A panoramic view of the skull base: systematic review of open and endoscopic endonasal approaches to four tumors

Christopher S. Graffeo · August R. Dietrich · Bartosz Grobelny ·
Meng Zhang · Judith D. Goldberg · John G. Golfinos · Richard Lebowitz ·
David Kleinberg · Dimitris G. Placantonakis

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Abstract Endoscopic endonasal surgery has been established as the safest approach to pituitary tumors, yet its role in other common skull base lesions has not been established. To answer this question, we carried out a systematic review of reported series of open and endoscopic endonasal approaches to four major skull base tumors: olfactory groove meningiomas (OGM), tuberculum sellae meningiomas (TSM), craniopharyngiomas (CRA), and clival chordomas (CHO). Data from 162 studies containing 5,701 patients were combined and compared for differences in perioperative mortality, gross total resection (GTR), cerebrospinal fluid (CSF) leak, neurological morbidity, post-operative

visual function, post-operative anosmia, post-operative diabetes insipidus (DI), and post-operative obesity/hyperphagia. Weighted average rates for each outcome were calculated using relative study size. Our findings indicate similar rates of GTR and perioperative mortality between open and endoscopic approaches for all tumor types. CSF leak was increased after endoscopic surgery. Visual function symptoms were more likely to improve after endoscopic surgery for TSM, CRA, and CHO. Post-operative DI and obesity/hyperphagia were significantly increased after open resection in CRA. Recurrence rates per 1,000 patient-years of follow-up were higher in endoscopy for OGM, TSM, and CHO. Trends for open and endoscopic surgery suggested modest improvement in all outcomes over time. Our observations suggest that endonasal endoscopy is a safe alternative to craniotomy and may be preferred for certain tumor types. However, endoscopic surgery is associated with higher rates of CSF leak, and possibly increased recurrence rates. Prospective study with long-term follow-up is required to verify these preliminary observations.

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C. S. Graffeo · A. R. Dietrich · B. Grobelny ·
J. G. Golfinos · D. G. Placantonakis (✉)
Department of Neurosurgery, New York University
School of Medicine, Skirball 8R-303, 530 1st Avenue,
New York, NY 10016, USA
e-mail: dimitris.placantonakis@nyumc.org

M. Zhang · J. D. Goldberg
Department of Population Health and Environmental Medicine,
New York University School of Medicine, 550 First Avenue,
New York, NY 10016, USA

R. Lebowitz
Department of Otolaryngology, New York University School of
Medicine, 550 First Avenue, New York, NY 10016, USA

D. Kleinberg
Department of Medicine, Division of Neuroendocrinology,
New York University School of Medicine, 550 First Avenue,
New York, NY 10016, USA

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Abbreviations

TSM	Tuberculum sellae meningioma
OGM	Olfactory groove meningioma,
CRA	Craniopharyngioma
CHO	Clival chordoma
CSF	Cerebrospinal fluid
GTR	Gross total resection
DI	Diabetes insipidus
CNS	Central nervous system

Introduction

Transnasal surgery entered the modern neurosurgical armamentarium in the late 1800s, with a subsequent clinical course focused on pituitary surgery that was marked by slow but persistent technical improvements leading to reduced morbidity and mortality, improved rates of gross total resection (GTR), and better overall patient outcomes [1]. The major technological innovations empowering these developments included the development of the surgical microscope and, more recently, the transnasal endoscope, which has been consistently associated with fewer complications in pituitary surgery, including decreased rates of post-operative diabetes insipidus (DI) and shorter hospital stays [2, 3]. In recent years, endoscopic transnasal approaches have been used in the resection of other tumors located along the skull base and accessible through the nose. However, the utility of endoscopy in the resection of non-pituitary skull base tumors relative to open craniotomy approaches has not been elucidated. Generally speaking, endoscopic approaches represent minimally invasive access to these tumors, but are technically challenging to most neurosurgeons and, additionally, are known for increased rates of CSF leak. In contrast, open approaches use microsurgical technique and extensive bony exposure to minimize brain retraction, although some manipulation of neural structures is typically still required [4, 5].

