± 65.8 min
Picht et al., 2016[29]	GBMs		12 of 93 (13%)	5 of 34 (15%)	57 of 93 (61.3%)	15 of 34 (44.1%)	/	/	206 (106-375) min	228 (110-390) min
Raffa et al., 2017[32]	LGGs		1 of 16 (6.2%) 0 of 9 (0%)* Motor-eloquent tumors only	7 of 16 (43.7%) 6 of 13(46.1%)* Motor-eloquent tumors only	/	/	/	/	/	/
Raffa et al., 2018[19]	20 LGGs 33 HGGs 9 METs 8 CMs	12 LGs 18 HGs 3 METs 2 CMs	7 of 70 (10%)° 7 of 62 (11.3%)* Brain tumors only	9 of 35 (25.7%)° 9 of 33 (27.3%)* Brain tumors only	35 of 62 (56.4%) Brain tumors only	14 of 33 (42.4%) Brain tumors only	24.7 ± 10.5 cm^2*	32.8 ± 12.6 cm^2	/	/

Abbreviations: / = not available, AVMs = artero-venous malformations, CMs = cavernous malformations, CST = corticospinal tract, f = female, GTR = gross total resection, LGGs = low grade gliomas, HGGs = high grade gliomas, m = male, M1 = primary motor cortex METs = metastasis, n/a = not available, nTMS = navigated transcranial magnetic stimulation, yo = years old.
*extracted from unpublished raw data.
°data are reported from all the study's population, including also vascular malformations and other lesions.
§the total sum is higher than the number of patients because tumors involved more than one lobe.

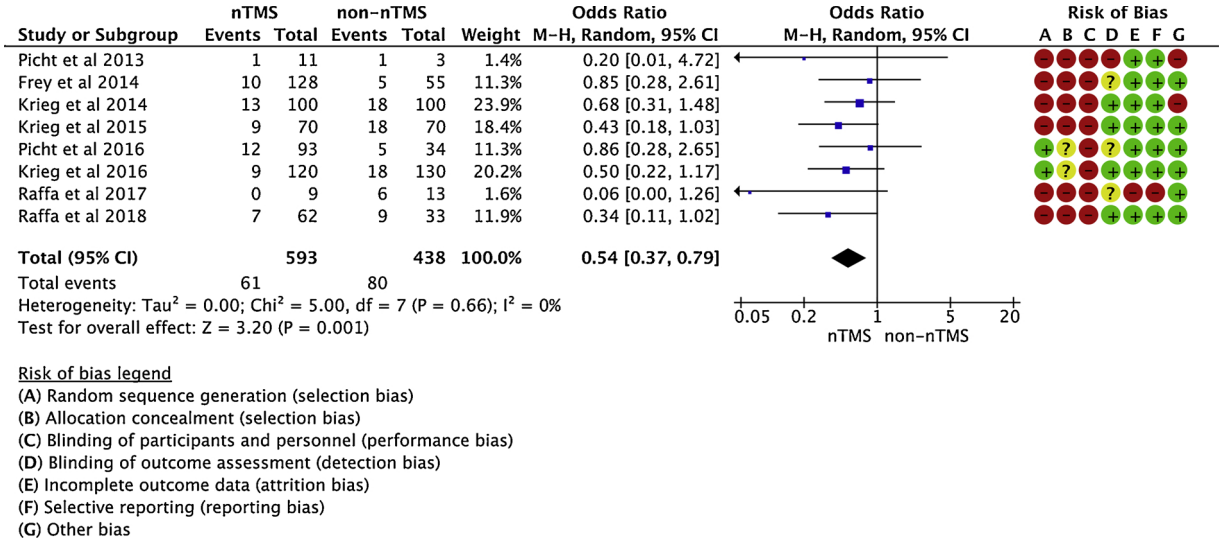

Fig. 2. Forest plot of pooled meta-analysis of the occurrence of postoperative new permanent motor deficits in nTMS vs. non-nTMS patients for each study (Mantel-Haenszel [(M−H)] random-effects model). Point estimates of odds ratio (OR) are indicated with boxes, the areas of which are proportional to the weight of each study. Ninety-five percent confidence intervals (CIs) are indicated by horizontal lines. The black diamond indicated the pooled effect of all studies. Risk of biases are indicated in last column on the right for each study and explained by the relative legend according to the Cochrane Collaboration's tool for assessing risk of bias [52]. The color of the circle for each bias indicates a low (green), unclear (yellow) or high (red) risk (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

