



Olfactory Groove Meningiomas: Comprehensive assessment between the different microsurgical transcranial approaches and the Endoscopic Endonasal Approaches, systematic review and metanalysis on behalf of the EANS skull base section



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Abbreviations:

ASBMs	Anterior Skull Base Meningiomas
ASFAs	Anterior Sub-frontal Approaches
CSF	Cerebrospinal Fluid
EEAs	Endoscopic Endonasal Approaches
GTR	Gross Total Resection
LSFAs	Lateral Sub-frontal Approaches
MITCAs	Minimally Invasive Transcranial Approaches
MTCAs	Microsurgical Transcranial Approaches
NND	New Neurological Deficit
OGMs	Olfactory Groove Meningiomas
PI	Pooled incidence
SIHAs	Superior Interhemispheric Approaches
STR	Subtotal Resection
TENC	Total Extra-Neurological Complications
TSC	Total Surgical Complications

1. Introduction

Meningiomas are estimated to account for about 13–38% of all intracranial tumours (Cea-Soriano et al., 2012), (Ostrom et al., 2020), (Marosi et al., 2008), reflecting a high variability which depends on the reference population with an annual incidence of 1.2/100.000 to 7.8/100.000 and an estimated prevalence of 50.4/100.000 to 70.7/100.000 (Baldi et al., 2018). Anterior Skull Base Meningiomas (ASBMs) such as Olfactory Groove Meningiomas (OGMs) (9–18%) (Demonte et al., 2011) (Liu et al., 2018) (Banu et al., 2016), planum sphenoidale and tuberculum sellae meningiomas (15%) (Bander et al., 2018) comprises an estimated of 20–30% of all intracranial meningiomas. Since described systematically by Cushing (Cushing y and Eisenhardt, 1938), more than 80 years ago, they remain technically challenging lesions to treat surgically.

Over the years, several Microsurgical Transcranial Approaches (MTCAs) have been described in the literature for the surgical resection of symptomatic OGMs, these included: the subfrontal bicoronal uni- or bilateral approach, the basal interhemispheric, the subcranial approach, the pterional, the frontolateral, the fronto-orbital approach and the superior interhemispheric. Emphasis has been placed to gradually develop the so called “Minimally Invasive” Transcranial Approaches (MITCAs), performed under the microscope with or without the aid of endoscopy such as frontal eye-brow, the lateral supraorbital, the eye-lid supraorbital or any variation keyhole supraorbital approaches (DeMonte, 1996), (Paterniti et al., 1999), (Turazzi et al., 1999), (Zevgaridis et al., 2001), (Welge-Luessen et al., 2001), (Obeid et al., 2003), (Mielke et al., 2014), (Spektor et al., 2005), (Tuna et al., 2005), (Bassiouni et al., 2007), (Nakamura et al., 2007), (Colli et al., 2007), (Gazzeri et al., 2008), (El-Bahy, 2009), (de Aguiar et al., 2009), (Romani et al., 2012), (Liu et al., 2018), (Arai et al., 2000), (Ohta et al., 2001), (Fahlbusch y and Schoot, 2002), (Goel et al., 2002), (Pamir et al., 2005), (Nakamura et al., 2006), (Bassiouni et al., 2006), (Ganna et al., 2009), (Hannequin et al., 2015), (Komotar et al., 2012), (Lu et al., 2018) (Reisch y and Perneckzy, 2005) (Reisch et al., 2003) (Roa Montes de Oca et al., 2017). Finally, alongside the MTCAs and MITCAs, the incorporation and spread of emerging Endoscopic Endonasal Approach (EEA) (Gardner et al., 2008), (De Divitiis et al., 2008) augmented the surgical armamentarium and surgical possibilities.

MTCAs may not result in the same rates of surgical success, functional outcomes, surgical complications avoidance, rates of resection or local tumour recurrence in OGMs. For this reason, it appears to us that it would be at some point artificial and not suitable to group all of them into a single group, which is a frequent bias when comparing results and surgical outcomes with series reporting on EEAs (Komotar et al., 2012), (Lu

et al., 2018), (Magill et al., 2018), (Khan et al., 2020). For this purpose, we have divided the surgical routes for OGM surgery as follows.

Anterior Sub-Frontal Approaches (ASFAs) include craniotomies and approaches that create a subfrontal corridor starting from the most ventral aspect of the ASB. These approaches often require a bicoronal incision with a bilateral or unilateral craniotomy. These approaches may be combined with or without orbital osteotomies. Other ASFAs also include the trans-frontal-sinus or trans-glabella subcranial approaches and the transbasal interhemispheric approaches.

Lateral Sub-frontal Approaches (LSFAs) involve all version of fronto-temporal craniotomies, the “so called” Pterional Craniotomies and their variations in size.

The Superior Interhemispheric Approaches (SIHAs) often involve a small bifrontal or a unilateral frontal craniotomy performed rostral to the FS (Roa Montes de Oca et al., 2017).

MITCAs include all the previously described frontal or fronto-temporal minimally invasive small-sized craniotomies that share the principle of the Keyhole Approach (Reisch et al., 2003), (Reisch y and Perneckzy, 2005) from a lateral (lateral supraorbital, fronto-lateral keyhole, supraorbital keyhole endoscopic approaches) or ventral routes (trans-eyebrow supraorbital or eyelid approaches) and can be performed with or without the aid of endoscopy.

EEAs comprise both endoscopic endonasal expanded transsphenoidal and trans-cribriform approaches.

Currently, debate continues regarding the best approach for OGM surgery, and the question remains if there is one approach in particular which can be tailored to these lesions. The goal of the present investigation is, to compare and assess if there are significant differences between the different MTCAs, MITCAs and EEAs, and we set out to weigh and compare clinical and surgical outcomes among the different surgical groups.

2. Methods and materials

On behalf of the EANS Skull Base Section a systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and meta-analysis protocols (PRISMA) (Moher et al., 2009).

2.1. Search strategy

A search strategy was performed using the keywords “meningioma AND (olfactory OR groove)” and “Anterior AND Skull AND Base AND Meningioma”. In Scopus Data Base and Pubmed/Medline from January 1st 1970 until the date of December 31st of 2021.

2.2. Inclusion criteria

- All published reports of patients with OGM in English, Spanish, French, Italian, Portuguese and German.
- All patients with de novo WHO Grade I OGM if distinction was made in the article.
- All patients undergoing surgery.
- All patients with reported surgical outcomes.

2.3. Exclusion criteria

- Animal studies.
- Cadaveric studies.
- Case reports, Letters to the editor/Comments, Reviews.
- Series of cases reporting only the surgical management of recurrences.
- Series of consecutive cases with less than 5 patients per approach.

For case series reporting different approaches, we excluded all the studies that did not report the surgical approach paired with their specific

surgical and functional outcomes.

If available in the reports reviewed, the outcomes of all patients with Grade II-III WHO meningioma and patients who received previous surgical treatment for OGM (recurrences) were excluded.

The searches were performed the August 20, 2022. Duplicate removal was performed with Mendeley Desktop 1.19.18 Software by Mendeley LTD 2008–2022. An independent Title/Abstract search and later full review of studies was performed by authors JCRM and JMGE, if there were any discrepancies in selection it was settled by mutual agreement.

2.4. Data extraction

The variables collected from articles meeting the inclusion criteria comprised the patients' administrative data (age, sex, and follow up). Preoperative clinical signs and symptoms, tumour radiological characteristics (measured in CT scans and/or MRI) were recorded such as size in diameter and/or volume. The following main functional and surgical outcomes were recorded: extent of resection *Gross Total Resection (GTR)*, *Subtotal Resection (STR)*, *Total New Neurological Deficits (NND)*, *Total Surgical Complications (TSC)*, *Total Extra-Neurological/Medical Complications (TENC)*, *Recurrence rates*, and *Mortality rates* as observed at the first 30 days. The following additional secondary surgical and functional outcomes were recorded when available: *Visual improvement*, *Visual stabilization or no change*, *Visual worsening*, *Olfactory Preservation*, *Olfactory Worsening*, *Frontal Syndrome Improvement*, *Postoperative Seizures*, *CSF leak*, *CSF Repairing Surgery*, *Total Hematomas* (this variable includes epidural hematomas, subdural hematomas, postoperative tumour bed hematoma and other surgery related hematomas such as basal ganglia and frontal contusion hematomas after manipulation), *Hydrocephalus*, *Moderate-Severe Postoperative Brain Edema*, *Postoperative Site Infection*, *Meningitis*, *Pulmonary Embolus*, *ACA complex Injury*, *Ischemic lesions* (accounted after ACA complex injury or contusions to frontal lobe) and *Mortality after 30 days and 6 months*.

The World Health Organization (WHO) Central Nervous System (CNS) Tumour Classification in 2016 included brain invasion as a criterion to upgrade Grade 1 tumours to Grade 2 (Louis et al., 2016) this was reaffirmed in 2021 WHO CNS Classification (Louis et al., 2021). All studies before 2016 that reported brain invasion amongst Grade 1 tumours were upgraded accordingly and excluded from the analysis. GTR referred to Simpson's resection grades 1 and 2.

Variables such as *visual improvement* and *frontal dysexecutive syndrome improvement* were in the context of those with preoperative visual and mental alterations/frontal dysexecutive syndrome only. Olfactory functional and/or anatomical preservation was recorded when available.

Visual improvement was recorded when authors reported any significant visual clinical improvement and/or when there was an improvement measured with visual acuity and/or visual fields or with VIS scale. Frontal lobe syndrome/mental alterations improvement were recorded when authors reported any significant clinical improvement in mental/behavioral or frontal dysexecutive syndrome.

New Neurological Deficit was the sum of all new neurological deficits reported such as *visual worsening*, *paresia/hemiparesia*, *postoperative seizures*, *memory problems*, *balance problems*, and some other rare deficits such as III or IV nerve palsy transient or permanent, in this variable we excluded *olfactory worsening*.

2.5. Risk of bias assessment

Publication bias risk was evaluated using Begg's (Begg y and Mazumdar, 1088) test and by generating funnel-plots with and without trim and fill method (Duval and Tweedie, 2000). Studies' quality properties were assessed using the New Castle-Ottawa Scale (NOS) (Wells et al.) which measures cohort and case control studies quality for systematic reviews and meta-analysis. The NOS scale evaluates 3 domains: sample selection, comparability and outcome reporting. An adaptation and modification of the scale was done by eliminating the comparability

domain as all the studies reviewed in this systematic revision were case series. The modified NOS (mNOS) as proposed elsewhere (Khan et al., 2020) with a maximum score of six points (3 points for Selection and 3 points for outcome reporting) with a low risk bias score equal or greater than 4.

