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Neuronavigation-Assisted versus Conventional Endoscopic Endonasal Transsphenoidal Surgery for Pituitary Adenomas: A Pilot Randomized Controlled Trial

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Abstract

Purpose

Evidence on the benefit of intraoperative neuronavigation in endoscopic endonasal transsphenoidal (EET) pituitary surgery remains mixed. We conducted a pilot randomized controlled trial comparing navigation-assisted and conventional EET surgery for pituitary adenomas, to estimate the effect size for a definitive multicentre trial.

Methods

At Ain Shams University (April 2025–February 2026), 57 patients with pituitary adenomas were assessed for eligibility; 7 were excluded for prior Gamma Knife radiosurgery. The remaining 50 were randomized 1:1 within strata of tumor size, functional status, and surgery status, with concealed computer-generated allocation. Outcome assessors, but not surgeons, were blinded. The primary outcome was extent of resection; secondary outcomes included operative time, blood loss, visual and hormonal outcomes, and complications.

Results

All 50 patients (25 per arm) were analyzed by intention-to-treat. Gross total resection was numerically higher with navigation (28.0% vs 16.0%; p = 0.496); adjusted for Knosp grade, the odds ratio was 2.66 (95% CI 0.41–17.06) versus a crude 2.04. Extent of resection was strongly associated with tumor size, functioning status, and Knosp grade; no giant adenoma achieved gross total resection. Blood loss was lower with navigation (median 250 vs 350 mL; p = 0.016), with no difference in operative time or added delay (p = 0.788).

Conclusion

Neuronavigation did not significantly improve extent of resection, though resection completeness trended favorably with navigation across most subgroups. The associated blood-loss reduction remains hypothesis-generating. A definitive, adequately powered multicentre trial is warranted.

Trial registration:

Pan African Clinical Trial Registry, PACTR202608562462156, registered retrospectively on 17 August 2026.

Introduction

Pituitary adenomas are among the most common intracranial tumors, with prevalence estimates ranging from 1 in 865 to 1 in 2,688 adults [1]. Although histologically benign, they can extend beyond the sella to compress the optic chiasm, cavernous sinus, and adjacent neurovascular structures, and their management requires a multidisciplinary approach spanning endocrinology, ophthalmology, and neurosurgery [2].

Surgical management of pituitary adenomas has shifted decisively toward endoscopic endonasal transsphenoidal (EET) surgery, now the standard approach at most centers. Even so, EET surgery is performed within a narrow corridor bounded by critical neurovascular structures — the internal carotid arteries, optic nerves, and cavernous sinuses — and its safety depends on reliable intraoperative orientation, particularly when normal anatomical landmarks are distorted by tumor extension, prior surgery, or anatomical variants such as a conchal, nonpneumatized sphenoid sinus. Intraoperative neuronavigation has been proposed as a further adjunct, translating preoperative MRI/CT into a real-time anatomical roadmap intended to help the surgeon maintain orientation within this corridor [3, 4]. A 2024 systematic review and meta-analysis of 42 studies (2,271 patients) found navigation-assisted resection associated with more than double the odds of gross total resection (OR 2.29) compared with non-navigated surgery, alongside a modest reduction in postoperative CSF leak, though with substantial between-study heterogeneity and few randomized comparisons [5].

Other single-center comparative series have found no measurable benefit of navigation on resection or complication rates in routine cases with well-defined anatomy [6], and the added cost and setup time remain reasonable objections to its routine adoption [7]. The role of navigation across varying degrees of tumor complexity has not been adequately evaluated in a prospective randomized study [8]. Reported complications after EET surgery include postoperative CSF leak, transient arginine vasopressin deficiency (AVP-D; previously termed diabetes insipidus), and, rarely, internal carotid artery (ICA) injury, occurring in approximately 0.1–2% of cases [9, 10].

We therefore conducted a prospective, single-center, randomized controlled trial at Ain Shams University comparing navigation-assisted and conventional EET surgery for pituitary adenomas. Because no a priori sample-size calculation was performed and recruitment was pragmatically fixed to an 11-month window, we present this as a pilot trial: the pre-specified primary hypothesis was that neuronavigation improves extent of resection, with operative efficiency, blood loss, visual and hormonal control, and complication profile as pre-specified secondary outcomes. We further examined whole-cohort determinants of extent of resection to interpret subgroup analyses and adjust the primary comparison for baseline imbalance between arms.

Materials and Methods

Trial design

This trial is a prospective, single-center, parallel-group randomized controlled trial with 1:1 allocation, conducted in the Department of Neurosurgery, Ain Shams University, Cairo, Egypt, between April 2025 and February 2026. No interim analyses were planned or performed, and no changes were made to eligibility criteria, interventions, or outcomes after the trial began. The study was approved by the Research Ethics Committee of Ain Shams University (approval no. FMASU-306/2025), and written informed consent was obtained from all patients or their legal guardians before enrolment. The trial was registered retrospectively (PACTR202608562462156) and is reported in accordance with the CONSORT 2010 statement [11].

Participants

Adults (≥ 18 years) of either sex undergoing EET resection of a primary or recurrent pituitary adenoma were eligible. Patients with terminal illness, histopathologically atypical adenoma (defined by Ki-67 index and mitotic count), or prior Gamma Knife radiosurgery were excluded by protocol; radiosurgery was excluded because treatment-induced fibrosis is a recognized independent determinant of resectability that would confound comparison of extent of resection between arms.

