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Endoscopic Endonasal Versus Endoscopic Supraorbital Keyhole Surgery for Craniopharyngioma Resection: A 15-Year Single-Center Retrospective Cohort Study

Ajit Phuyal
King Edward Medical University
Burhan Ulhaq
King Edward Medical University
Hammad Nasir Malik
King Edward Medical University
Simon John
drsimonjohn7@gmail.com
United Medical & Dental College https://orcid.org/0009-0003-8131-9506
Kanwal Ali
Indus Medical College & Hospital
Asim Andrabi
King Edward Medical University

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Abstract

Background.

Craniopharyngioma is a WHO grade I epithelial tumor arising from Rathke's pouch remnants. Despite its benign histology, its proximity to the optic apparatus, hypothalamus, and major neurovascular structures makes surgical management challenging. Comparative data on minimally invasive approaches from lower-middle-income countries remain limited.

Methods.

We performed a single-center retrospective cohort study at Mayo Hospital, Lahore, Pakistan, including consecutive patients who underwent surgery for craniopharyngioma between June 2007 and September 2022. 60 eligible patients (5–65 years) were included: 30 underwent an extended endoscopic endonasal approach (Group A) and 30 an endoscopic supraorbital eyebrow keyhole craniotomy (Group B). Primary outcomes were gross-total resection (GTR) on 48-hour postoperative MRI and visual improvement at 3 months. Secondary outcomes included cerebrospinal fluid (CSF) leak, new endocrine deficits, and recurrence. Relative risks (RRs) with 95% confidence intervals (CIs) were calculated.

Results.

Suprasellar/intrasellar tumors were more common in Group A (73.3% vs. 33.3%), whereas retrochiasmatic/intraventricular lesions predominated in Group B (40.0% vs. 13.3%). GTR was achieved in 83.3% of Group A versus 60.0% of Group B (p = 0.045; RR 1.39, 95% CI 1.00–1.93). Visual improvement occurred in 86.7% and 63.3%, respectively (p = 0.037; RR 1.37, 95% CI 1.03–1.82). CSF leaks were more frequent in Group A (13.3% vs. 3.3%), while endocrine outcomes and recurrence were comparable.

Conclusions.

The endoscopic endonasal approach was associated with higher rates of GTR and visual improvement than the supraorbital keyhole approach. Both techniques remain complementary, and approach selection should be individualized according to tumor anatomy, hypothalamic involvement, and surgical expertise. Prospective multicenter studies are needed to validate these findings.

Introduction

Craniopharyngioma is a WHO grade I epithelial tumor arising from squamous cell remnants of Rathke's pouch along the craniopharyngeal duct.[1–3] Despite its histologically benign classification, it is widely regarded as one of the most surgically demanding intracranial neoplasms owing to its anatomical proximity to the optic chiasm, hypothalamus, pituitary stalk, and major cerebral vessels. The reported

incidence is approximately 0.5–2.5 per 100,000 population annually, with a bimodal age distribution peaking in children aged 5–14 years and again in adults aged 50–75 years.[1,2] The adamantinomatous subtype predominates in the pediatric population, whereas the papillary subtype is almost exclusively encountered in adults.

Despite generally favorable long-term survival, patients with craniopharyngioma bear a disproportionate burden of morbidity, including progressive visual deterioration from optic apparatus compression, hypothalamic dysfunction manifesting as obesity and thermoregulatory failure, panhypopituitarism, and neuropsychological sequelae that profoundly impair quality of life.[2,4] Surgical resection remains the cornerstone of management; however, the optimal operative strategy with respect to both approach selection and intended extent of resection continues to be debated.[5,6]

Traditional transcranial approaches (pterional, subfrontal, orbitozygomatic) provide wide exposure of the suprasellar compartment but are associated with significant brain retraction, manipulation of neurovascular structures, and associated perioperative morbidity.[5,6] The evolution of endoscopic skull base surgery over the past two decades has refined two competing minimally invasive paradigms: the extended endoscopic endonasal transplanum-transtuberculum approach, which exploits the natural midline corridor to provide a direct inferior-to-superior trajectory to the suprasellar space; and the endoscopic supraorbital eyebrow keyhole craniotomy, which offers a lateral subfrontal corridor with endoscope augmentation. [6,7,11,12,22]

Published comparative series have yielded conflicting conclusions. Several institutional reports document higher rates of GTR and visual recovery with the endonasal route in appropriately selected midline lesions,[8–10,19,20,] whereas others advocate individualized transcranial strategies for tumors with significant lateral, intraventricular, or retrochiasmatic extension.[6,13,22] Comparative evidence from lower-middle-income settings, where resource constraints may influence technique adoption and outcomes, remains sparse.