management of patients included in the two study groups (nTMS vs. non-nTMS) [26]. The second one was probably biased by the inclusion of few cases of vascular malformations in the analysis of the considered outcomes [28] (Fig. 2). Moreover, the same study performed in 2014 probably included some patients that have been enrolled also in later studies published by the same authors' group, thus leading to a possible duplicate reporting bias. In particular, some HGGs and METs patients probably have been included in two studies published respectively in 2015 [30] and 2016 [31].

3.4. Occurrence of postoperative new permanent motor deficits

A total of 1031 patients from 8 studies were included [19,26–32]. Five hundred ninety-three were submitted to preoperative nTMS motor mapping, whereas 438 were operated without performing preoperative nTMS mapping.

In the pooled meta-analysis, the use of preoperative nTMS motor mapping significantly reduced the risk of the occurrence of postoperative new permanent motor deficits as compared to the non-nTMS group (OR = 0.54, 95% CI 0.37–0.79, p = 0.001). There was no significant heterogeneity (I^2 = 0%, p = 0.66) (Fig. 2).

3.5. GTR rate

A total of 1009 patients were described in 7 studies [19,26–31]. In particular, 584 patients were included in the nTMS group and 425 in the non-nTMS group. All studies consistently defined the GTR as the removal of the 100% of the tumor tissue at the early postoperative MR scan. The pooled analysis revealed that preoperative nTMS motor mapping was associated with a significantly higher probability (more than two-fold) to achieve the GTR of the tumor (OR = 2.32, 95% CI 1.73–3.10, p < 0.001). No significant heterogeneity was observed (I^2 = 0%, p = 0.59) (Fig. 3A).

Moreover, a further subgroup analysis was performed after excluding one study that analyzed the GTR rate including also few cases of vascular lesions (6 cases in each arm) [28]. The new pooled analysis on 6 studies confirmed previous results, showing a still significant two-fold increased probability to achieve a GTR in patients submitted to preoperative nTMS motor mapping (OR 2.25; 95% CI 1.62–3.13, p < 0.001), with no significant heterogeneity (I^2 = 0%, p = 0.48) (Fig.3B).

3.6. Size of craniotomy and length of surgery

Four studies [19,28,30,31] including 695 patients reported data regarding the size of craniotomy in patients submitted to nTMS motor mapping prior to surgery (360 patients) vs. patients operated without nTMS mapping (335 patients). A fifth study reported a reduced size of craniotomy in the nTMS group, but raw data were not available and the study was excluded [27].

The pooled analysis showed that patients in the nTMS group received significantly smaller craniotomies as compared to the non-nTMS group (inverse variance model with random effect: mean difference = -6.24 cm^2, 95% CI between -8.31 and -4.17 cm^2, p < 0.001). The heterogeneity was slight but not significant (I^2 =27%, p = 0.25) (Fig. 4).

Three studies [28,30,31] including 590 patients provided data regarding the length of the surgical procedure in the two groups (290 in the nTMS vs. 300 in the non-nTMS group). A fourth study reported only the mean values of the craniotomy size, and therefore it was excluded [29]. Patients submitted to nTMS had a shorter duration of surgery but the difference was not statistically significant (mean difference = -10.30 min, 95% CI between -33.11 and + 12.52 min, p = 0.38). For this specific outcome the heterogeneity was very high and significant (I^2 =82%, p = 0.004) (Fig. 5).

3.7. Assessment of publication biases

Visual inspection of funnel plots disclosed asymmetries for the outcomes "occurrence of postoperative new permanent motor deficits" and "GTR rate" (Fig. 6), suggesting the possibility of a small-study effect.

