CSF Rhinorrhoea after Endonasal Intervention to the Skull Base (CRANIAL): A Multicentre Prospective Observational Study

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Counts:

Abstract: 347 words

Manuscript: 2975 words - excluding references, tables, figures.

Figures: 3

Tables: 2

Supplementary Materials: 6

Number of references: 40

Acknowledgements:

The authors would like to thank the Neurology and Neurosurgery Interest Group (NANSIG) and the British Neurosurgical Trainee Research Collaborative (BNTRC) without which this study would not have been possible. A special thanks to the data validation team for ensuring data accuracy (Supplementary Material 1). No specific funding was received for this study. HJM is supported by the Wellcome (203145Z/16/Z) EPSRC (NS/A000050/1) Centre for Interventional and Surgical Sciences, University College London. HJM is also funded by the NIHR Biomedical Research Centre at University College London. DZK is supported by an NIHR Academic Clinical Fellowship.

Abstract

Objective

Despite progress in endonasal skull-base neurosurgery, cerebrospinal fluid (CSF) rhinorrhoea remains common and significant. The CRANIAL study sought to determine 1) the scope of skull-base repair methods used, and 2) corresponding rates of postoperative CSF rhinorrhoea in the endonasal transsphenoidal approach (TSA) and the expanded endonasal approach (EEA) for skull-base tumors.

Methods

A prospective observational cohort study of 30 centers performing endonasal skull-base neurosurgery in the UK and Ireland (representing 91% of adult units). Patients were identified for 6 months and followed up for 6 months. Data collection and analysis was guided by our published protocol and pilot studies. Descriptive statistics, univariate and multivariable logistic regression models were used for analysis.

Results

A total of 866 patients were included - 726 TSA (84%) and 140 EEA (16%). There was significant heterogeneity in repair protocols across centers. In TSA cases, nasal packing (519/726, 72%), tissue glues (474/726, 65%) and hemostatic agents (439/726, 61%) were the most common skull base repair techniques. Comparatively, pedicled flaps (90/140, 64%), CSF diversion (38/140, 27%), buttresses (17/140, 12%) and gasket sealing (11/140, 9%) were more commonly used in EEA cases. CSF rhinorrhoea (biochemically confirmed or requiring re-operation) occurred in 3.9% of TSA (28/726) and 7.1% of EEA (10/140) cases. A significant number of patients with CSF rhinorrhoea (15/37, 41%) occurred when no intraoperative CSF leak was reported. On multivariate analysis, there may be marginal benefits with using tissue glues in TSA (OR: 0.2, CI: 0.1-0.7, $p<0.01$), but no other technique reached significance. There was evidence that certain characteristics make CSF rhinorrhoea more likely – such as previous endonasal surgery and the presence of intraoperative CSF leak.

Conclusions

There is a wide range of skull base repair techniques used across centers. Overall, CSF rhinorrhoea rates across the UK and Ireland are lower than generally reported in the literature. A large proportion of postoperative leaks occurred in the context of occult intraoperative CSF leaks, and decisions for universal sellar repairs should consider the risks and cost-effectiveness of repair strategies. Future work could include longer-term, higher-volume studies, such as a registry; and high-quality interventional studies.

Introduction

Endonasal approaches have revolutionized skull-base neurosurgery[1,25]. The most commonly utilized approach is the transsphenoidal approach (TSA), frequently used for sellar lesions. More recently, the development of the expanded endonasal approach (EEA) has allowed access to pathologies extending beyond the sella, with growing indications as this technique evolves[6,19].

An international expert consensus on TSA workflow highlighted the potential for practice variations, particularly in closure, due to a variety of skull-base repair options[27]. Previous systematic reviews examining skull-base repair techniques across endonasal skull-base neurosurgery found absolute heterogeneity across studies and centers, likely due to a paucity of high-level comparative evidence[21]. Similarly, there is variance in postoperative cerebrospinal fluid (CSF) rhinorrhoea rates, one of the commonest postoperative complications – generally up to 5% in TSA and 20% in EEA[6,10,11,17,28,31,35]. CSF rhinorrhoea has potentially serious consequences including pneumocephalus, meningitis, and prolonged hospital admission or re-admission[17,23,26].

CRANIAL (CSF Rhinorrhoea After Endonasal Intervention to the Skull Base) was a prospective, multicentre observational study seeking to determine the: (1) scope of the methods of skull-base repair; and (2) corresponding rates of postoperative CSF rhinorrhoea in the UK and Ireland[4,5,22]. CRANIAL was a collaboration between three bodies: students and junior doctors via NANSIG (The Neurology and Neurosurgery Interest Group), neurosurgical trainees via BNTRC (British Neurosurgical Trainee Research Collaborative) and skull-base consultants (neurosurgery and otorhinolaryngology) via the CRANIAL Steering Committee.

After piloting at 12 centers, preliminary results suggested practice heterogeneity[4,5]. Thus, the study was expanded UK and Ireland wide, and herein, we present the results.

Methods

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement guided this report[36].

Study Design

A multicentre, prospective, observational cohort study design was conducted across tertiary neurosurgical units with 2 pilot phases (Phase 1, 4 centers, 01/11/2019-22/03/2020; Phase 2, 12 centers, 23/03/2020-31/07/2020) and a full study period[4,5,22]. The full study included 30 centers, representing 91% (29/32, of adult neurosurgical centers performing endonasal skull-base neurosurgery in the UK and Ireland). One pediatric center was included, whilst others provided both adult and pediatric services. The study period included 6 months of consecutive case recruitment (10/08/20–10/02/21) and 6 months of follow-up (10/02/21–10/08/21).

Cases included patients of all ages undergoing TSA for sellar tumors and EEA for skull base tumors[22]. TSA was defined as surgical access to the sella alone (transsphenoidal) whilst EEA was defined as acquiring surgical access to an area not limited to the sella (e.g., transplanum or transcribriform)[20,22]. Exclusion criteria were patients undergoing transcranial surgery and those with preoperative CSF rhinorrhoea.

Ethical approval

Formal institutional ethical board review and informed consent from human participants was not required owing to the nature of the study (seeking to evaluate local services as an observational study) and this was confirmed with the Health Research Authority, UK.

Data collection

Each center registered the project as a service evaluation with appropriate approvals. Following the BNTRC model[3], the local team consisted of consultant lead(s) with overall project responsibility, with trainee lead(s) and student lead(s) for data collection via a secure web-based central database (Castor Electronic Data Capture). NANSIG and the BNTRC provided project support, overseen by the CRANIAL consultant steering committee.

Data were collected as per protocol[4,5,22]. The Esposito-Kelly system graded intraoperative CSF leak if present[9]. Local teams aimed to collect data within 30 days of operation for admission data, and at the end of the 6-month follow-up window for follow-up data[22]. Primary outcomes were: (1) methods of intraoperative skull-base reconstruction, and (2) postoperative CSF rhinorrhoea biochemically confirmed or requiring intervention (CSF diversion and/or operative repair)[22].

Data validation

Data were confirmed with operating surgeons or senior team members before final submission. An independent local data validator screened a random 10% of submitted cases at each center. The primary validation target was >95% accuracy across audited data[22]. Finally, each local team reviewed their final validated dataset before analysis.

Data analysis

Pre-processing included re-categorizing free-text entries. Descriptive statistics summarized baseline characteristics (demographic, tumour, and operative characteristics) and surgical outcomes, using Microsoft Excel (Version 16.54). The incidence density of repair methods and combinations within TSA/EEA and CSF leak grade subgroups were calculated.

Corresponding postoperative CSF rhinorrhoea rates were summarized as incidence percentages per TSA/EEA subgroups and repair method used. Univariate and multivariable logistic regression models assessed the impact of baseline characteristics (from the literature) on skull-base repair methods, and the influence of baseline characteristics and skull-base repair methods on CSF rhinorrhoea incidence, with odds ratios and 95% confidence intervals reported (Stata, Version 16, StataCorp, USA)[22] . Fisher's exact test was used to compare repair methods used with and without intraoperative CSF leak.

Results

866 patients (726 TSA, 140 EEA) were included across 30 centers. All centers completed data validation, with >95% record accuracy in audited cases and no duplicates included.

Patient characteristics

The median patient age was 53 years (range: 5–84), 23% (198/866) were older than 65. There were 416 male patients and 450 female patients; 238 (TSA: 210/726; EEA: 28/140) patients were obese (body mass index >30) (Tables 1 & 2). Pre-operative visual deficits (acuity and/or field) were present in 464 patients (TSA: 374/726; EEA: 91/140); 6 were blind with binocular <6/60 acuity (TSA: 9/374; EEA: 3/91) (Table 3). Pre-operative anterior hypopituitarism (requiring hydrocortisone supplementation) was present in 215 cases (TSA: 184/726; EEA: 31/140), and posterior hypopituitarism (requiring desmopressin supplementation) in 36 cases (TSA: 28/726; EEA: 8/140). The commonest TSA pathologies were non-functioning pituitary adenoma (410/726), functioning pituitary adenoma (249/726), and Rathke's cleft cyst (26/726) (Supplementary Material 3). For EEA, craniopharyngioma (38/140), meningioma (25/140) and non-functioning pituitary adenoma (23/140) were the commonest. Most tumors were >1cm in maximum diameter (TSA: 607/726; EEA: 131/140).

