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Muskens, I.S.

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The endoscopic endonasal approach is not superior to the microscopic transcranial approach for anterior skull base meningiomas

Ivo S. Muskens MD, Vanessa Briceno MSc, Tom L. Ouwehand MD, William B. Gormley MD MPH MBA, Linda S. Aglio MD MS, Amir H. Zamanipoor Najafabadi BSc, Wouter R. van Furth MD PhD, Timothy R. Smith MD PhD MPH, Rania. A Mekary MSc PhD, Marike L.D. Broekman MD PhD JD

Introduction: In the past decade, the endonasal transsphenoidal approach (eTSA) has become an alternative to the microsurgical transcranial approach (mTCA) for tuberculum sellae meningiomas (TSMs) and olfactory groove meningiomas (OGMs). The aim of this meta-analysis was to evaluate which approach offered the best surgical outcomes. **Methods***: A systematic review of the literature from 2004 and meta-analysis were conducted in accordance with the PRISMA guidelines. Pooled incidence was calculated for gross total resection (GTR), visual improvement, cerebrospinal fluid (CSF) leak, intraoperative arterial injury, and mortality, comparing eTSA and mTCA, with p-interaction values.* **Results***: Out of 1684 studies, 64 case series were included in the meta-analysis. Using the fixed-effects model, GTR rate was significantly higher among mTCA patients for OGM (eTSA:*

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70.9% vs. mTCA: 88.5%, p-interaction< 0.01), but not significantly higher for TSM (eTSA: 83.0% vs. mTCA: 85.8%, p-interaction=0.34). Despite considerable heterogeneity, visual improvement was higher for eTSA than mTCA for TSM (p-interaction<0.01), but not for OGM (p-interaction=0.33). CSF leak was significantly higher among eTSA patients for both OGM (eTSA: 25.1% vs. mTCA: 10.5%, p-interaction<0.01) and TSM (eTSA: 19.3%, vs. mTCA: 5.81%, p-interaction<0.01). Intraoperative arterial injury was higher among eTSA (4.89%) than mTCA patients (1.86%) for TSM (p-interaction=0.03), but not for OGM resection (p-interaction=0.10). Mortality was not significantly different between eTSA and mTCA patients for both TSM (p-interaction=0.14) and OGM resection (p-interaction=0.88). Random-effect models yielded similar results. **Conclusions**: *In this meta-analysis, eTSA was not shown to be superior to mTCA for resection of both OGMs and TSMs.*

Introduction

The mainstay of treatment for tuberculum sellae meningiomas (TSMs) and olfactory groove meningiomas (OGMs) is surgery. Goals of surgery include obtaining tissue for histopathological diagnosis and relieving pressure caused by the tumor on neighboring structures such as the olfactory nerves, anterior cerebral arteries, optic nerves, and the pituitary gland. At the same time, these structures are very susceptible to manipulation and damage to these structures can lead to great morbidity[51]

Traditionally, TSMs and OGMs are resected using a microscopic transcranial approach (mTCA). Various approaches have been described, including interhemispheric, pterional, bifrontal, and subfrontal mTCA[1, 2, 5-7, 9, 47, 51, 56, 64, 70] In the last decade, however, as a result of the evolution of endoscopic surgery for pituitary adenomas, these meningiomas have been increasingly resected using an endonasal endoscopic transsphenoidal approach (eTSA), as first described by Jho et al. in 2004[38] Although the endoscopic approach is generally viewed as less invasive, with some studies suggesting that eTSA caused fewer post-operative changes on magnetic resonance imaging (MRI) compared to mTCA possibly indicating less manipulation,[22] it has been suggested that eTSA results in higher rates of CSF leaks, and potentially different outcomes (e.g. less GTR)[18, 42] However, a direct comparison between eTSA and mTCA is currently lacking. Therefore, the aim of this systematic review and meta-analysis was to evaluate which approach (eTSA vs. mTCA) offers the best surgical outcomes.

Methods

Search strategy and paper selection

In order to identify studies reporting on outcomes of surgically-treated TSMs and OGMs, a systematic review of the literature was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement[54] Both PubMed and Embase databases were searched on September 12, 2016. Because the outcomes of endoscopic surgery were first described in 2004 and microscopic resection has seen a continuous improvement, only articles published in 2004 or later were included[26, 38] The search strategy was drawn up using the keywords "Meningioma", "Tuberculum Sellae", "Olfactory Groove" and synonyms

(**Supplementary Table 3.5**). Duplicates were removed using Endnote X7.5.

Figure 3.1: Flowchart
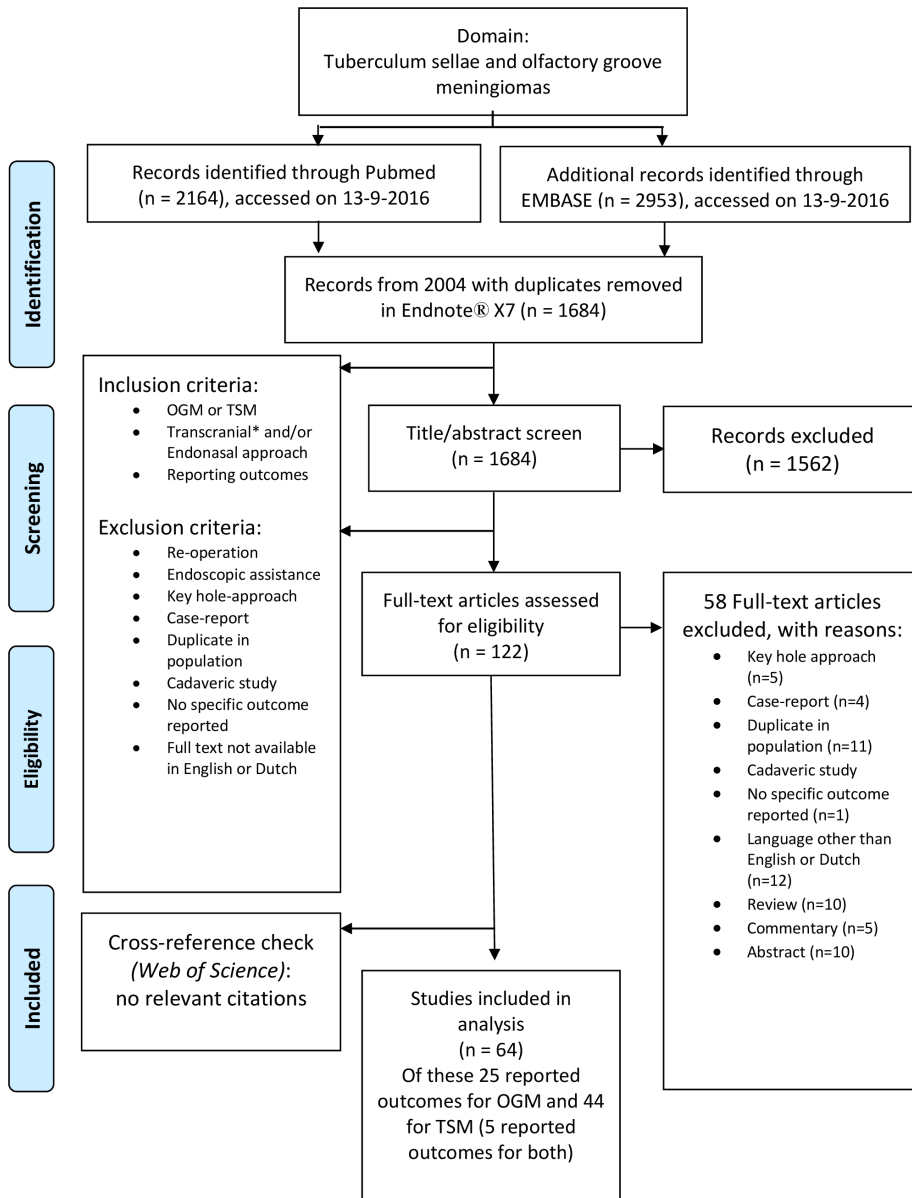
Legend: Abbreviations: OGM: olfactory groove meningioma, TSM: tuberculum sellae meningioma

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Table 3.1: Study characteristics of tuberculum sellae menigoma (TSM) studies