Concerning the occurrence of permanent motor deficits, two studies were excluded because they were located at the bottom left corner of the funnel plot [26,32]. The new pooled analysis still showed a reduced probability to have new permanent motor deficits in the nTMS group (OR = 0.57, 95% CI 0.39-0.83, p = 0.004; I^2 = 0%, p = 0.77) (Fig. 6A).

Concerning the GTR rate, one study located at the bottom right

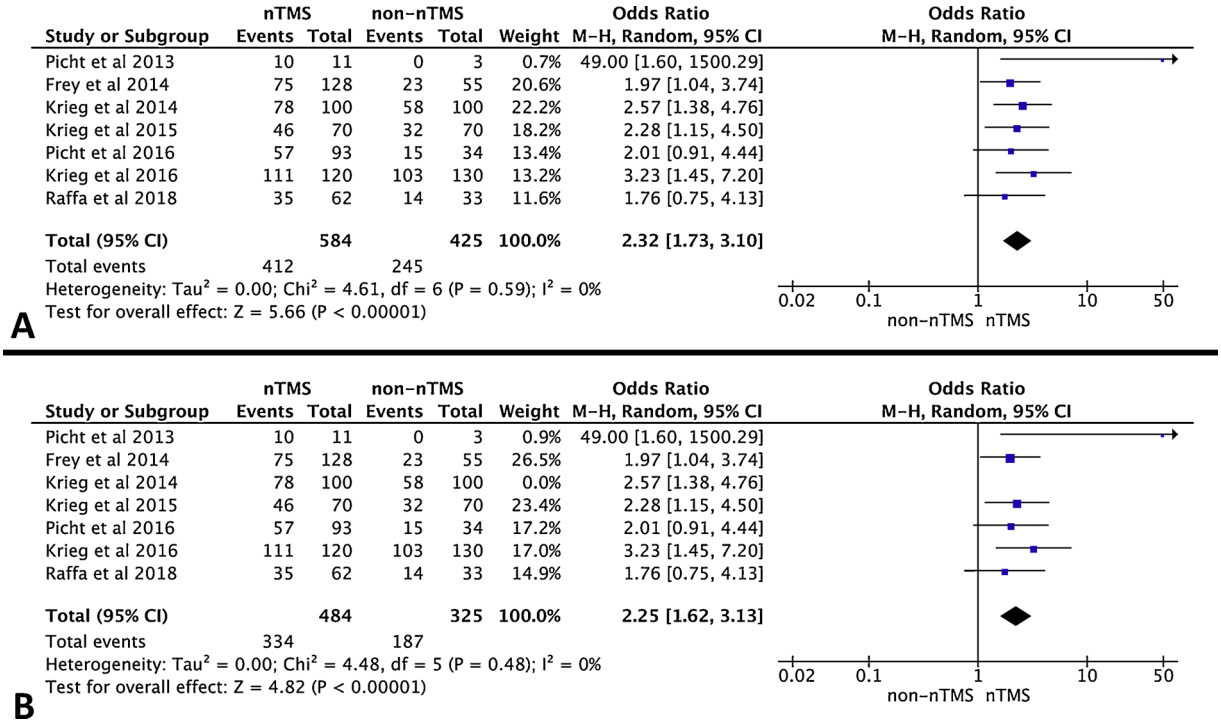

Fig. 3. Forest plot of pooled meta-analysis of the GTR rate in nTMS vs. non-nTMS patients for each study (Mantel-Haenszel [(M − H)] random-effects model) (A). Subgroup pooled analysis after the exclusion of the study published by Krieg et al. in 2014 including also vascular malformations (B). Point estimates of odds ratio (OR) are indicated with boxes, the areas of which are proportional to the weight of each study. Ninety-five percent CIs are indicated by horizontal lines. The black diamond indicates the pooled effect of all studies.

corner of the funnel plot was removed [26]. Nevertheless, the probability of GTR was still significantly increased in the nTMS group (OR = 2.27, 95% CI 1.69–3.04, p < 0.001; I^2 = 0%, p = 0.91) (Fig. 6B).