Operation characteristics

Of TSA cases, endoscopic was most prevalent (615/726), followed by microscopic (80/726), and a combined approach (32/726) method. Revision surgery was infrequent (TSA 98/726; EEA 21/140). On multivariate logistic regression, TSA was less likely to be used for larger tumors (maximum diameter >1cm) compared to EEA, aligning with indications for these approaches (OR: 0.4, CI: 0.2-0.9, p=0.03). Most TSA surgeries were performed by neurosurgeons alone (458/726), whereas most EEA cases were performed with both neurosurgery and otorhinolaryngology specialists (90/140). Infrequently cases were performed by otorhinolaryngologists alone (TSA: 22/726; EEA: 3/140). The median operation duration was 110 minutes for TSA (range: 29–540 minutes) and 220 minutes for EEA (range: 30–795 minutes).

Intraoperative CSF leak was reported in 214 TSA cases (214/726) and 79 EEA cases (79/140). Intraoperative CSF leaks were most commonly low-flow in TSA (131/214 grade 1) and high-flow in EEA (39/79 grade 3) (Tables 1 & 2).

Skull-base reconstruction overview

A taxonomy for skull-base repair was adapted from a systematic review of the literature (Supplementary Material 2)[20,21]. Heterogeneity of repair technique choice across both approaches was evident (Figures 1 and 2).

In TSA, the commonest techniques were nasal packing (519/726), tissue glues (474/726) and hemostatic agents (439/726) (Table 1, Supplementary Material 4). The most prevalent nasal packing was Nasopore® (369/519), Merocel® (94/519) and Rapid Rhinos® (33/519). Tissue glues most frequently used were Adherus® (146/489), Duraseal® (137/489) and Tisseel® (126/489); whilst common hemostatic agents included Surgicel® (189/439), Surgiflo® (141/439) and Floseal® (91/439). Tissue grafts were used in 221 cases (221/726), usually fat (189/221, most commonly abdominal), fascia (27/221, most often fascia lata) and mucosa (28/221, usually middle turbinate). Synthetic grafts (204/726) included Spongostan™ (181/204), Tachosil® (21/204) and Gelfoam® (2/204). The button technique was used with these grafts in 20 cases (20/726). There was overlap between these graft materials and dural replacement (or reconstruction via layering) strategies (196/726) which usually consisted of Duragen® (136/196), fascia lata (18/196) or Lyoplant® (17/196). Pedicled flaps were used in 116 cases (116/726), most frequently nasoseptal flaps (105/116). Rigid buttresses were used in 31 cases (31/726), commonly Medpor® (15/31), autologous bone (14/31, usually septal) and autologous cartilage (1/31). These buttresses were used with a gasket seal technique in 15 cases (15/726), usually with fascia lata.

Comparatively, pedicled flaps (90/140), CSF diversion (38/140), buttresses (17/140), and gasket sealing (11/140) were more commonly used in EEA cases (Table 1, Supplementary Material 4). Nasoseptal flaps (87/90) were again the most frequent pedicled flaps. Like TSA, supportive buttresses were often Medpor® (10/17) or autologous bone (5/17), the majority of these being used with the gasket seal technique (11/17). Additionally, nasal packs (116/140), tissue glue (114/140) and hemostatic agents (93/140) were prevalent. The commonest nasal packs were Nasopore® (86/116), Merocel® (20/116) and Bismuth-Soaked Ribbon Gauze (11/116). Again, Tisseel® (32/99), Adherus® (22/99) and Duraseal® (22/99) were the most used tissue glues; whilst Surgicel® (51/93), Surgiflo® (24/93) and Floseal® (13/93) were common hemostatic agents. Tissue grafts (65/140,) were frequently fat (45/65), fascia (36/65) and mucosa (8/65), akin to TSA. Similarly, synthetic grafts (47/140) included Spongostan™ (39/47) and Tachosil® (5/47). The button technique was sometimes used with these grafts (47/140). Finally, common dural replacement (66/140) strategies included Duragen® (43/66), fascia lata (12/66) and Tutoplast® (6/66).

Factors affecting repair technique choice

Repair method appeared to be tailored according to postoperative CSF leak risk (Table 1 for descriptive analyses, Supplementary material 5 for further statistical analyses). In cases with intraoperative CSF leak, there was a statistically significant (via Fisher's exact test) increased use of tissue grafts ($p<0.01$), pedicled flaps ($p<0.01$), tissue glues ($p<0.01$) and CSF diversion (TSA $p<0.01$; EEA $p<0.05$) for both TSA and EEA on univariate analysis. Additionally, dural replacements ($p<0.01$), hemostatic agents ($p=0.01$) and buttresses ($p<0.01$) were also more in EEA (but not TSA) with intraoperative CSF leak. Similarly, the use of pedicled flaps (OR: 2.3, CI: 1.3-4.2, $p=0.01$), dural replacement (OR: 2.1, CI: 1.3-3.4, $p<0.01$) and tissue glues (OR: 1.36, CI: 1.1-2.5, $p=0.02$) were statistically associated with operations for larger tumors (maximum diameter >1cm) on multivariate logistic regression. Regarding surgical specialty, the use of pedicled flaps (OR: 4.5, CI: 3.1-6.3, $p<0.01$) and hemostatic agents (OR: 1.9, CI: 1.5-2.7, $p<0.01$) were statistically associated with otorhinolaryngology involvement, whilst the use of tissue grafts (OR: 0.3, CI: 0.2-0.5, $p<0.01$) and tissue glues (OR: 0.6, CI: 0.4-0.8, $p<0.01$) was reduced on multivariate logistic regression.

CSF diversion

67 cases used CSF diversion (TSA: 29/726; EEA: 38/140). In TSA, lumbar drainage was most common (27/29) with one of these patients subsequently requiring a ventriculoperitoneal shunt (VPS). The remainder underwent lumbar puncture (1/29), or external ventricular drain (EVD) placement (1/29). Lumbar drains were usually placed under the same anesthetic (pre-procedure, 15/29; post-procedure, 7/29), with regimes (if specified) volume-led (14/29, usually 5-10mls/hr), pressure-led (6/29) or using a LiquoGuard® system (1/29). Three drains inserted pre-procedure were removed before any effective postoperative CSF drainage (used for intraoperative saline injection or inserted prophylactically in case of subsequent CSF rhinorrhoea). Excluding these, the median length of drainage via lumbar drain was five days (range: 2-11).

Regarding EEA surgeries, all CSF diversion was performed via lumbar drain with most placed under the same anesthetic (immediately pre-procedure: 22/38; or immediately post-procedure: 8/38). The most common drainage regime was volume-led (21/22), with 5-10mls/hr the commonest protocol. One case also had an EVD placed one week before tumour resection for acute hydrocephalus. Three pre-procedure drains inserted were removed before any effective postoperative CSF drainage. Excluding these, the median length of drainage was five days (range: 1-7).

Postoperative management

The median patient stay was four days (range: 1–37) for TSA and seven days (range: 1–35) for EEA. Regarding conservative measures, bed rest was advised in 20% (147/726) TSA cases (head elevated: 72/147; head flat: 5/147; unspecified height: 70/152) and 40% (52/140) EEA cases (head elevated: 37/52; head flat: 3/52; unspecified height: 12/52); avoiding straining (e.g., lifting, sneezing, etc.) was advised in most TSA (502/726) and EEA (91/140) cases. Stool softeners were prescribed in 191 TSA cases (191/726) and 30 EEA cases (30/140). Rarely, acetazolamide (TSA: 1/726; EEA 1/140) was offered. Visual outcomes, endocrine outcomes and complications at 6 months follow-up are summarized in Supplementary Material 6.

Postoperative CSF rhinorrhoea

CSF rhinorrhoea (biochemically confirmed or requiring re-operation) occurred in 3.9% of TSA (28/726) and 7.1% of EEA (10/140) cases.

In TSA, most cases occurred during the index admission (21/28), presenting a median of 2 days postoperatively (range: 1-17), whereas those presenting during follow-up (7/28) a median of 10 days postoperatively (range: 2-84). Almost all were managed operatively (index: 18/21; follow-up: 6/7). Initial surgical treatment included lumbar drain & endonasal repair (8/24), direct endonasal repair alone (6/24), lumbar drain alone (8/24), or VPS alone (2/24). Five cases required further operations for recurrent CSF rhinorrhoea. Regarding EEA, CSF rhinorrhoea occurred during the index admission for eight cases, and 2 cases during follow-up. All cases were managed operatively (lumbar drain & endonasal repair: 6/10; lumbar drain alone 3/10; endonasal repair alone: 1/10). Two cases required further operations for recurrent CSF rhinorrhoea. Cases presenting during index admission were detected at a median of 2 days postoperatively (range: 1-11), whilst those detected during follow-up were found at a median of 19 days postoperatively (range: 8-54).

On univariate logistic regression analysis, displayed in Figure 3, the following variables were associated with CSF rhinorrhoea: revision surgery (TSA), presence of intraoperative CSF leak (TSA), and the absence of neurosurgery involvement (TSA) (Table 2, Figure 3, Supplementary material 5). On multivariate analysis, revision surgery and the presence of intraoperative CSF leak remained a predictor of CSF rhinorrhoea in TSA (Table 2, Figure 3, Supplementary material 5). No specific technique category (including CSF diversion) considerably impacted the odds of CSF rhinorrhoea for EEA. However, tissue glues in TSA (OR: 0.2, CI: 0.1-0.7, $p<0.01$) may be related to a slight decrease in CSF rhinorrhoea rates on multivariate analyses (Table 2, Figure 3, Supplementary material 5).