We therefore undertook this 15-year retrospective cohort study to characterize our institutional experience with both approaches, compare co-primary outcomes of GTR and visual improvement, and report complications and medium-term recurrence rates. We explicitly acknowledge that a non-random approach to allocation limits causal inference, and we frame our findings as hypothesis-generating observations for the planning of prospective comparative trials.

Methods

Study Design and Setting

This single-center retrospective cohort study was conducted at the Department of Neurosurgery, Mayo Hospital, Lahore, Pakistan. Consecutive surgical records from June 2007 to September 2022 were reviewed. The study was reported in accordance with the STROBE (Strengthening the Reporting of

Observational Studies in Epidemiology) guidelines. All patient data were anonymized before analysis. Given the retrospective design and use of de-identified data, formal ethical approval and the requirement for informed consent were waived by the Institutional Ethics Committee of Mayo Hospital. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Selection

A total of 67 consecutive patients with craniopharyngioma were identified between June 2007 and September 2022. After applying predefined eligibility criteria, 60 patients were included in the final analysis (Fig. 1). Inclusion criteria were: (i) age 5–65 years; (ii) radiologically confirmed craniopharyngioma on preoperative contrast-enhanced MRI; (iii) documented preoperative visual impairment; and (iv) primary surgical treatment at our institution using one of the study approaches. Exclusion criteria included prior resection at an external institution, incomplete clinical or imaging records, and insufficient postoperative follow-up. Seven patients were excluded: four due to incomplete records, two because of prior surgery elsewhere, and one owing to inadequate follow-up.

Surgical Approach, Allocation, and Selection Bias

Patients were allocated to one of two groups based on the operative approach selected by a multidisciplinary consensus incorporating tumor morphology on preoperative MRI (size, extension, chiasm displacement, calcification pattern), degree of hypothalamic and stalk involvement, availability of an adequate surgical corridor, and operating surgeon expertise. Retrochiasmatic and predominantly intraventricular tumors were preferentially directed to the supraorbital keyhole approach. All cases were performed by one of two fellowship-trained skull base neurosurgeons.

This non-random allocation constitutes an inherent and acknowledged source of selection bias. More anatomically favorable midline suprasellar lesions were systematically directed to the endonasal route, while more surgically challenging tumors with retrochiasmatic or intraventricular extension were preferentially assigned to Group B. Accordingly, all outcome comparisons should be interpreted as reflecting both approach-specific and tumor-specific effects; the observed differences in GTR and visual outcomes cannot be attributed solely to surgical approach. This limitation is explicitly addressed in the Discussion.

Surgical Techniques

Group A, Endoscopic Endonasal Approach

Surgery was performed under general anesthesia with the patient supine, head extended 15–20°. A binostril, four-handed endoscopic technique was employed using 0° and 30° rigid endoscopes (4 mm diameter; Karl Storz, Tuttlingen, Germany). Sequential sphenoidotomy, posterior septectomy, and

bilateral posterior ethmoidectomy were performed to expose the sellar and parasellar anatomy. The planum sphenoidale and tuberculum sellae were drilled with a high-speed diamond burr to create the transplanum-transtuberculum bone window. The superior intercavernous sinus was coagulated and divided where necessary to optimize access. The tumor was debulked internally and dissected from the optic nerves, chiasm, and hypothalamic perforators under direct endoscopic visualization. Skull base reconstruction was performed in all cases using a vascularized pedicled nasoseptal flap reinforced with an abdominal fat graft and fibrin sealant.