Authors	TSM (N)	Mean age (range)	Meningioma Grade: WHOII and WHOIII (N)	% Male	Meningioma size	Approach	Mean Follow-up (years)	Modified NOS*
Ali et al.[3]	30	48 (34-63)	0 & 0	43	NR	mTCA	2.5 (range: 0.5 − 4)	3
Bassiouni et al.[5]	62	53 (29-81)	NS	26	NR	mTCA	6 (range: 1.5 − 14)	3
Bohman et al.[9]	5	53 (24-77)	NS	40	Mean DM: 4.74 cm	eTSA	0.65 (range: 0.18 − 1.42)	4
Bowers et al.[11]	27	54 (23-77)	NS	18.5	NR	mTCA + eTSA	NR	3
Ceylan et al.[12]	23	52.9 (23-77)	NS	18.5	Mean DM 2.55 cm	eTSA	1.82 (range: 0.17 − 2.42)	3
Chen et al.[13]	6	49.8 (4-78)	NS	33	NR	mTCA	2.44 (range: 0.5 − 4.04)	4
Chokyu et al.[15]	34	55.7 (23-78)	0 & 0	15	Mean DM: 2.43 cm	mTCA	7.98 (range: 1.25 − 16.2)	3
Chowdhury et al.[16]	6	39.5 (29-52)	NS	33	Mean DM: 3.5 cm	eTSA	0.58 (range: 0.16 − 1)	4
cook et al.[20]	3	40.3 (32-55)	NS	0	NR	eTSA	NR	3
Curey et al.[21]	20	59.1 (SD: 11.1)	0 & 0	15	Mean DM: 3.25 (SD: 1.38 cm)	mTCA	4.69 (SD: 2.83)	4
De Divitiis et al.[23]	51	NS	NS	20	DM: 6: < 2cm, 33: 2-4cm, 5: >4 cm	mTCA + eTSA	Range: 0.75 - 21	4
Della puppa et al.[25]	23	NS	NS	0	NR	mTCA	3.42 (range: 0.25 − 6.42)	3
Fatemi et al.[29]	23	40 (SD: 22)	NS	30	Mean DM:3.08 cm	mTCA + eTSA	eTSA: 1.67 (range: 0.25 − 5), mTCA: 1.17 (range: 0.92 − 1.5)	4
Gadgil et al.[30]	5	51 (31-66)	0 & 0	40	Mean volume: 6.3 cm^3	eTSA	1.25 (range: 0.25 − 2.25)	4
Ganna et al.[32]	24	53.8 (33-80)	0 & 0	17	Mean DM: 2.63 cm	mTCA	4.33 (range: 1.5 − 7.67)	3
Goel et al.[34]	85	NS	NS	NS	NR	mTCA	4 (range 0.5 − 9)	4
Hayhurst et al.[35]	9	48.7 (29-65)	0 & 0	42	NR	eTSA	Median follow-up 38.6 (range 12 − 60 months)	4
Jang et al.[35]	24	49.5 (25-70)	NS	21	Mean DM: 2.06 cm	mTCA	1.73 (range: 0.25 − 4.5)	3
Khan et al.[40]	20	56.5 (31-81)	0 & 0	30	Mean volume: 11.98 cm^3	eTSA	NS	3
Kitano et al.[41]	28	Median: 55 (range:-42-76)	NS	14%	Mean volume: 8.1 mm3 (range 0.7–31.4 mm3)	mTCA + eTSA	NS	3
Koutourousiou et al.[43]	70	57.3 (36-88)	0 & 0	16	Mean DM: 2.3 cm	eTSA	2.42 (range: 0.083 − 8.17	3
Landeiro et al.[45]	23	56.2 (38-77)	NS	35	NR	mTCA	2.6 (range: 0.5 − 10.3)	3
Leveque et al.[47]	18	63.8 (31-88)	NS		DM <4.0 cm: 11, >4.0 cm: 7	mTCA	4.74 (SD: 2.74)	4
Li et al.[48]	43	53.8 (24-68)	NS	28	DM: <2 cm: 8, 2-4 cm: 22, >4 cm: 13	mTCA	5.4 (range: 2 − 10)	3
Li-Hua et al.[49]	67	48.7 (28-76)	NS	42	DM: <3 cm: 29, >3cm: 38	mTCA	2.44 (range: 0.5 − 4.04)	4
Liu et al.[50]	19	NS	NS	NR	NR	mTCA	1.24 (range: 0.33 − 3.83)	4
Mahmoud et al.[51]	58	56 (13-80)	NS	31	Mean DM: 2.9	mTCA	1.92 (up to 12 years)	4
Margalit et al.[52]	51	57.1 (28 -83)	NS	32	Mean max DM 2.94 cm (SD: 1.07)	mTCA	3.51 (range 0.17 − 7)	3
Mathiesen et al.[55]	29	58.3 (30 -84)	0 & 0	21	Mean max DM: 23.9 cm	mTCA	6 (1.5 - 10)	4
Nakamura et al.[56]	72	54.3 (30 -86)	1 & 0	24	Mean max 2.5 cm	mTCA	3.8 (range: 0.33 − 19.8)	3
Nanda et al.[58]	24	NS	NS	NS	DM: <3 cm: 3, 3-5 cm: 6, >5 cm: 21	mTCA	Median: 1.5	4
Ogawa et al.[61]	29	58.9 (43 -79)	2 & 0	26	NR	eTSA	2.98 (range: 0.5 − 4.92)	3
Padhye et al.[62]	3	66 (65 -66)	0 & 0	0	Mean volume 25.7 cm^3	eTSA	1.83 (range: 0.25 − 6)	4

Abbreviations: WHO: World Health Organization, SD: Standard deviation, NR: Not Reported, DM: diameter, NS: not specified, mTCA: microscopic transsphenoidal approach, eTSA: endoscopic transsphenoidal approach, NOS: New-Castle Ottawa Scale.*The modified NOS score varied between 3 and 4; the difference was mainly caused by variation in specifying completeness of follow-up.

Table 3.1: Study characteristics of tuberculum sellae menigoma (TSM) studies (continued)

Study								
Palani et al.[63]	41	NR	NR	37	NR	mTCA	Range: 0.5 – 4	4
Pamir et al.[65]	42	3 & 1	53 (24-79)	33	Range 7.5-210 mm³	mTCA	3.13 (range: 0.25 0 16)	3
Park et al.[66]	21	NS	51	14	Mean volume: 12.4 cm³	mTCA	6.33 (range: 1 – 12.6)	4
Refaat et al.[68]	16	NS	NS	19	Mean DM: 2.5cm	mTCA	1.17 (range: 0.67 – 1.5)	3
Romani et al.[69]	52	1 & 0	Median: 59 (14-87)	19	Mean DM: 3.1 cm	mTCA	Median: 4.91 (range: 0.08 – 11.1)	3
Schick et al.[72]	53	NS	52.6 (27-78)	25	Mean DM 2.6 cm	mTCA	2.49 (range: 0.5 – 9)	4
Seol et al.[73]	86	NS	49 (24-75)	23	Mean Dm: 2.41	mTCA	3.25 (range: 0.6 – 12.2)	3
Terasaka et al.[77]	9	0 & 0	64 (57-83)	11	NR	mTCA	2.1 (0.5 - 5.92)	4
Wang et al.[79]	12	0 & 0	56.7 (40 -67)	33	Mean DM: 3.03 cm	eTSA	2.1 (range: 0.5 – 5)	3
Wilk et al.[81]	18	0 & 0	50.5 (30 – 73)	17	Mean volume 6.915 mm³	mTCA	1.96 (range: 0.5 – 3.25)	4
Zhou et al.[82]	56	NS	42.5 (21-69)	46	DM: <3 cm: 24, 3-5 cm: 26 > 5m: 6	mTCA	2.29 (range: 0.08 – 3)	4

Data extraction

Two authors (IM and TO) independently screened the titles and abstracts of the articles for papers reporting surgical outcomes of resected OGMs and TSMs. After full-text screening, articles that reported outcomes of surgically-treated OGMs and TSMs were included. Case reports, commentaries, congress abstracts, reviews, animal studies, studies describing an endoscopically-assisted approach, studies reporting on the use of a keyhole-approach, studies in pediatric patients (<18 years old), re-operations, and cadaveric studies were excluded. Only literature in English and Dutch was reviewed. Discrepancies in selection were sorted out by discussion, and a senior author (MB) was consulted if the discrepancy could not be solved by discussion.

The following study characteristics were extracted from the full text of the selected studies: study design, number of patients, follow-up duration, study geographic location, percentage of WHO II and III meningiomas, percentage of males in the study population, mean age of the study population, and surgery type (transcranial or endoscopic endonasal). The following outcomes were extracted: number of patients with GTR (defined as Simpson grade I or II), number of patients with pre-operative visual problems, number of patients with improved vision post-surgery, post-operative cerebrospinal fluid (CSF) leakage, number of intraoperative arterial injury, and all-cause mortality (within 30 days after resection). Furthermore, perioperative blood loss, hospital length of stay, and operation length were extracted. Study quality was assessed with the adjusted New-Castle Ottawa Scale (NOS)[80] If the study in question was a case series, comparability was ignored.