Discussion

Principal findings

This multicentre, prospective, observational study represents the first study of its kind, exploring skull base repair techniques and CSF rhinorrhoea rates in a collaborative project involving almost all neurosurgical centers in the UK and Ireland.

There is clear heterogeneity in skull-base repair regimes across centers, with no two sharing the same protocol. Additionally, no specific type of repair technique made a significant difference in postoperative CSF rates, although there may be marginal benefits with tissue glue in TSA. Certain characteristics appear to make CSF rhinorrhoea more likely – previous endonasal surgery and intraoperative CSF leak. This translates into the tailoring of repair strategies. For example, in EEA, multilayer regimes using pedicled flaps, rigid buttresses (often with gasket sealing) and CSF diversion were frequent. Similarly, with intraoperative CSF leak, tissue grafts, tissue glues, pedicled flaps and CSF diversion were used more often. Larger tumors (maximum diameter >1cm) were associated with the use of pedicled flaps, dural replacement and tissue glues. Surgeon preference or training may also factor in, with pedicled flaps and hemostatic agents used less in the absence of otorhinolaryngologists. Tissue grafts, tissue glues, and construct support strategies (e.g., rigid buttresses and CSF diversion) were less frequent in the absence of neurosurgical involvement.

CSF rhinorrhoea for both TSA (28/726, 3.9%) and EEA (10/140, 7.1%) is lower than generally reported in the literature[10,17,21,24,28,35]. This may reflect the ongoing improvement in endonasal skull-base repair and CSF rhinorrhoea rates, demonstrated by recent meta-analyses over time[38]. Additionally, the UK and Ireland have consolidated pituitary services into dedicated "centers of excellence", which may influence surgical outcomes[2]. Furthermore, as a prospective series, surgeons were aware of the monitoring of this outcome, perhaps influencing their management via the *Hawthorne effect*[7]. Importantly, a significant proportion of postoperative CSF rhinorrhoea cases had no recorded intraoperative CSF leak (Total: 15/38; TSA: 11/28; EEA: 4/9), suggesting occult intraoperative leak, or possibly a thinned and vulnerable diaphragma which tears postoperatively in the absence of support. In our series, this subgroup had the lowest frequency of almost every repair method category (except synthetic grafts and hemostatic agents). This phenomenon is described in other case series, with many authors advocating for universal sellar repair for this reason, and some recommending routine use of intrathecal fluorescein[18,33]. However, these strategies should be balanced against the increased operative time, cost-effectiveness, and additional repair-related morbidity (e.g., donor site injuries or scars)[18,33].

Findings in the context of literature

Recent systematic reviews of skull-base repair techniques have highlighted the variations across surgeons and centers, likely related to the lack of high-level comparative evidence[14,15,21,30]. There is an ever-expanding list of repair options, with most modern protocols adapting reconstruction to postoperative CSF rhinorrhoea risk[6,8,12,13,21,28,29,32,37,39]. Techniques reported commonly for low-risk cases include fat grafts, fascia lata grafts and synthetic grafts; whereas multilayer regimes with vascularized flaps, gasket-sealing, and lumbar drains are commoner in higher-risk cases[15,16,21,34]. The only high-level evidence is a randomized controlled trial investigating perioperative lumbar drainage (combined with nasoseptal flap repair) in EEA with high-flow intraoperative CSF leak[40]. Lumbar drains were inserted immediately postoperatively (under the same anesthetic), draining 10 ml/h for 3 days, resulting in a decrease in CSF rhinorrhoea rates (8.2% with lumbar drainage vs. 21.2% without; $p = 0.03$)[40].

Strengths and limitations

The strengths of this study are its prospective, consecutive recruitment (despite COVID-19), and the creation of a collaborative network of neurosurgeons and otorhinolaryngologists with a specialist interest in skull-base and pituitary, spanning almost every adult neurosurgical center in the UK and Ireland. There are several limitations. Firstly, the study is observational and occurred during a pandemic wave, possibly hampering case recruitment. Due to pandemic-related pressures and redeployments, several centers uploaded data in retrospect but submitted cases were reviewed in detail by supervising consultants. Only one dedicated pediatric center was included, although 6 centers (joint adult and pediatric) included patients less than 16 years old. CSF rhinorrhoea was infrequent, whilst there was a wide array of combinations for relevant variables (particularly skull-base repair methods) making statistical analysis challenging.

Conclusions

Heterogeneity of skull-base repair techniques exists across centers. Multilayer regimes with vascularized flaps, CSF diversion and rigid buttresses appear commoner in higher-risk cases, such as in EEAs. Overall, corresponding CSF rhinorrhoea rates across the UK and Ireland are lower than generally reported in the literature. A large proportion of postoperative leaks occurred in the context of occult intraoperative CSF leaks, and decisions for universal sellar repairs should consider the risks and cost-effectiveness of repair methods used. Future work could include longer-term, higher-volume studies, such as a registry; and high-quality interventional studies.

Tables

Table 1: Incidence of repair technique categories across surgical approaches, intraoperative CSF leak presence/grade, tumour diameter, BMI and age. CSF = cerebrospinal fluid, BMI=body mass index.

Table 2: Summary of CSF rhinorrhoea incidence per baseline and operative risk factor subgroups – incidence and statistical analysis via multivariate logistic regression.

Figure legends

Figure 1: Heat map highlighting frequency of repair technique category use per centre for transsphenoidal cases.

Figure 2: Heat map highlighting frequency of repair technique category use per centre for expanded endonasal cases.

Figure 3: Summary of univariate and multivariate logistic regression of baseline characteristics and operative technique against CSF rhinorrhoea across transsphenoidal (3a, 3b) and expanded endonasal (3c, 3d) appraoches. CSF = cerebrospinal fluid, BMI=body mass index, TSA=transsphenoidal approach, EEA=expanded endonasal approach. *=statistically significant relationships ($p<0.05$, see Table 2 and Supplementary Information 3).

Supplementary material

Supplementary material 1: List of authors and collaborators.

Supplementary material 2: Levels for skull base repair from which study repair technique taxonomy was derived. Adapted with permission from: Skull base repair following endonasal pituitary and skull base tumour resection: a systematic review, Pituitary, 2021, Khan DZ et al.

Supplementary material 3: Table of tumour types included by approach.

Supplementary material 4: Full list of all repair methods per category by approach.

Supplementary material 5a. Summary of baseline and operative risk factors for CSF rhinorrhoea – incidence and statistical analysis via univariate logistic regression.

Supplementary material 5b. Summary of operative technique and intra-operative CSF leak – incidence and statistical analysis via Fisher’s exact test.

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Figures

Figure 1: Heat map highlighting frequency of repair technique category use per centre for transsphenoidal cases.

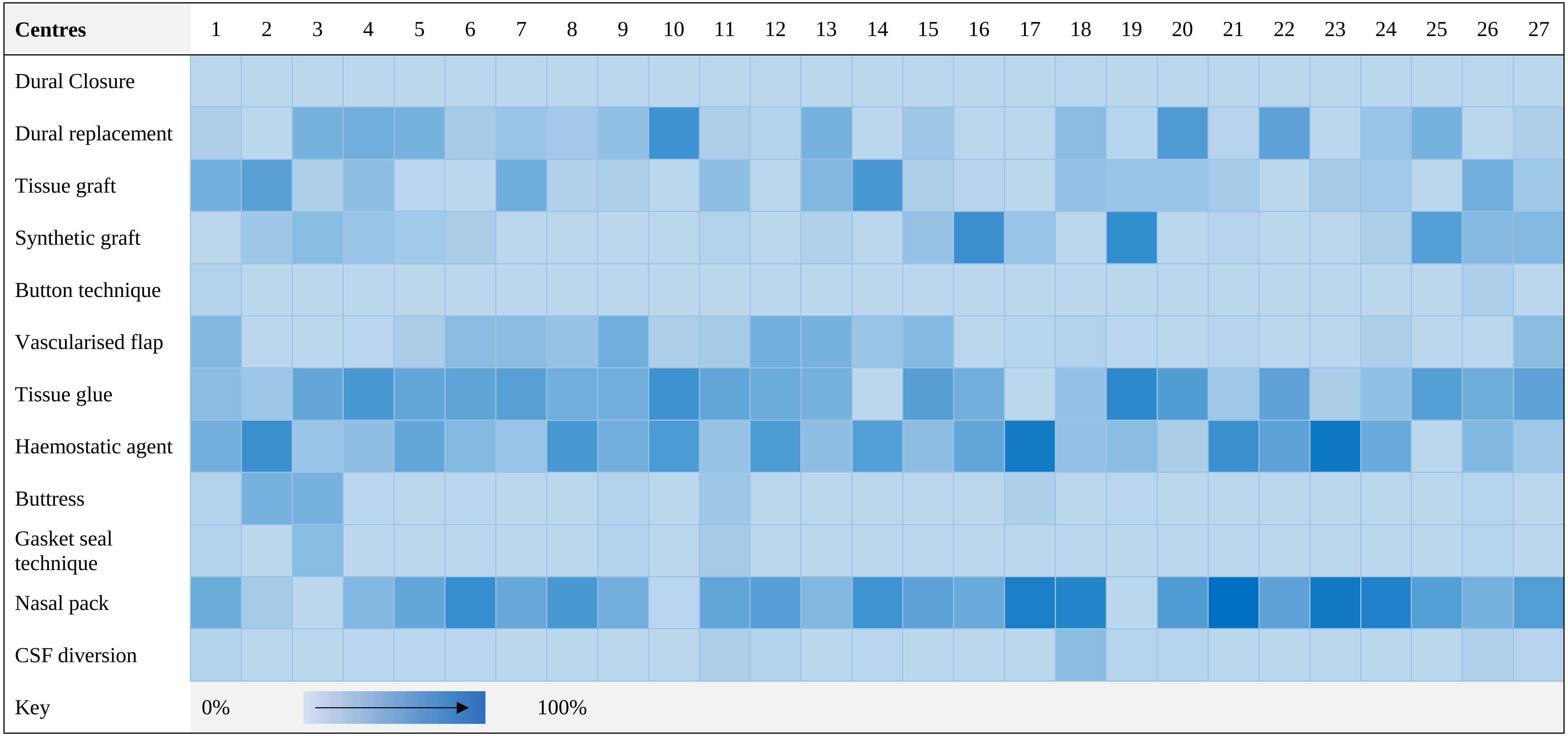


Figure 2: Heat map highlighting frequency of repair technique category use per centre for expanded endonasal cases.

