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*Original Article*

# Preoperative radiographic and clinical factors associated with the visualization of intraoperative cerebrospinal fluid during endoscopic transsphenoidal resection of pituitary adenomas

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## ABSTRACT

**Background:** Intraoperative visualization of cerebrospinal fluid (CSF) during endoscopic endonasal resection of skull base tumors is the most common factor contributing to the development of postoperative CSF leaks. No previous studies have solely evaluated preoperative factors contributing to intraoperative CSF visualization. The purpose of this study was to identify preoperative factors predictive of intraoperative CSF visualization.

**Methods:** Retrospective review of patients who underwent transsphenoidal resection of pituitary adenomas was conducted. Clinical and radiographic variables were compared for those who had CSF visualized to those who did not. Nominal logistic regression models were built to determine predictive variables.

**Results:** Two hundred and sixty patients were included in the study. All significant demographic and radiographic variables on univariate analysis were included in multivariate analysis. Two multivariate models were built, as tumor height and supraclinoid extension were collinear. The first model, which considered tumor height, found that extension into the third ventricle carried a 4.60-fold greater risk of CSF visualization ($P = 0.005$). Increasing tumor height showed a stepwise, linear increase in risk; tumors >3 cm carried a 19.02-fold greater risk of CSF visualization ($P = 0.003$). The second model, which considered supraclinoid tumor extension, demonstrated that extension into the third ventricle carried a 4.38-fold increase in risk for CSF visualization ($P = 0.010$). Supraclinoid extension showed a stepwise, linear increase in intraoperative CSF risk; tumors with >2 cm of extension carried a 9.26-fold increase in risk ($P = 0.017$).

**Conclusion:** Our findings demonstrate that tumor height, extension into the third ventricle, and extension above the clinoids are predictive of intraoperative CSF visualization.

**Keywords:** Cerebrospinal fluid leak, Complications, Endoscopic transsphenoidal surgery, Pituitary adenoma, Skull base

## INTRODUCTION

Advances in endoscopic skull base surgery have allowed for the resection of larger and more complex pathologies, leading to larger skull base defects, necessitating the development of complex skull base repair techniques.[7,14,20,21] The pedicled nasal septal flap (NSF) is the current reconstructive technique of choice.[7,9,13,20,25]

Postoperative CSF leak is the most common complication following endoscopic skull base surgery, with significant impact on patient morbidity and medical costs.[1,10] Intraoperative CSF visualization is felt to be the most significant risk factor for the development of a postoperative CSF leak with intraoperative CSF visualization rates ranging from 10 to 71%.[2,5,11,12,13,15,16,22,24,26]

While no gold standard protocol exists for management in the setting of visualized intraoperative CSF, most surgical teams favor complex skull base repair, typically through NSF.[5,20,26] While overall morbidity of NSF reconstruction is low, there is added postoperative burden on patients, including antibiotic treatment, nasal packing/crusting, and closer follow-up;[17] additionally, NSF placement is typically performed by an otolaryngologist, thus making for a more complicated operative planning process. Understanding the preoperative risk factors that predict the visualization of intraoperative CSF and subsequent possible need for complex skull base repair is critical for preoperative planning and patient counseling.

Despite its importance, few studies have endeavored to analyze this clinical question, and none have solely looked at preoperative predictors. In addition, major variations in tumor measurement methodologies between these previous studies have caused the relationship between tumor "size" and CSF visualization to remain poorly defined.[8,11,12,22,26]

The purpose of this study is to analyze preoperative clinical and radiographic variables to better understand their association with the risk of visualizing CSF intraoperatively. This information will be valuable to surgical teams for counseling patients and operative planning, as patients at higher risk for intraoperative CSF visualization are also more likely to require complex skull base repairs.

## MATERIALS AND METHODS

### Patient selection

All patients who underwent endoscopic transsphenoidal resection of pituitary adenoma between January 2009 and April 2019 were eligible for inclusion. Patients were excluded if there was no intraoperative documentation of the presence or absence of CSF visualization on review of surgical operative reports. This study was approved by the University of Alabama-Birmingham Institutional Review Board, protocol number 150610001, assurance number FWA00005960.