No evident asymmetries were observed for the craniotomy size (Fig. 7A) and length of surgery (Fig. 7B).

4. Discussion

The main result of the present meta-analysis is that to date only few studies have attempted to compare the clinical impact of preoperative nTMS-based mapping and planning on surgery of motor-eloquent intrinsic brain tumors vs. results achieved without the support of nTMS.

Nevertheless, data from the currently available literature clearly favors the use of preoperative nTMS motor mapping, since it seems to improve the surgical management of patients affected by motor-eloquent brain tumors.

4.1. Postoperative new permanent motor deficits

Data regarding the occurrence of postoperative new permanent motor deficits were available from 8 studies [19,26–32]. Among these, the study published by Krieg et al. in 2014 had the greatest impact on the pooled analysis (23.9%) [28]. Nevertheless, the results of this paper were for some aspects biased by the inclusion of few patients with vascular malformations. A similar bias was also found in the other two studies [19,27], but it was easily overpassed thanks to the report of data regarding gliomas only in the paper of Frey et al. [27], and to the availability of raw unpublished data regarding brain tumors only from the study of our group published in 2018 [19].

The inclusion in the study population of patients affected by vascular malformations could be considered not properly correct when analyzing the impact of nTMS on motor outcome. Nonetheless, the role of the nTMS motor mapping should be to identify the spatial relationship between the tumor and the surrounding motor-eloquent brain parenchyma, and to guide the IONM and the safe resection regardless of the nature of the lesion. As a matter of fact, this strategy may be used also during resection of vascular lesions such as CMs or the nidus of AVMs. Therefore the role of nTMS planning in preserving the motor pathway and reducing the occurrence of new motor deficits could be assessed regardless of the histology of lesions, thus including also few cases of vascular malformations in the study population.

The remaining five studies analyzed homogenous series consisting of LGGs [26,32], HGGs [30], GBMs [29], and metastasis [31]. Among

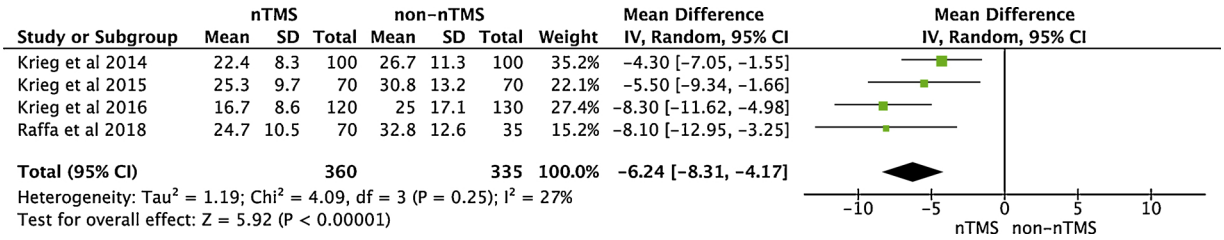

Fig. 4. Forest plot of pooled meta-analysis of the craniotomy size in nTMS vs. non-nTMS patients for each study (inverse variance with random-effects model). Point estimates of the mean difference are indicated with boxes, the areas of which are proportional to the weight of each study. Ninety-five percent CIs are indicated by horizontal lines. The black diamond indicates the pooled effect of all studies.

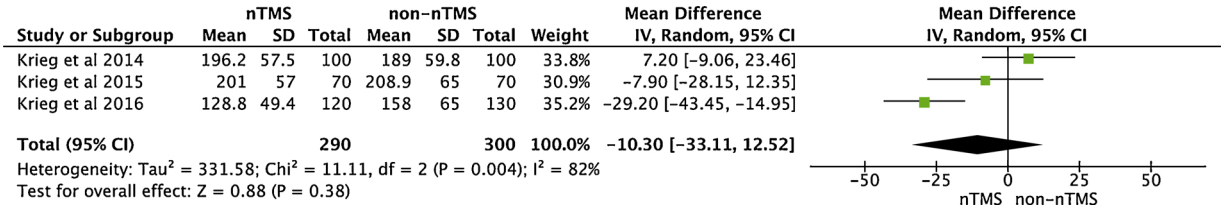

Fig. 5. Forest plot of pooled meta-analysis of the length of surgery in nTMS vs. non-nTMS patients for each study (inverse variance with random-effects model). Point estimates of the mean difference are indicated with boxes, the areas of which are proportional to the weight of each study. Ninety-five percent CIs are indicated by horizontal lines. The black diamond indicates the pooled effect of all studies.