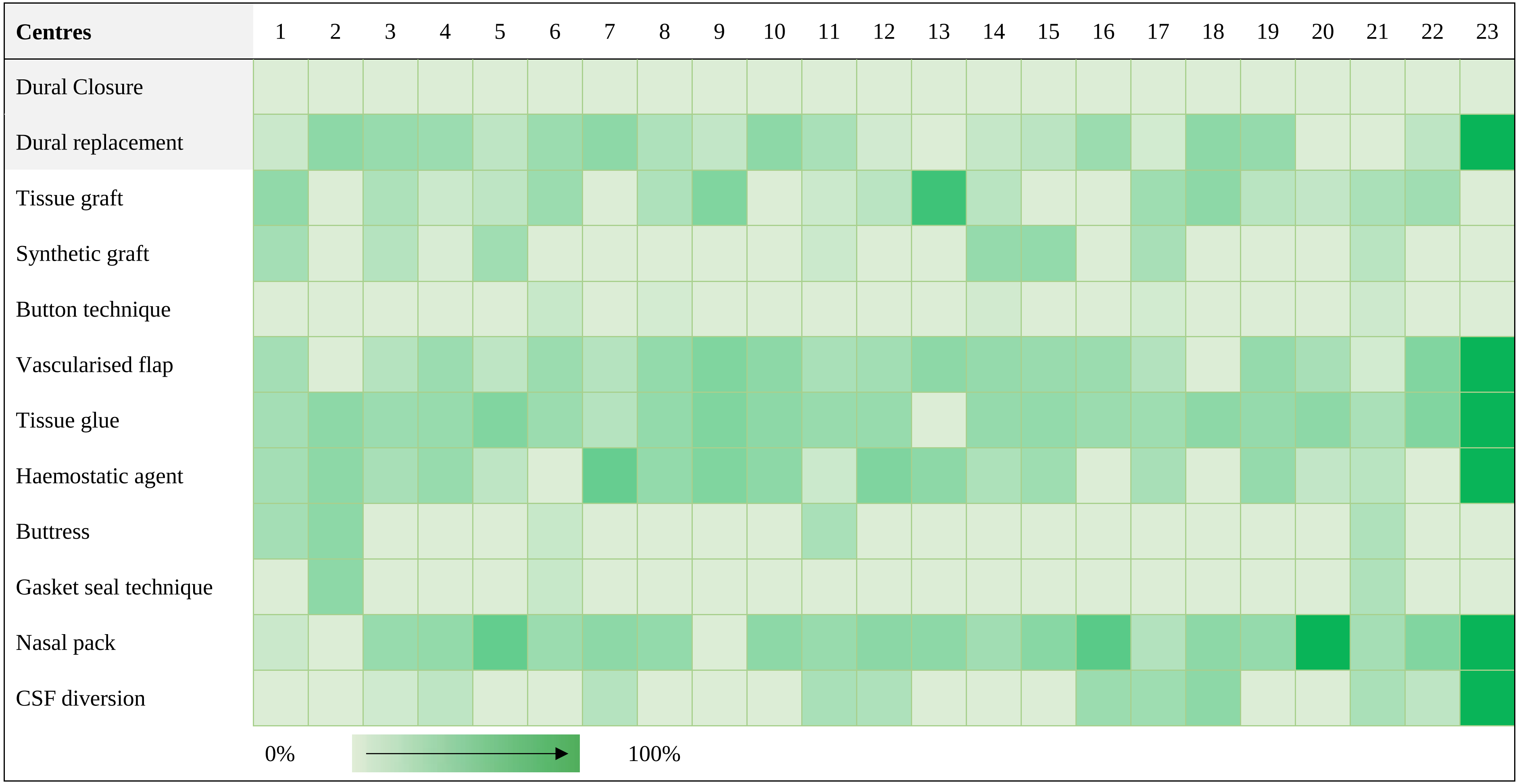
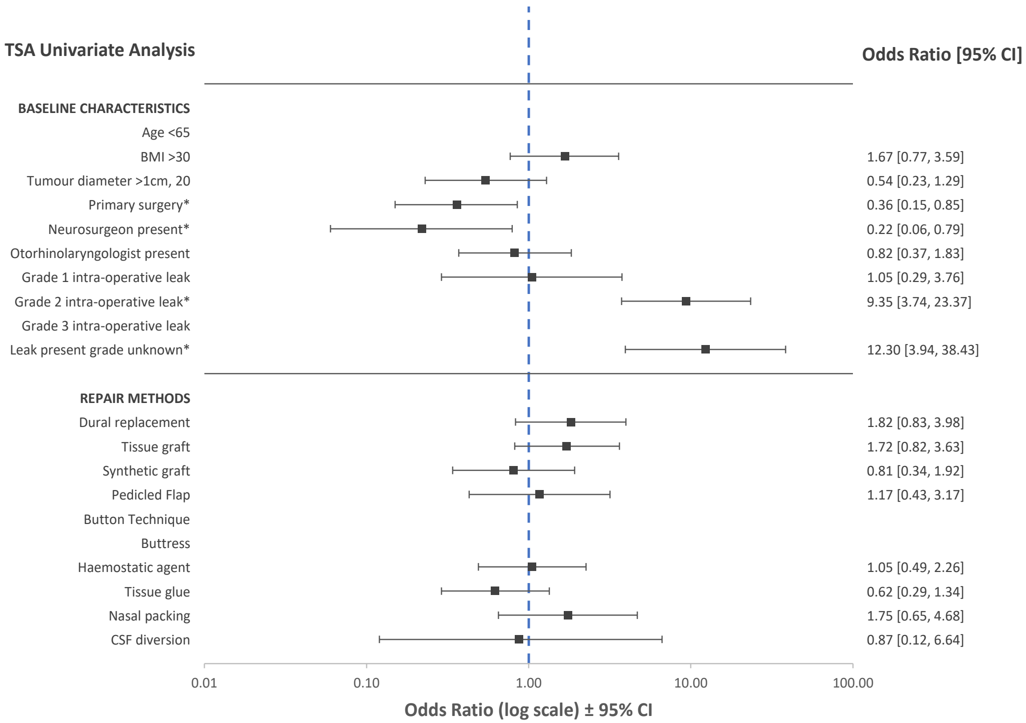
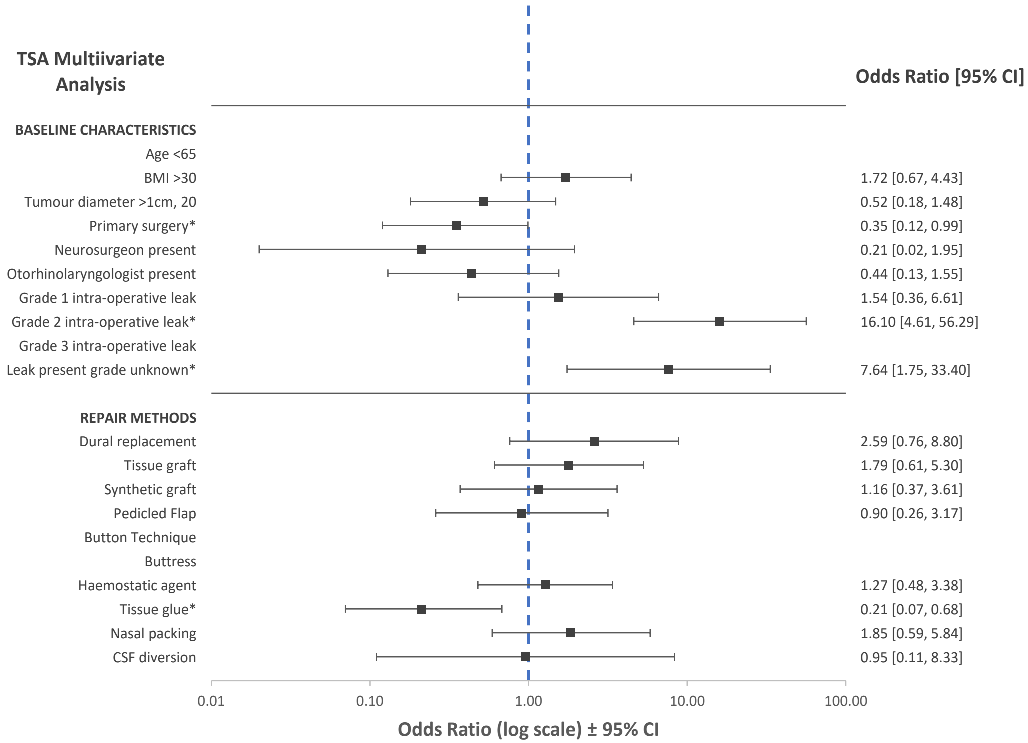