In an effort to understand how transnasal endoscopy compares to open craniotomy for the resection of non-pituitary skull base tumors, we performed a systematic review of the literature describing these techniques. Our study focused on four of the most common non-pituitary skull base lesions: olfactory groove meningiomas (OGM), tuberculum sellae meningiomas (TSM), craniopharyngiomas (CRA), and clival chordomas (CHO). Meningiomas are common, benign, slow-growing, extra-axial tumors arising from the arachnoid cap cells that make up 35.2 % of all primary central nervous system (CNS) tumors [6]. 14.2 % arise from the tuberculum sellae or planum sphenoidale, and 3.7 % from the olfactory groove [7]. Craniopharyngiomas are suprasellar lesions derived from remnants of Rathke's pouch, which constitute 4.1 % of all pediatric CNS tumors and occur with a bimodal distribution peaking at 5–14 and 65–74 years-of-age [6, 8]. Survival rates are generally good—99 % at 5 years for patients diagnosed under 20 years-of-age, and 80 % for patients diagnosed between 20 and 64. However, recurrence rates are also high—33 % at 10 years, and 40 % at 15 years [8, 9]. Chordomas are rare malignant primary CNS tumors that arise from remnants of the primitive notochord, with an incidence of 0.08 per 100,000, 32 % of which occur at the skull base [10]. Extracranial metastasis is rare, but recurrence is common at 35 % within 5 years for skull base chordomas [11].

Even as endoscopic endonasal surgery has become more widely adopted, research evaluating its safety and efficacy remains limited. Although the available data in our study are constrained by methodological compromises including lack of randomization, retrospective analysis, heterogeneity between studies regarding how outcomes were defined and recorded, short follow-up after endoscopic resection, and small study sizes, our aim was to use a large review to make basic comparisons between open and endoscopic endonasal approaches in these tumors. Perhaps most importantly, we hoped to highlight the weaknesses in the current knowledge base and the need for prospective research with long-term follow-up to help answer a clinical question of growing importance.

Methods

Article selection

Online searches were performed using the MEDLINE (PubMed) and Embase databases for English-language articles using the following MESH headings, alone and in combination: “craniotomy,” “endoscopic,” “endoscopy,” “olfactory groove,” “tuberculum sellae,” “clivus,” “meningioma,” “craniopharyngioma” and “chordoma.” Article bibliographies were reviewed using identical search terms for sources not captured by primary screen.

Table 1 details our inclusion and exclusion criteria. Inclusion was limited to original articles published since January 1, 1990. Case reports, retrospective case series, and prospective studies of primary resections were considered eligible. Reports including multiple pathologies or studies comparing open and endoscopic endonasal techniques were included, provided that data were reported separately. In keeping with related reports, data from articles on tuberculum sellae and planum sphenoidale meningiomas were combined [5, 12–14]. Reoperations, planned limited resections to be followed by radiation therapy, articles reporting only pooled data, and review articles were excluded. Transnasal microscopic approaches were excluded.

From the initial screen of more than 2,500 articles, 162 satisfied inclusion criteria and were subject to full analysis, yielding 176 data sets containing information on 5,701 patients. Table 2 summarizes the distribution of articles and patient data points by tumor type, approach, and study size.

Data extraction

Primary endpoints examined in all tumor types included rate of GTR, perioperative mortality, CSF leak, neurological morbidity (defined as new or worsened cranial nerve deficits, intraoperative or immediate postoperative cerebrovascular

Table 1 Study criteria

Inclusion criteria	Exclusion criteria
Case reports, retrospective case series, and prospective studies	Reoperations
Primary resections of TSM, OGM, CRA, or CHO	Planned limited resections followed by radiation therapy
Published 1990 or later	Published 1989 or earlier
Pure open or endoscopic approaches	Transnasal microscopic approaches
For reports including multiple pathologies and/or approaches, data reported separately	Articles reporting only pooled data from multiple pathologies, approaches, or primary and recurrent resections
English language	Review or editorial articles summarizing other previously-reported series without original patient data

Table 2 Summary of studies included in the analyses by tumor type (OGM, TSM, CRA, or CHO) and surgical approach

	OGM-O	OGM-E	TSM-O	TSM-E	CRA-O	CRA-E	CHO-O	CHO-E
No of series	30	9	41	14	47	13	3	18
No of patients	782	30	1464	90	3014	104	95	122
Range of study size	1–91	1–12	5–112	1–13	22–309	1–18	6–46	1–20
Mean of study size	25	3	35	6	64	8	32	7
Standard deviation of study size	25	3	23	4	54	5	22	6

O: open surgical approach, E: endoscopic surgical approach

accident resulting in a permanent motor or sensory deficit, or a new or worsened seizure disorder), postoperative visual function (defined as improvement, worsening, or no change in existing visual field defects or visual acuity, or the occurrence of new symptoms in previously asymptomatic patients), and recurrence/progression. Secondary endpoints—examined in appropriate tumor types—included post-operative anosmia, DI, and obesity/hyperphagia. Supplemental Tables 1–8 contain the complete data sets extracted from all included studies.