The 50 eligible patients (Fig. 1) were stratified according to three predefined prognostic variables — tumor size (macroadenoma, large adenoma, or giant adenoma), tumor functional status (functioning or non-functioning), and surgery status (primary or recurrent) — before randomization. Of the 12 nominal strata defined by these variables, patients were allocated within 6 (Supplementary Table S2); the remaining 6 were structurally empty in this cohort, as no functioning giant adenomas and no non-functioning macroadenomas were enrolled. One patient in the conventional group required a staged operation following an intraoperative internal carotid artery injury during the initial aborted procedure; that initial procedure was not included in any statistical analysis, and outcome measures were recorded from the definitive second operation only.

Interventions: preoperative assessment

All patients underwent a standardized preoperative work-up comprising neurological and general examination, formal visual field assessment by an independent ophthalmologist, and a pituitary hormonal profile (prolactin, growth hormone, IGF-1, TSH, free T3/T4, diurnal cortisol, and ACTH). Contrast-enhanced MRI of the brain and sella and CT of the paranasal sinuses were obtained in all patients to characterize tumor size, cavernous sinus invasion (Knosp grade), and extension into adjacent compartments; maximal tumor diameter was measured using calibrated image-analysis software (Digimizer®, MedCalc Software, Ostend, Belgium).

Interventions: surgical technique

All procedures were performed via a binostril EET approach using 0° and 30° rigid endoscopes. In the navigation group, preoperative high-resolution MRI was registered to the Medtronic StealthStation® S8 platform, and the navigation probe was used to confirm midline orientation and the position of the sellar floor, internal carotid arteries, and optic nerves (Fig. 2I). In the conventional group, surgery used standard anatomical landmarks alone, without intraoperative image guidance. Skull base reconstruction, when required, used a multilayer fat/fascia graft with or without a vascularized nasoseptal flap; lumbar drainage was reserved for high-flow intraoperative CSF leaks.

Outcomes

The pre-specified primary outcome was extent of resection, assessed on postoperative MRI (at the 3-month visit) and categorized, based on volumetric assessment, as gross total resection (GTR, no visible tumor residual), near-total resection (NTR, ≥ 90% reduction in size), subtotal resection (STR, 70–90%), or partial resection (< 70%), according to Juraschka et al. [12]. Extent of resection was independently confirmed by a senior consultant neurosurgeon and by an independent neuroradiologist blinded to treatment allocation (Fig. 2A–H).

Pre-specified secondary outcomes were: operative time (minutes); estimated blood loss (mL), measured as suction-canister volume plus the weighed increment of surgical sponges, minus total irrigation volume; use of an intraoperative lumbar drain; postoperative complications (sinusitis, cranial nerve palsies, internal carotid artery injury, transient AVP-D, and intra- or post-operative CSF leak); visual outcome (improved or stable, among patients with a baseline deficit) assessed by an independent, blinded ophthalmologist; and hormonal control among patients with a functioning adenoma. All patients were followed up at a minimum of 2 weeks, 3 months, and 6 months postoperatively.

Hormonal control was assessed by structured biochemical follow-up. For acromegaly, serum IGF-1 was sampled at 48 hours postoperatively and at the 2-week, 3-month, and 6-month visits; control was defined as a normalized age- and sex-adjusted IGF-1 at 3 months together with satisfactory resection on follow-up MRI. For Cushing's disease, serum cortisol was screened at 24, 48, and 72 hours postoperatively to detect early adrenal insufficiency and reassessed at the same visits; control was likewise defined as a normalized cortisol level at 3 months.

Baseline and stratification variables

Preoperative variables included age, sex, visual field status, maximum tumor diameter on MRI (macroadenoma [< 30 mm], large [30–39 mm], or giant [≥ 40 mm]), Knosp grade (1–4, also dichotomized as low [1–2] or high [3–4]), functioning status (functioning [acromegaly, Cushing's disease] or nonfunctioning), and surgery status (primary or recurrent). Tumor size, functioning status, and surgery status were the three stratification variables used for randomization.

Sample size

No formal a priori sample-size or power calculation was performed. The trial enrolled all consecutive eligible patients presenting during a pragmatically fixed 11-month recruitment window, yielding 25 patients per group. Using the extent-of-resection rates observed here (28.0% vs 16.0% gross total resection), a definitive two-arm trial would require approximately 185 patients per arm to detect this difference with 80% power at a two-sided α of 0.05 (approximately 247 per arm for 90% power).

Randomization: sequence generation

Within each of the 12 nominal strata, patients were allocated 1:1 to the neuronavigation-assisted or conventional surgery group using a computer-generated randomization sequence, generated separately for each stratum with the random-number generator in SPSS version 26. No block randomization was used; because several strata contained few patients (Supplementary Table S2), this stratified-but-unblocked design did not guarantee balance within every stratum (see Results, Discussion).

Randomization: allocation concealment mechanism

The allocation sequence was concealed using sequentially numbered, opaque, sealed envelopes (SNOSE), prepared in advance for each stratum.

Randomization: implementation

The randomization sequence was generated, and the envelopes prepared, by a research coordinator independent of the surgical team, who had no role in patient enrolment, surgery, or outcome assessment. Patients were enrolled and the corresponding envelope opened, in sequence, by the treating surgical team only after eligibility was confirmed and consent obtained, so allocation could not be anticipated.