### Preoperative and intraoperative workflow considerations

At our center, a neurosurgeon (KR) performs almost all pituitary procedures for the institution, and nearly, all cases are performed endoscopically. Surgical indications for tumor resection include apoplexy, endocrinopathy, and visual dysfunction. All cases not undergoing more extensive skull base repairs are repaired using a multilayer approach involving placement of an autologous fat graft in the intradural space, epidural overlay of a duraplasty made of porcine small intestine submucosa (Biodesign®, Cook Medical, Bloomington, IN), followed by bolstering with a synthetic high-density polyethylene implant (MedPor TSI, Medtronic). If preoperative MRI suggests a defect larger than 2 cm, NSF is considered, and patients are counseled accordingly. When an NSF is planned, the case is scheduled in coordination with an otolaryngologist (BW). Flap harvest is typically completed at the beginning of the case and placed in position on its conclusion. In cases where NSF is possible but not guaranteed, or in cases where NSF is not considered, neurosurgery proceeds with the approach and free graft repair is attempted. Otolaryngology is contacted for NSF repair in the setting of easy free graft dislodgement following a "tug test," evidence of CSF leaking around the free graft during a Valsalva maneuver, and/or inability to adequately secure free graft material under a bony edge on at least three sides. High volume of CSF visualized intraoperatively and repeat surgeries is the setting in which unplanned rescue flaps are most frequently used.

### Data collection

Electronic medical record review was conducted. Data were collected regarding patient demographics, presenting symptoms, prior operative history, tumor measurements, tumor pathologic characteristics, preoperative and postoperative endocrinological status, skull base repair technique, presence or absence of intraoperative visualized CSF, and presence of postoperative CSF leak. The presence of intraoperative CSF was determined from operative reports. Postoperative CSF leak was defined by persistent leakage of clear fluid from the nares spontaneously or with forward head tilt of 30°. Leaks were confirmed with patient clinical history and imaging findings. Confirmatory laboratory tests, such as beta-2 transferrin, were not commonly used as the results are not available in a timely manner so as to be useful in clinical decision-making. Cases were defined as patients having an intraoperative CSF visualized, while controls were subjects who did not have a visualized intraoperative CSF.

### Tumor measurements

Qualitative and quantitative measures of tumor size were calculated for all patients. All measures were performed using contrasted MRI sequences. For patients unable to obtain an MRI, a CT was used. Independent statistical analysis was conducted for both MRI and CT measurements. No statistically significant difference was found between MRI and CT measurements and statistical analysis using both

imaging modalities demonstrated nearly identical findings. As most patients are evaluated with MRI for pituitary tumors, only MRI data are presented in this study.

Qualitative descriptors included erosion (thinning) of the sella turcica without extension of tumor beyond sellar boundaries, tumor extension through the sella turcica into the sphenoid sinus, tumor extension into the third ventricle, and >2 cm predicted sellar defect as determined by radiographic tumor appearance/measured width. Intraoperative factors, such as tumor texture, were not considered, as the purpose of this study is to solely evaluate preoperative predictors. Quantitative measures of tumor size included maximal tumor height, maximal tumor width, and tumor extension above the anterior clinoids (all reported in mm).

Multivariate analysis of continuous variables often lacks the clinical utility to meaningfully guide clinical decision-making. When considering which patients to counsel for heightened risk of CSF leak and potential need for NSF, ease of use becomes important. Therefore, additional analyses were performed, subdividing continuous MRI radiographic variables into ordinal categories. Categories for tumor height and width included <1 cm, 1–2 cm, and >3 cm. Categories for extension above the anterior clinoid included no extension, <1 cm, 1–2 cm, and >2 cm.

### Statistical analysis

All statistical analyses were conducted using JMP® 14 Statistical Software (SAS Institute, Cary, North Carolina, USA). Continuous variables are presented as mean ± standard deviation and were compared using *t*-tests. Categorical variables are presented as frequency and percentage and were compared using Chi-square tests. All variables that were found to significantly differ between groups were retained. Nominal logistic regression models were used to determine which the retained variables were predictive of intraoperative CSF egress. This manuscript was prepared using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist. $P < 0.05$ was considered statistically significant.