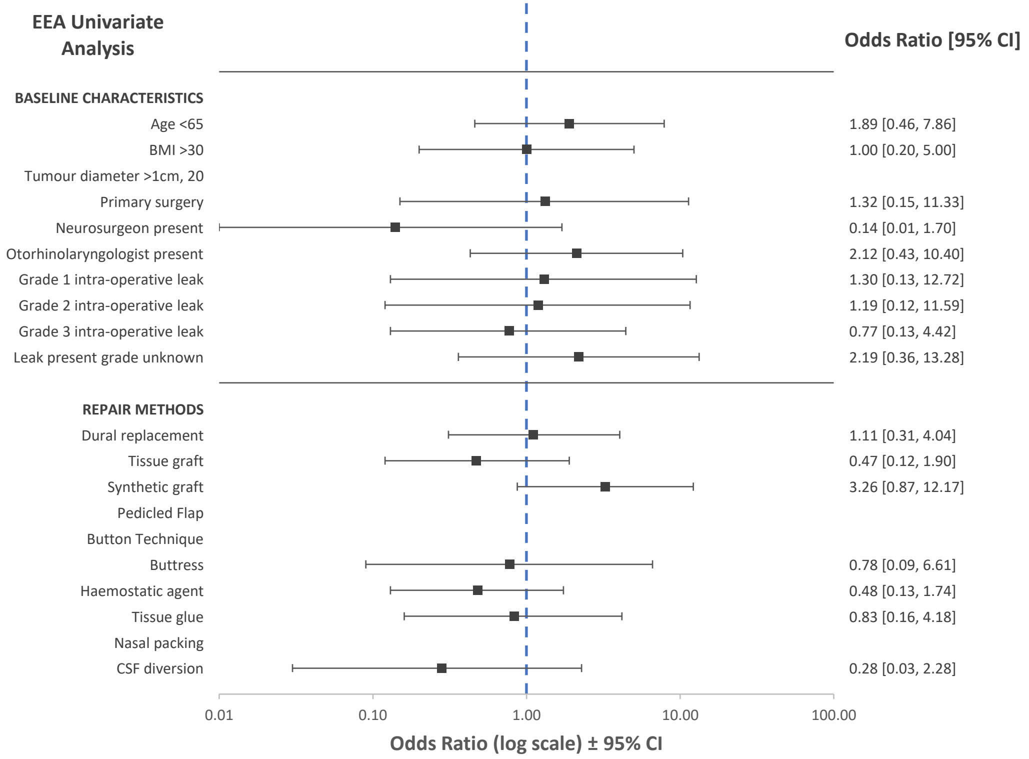
Figure 3: Summary of univariate and multivariate logistic regression of baseline characteristics and operative technique against CSF rhinorrhoea across transsphenoidal (3a, 3b) and expanded endonasal (3c, 3d) appraoches. CSF = cerebrospinal fluid, BMI=body mass index, TSA=transsphenoidal approach, EEA=expanded endonasal approach. *=statistically significant relationships (p<0.05, see Table 2 and Supplementary Information 3).

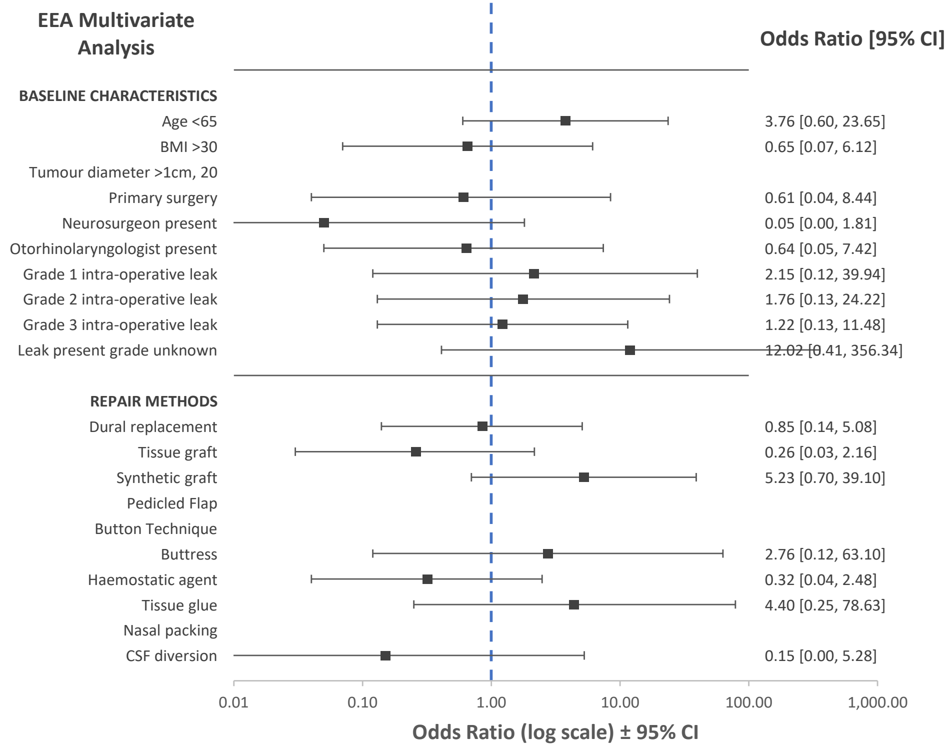
Transsphenoidal approach (TSA) univariate analysis (3a) and multivariate analysis (3b)





Expanded endonasal approach (EEA) univariate analysis (3c) and multivariate analysis (3d)





Tables

Table 1: Incidence of repair technique categories across surgical approaches, intraoperative CSF leak presence/grade, tumour diameter, BMI and age. CSF = cerebrospinal fluid, BMI=body mass index.

Category	Dural Closure	Dural replacement	Tissue graft	Synthetic graft	Button Technique	Pedicled Flap	Tissue Glue	Haemostatic agent	Buttress	Gasket sealing	Nasal packing	CSF diversion	CSF Rhinorrhoea
Approach													
TSA (N = 726), n/N (%)	0 (0%)	196 (27%)	221 (30.4%)	204 (28.1%)	20 (2.8%)	116 (16%)	474 (65.3%)	439 (60.5%)	31 (4.3%)	15 (2.1%)	519 (71.5%)	29 (4%)	28 (3.9%)
EEA (N = 140), n/N (%)	0 (0%)	66 (47.1%)	65 (46.4%)	47 (33.6%)	7 (5%)	90 (64.3%)	114 (81.4%)	93 (66.4%)	17 (12.1%)	11 (7.9%)	116 (82.9%)	38 (27.1%)	10 (7.1%)
Intraoperative CSF leak grade													
Grade 0 (N = 573), n/N (%)	0 (0%)	136 (23.7%)	106 (18.5%)	163 (28.4%)	9 (1.6%)	88 (15.4%)	335 (58.5%)	358 (62.5%)	19 (3.3%)	11 (1.9%)	403 (70.3%)	19 (3.3%)	15 (2.6%)
Grade 1 (N = 143), n/N (%)	0 (0%)	54 (37.8%)	89 (62.2%)	45 (31.5%)	7 (4.9%)	37 (25.9%)	124 (86.7%)	82 (57.3%)	7 (4.9%)	3 (2.1%)	114 (79.7%)	13 (9.1%)	4 (2.8%)
Grade 2 (N = 67), n/N (%)	0 (0%)	27 (40.3%)	41 (61.2%)	18 (26.9%)	7 (10.4%)	33 (49.3%)	55 (82.1%)	33 (49.3%)	10 (14.9%)	4 (6%)	52 (77.6%)	8 (11.9%)	10 (14.9%)
Grade 3 (N = 44), n/N (%)	0 (0%)	23 (52.3%)	33 (75%)	15 (34.1%)	3 (6.8%)	30 (68.2%)	44 (100%)	28 (63.6%)	9 (20.5%)	6 (13.6%)	31 (70.5%)	16 (36.4%)	2 (4.5%)
Grade unknown (N = 39), n/N (%)	0 (0%)	22 (56.4%)	17 (43.6%)	10 (25.6%)	1 (2.6%)	18 (46.2%)	30 (76.9%)	31 (79.5%)	1 (2.6%)	2 (5.1%)	18 (46.2%)	46.2 (30%)	7 (17.9%)
Specialty													
Neurosurgery only (N=505), n (%)	0 (0%)	154 (30.5%)	219 (43.4%)	164 (32.5%)	24 (4.8%)	63 (12.5%)	361 (71.5%)	274 (54.3%)	33 (6.5%)	21 (4.2%)	297 (58.8%)	40 (7.9%)	21 (4.2%)
Otorhinolaryngology only (N=25), n (%)	0 (0%)	17 (68%)	2 (8%)	14 (56%)	0 (0%)	5 (20%)	25 (100%)	25 (100%)	0 (0%)	0 (0%)	25 (100%)	0 (0%)	4 (16%)
Multidisciplinary (N=336), n (%)	0 (0%)	91 (27.1%)	65 (19.3%)	73 (21.7%)	3 (0.9%)	138 (41.1%)	202 (60.1%)	233 (69.3%)	15 (4.5%)	5 (1.5%)	313 (93.2%)	27 (8%)	13 (3.9%)
Tumour diameter													
>1cm (N=738), n/N (%)	0 (0%)	238 (32.2%)	243 (32.9%)	218 (29.5%)	26 (3.5%)	190 (25.7%)	510 (69.1%)	456 (61.8%)	44 (6%)	24 (3.3%)	546 (74%)	61 (8.3%)	31 (4.2%)
<1cm (N=128), n/N (%)	0 (0%)	24 (18.8%)	43 (33.6%)	33 (25.8%)	1 (0.8%)	16 (12.5%)	78 (60.9%)	76 (59.4%)	4 (3.1%)	2 (1.6%)	89 (69.5%)	6 (4.7%)	7 (5.5%)
BMI													
<30 (N=628), n/N (%)	0 (0%)	190 (30.3%)	211 (33.6%)	181 (28.8%)	20 (3.2%)	148 (23.6%)	416 (66.2%)	378 (60.2%)	41 (6.5%)	24 (3.8%)	456 (72.6%)	51 (8.1%)	25 (4%)
>30 (N=238), n/N (%)	0 (0%)	72 (30.3%)	75 (31.5%)	70 (29.4%)	7 (2.9%)	58 (24.4%)	172 (72.3%)	154 (64.7%)	7 (2.9%)	2 (0.8%)	179 (75.2%)	16 (6.7%)	13 (5.5%)
Age													
<65 (N=668), n/N (%)	0 (0%)	201 (30.1%)	216 (32.3%)	197 (29.5%)	19 (2.8%)	168 (25.1%)	462 (69.2%)	419 (62.7%)	35 (5.2%)	17 (2.5%)	493 (73.8%)	54 (8.1%)	35 (5.2%)
>65 (N=198), n/N (%)	0 (0%)	61 (30.8%)	70 (35.4%)	54 (27.3%)	8 (4%)	38 (19.2%)	126 (63.6%)	113 (57.1%)	13 (6.6%)	9 (4.5%)	142 (71.7%)	13 (6.6%)	3 (1.5%)