Blinding

Given the nature of the intervention, patients and the surgical team could not be blinded. To limit assessment bias, extent of resection on postoperative MRI was adjudicated by an independent neuroradiologist blinded to allocation, in addition to a senior consultant neurosurgeon, and visual field outcome was assessed by an independent ophthalmologist also blinded to allocation. Statistical analysis was unblinded.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range), and categorical variables as number (%). Because patients were allocated using stratified randomization, baseline characteristics (Table 1) are presented descriptively, and differences remaining numerically present despite stratification are discussed rather than formally tested, per CONSORT guidance.

Between-group comparisons used the independent-samples t-test or the Mann–Whitney U test; the Hodges–Lehmann estimator with bootstrap 95% confidence interval is additionally reported for blood loss. Categorical variables were compared using Fisher's exact test (2×2 tables) or an exact permutation test (Monte Carlo estimate, 20,000 resamples) for the 2×4 extent-of-resection comparison, since expected cell counts were below 5 in several cells, making the chi-square approximation unreliable there.

Table 1
Baseline demographic, preoperative visual, and tumor characteristics of the study cohort

Variable	Whole cohort (n = 50)	With Navigation (n = 25)	Without Navigation (n = 25)
Age, years, mean ± SD (median)	44.2 ± 10.3 (45.0)	45.6 ± 10.5 (47.0)	42.8 ± 10.0 (42.0)
Male sex, n/N (%)	31/50 (62.0)	15/25 (60.0)	16/25 (64.0)
Baseline visual deficit, n/N (%)	42/50 (84.0)	19/25 (76.0)	23/25 (92.0)
Max tumor diameter, mm, mean ± SD (median)	37.6 ± 10.8 (39.5)	36.7 ± 11.6 (39.0)	38.6 ± 10.0 (40.0)
Macroadenoma (< 30 mm), n (%)	10 (20.0)	5 (20.0)	5 (20.0)
Large (30–39 mm), n (%)	15 (30.0)	8 (32.0)	7 (28.0)
Giant (≥ 40 mm), n (%)	25 (50.0)	12 (48.0)	13 (52.0)
Knosp grade 1, n (%)	9 (18.0)	4 (16.0)	5 (20.0)
Knosp grade 2, n (%)	2 (4.0)	2 (8.0)	0 (0.0)
Knosp grade 3, n (%)	4 (8.0)	4 (16.0)	0 (0.0)
Knosp grade 4, n (%)	35 (70.0)	15 (60.0)	20 (80.0)
Functioning adenoma, n/N (%)	13/50 (26.0)	8/25 (32.0)	5/25 (20.0)
Non-functioning, n (%)	37 (74.0)	17 (68.0)	20 (80.0)
Acromegaly (GH-secreting), n (%)	8 (16.0)	5 (20.0)	3 (12.0)
Cushing's disease (ACTH-secreting), n (%)	5 (10.0)	3 (12.0)	2 (8.0)
Recurrent surgery, n/N (%)	10/50 (20.0)	6/25 (24.0)	4/25 (16.0)

As a pre-specified secondary sensitivity analysis, the primary outcome was additionally estimated after adjustment for Knosp grade (low [1–2] versus high [3–4]) using the Cochran–Mantel–Haenszel method and logistic regression; this covariate was chosen because Knosp grade was both strongly associated with extent of resection and numerically imbalanced between arms. A case-mix standardization, applying the whole cohort's functioning-status-specific gross-total-resection rates to each arm's actual composition, quantifies the contribution of baseline imbalance to the crude between-arm difference.

Analyses followed the intention-to-treat principle: all randomized patients were analyzed in their originally assigned group. For the one patient whose initial procedure was aborted, intraoperative and extent-of-resection outcomes were taken from the definitive second-stage procedure only, per protocol. Risk differences and, for binary outcomes with events in both arms, risk ratios are reported with 95% confidence intervals (Newcombe/Wilson method for proportions; Welch's t-based interval for operative time); secondary, adjusted, and subgroup estimates were not adjusted for multiplicity and are descriptive and hypothesis-generating. A two-tailed $p < 0.05$ was considered significant. Analyses used SPSS version 26 (IBM Corp., Armonk, NY).

Results

Participant flow (Fig. 1)

Of 57 consecutive patients assessed for eligibility between April 2025 and February 2026, 7 were excluded because of prior Gamma Knife radiosurgery for recurrent disease, and the remaining 50 were randomized (25 per arm); no eligible patient declined participation. One patient in the conventional group sustained an intraoperative internal carotid artery injury during the initial attempt; the procedure was aborted, the injury was managed by emergency endovascular embolization, and definitive resection was performed one month later using the same allocated technique. All 50 patients completed a minimum of 6 months' follow-up and were analyzed in their originally assigned group; none were lost to follow-up or discontinued the allocated intervention.

Baseline characteristics (Table 1)

The whole cohort had a mean age of 44.2 ± 10.3 years, and 62.0% were male. Most patients (84.0%) presented with a baseline visual field deficit, most commonly bitemporal hemianopsia. Nonfunctioning adenomas comprised 74.0% of the cohort; the remainder were GH-secreting (16.0%) or ACTH-secreting (10.0%) functioning adenomas. Half of all tumors (50.0%) were giant (≥ 40 mm), and 70.0% were Knosp grade 4. One-fifth of patients (20.0%) underwent surgery for recurrent disease.