Analysis

Average values for each outcome weighted by study size were calculated by tumor type and surgical approach, with 95 % confidence intervals (Tables 3, 4, 5, 6; Fig. 1). Comparisons between open and endoscopic approaches for each tumor type were made using Fisher's exact test or Yate's continuity corrected χ^2 test. Although multiple endpoints were involved for each of the comparisons, no formal multiplicity adjustments were made. Instead, a conservative threshold of $p < 0.005$ was considered an indication of statistical significance, so as to avoid false positive results (Tables 3, 4, 5, 6). Weighted averages combined from all studies were plotted by year to depict overall trends in open and endoscopic surgery during the study period (Fig. 2). Recurrence rates per 1,000 patient-years of follow up were calculated by dividing the number of observed recurrences within each study by the sum of each study's mean follow-up multiplied by the number of

patients in that study. All calculations were completed using Microsoft Excel (Office 2011 for Mac, v14.2.5) or GraphPad Prism 5 for Mac.

Results

Primary outcomes

Weighted averages with confidence intervals for all outcomes by tumor type and approach are presented in Tables 3, 4, 5, 6 and in Fig. 1. Comparisons between open and endoscopic approaches are presented as p values in Tables 3, 4, 5, 6. Estimated recurrence rates per 1,000 patient-years of follow-up are presented in Table 7. Our observations follow below.

Differences in GTR, perioperative mortality, and worsened visual function were not significant for any tumors.

CSF leak was significantly increased after endoscopic surgery for both TSM (21.5 vs. 4.4 %, $p < 0.001$) and CRA (33.1 vs. 7.6 %, $p < 0.001$).

Improvement of visual function symptoms was significantly higher after endoscopy in TSM (87.0 vs. 61.0 %, $p = 0.001$), CRA (86.7 vs. 44.9 %, $p < 0.001$), and CHO (78.4 vs. 52.0 %, $p = 0.004$). Unchanged visual function was significantly higher after open surgery in TSM (28.1 vs. 10.5 %, $p < 0.001$), CRA (36.4 vs. 9.5 %, $p < 0.001$), and CHO (48.0 vs. 18.9 %, $p = 0.001$).

Neurological morbidity was significantly higher after endoscopic surgery in CRA (24.1 vs. 8.9 %, $p < 0.001$).

Table 3 OGM weighted averages confidence intervals and *p* values

	OGM-O (%)	95 % CI	OGM-E (%)	95 % CI	<i>p</i> value
Rate of GTR	93.6	[92.4–94.7 %]	89.7	[84.5–94.8 %]	0.433
Perioperative mortality	3.1	[2.8–3.4 %]	0.0	[0.0–0.0 %]	1.000
CSF leak	9.2	[8.4–10.0 %]	21.9	[6.8–37.0 %]	0.054
Neurological morbidity	4.2	[3.6–4.8 %]	5.9	[4.9–6.8 %]	0.531
Visual function improved	63.8	[60.6–66.9 %]	78.9	[64.9–93.0 %]	0.225
Visual function unchanged	29.3	[26.0–32.6 %]	21.1	[– 5.2–47.3 %]	0.601
Visual function deteriorated	2.7	[2.3–3.2 %]	0.0	[0.0–0.0 %]	1.000
Recurrence/progression	5.8	[4.9–6.8 %]	3.7	[0.9–6.5 %]	1.000
Post-Op DI	–	–	–	–	–
Post-Op anosmia	33.8	[27.6–39.9 %]	25.0	[– 3.1–53.1 %]	1.000
Obesity/hyperphagia	–	–	–	–	–

Table 4 TSM weighted averages, confidence intervals, *p* values

	TSM-O (%)	95 % CI	TSM-E (%)	95 % CI	<i>p</i> value
Rate of GTR	85.3	[84.5–86.0 %]	79.9	[76.5–83.2 %]	0.1735
Perioperative mortality	2.9	[2.7–3.1 %]	2.2	[1.0–3.4 %]	1.000
CSF leak	4.4	[3.8–5.0 %]	21.5	[18.4–24.7 %]	<0.001*
Neurological morbidity	7.6	[7.1–8.1 %]	4.4	[2.5–6.3 %]	0.396
Visual function improved	61.0	[60.0–62.0 %]	87.0	[83.7–90.3 %]	<0.001*
Visual function unchanged	28.1	[27.2–29.1 %]	10.5	[8.3–12.8 %]	<0.001*
Visual function deteriorated	11.4	[11.0–11.8 %]	2.1	[1.0–3.2 %]	0.009*
Recurrence/progression	4.2	[3.9–4.5 %]	5.0	[1.5–8.4 %]	0.147
Post-Op DI	–	–	11.7	[6.5–16.9 %]	–
Post-Op anosmia	–	–	–	–	–
Obesity/hyperphagia	–	–	–	–	–