## RESULTS

### Patient demographics and clinical characteristics

Two hundred and ninety-eight patients were screened for inclusion in this study. Thirty-eight patients were excluded due to lack of documentation of the presence or absence of CSF visualization on review of surgical operative reports. Two hundred and sixty patients were included in the final analysis, 138 (53.1%) were documented to have intraoperative CSF visualized, which is consistent with rates previously been documented in the literature. Average age at time of surgical resection was 53.2 years and 46.1% of patients were female. About 75.8% of tumors were nonfunctional, 53.1% of patients had visual abnormalities present on admission, 12.7% presented with pituitary apoplexy, and 9.6% had previously undergone transsphenoidal resection of a pituitary mass [Table 1]. Of the clinical characteristics analyzed, only the presence of visual abnormalities on presentation and tumor functionality was found to significantly differ between cases and controls, with patients who had intraoperative CSF visualized being significantly more likely to have presented with visual impairment (59.4% vs. 45.9%, $P = 0.029$, Table 1), and patients with CSF visualization being significantly more likely to have a nonfunctioning pituitary mass (81.2% vs. 69.7%, $P = 0.031$, Table 1).

### Operative management and postoperative characteristics

Of the patients with intraoperative CSF visualized, management included eight multilayer repairs, 92 multilayer repairs with autologous abdominal fat graft, four multilayer repairs with NSF, and 34 multilayer repairs with NSF and autologous abdominal fat graft ($P < 0.0001$, Table 2, Figure 1). Fifty patients underwent NSF placement for skull base repair; 38 (76.0%) had CSF visualized intraoperatively, as compared to 12 (24.0%) who did not ($P = 0.0003$, Table 2).

Nine patients (3.5%) developed postoperative CSF leaks. The postoperative leak rate in those with visualized CSF intraoperatively was 5.8% as compared to 0.8% in those without the presence of an intraoperative CSF ($P = 0.028$, Table 2). Of the nine patients who developed postoperative CSF leaks, 8 (88.9%) had visualized intraoperative CSF. The one patient with a postoperative leak who did not have intraoperative CSF visualized was treated with several days of CSF diversion through lumbar drain followed by operative repair with NSF. Of the eight patients with concomitant intraoperative CSF visualization and postoperative CSF leak, only one had been initially treated with an NSF, this patient's postoperative leak was treated with lumbar drain and operative repair of NSF. Only one patient developed postoperative CSF leak in the setting of multilayer repair without fat grafting. This patient was treated with CSF diversion through lumbar drain alone. Of the six patients with intra- and postoperative CSF egress initially treated with multilayer repair with abdominal fat graft, postoperative leak was treated with CSF drainage through lumbar drain alone for a one patient, CSF diversion (through lumbar drain and external ventriculostomy drain) followed by NSF for two patients, NSF alone for one patient, and operative repair of initial multilayer repair for two patients. No recurrence of CSF leak occurred after secondary repair for any of the patients [Figure 1].

Postoperative leak rates and repair strategies were not included in multivariate analysis as the purpose of this