Despite stratified randomization, several baseline variables differed numerically between arms (Table 1). Because randomization was stratified but unblocked within 12 nominal strata — only 6 of which were populated, several with very few patients (Supplementary Table S2) — it did not guarantee balance in every stratum. As tumor size, functioning status, and Knosp grade were each strongly associated with extent of resection, this residual imbalance is addressed in the adjusted analysis that follows.

Whole-cohort determinants of extent of resection (Table 2)

Table 2
Extent of resection in the whole cohort (N = 50), stratified by tumor size, functioning status, Knosp grade (dichotomized), and surgery status, irrespective of navigation use

Variable	Category	N	GTR	NTR	STR	Partial	p-value
Tumor size	Macroadenoma (< 30 mm)	10	7 (70%)	1 (10%)	0 (0%)	2 (20%)	
	Large (30–39 mm)	15	4 (27%)	7 (47%)	3 (20%)	1 (7%)	< 0.001
	Giant (≥ 40 mm)	25	0 (0%)	5 (20%)	8 (32%)	12 (48%)	
Tumor type	Functioning	13	8 (62%)	3 (23%)	0 (0%)	2 (15%)	0.001
	Non-functioning	37	3 (8%)	10 (27%)	11 (30%)	13 (35%)	
Knosp grade	Low grade (1–2)	11	8 (73%)	1 (9%)	0 (0%)	2 (18%)	< 0.001
	High grade (3–4)	39	3 (8%)	12 (31%)	11 (28%)	13 (33%)	
Surgery status	Primary	40	10 (25%)	11 (28%)	8 (20%)	11 (28%)	0.673
	Recurrent	10	1 (10%)	2 (20%)	3 (30%)	4 (40%)	

Before evaluating the primary comparison, we examined the association between established tumor characteristics and extent of resection across the whole cohort (N = 50), irrespective of navigation status. Tumor size, functioning status, and Knosp grade were each strongly associated with extent of resection (size and Knosp grade $p < 0.001$; functioning status $p = 0.001$; Table 2). GTR was achieved in 70% of macroadenomas, 27% of large tumors, and 0% of giant tumors; in 62% of functioning versus 8% of non-functioning adenomas; and in 73% of low-grade Knosp (1–2) versus 8% of high-grade Knosp (3–4) tumors. Surgery status was not significantly associated with extent of resection (GTR 25% vs 10%, $p = 0.673$).

Primary outcome: extent of resection with navigation (Table 3)

Table 3
Intraoperative data, extent of resection, and complications: navigation-assisted versus conventional endoscopic endonasal transsphenoidal surgery

Variable	With Navigation (n = 25)	Without Navigation (n = 25)	Whole cohort (n = 50)	p	Effect size (95% CI)
Operative time, min, mean ± SD	231.9 ± 36.0	235.6 ± 58.6	233.7 ± 48.2	0.788	MD − 3.7 (− 31.5 to 24.1)
Estimated blood loss, mL, median (IQR)	250 (250–350)	350 (300–420)	—	0.016	HL − 100 (− 150 to 0)
Intraoperative lumbar drain, n (%)	4 (16.0)	5 (20.0)	9 (18.0)	1.000	RD − 4.0 (− 25.4 to 17.7)
GTR, n (%)	7 (28.0)	4 (16.0)	11 (22.0)		
NTR, n (%)	8 (32.0)	5 (20.0)	13 (26.0)		
STR, n (%)	6 (24.0)	5 (20.0)	11 (22.0)		
Partial, n (%)	4 (16.0)	11 (44.0)	15 (30.0)		
Extent of resection, overall (4-category)				0.199	
GTR achieved, n (%) — primary outcome	7 (28.0)	4 (16.0)	11 (22.0)	0.496	RD 12.0 (− 11.2 to 33.8); RR 1.75 (0.58–5.24)
Knosp-adjusted (CMH) OR for GTR				0.30	OR 2.66 (0.41–17.06)
Postoperative sinusitis, n (%)	3 (12.0)	1 (4.0)	4 (8.0)	0.609	RD 8.0 (− 9.4 to 26.3)
Transient 6th nerve palsy, n (%)	0 (0.0)	3 (12.0)	3 (6.0)	0.235	RD − 12.0 (− 30.0 to 3.5)
Internal carotid artery injury, n (%)	0 (0.0)	1 (4.0)	1 (2.0)	1.000	RD − 4.0 (− 19.5 to 9.7)
Transient AVP-D, n (%)	3 (12.0)	2 (8.0)	5 (10.0)	1.000	RD 4.0 (− 14.7 to 22.9)
Intraoperative CSF leak, n (%)	4 (16.0)	5 (20.0)	9 (18.0)	1.000	RD − 4.0 (− 25.4 to 17.7)
Any complication, n (%)	8 (32.0)	11 (44.0)	19 (38.0)	0.561	RD − 12.0 (− 36.0 to 14.2); RR 0.73 (0.35–1.50)
Visual improvement, n/N (%)	14/19 (73.7)	16/23 (69.6)	30/42 (71.4)	1.000	RD 4.1 (− 22.8 to 29.2)

Variable	With Navigation (n = 25)	Without Navigation (n = 25)	Whole cohort (n = 50)	p	Effect size (95% CI)
Hormonal control, n/N (%)	6/8 (75.0)	5/5 (100.0)	11/13 (84.6)	0.487	RD − 25.0 (− 59.1 to 22.0)

Extent of resection showed a favorable but not statistically significant trend with navigation on the pre-specified (crude) comparison: gross total resection was achieved in 28.0% versus 16.0% of patients (risk difference 12.0 percentage points, 95% CI − 11.2 to 33.8; risk ratio 1.75, 95% CI 0.58–5.24; p = 0.496), and partial resection occurred less often (16.0% vs 44.0%); the overall four-category comparison did not reach significance by exact permutation test (p = 0.199, 20,000 Monte Carlo resamples; consistent with the chi-square approximation, p = 0.182, though the latter is unreliable given sparse cell counts).