these, the paper published by Picht et al in 2013 [26] suffered from a clear bias related to the small number of patients and by their different clinical and surgical management. Indeed, all 11 patients included in the nTMS group underwent surgical treatment within the first year from diagnosis. Conversely, only 3 out of 11 patients in the control group received surgery during the same timeframe. That clearly affected the comparison between the two groups. As well, the study of our group published in 2017 [32] suffered from a similar bias (small number of patients) and from a clear attrition and reporting bias: postoperative outcome was reported without a clear distinction between motor- and language-eloquent tumors. Nonetheless, this bias was overpassed thanks to the use of unpublished raw data.

Collectively, the pooled analysis demonstrated the possibility to reduce the occurrence of postoperative new permanent motor deficits by using the preoperative nTMS motor mapping. It could be argued that other factors could influence the occurrence of postoperative motor deficits, such as the use of IONM during surgery [33,34]. However, in all the analyzed studies the authors reported the use of IONM during the surgical procedure in both groups (nTMS and non-nTMS). Therefore, these results should be considered as related to a particular attention paid to the motor pathway during planning and lesion resection, thanks to the availability of preoperative nTMS mapping. Indeed, the reduced occurrence of postoperative motor deficits may be considered as the result of a customized planning that could modify the surgical strategy. As a matter of fact, knowing about functionally important regions surrounding the tumor may be essential to plan the approach through non-essential tissue, thus avoiding damage to the functional motor pathway. In our previous experiences, the use of the nTMS-based motor mapping increased the awareness of high risk areas, inducing a change of the previously hypothesized plan based on standard MR in a percentage ranging from 17.1% to 56% of cases [19,32]. Another authors' group reported that nTMS was significantly able to modify the surgical indication and planned extent of resection (EOR; both in terms of increasing or restricting the planned resection) in a range of 10%–68% of cases [26,27,29]. Unfortunately, the methods used to analyze the impact of nTMS on surgical strategy and planning were not consistent among different studies, thus precluding us from performing a quantitative pooled analysis.

Nevertheless, it must be considered that the occurrence of new neurological deficits does not depend only on the direct damage to the motor pathway, but also on an eventual indirect vascular damage that could result in an ischemic insult to the M1 and/or corticospinal tract (CST) [35–41]. That aspect is difficult to analyze and is poorly considered in the literature: as well, it has not been analyzed by the included studies.