Group B, Endoscopic Supraorbital Keyhole Craniotomy

Surgery was performed under general anesthesia with the patient supine, head rotated 15–20° contralateral to the side of dominant tumor extension, and fixed in a Mayfield three-point head holder. A 3–4 cm incision was placed within the natural skin crease of the lateral two-thirds of the ipsilateral eyebrow. A keyhole craniotomy (approximately 2.5 × 1.5 cm) was fashioned at the frontal-orbital junction using a pneumatic craniotome. A 30° 4-mm rigid endoscope was introduced through the subfrontal corridor following arachnoid dissection along the basal cisterns. Tumor resection was performed under endoscope-assisted microsurgical guidance, with dynamic retraction of the optic nerves and preservation of hypothalamic perforators. Watertight dural closure was achieved with 4 − 0 Prolene suture supplemented by Tisseel fibrin sealant (Baxter Healthcare, Deerfield, IL, USA).

Outcome Measures

Co-primary outcomes were: (i) Extent of resection, classified as gross-total resection (GTR; no contrast-enhancing tumor on postoperative MRI) or subtotal resection (STR; any residual enhancement), assessed on gadolinium-enhanced MRI within 48 hours of surgery by a board-certified neuroradiologist blinded to the operative approach; and (ii) Visual improvement, defined as improvement in best-corrected visual acuity of ≥ 2 Snellen lines in at least one eye, or a clinically meaningful improvement in visual field (≥ 1 quadrant), assessed by an independent ophthalmologist at 3 months postoperatively.

Predefined secondary outcomes comprised: CSF leak requiring intervention; new-onset diabetes insipidus; new pituitary insufficiency; clinical evidence of hypothalamic injury; surgical site infection; 30-day reoperation rate; mean hospital length of stay; and radiological recurrence at last available follow-up. These endpoints are presented in Table 3 for descriptive purposes; the study was not powered to detect between-group differences in individual secondary endpoints, and all secondary comparisons should be regarded as exploratory.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean ± standard deviation (SD) and were compared using the independent-samples *t*-test after confirming normality by the Shapiro–Wilk test. Categorical variables are reported as frequencies and percentages and were compared using the Pearson chi-square

test or Fisher's exact test where expected cell counts were less than 5. Relative risk (RR) with 95% CI was calculated for each primary outcome. Subgroup analyses were performed for tumor size (≤ 30 mm vs. >30 mm) and age group (≤ 50 years vs. >50 years); these subgroup comparisons were exploratory and were not adjusted for multiple comparisons. Given the retrospective observational design and acknowledged selection bias, no formal multivariate adjustment was performed; however, we note that multivariable logistic regression adjusting for tumor location and size would be a priority analysis for any future prospective study. No imputation was performed for missing data. A two-tailed p-value of ≤ 0.05 was considered statistically significant for primary outcomes.

Results

Of 67 patients assessed for eligibility between June 2007 and September 2022, 60 were included in the final analysis (30 per group). Seven patients were excluded: four due to incomplete medical records, two due to prior surgery at an external institution, and one due to insufficient follow-up (Fig. 1). Baseline demographic and clinical characteristics are summarized in Table 1.

Mean age was 50.1 ± 13.9 years in Group A and 51.0 ± 14.2 years in Group B (p = 0.81). Sex distribution (53.3% male in Group A vs. 50.0% male in Group B; p = 0.79), mean tumor diameter (28.4 ± 9.1 mm vs. 29.7 ± 10.3 mm; p = 0.59), symptom duration (7.2 ± 3.1 months vs. 7.8 ± 3.4 months; p = 0.47), and preoperative Karnofsky Performance Status (72.4 ± 8.2 vs. 71.8 ± 8.6; p = 0.78) were comparable between groups.

Tumor location, however, differed significantly by design. Suprasellar or intrasellar lesions predominated in Group A (22/30, 73.3%) compared with Group B (10/30, 33.3%; p < 0.001). Retrochiasmatic tumors were more frequent in Group B (12/30, 40.0% vs. 4/30, 13.3%; p = 0.018). Intraventricular extension was present in 4 Group A patients (13.3%) and 8 Group B patients (26.7%; p = 0.18). Grade ≥ 2 hypothalamic invasion (per the modified DeLellis-Müller classification) was present in 8 Group A (26.7%) and 14 Group B patients (46.7%; p = 0.10). Histological subtype and cystic composition did not differ significantly between groups (Table 1). These differences in tumor location are a direct consequence of the approach-allocation strategy and represent the primary confounding factor in this study.