* $p < 0.005$ considered significant for this analysis

Table 5 CRA weighted averages, confidence intervals, *p* values

	CRA-O (%)	95 % CI	CRA-E (%)	95 % CI	<i>p</i> value
Rate of GTR	61.4	[60.3–62.6 %]	59.0	[52.4–65.6 %]	0.696 [†]
Perioperative mortality	2.5	[2.4–2.7 %]	1.0	[0.0–1.9 %]	0.499 [†]
CSF leak	7.6	[6.9–8.3 %]	33.1	[27.0–39.1 %]	<0.001*
Neurological morbidity	8.9	[8.5–9.2 %]	24.1	[18.0–30.1 %]	<0.001 [†] ,*
Visual function improved	44.9	[43.8–46.1 %]	86.7	[84.3–89.2 %]	<0.001*
Visual function unchanged	36.4	[35.2–37.7 %]	9.5	[7.6–11.3 %]	<0.001*
Visual function deteriorated	12.8	[12.3–13.4 %]	3.7	[2.2–5.3 %]	0.020 [†]
Recurrence/progression	16.1	[15.4–16.9 %]	7.4	[6.4–8.5 %]	0.003 [†] ,*
Post-Op DI	68.8	[67.7–69.9 %]	29.3	[22.0–36.7 %]	<0.001*
Post-Op anosmia	–	–	–	–	–
Obesity/hyperphagia	30.1	[29.0–31.2 %]	5.1	[2.5–7.7 %]	<0.001*

[†] Yate's continuity corrected Chi squared test performed. All other *p* values calculated using Fisher's exact test

* $p < 0.005$ considered significant for this analysis

Table 6 CHO weighted averages, confidence intervals, *p* values

	CHO-O (%)	95 % CI	CHO-E (%)	95 % CI	<i>p</i> value
Rate of GTR	63.9	[59.9–68.0 %]	58.8	[54.5–63.2 %]	0.481
Perioperative Mortality	3.5	[3.2–3.7 %]	2.5	[1.3–3.6 %]	1.000
CSF Leak	26.5	[26.5–26.5 %]	16.2	[9.7–22.6 %]	0.140
Neurological Morbidity	50.5	[46.1–55.0 %]	6.9	[4.2–9.5 %]	<0.001*
Visual Function Improved	52.0	[52.0–52.0 %]	78.4	[74.3–82.6 %]	0.004*
Visual Function Unchanged	48.0	[48.0–48.0 %]	18.9	[14.3–23.4 %]	0.001*
Visual Function Deteriorated	16.7	[16.7–16.7 %]	4.0	[0.4–7.6 %]	0.269
Recurrence/Progression	9.3	[9.3–9.3 %]	6.8	[4.4–9.1 %]	0.748
Post-Op DI	—	—	—	—	—
Post-Op Anosmia	—	—	—	—	—
Obesity/Hyperphagia	—	—	—	—	—

* *p* < 0.005 considered significant for this analysis **Fig. 1** Weighted averages of outcomes

Recurrences were higher on average after open surgery in CRA (16.1 vs. 7.4 %, *p* = 0.003), and approximately equal in OGM (5.8 vs. 3.7 %, *p* = 1.0), TSM (4.2 vs. 5.0 %, *p* = 0.147), and CHO (9.3 vs. 6.8 %, *p* = 0.748).

However, estimated recurrences per 1,000 patient-years of follow-up were approximately equal in CRA (35 vs. 34), but higher after endoscopic surgery for OGM (34 vs. 12), TSM (27 vs. 8), and CHO (50 vs. 17). This discrepancy is

Fig. 2 Trends in specific outcomes by five-years periods

Table 7 Estimated recurrences

	OGM-O	OGM-E	TSM-O	TSM-E	CRA-O	CRA-E	CHO-O	CHO-E
Mean follow-up (months)	62	24	62	20	72	25	56	17
Estimated total follow-up (patient-years)	2,630	30	6,428	105	13,668	190	412	161
Actual recurrences	30	1	58	3	424	6	4	8
Estimated recurrence (per 1,000 patient-years)	12	34	8	27	35	34	17	50

most likely ascribable to the fact that follow-up is shorter in the endoscopic group, thereby underestimating the actual recurrence rate, as discussed below.

Secondary outcomes

In OGM, post-operative anosmia was higher on average after open surgery, but the difference was not significant (33.8 vs. 25.0 %, $p = 1.0$). In CRA, both post-operative DI and obesity/hyperphagia were significantly higher after open surgery (68.8 vs. 29.3 %, $p < 0.001$; 30.1 vs. 5.1 %, $p < 0.001$).