2.6. Meta-analysis

Using the library "Meta" of R's Software, version 4.0.0 (R-Team, 2020) a meta-analysis was performed. The pooled incidence of the categorical variables for each surgical approach (ASFA, LSFA, SIHA, MITCA, EEA) was calculated. The random-effects model of Der Simonian and Laird was used in the presence of heterogeneity, the fixed-effects model was utilised when the heterogeneity was not significant (DerSimonian y and Laird, 1986) (DerSimonian y and Laird, 2015). Heterogeneity assessment was performed using the *I*-squared values and the Cochran's *Q* test and it was considered significant when $I^2 > 50\%$ and/or Cochran's $Q = p < 0,10$ (COCHRAN, 1950) (Hozo et al., 2005). A graphic representing the Pooled Incidences (PI) with the Confidence Interval (CI) 95% of the analysed variables according to each surgical group (ASFA, LSFA, SIHA, MITCA and EEA) group was created for qualitative analysis.

We set an arbitrary threshold of 4 cm tumour diameter (<4 cm small and ≥ 4 cm big) as some case series did (Turazzi et al., 1999) (Nakamura et al., 2007) (El-Bahy, 2009) (Lévêque et al., 2011) (Musluman et al., 2012) (Padhye et al., 2012), to set out if there were statistically significant differences in OGM sizes in the qualitative analysis between the surgical approaches.

Likewise, in order to weigh the influence of median tumour size (cross sectional diameter), median age and male sex percentage over each approach and the outcome combination a univariate meta-regression was performed. Although 10 is the minimal ideal threshold, we performed meta-regression if 3 or more studies were available for the approach and secondary outcome combinations and at least 5 studies for approach and main outcome combination on a pragmatic basis to reflect the relative scarce and paucity of main and secondary outcomes in OGM case report series.

3. Results

3.1. Search results

A total of 2741 studies were identified on the primary searches and after duplicate removal 670 studies were screened. Applying the inclusion and exclusion criteria 513 studies were excluded and full text article reviews included 157 studies of which 104 were excluded for different reasons detailed in PRISMA flow diagram and finally 53 studies were included for final data collection and review; for ASFA group the studies reviewed were (Bakay, 1984), (Bakay y and Cares, 1972), (Tsikoudas y and Martin-Hirsch, 1999), (Tamaki y and Yin, 1999), (El Gindi, 2000), (Welge-Luessen et al., 2001), (Lagares et al., 2001), (Hallacq et al., 2001), (DeMonte, 2003), (Obeid et al., 2003), (Spektor et al., 2005), (De Tella et al., 2006), (Bassiouni et al., 2007), (Colli et al., 2007), (Nakamura et al., 2007), (Gazzeri et al., 2008), (Bouaziz et al., 2009), (González-Darder et al., 2011), (Refaat et al., 2015), (De Almeida et al., 2015), (Pallini et al., 2015), (Nanda et al., 2016), (Barzaghi et al., 2017), (Guduk et al., 2017), (Farooq et al., 2018), (Goel et al., 2018), (Liu et al., 2018), (Patel et al., 2019), (Xu et al., 2019), (Zenga et al., 2020), (Ottenhausen et al., 2018), for LSFA; (Schaller et al., 1994), (Zentner, 1989), (Turazzi et al., 1999), (Paterniti et al., 1999), (Spektor et al., 2005), (Bassiouni et al., 2007), (Nakamura et al., 2007), (Tomasello et al., 2011), (Bitter et al., 2013), (Della Puppa et al., 2015), (Nanda et al., 2016), (Pallini et al., 2015), (Guduk et al., 2017), for SIHA; (Lévêque et al., 2011), (Mayfrank y and Gilsbach, 1996), (Mielke et al., 2014), (Musluman et al., 2012), for MITCAs; (Bassiouni et al., 2007), (Nakamura et al., 2007), (El-Bahy, 2009), (Romani et al., 2009), (Telera et al., 2012), (Banu et al., 2016), (Eroglu et al., 2019), (Dedeciusova et al., 2020),

Table 1
Summary of the administrative and general clinical variables.

	n	ASFAs	LSFAs	SIHAs	MITCAs	EEAs
<i>Administrative Data</i>						
N° of studies	64	31	12	3	11	7
N° of patients	1555	864	309	118	181	83
Median Female % (min-max) (N Studies)	69.2 (61.2–79.4) (61)	72.7 (60.0–80.0) (29)	66.6 (65.4–71.8) (12)	64.2 (360.7–71.8) (0)	66.6 (56.3–76.7) (11)	80 (72.5–95) (6)
Median Male % (min-max) (N° Studies)	30.7 (21.0–40.2) (59)	26.7 (20.0–40.4) (28)	33.3 (30.3–34.9) (11)	35.7 (328.1–39.2) (0)	33.3 (23.3–48.5) (11)	20 (5–27.5) (6)
Median Mean Age (min-max) (N° Studies)	56.0 (51.0–59.0) (58)	54.0 (51.0–56.7) (27)	57.0 (53.5–59.5) (11)	62.0 (360.5–62.9) (0)	57.0 (53.5–59) (11)	55.0 (53.2–64.7) (6)
Median Mean Months of clinical following (min-max) (N° Studies)	45.0 (31.5–63.4) (49)	59.2 (39.5–67.2) (21)	65.3 (46.2–76.4) (8)	54.4 (253.2–55.6) (0)	31.5 (24.8–39.4) (11)	32.0 (23.3–45.5) (7)
Median Mean Years of clinical following (min-max) (N° Studies)]	4.0 (2.6–5.3) (52)	4.9 (3.2–5.5) (22)	5.4 (4.3–7.0) (10)	4.5 (4.4–4.6) (2)	2.6 (2.0–3.2) (11)	2.6 (71.9–3.8) (0)
<i>Clinical Data</i>						
Median Visual Disturbances % (min-max) (N° Studies)	38.3 (27.5–47.1) (40)	44.5 (37.8–60.0) (20)	40.2 (31.1–42.8) (6)	38.2 (35.7–46.5) (3)	26.6 (21.5–28.1) (7)	25.3 (19.1–32.9) (4)
Median Hiposmia/Anosmia % (min-max) (N° Studies)	57.2 (38.3–74.7) (40)	58.2 (41.6–74.5) (20)	64.7 (52.5–93.2) (6)	55.8 (50.5–60.1) (3)	55.9 (39.5–71.4) (6)	20.0 (16.6–100) (5)
Median Mental Alterations % (min-max) (N° Studies)	50.0 (35.1–66.6) (36)	51.7 (34.0–65.1) (19)	71.4 (41.4–72.9) (5)	52.3 (51.1–59.5) (3)	42.2 (20.0–56.1) (6)	36.7 (28.3–43.3) (3)
<i>Tumor diameter</i>						
Median Size <40 mm % (min-max) (N° Studies)	34.7 (0.0–55.7) (38)	14.7 (0.0–23.4) (19)	38.3 (12.4–50.7) (7)	25.8 (19.2–33.8) (2)	48.1 (35.6–59.1) (7)	46.8 (42.4–55.7) (3)
<i>Quality of the studies</i>						
Median mNOS score		5.0	5.1	5,6	5.0	5.0

(Youngerman et al., 2020), (Gandhoke et al., 2017), (de Paiva-Neto y and Tella, 2010) for EEAs (Padhye et al., 2012), (Koutourousiou et al., 2014), (De Almeida et al., 2015), (Zoli et al., 2018), (Liu et al., 2018), (Banu et al., 2016), (Gardner et al., 2008), (Ottenhausen et al., 2018). All of the articles were retrospective except in one case (Dedeciusova et al., 2020).

The studies that reported different approaches paired with the different outcomes for each approach were statistically treated as multiple studies. Those studies were: (Spektor et al., 2005), (Bassiouni et al., 2007), (Nakamura et al., 2007), (De Almeida et al., 2015), (Pallini et al., 2015), (Nanda et al., 2016), (Guduk et al., 2017), (Liu et al., 2018), (Banu et al., 2016), (Ottenhausen et al., 2018). Duplicate cohort studies published in subsequent years by same authors were reviewed and treated as a single study (Gardner et al., 2008) (Koutourousiou et al., 2014); (Mayfrank y and Gilsbach, 1996) (Mielke et al., 2014); (Schaller et al., 1994) (Zentner, 1989) and (Ottenhausen et al., 2018) (Youngerman et al., 2020), with the objective of collecting all variables and avoid possible bias or omissions in the last studies.

In total, while the data was extracted from 53 articles, accounting the multi-approaches studies as multiple studies and reducing duplicate cohort studies as single studies a total of 64 studies were statistically treated for qualitative analysis.

3.2. Administrative, clinical and quality results

The measures of central tendency and dispersion used were the Median (M) and the Interquartile Range (IR). A total of 64 studies and 1555 patients were included in this review. Median female rate was 69% and median mean age was 56 years old. Median Follow-up was 45 months. Median rate for visual disturbances was 38%, for hyposmia/Anosmia it was 57%, for mental alterations it was 50%. A median tumour size <40 mm was present in 24% of patients and the median mean diameter of OGMs was 46 mm. Summary characteristics per approach are shown in Table 1.

Overall quality of the studies was appropriate (punctuation >4) and homogeneous between surgical groups (mean = 5), according to the criteria of the modified NOS scale criteria (Table 1).

3.3. Meta-analysis and meta-regression results

The following section describes the results of the PI of each variable as

it relates to the distinct surgical groups. To study the differences of PI between each surgical group, a CI of 95% was used. Each variable is presented in a graphic forest plot with the PI by approach and their respective CI at 95% in Figs. 1 and 2. If the CIs overlapped, statistically significant differences were not considered valid. All comparisons were reported and no mathematical correction was made for multiple comparisons.

For the purpose of a practical read we decided to describe only the main and secondary surgical outcomes that resulted in a statistically significant difference. Surgical outcomes are shown in: Fig. 1 (forest plot PI of main outcomes), Fig. 2 (forest plot PI of secondary outcomes), appendix A (meta-regression results), appendix B (PI and heterogeneity measures), Appendix C (Begg's test results), Appendix D and E (raw funnel plots and forest plots respectively) and most importantly Table 2 which contains all the summarized data.