Table 1
Baseline Demographic, Clinical, and Tumor Characteristics.

Variable	Group A – Endonasal (n = 30)	Group B – Supraorbital (n = 30)	p-value
Mean age, years ± SD	50.1 ± 13.9	51.0 ± 14.2	0.81
Age 5–30 years, n (%)	3 (10.0)	3 (10.0)	> 0.99
Age 31–50 years, n (%)	10 (33.3)	10 (33.3)	> 0.99
Age 51–65 years, n (%)	17 (56.7)	17 (56.7)	> 0.99
Male sex, n (%)	16 (53.3)	15 (50.0)	0.79
Tumor location			
Suprasellar/intrasellar, n (%)	22 (73.3)	10 (33.3)	< 0.001
Retrochiasmatic, n (%)	4 (13.3)	12 (40.0)	0.018
Intraventricular, n (%)	4 (13.3)	8 (26.7)	0.18
Histological subtype			
Adamantinomatous, n (%)	21 (70.0)	19 (63.3)	0.58
Papillary, n (%)	9 (30.0)	11 (36.7)	0.58
Cystic/mixed composition, n (%)	19 (63.3)	17 (56.7)	0.60
Mean tumor diameter, mm ± SD	28.4 ± 9.1	29.7 ± 10.3	0.59
Tumor > 30 mm, n (%)	12 (40.0)	13 (43.3)	0.79
Hypothalamic invasion (Grade ≥ 2), n (%)	8 (26.7)	14 (46.7)	0.10
Mean symptom duration, months ± SD	7.2 ± 3.1	7.8 ± 3.4	0.47
Mean preoperative KPS ± SD	72.4 ± 8.2	71.8 ± 8.6	0.78
Preoperative visual deficit, n (%)	30 (100)	30 (100)	—

KPS = Karnofsky Performance Status; SD = standard deviation. Tumor location differences between groups reflect a deliberate allocation strategy (see Methods) and represent a key source of confounding. All other between-group comparisons non-significant (p > 0.05).

Primary Outcomes

Primary outcome data are presented in Table 2. GTR was achieved in 25 of 30 patients (83.3%) in Group A compared with 18 of 30 (60.0%) in Group B ($\chi^2 = 4.02$; p = 0.045; RR 1.39, 95% CI 1.00–1.93). The

absolute risk difference was 23.3 percentage points (95% CI 2.5–44.1). It bears emphasis that the confidence interval for the RR just excludes 1.00 (borderline significance), and that this difference is influenced by the preferential allocation of anatomically favorable tumors to Group A.

Visual improvement at 3 months was documented in 26 of 30 patients (86.7%) in Group A versus 19 of 30 (63.3%) in Group B ($\chi^2 = 4.43$; $p = 0.037$; RR 1.37, 95% CI 1.03–1.82). The absolute risk difference was 23.4 percentage points (95% CI 4.6–42.2).

Table 2
Primary Outcome Measures.

Outcome	Group A n = 30	Group B n = 30	χ^2	p-value	RR (95% CI)
Gross-total resection, n (%)	25 (83.3%)	18 (60.0%)	4.02	0.045*	1.39 (1.00–1.93)
Subtotal resection, n (%)	5 (16.7%)	12 (40.0%)	—	—	—
Absolute risk difference (GTR)	23.3%	(95% CI: 2.5–44.1%)	—	—	—
Visual improvement at 3 months, n (%)	26 (86.7%)	19 (63.3%)	4.43	0.037*	1.37 (1.03–1.82)
Absolute risk difference (visual)	23.4%	(95% CI: 4.6–42.2%)	—	—	—

*RR = relative risk; CI = confidence interval. GTR is defined as no contrast-enhancing tumor on 48-hour postoperative gadolinium-enhanced MRI. * Statistically significant at $p \leq 0.05$ (chi-square test); confidence intervals are borderline and should be interpreted cautiously given the modest sample size and non-random allocation.*

Subgroup Analysis

Subgroup analyses stratified by tumor size (≤ 30 mm vs. >30 mm) and age group (≤ 50 years vs. >50 years) revealed consistent numerical trends favoring the endonasal approach across all strata. For tumors exceeding 30 mm, GTR was achieved in 10 of 12 Group A patients (83.3%) versus 7 of 13 Group B patients (53.8%); visual improvement rates were 83.3% and 53.8%, respectively. In patients older than 50 years, GTR rates were 81.3% (13/16) versus 58.8% (10/17). None of these subgroup comparisons reached statistical significance ($p = 0.08$–0.14), attributable to substantially reduced stratum-level sample sizes. No adjustment for multiple comparisons was applied to these exploratory analyses. These findings should be treated as hypothesis-generating only.