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Table 3.2: Study characteristics of olfactory groove meningioma (OGM) studies

Authors	TSM (N)	Mean age (range)	Meningioma Grade: WHOII and WHOIII (N)	% Male	Meningioma size	Approach	Mean Follow-up (years)	Modified NOS*
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Liu et al.[50]	19	NS	NS		NR	mTCA	1.24 (range: 0.33 – 3.83)	4
Mahmoud et al.[51]	58	56 (13-80)	NS	31	Mean DM: 2.9	mTCA	1.92 (up to 12 years)	4
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Nanda et al.[58]	24	NS	NS	NS	DM: <3 cm: 3, 3–5 cm: 6, >5 cm: 21	mTCA	Median: 1.5	4
Ogawa et al.[61]	29	58.9 (43 -79)	2 & 0	26	NR	eTSA	2.98 (range: 0.5 – 4.92)	3
Padhye et al.[62]	3	66 (65 -66)	0 & 0	0	Mean volume 25.7 cm^3	eTSA	1.83 (range: 0.25 – 6)	4

Legend: Abbreviations; NS: Not specified, NR: not reported, DM: diameter, eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach, SD: Standard deviation, NOS: New-Castle Ottawa Scale.*The modified NOS score varied between 3 and 4; the difference was mainly caused by not specifying the completeness of follow-up.† One OGM study (ref 13) compared eTSA to mTCA and was given 5 stars

Meta-analysis

Comprehensive meta-analysis (CMA) version 3 was used to calculate separate overall incidence using the fixed-effect model with the inverse variance method and the random-effect model according to the method of DerSimonian and Laird,[27] in the endonasal endoscopic and transcranial approach for the following variables: GTR, arterial injury, visual improvement, CSF leakage, and mortality. A resulting p-interaction value from the subgroup analysis comparing eTSA and mTCA was considered significant if < 0.05. Study heterogeneity was assessed by calculating I-squared values and P-values from the Cochrane Q test. Publication bias was assessed with Begg's tests and was corrected for by a trim-and-fill method. Finally, a meta-regression was conducted on each of age, gender (dichotomized by male percentage below/above the median category), and continent (North America as the reference) for eTSA and mTCA separately. For visual outcomes, only continent could be assessed as a source of heterogeneity as not all patients presented with visual problems and baseline characteristics from this subgroup were not available. A subgroup analysis for tumor size and grade was not possible due to great variance in reporting.

Results

After removing duplicates, 1684 articles were identified. After screening for titles and abstracts, 1426 articles were excluded and 216 full texts were reviewed (Figure 3.1). For TSM, 44 case series (of which 11 in eTSA, 29 in mTCA, and 4 in both) were included in the meta-analysis for the different outcomes, including a total of 1444 patients[3, 5, 8, 11-13, 15, 16, 20, 21, 23, 25, 29, 30, 32, 34-36, 40, 41, 43, 45, 47-53, 56, 58, 61-63, 65, 66, 68, 69, 72, 73, 77, 79, 81, 82] As for OGM, 25 case series (of which 6 in eTSA, 18 in mTCA, and 1 in both) were included describing outcomes in 891 patients[2, 4, 6, 7, 17, 19, 22, 24, 25, 35, 37, 40, 44, 47, 55, 57, 60, 62, 64, 67, 68, 70, 75, 76, 78]

The median number of patients per study was 24 for TSM (**Table 3.1**) and 29 for OGM (**Table 3.2**). The average percentage of male patients was 27% for TSM and 32% for OGM. The median age was 51.0 for TSM and 52.0 for OGM. The median follow-up time was 6.0 years based on 35 studies for TSM[3, 5, 8, 12, 13, 15, 16, 21, 25, 29, 30, 32, 34, 36, 43, 45, 47-53, 56, 61, 62, 65, 66, 68, 72, 73, 77, 79, 81, 82] and 7.0 years based on 20 studies for OGM[2, 4, 6, 7, 17, 19, 22, 24, 25, 37, 44, 47, 55, 57, 60, 62, 67, 68, 76, 78] The modified NOS score varied between 3 and 4 out of 7 among the TSM and OGM case series[3, 5, 8, 11-13, 15, 16, 20, 21, 23, 25, 29, 30, 32, 34-36, 40, 41, 43, 45, 47-53, 56, 58, 61-63, 65, 66, 68, 69, 72, 73, 77, 79, 81, 82] Outcomes of the meta-analysis for TSM (**Table 3.3**) and OGM (**Table 3.4**) are shown.

Gross Total Resection

For TSM, GTR after eTSA was reported in 14 studies[8, 11-13, 16, 20, 23, 29, 30, 40, 43, 61, 62, 79] and after mTCA was reported in 31 studies[3, 5, 11, 13, 15, 21, 23, 25, 29, 32, 34, 36, 45, 47-49, 51-53, 56, 58, 63, 65, 66, 68, 69, 72, 77, 79, 81, 82] In a fixed effect model, the overall incidence for GTR was not significantly different comparing eTSA (incidence=83.0%; 95%-CI=76.7-88.0%, p-heterogeneity=0.74, I²=0%, 221 patients) to mTCA (incidence=85.8% (95%-CI=83.6-87.9%, p-heterogeneity=0.07, I²:

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Table 3.3: Outcomes of the tuberculum sellae meningioma (TSM) meta-analysis

Outcomes in TSM	# of studies	prevalence % (95% CI) Fixed & random	P-interaction Fixed & Random effectS	I² (%)	Cochrance Q test (p-value)	Begg's test (p-value) for publication bias	Meta-regression on age,	Meta-regression on Gender, (<27% vs. ≥27% males) COEFFICIENT (P-VALUE); RANDOM EFFECT	Meta-regression on continent (north america as reference) OVERALL P-VALUE; RANDOM EFFECT
GTR									
eTSA: FIXED	14	83.0 (76.7-88.0)	0.34						
RANDOm		83.1 (76.2-88.3)	0.33	0.00	0.74		0.05 (0.26)	0.28 (0.50)	0.62
MTCA: FIXED	31	85.8 (83.6-87.9)							
RANDOm		86.1 (83.5-88.4)		28.4	0.07	0.31	0.01 (0.78)	**0.49 (0.03)**	**0.02**
Visual improvement									
eTSA: FIXED	12	77.7 (70.3-83.7)	**<0.01**						
RANDOm		77.0 (64.8-85.9)	**0.04**	7.90	0.37		*	*	0.42
MTCA: FIXED	28	60.7 (57.3-64.0)							
RANDOm		62.6 (55.2-69.3)		77.4	**<0.01**	0.14	*	*	0.30
CSF Leak									
eTSA: FIXED	15	19.3 (14.1-25.8)	**<0.01**						
RANDOm		19.3 (14.1-25.8)	**<0.01**	0.00	0.50		0.01 (0.77)	0.27 (0.51)	0.16
MTCA: FIXED	24	5.81 (4.33-7.75)							
RANDOm		5.81 (4.33-7.75)		0.00	0.93	0.98	0.03 (0.52)	0.02 (0.96)	0.94
Arterial Injury									
eTSA: FIXED	12	4.89 (2.33-9.94)	**0.03**						
RANDOm		4.89 (2.33-9.94)	**0.03**	0.00	0.97		-0.04 (0.54)	-0.51 (0.52)	0.69
MTCA: FIXED	27	1.86 (1.13-3.05)							
RANDOm		1.86 (1.13-3.05)		0.00	0.99	**<0.01†**	-0.01 (0.96)	-0.14 (0.79)	0.78
Mortality									
eTSA: FIXED	10	5.15 (2.39-10.8)	0.14						
RANDOm		5.15 (2.39-10.8)	0.14	0.00	0.85		-0.02 (0.81)	0.00 (0.99)	0.91
MTCA: FIXED	30	2.67 (1.77-4.02)							
RANDOm		2.67 (1.77-4.02)		0.00	0.99	**<0.01‡**	-0.02 (0.76)	-0.34 (0.43)	0.99

Legend: Abbreviations: GTR, gross total resection; mTCA: microscopic transcranial approach, eTSA: endoscopic transsphenoidal approach; CSF, cerebrospinal fluid; *meta-regression for age and gender was not possible for visual outcomes because the numbers were given for all subjects in the study and not all patients presented with visual problems †The Egger's p-value for publication bias was 0.35, non-significant. ‡The Egger's p-value for publication bias was 0.45, non-significant.