3.4. Gross Total Resection

GTR PI was greater in LSFAs 99.1% (95% CI 97.5–100) followed by SIHAs with 98.6% (95% CI 96.1–100); ASFAs with 93.0% (95% CI 89.9–96.2); MITCAs with 84.7% (95% CI 62.8–100) and EEAs with 78.8% (95% CI 62.1–95.6). Study heterogeneity was likely in ASFAs ($I^2 = 75.4%$, Cochran $p < 0.001$); in MITCAs ($I^2 = 97.3%$, Cochran $p < 0.001$) and EEAs ($I^2 = 64.3%$, Cochran $p = 0.009$). Begg's test suggested publication bias in ASFAs ($p = 0.001$) and LSFAs ($p = 0.003$). Raw funnel plots showed marked asymmetry in MITCAs with some changes in summary effects (likely reflective of heterogeneity and publication bias). **Statistically significant differences were found between studies reporting on LSFAs and those of ASFAs and EEAs with a greater PI in the LSFA group. Similarly, statistically significant differences were observed between SIHAs and EEAs with a greater PI in the SIHAs group. Meta-regression in the domain of GTR shows in EEAs group a trend to statistical significance for younger aged patients $p = 0.055$ (-0.032 95% CI - 0.065–0.001) and statistically significant differences minor tumour diameter $p = 0.010$ (-0.042 CI 95% -0.074 - -0.001).**

3.5. Subtotal Resection

STR PI was greater in EEAs with 21.1% (95% CI 4.4–37.8) followed

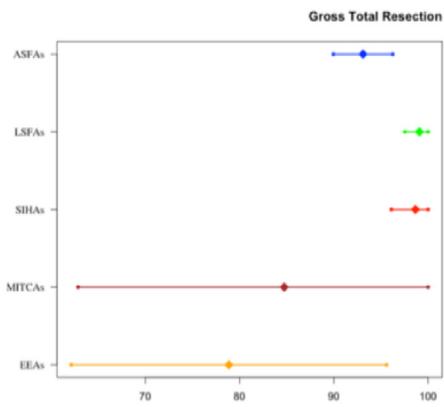


Figure 1A. Mean Pooled Incidence at 95% CI of GTR
+++

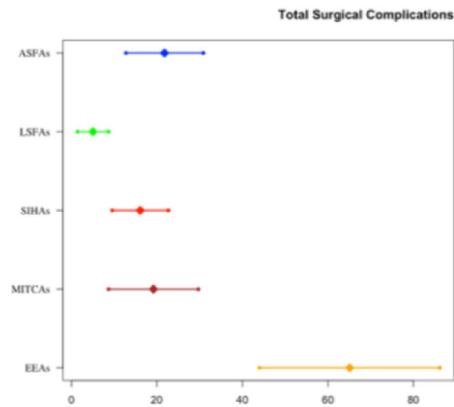


Figure 1E. Mean Pooled Incidence at 95% CI of Total Surgical Complications
+++

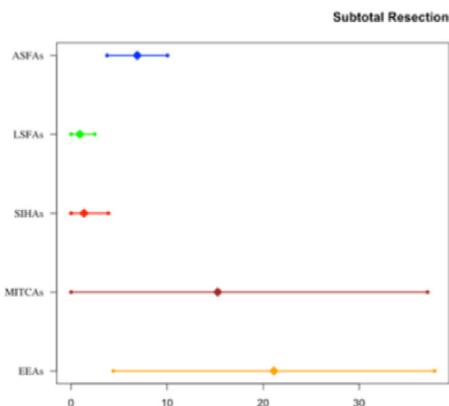


Figure 1B. Mean Pooled Incidence at 95% CI of STR
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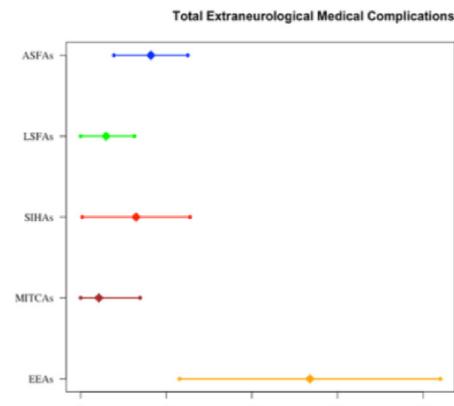


Figure 1F. Mean Pooled Incidence at 95% CI of Total extra neurological Medical Complications
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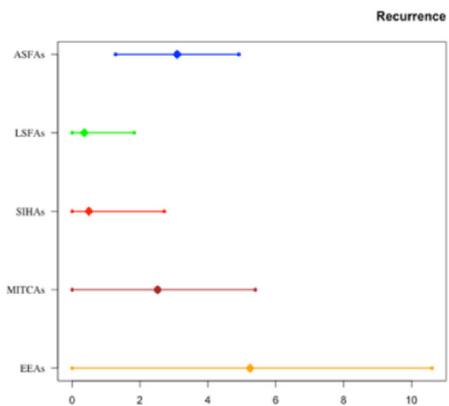


Figure 1C. Mean Pooled Incidence at 95% CI of Recurrence

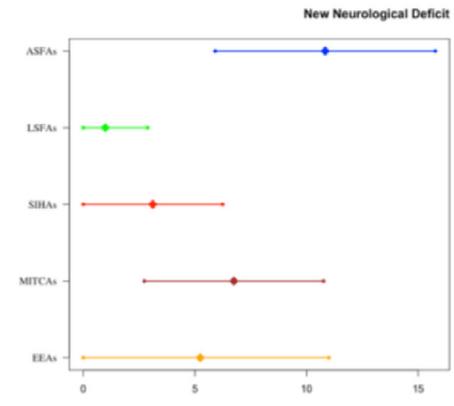


Figure 1G. Mean Pooled Incidence at 95% CI of 95% New Neurological Deficits.
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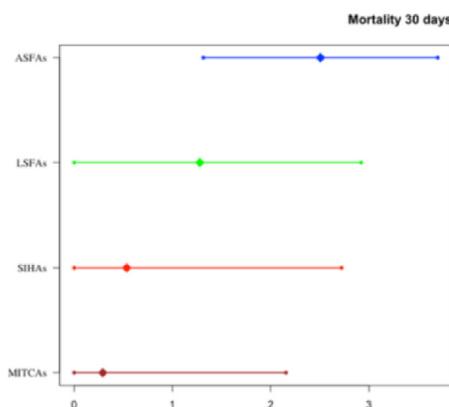


Figure 1D. Mean Pooled Incidence at 95% CI of Mortality at 30 days.

+++ = Statistically Significant Differences in PI

Fig. 1. Main Outcomes.

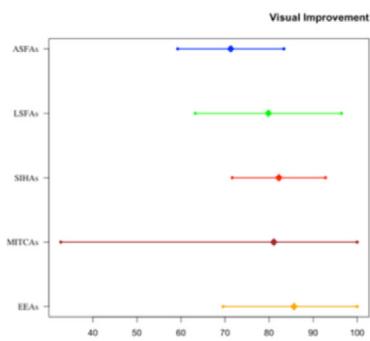


Figure 2A. Mean Pooled Incidence at 95% CI of Visual Improvement.

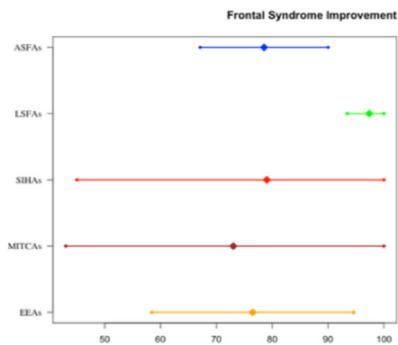


Figure 2F. Mean Pooled Incidence at 95% CI of Frontal Dysexecutive Syndrome Improvement
+++

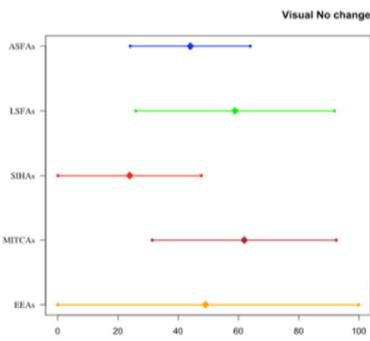


Figure 2B. Mean Pooled Incidence at 95% CI of Visual No Change.

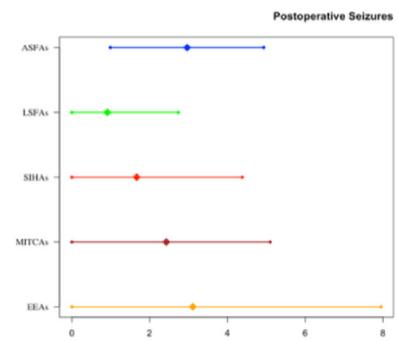


Figure 2G. Mean Pooled Incidence at 95% CI of Postoperative Seizures.

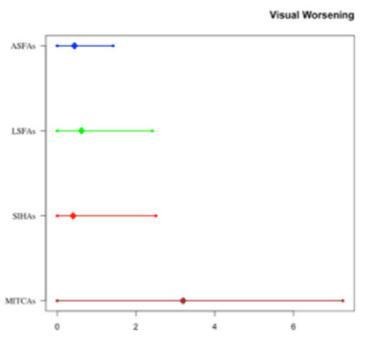


Fig. 2C. Mean Pooled Incidence at 95% CI of Visual Worsening.

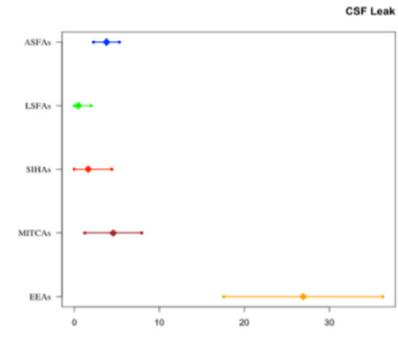


Figure 2H. Mean Pooled Incidence at 95% CI of CSF Leak
+++

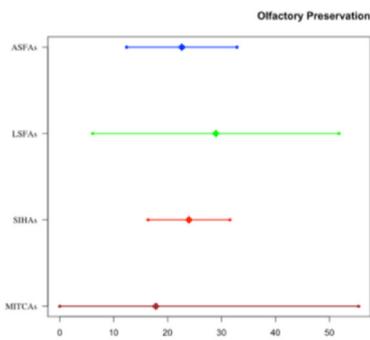


Figure 2D. Mean Pooled Incidence at 95% CI of Olfactory Preservation.

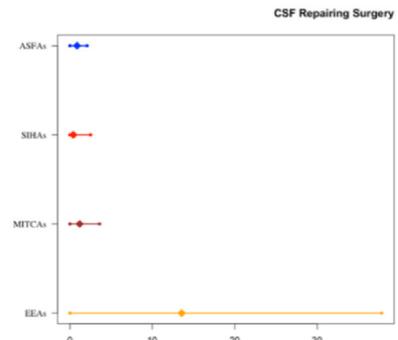


Figure 2I. Mean Pooled Incidence at 95% CI of CSF Leak Repairing Surgery.

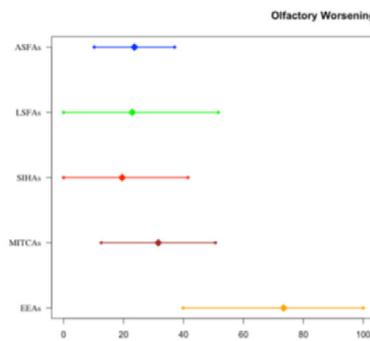


Figure 2E. Mean Pooled Incidence at 95% CI of Olfactory Worsening.
+++

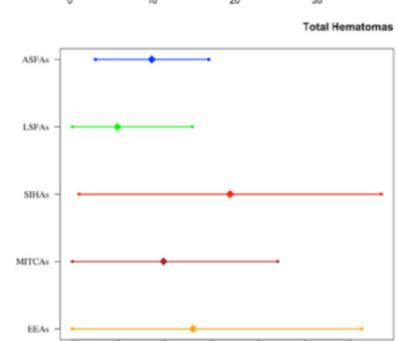


Figure 2J. Mean Pooled Incidence at 95% CI of Total Hematomas.

Fig. 2. Secondary Outcomes.