Table 2: Summary of CSF rhinorrhoea incidence per baseline and operative risk factor subgroups – incidence and statistical analysis via multivariate logistic regression.

	Transsphenoidal approach		*Expanded Endonasal Approach*	
	CSF Rhinorrhoea rate	**Multivariate Analyses (OR, CI, p-value)**	**CSF Rhinorrhoea rate**	**Multivariate Analyses (OR, CI, p-value)**
Approach				
TSA	28/726 (3.9%)	-	-	-
EEA	-	-	10/140 (7.1%)	-
Baseline characteristics				
Age >65	0/172 (0.0%)	-	3/27 (11.1%)	OR: 3.8, CI: 0.6–23.7, p =0.16
Age <65	28/553 (5.1%)	Reference	7/113 (6.2%)	Reference
BMI >30	11/210 (5.2%)	OR: 1.7, CI: 0.7-4.4, p=0.26	2/28 (7.1%)	OR: 0.7, CI: 0.1-6.1, p=0.7
BMI<30	17/516 (3.3%)	Reference	8/112 (7.1%)	Reference
Tumour diameter >1cm	21/607 (3.5%)	OR:0.5; CI: 0.2 – 1.5, p=0.22	10/131 (7.6%)	-
Tumour diameter <1cm	7/119 (6.0%)	Reference	0/9 (0%)	Reference
Primary surgery	8/98 (8.2%)	**OR:0.4, CI: 0.1-0.9, p=0.05**	1/21 (4.8%)	OR: 0.6, CI; 0.1-8.4, p=0.71
Revision surgery	19/573 (3.3%)	Reference	7/113 (6.2%)	Reference
Presence of Otorhinolaryngologist	9/268 (3.4%)	OR: 0.4, CI: 0.1-1.6, p=0.2	8/93 (8.6%)	OR: 0.6, CI: 0.1-7.4, p=0.72
Presence of Neurosurgeon	25/704 (3.6%)	OR: 0.2, CI: 0.1-1.9, p=0.17	9/137 (6.6%)	OR: 0.1, CI: 0-1.8, p=0.1
Intra-operative CSF leak grade				
Grade 0	11/512 (2.1%)	Reference	4/61 (6.6%)	Reference
Grade 1	3/131 (2.3%)	OR: 1.5, CI: 0.4-6.6, p=0.56	1/12 (8.3%)	OR: 2.2, CI: 0.1-39.9, p= 0.61
Grade 2	9/54 (16.7%)	**OR: 16.1, CI: 4.6-56.3, p<0.01**	1/13 (7.7%)	OR: 1.8, CI: 0.1-24.2, p=0.67
Grade 3	0/5 (0%)	-	2/39 (5.6%)	OR: 1.2, CI: 0.1-11.5, p=0.87
Leak present, grade unknown	5/24 (20.8%)	**OR: 7.6, CI: 1.8-33.4, p<0.01**	2/15 (13.3%)	OR: 12, CI: 0.4-356.3, p=0.15
Repair methods				
Dural closure	-	-	-	-
Dural replacement	11/196 (5.6%)	OR: 2.6, CI: 0.8-8.8, p=0.13	5/66 (7.6%)	OR: 0.9, CI: 0.1-5.1, p=0.85
Tissue graft	13/221 (5.9%)	OR: 1.8, CI: 0.6-5.3, p=0.29	3/65 (4.6%)	OR: 0.3, CI: 0.1-2.2, p=0.21
Synthetic graft	7/204 (3.4%)	OR: 1.2, CI: 0.4-3.6, p=0.79	6/47 (12.8%)	OR: 5.2, CI: 0.7-39.1, p=0.11
Button Technique	0/20 (0%)	-	0/7 (0%)	-
Pedicled Flap	5/116 (4.3%)	OR: 0.9, CI: 0.3-3.2, p=0.87	8/90 (8.9%)	-
Tissue Glue	15/474 (3.2%)	**OR: 0.2, CI: 0.1-0.7, p<0.01**	8/114 (7.0%)	OR: 4.4, CI: 0.3-78.6, p=0.31
Haemostatic agent	18/439 (4.1%)	OR: 1.3, CI: 0.5-3.4, p=0.63	5/93 (5.4%)	OR: 0.3, CI: 0.1-2.5, p=0.27
Buttress	0/31 (0%)	-	1/17 (5.9%)	OR: 2.8, CI: 0.1-63.1, p=0.53
Gasket sealing	0/15 (0%)	-	0/11 (0%)	-
Nasal packing	22/519 (4.2%)	OR: 1.9, CI: 0.6-5.8, p=0.29	10/116 (8.6%)	-
CSF diversion	1/29 (3.4%)	OR: 0.9, CI: 0.1-8.3, p=0.96	1/38 (2.6%)	OR: 0.2, CI: 0-5.3, p =0.298

Supplementary Materials:

Supplementary material 1: List of authors and collaborators

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Supplementary material 2: Levels for skull base repair from which study repair technique taxonomy was derived. Adapted with permission from: Skull base repair following endonasal pituitary and skull base tumour resection: a systematic review, Pituitary, 2021, Khan DZ et al.

Overall function	Anatomical level	Technique		Materials: Autologous examples	Materials: Allogenic/synthetic/xenograft examples	Grade of recommend-ation
Barrier-restoring	**Intra-dural (dural inlay)**	Layering		Fat (abdominal, thigh), muscle (lateral rectus)	Collagen sponge, gelatin sponge, surgicel	C
		Button technique		Fascia lata, rectus fascia	Sutures (nylon, prolene)	C
	Dural (dural onlay or overlay)	Layering		Fascia lata, rectus fascia, autologous fibrin glue	Duragen, Durepair, Duramatrix, Tutopatch, Tisseel, Adherus, Evicel, Bioglue	C
		Primary closure			Sutures (nylon, prolene), Clips (nitinol, titanium)	C
		Gasket seal technique		Bone (vomer, septal, turbinate), cartilage (septal), fascia lata	Medpor, Lactosorb, cadaveric fascia	C
	Bony skullbase	Layering		Bone (vomer, septal, turbinate), cartilage (septal)	Medpor, Lactosorb, titanium, cadaveric iliac bone, cement, Surgiflo, Floseal, Surgicel, Duraseal,	C
	Nasal	Vascularized repair	Nasal flap	NSF (traditional, rescue, extended), turbinates, lateral nasal	-	C
			Extra-nasal flap	Pericranial, temporoparietal, buccinator, palatal, occipital, radial	-	C
		Construct stabilization	Temporary	Balloon (Foley, Merocel), non-balloon (Nasopore, BSRG, gelfoam)	-	C
			Permanent	Bone (vomer, septal, turbinate), cartilage (septal)	Medpor, Lactosorb, titanium, cadaveric iliac bone	C
Pressure-reducing	CSF diversion	Short term drainage			Lumbar puncture, lumbar drain, external ventricular drain	**B**
		Long term drainage			Ventriculoperitoneal shunt, lumbar shunt	C

Supplementary material 3: Table of tumour types included by approach.