**Table 1:** Patient demographics and clinical characteristics.

| | All patients (*n*=260) | Intraoperative CSF seen (*n*=138) | No intraoperative CSF seen (*n*=122) | *P* value |
|---|---|---|---|---|
| Age (mean±SD) | 53.2 (14.7) | 53.3 (15.1) | 53.1 (14.4) | 0.891 |
| Gender, *n* (%) | | | | 0.186 |
| Male | 120 (46.1) | 69 (50.0) | 51 (41.8) | |
| Female | 140 (53.9) | 69 (50.0) | 71 (58.2) | |
| Race, *n* (%) | | | | 0.366 |
| Caucasian | 167 (64.2) | 87 (63.0) | 80 (65.6) | |
| African-American | 86 (33.1) | 45 (32.6) | 41 (33.6) | |
| Non-White Hispanic | 6 (2.3) | 5 (3.6) | 1 (0.8) | |
| Asian | 1 (0.4) | 1 (0.8) | 0 (0.0) | |
| BMI (mean, ±SD) | 32.8 (7.4) | 32.9 (7.2) | 32.6 (7.6) | 0.772 |
| Visual abnormality, *n* (%) | | | | 0.029 |
| Present | 138 (53.1) | 82 (59.4) | 56 (45.9) | |
| Absent | 122 (46.9) | 56 (40.6) | 66 (54.1) | |
| Apoplexy on presentation, *n* (%) | | | | 0.856 |
| Yes | 33 (12.7) | 18 (13.0) | 15 (12.3) | |
| No | 227 (87.3) | 120 (87.0) | 107 (87.7) | |
| Previous endoscopic transsphenoidal surgery, *n* (%) | | | | 0.758 |
| Yes | 25 (9.6) | 14 (10.1) | 11 (9.0) | |
| No | 235 (90.4) | 124 (89.9) | 111 (91.0) | |
| Previous craniotomy for sellar pathology, *n* (%) | | | | 0.500 |
| Yes | 6 (2.3) | 4 (2.9) | 2 (1.6) | |
| No | 254 (97.7) | 134 (97.1) | 120 (98.4) | |
| Previous sellar radiation, *n* (%) | | | | 0.901 |
| Yes | 4 (1.5) | 2 (1.5) | 2 (1.6) | |
| No | 256 (98.5) | 136 (98.5) | 120 (98.4) | |
| Preoperative hormone replacement, *n* (%) | | | | 0.439 |
| Yes | 98 (37.7) | 49 (35.5) | 49 (40.2) | |
| No | 162 (62.3) | 89 (64.5) | 73 (59.8) | |
| Functioning pituitary mass, *n* (%) | | | | 0.031 |
| Yes | 63 (24.2) | 26 (18.8) | 37 (30.3) | |
| No | 197 (75.8) | 112 (81.2) | 85 (69.7) | |

BMI: Body mass index, CSF: Cerebrospinal fluid, SD: Standard deviation

study is to analyze solely preoperative variables predictive of intraoperative CSF visualization with the goal of assisting surgical teams in determining which patients are at risk of requiring more complex skull base repairs. Including postoperative leak rates and intraoperative repairs would alter our results and detract from this study's purpose.

### Preoperative radiographic characteristics

On review of preoperative imaging characteristics, patients with intraoperative CSF visualization were found to have larger tumor width (24.8 vs. 21.2 mm, $P = 0.0008$), tumor extension above the anterior clinoids (11.5 vs. 7.3 mm, $P < 0.0001$), and tumor height (27.4 vs. 20.7 mm, $P < 0.0001$) as compared to patient with no intraoperative CSF [Table 2]. Patients with visualized intraoperative CSF were also more likely to have tumor extension into the third ventricle (25.2% vs. 5.0%, $P < 0.0001$) and >2 cm predicted sellar defect on preoperative imaging (78.8% vs. 65.6%, $P = 0.028$) as compared to those without intraoperative CSF [Table 2]. There was no significant difference between visualized CSF and no visualized CSF groups with respect to extension of tumor through the sella into the sphenoid sinus (53.0% vs. 42.7%, $P = 0.105$) and sellar erosion without extension into the sphenoid sinus (86.5% vs. 81.3%, $P = 0.257$, Table 2).

### Bivariate analysis of variables when subdivided into ordinal categories

Continuous MRI radiographic variables were subdivided into ordinal categories to improve the ease of use and utility of the results in clinical decision-making. On bivariate analysis, intraoperative CSF visualization was significantly associated with tumor height (<1 cm, 1–2 cm, 2–3 cm, and >3 cm, $P = 0.0002$), tumor extension above the anterior clinoids (none, <1 cm, 1–2 cm, and >2 cm, $P < 0.0001$), and tumor width (<1 cm, 1–2 cm, 2–3 cm, and >3 cm, $P = 0.007$, Table 3).