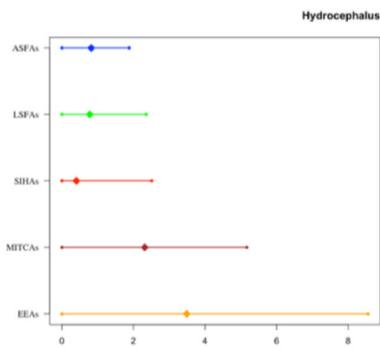


Figure 2K. Mean Pooled Incidence at 95% CI of Hydrocephalus.

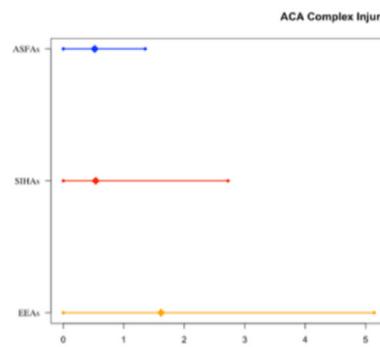


Figure 2O. Mean Pooled Incidence at 95% CI of ACA Complex Injury.

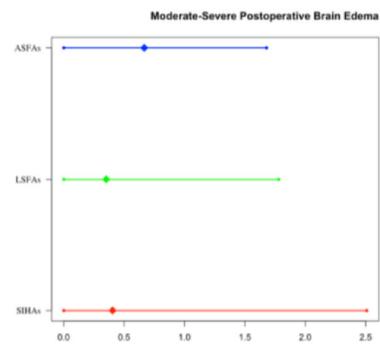


Figure 2L. Mean Pooled Incidence at 95% CI of Postoperative Brain Edema.

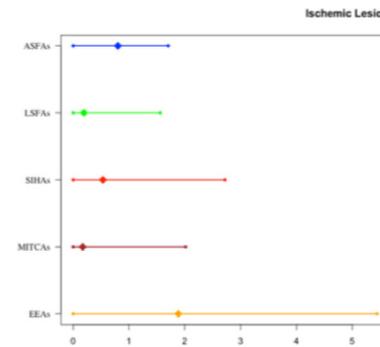


Figure 2P. Mean Pooled Incidence at 95% CI of Ischemic Lesion.

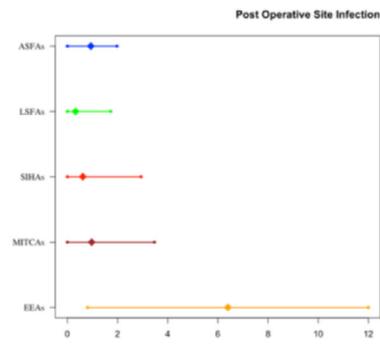


Figure 2M. Mean Pooled Incidence at 95% CI of Postoperative Site Infection.

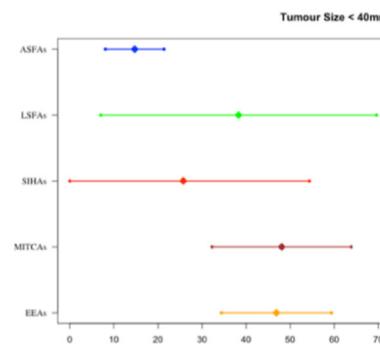


Figure 2Q. Mean Pooled Incidence at 95% CI of Tumour Size < 40mm. +++

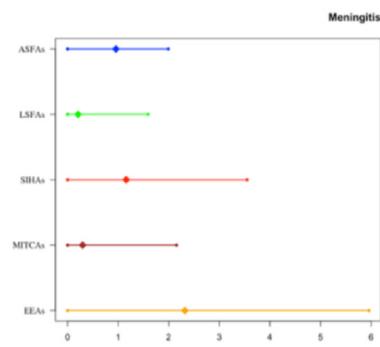


Figure 2N. Mean Pooled Incidence at 95% CI of Meningitis.

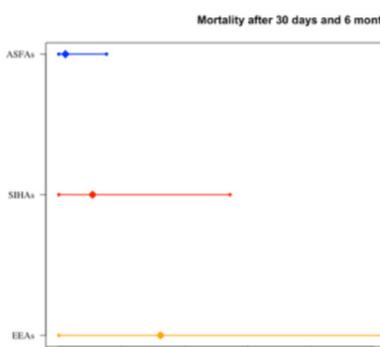


Figure 2R. Mean Pooled Incidence at 95% CI of Mortality after 30 days and 6 months

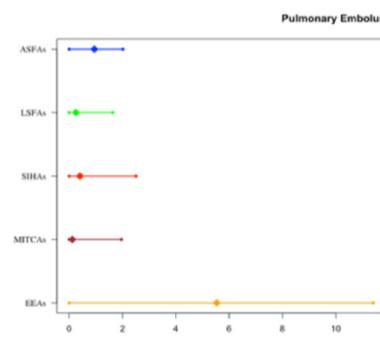


Figure 2Ñ. Mean Pooled Incidence at 95% CI of Pulmonary Embolus.

+++ = Statistically Significant Differences in

Fig. 2. (continued).

Table 2

	ASFAs	LSFAs	SIHAs	MITCAs	EEAs
Gross Total Resection					
N° studies/patients	30/839	12/309	3/118	11/181	7/83
Pooled Incidence	93.0%	99.1%*	98.6%*	84.7%	78.8%
Statistically significant heterogeneity	p<0.001	NS	NS	p<0.001	p=0.009
PI Statistically significant differences					
PI Statistically significant differences					
Begg's test	p=0.001	p=0.003	p=0.117	p=0.052	p=0.759
Subtotal Resection					
N° studies/patients	30/839	12/309	3/118	11/181	7/83
Pooled Incidence	6.9%*	0.9%	1.3%	15.2%	21.1%*
Statistically significant heterogeneity	p<0.001	NS	NS	p<0.001	p=0.010
Statistically significant differences at 95% CI in PI	NS			NS	
Statistically significant differences at 95% CI in PI			NS	NS	NS
Begg's test	p=0.001	p=0.003	p=0.117	p=0.052	p=0.759
Recurrence					
N° studies/patients	26/800	11/281	3/118	11/181	7/83
Pooled Incidence	3.1%	0.3%	0.5%	2.5%	5.2%
Statistically significant heterogeneity	p=0.017	NS	NS	NS	NS
Statistically significant differences at 95% CI	NS	NS	NS	NS	NS
Begg's test	p=0.036	p=0.001	p=0.157	p=0.139	p=0.271
Mortality at 30 days					
N° studies/patients	31/864	12/309	3/118	11/181	7/83
Pooled Incidence	2.5%	1.2%	0.5%	0.3%	++
Statistically significant heterogeneity	NS	NS	NS	NS	++
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	++
Begg's test	p=0.025	p=0.170	p=0.117	p=0.003	++
Total Surgical Complications					
N° studies/patients	30/854	12/309	3/118	11/181	7/83
Pooled Incidence	21.8%*	5.0%	16.1%*	19.2%	65.0%*
Statistically significant heterogeneity	p<0.001	p=0.020	NS	p<0.001	p<0.001
Statistically significant differences at 95% CI in PI					
Statistically significant differences at 95% CI in PI	NS			NS	NS
Statistically significant differences at 95% CI in PI			NS	NS	NS
Begg's test	p=0.038	p=0.040	p=0.602	p=0.586	p=0.759
Total Extra-Neurological Medical Complications					
N° studies/patients	29/725	12/309	3/118	11/181	7/83
Pooled Incidence	4.1%	1.4%	3.2%	1.1%	13.4%*
Statistically significant heterogeneity	p=0.008	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS				
Begg's test	p=0.006	p=0.020	p=0.157	p=0.028	p=0.759
New Neurological Deficit					
N° studies/patients	22/475	9/230	3/118	11/181	6/78
Pooled Incidence	10.8%*	0.9%	3.1%	6.7%	5.2%
Statistically significant heterogeneity	p=<0.001	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI			NS	NS	NS
Begg's test	p=0.007	p=0.037	p=0.117	p=0.876	p=0.573
Visual Improvement					
N° studies/patients	12/328	5/177	3/118	5/100	3/60
Pooled Incidence	71.3%	79.8%	82.2%	81.0%	85.6%
Statistically significant heterogeneity	p<0.001	p=0.002	NS	p<0.001	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p=0.674	p=0.327	p=0.602	p=0.624	p=0.602
Visual No Change					
N° studies/patients	12/202	6/191	3/118	5/100	4/63
Pooled Incidence	44.0%	58.8%	23.8%	61.9%	49.0%
Statistically significant heterogeneity	p<0.001	p<0.001	p<0.001	p<0.001	p<0.001
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p=0.273	p=0.348	p=0.117	p=1.000	p=0.279
Visual Worsening					

N° studies/patients	15/369	6/191	3/118	6/113	7/83
Pooled Incidence	0.4%	0.6%	0.4%	3.2%	++
Statistically significant heterogeneity	NS	NS	NS	NS	++
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	++
Begg's test	p=0.017	p=0.039	p=0.157	p=0.573	++
Olfactory Preservation					
N° studies/patients	9/153	4/124	3/118	2/20	7/83
Pooled Incidence	22.6%	29.0%	24.0%	17.8%	++
Statistically significant heterogeneity	p=0.014	p<0.001	NS	p=0.016	++
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	++
Begg's test	p=0.835	p=0.497	p=0.602	-	++
Olfactory Worsening					
N° studies/patients	10/166	3/73	3/118	5/104	6/73
Pooled Incidence	23.6%	22.9%	19.5%	31.6%	73.4%*
Statistically significant heterogeneity	p<0.001	p<0.001	p<0.001	p=0.002	p<0.001
Statistically significant differences at 95% CI in PI					
Begg's test	0.009	0.602-	0.117	0.142	0.573
Frontal Dysexecutive Syndrome Improvement					
N° studies/patients	11/314	4/124	2/84	5/56	2/55
Pooled Incidence	78.5%	97.3%*	79.0%	73.0%	76.5%
Statistically significant heterogeneity	p<0.001	NS	p<0.001	p=0.03	NS
Statistically significant differences at 95% CI in PI			NS	NS	NS
Begg's test	p=0.312	p=0.042	-	p=0.142	-
Postoperative Seizures					
N° studies/patients	23/605	10/251	3/118	11/181	6/73
Pooled Incidence	2.9%	0.9%	1.6%	2.4%	3.1%
Statistically significant heterogeneity	p=0.04	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p=0.050	p=0.025	p=0.117	p=0.060	p=0.545
CSF Leak					
N° studies/patients	28/713	12/309	3/118	11/181	7/83
Pooled Incidence	3.8%*	0.4%	1.6%	4.5%	26.9%*
Statistically significant heterogeneity	NS	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI			NS	NS	NS
Begg's test	p=0.005	p=0.002	p=0.602	p=0.159	p=0.539
CSF Repairing Surgery					
N° studies/patients	21/508	12/309	3/118	11/181	3/56
Pooled Incidence	0.8%	++	0.4%	1.1%	13.5%
Statistically significant heterogeneity	NS	++	NS	NS	p=0.038
Statistically significant differences at 95% CI in PI	NS	++	NS	NS	NS
Begg's test	p=0.002	++	p=0.157	p=0.016	p=0.602
Total Hematomas					
N° studies/patients	28/713	12/309	3/118	11/181	7/83
Pooled Incidence	1.7%	0.9%	3.4%	1.9%	2.6%
Statistically significant heterogeneity	NS	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p=0.018	p=0.009	p=0.117	p=0.433	p=0.006
Hydrocephalus					
N° studies/patients	28/713	12/309	3/118	11/181	7/83
Pooled Incidence	0.8%	0.8%	0.4%	2.3%	3.5%
Statistically significant heterogeneity	NS	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p<0.001	p=0.006	p=0.157	p=0.273	p=0.271
Moderate-Severe Postoperative Brain Edema					
N° studies/patients	28/713	12/309	3/118	11/181	7/83
Pooled Incidence	0.6%	0.4%	0.3%	++	++
Statistically significant heterogeneity	NS	NS	NS	++	++
Statistically significant differences at 95% CI in PI	NS	NS	NS	++	++
Begg's test	p<0.001	p<0.001	p=0.157	++	++
Post-Operative Site Infection					
N° studies/patients	28/713	12/309	3/118	11/181	7/83