Trends

Mortality and CSF leak in endoscopic approaches reached a maximum in the mid-2000s, followed by a decrease

through subsequent years. With regard to GTR, endoscopy showed decreased GTR rates in 2005–2010, followed by a small increase since 2010 (Fig. 2). Neurologically morbidity rates have been increasing since 2000 (Fig. 2).

Discussion

Our observations suggest that endonasal endoscopy is a safe alternative to open surgery, and a technique that has improved markedly beyond its clinical infancy.

With respect to perioperative mortality and rate of GTR, our analysis did not show a significant difference between open and endoscopic approaches. Although these findings must be taken in the context of small data sets and limited

statistical tests, we also observed a subtle trend in the weighted averages suggesting increased mortality after open surgery, possibly due to more aggressive resection.

Our review indicates that CSF leak is the major complication associated with endoscopic endonasal surgery, a finding that has been observed in numerous other studies—especially in TSM and CRA [15, 16]. Anatomic access to the clivus in CHO operations is a technical challenge, and the risk of CSF leak is considerable by either approach; as such, our observation that the open and endoscopic groups had similar rates of CSF leak is not surprising [11, 17]. In OGM, the weighted averages showed 9.2 % CSF leak among open patients, versus 21.9 % CSF leak among endoscopic patients, a difference that was not significant in our review, but which could be significant in a larger, prospective study.

Neurological morbidity was statistically equivalent in OGM and TSM. In CRA, neurological morbidity was significantly higher after endoscopic resection; however, this finding may be confounded by our definition of neurological morbidity, which excluded DI and obesity/hyperphagia. For consistency, we maintained this definition in CRA despite the fact that DI and obesity/hyperphagia constitute the overwhelming majority of post-operative morbidity, due to manipulation of the pituitary stalk and hypothalamus. Although the higher rate of neurological morbidity we observed after endoscopic resection could be due to differences in vascular control, a more accurate picture of the morbidity burden in CRA is captured by our secondary outcomes, which showed significantly higher rates of both DI and obesity/hyperphagia after open surgery.

In CHO, we observed significantly higher neurological morbidity after open surgery (50.5 vs. 6.9 %, $p < 0.001$). The difference is not surprising, as open access to the clivus is operatively complex and associated with significant exposure of the cranial nerves and the brainstem, as well as their manipulation in order to reach ventrally located tumor. In contrast, endoscopic endonasal surgery provides direct access to these ventral tumors.

Recurrence may be the most important question in judging the efficacy of endoscopic surgery, yet given the limited data available on a relatively young technique, the similarity in average recurrence rates observed in OGM, TSM, and CHO may not accurately represent the clinical reality. Correspondingly, we chose to estimate the recurrence rates per 1,000 patient-years of follow-up, which predicted nearly three times as many recurrences in OGM, TSM, and CHO after endoscopic surgery as compared to open surgery (Table 7). It is clear that further study is required to determine recurrence rates in the two approaches and that the continuous evolution of endoscopy may someday match open craniotomy with regard to risk for recurrence.

During the earliest years of endoscopic surgery, adverse outcomes initially increased over time, yet within a decade that trend reversed. In parallel, the rate of GTR initially decreased, then increased, suggesting an underlying “learning curve” as neurosurgeons became more comfortable with the limitations of the technology. These boundaries are defined by the balance between extent-of-resection and complication risk, two opposing forces whose interplay and patient-to-patient variation is only learned with experience. Of particular note, the trends we observed in rate of CSF leak are consistent with other published observations on learning endoscopic endonasal neurosurgery [18].

In spite of its limitations, our study is the most broad-reaching and diverse investigation of safety in endoscopic endonasal skull base surgery that we are aware of, and we believe that it will aid informed clinical decision-making and guide future research. Given the complexities surrounding randomization, we are considering a longitudinal patient registry as an alternative to a randomized, controlled trial that would ensure standardized criteria and long-term, prospective follow-up.

We believe that our findings support the safety of endoscopy in appropriate patients. The major risk of endoscopy is CSF leak—an observation consistent with clinical wisdom and the skull base literature at large. Notwithstanding, our observations suggest that endoscopic surgery may offer patients a better chance at improved post-operative visual function, and possibly less risk of DI or obesity/hyperphagia in CRA. In summary, although we believe that our review provides new insight and support for current clinical practices, our chief finding is that additional study is required to definitively address unresolved concerns. Nevertheless, in experienced hands endoscopic surgery is likely to remain an important neurosurgical tool, and one whose indications and applications will continue to expand in parallel with surgeon experience and technological capability.

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