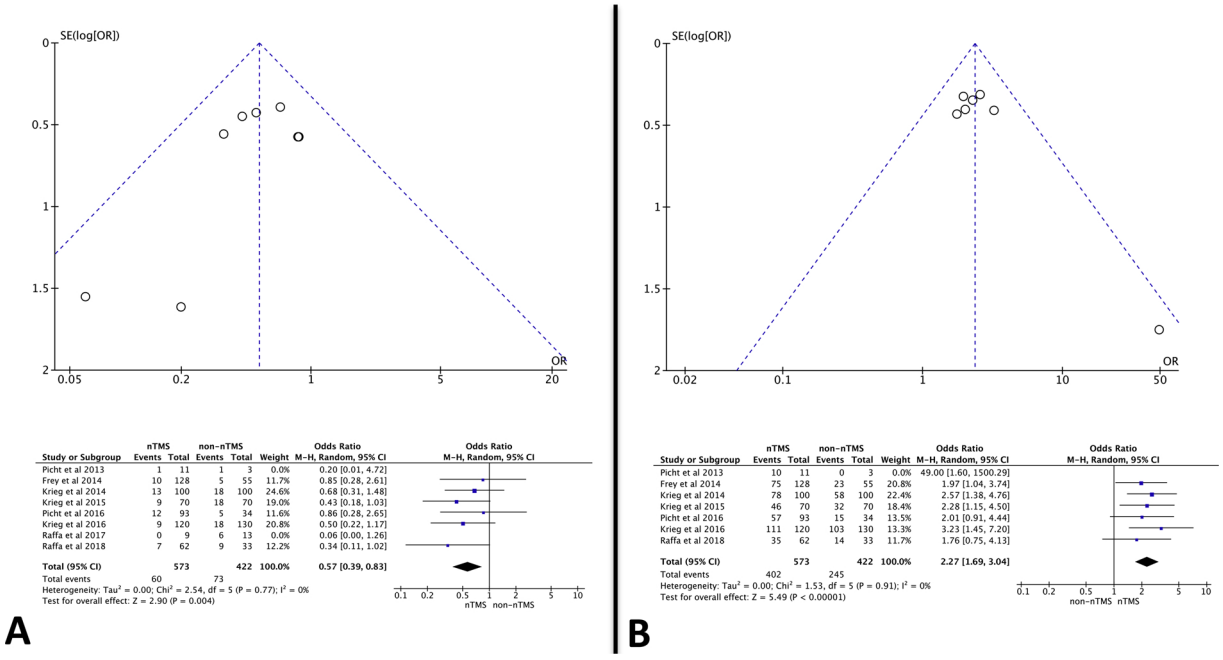

Fig. 6. Publication bias of the studies eligible for the analysis of the outcome "occurrence of postoperative new permanent motor deficits" (A) and "GTR rate" (B). The funnel plot in the panel A showed a clear asymmetry because of two studies located at the bottom left corner. A further pooled analysis was performed removing the two studies and is reported at the bottom of the panel A: nonetheless, nTMS patients continued to have a reduced risk of the occurrence of postoperative new motor deficits (OR = 0.57; p = 0.004); similarly, the funnel plot in the panel B showed an asymmetry due to the presence of one study located at the bottom right corner. After removing the study, the probability to achieve a GTR of the tumor was still higher in the nTMS group (OR 2.27; $p < 0.001$).