Pooled Incidence	0.9%	0.3%	0.6%	0.9%	6.4%
Statistically significant heterogeneity	NS	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p<0.001	p<0.001	p=0.117	p=0.005	p=0.453
Meningitis					
N° studies/patients	28/713	12/309	3/118	11/181	7/83
Pooled Incidence	0.9%	0.2%	1.1%	0.3%	2.3%
Statistically significant heterogeneity	NS	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p<0.001	p<0.001	p=0.117	p<0.001	p=0.125
Pulmonary Embolus					
N° studies/patients	28/713	12/309	3/118	11/181	7/83
Pooled Incidence	0.9%	0.2%	0.4%	0.1%	5.5%
Statistically significant heterogeneity	NS	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p=0.001	p<0.001	p=0.157	p<0.001	p=0.357
ACA complex injury					
N° studies/patients	29/842	12/309	3/118	11/181	7/83
Pooled Incidence	0.5%	++	0.5%	++	1.6%
Statistically significant heterogeneity	NS	++	NS	++	NS
Statistically significant differences at 95% CI in PI	NS	++	NS	++	NS
Begg's test	p<0.001	++	p=0.117	++	p=0.271
Ischemic Lesion					
N° studies/patients	29/842	12/309	3/118	11/181	7/83
Pooled Incidence	0.8%	0.2%	0.5%	0.1%	1.9%
Statistically significant heterogeneity	NS	NS	NS	NS	NS
Statistically significant differences at 95% CI in PI	NS	NS	NS	NS	NS
Begg's test	p<0.001	p<0.001	p=0.117	p<0.001	p=0.219
Tumour Diameter Size <40mm					
N° studies/patients	19 /639	7/205	2/76	7/134	3/60
Pooled Incidence	14.7%	38.2%	25.8%	48.1%*	46.8%*
Statistically significant heterogeneity	p<0.001	p<0.001	p=0.003	p=0.005	NS
Statistically significant differences at 95% CI in PI		NS	NS	NS	
Statistically significant differences at 95% CI in PI		NS	NS		NS
Begg's test	p=0.123	p=0.176	-	p=0.051	p=0.602
Mortality after 30 days and 6 months					
N° studies/patients	31/864	12/309	3/118	7/83	7/83
Pooled Incidence	0.1%	++	0.5%	++	1.6%
Statistically significant heterogeneity	NS	++	NS	++	NS
Statistically significant differences at 95% CI in PI	NS	++	NS	++	NS
Begg's test	p<0.001	++	p=0.117	++	p=0.271

Studies:

- Red color = statistically significant heterogeneity.
- Bold (red or black color) = statistically significant differences in Begg's test
- * = Statistical difference at 95% CI in PI.
- Green colored square = statistically significant differences at 95% CI PI meaning a better outcome than the red colored square approach.
- Red colored square = statistically significant differences at 95% CI PI meaning a worse outcome than the green colored squared approach.
- - = Not available for analysis
- NS = No Statistical Significance.
- NV= No variability (no heterogeneity)
- ++ Non calculable since value=0

by MITCAs with 15.3% (95% CI 0–37.1); ASFAs with 6.9% (95% CI 3.7–10.0); SIHAs with 1.3% (95% CI 0–3.8) and LSFAs with 0.9% (95% CI 0–2.4). Study heterogeneity was likely in ASFAs ($I^2 = 75.4%$, Cochran $p < 0.001$); MITCAs ($I^2 = 97.3%$, Cochran $p < 0.001$) and EEAs ($I^2 = 67.8%$, Cochran $p = 0.009$). Begg's test suggested publication bias in ASFAs ($p = 0.001$) and LSFAs ($p = 0.003$). ASFAs and MITCAs presented asymmetry in raw funnel plots with some changes in summary effects (likely reflective of heterogeneity and publication bias). **Statistically significant differences were found between EEAs and the two groups representing LSFAs and SIHAs with a greater PI of STR for EEAs. Similarly, a statistically significant difference was found between LSFAs and ASFAs with greater PI of STR in the latter. Meta-regression showed a trend to statistical significance for subtotal resection in the EEA group in older ages $p = 0.055$ (0.032 95% CI - 0.001–0.065) and statistically significant differences for subtotal resection in patients with greater tumour diameters $p = 0.010$ (0.042 CI 95% 0.01–0.074).**

3.6. Total Surgical Complications

The PI was greater in EEAs with 65.0% (95% CI 43.9–86.1) followed by ASFAs with 21.8% (95% CI 12.7–30.8); MITCAs 19.2% (95% CI 8.6–29.7); SIHAs with 16.1% (95% CI 9.5–22.7) and LSFAs 5.0% (95% CI 1.3–8.7). Heterogeneity was likely in ASFAs ($I^2 = 93.7%$, Cochran $p < 0.001$); LSFAs ($I^2 = 52%$, Cochran $p < 0.019$); MITCAs ($I^2 = 70.2%$, Cochran $p < 0.001$) and EEAs ($I^2 = 75.7%$, Cochran $p < 0.001$). Begg's test suggested publication bias in ASFAs ($p = 0.038$), LSFAs ($p = 0.040$). Asymmetry was observed particularly in ASFAs and MITCAs in raw funnel plots without major changes in summary effects (likely reflective of heterogeneity and publication bias). **Statistically significant differences in the PI between EEAs and the rest of approaches were found being the PI greater in the EEAs. Such difference was also detected between LSFAs and the groups of SIHAs and ASFAs with a minor PI in the LSFAs group. Meta-regression showed in EEAs statistically significant differences for female sex $p = 0.002$ (-1.06 95% CI - 1.721 - -0.398) as well as for older aged patients $p = 0.037$ (0.023 CI**

95% 0.001–0.044).

3.7. Total extra-neurological medical complications

The PI was greater in EEAs with 13.4% (95% CI 5.7–21.0) followed by ASFAs with 4.1% (95% CI 1.9–6.2); SIHAs with 3.2% (95% CI 0.1–6.4); LSFAs with 1.4% (95% CI 0–3.1) and MITCAs with 1.0% (95% CI 0–3.4). Heterogeneity was likely in ASFAs ($I^2 = 43.0\%$, Cochran $p = 0.008$). Begg's test suggests publication bias in ASFAs ($p = 0.006$), LSFAs ($p = 0.020$) and MITCAs ($p = 0.028$). Mild asymmetry is evident in ASFAs and LSFAs in raw funnel plots without major changes in summary effects (likely reflective of heterogeneity). **Statistically significant differences were identified in PI between EEAs and the groups of LSFAs and MITCAs with a lesser PI in the latter. Meta-regression showed in EEAs statistically significant differences for older age $p = 0.029$ (0.028 95% CI 0.003–0.052) and for larger tumour diameter $p = 0.007$.**

3.8. New neurological deficits

The PI was greater in ASFAs with 10.8% (95% CI 5.9–15.7), followed by MITCAs with 6.7% (95% CI 2.7–10.7); EEAs with 5.2% (95% CI 0–11.0); SIHAs with 3.1% (95% CI 0.0–6.2) and for LSFAs 0.9% (95% CI 0–2.9). Heterogeneity was likely in ASFAs ($I^2 = 76.8\%$, Cochran $p < 0.001$). Begg's test suggested publication bias in ASFAs ($p = 0.007$) and LSFAs ($p = 0.037$). Raw funnel plots showed in ASFAs asymmetry with some changes in summary effects using trim and fill method (Likely reflective of heterogeneity and publication bias). **Statistically significant were found between ASFAs and LSFAs with a minor PI of New Neurological Deficit in the latter.**

3.9. Olfactory Worsening

The PI was greater in EEAs with 73.4% (95% CI 39.8–100) followed by MITCAs with 31.6% (95% CI 12.5–50.6); ASFAs with 23.6% (95% CI 10.2–37.1); LSFAs with 22.9% (95% CI 0–51.6) and SIHAs with 19.5% (95% CI 0–41.5). Heterogeneity was likely in ASFAs ($I^2 = 87.1\%$, Cochran $p = 0.001$); LSFAs ($I^2 = 91.6\%$, Cochran $p < 0.001$); SIHAs ($I^2 = 91.9\%$, Cochran $p < 0.001$); MITCAs ($I^2 = 76.1\%$, Cochran $p = 0.002$) and EEAs ($I^2 = 92.7\%$, Cochran $p < 0.001$). Begg's tests results do not show publication bias, nevertheless, asymmetry was observed in raw funnel plots with changes in summary effects using trim and fill method possibly reflecting publication bias and heterogeneity in all of the surgical groups. **Statistically significant differences of PI at CI 95% were found between ASFAs and EEAs with a greater PI of olfactory worsening in the latter. Meta-regression suggests higher Olfactory Worsening in the ASFAs subgroup for older aged patients; $p = 0.047$ (0.071 CI 95% 0.001–0.141) and for patients with smaller tumour diameter $p < 0.001$ (–0.013 CI 95% –0.019 – 0.001).**

3.10. Frontal dysexecutive syndrome/mental alterations improvement

The PI was greater in LSFAs with 97.3% (95% CI 93.4–100) followed by SIHAs with 79.0% (95% CI 45.0–100); ASFAs with 78.5% (95% CI 67.1–90.0); EEAs with 76.5% (95% CI 58.4–94.5) and MITCAs with 73.0% (95% CI 43.0–100). Heterogeneity was likely in ASFAs ($I^2 = 82.3\%$, Cochran $p < 0.001$), in SIHAs ($I^2 = 91.3\%$, Cochran $p < 0.001$) and in MITCAs ($I^2 = 62.6\%$, Cochran $p = 0.03$). Begg's test suggests publication bias for LSFAs ($p = 0.042$). Conversely, asymmetry was observed in raw funnel plots with some changes in summary effects using trim and fill method in ASFAs, LSFAs and MITCAs groups possibly reflecting publication bias. **Statistically significant differences were found at 95% CI between ASFAs and LSFAs with a greater PI of Frontal Syndrome Improvement in the LSFAs. Meta-regression suggests significant frontal syndrome improvement in the ASFAs subgroup for older aged patients; $p = 0.006$ (0.071 CI 95%**

0.021–0.122).