Secondary Outcomes and Complications

Secondary outcomes are summarized in Table 3. CSF leak requiring intervention occurred in 4 Group A patients (13.3%) and 1 Group B patient (3.3%; $p = 0.16$), consistent with the known higher CSF leak risk of

endonasal skull base surgery. New-onset diabetes insipidus was observed in 9 Group A (30.0%) and 7 Group B patients (23.3%; p = 0.55). New pituitary insufficiency occurred in 11 (36.7%) and 9 (30.0%) patients, respectively (p = 0.58). Clinical hypothalamic injury was documented in 3 Group A (10.0%) and 4 Group B patients (13.3%; p = 0.69). Surgical site infection and 30-day reoperation rates were low and comparable. None of the individual secondary endpoint comparisons reached statistical significance, and given the sample size and exploratory nature, these data should be interpreted as descriptive rather than inferential.

Median follow-up was 38 months (IQR 18–72) in Group A and 41 months (IQR 22–78) in Group B (p = 0.62). Radiological recurrence at last follow-up was detected in 6 Group A patients (20.0%) and 8 Group B patients (26.7%; p = 0.54). The absence of a statistically significant difference in recurrence rates should be interpreted with caution, given the modest follow-up duration and the non-random allocation design.

Table 3
Secondary Outcomes and Complication Profile.

Outcome	**Group A – Endonasal (n = 30)**	**Group B – Supraorbital (n = 30)**	**p-value**
CSF leak requiring intervention, n (%)	4 (13.3)	1 (3.3)	0.16
New-onset diabetes insipidus, n (%)	9 (30.0)	7 (23.3)	0.55
New pituitary insufficiency, n (%)	11 (36.7)	9 (30.0)	0.58
Hypothalamic injury (clinical), n (%)	3 (10.0)	4 (13.3)	0.69
Surgical site infection, n (%)	1 (3.3)	1 (3.3)	> 0.99
30-day reoperation, n (%)	2 (6.7)	1 (3.3)	0.55
Mean hospital stay, days ± SD	7.4 ± 2.1	6.8 ± 2.3	0.30
Median follow-up, months (IQR)	38 (18–72)	41 (22–78)	0.62
Radiological recurrence at last follow-up, n (%)	6 (20.0)	8 (26.7)	0.54

IQR = interquartile range. All between-group comparisons for secondary outcomes are exploratory; the study was not powered to detect differences in individual secondary endpoints.

Discussion

This 15-year single-center retrospective cohort study compared endoscopic endonasal and endoscopic supraorbital keyhole approaches for craniopharyngioma resection in 60 patients with comparable demographic profiles. The principal findings were that the endonasal approach was associated with higher rates of both GTR (83.3% vs. 60.0%; p = 0.045) and visual improvement at 3 months (86.7% vs.

63.3%; p = 0.037). These findings must, however, be interpreted in the context of a fundamental and acknowledged limitation: the preferential allocation of anatomically favorable midline suprasellar tumors to the endonasal approach and more challenging retrochiasmatic or intraventricular tumors to the supraorbital approach. Selection bias remains the key limitation of this study, and the differences in primary outcomes reflect, at least in part, differences in tumor characteristics rather than surgical approach alone.