Table 3.4: Outcomes of the olfactory groove meningioma (OGM) meta-analysis

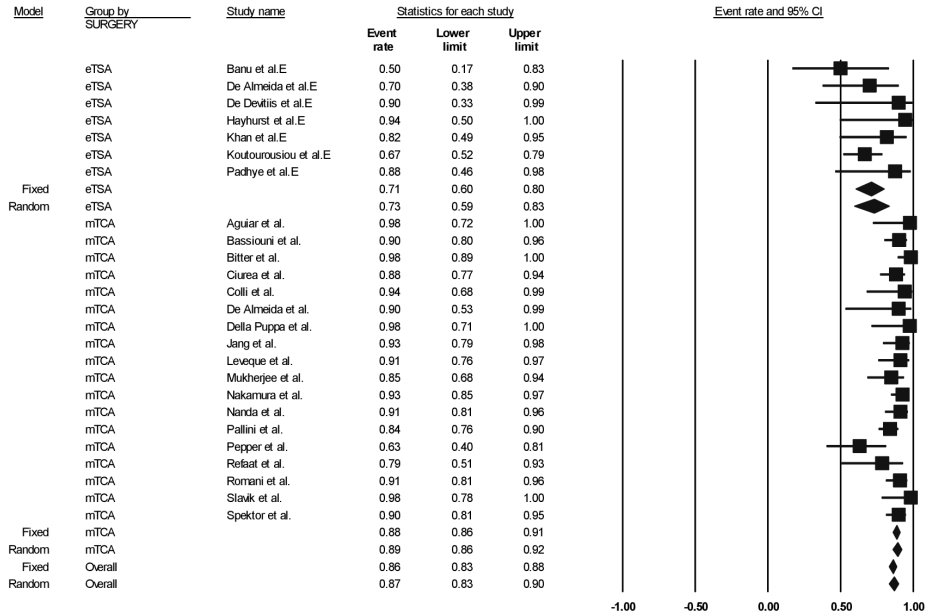| Outcomes in OGM	# of studies	Fixed & random prevalence % (95% CI)	P-interaction Fixed & Random effectS	I² (%)	Cochrane Q test (p-value)	Begg's test (p-value) for publication bias	Meta-regression on age, COEFFICIENT (P-VALUE); RANDOM EFFECT	Meta-regression on Gender, (<29% vs. ≥29% males) COEFFICIENT (P-VALUE); RANDOM EFFECT	Meta-regression on continent (north america as reference) OVERALL P-VALUE; RANDOM EFFECT
GTR									
eTSA: FIXED	7	70.9 (60.3-79.7)	**<0.01**						
RANDOm		72.9 (59.4-83.2)	**<0.01**	0.00	0.45		**-0.18 (0.05)**	0.52 (0.44)	0.15
MTCA: FIXED	18	88.5 (85.9-90.7)				0.48			
RANDOm		89.1 (85.8-91.8)		36.5	0.06		0.05 (0.17)	0.11 (0.82)	0.30
Visual improvement									
eTSA: FIXED	4	64.5 (37.9-84.4)	0.33						
RANDOm		63.3 (30.9-87.0)	0.40	65.5	0.03	0.25	*	*	0.34
MTCA: FIXED	9	50.6 (42.9-58.4)							
RANDOm		47.4 (31.9-63.5)		68.6	<0.01		*	*	0.57
CSF Leak									
eTSA: FIXED	7	25.1 (17.5-34.8)	**<0.01**						
RANDOm		20.1 (10.4-35.1)	**0.04**	25.8	0.22	0.30	0.01 (0.94)	-0.30 (0.60)	0.54
MTCA: FIXED	17	10.5 (8.22-13.4)							
RANDOm		9.11 (6.01-13.6)		60.2	**<0.01**		**-0.12 (<0.01)**	0.07 (0.91)	0.22
Arterial Injury									
eTSA: FIXED	7	3.88 (1.55-9.43)	0.12						
RANDOm		3.89 (1.55-9.43)	0.12	0.00	0.98	**<0.01†**	-0.06 (0.67)	0.97 (0.38)	0.79
MTCA: FIXED	17	1.62 (0.87-2.98)		0.00	0.99				
RANDOm		1.62 (0.87-2.98)					-0.10 (0.22)	0.22 (0.81)	0.87
Mortality									
eTSA: FIXED	7	4.27 (1.50-11.6)	0.88						
RANDOm		4.27 (1.50-11.6)	0.88	0.00	0.94	0.21	-0.06 (0.68)	1.20 (0.34)	0.78
MTCA: FIXED	19	3.92 (2.66-5.75)		0.00	0.74				
RANDOm		3.92 (2.66-5.75)					-0.04 (0.44)	**1.02 (0.02)**	0.08

Legend: Abbreviations: GTR, gross total resection; mTCA: microscopic transcranial approach, eTSA: endoscopic transsphenoidal approach; CSF, cerebrospinal fluid; *meta-regression for age and gender was not possible for visual outcomes because the numbers were given for all subjects in the study and not all patients presented with visual problems †The Egger's p-value for publication bias was 0.50, non-significant.

Figure 3.2: Pooled prevalence of gross total resection by approach for olfactory groove meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach.

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Model	Group by SURGERY	Study name	Event rate	Lower limit	Upper limit	Event rate and 95% CI
	eTSA	Banu et al.E	0.50	0.17	0.83	
	eTSA	De Almeida et al.E	0.70	0.38	0.90	
	eTSA	De Devitiis et al.E	0.90	0.33	0.99	
	eTSA	Hayhurst et al.E	0.94	0.50	1.00	
	eTSA	Khan et al.E	0.82	0.49	0.95	
	eTSA	Koutourousiou et al.E	0.67	0.52	0.79	
	eTSA	Padhye et al.E	0.88	0.46	0.98	
Fixed	eTSA		0.71	0.60	0.80	
Random	eTSA		0.73	0.59	0.83	
	mTCA	Aguiar et al.	0.98	0.72	1.00	
	mTCA	Bassiouni et al.	0.90	0.80	0.96	
	mTCA	Bitter et al.	0.98	0.89	1.00	
	mTCA	Ciurea et al.	0.88	0.77	0.94	
	mTCA	Colli et al.	0.94	0.68	0.99	
	mTCA	De Almeida et al.	0.90	0.53	0.99	
	mTCA	Della Puppa et al.	0.98	0.71	1.00	
	mTCA	Jang et al.	0.93	0.79	0.98	
	mTCA	Leveque et al.	0.91	0.76	0.97	
	mTCA	Mukherjee et al.	0.85	0.68	0.94	
	mTCA	Nakamura et al.	0.93	0.85	0.97	
	mTCA	Nanda et al.	0.91	0.81	0.96	
	mTCA	Pallini et al.	0.84	0.76	0.90	
	mTCA	Pepper et al.	0.63	0.40	0.81	
	mTCA	Refaat et al.	0.79	0.51	0.93	
	mTCA	Romani et al.	0.91	0.81	0.96	
	mTCA	Slavik et al.	0.98	0.78	1.00	
	mTCA	Spektor et al.	0.90	0.81	0.95	
Fixed	mTCA		0.88	0.86	0.91	
Random	mTCA		0.89	0.86	0.92	
Fixed	Overall		0.86	0.83	0.88	
Random	Overall		0.87	0.83	0.90	

-1.00   -0.50   0.00   0.50   1.00

P-interaction value < 0.01. Abbreviations: eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

28.4%, 1223 patients); (p-interaction value=0.34). In meta-regression, TSM studies with lower percentage of males had a higher rate of GTR (p=0.03). Studies conducted in Europe and Africa had significantly higher rates of GTR than North America (p=0.02). Begg's test for publication bias was non-significant (p=0.31, **Table 3.3**).[4, 22, 24, 35, 40, 44, 62] studies and 18 mTCA studies[2, 6, 7, 17, 19, 22, 25, 37, 47, 55, 57, 60, 64, 67, 68, 70, 75, 76] Unlike TSM, the overall fixed incidence of GTR was significantly lower in eTSA (incidence=70.9%; 95%-CI=60.3-79.9%, p-heterogeneity=0.45, I^2=0%, 86 patients) compared to mTCA (88.5%; 95%-CI=85.9-90.7%, p-heterogeneity=0.06, I^2:36.5%, 786 patients); (p-interaction<0.01; Figure 3.2). In meta-regression, only higher age was associated with lower GTR in resected OGM with the eTSA approach with borderline significance (p=0.05). Begg's test for publication bias was non-significant (p=0.48) (**Table 3.4**).