3.11. CSF leak

The PI was greater in EEAs with 26.9% (95% CI 17.5–36.3) followed by MITCAs with 4.5% (95% CI 1.2–7.9); ASFAs with 3.8% (95% CI 2.2–5.3); SIHAs 1.6% (95% CI 0–4.4) and LSFAs 0.5% (95% CI 0.0–1.9). Heterogeneity was not likely in any surgical group. Begg's test suggests publication bias in ASFAs ($p = 0.005$) and LSFAs ($p = 0.002$). Mild asymmetry was observed in SIHAs and EEAs in raw funnel plots with some changes in summary effects using trim and fill method possibly reflecting heterogeneity and publication bias. **Between EEAs and all other open surgical groups, statistically significant differences were found at 95% CI with a greater PI of CSF leak in the EEAs. Statistically significant differences at 95% CI were also detected between LSFAs and ASFAs with a greater PI of CSF leak in the latter.**

3.12. Tumour diameter size < 40 mm

The PI of patients with tumours diameters smaller than 40 mm was greater in MITCAs with a PI of 48.1% (95% CI 32.3–63.8) followed by EEAs with 46.8% (95% CI 34.3–59.3); LSFAs with 38.3% (95% CI 7.0–69.6); SIHAs with 25.8% (95% CI 0.0–53.9%) and ASFAs with 14.7% (95% CI 7.6–19.9). Heterogeneity was likely in ASFAs ($I^2 = 87.8\%$, Cochran $p < 0.001$), in LSFAs ($I^2 = 98.2\%$, Cochran $p < 0.001$), in SIHAs ($I^2 = 88.7\%$, Cochran $p = 0.003$) and MITCAs ($I^2 = 67.9\%$, Cochran $p = 0.005$). Begg's test did not show publication bias; however, asymmetry was observed ASFAs, LSFAs and MITCAs groups in raw funnel plots with mild changes in summary effects using trim and fill method possibly suggesting publication bias. **Statistically significant differences were found at 95% CI in PI in patients with tumour sizes lesser than 40 mm between ASFAs and the groups of MITCAs and EEAs with a greater PI in the latter. Meta-regression showed in ASFAs statistically significant differences for male sex $p = 0.032$ (0.631 95% CI 0.053–1.209) and a tumour diameter <40 mm. Similarly, in MITCAs there was a trend to statistical significance for younger age and tumour diameter < 40 mm $p = 0.063$ (–0.053 95% CI –0.109–0.003).**

4. Discussion

4.1. Main findings

To date, some systematic reviews on OGMs included also tuberculoma sellae meningiomas collectively grouped into ASBMs operated through various transcranial approaches summarized as MTCA (Khan et al., 2020) (Komotar et al., 2012) (Lu et al., 2018) (Muskens et al., 2018) (Purohit et al., 2019) (Ruggeri et al., 2016) (Shetty et al., 2017) (Tables 3 and 4). This situation is rather simplistic and introduces an important bias in the proper assessment of the role of the different MTCAs in OGM surgery as undertaken in this review. The objective of this analysis was to differentiate OGM among other ASBMs and to perform a specific analysis among the various transcranial procedures, in order to extend the discussion more than to a debate “from above or from below”. Until now, it has been difficult to distinguish which single approach/surgical route was superior or inferior with respect to a particular aspect of interest, or if they were all equal because the MTCAs were grouped into a single aggregate.

In the primary and secondary surgical and functional outcomes of OGM surgery assessed in this review, statistically significant differences were found in respectively 5 and 4 variables: GTR, STR, TSC, TEMC, NND, olfactory worsening, frontal dysexecutive syndrome improvement, CSF leakage and tumour size diameter.

In term of GTR, the analysis of the data collected in our study indicate that LSFAs and SIHAs appear superior to EEAs, and with LSFAs superior to ASFAs, though no statistically significant differences were found

Table 3
Comparison with other Systematic Reviews for OGM surgery. MTCAs and MITCAs.

Author	GTR	Recurrence	Mortality 30 days	Visual Improvement	Visual no changes	Visual Worsening	Olfact Preservation	Olfact Worsening	CSF Leak	ACA Injury	Ischemic lesion	Postop Hematomas	Postop Hydrocephalus	Postop Meningitis	Postop Site Infection	Pulmonary embolism	Postop Seizures
MTCAs																	
Komotar	92.8%	5%*	3.3%	54.2%	41.5%	4.3%	-	8.8%	6%	-	-	5%	4%	3%	4%	2.2%	-
Ruggeri +	88.1%	-	2.9%	61.8%	35.1%	10.8%	-	-	5.9%	-	-	-	-	-	-	-	6.4%
Shetty	90.9%	7%**	2.4%	12.8%	17.2%	6.6%	-	61.9%	6.3%	-	6.3%	-	2%	1.1%	2%	-	4.2%
Muskens	88.5%	-	3.9%	50.6%	-	-	-	-	10.5%	3.8%	-	-	-	-	-	-	-
Lu	85%	-	-	-	-	20%	-	-	-	-	-	-	-	-	-	-	-
Khan	91.1%	-	0.9%	45.7%	-	-	-	-	6.4%	0.1%	-	-	-	-	-	-	-
Our Review:																	
ASFAs	93%	3.1%	2.5%	71.3%	44.0%	0.4%	22.6%	23.6%	3.8%	0.5%	0.8%	1.7%	0.8%	0.9%	0.9%	0.9%	2.9%
LSFAs	99.1%	0.3%	1.2%	79.8%	58.8%	0.6%	29%	22.9%	0.4%	0%	0.2%	0.9%	0.8%	0.2%	0.3%	0.2%	0.9%
SIHAs	98.6%	0.5%	0.5%	82.2%	23.8%	0.4%	24%	19.5%	1.6%	0.5%	0.5%	3.4%	0.4%	1.1%	0.6%	0.4%	1.6%
MITCAs																	
Khan	84.9%	-	0.4%	52.9%	-	-	-	-	1.61%	0%	-	-	-	-	-	-	-
Our review	84.7%	2.5%	0.3%	81%	61.9%	3.2%	17.8%	31.6%	4.5%	0%	0.1%	1.9%	2.3%	0.3%	0.9%	0.1%	2.4%

+Combined OGM and TSM as a single entity.

-No data available.

*Median follow-up of 68.5 months.

**Median follow-up of 65.4 months.

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Table 4
EEAs Comparison with other Systematic Reviews for OGM surgery.

Author	GTR	Recurrence	Mortality 30 days	Visual Improvement	Visual no change	Visual Worsening	Olfact Preservation	Olfact Worsening	CSF Leak	ACA Injury	Ischemic lesion	Postop Hematomas	Postop Hydrocephalus	Postop Meningitis	Postop Site Infection	Pulmonary embolism	Postop Seizures
Komotar	63.2%	0%*	0%	20%	80%	0%	-	0%	31.6%	-	-	0%	0%	0%	0%	0%	-
Ruggeri +	78.4%	-	1%	80%	37%	2.4%	-	-	18.8%	-	-	-	-	-	-	-	2.1%
Shetty	70.2%	7.7%**	0%	80.7%	19.2%	0%	-	-	25.7%	-	2.9%	-	3.9%	4.9%	3.9%	-	2.0%
Muskens	70.9%	-	4.2%	64.5%	-	-	-	-	25.1%	1.6%	-	-	-	-	-	-	-
Lu	71%	-	-	-	-	8%	-	-	-	-	-	-	-	-	-	-	-
Khan	82.7%	-	0%	54.5%	-	-	-	-	14.4%	1.2%	-	-	-	-	-	-	-
Our Review:	78.8%	5.2%	0%	85.6%	49.0%	0%	0%	73.4%	26.9%	1.6%	1.9%	2.6%	3.5%	2.3%	6.4%	5.5%	3.1%

-No data available.

+Combined OGM and TSM as a single entity.

*Median follow-up 9.8 months.

**Median follow-up 22.6 months.

between EEAs, MITCAs and ASFAs.

A greater STR-rate in MITCAs vs ASFAs is somewhat incongruent with the observation of a higher (not statistically significant) number of recurrences seen in ASFAs over MITCAs, but this conflict may be explained by the fact that the median duration of clinical follow-up was almost half the period in MITCAs (31.5 months) than that reported in ASFAs (59.2 months), and also shorter than the rest of the MTCAs (LSFAs 65.3; SIHAs 54.4) unmasking the results from the MITCAs group as a likely “artificial” lower PI of recurrence.

The aggregate number of observed surgical complications was statistically significantly higher in EEAs than in the other surgical groups, primarily influenced by the higher rate of postoperative CSF leakage. Of note, further differences were found with events encountered in MTCAs with a lower incidence of surgical complications seen in LSFAs when compared to SIHAs and ASFAs.

The number of extra-neurological/medical postoperative complications ensuing postoperatively was significantly higher in EEAs than in LSFAs and MITCAs, again with LSFAs demonstrating a particular superiority when compared to the rest of the MTCAs. Finally, mortality within the first 30 days after surgery showed no statistically significant differences between any of the surgical groups, and no mortality was reported in EEAs either.

The number of postoperative NNDs were statistically significantly higher in the group of ASFAs (10.8%) than that seen in LSFAs (0.9%). Similarly, a trend to statistical significance of a lower PI of new neurological deficit was observed in SIHAs compared to ASFAs when allowing for each CI range.

Regarding the postoperative olfactory function, considering the importance and the impact of olfaction in the quality of life of the humans, there was a paucity of data and it was not methodically reported in most of the studies included in this review. In this variable EEAs showed olfactory worsening in 73%, which is statistically significantly higher than that seen in ASFAs. Of note in EEAs studies, 27% of the patients were already anosmic when taken to surgery so, additional loss of function was not expected. Among MTCAs and MITCAs, postoperative olfactory worsening was not statistically significantly different. From those studies that did assess olfactory preservation (olfactory function preservation and/or at least one olfactory nerve anatomically preserved) we found that the highest rate was reported in LSFAs (29%) followed by SIHAs (24%) and ASFAs (22%) with lower numbers seen in MITCAs (17%) and with no preservation reported from EEAs. Nevertheless, no statistically significant differences were detected between the surgical groups.

Frontal lobe dysexecutive syndrome and mental alterations improvement was statistically significantly more frequently observed in LSFAs (97%) over ASFAs (79%) with a similar value > 70% found in the other surgical groups.

In our study we did not only replicate the same findings in the literature like a statistically significantly more observed difference of CSF leaks in EEAs over MTCAs and MITCAs, but we also found statistically significant differences among MTCAs with more CSF leaks occurring in ASFAs over LSFAs. If the occurrence of a postoperative CSF leak constitutes a significant disadvantage with still a fairly high prevalence in EEAs, there was a higher non statistically significant number of CSF repair surgeries (13.5%; 95% CI 0–37.8) in EEAs over MTCAs and MITCAs (Fig. 2I), as well as higher non statistically significant rate of complications such as postoperative site infection, meningitis, hydrocephalus and pulmonary emboli.