The anatomical rationale for favorable resection outcomes with the endonasal route in midline suprasellar tumors is well established.[11–13] The extended transplanum-transtuberculum corridor provides a direct inferior-to-superior trajectory enabling early decompression of the optic chiasm before tumor capsule manipulation, affording excellent visualization of the tumor–hypothalamic interface and the perforating vessels of the anterior communicating artery complex. By contrast, the supraorbital keyhole corridor is a unilateral lateral-to-medial approach that may require greater displacement of the optic apparatus for lesions with significant medial or inferior extension.[7,20,22] Studies have demonstrated that the degree of intraoperative chiasm mobilization is an independent predictor of visual outcome following craniopharyngioma surgery.[16,17]

Our GTR rate of 83.3% with the endonasal approach is consistent with—or at the higher end of—published series. Koutourousiou et al. reported GTR in 62% of 64 patients,[11] Cavallo et al. achieved GTR in 73% of a predominantly recurrent cohort,[12] and Fan et al. reported GTR in 68% of the endonasal group in a comparative series of 112 patients.[8] A recent systematic review and meta-analysis reported pooled GTR rates of approximately 65–70% for the endonasal approach across selected case series, acknowledging substantial heterogeneity in patient selection.[18] The relatively high GTR rate in our endonasal cohort likely reflects the stringent selection policy directing lesions with favorable intrasellar or suprasellar midline extension to this route.

The 86.7% rate of visual improvement in Group A is consistent with published endonasal series documenting visual recovery in 62–88% of patients.[18–20] The mechanistic basis for the close relationship between GTR and visual improvement is compelling: complete tumor removal eliminates ongoing compressive and ischemic insult to the optic apparatus, while the inferior operative trajectory enables earlier and gentler chiasm decompression.

The supraorbital keyhole approach achieved GTR in 60% and visual improvement in 63.3% of patients. These outcomes are consistent with published transcranial series.[22] Fatemi et al., comparing the two approaches directly in 31 patients, documented GTR in 58% of the endonasal group versus 50% of the supraorbital cohort, with visual improvement in approximately 60–65% of both groups.[22] Our study broadly corroborates these trends, with numerical differences also reaching statistical significance in this larger series. Given the borderline p-values (0.045 and 0.037) and wide confidence intervals, however, we caution against overstating the clinical magnitude of these differences. A type I error cannot be excluded.

The complication profile of the two approaches in this cohort reflects known anatomical vulnerabilities. The numerically higher CSF leak rate in Group A (13.3% vs. 3.3%)—a well-recognized risk of endonasal skull base surgery—did not reach statistical significance (p = 0.16), likely reflecting insufficient power for this secondary endpoint. Endocrine outcomes and recurrence rates were comparable, consistent with evidence that long-term endocrine morbidity is driven more by tumor biology and hypothalamic involvement than by surgical approach.[21]

Limitations

Several limitations should be considered when interpreting these findings. Most importantly, the retrospective design and non-random treatment allocation introduced unavoidable selection bias. Tumor location influenced surgical approach selection, with midline suprasellar lesions preferentially treated via the endonasal route and retrochiasmatic or intraventricular tumors more often managed through the supraorbital approach. Consequently, differences in outcomes likely reflect both surgical approach and underlying tumor characteristics. Although multivariable adjustment for tumor location would have been desirable, the sample size was insufficient to support robust regression analysis.

Second, the study was not powered to detect differences in secondary outcomes; therefore, complication and recurrence data should be interpreted descriptively. Third, the modest sample size (n = 30 per group) limits statistical precision. Fourth, standardized grading of hypothalamic involvement was not consistently available, precluding adjustment for an important determinant of resectability and long-term outcome. Fifth, primary outcomes were assessed at 3 months, and long-term visual, endocrine, recurrence, and quality-of-life outcomes were not systematically collected. Finally, this was a single-center study, which may limit generalizability to other institutions and healthcare settings.

Despite these limitations, this study provides real-world comparative data from a high-volume tertiary skull base center over 15 years and represents one of the largest single-center comparisons of these minimally invasive approaches reported from this region. Future prospective multicenter studies incorporating standardized treatment allocation, multivariable adjustment, comprehensive complication reporting, and validated quality-of-life measures are needed to confirm these findings.

Conclusion

In this 15-year retrospective institutional series, the endoscopic endonasal approach was associated with higher rates of gross-total resection and visual improvement compared with the endoscopic supraorbital keyhole approach for craniopharyngioma resection. While these associations are statistically significant, they must be interpreted with caution as they partially reflect systematic differences in tumor location arising from non-random surgical allocation. Ultimately, both techniques remain complementary tools in the skull base surgeon's armamentarium. The optimal surgical strategy should be individualized based on tumor morphology, institutional expertise, and the extent of hypothalamic and chiasmal involvement. Prospective, multicenter studies utilizing standardized

allocation, robust multivariable analysis, and patient-centered outcome assessments are required to definitively establish the relative merits of each approach.