**Table 2:** Radiographic, operative, and postoperative characteristics.

| | All | Intraoperative CSF seen | No intraoperative CSF seen | *P* value |
|---|---|---|---|---|
| Tumor extension above anterior clinoids, mean in mm (±SD) | 9.4 (7.2) | 11.5 (7.5) | 7.3 (6.2) | 0.0001 |
| Greatest tumor width, mean in mm (±SD) | 23.1 (8.3) | 24.8 (7.9) | 21.2 (8.3) | 0.0008 |
| Greatest tumor height, mean in mm (±SD) | 24.2 (11.0) | 27.4 (10.8) | 20.7 (10.2) | 0.0001 |
| Sellar erosion without extension into sphenoid sinus, *n* (%) | | | | 0.257 |
| Yes | 210 (84.0) | 115 (86.5) | 95 (81.2) | |
| No | 40 (16.0) | 18 (13.5) | 22 (18.8) | |
| Tumor extension into sphenoid sinus, *n* (%) | | | | 0.105 |
| Yes | 120 (48.2) | 70 (53.0) | 50 (42.7) | |
| No | 129 (51.8) | 62 (47.0) | 67 (57.3) | |
| Tumor extension into third ventricle, *n* (%) | | | | 0.0001 |
| Yes | 40 (15.6) | 34 (25.2) | 6 (5.0) | |
| No | 216 (84.4) | 101 (74.8) | 115 (95.0) | |
| >2 cm predicted sellar defect, *n* (%) | | | | 0.017 |
| Yes | 188 (72.6) | 108 (78.8) | 80 (65.6) | |
| No | 71 (27.4) | 29 (21.2) | 42 (34.4) | |
| Postoperative CSF leak, *n* (%) | | | | 0.028 |
| Yes | 9 (3.5) | 8 (5.8) | 1 (0.8) | |
| No | 251 (96.5) | 130 (94.2) | 121 (99.2) | |
| Nasoseptal flap (NSF) placement, *n* (%) | | | | 0.0003 |
| Yes | 50 (19.2) | 38 (27.5) | 12 (9.8) | |
| No | 210 (80.8) | 100 (72.5) | 110 (90.2) | |
| Skull base repair technique, *n* (%) | | | | 0.0001 |
| Multilayer repair, – fat graft | 42 (16.2) | 8 (5.8) | 34 (27.9) | |
| Multilayer repair, + fat graft | 168 (64.6) | 92 (66.7) | 76 (62.3) | |
| Multilayer repair, – fat graft, + NSF | 5 (1.9) | 4 (2.9) | 1 (0.8) | |
| Multilayer repair, + fat graft, + NSF | 45 (17.3) | 34 (24.6) | 11 (9.0) | |

CSF: Cerebrospinal fluid, SD: Standard deviation

**Table 3:** Bivariate analysis of tumor characteristics when divided into ordinal categories.

| | All patients | Intraoperative CSF seen | No intraoperative CSF seen | *P* value |
|---|---|---|---|---|
| Tumor extension above anterior clinoids, *n* (%) | | | | <0.0001 |
| None | 44 (17.0) | 10 (7.3) | 34 (27.9) | |
| <1 cm | 86 (33.2) | 50 (36.5) | 36 (29.5) | |
| 1–2 cm | 107 (41.3) | 58 (42.3) | 49 (40.1) | |
| >2 cm | 22 (8.5) | 19 (13.9) | 3 (2.5) | |
| Greatest tumor width, *n* (%) | | | | 0.007 |
| <1 cm | 15 (6.3) | 3 (2.4) | 12 (10.5) | |
| 1–2 cm | 57 (23.9) | 30 (24.2) | 27 (23.7) | |
| 2–3 cm | 133 (55.9) | 67 (54.0) | 66 (57.9) | |
| >3 cm | 33 (13.9) | 24 (19.4) | 9 (7.9) | |
| Greatest tumor height, *n* (%) | | | | 0.0002 |
| <1 cm | 30 (11.6) | 6 (4.4) | 24 (19.7) | |
| 1–2 cm | 48 (18.5) | 24 (17.5) | 24 (19.7) | |
| 2–3 cm | 109 (42.1) | 58 (42.3) | 51 (41.8) | |
| >3 cm | 72 (27.8) | 49 (35.8) | 23 (18.8) | |

CSF: Cerebrospinal fluid

### Nominal logistic regression modeling

Multivariate logistic regression models were constructed, consisting of the preoperative variables significantly associated with intraoperative CSF visualization on bivariate analysis. As tumor height and tumor extension above the anterior clinoids are collinear variables, two separate models were constructed to avoid data skewing. Model number