Visual improvement

Visual outcomes were reported in 12 studies for eTSA[8, 12, 16, 23, 29, 30, 35, 40, 43, 61, 62, 79] and 28 studies for mTCA[3, 5, 13, 15, 21, 23, 25, 29, 32, 34, 36, 47-51, 56, 63, 65, 66, 68, 69, 72, 73, 77, 81, 82] with a total of 1139 patients presenting with visual

problems.[3, 5, 8, 12, 13, 15, 16, 21, 23, 25, 29, 30, 32, 34-36, 40, 43, 47-51, 53, 56, 61-63, 65, 66, 68, 69, 72, 73, 77, 79, 81, 82]
Post-operative visual improvement was significantly higher for eTSA (incidence=
77.7%; 95%-CI=70.3-83.7%, p-heterogeneity=0.37, I^2=7.90%, 167 patients) than
mTCA (incidence=60.7% (95%-CI=57.3-64.0, p-heterogeneity< 0.01, I^2=77.4%, 1139
patients) in fixed-effect models (p-interaction < 0.01). Because age and male per-
centage were not provided for this subgroup of patients who presented with visual
problems, only continent could be assessed as a source of heterogeneity, which was
not a significant source of heterogeneity for TSM resection using eTSA or MTCA.
Begg's test for publication bias was non-significant (p=0.14, **Table 3.3**). One study
specifically addressed visual improvement per approach in TSM resection, finding
that eTSA was associated with more visual acuity improvement (≥5%; p-value: 0.01),
but not with improvement of visual field deficits (p-value=0.61)[41]

Visual improvement in OGM patients was described 4 eTSA studies[4, 40, 44, 62] and
9 mTCA studies[6, 7, 47, 57, 60, 68, 70, 75, 78] with 224 patients presenting with visual symp-
toms. The resulting fixed overall improvement rate was 64.5% (95%-CI: 37.9-84.4%,
p-heterogeneity=0.03; I^2=65.5%) for eTSA compared to 50.6% (95%-CI=42.9-58.4%,
p-heterogeneity <0.01, I^2=68.6%) for mTCA; however, this difference was not signifi-
cant (p-interaction value: 0.33). Continent was not identified as a significant source
of heterogeneity for eTSA (p=0.34) and mTCA (p=0.57). Begg's test for publication
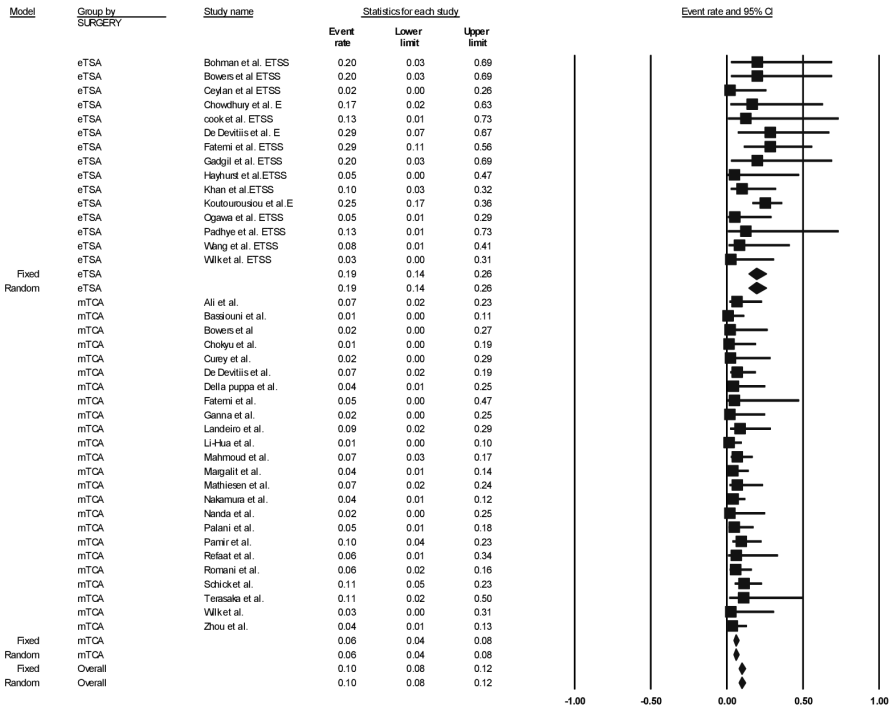bias was non-significant (p=0.25, **Table 3.4**).

Cerebrospinal fluid leakage

CSF leak occurrence after TSM resection was extracted from 15 eTSA
studies[8, 11, 16, 20, 23, 29, 30, 35, 40, 43, 61, 62, 79, 81] and 24 mTCA studies. The overall incidence
of post-operative CSF leakage was significantly higher in patients treated with
the eTSA approach (incidence=19.3%; 95%-CI=14.1-25.8%, p-heterogeneity=0.50,
I^2=0%, 225 patients) than with mTSA (incidence= 5.81%; 95%-CI=4.33-7.75%,
p-heterogeneity=0.93, I^2=0%, 879 patients) in fixed models (p-interaction value
<0.01, Figure **??**). Age, gender and continent were not identified as sources of
heterogeneity using meta-regression (all p-value > 0.05). Begg's test revealed no
significant publication bias (p=0.98) (**Table 3.3**).

In OGM, 7 eTSA studies[4, 22, 24, 35, 40, 44, 62] and 17 mTCA
studies[2, 6, 7, 17, 19, 22, 25, 37, 55, 57, 60, 64, 67, 68, 70, 75, 76, 78] including 889 patients described
whether patients postoperatively developed a CSF leak. The overall incidence in
fixed models was statistically significantly higher (p-interaction<0.01) for eTSA
(incidence=25.1%; 95%-CI=17.5-34.8%, p-heterogeneity=0.22, I^2=25.8%) than mTCA
(incidence=10.5%; 95%-CI=8.22-13.4%, p-heterogeneity <0.01, I^2=60.2%) (Figure
3.3). In meta-regression, only older age was significantly associated with lower CSF
leakage rate for mTCA (p<0.01). For eTSA, age, gender, and continent were not
identified as potential effect modifiers (p-interaction for all > 0.05). Begg's test
indicated no significant publication bias (p=0.30, **Table 3.4**).

Figure 3.3: Pooled prevalence of cerebrospinal fluid leak by approach for tuberculum sellae meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach

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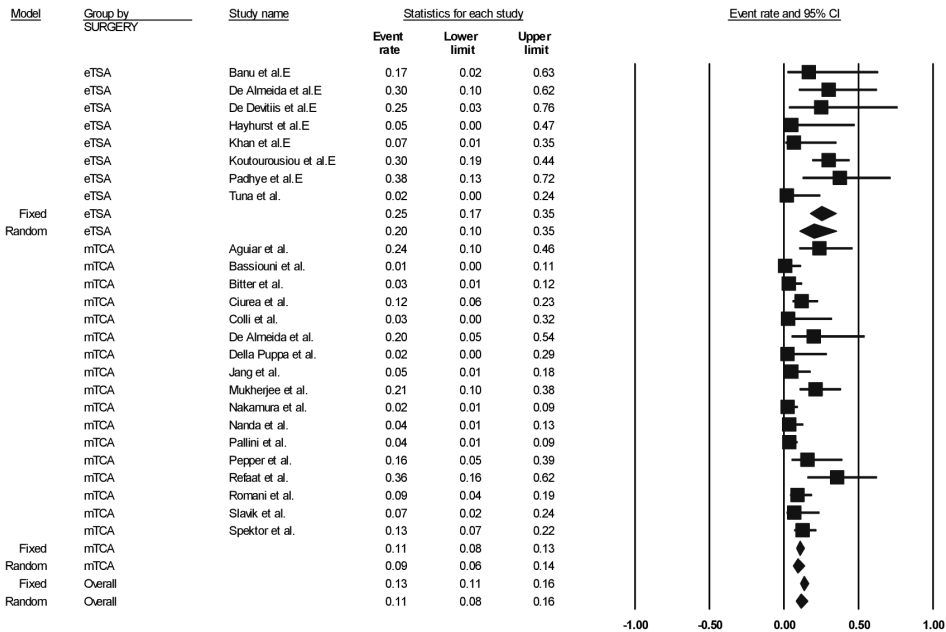| Model	Group by SURGERY	Study name	Event rate	Lower limit	Upper limit	Event rate and 95% CI
	eTSA	Bohman et al. ETSS	0.20	0.03	0.69	
	eTSA	Bowers et al ETSS	0.20	0.03	0.69	
	eTSA	Ceylan et al ETSS	0.02	0.00	0.26	
	eTSA	Chowdhury et al. E	0.17	0.02	0.63	
	eTSA	cook et al. ETSS	0.13	0.01	0.73	
	eTSA	De Devitiis et al. E	0.29	0.07	0.67	
	eTSA	Fatemi et al. ETSS	0.29	0.11	0.56	
	eTSA	Gadgil et al. ETSS	0.20	0.03	0.69	
	eTSA	Hayhurst et al.ETSS	0.05	0.00	0.47	
	eTSA	Khan et al.ETSS	0.10	0.03	0.32	
	eTSA	Koutourousiou et al.E	0.25	0.17	0.36	
	eTSA	Ogawa et al. ETSS	0.05	0.01	0.29	
	eTSA	Padhye et al. ETSS	0.13	0.01	0.73	
	eTSA	Wang et al. ETSS	0.08	0.01	0.41	
	eTSA	Wilk et al. ETSS	0.03	0.00	0.31	
Fixed	eTSA		0.19	0.14	0.26	
Random	eTSA		0.19	0.14	0.26	
	mTCA	Ali et al.	0.07	0.02	0.23	
	mTCA	Bassiouni et al.	0.01	0.00	0.11	
	mTCA	Bowers et al	0.02	0.00	0.27	
	mTCA	Chokyu et al.	0.01	0.00	0.19	
	mTCA	Curey et al.	0.02	0.00	0.29	
	mTCA	De Devitiis et al.	0.07	0.02	0.19	
	mTCA	Della puppa et al.	0.04	0.01	0.25	
	mTCA	Fatemi et al.	0.05	0.00	0.47	
	mTCA	Ganna et al.	0.02	0.00	0.25	
	mTCA	Landeiro et al.	0.09	0.02	0.29	
	mTCA	Li-Hua et al.	0.01	0.00	0.10	
	mTCA	Mahmoud et al.	0.07	0.03	0.17	
	mTCA	Margalit et al.	0.04	0.01	0.14	
	mTCA	Mathiesen et al.	0.07	0.02	0.24	
	mTCA	Nakamura et al.	0.04	0.01	0.12	
	mTCA	Nanda et al.	0.02	0.00	0.25	
	mTCA	Palani et al.	0.05	0.01	0.18	
	mTCA	Pamir et al.	0.10	0.04	0.23	
	mTCA	Refaat et al.	0.06	0.01	0.34	
	mTCA	Romani et al.	0.06	0.02	0.16	
	mTCA	Schick et al.	0.11	0.05	0.23	
	mTCA	Terasaka et al.	0.11	0.02	0.50	
	mTCA	Wilk et al.	0.03	0.00	0.31	
	mTCA	Zhou et al.	0.04	0.01	0.13	
Fixed	mTCA		0.06	0.04	0.08	
Random	mTCA		0.06	0.04	0.08	
Fixed	Overall		0.10	0.08	0.12	
Random	Overall		0.10	0.08	0.12	