Row Labels	***Transsphenoidal Approach***	***Expanded Endoscopic Endonasal Approach***	***Grand Total***
Apoplexy	7 (1.0%)	1 (0.7%)	8 (0.9%)
Arachnoid cyst	3 (0.4%)	1 (0.7%)	4 (0.5%)
Chordoma	0 (0%)	15 (10.7%)	15 (1.7%)
Craniopharyngioma	3 (0.4%)	38 (27.1%)	41 (4.7%)
Dermoid cyst	0 (0%)	1 (0.7%)	1 (0.1%)
Germinoma	1 (0.1%)	0 (0%)	1 (0.1%)
Hypophysitis	1 (0.1%)	0 (0%)	1 (0.1%)
Meningioma	3 (0.4%)	25 (17.9%)	28 (3.2%)
Meningoencephalocele	0 (0%)	1 (0.7%)	1 (0.1%)
Neuroendocrine tumour	1 (0.1%)	0 (0%)	1 (0.1%)
Other	3 (0.4%)	1 (0.7%)	4 (0.5%)
Pituitary adenoma (Cushing's)	249 (34.3%)	14 (10.0%)	69 (8%)
Pituitary adenoma (Non-functioning)	410 (56.5%)	23 (16.4%)	433 (50%)
Rathke's Cleft Cyst	26 (3.6%)	2 (1.4%)	28 (3.2%)
Sinonasal endocrine tumour	0 (0%)	1 (0.7%)	1 (0.1%)
Squamous cell carcinoma	0 (0%)	1 (0.7%)	1 (0.1%)
Lymphocytic Hypophysitis	6 (0.8%)	0 (0%)	6 (0.7%)
Mucocele	1 (0.1%)	0 (0%)	1 (0.1%)
Epidermoid cyst	1 (0.1%)	0 (0%)	1 (0.1%)
Pituitary abscess	2 (0.3%)	0 (0%)	2 (0.2%)
Low grade spindle cell sarcomatous tumour	1 (0.1%)	0 (0%)	1 (0.1%)
Simple cyst	1 (0.1%)	0 (0%)	1 (0.1%)
Sellar Rhabdoid	1 (0.1%)	0 (0%)	1 (0.1%)
Cyst (Uncertain aetiology)	1 (0.1%)	0 (0%)	1 (0.1%)
Pituicytoma	1 (0.1%)	0 (0%)	1 (0.1%)
Metastasis (Lung)	1 (0.1%)	1 (0.7%)	2 (0.2%)
Pterygoid-maxillary tumour	0 (0%)	2 (1.4%)	2 (0.2%)
Chondrosarcoma	0 (0%)	5 (3.6%)	5 (0.6%)
Hemangiopericytoma	0 (0%)	1 (0.7%)	1 (0.1%)
Adenocarcinoma (Sinonasal)	0 (0%)	5 (3.6%)	5 (0.6%)
Metastasis (Melanoma)	1 (0.1%)	1 (0.7%)	2 (0.2%)
Metastasis (Other)	0 (0%)	1 (0.9%)	1 (0.1%)
Cavernous haemangioma	1 (0.1%)	0 (0%)	1 (0.1%)
Metastasis (Prostate)	1 (0.1%)	0 (0%)	1 (0.1%)
Grand Total	**726**	**140**	**866**

Supplementary material 4: Full list of all repair methods per category by approach.

Repair Technique	*Transsphenoidal Approach*	*Expanded Endoscopic Endonasal Approach*
Dural Closure	**0**	**0**
Sutures	0	0
Clips	0	0
Dural Replacement	**196**	**66**
Duragen®	136	43
Fascia Lata	18	12
Lyoplant®	17	0
Duramend®	7	0
Tachosil®	6	6
Tutoplast®	0	6
Durarepair®	4	1
Redura®	1	3
Neuropatch®	3	0
Haemopatch®	3	0
Duraform®	0	2
Duraguard®	1	0
Durapore®	1	0
Ethisorb®	1	0
Fibrillar	3	0
Tissue Graft	**221**	**65**
Autologous Fat	189 (abdomen 145, thigh 44)	45 (abdomen 20, thigh 20, unspecified 5)
Autologous Fascia	27 (Lata 25, unspecified 2)	36 (Lata 32, temporalis 3, unspecified 1)
Autologous Mucosa	28 (middle turbinate 10, septal 4, sphenoid 13, nasal unspecified 1)	8 (middle turbinate 1, septal 4, sphenoid 1, nasal unspecified 2)
Autologous Bone	8 (septum 7, vomer 2)	4 (vomer 2, septum 1, unspecified 1)
Autologous Muscle	4 (thigh 4)	0
Autologous Cartilage	1 (septal)	0
Autologous Periosteum	0	1 (pericranium)
Synthetic Graft	**204**	**47**
Spongostan™	181	39
Tachosil®	21	5
Gelfoam®	2	1
Collagen sponge	1	0
Gliadel® wafers	1	0
Redura®	0	1
Tutoplast®	0	1
Pedicled Vascular Flap	**116**	**90**
Nasoseptal flaps	105	87
Middle turbinate flaps	11	2
Mucoperichondrial	0	1
Temporoparietal	0	1
Tissue Glue	489	99
Adherus®	146	22
Duraseal®	137	22
Tisseel®	126	32
Evicel®	43	16
Bioglue®	40	7
Stammberger foam®	2	1

Floseal®	1	0
Haemostatic Agents	**439**	**93**
Surgicel®	189	51
Surgiflo®	141	24
Floseal®	91	13
Fibrillar®	48	3
Gelfoam®	0	5
Lyostypt®	7	2
Haemopatch®	2	2
Thrombin product unspecified	1	0
Buttress	**31**	**17**
Medpor® polyethylene	15	10
Autologous Bone	14 (septal 10, sphenoid 4)	5 (septal 4, unspecified 1)
Autologous Cartilage	1 (unspecified 1)	2 (septal 1, unspecified 1)
Silastic splint	1	0
Nasal Pack	**519**	**116**
Nasopore®	369	86
Merocel®	94	20
Bismuth-soaked ribbon gauze	34	11
Rapid Rhinos®	33	10
Posisep®	10	5
Stammberger foam®	9	5
Netcell®	8	4
Foley Catheter	2	10
Bactroban®-soaked ribbon gauze	0	7
Sinofoam®	2	0
Parrafin-soaked ribbon gauze	1	0
Unspecified	3	2
CSF diversion	**29**	**38**
Lumbar drain	27	38
External ventricular drain	1	1
Lumbar puncture	1	0
Ventriculoperitoneal shunt	1	0

Supplementary material 5:
Table 5a. Summary of baseline and operative risk factors for CSF rhinorrhoea – incidence and statistical analysis via univariate logistic regression.

	Transsphenoidal approach		*Expanded Endonasal Approach*	
	CSF Rhinorrhoea rate	**Univariate Analyses (OR, CI, p-value)**	**CSF Rhinorrhoea rate**	**Univariate Analyses (OR, CI, p-value)**
Approach				
TSA	28/726 (3.9%)	OR: 0.52, CI: 0.25-1.01, p=0.087	-	-
EEA	-	-	10/140 (7.1%)	OR: 1.92, CI: 0.91-4.04, p=0.087
Baseline characteristics				
Age >65	0/172 (0.0%)	-	3/27 (11.1%)	OR: 1.89, CI: 0.46-7.86, p=0.380
Age <65	28/553 (5.1%)	Reference	7/113 (6.2%)	Reference
BMI >30	11/210 (5.2%)	OR: 1.67, CI: 0.77-3.59, p=0.192	2/28 (7.1%)	OR: 1.00, CI: 0.20-5.00, p=1.000
BMI<30	17/516 (3.3%)	Reference	8/112 (7.1%)	Reference
Tumour diameter >1cm	21/607 (3.5%)	OR: 0.54, CI: 0.23–1.29, p = 0.167	10/131 (7.6%)	-
Tumour diameter <1cm	7/119 (6.0%)	Reference	0/9 (0%)	Reference
Primary surgery	8/98 (8.2%)	**OR: 0.36, CI: 0.15-0.85, p=0.019**	1/21 (4.8%)	OR: 1.32, CI: 0.15 – 11.33, p=0.800
Revision surgery	19/573 (3.3%)	Reference	7/113 (6.2%)	Reference
Presence of Otorhinolaryngologist	9/268 (3.4%)	OR: 0.82, CI: 0.37-1.83, p=0.634	8/93 (8.6%)	OR: 2.12, CI: 0.43-10.40, p=0.355
Presence of Neurosurgeon	25/704 (3.6%)	**OR: 0.22, CI: 0.06-0.79, p=0.021**	9/137 (6.6%)	OR: 0.14, CI: 0.01-1.70, p=0.123
Intra-operative CSF leak grade				
Grade 0	11/512 (2.1%)	Reference	4/61 (6.6%)	Reference
Grade 1	3/131 (2.3%)	OR: 1.05, CI: 0.29-3.76, p=0.944	1/12 (8.3%)	OR: 1.30, CI: 0.13-12.72, p=0.824
Grade 2	9/54 (16.7%)	**OR: 9.35, CI: 3.74-23.37, p < 0.001**	1/13 (7.7%)	OR: 1.19, CI: 0.12-11.59, p=0.882
Grade 3	0/5 (0%)	-	2/39 (5.6%)	OR: 0.77, CI: 0.13-4.42, p=0.770
Leak present, grade unknown	5/24 (20.8%)	**OR: 12.3, CI: 3.94-38.43, p < 0.001**	2/15 (13.3%)	OR: 2.19, CI: 0.36-13.28, p=0.393
Repair methods				
Dural closure	-	-	-	-
Dural replacement	11/196 (5.6%)	OR:1.82, CI: 0.83-3.98 p=0.136	5/66 (7.6%)	OR: 1.11, CI: 0.31-4.04, p=0.869
Tissue graft	13/221 (5.9%)	OR: 1.72, CI: 0.82-3.63, p=0.154	3/65 (4.6%)	OR: 0.47, CI: 0.12-1.90, p=0.289
Synthetic graft	7/204 (3.4%)	OR: 0.81, CI: 0.34-1.92, p=0.628	6/47 (12.8%)	OR: 3.26, CI: 0.87-12.17 p=0.079
Button Technique	0/20 (0%)	-	0/7 (0%)	-
Pedicled Flap	5/116 (4.3%)	OR: 1.17, CI: 0.43-3.17, p=0.756	8/90 (8.9%)	-
Tissue Glue	15/474 (3.2%)	OR: 0.62, CI: 0.29-1.34, p=0.226	8/114 (7.0%)	OR: 0.83, CI: 0.16-4.18, p=0.821
Haemostatic agent	18/439 (4.1%)	OR: 1.05, CI: 0.49-2.26, p=0.896	5/93 (5.4%)	OR: 0.48, CI: 0.13-1.74, p=0.262
Buttress	0/31 (0%)	-	1/17 (5.9%)	OR: 0.78, CI: 0.09-6.61, p=0.789
Gasket sealing	0/15 (0%)	-	0/11 (0%)	-
Nasal packing	22/519 (4.2%)	OR: 1.75, CI: 0.65-4.68, p=0.266	10/116 (8.6%)	-
CSF diversion	1/29 (3.4%)	OR: 0.87, CI: 0.12-6.64, p=0.896	1/38 (2.6%)	OR: 0.28, CI: 0.03-2.28, p =0.234