Because Knosp grade and functioning status differed numerically between arms despite stratification, we performed a secondary sensitivity analysis adjusting the primary comparison for Knosp grade. The Knosp-stratified (Cochran–Mantel–Haenszel) odds ratio for gross total resection with navigation was 2.66 (95% CI 0.41–17.06, p = 0.30), directionally larger than the crude odds ratio (2.04) though similarly imprecise; logistic regression gave a consistent estimate (OR 2.68).

A case-mix standardization using the whole cohort's functioning-status-specific GTR rates (62% functioning, 8% non-functioning) predicted 6.3 gross total resections in the navigation arm and 4.7 in the conventional arm from case-mix alone, against 7 and 4 observed, indicating that roughly half of the crude 12-percentage-point difference is attributable to baseline imbalance in the proportion of functioning tumors rather than to navigation itself.

Secondary outcomes (Table 3)

Operative time did not differ significantly between groups (231.9 ± 36.0 vs 235.6 ± 58.6 min; mean difference − 3.7 min, 95% CI − 31.5 to 24.1; p = 0.788). Estimated blood loss was lower with navigation (median 250 [IQR 250–350] vs 350 [IQR 300–420] mL; Hodges–Lehmann median difference − 100 mL, p = 0.016 by Mann–Whitney U test).

Complication rates did not differ significantly for any individual complication or for the composite rate (32.0% vs 44.0%; risk difference − 12.0 percentage points, 95% CI − 36.0 to 14.2; p = 0.561). No patient in the navigation group developed transient sixth cranial nerve palsy, versus 12.0% conventionally (risk difference − 12.0 percentage points, 95% CI − 30.0 to 3.5; p = 0.235), and no internal carotid artery injury occurred with navigation versus one event (4.0%) conventionally (risk difference − 4.0 percentage points, 95% CI − 19.5 to 9.7; p = 1.000). Visual improvement (73.7% vs 69.6%) and hormonal control (75.0% vs 100.0%; p = 0.487) were comparable, though the small number of functioning adenomas (n = 13) limits the latter. No patient developed a new visual deficit or permanent anterior pituitary hormone deficit; only transient AVP-D was observed.

Subgroup (effect-modification) comparisons (Supplementary Table S1)

Subgroup comparisons are reported as exploratory and hypothesis-generating. Repeated within each tumor type, size, and surgery-status stratum, the blood-loss benefit of navigation was present among nonfunctioning adenomas (300 vs 350 mL, p = 0.040) and primary cases (250 vs 350 mL, p = 0.031). Because macroadenomas in this cohort were exclusively functioning tumors, and the recurrent-case subgroup overlapped substantially with the large-tumor subgroup, several subgroup estimates coincide numerically by construction rather than by chance (see Supplementary Table S1). In giant tumors (≥ 40 mm), GTR was 0% in both groups, indicating navigation did not overcome this ceiling. No other subgroup comparison reached statistical significance, and operative time and the composite complication rate did not differ within any subgroup (all p > 0.05).

Discussion

Baseline comparability and tumor case-mix

Despite stratified randomization, the navigation and conventional groups differed numerically at baseline in Knosp grade distribution, functioning-tumor proportion, and baseline visual deficit (Table 1). Stratified randomization without blocking constrains balance only in expectation; in a single trial this size it does not guarantee balance in any stratum. We address this directly with the Knosp-adjusted sensitivity analysis and case-mix standardization, rather than asserting a baseline comparability the data do not fully support.

Giant adenomas (≥ 40 mm) comprised half the cohort, and high-grade (Knosp 3–4) tumors 78% — considerably heavier than the 10–15% giant-tumor proportion typically reported in operated series [13]. Our trial therefore compared navigation and conventional surgery predominantly in anatomically challenging tumors, where any incremental benefit would be most clinically relevant — a complex cohort underrepresented in prior navigation series dominated by smaller, more straightforward tumors.

Determinants of resection extent

Tumor functional type, size, and Knosp grade were each strongly associated with extent of resection (functioning status p = 0.001; size and Knosp grade p < 0.001) (Supplementary Fig. S1), and no giant adenoma in either arm achieved gross total resection. Because these variables were highly collinear in our cohort, they are read as one axis of tumor invasiveness rather than as independent predictors. This mirrors the wider giant-adenoma literature: a series of 239 cases achieved GTR in only 19.3%, with diameter and Knosp grade the dominant limiting factors [14], and a multicenter series of 64 giant adenomas found GTR ranging from 64% in round tumors to 8% in multilobular ones [15]. Cavernous sinus invasion imposes a resectability ceiling that no surgical adjunct can fully overcome [16, 17]; pooled

data show Knosp grade 3–4 discriminates cavernous sinus invasion with an AUC of 0.86 across more than 3,000 patients [18].