P-interaction value < 0.01. Abbreviations: CSF: cerebrospinal fluid eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

Intraoperative arterial injury

For intraoperative arterial injury, outcomes were extracted from 12 eTSA studies[8, 11, 16, 23, 29, 30, 35, 40, 43, 61, 62, 79] and 27 mTCA studies for TSM[3, 5, 11, 12, 15, 21, 23, 25, 29, 32, 36, 45, 48, 49, 51, 52, 56, 58, 63, 65, 68, 69, 72, 77, 81, 82] The overall incidence of intraoperative arterial injury was significantly higher for eTSA (incidence=4.89%; 95%-CI=2.33-9.94%, p-heterogeneity=0.97, I^2=0%, 225 patients) than for MTCA (incidence=1.86%; 95%-CI=1.13-3.05%, p-heterogeneity=0.99, I^2 =0%, 225 patients) in fixed effect models (p-interaction value=0.03; Figure 3.4). Trial-level covariates such as age, continent, and gender did not significantly contribute to any heterogeneity in the models, both for eTSA and mTCA (all p-interaction values>0.05). There was a significant publication bias, indicating that study results with higher arterial injury incidence tended not to be published (Begg's test p-value<0.01 **Table 3.3**). However, the imputed overall incidence estimate for TSM was not materially different from the original incidence rate (not shown).
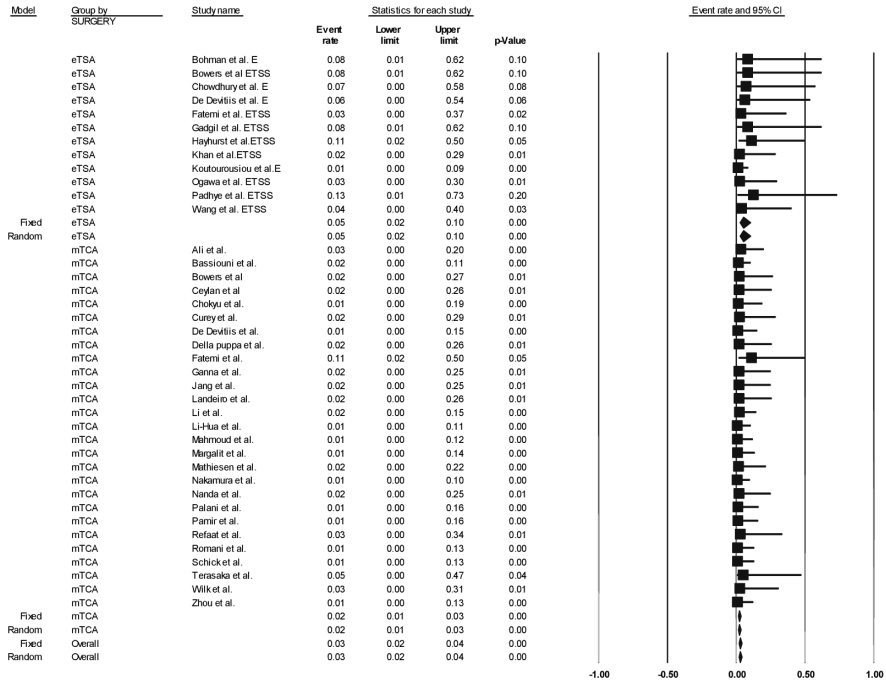
Figure 3.3: Pooled prevalence rates of cerebrospinal fluid leak by approach for olfactory groove meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach

Model	Group by SURGERY	Study name	Event rate	Lower limit	Upper limit	Event rate and 95% CI
	eTSA	Banu et al.E	0.17	0.02	0.63	
	eTSA	De Almeida et al.E	0.30	0.10	0.62	
	eTSA	De Divitiis et al.E	0.25	0.03	0.76	
	eTSA	Hayhurst et al.E	0.05	0.00	0.47	
	eTSA	Khan et al.E	0.07	0.01	0.35	
	eTSA	Koutourousiou et al.E	0.30	0.19	0.44	
	eTSA	Padhye et al.E	0.38	0.13	0.72	
	eTSA	Tuna et al.	0.02	0.00	0.24	
Fixed	eTSA		0.25	0.17	0.35	
Random	eTSA		0.20	0.10	0.35	
	mTCA	Aguiar et al.	0.24	0.10	0.46	
	mTCA	Bassiouni et al.	0.01	0.00	0.11	
	mTCA	Bitter et al.	0.03	0.01	0.12	
	mTCA	Ciurea et al.	0.12	0.06	0.23	
	mTCA	Colli et al.	0.03	0.00	0.32	
	mTCA	De Almeida et al.	0.20	0.05	0.54	
	mTCA	Della Puppa et al.	0.02	0.00	0.29	
	mTCA	Jang et al.	0.05	0.01	0.18	
	mTCA	Mukherjee et al.	0.21	0.10	0.38	
	mTCA	Nakamura et al.	0.02	0.01	0.09	
	mTCA	Nanda et al.	0.04	0.01	0.13	
	mTCA	Pallini et al.	0.04	0.01	0.09	
	mTCA	Pepper et al.	0.16	0.05	0.39	
	mTCA	Refaat et al.	0.36	0.16	0.62	
	mTCA	Romani et al.	0.09	0.04	0.19	
	mTCA	Slavik et al.	0.07	0.02	0.24	
	mTCA	Spektor et al.	0.13	0.07	0.22	
Fixed	mTCA		0.11	0.08	0.13	
Random	mTCA		0.09	0.06	0.14	
Fixed	Overall		0.13	0.11	0.16	
Random	Overall		0.11	0.08	0.16	

-1.00   -0.50   0.00   0.50   1.00

P-interaction value < 0.01; Abbreviations: CSF: cerebrospinal fluid eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

For OGM, the incidence of intraoperative arterial injury was extracted from 858 patients in 7 eTSA studies[4, 22, 24, 35, 44, 62] and 17 mTCA studies[2, 6, 7, 17, 19, 22, 25, 37, 55, 57, 60, 64, 67, 68, 70, 75, 76, 78] For eTSA, the fixed overall incidence of intraoperative arterial injury was 3.88% (95%-CI=1.55-9.43%, p-heterogeneity=0.98, I^2=0%). Although lower, the incidence for mTCA was 1.62% (95%-CI=0.87 - 2.98%, p-heterogeneity=0.99, I^2=0%) but not significantly different (p-interaction = 0.12). Covariates such as age, gender, and continent were not identified as sources of heterogeneity for both eTSa and mTCA procedures (all p-interaction> 0.05). Although Begg's Test for publication bias indicated the presence of publication bias (p-value < 0.01), Egger's test did not (p-value=0.50,**Table 3.4**). Moreover, the imputed overall incidence estimates for OGM were not materially different from the original incidence values (not shown).