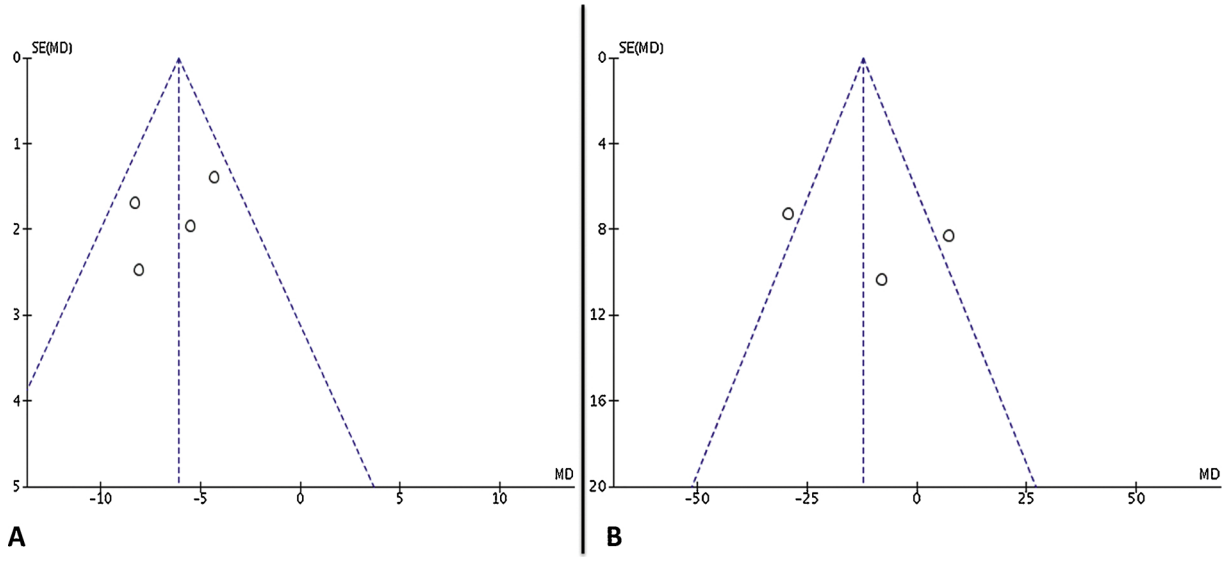

Fig. 7. Analysis of the publication bias through Funnel Plots regarding the craniotomy size (A) and the length of surgery (B). No evident asymmetries are visible.

4.2. GTR rate

All 7 included studies reported a higher GTR rate using nTMS motor mapping [19,26–31]. The study of Krieg et al. published in 2014 [28] has the highest impact on the pooled analysis (22.2%) but, as already previously pointed out, it was biased by the inclusion of few vascular malformations also for the computation of the GTR rate. Nevertheless, in both the analyzed groups (100 patients each), vascular lesions affected only 6 patients. Such a bias was corrected in the study of Frey et al. [27] that reported the GTR rate for gliomas only (58.6% in the nTMS group vs. 41.8% in the non-nTMS group), and in the study of our group [19] that described the GTR rate in brain tumors only (56.4% for nTMS vs. 42.4% for non-nTMS). Other papers analyzed the GTR rate in homogenous groups, reporting similar results [26,29,27–31].

Other technologies such as IONM, intraoperative fluorescence, iMRI, and others could influence the achieved GTR rate [33,42–46]. Nevertheless IONM was always used in all studies, whereas fluorescence-guided surgery or other technologies that could increase the EOR have never been used in any study. Therefore, the observed increase of the GTR rate should be explained with a higher awareness of the spatial relationship between the tumor and the motor pathway disclosed by the nTMS-based planning. This could lead to the identification of safe areas that could be further resected, thus resulting in an increased EOR without inducing new motor deficits [19]

4.3. Size of craniotomy and length of surgery

The impact of nTMS on tailoring surgical strategy was poorly analyzed. Only 4 studies assessed the impact of nTMS motor mapping on the craniotomy size [19,28,30,31], and three studies were published by a single group [28,30,31]. The comparison of the actual craniotomy size (mean ± SD) between the two arms of each study resulted in a pooled quantitative analysis that demonstrated a reduced size in patients treated using nTMS vs. controls. This could be explained by the preoperative identification of the spatial relationship between the M1 and the tumor, that could help the neurosurgeon to plan a customized craniotomy, even smaller, without the need to expose unnecessary brain cortex to perform extensive intraoperative mapping. Indeed, as reported by Krieg et al., a possible explanation of these results could be that when nTMS motor mapping is available, the surgeon' s task is just to confirm nTMS data by circumscribed cortical mapping [30].

Three studies described the influence of the nTMS on the length of surgery [28,30,31]. An initial study by Krieg et al. in 2014 [28] reported a longer duration for surgery in the nTMS group. Probably this result was due to the learning-curve related to the use of nTMS data during surgery in the early experience of the authors with this technology. The remaining two studies, published by the same group of authors, reported a shorter duration of surgery in the nTMS group [30,31].

These findings could be explained by the possibility to perform a customized surgical approach, reducing the size of craniotomy and the time necessary for IONM that does not need to be extensive, but simply tailored to the preoperative nTMS mapping.

On the other hand, it must be emphasized that nTMS mapping needs to be performed by well-trained personnel to avoid that time spent in planning may outweigh the benefits that could derive from the customized strategy, including the shorter surgical time and reduced craniotomy size. For this purposes, some studies have been published describing specific mapping protocols and suggesting the best way for the implementation of nTMS mapping in the workflow for management of brain tumor patients in Neurosurgical departments [47,48]. Indeed, a standardized strategy to optimize nTMS integration in the clinical workflow has been already reported and could serve as a guide for centers beginning to use nTMS data in neurosurgical patients' care. That may avoid excessively time-consuming nTMS investigations that could reduce the advantages of the nTMS-based planning.