Effect of navigation after accounting for baseline case-mix

When resection completeness was examined within tumor-characteristic strata, navigation showed a numerically higher completeness rate in most cases, most prominently in functioning adenomas, macroadenomas, and low-grade Knosp tumors — tumors not already at the anatomical ceiling of resectability (Supplementary Fig. S2). This pattern, together with the Knosp-adjusted odds ratio (2.66) exceeding the crude estimate (2.04), is consistent with the incremental value of intraoperative imaging deriving from identifying small, occult residual tumor when complete removal is anatomically feasible, rather than from overcoming invasion beyond the reach of conventional techniques [19, 20].

Recurrent cases showed a lower GTR rate than primary cases (10% vs 25%, Table 2), though this cohort included only 10 recurrent procedures and the comparison was not significant ($p = 0.673$). This is notable because revision surgery, where landmarks are most distorted, is precisely where navigation is most often argued to add value [4]; this remains an important target for a dedicated trial.

Operative efficiency and blood loss

Operative time did not differ by navigation status, consistent with Achey et al.'s finding that navigation setup does not add meaningful delay [6]. Blood loss was lower with navigation (Hodges–Lehmann median difference − 100 mL; $p = 0.016$). This diverges from Achey et al., who found no blood-loss difference [6]; blood loss is also not a standard outcome across most of the intraoperative MRI literature synthesized by Huang et al. [5], limiting direct comparison. Mechanistically, more precise anatomical orientation may permit more direct dissection with fewer exploratory maneuvers along the parasellar corridor, plausibly reducing incidental mucosal and venous-plexus injury; this complements perioperative strategies previously described to reduce blood loss in transsphenoidal surgery [21]. The clinical significance of a 100 mL median difference remains uncertain; we did not record transfusion requirements or postoperative hemoglobin change, and future trials should assess whether this difference translates into measurable clinical benefit.

Safety: cranial nerve and vascular injury

Rates of sinusitis, AVP-D, and intra-operative CSF leak did not differ by navigation status. No patient in the navigation arm developed transient sixth cranial nerve palsy or ICA injury, versus 12% and 4% respectively in the conventional arm. Our sixth-nerve palsy rate exceeds that of a comparably Knosp-4-heavy series (6.8%) [22], plausibly reflecting our higher proportion of high-grade tumors (78%). The single ICA injury (2% of the whole cohort) lies within the range reported in large contemporary series [9, 10, 23]. The literature on navigation's protective role against carotid injury is not unanimous — a systematic review found no evidence that image guidance mitigates this risk [24] — so our finding is hypothesis-generating given the rarity of the event.

Visual and functional outcomes

Visual outcomes were reassuring: no patient in either group developed a new or worsened visual deficit. Among the 42 patients with a baseline visual field deficit, 30 (71.4%) improved and 12 (28.6%) remained stable, with comparable outcomes between arms (73.7% vs 69.6%, p = 1.000). This mirrors prior series of large and giant adenomas, in which 80% improved, 20% remained stable, and none deteriorated [25, 26, 27]. The absence of deterioration is notable set against pooled estimates from the wider endoscopic literature, where improvement occurs in a similar proportion (80.8%, 95% CI 77.7–83.6%) but deterioration is still reported in approximately 2.3% (95% CI 1.1–4.7%) of cases [28]. That neither arm, despite its heavy giant-tumor and high Knosp-grade case-mix, produced a single instance of visual worsening likely reflects a conservative philosophy of safe optic-pathway decompression, with maximal resection pursued only when it did not compromise patient safety [25]. Visual and hormonal outcomes did not differ by navigation status, consistent with reports that functional recovery is governed primarily by degree of decompression and preoperative deficit severity rather than by the surgical adjunct used [25–27].

Conclusions

In this pilot randomized controlled trial, extent of resection did not differ significantly between navigation-assisted and conventional EET surgery on either the crude or the Knosp-adjusted comparison, though the adjusted estimate favored navigation more strongly. Extent of resection was determined predominantly by tumor size, functioning status, and Knosp grade rather than by surgical adjunct, though resection completeness trended favorably with navigation across most subgroups, with the exception of giant adenomas, in which no gross total resection was achieved in either group. Among secondary outcomes, neuronavigation did not prolong operative time and was associated with reduced intraoperative blood loss, and no transient sixth cranial nerve palsy or internal carotid artery injury occurred in the navigation group. Using the effect size observed here, a definitive, adequately powered, prospectively registered multicentre trial — requiring approximately 185 patients per arm — is warranted.

Limitations

This trial has several limitations. It was not prospectively registered; we registered it in PACTR retrospectively. No formal sample-size calculation was performed beforehand; recruitment was pragmatic, comprising all consecutive eligible patients over a fixed 11-month period. The resulting sample of 25 per arm limited power to detect a difference in the primary outcome and contributed to several secondary outcomes favoring navigation numerically without reaching significance.

The stratified randomization was unblocked, and with 25 patients per arm across 6 populated strata it did not guarantee balance within every stratum. We addressed this with a Knosp-adjusted sensitivity analysis and case-mix standardization rather than treating the crude comparison as unconfounded; a future trial should use block randomization within strata, or minimization, to prevent this prospectively.