3. The endoscopic endonasal approach is not superior to the microscopic transcranial
approach for anterior skull base meningiomas

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Figure 3.4: Pooled prevalence rates of intra operative arterial injury by approach for tuberculum sellae meningioma resection: endoscopic transsphenoidal approach vs. microscopic transcranial approach.

Model	Group by SURGERY	Study name	Event rate	Lower limit	Upper limit	p-Value
	eTSA	Bohman et al. E	0.08	0.01	0.62	0.10
	eTSA	Bowers et al ETSS	0.08	0.01	0.62	0.10
	eTSA	Chowdhury et al. E	0.07	0.00	0.58	0.08
	eTSA	De Devitiis et al. E	0.06	0.00	0.54	0.06
	eTSA	Fatemi et al. ETSS	0.03	0.00	0.37	0.02
	eTSA	Gadgil et al. ETSS	0.08	0.01	0.62	0.10
	eTSA	Hayhurst et al.ETSS	0.11	0.02	0.50	0.05
	eTSA	Khan et al.ETSS	0.02	0.00	0.29	0.01
	eTSA	Koutourousiou et al.E	0.01	0.00	0.09	0.00
	eTSA	Ogawa et al. ETSS	0.03	0.00	0.30	0.01
	eTSA	Padhye et al. ETSS	0.13	0.01	0.73	0.20
	eTSA	Wang et al.ETSS	0.04	0.00	0.40	0.03
Fixed	eTSA		0.05	0.02	0.10	0.00
Random	eTSA		0.05	0.02	0.10	0.00
	mTCA	Ali et al.	0.03	0.00	0.20	0.00
	mTCA	Bassiouni et al.	0.02	0.00	0.11	0.00
	mTCA	Bowers et al	0.02	0.00	0.27	0.01
	mTCA	Ceylan et al	0.02	0.00	0.26	0.01
	mTCA	Chokyu et al.	0.01	0.00	0.19	0.00
	mTCA	Curey et al.	0.02	0.00	0.29	0.01
	mTCA	De Devitiis et al.	0.01	0.00	0.15	0.00
	mTCA	Della puppa et al.	0.02	0.00	0.26	0.01
	mTCA	Fatemi et al.	0.11	0.02	0.50	0.05
	mTCA	Ganna et al.	0.02	0.00	0.25	0.01
	mTCA	Jang et al.	0.02	0.00	0.25	0.01
	mTCA	Landeiro et al.	0.02	0.00	0.26	0.01
	mTCA	Li et al.	0.02	0.00	0.15	0.00
	mTCA	Li-Hua et al.	0.01	0.00	0.11	0.00
	mTCA	Mahmoud et al.	0.01	0.00	0.12	0.00
	mTCA	Margalit et al.	0.01	0.00	0.14	0.00
	mTCA	Mathiesen et al.	0.02	0.00	0.22	0.00
	mTCA	Nakamura et al.	0.01	0.00	0.10	0.00
	mTCA	Nanda et al.	0.02	0.00	0.25	0.01
	mTCA	Palani et al.	0.01	0.00	0.16	0.00
	mTCA	Pamir et al.	0.01	0.00	0.16	0.00
	mTCA	Refaat et al.	0.03	0.00	0.34	0.01
	mTCA	Romani et al.	0.01	0.00	0.13	0.00
	mTCA	Schick et al.	0.01	0.00	0.13	0.00
	mTCA	Terasaka et al.	0.05	0.00	0.47	0.04
	mTCA	Wilk et al.	0.03	0.00	0.31	0.01
	mTCA	Zhou et al.	0.01	0.00	0.13	0.00
Fixed	mTCA		0.02	0.01	0.03	0.00
Random	mTCA		0.02	0.01	0.03	0.00
Fixed	Overall		0.03	0.02	0.04	0.00
Random	Overall		0.03	0.02	0.04	0.00

Legend: P-interaction value: 0.03. Abbreviations: eTSA: endoscopic transsphenoidal approach, mTCA: microscopic transcranial approach.

Mortality

Mortality after TSM surgery was described in a total of 10 eTSA studies[8, 11, 23, 29, 40, 43, 61, 62, 79] and 30 mTCA studies[3, 5, 11-13, 15, 21, 23, 25, 29, 30, 35, 36, 45, 48, 49, 51-53, 56, 58, 63, 65, 68, 69, 72, 77, 81, 82] eTSA resulted in a 30-day mortality incidence of 5.15% (95%-CI=2.39-10.8, p-heterogeneity=0.85, I^2=0%, 194 patients), which was not significantly different from mTCA (incidence=2.67%; 95%-CI=1.77-4.02, p-heterogeneity=0.99, I^2=0%, 962 patients) in fixed models (p-interaction=0.14). Age, gender, and continent did not appear to have different incidence values based on the meta-regression results for both eTSA and mTCA (all p>0.05). Begg's test p-value for publication bias was significant indicating that articles with higher mortality rates tend not to be published (p < 0.01, **Table 3.3**); however, the trim-and-fill method suggested that the imputed overall incidence estimates for TSM were not materially different from the original incidence values (not shown).

For OGM, 7 eTSA studies[4, 22, 24, 35, 40, 44, 62] and 19 mTCA studies[2, 6, 7, 17, 19, 22, 25, 37, 47, 55, 57, 60, 64, 67, 68, 70, 75, 76, 78] including described mortality incidence. For eTSA, the overall 30-day mortality incidence was 4.27%

(95%-CI=1.50-11.6%, p-heterogeneity=0.94; I^2=0%; 82 patients), which was not significantly different from the mortality incidence in the mTCA group (incidence = 3.92%, 95%-CI=2.66-5.75, p-heterogeneity=0.74, I^2=0%; 779 patients) in fixed models (p-interaction=0.88). In a meta-regression for gender, it was identified that studies with a lower male percentage were significantly associated with a higher mortality incidence for mTCA (p=0.02) but not for eTSA (p=0.34), while age and continent were not. Begg's test for publication bias was non-significant (p=0.21) (**Table 3.4**).

Random-effect models
For all the above-mentioned results, the random-effect models yielded similar results (**Table 3.3 and 3.4**).

Blood loss, operating time, and length of stay in hospital
For blood loss, operating time and length of hospital stay, a quantitative meta-analysis was not feasible because of the paucity of studies reporting them; hence, these few studies were systematically reviewed. In TSM, mean blood loss ranged from 448 to 970 mL in three studies describing mTCA, compared to 200 to 617 mL for eTSA[21, 30, 41, 47] The mean operating time ranged from 375 to 444 minutes for eTSA in two studies, and from 116 to 426 minutes for mTCA in four studies[21, 23, 41, 47, 69] Hospital length of stay ranged from 6 to 21 days in one study in patients treated by an eTSA[23]

For OGM, blood loss was only reported in one case series in patients operated with an interhemispheric approach (mean: 570.9 ml, SD: 442)[47] The mean hospital length of stay for eTSA ranged from 11 to 13.5 days in 2 studies 9, 13, compared to 8.5 to 18 days for mTCA[7, 22, 24, 78] Of these studies, one described the mean length of stay in both approaches, with a mean length of stay of 11 days for eTSA compared to 8.5 days in mTCA (p=0.54)[22] Operating time ranged from six to ten hours in one study reporting outcomes from eTSA[24] In a study examining patients with an interhemispheric approach, the mean operating time was 209 minutes (standard deviation: 103)[47]

Discussion
In this meta-analysis, eTSA was not shown to be superior to mTCA for resection of both OGMs and TSMs. Only in patients with preoperative visual deficits due to TSM, eTSA seems superior to mTCA, but with great hetereogeneity. In patients with TSM, eTSA resulted in higher rates of visual improvement, similar rates of GTR and more CSF leaks and intraoperative arterial injury. While in patients with OGM, results of both techniques were similar for visual improvement and intraoperative arterial injury, but worse in patients operated with eTSA for GTR and CSF leaks. There seems to be no substantial difference in peri-operative blood loss, operating time, or length of hospital stay between the two approaches. There was no substantial difference between in incidence rates between in fixed- and random-effect models. This could be explained by a relative lack of difference between the study populations in the studies, which could have been implicated in the case of a difference between the models. However, mTCA was associated with considerable heterogeneity for out-

comes visual improvement in TSMs and CSF leak for OGMs which could reflect a relatively greater inter-study variability for these outcomes.