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Figures

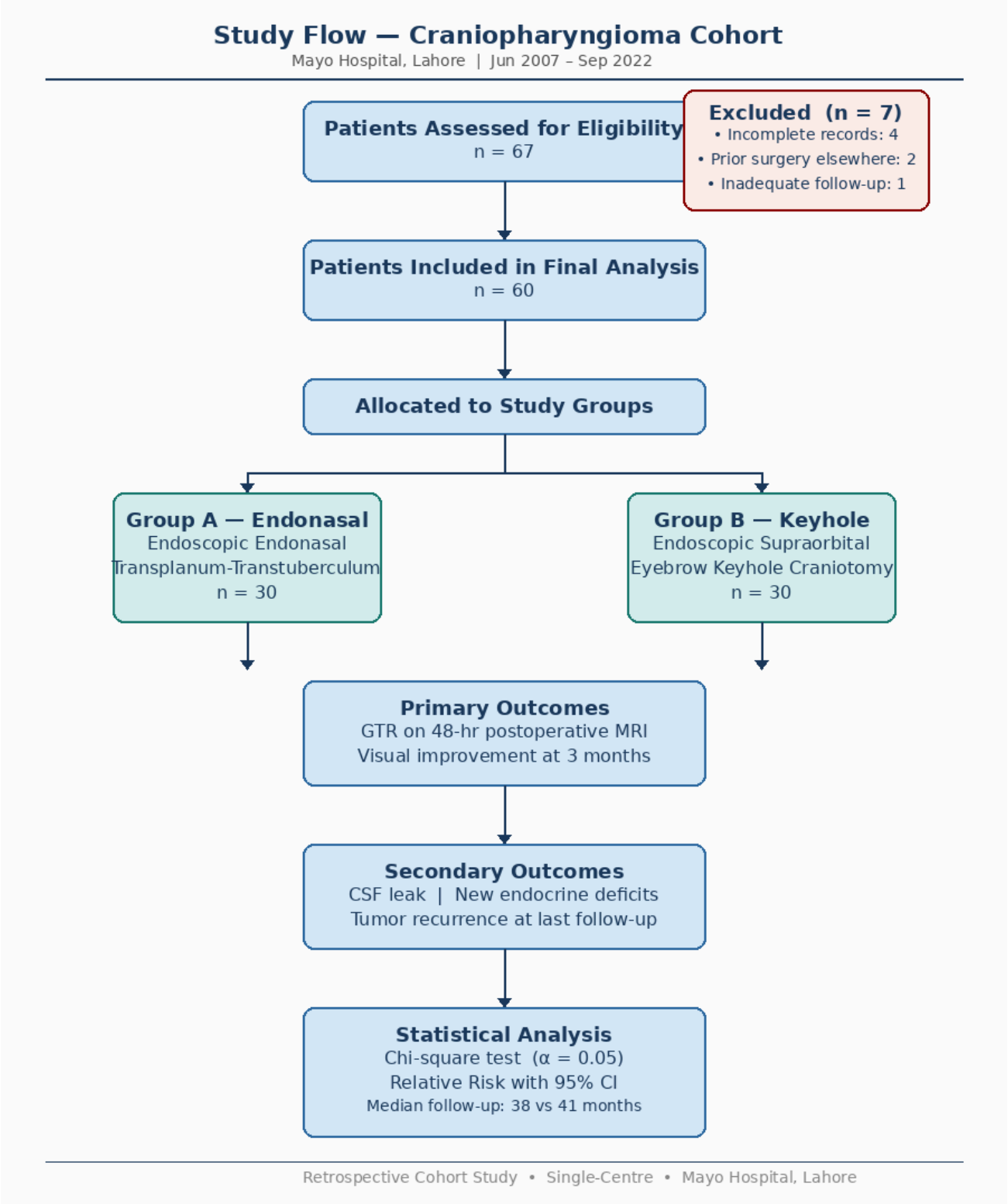


Figure 1

Patient selection and Allocation flowchart