We likewise did not collect navigation-specific process measures — registration accuracy, setup time, or instances of navigation failure or drift — that would help determine whether our results reflect navigation's inherent value or a particular implementation. The single-center, single-team design maximizes technical homogeneity but limits generalizability, and our high proportion of giant and high-Knosp-grade tumors likely reflects tertiary referral patterns. Although allocation concealment was maintained and outcome assessors blinded, blinding of surgeons and patients was not feasible — an inherent limitation of surgical trials. Finally, follow-up at 2 weeks, 3, and 6 months is adequate for perioperative and early biochemical outcomes but too short to capture long-term recurrence or delayed endocrinological outcomes; cost-effectiveness and learning-curve effects were also not evaluated.

Declarations

Funding

The authors did not receive support from any organization for the submitted work.

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki and is reported in accordance with the CONSORT 2010 statement for randomized trials. Approval was granted by the Research Ethics Committee of Ain Shams University (approval no. FMASU-306/2025).

Protocol

A separate, standalone trial protocol was not published. Full methodological detail, including the pre-specified primary and secondary outcomes, is reported in this manuscript; further detail is available from the corresponding author on reasonable request.

Consent to participate

Informed consent was obtained from all individual participants, or their legal guardians, included in the study, after the nature of the study was fully explained.

Consent to publish

Written informed consent for publication of accompanying images was obtained from the patients depicted in Fig. 2; each patient was assigned a coded study identifier, and no patient is identified by name in this manuscript.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request, subject to patient confidentiality considerations.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Michael Zohney and Mohamed M. Aziz. The first draft of the manuscript was written by Michael Zohney, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

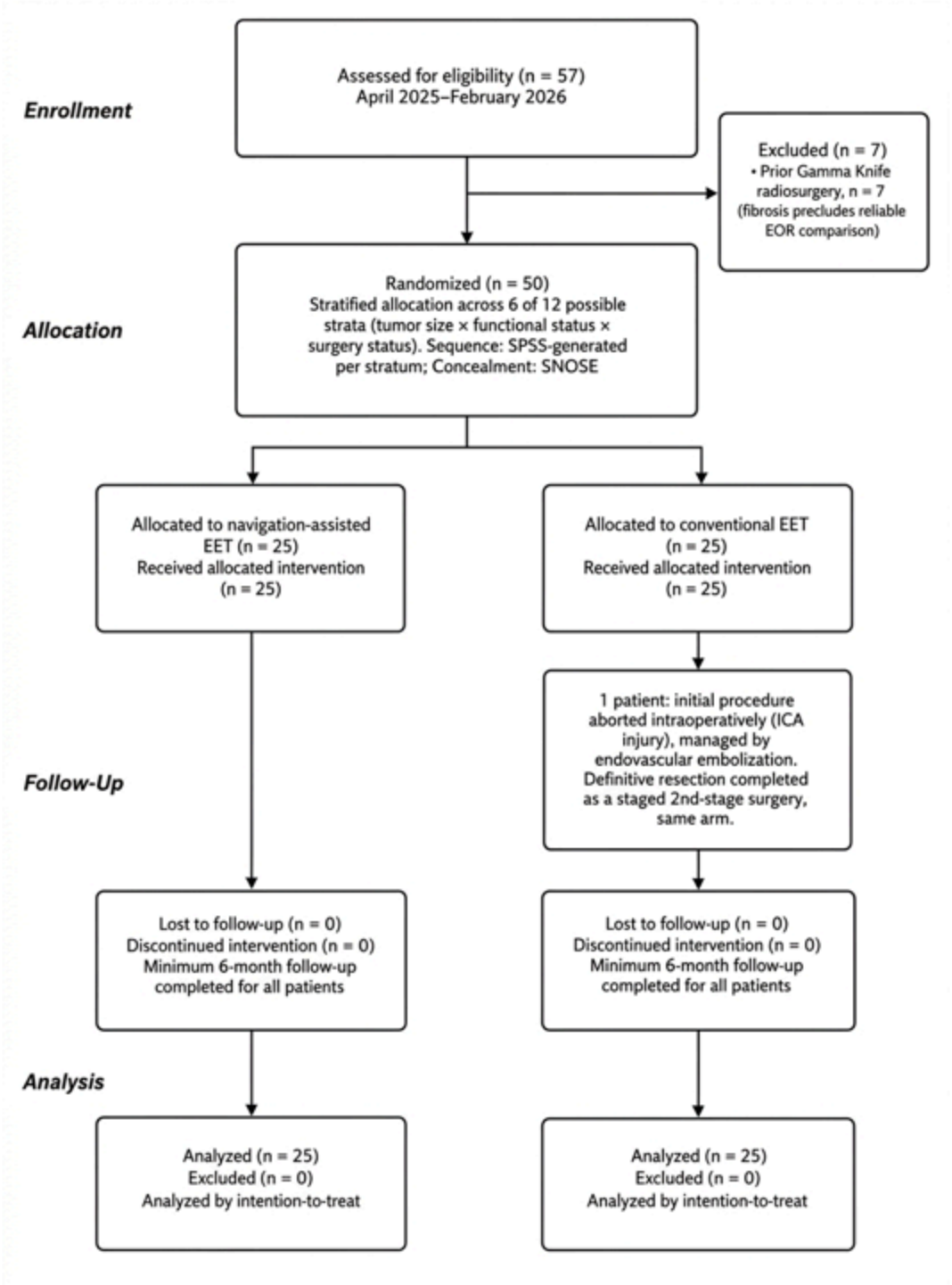


Figure 1

CONSORT participant flow diagram

Of 57 patients assessed for eligibility during the study period (April 2025–February 2026), 7 were excluded (prior Gamma Knife radiosurgery, all recurrent disease, n = 7), and the remaining 50 met the eligibility criteria and were randomized 1:1 within strata of tumor size, functional status, and surgery status (stratified randomization; sequence generated in SPSS; concealed using sequentially numbered,

opaque, sealed envelopes) to navigation-assisted (n = 25) or conventional (n = 25) EET surgery. One patient in the conventional group had an initial procedure aborted intraoperatively because of an internal carotid artery injury, managed by endovascular embolization, with definitive resection completed as a staged second-stage surgery under the same allocation; this initial procedure was excluded from all statistical analyses. All 50 randomized patients completed a minimum 6-month follow-up and were analyzed in their originally assigned group (intention-to-treat); none were lost to follow-up or discontinued the allocated intervention