Table 5b. Summary of operative technique and intra-operative CSF leak – incidence and statistical analysis via Fisher's exact test.

	Intra-operative CSF leak grade during Expanded Endonasal Approach (N = 140)						***Intra-operative CSF leak grade during Transsphenoidal approach (N = 726)***					
Repair methods	Grade 0	Grade 1	Grade 2	Grade 3	Leak present, grade unknown	p-value	Grade 0	Grade 1	Grade 2	Grade 3	Leak present, grade unknown	p-value
Dural closure	0/60 (0%)	0/12 (0%)	0/13 (0%)	0/39 (0%)	0/13 (0%)	-	0/505 (0%)	0/130 (0%)	0/54 (0%)	0/5 (0%)	0/24 (0%)	-
Dural replacement	23/61 (37.7%)	7/12 (58.3%)	8/13 (61.5%)	19/39 (48.7%)	9/14 (64.2%)	0.236	113/509 (22.2%)	47/130 (36.2%)	19/54 (35.2%)	4/5 (80.0%)	13/24 (54.2%)	**<0.001**
Tissue graft	18/61 (29.5%0	9/12 (75.0%)	4/13 (30.8%)	28/39 (71.8%)	6/15 (40.0%)	**<0.001**	88/512 (17.2%)	80/131 (61.1%)	37/54 (68.5%)	5/5 (100.0%)	11/24 (45.8%)	**<0.001**
Synthetic graft	22/61 (36.1%)	4/13 (33.3%)	4/13 (30.8%)	13/39 (33.3%)	4/15 (26.7%)	0.985	141/512 (27.5%)	41/131 (31.3%)	14/54 (25.9%)	2/5 (40.0%)	6/24 (25.0%)	0.835
Button Technique	2/26 (7.7%)	0/11 (0%)	1/7 (14.3%)	3/30 (10.0%)	1/5 (20.0%)	0.560	7/171 (4.1%)	7/89 (7.9%)	9/54 (16.7%)	0/5 (0%)	1/24 (4.2%)	0.119
Pedicled Flap	30/60 (50.0%)	8/12 (66.7%)	12/13 (92.3%)	29/38 (76.3%)	11/11 (100.00%)	**0.001**	58/475 (12.2%)	29/121 (24.0%)	21/47 (44.7%)	1/4 (25.0%)	7/24 (29.2%)	**<0.001**
Tissue Glue	41/61 (67.2%)	12/12 (100%)	12/13 (92.3%)	39/39 (100.0%)	10/13 (76.9%)	**<0.001**	294/509 (57.8%)	112/130 (86.2%)	43/54 (79.6%)	5/5 (100.0%)	20/24 (83.3%)	**<0.001**
Haemostatic agent	38/61 (62.3%)	9/12 (75.0%)	7/13 (53.9%0	27/39 (69.2%)	12/15 (80.0%)	0.553	320/512 (62.5%)	73/131 (55.7%)	26/54 (48.1%)	1/5 (20.0%)	19/24 (79.2%0	**0.013**
Buttress	5/61 (8.2%)	0/12 (0%)	1/13 (7.7%)	9/39 (23.1%)	2/14 (14.3%0	0.147	14/508 (2.8%)	7/129 (5.4%)	9/54 (16.7%)	0/5 (0%)	1/24 (4.2%)	**0.001**
Gasket sealing	3/6 (50.0%)	-	0/2 (0.0%)	6/9 (66.7%)	2/2 (100.0%)	0.267	8/19 (42.1%)	3/8 (37.5%)	4/10 (40.0%)	-	0/1 (0%)	1.000
Nasal packing	50/61 (82.0%)	12/12 (100.0%)	12/13 (92.3%)	28/39 (71.8%)	14/14 (100.0%)	**0.046**	353/494 (71.5%)	102/128 (79.7%)	40/53 (75.5%)	3/4 (75.0%)	21/24 (87.5%)	0.175
CSF diversion	8/61 (13.1%)	1/12 (8.3%0	4/13 (30.8%)	16/39 (41.0%)	9/15 (60.0%)	**<0.001**	11/512 (2.1%)	12/131 (9.2%)	4/54 (7.4%)	0/5 (0%)	2/24 (8.3%)	**0.002**
TOTAL	61	12	13	39	15		512	131	54	5	24	

Supplementary material 6: Summary of visual, endocrine and general outcomes with up to 6 months follow up for transsphenoidal and expanded endonasal cases (if available). SIADH = syndrome of inappropriate anti-diuretic hormone, DI = diabetes insipidus.

	Transsphenoidal approach		*Expanded Endonasal Approach*	
	Pre-operative	**Post-operative (if available)**	**Pre-operative**	**Post-operative (if available)**
Visual & Endocrine Outcomes at 6 months				
Visual deficits (acuity or field)	All deficits: 360/726 (51.7%) Blind: 9/360 (2.4%)	Worse: 10/239 (4.2%) Stable: 53/239 (22.2%) Improved: 176/239 (73.6%)	All deficits: 91/140 (65.0%) Blind: 3/91 (3.3%)	Worse: 7/56 (12.5%) Stable: 11/56 (19.6%) Improved: 38/56 (67.9%)
Anterior hypopituitarism requiring steroid replacement	184/724 (25.4%)	Worse: 131/427 (30.7%) Stable: 263/427 (61.6%) Improved: 33/427 (7.7%)	31/140 (22.1%)	Worse: 22/73 (30.1%) Stable: 46/73 (63.0%) Improved: 5/73 (6.8%)
Posterior hypopituitarism requiring desmopressin replacement	28/722 (3.9%)	Worse: 49/421 (11.6%) Stable: 367/421 (87.2%) Improved: 5/421 (1.2%)	8/140 (5.7%)	Worse: 13/74 (17.6%) Stable: 59/74 (79.7%) Improved: 2/74 (2.7%)
Postoperative Complications				
*Residual/recurrent disease**	-	73/726 (3.3%)	-	10/140 (7.1%)
New DI (transient or permanent)	-	50/726 (6.9%)	-	15/140 (10.7%)
Nasal crusting	-	45/726 (6.2%)	-	11/108 (7.9%)
SIADH	-	22/726 (3.0%)	-	4/140 (2.9%)
Hyponatraemia (unspecified)	-	14/726 (1.9%)	-	2/140 (1.4%)
CNS infection	-	10/726 (1.4%)	-	4/140 (2.9%)
New focal neurological deficit	-	12/726 (1.7%)	-	2/140 (1.4%) 7/140 (5.0%)
Epistaxis (requiring surgical intervention)	-	9/726 (1.2%)	-	0/140 (0%)
All-cause mortality	-	6/726 (0.8%)	-	2/140 (1.4%)
Hypernatraemia (unspecified)	-	4/726 (0.6%)	-	2/140 (1.4%)
Seizures	-	2/726 (0.3%)	-	0/140 (0%)
Major blood vessel injury (e.g. carotids)	-	3/726 (0.4%)	-	0/140 (0%)
Other	-	20[a]/726 (2.8%)	-	5[b]/140 (3.6%)

* Independent of surgical intention. Includes functional recurrence if functioning tumour.

[a] Abdominal wall haematoma x2, psychosis/delirium/confusion x1, sepsis x5, wound breakdown x1, ketosis x1, respiratory infection x4, hyperglycaemia x1,, nasal discharge x1, obstructive hydrocephalus x1, arrythymia x2, otitis media x1

[b] Lumbar drain leak & intracranial hypotension x1, pulmonary embolus x1, pneumocephalus x1, psychosis/delirium/confusion x2, septal perforation x1,