4.4. Limitations, other biases, and future directions

The present meta-analysis suffers from several limitations. First, the lack of well-conducted RCTs in this specific literature may reduce the power of our results. This forced us to perform a meta-analysis of observational studies, therefore having an increased risk of biases, that could anyway be helpful as a summary of the current literature on the topic [49].

Moreover, the population analyzed for each outcome is not homogeneous. Nevertheless, the non-homogenous histology of tumors included in the eligible studies should not influence the evaluation of the nTMS ability in preserving the motor eloquent brain parenchyma during surgery.

On the other hand, the lack of homogeneity in some series could represent a further source of biases when analyzing specific outcomes. Indeed, the inclusion of patients with vascular malformations in the analysis of the GTR rate may affect the quantitative pooled analysis and should be avoided.

Another bias that could affect this meta-analysis is duplicate

reporting. That has been hypothesized for some studies published by the same authors' group, but it has been impossible to confirm or rule it out.

The lack of the use of 5-ALA or sodium-fluorescein to increase the extent of tumor resection in the included studies may be considered a further limitation. Indeed, fluorescence-guided resection using 5-ALA [42,50] or sodium-fluorescein [44] is a widely accepted and used technique that, if combined with nTMS motor mapping and planning, could further increase the achieved EOR. Probably, the authors excluded patients treated by fluorescence-guided resection to avoid confounding factors in the evaluation of the nTMS impact on the EOR.

Only limited data have been reported regarding the influence of nTMS mapping on the craniotomy size and length of surgery, thereby no firm conclusions can be drawn. Indeed, most of the studies (3 out of 4) analyzing these two parameters have been published by the same authors' group, thus increasing the possibility of reporting biases.

Despite all these limitations, the present meta-analysis of observational studies [49] must be interpreted as a mere attempt to perform a critical evaluation of the available literature with the aim to push towards the necessity of performing new well-designed studies to reach a higher level of evidence on the emerging topic of nTMS motor mapping in brain tumor surgery.

Indeed, this critical reappraisal of the current literature should serve to reduce the occurrence of the most common biases observed in the currently available papers. In particular, prospective studies are desirable and a higher attention should be paid in the selection of the study populations: the analysis of specific outcomes should be performed on homogeneous populations of brain tumor patients, distinguishing between brain tumor patients with different histology (i.e. HGGs, LGGs, METs, and so on), and patients with other intracranial diseases (e.g. vascular malformations).

Moreover, higher attention must be paid to avoid the inclusion in different studies of some patients enrolled during partially overlapping time periods, thus reducing the possibility of duplicate reporting biases.

Future studies should also try to reduce performance biases that are usually due to the difficult blinding of patients and personnel. As already reported in a previous study on nTMS language mapping [51], a possible solution would consist in performing the nTMS mapping and planning in both the study arms (nTMS and non-nTMS); afterwards, data from planning should be available only for surgery of patients included in the nTMS group. Then, external personnel blind to the preoperative and intraoperative data should evaluate outcomes. Probably, a similar study design might really reduce performance biases.

Lastly, it may be considered appropriate that next studies will evaluate also whether the combination of nTMS planning and fluorescence-guided resection may further increase the EOR.

5. Conclusions

The present meta-analysis demonstrates for the first time that, in patients affected by motor-eloquent intrinsic brain tumors, the use of nTMS motor mapping and planning prior to surgery may be associated with a reduced risk of postoperative new permanent motor deficits and with a higher probability to achieve a gross total resection of the tumor than in cases of surgery performed without the support of nTMS. Moreover, limited data suggest a possible role for nTMS in tailoring the surgical approach and procedure, as expressed by the reduction of the craniotomy size and the length of surgery. Nonetheless, a growing need of high-level evidence about nTMS motor mapping in brain tumor surgery is perceived. Well-designed randomized controlled studies from multiple Institutions are clearly advocated to continue to shed a light on this emerging topic.

Conflict of interest

None.

Disclosure of funding

None.

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