Figure 2

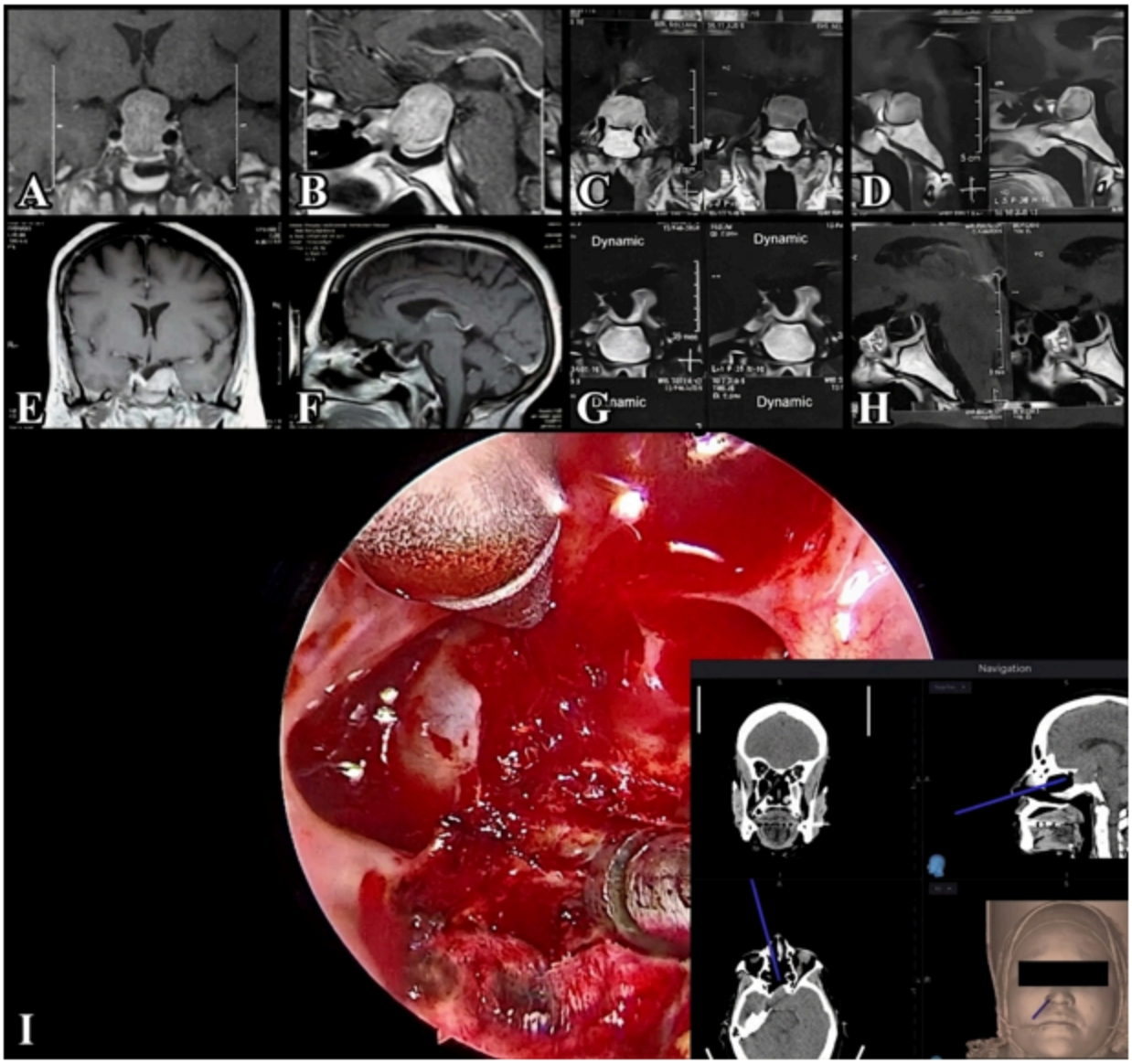


Figure 2

Illustrative case material

a–h Sagittal T1-weighted contrast-enhanced MRI in two representative patients undergoing endoscopic endonasal transsphenoidal resection of a pituitary adenoma, showing paired preoperative (a, b Patient 1;

c, d Patient 2) and postoperative (e, f Patient 1; g, h Patient 2) images at corresponding sagittal levels, demonstrating tumor resection with restoration of normal sellar and suprasellar anatomy. i Intraoperative endoscopic view (main panel) with the corresponding real-time Medtronic StealthStation® S8 navigation display (inset) from a separate, navigation-assisted case with a distorted surgical corridor; the tracked navigation probe (blue trajectory line, inset panels) was used to confirm anatomical orientation before proceeding with dissection.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORTchecklist.pdf
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