The assessment of reported recurrence rates of OGM revealed a descending order (EEA = 5.2% > ASFAs = 3.1% > MITCAs = 2.5% > SIHAs = 0.5% > LSFAs = 0.3%) similar (and likely related) to the STR rates, except for MITCAs (15.2%) and ASFAs (6.9%) which revealed inverted values (EEAs > MITCAs > ASFAs > SIHAs > LSFAs). The difference observed did not reach any statistically significant difference.

No statistically significant differences were detected in the 30-day postoperative mortality rate between the surgical groups in our review.

Mortality after 30 days and 6 months was only recorded in EEAs, SIHAs and ASFAs with values indicating rates lower than 2% with no statistically significant differences among them (Fig. 2R).

It has been previously reported that EEAs yield better postoperative results regarding visual improvement in OGM patients with preoperative visual disturbances (Lu et al., 2018) (Shetty et al., 2017). This was replicated in our findings in this systematic review, with reported EEAs resulting in visual improvement in nearly 86%. However, those results did not reach statistical significance when compared to the rest of the MTCAs (SIHAs 82.2%, LSFAs 79.8%, ASFAs 71.3%) or MITCAs (81%) hence yielding similar outcomes with respect to visual improvement with overlapping of CIs. Likewise, no statistically significant differences were found in the visual no change/visual stabilization category, nor in the variable assessing worsening of visual function. Regarding the latter, no visual worsening was detected in the group of EEAs.

4.2. Comparison with other reviews

As seen in Table 3 and Table 4, GTR were reported by Komotar et al. in as high as 92.8% for MTCAs and 63.2% for EEAs (Komotar et al., 2012). Ruggeri et al. found a more profound and also statistically significant differences in GTR rates for OGM and TSM when MTCAs are compared to EEAs (88.1% vs. 78.4% respectively) (Ruggeri et al., 2016). Shetty et al. in their review on OGM surgery, also recorded a 90.9% of GTR in MTCAs as compared to a 70.2% GTR in EEAs, a difference highly statistically significant (Shetty et al., 2017), which is similar to the results reported by Muskens et al., 88.5% (CI 85.9–90.7) for MTCAs vs. 70.9% (CI 60.3–79.9%) for EEAs (Muskens et al., 2018). This is corroborated by Lu et al. who found a lower GTR of EEAs (71%) vs 85% for open approaches to OGM (Lu et al., 2018) and finally Khan et al. found GTR for OGMs at a rate of 91.1% (CI 87.9–94.2) for MTCAs which compared to 84.9% (CI 50.4–100) for MITCAs and 82.7% (CI 72.3–93.2) for EEAs (Khan et al., 2020).

All these reports are consistent with our findings, reflecting an overwhelming superiority in GTR of MTCAs over MITCAs and EEAs. However, when grouping the MTCAs into a single aggregate, as previous authors did, it remained impossible to distinguish which single approach/surgical route may be superior or inferior with respect to a particular aspect of interest, or if they were all equal. To this end, the analysis of the data collected in our study revealed that LSFAs and SIHAs appear superior over EEAs, and with LSFAs superior to ASFAs, though no statistically significant differences were found between EEAs, MITCAs and ASFAs.

Recurrence rates were not consistently reported in previous reviews. Komotar et al. found a recurrence rate of 5% in MTCAs and no recurrence in EEAs with a mean follow up of 68.5 months in MTCAs vs 9.8 months in EEAs (Komotar et al., 2012). Shetty et al. reported 7% in MTCAs vs 7.7% in EEAs though the former had a significantly longer mean follow-up (65.4 ± 29.2 months) than the latter (22.6 ± 17 months) (Shetty et al., 2017). Similarly in our review mean duration of follow-up of EEAs and MITCAs was significantly shorter when compared to all other surgical groups (see Table 1). However, although no statistically significant differences in recurrence rates were found between groups in our systematic review, they were reported as 5.2% in EEAs vs, 3.1% in ASFAs, with MITCAs at 2.5%, SIHAs at 0.5% and LSFAs at 0.36% as illustrated in Fig. 1C. In the future it would be valuable to update the recurrence data of EEAs and MITCAs surgical series to determine and compare recurrence rates matching mean months of follow-up of MTCAs assessing the differences properly.

Peri-operative mortality (at 30 days) was reported by Komotar et al. in MTCAs as high as 3.3% vs 0% for EEAs (Komotar et al., 2012). Ruggeri et al. found a 2.9% of mortality in MTCAs over that seen in EEAs with 1% (however, this authors were jointly grouping OGM and TSM) (Ruggeri et al., 2016). Shetty et al. detected a 2.4% of mortality rate in MTCAs over a rate of 0% in EEAs, with no statistically significant differences (Shetty et al., 2017). Conversely Muskens et al. reported these values higher at

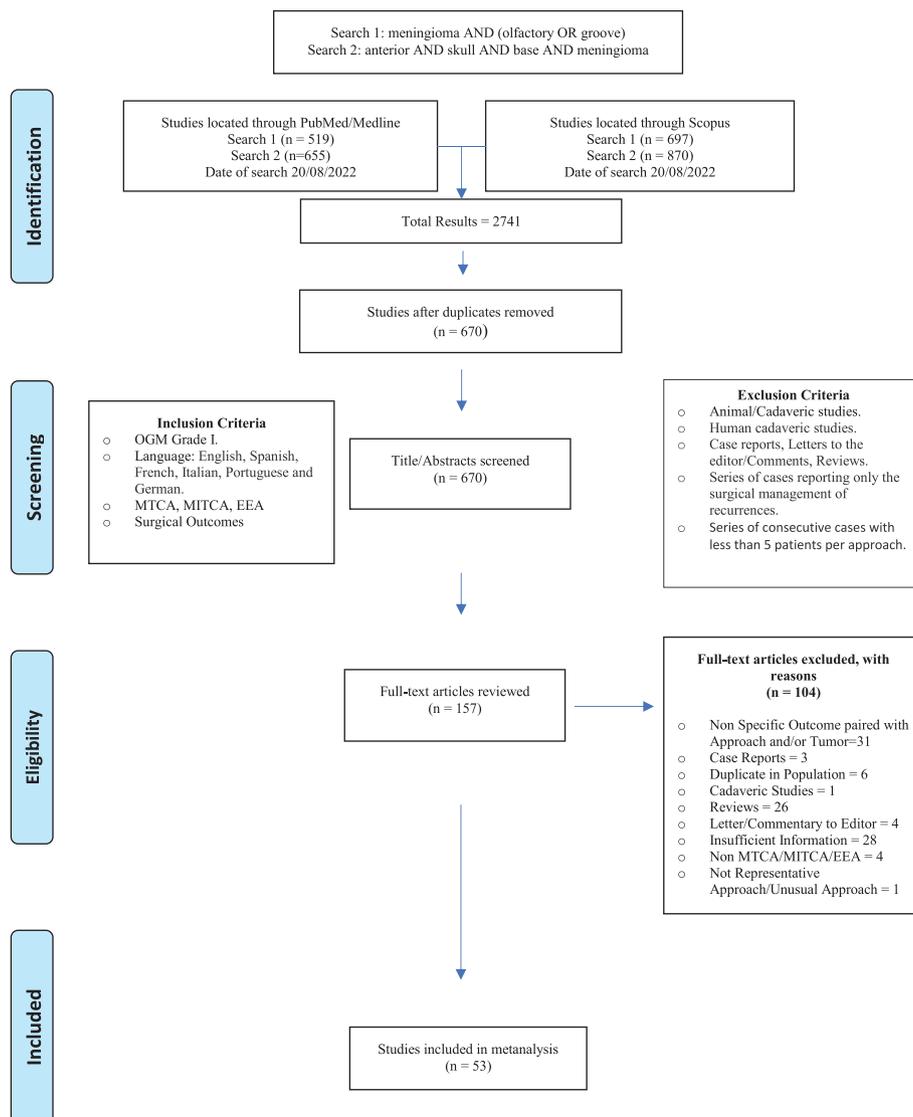
3.9% (95% CI 2.6–5.7) for MTCAs and at 4.2% (95% CI 1.5–11.1) for EEAs, not detecting statistically significant differences (Muskens et al., 2018). Further investigation by Khan et al. found the mortality rate to be at 0.9% (CI 0.2–1.5) in MTCAs, and 0% (95% CI 0–2.3) in EEAs with a comparable rate of 0.4% (95% CI 0–4) in MITCAs (Khan et al., 2020). Coherent with this previous reports, no statistically significant differences in mortality rates were detected between surgical groups in our review as can be seen in Fig. 1D. No mortality at 30 days was found reported in EEAs. Correspondingly, mortality after 30 days and 6 months was only detected in EEAs, SIHAs and ASFAs with values indicating rates at less than 2% with no statistically significant differences among them (Fig. 2R).

Regarding visual outcomes, Komotar et al. reported in MTCAs an improvement seen in 54.2%, with 41.5% showing stabilization/no changes and only 4.3% with documented worsening (Komotar et al., 2012). For surgical cases after EEAs these numbers are: 20.0% for improvement, 80.0% for stabilization and no cases with worsening (Komotar et al., 2012). Conversely, Ruggeri et al. found in MTCAs documented improvement in 61.8%, stabilization/no change in 35.1% and worsening in 10.8% (Ruggeri et al., 2016). For EEAs (here grouping OGM/TSM as a single entity) these authors reported improvement in 80.0%, stabilization/no change in 37.0% and worsening in 2.4% (Ruggeri et al., 2016). For the same parameters, Shetty et al. found statistically

significant differences in visual improvement between EEAs (80.7%) and MTCAs (12.8%), though no differences were detected in patients rates showing visual stabilization (MTCAs 17.2%, EEAs 19.2%) nor in visual function worsening (EEAs 0.0% vs MTCAs 6.6%) (Shetty et al., 2017). Muskens et al. detected less frequently visual improvement in surgical cases of MTCAs (50.6%; CI 95% 42.9–58.4%) vs. 64.5% (CI 95% 37.9–84.4%) for EEAs, though differences remained statistically not significant (Muskens et al., 2018). Likewise, Khan et al. found a higher fraction of patients showing visual improvement after EEAs 54.5% (95% CI 20.4–88.7%) followed by MITCAs 52.9% (CI 95% 0–100) and MTCAs 45.7% (95% CI 24.5–66.8), again with no statistically significant differences (Khan et al., 2020).

Our results in the variable reporting visual improvement are similar to the findings by Muskens and Khan showing no statistically significant differences between MTCAs (ASFAs, SIHAs, LSFAs) MITCAs and EEAs as can be seen in Fig. 2A. Regarding the categories of visual stabilization/no change and visual worsening (as seen in Fig. 2B and C respectively) also showed no statistically significant differences between surgical groups replicating the findings by Shetty et al. and Ruggeri et al. These results remain in contrast with the study results of Komotar et al. where the incidence of visual stabilization/no change was found to be higher in EEAs (Komotar et al., 2012).