Although no significant difference was identified in GTR rate for TSM, mTCA resulted in higher GTR rates in OGM. As OGMs are located more anterior than TSM an extended eTSA approach is needed for OGM which requires more extensive drilling of the anterior skull base and a potential suboptimal view because of the angle of the scope. However, it should also be noted that GTR was not always the primary the goal of surgery (e.g. the goal could be preserving vision)[43, 72] Furthermore, many other factors seem to influence GTR rate. One factor may be the learning curve associated with eTSA, as seen with pituitary adenoma resection[10, 14, 46] Also, tumor factors such as large size and vascular enhancement can significantly lower GTR rate for eTSA, as seen in one study in TSM[43] Furthermore, presence of a "cortical cuff" (a layer of brain between the tumor capsule and cerebral vessels) on MRI was associated with more GTR in OGM[40]

For visual improvement, it remains to be determined whether eTSA is truly associated with more visual improvement than mTCA in TSM, as the heterogeneity among mTCA studies could not be corrected for. Therefore, the difference witnessed may very well be insignificant as seen with OGM. Furthermore, as the variance in reporting of tumor size did not allow for it to be incorporated in a meta-regression, the TSMs in the eTSA group may very well be smaller compared to the mTCA group. However, regarding visual outcomes, one study looking at the mTCA approach suggests that visual outcomes are associated with age and duration of visual symptoms but not with actual tumor size[28]

Both for OGM and TSM, eTSA was significantly associated with more CSF leakage. However, prophylactic lumbar drain placement varied greatly; in some studies almost all patients were given a prophylactic pre-operative lumbar drain, while in other studies none of the included patients were drained[8, 24, 30, 35, 40, 44] Also, the different studies used different reconstruction techniques (e.g. introduction of a vascularized flap and use of certain glues), although this caused no considerable heterogeneity among the studies[40, 44, 62]Another factor in the post-operative CSF leakage rate may be the level of neurosurgeon's experience. Although the difference was not significant and in a small number of patients, one group had two leaks in their first group of patients (n=8), compared to none in the latter group (n=12)[40] Also, the use of a vascularized flap for reconstruction of the skull base seems to bring CSF leakage rate down considerably[40, 43, 62] Still, this rate is considerably higher than overall incidence calculated for mTCA. Further improvement with more sophisticated reconstruction techniques following eTSA may bring the rate of CSF leakage down to those reported for mTCA.

MTCA for TSM resulted in a significantly lower rate of intraoperative arterial injury compared to eTSA. However, this seems not to have caused a significant difference in mortality. Nevertheless, a relative low number of patients treated with an eTSA may have caused a relatively low power, as the p-interaction value for mortality for TSM approaches significance (p=0.14). A significant association between intraoperative arterial injury and eTSA was not seen in OGM, again this may be explained by low power and a low number of studies, but also because of the anterior location

of the tumor. Previously, two reviews have described a comparison between eTSA and mTCA for both TSM and OGM. The first review identified higher GTR rate and less CSF leak associated with mTCA for both OGM and TSM (p<0.01 for both, using chi-squared test and Fisher's exact test respectively), which is similar to our findings except for the GTR rate for TSM[42] A second review found significantly more visual improvement (p<0.01) and CSF leakage (p<0.01) for eTSA and no difference in mortality (p=0.15) for TSM and OGM together, which is similar to our findings. eTSA was also found to be associated with a lower GTR rate (p<0.01) compared to mTCA, which was only the case in OGM in this meta-analysis[71] Finally, the authors of a meta-analysis for TSM found that eTSA was significantly associated with CSF leakage (OR: 3.9; 95%-CI: 1.15-15.75, p<0.05) and visual improvement (OR 1.5; 95%-CI 1.18, 1.82, p<0.05), which again is similar to our results[18]

Strengths of this study include an extensive review of the literature and evaluation of outcomes such as arterial injury, length of hospital stay, and blood loss. The use of both fixed- and random-effect models, evaluation of heterogeneity between the included studies, and assessment of publication bias ensures a rigorous evaluation of outcomes with appropriate valuation of the results. All outcomes were also subjected to meta-regression for various study characteristics where possible to try to identify sources of heterogeneity between the studies.

There are several limitations of this meta-analysis. First, the decision of discarding studies published before 2004 produces limitation. The decision to do so was based on the assumption that also mTCA outcomes improve over time with continual innovation and that meningiomas were not reported to be resected with an eTSA before that time[26, 38] Regarding the included studies, only case series were identified, resulting in the inability of calculation overall odds ratios. There is probably also a great difference between the population of patients that were deemed eligible for a eTSA resection, compared to those resected with mTCA, due to size, extension and invasion of the tumors (confounding by indication). Furthermore, one could argue that only looking at perioperative outcomes may not be conclusive, as especially recurrence happens during follow-up. However, as GTR and World Health Organization (WHO) grade remain the main prognostic factors for predicting recurrence, opting for eTSA should be done with great caution, as high grade meningiomas may be harder to resect completely[59, 74] However, it was not possible to correct for meningioma size, which is unfortunate as very small meningiomas may show very different results. Furthermore, it was no possible to correct for WHO grade, which could theoretically alter the results[31] Also, the choice of approach varied greatly among mTCA approach studies[1, 2, 5-7, 9, 47, 51, 56, 64, 70]

Indications for eTSA vary between groups. One group reported to operate all midline meningiomas regardless of size, extension, or configuration except for those tumors that extend from the anterior clinoid process[43] It has also been suggested that if the tumor extends laterally over the internal carotid artery, chances of GTR are limited[61] Others have suggested that larger tumors, tumors that extend laterally, involve vasculature or are calcified are also lesser candidates[23, 44] Therefore, confounding by indication cannot be ruled out, especially since the patients in these studies were not randomized to either treatment. As a result, the exact indications and

contra-indications for eTSA remain to be determined.

Future studies should, therefore, focus on identifying clear indications for eTSA for OGM and TSM and its safety by direct comparison in a randomized study. Such a study should ideally be conducted in a research setting by experienced surgeons, as its safety has not been prospectively compared to mTCA and as both approaches seem to come with a considerable learning curve which results in different outcomes[43] Given the observation that younger patients seem to benefit more from eTSA compared to older patients (p=0.02, n=34), it is not unlikely that specific groups might benefit more from one of the approaches[39] Probably, patients with relatively small (<3 cm), midline TSMs would probably be the best early candidates. These patients may benefit from a potential higher incidence of visual improvement postoperatively and the relative invasiveness of the eTSA approach. Further evaluation could be focused at characteristics such as size, a cortical cuff, and WHO grading to identify the best potential candidates for either approach[40] However, due to the low incidence of TSMs and OGMs in general and the great variety in anatomical characteristics among them this may very well be challenging. Therefore, other trial designs - e.g. a registry - should be considered when answering this question. Also, future improvement of the instruments used (e.g. 3D-endoscopes or glues) may improve results obtained by eTSA over time[33]

Conclusion

This meta-analysis indicates that the endoscopic transsphenoidal approach (eTSA) has not been shown to be superior to the microscopic transsphenoidal approach (mTCA) for both olfactory groove meningiomas (OGMs) and tuberculum sellae menigniomas (TSMs). More specifically, eTSA was associated with lower GTR rate for OGMs compared to eTSA and higher rate of arterial injury in TSMs. Furthermore, eTSA was associated with more CSF leaks in in both OGMs and TSMs compared to mTCA. On the other hand, eTSA was associated with a higher rate of visual improvement postoperatively compared to mTCA, which was not observed for OGMs. All conclusions should, however, be interpreted with caution due to limitations of this study.

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Table 3.5: Search syntax

Pubmed (09-12-2016) from 2004
(Tuberculum[Title/Abstract] OR Suprasellar[Title/Abstract] OR sellar[Title/Abstract] OR sella[Title/Abstract] OR sellae[Title/Abstract] OR cribriform[Title/Abstract] OR Planum[Title/abstract] OR Sphenoid*[Title/abstract] OR olfactory[Title/abstract] OR sphenoid bone[MeSH Terms] OR anterior skull base[Title/Abstract] OR "Cranial Fossa, Anterior"[Mesh]) AND (Meningioma*[Title/Abstract] OR meningioma[MeSH Terms] OR meningeoma*[Title/abstract] OR meningeal neoplasms[MeSH Terms] OR TSM[Title/abstract] OR OGM[Title/abstract] OR PSM[Title/abstract])

Embase (09-12-2016) from 2004
(Olfactory:ab,ti OR tuberculum:ab,ti OR suprasellar:ab,ti OR sellar:ab,ti OR sella:ab,ti OR Sellae:ab,ti OR planum:ab,ti OR cribriform:ab,ti OR sphenoid*:ab,ti OR 'sphenoid'/exp OR 'anterior skull base':ab,ti) AND (meningioma*:ab,ti OR 'meningioma'/exp OR meningeoma*ab,ti OR TSM:ab,ti OR OGM:ab,ti OR PSM:ab,ti)