Olfactory outcomes were scarcely reported in most of the case series



reviewed in this study. This has been noted in previous systematic reviews, e.g., by Komotar et al. who found 8.8% of reported postoperative anosmia in MTCAs and 0% in EEAs (Komotar et al., 2012). However, Shetty et al. found postoperative anosmia in MTCAs at 61.9%, yet these authors did not report outcomes in EEAs assuming a postoperative loss in all cases (Shetty et al., 2017). In our review, olfactory preservation was noted in MTCAs (LSFAs 29% >SIHAs 24% >ASFAs 23%) and MITCAs (17.8%) with no statistically significant differences among these surgical approaches, which clearly contrasts with no reported preservation of olfactory function with EEAs, no preservation of olfactory function with EEAs. This is mirrored by the fact that the PI of olfactory worsening was the highest in EEAs (73%) followed by MITCAs (32%), ASFAs (24%), LSFAs (23%) and SIHAs (19%) as seen in Fig. 2D and E.

Surgical Complications such as CSF leakage was reported by Komotar et al. as statistically significantly different in MTCAs vs. EEAs with rates of 6% and 31.6% respectively (Komotar et al., 2012). Ruggeri et al. (with TSM and OGM patients grouped together) found a higher incidence of CSF leaks after EEAs 18.8% vs. 5.9% after MTCAs (Ruggeri et al., 2016). Shetty et al. discovered similarly a lower incidence of CSF leaks when MTCAs were compared to EEAs (6.3% vs 25.7%) (Shetty et al., 2017). This matches the observations by Muskens et al. who found statistically significant differences in CSF leak rates, with lower incidences observed in MTCAs 10.5% (CI 95% 8.2–13.1) vs. 25.1% (CI 95% 17.5–34.8) for EEAs (Muskens et al., 2018). Finally, Khan et al. reported the same findings for EEAs with a 14.4% (CI 95% 4.8–24.1) leakage rate over MTCAs with a rate as around 6.4% (95% CI 3.9–8.9) and numbers as low as 1.6% (CI 95% 0–7.3) for MITCAs (Khan et al., 2020). (Fig. 2H)

In our study we did not only replicate the same findings with a statistically significant more observed difference of CSF leaks in EEAs over MTCAs and MITCAs, but we also found statistically significant differences in MTCAs with more leaks occurring in ASFAs vs. LSFAs.

If the occurrence of a postoperative CSF leak constitutes a significant disadvantage with still a fairly high prevalence in EEAs, there was a higher non statistically significant number of CSF repair surgeries (13.5%; 95% CI 0–37.8) in EEAs over MTCAs and MITCAs (Fig. 2I), as well as higher non statistically significant rate of complications such as postoperative site infection, meningitis, hydrocephalus and pulmonary emboli. Future studies should address the relationship of CSF leaks occurring in EEA surgeries with the latter complications since an association of e.g., leak rate and meningitis is anticipated, but may escape the reporting standards.

4.3. Global surgical insight

Study heterogeneity and possibly publication bias were common denominators existing in many of the outcomes scrutinised in the different studies reviewed. It remains to be determined whether patient selection (based on clinical/radiological characteristics) or the surgical technique or both factors combined, may influence differences in the outcomes when approaches are compared. Patients baseline characteristics described in this review seemed similar in each group of approaches, except for the median follow-up (shorter in MITCAs and EEAs) and for the median tumour diameter size, with a higher rate of tumour sizes <40 mm statistically significantly higher in MITCAs (48.1%) and EEAs (46.9%) than in the other surgical groups. It seems thus unlikely that surgical success remains strictly on patient's baseline characteristics selection. According to these results, the surgical route to address OGMs may have the greatest influence in the success of the outcomes.

ASFAs involve the opening of the frontal sinus and the splitting of the superior sagittal sinus (SSS). Various orbital osteotomies are described but may not be routinely implemented (as many of the case-series comprised in this review). This approach allows an early devascularization of the tumour. The wide exposure and elevation of frontal lobes may produce significant retraction to a typically oedematous frontal lobe parenchyma, precluding the preservation of frontal bridging veins with direct cerebral damage from surgical manoeuvres performed. This could

explain among other factors a statistically significant lower rate of frontal lobe dysexecutive syndrome improvement or the higher rates of cumulative surgical complications when compared to the LSFAs. The decompression of neurovascular complex is achieved late in surgery and from a relatively far distance when compared to LSFAs, MITCAs and SIHAs.

LSFAs provide a relatively wide exposure allowing an early opening of the carotid cistern improving the brain relaxation and retraction from the beginning of the surgery. This unilateral approach results in less trauma to the contralateral frontal lobe and the possibility of anatomical sparing of the contralateral olfactory nerve. It has also the advantage of providing an adequate corridor for reconstruction at any location of the ASB. These advantages may be responsible for the surgical success of this approach over the others as described above, irrespective of the baseline characteristics of the population exposed to LSFAs for OGM surgery.

MITCAs with or without the aid of endoscopy share the same advantages as seen in the LSFAs. Reconstruction of ASB might nevertheless be more challenging. Nonetheless, while in the past extensive resection of the tumoral base with drilling of the infiltrated bone was advocated to reduce the recurrence rate even at the prize of an increased morbidity, the current surgical strategy has evolved over the years favouring a less aggressive skull base resection to decrease the surgical morbidity and favouring a subsequent stereotactic radio-surgical procedures in case of evolutive remnant (Ge et al., 2019) (Karaaslan et al., 2021). Large tumour diameter could be potentially another limiting factor, as seen in the statistically significant proportion of patients with tumours <4 cm. The advantages of using MITCAs may result in no inferiority when compared to MTCAs (in <4 cm tumours) and superiority to EEAs in avoidance of surgical and extra-neurological medical complications as well as a lower CSF leak rate.

SIHAs allow a limited unilateral fastly-performed craniotomy (Roa Montes de Oca et al., 2017). The sparing of the frontal sinus, of the superior sagittal sinus and the bridging veins participate to the decrease of the postoperative morbidity. Large tumours create a large surgical corridor by themselves. Starting straightforwardly with an anterior debulking in the midline allows a rapid decrease of the mass effect and to reach the cranial base to perform an early devascularization. The resection of the falx cerebri can be performed to gain contralateral access in early or mid-stages of surgery if needed. At the last steps of the procedure, the most sensitive structures like the olfactory nerves, the ACA complex and the optic apparatus can be visualized and dissected carefully since the mass effect has been released by the tumour debulking. The side of the approach is selected according to the side that shows the larger portion of tumour burden and to the location of the bridging veins. The advantages of this approach may be responsible for the high rate of surgical success in GTR, the avoidance of surgical complications with a lesser rate of CSF leakage.

The EEAs benefit from an early attack to ASB and from an early devascularization and decompression of the internal aspects of the bilateral optic canals during surgery. However, GTR may be unwarranted if tumour's extension goes laterally (beyond the midorbital vertical meridian line (Gardner et al., 2012) or more than 1 cm away from lamina papyracea (Banu et al., 2016)) or anteriorly far enough (around the back wall of the frontal sinus (Banu et al., 2016) (Ottenhausen et al., 2018)) or if a firm attachment/encasement to ACA complex or carotid arteries are detected, not to mention the drawbacks of the higher frequency of CSF leaks and the complete loss of olfaction. Consequently, these anatomical criteria can be obviated in the other surgical approaches to achieve similar or better surgical outcomes not only in GTR but in the variables mentioned above due to the inherent anatomical particularities and mainly due to the preservation of ASB and easier preservation of neurovascular structures during surgical manoeuvres.

5. Limitations

According to the surgical route and type of craniotomy performed for OGM surgeries, we arbitrarily divided the classical microsurgical

transcranial approaches into: anterior, lateral and superior interhemispheric access routes for the reasons exposed above. The price of this particular arrangement can bring a paucity of surgical outcomes reports that is compensated when rearranging into one big surgical group as previous authors did. Consequently, most results in our meta-regression were done with a minimum of 3 or 5 studies potentially adding confounding factors (except in most of ASFAs variables, where outcomes counted were based on at least 10 studies per outcome).

Heterogeneity and publication bias are very likely to be present in the data set analysed for our systematic review, as reflected in I^2 and Cochran Q tests derived for most of the surgical outcomes. This is also seen in Begg's test chart as well as the asymmetry shown in some funnel plots.

Olfactory outcomes were very scarce and not correlated with preoperative anosmia or hyposmia of patients in most of the studies. Accordingly, we attempted to take into account indistinctly anatomic preservation and/or olfactory function if available when grouping patients into olfactory preservation or olfactory worsening variables and we calculated PI at 95% CI of each variable from the total of patients of each series as it was not possible to correlate with preoperative hyposmia/anosmia as most series made no distinction between preoperative hyposmia or anosmia grouping patients indistinctly. Consequently, there might be an important bias when grouping olfactory outcomes in such a fashion as we have done, nevertheless we believe this offers at least a brief and fair summarized estimation of what to expect when in terms of olfactory outcomes when using each of the surgical approaches researched.

The effect of time may have an impact in the outcomes since older case series may not have benefited from the best radiological imagery, the development of newer surgical techniques and tools, nor from the improvements in anaesthetics and post-surgical intensive-care units. These factors should be studied in another dedicated series.

Individual data of each patient was not available since most authors reported global results from their case series. Quality of life was not systematically reported.

6. Conclusions

With the information gained at hand, we put forward the notion that LSFAs and SIHAs seem superior to EEAs for OGM of all sizes and configuration in terms of GTR, STR, with a lower incidence of surgical complications, lower rates of extra-neurological/medical complications, and less occurrence of CSF leaks.

Moreover, among MTCAs, some other differences were found in surgical outcomes: LSFAs were superior to ASFAs with respect to GTR rates, CSF leaks and new neurological deficits and seemed also superior to ASFAs and SIHAs since it resulted in fewer surgical complications. Similarly, frontal dysexecutive syndrome/mental alterations improvement showed better results in LSFAs than in ASFAs.

MTCAs appeared not to be inferior to ASFAs, SIHAs nor LSFAs in the variables studied. However, it may have its main role in OGM of smaller than 40 mm diameter. MTCAs also appear superior to EEAs in avoiding surgical complications and resulted in fewer extra-neurological medical complication, and showed a lower incidence of CSF leaks.

EEAs may also have its role especially in anosmic patients with small diameter tumours (<40 mm), and in patients with tumours bigger than 40 mm with complete anosmia in whose GTR may not be main goal of the surgery.

All facts considered, and according to the data reviewed here, we consider LSFAs and SIHAs the most superior, versatile, suitable and effective approaches for addressing this complex surgical entity.

Future case series on OGM surgical outcomes should harmonize the reporting fashion in a unanimous and universal trend to avoid heterogeneity and publication bias. Identical tools should be used for measuring on patient's clinical, radiological aspects, and for surgical outcomes. Important assessments such as olfactory outcomes, quality of life and neuropsychological measures should not be neglected as most of these

critical aspects were not frequently assessed, not even in most recent case series. Data-bases of these studies should be open patient by patient for future research and for more detailed future meta-analysis.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bas.2022.101661>.

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