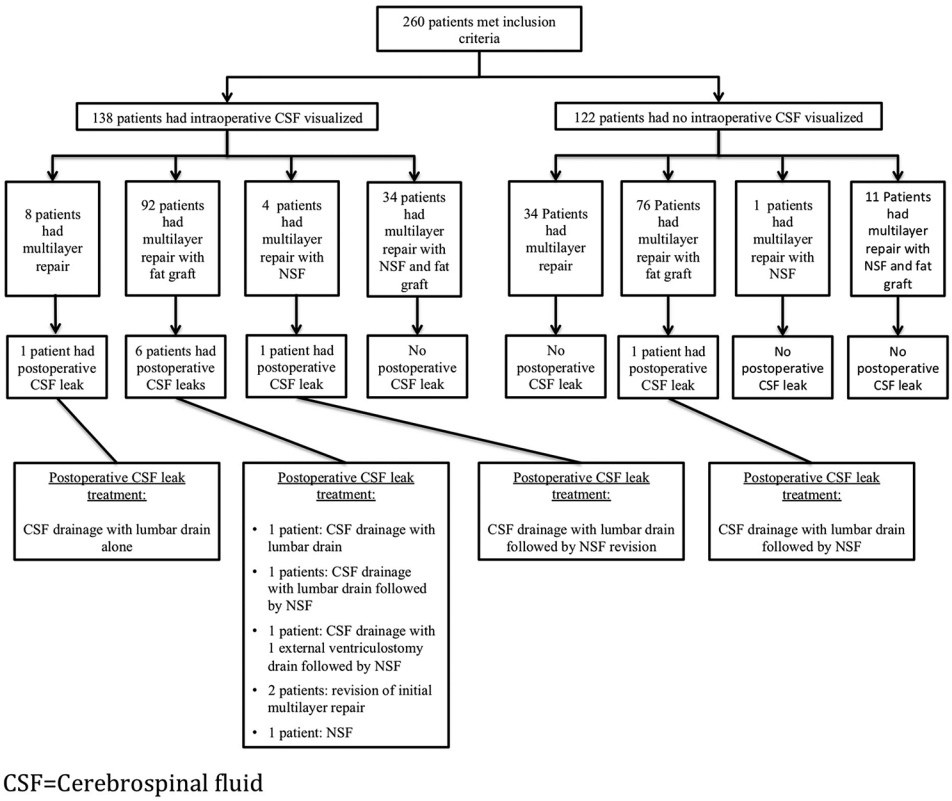


**Figure 1:** Initial skull base repair technique for all 260 patients subdivided by the presence or absence of visualized intraoperative CSF. Subsequent postoperative CSF leaks with associated management strategies are displayed. No recurrence of CSF leak was seen after secondary repair.

one included all significant variables and tumor height, but did not include tumor extension above the clinoids. In this model, extension into the third ventricle carried a 4.60-fold greater risk of CSF visualization ($P = 0.005$), while increasing tumor heights showed a stepwise, linear increase in risk of CSF visualization. Relative to tumors <1 cm in size, tumors >3 cm carried a 19.02-fold greater risk of CSF visualization ($P = 0.003$, Table 4).

The second model included all significant variables and extension above the clinoids, but did not include tumor height. In this model, tumor extension into the third ventricle carried a 4.38-fold greater risk of CSF visualization ($P = 0.010$), while supraclinoid extension showed a stepwise linear increase in risk of CSF visualization. Relative to tumors with no extension, tumors with >2 cm of extension carried a 9.26-fold increase in risk for CSF visualization ($P = 0.017$, Table 4).

## DISCUSSION

### Demographic variables and intraoperative CSF visualization

In our study, postoperative CSF leak rates were significantly higher for those with intraoperative CSF visualized than those without, with an overall rate of CSF visualization during tumor resection of 53.1% and a postoperative CSF leak rate of 3.5%. This is reflective of what has been previously published in the literature, reconfirming the importance of intraoperative CSF visualization as a contributing factor in the development of postoperative CSF leaks.[5,9,11,12,13,15,20,22,24]

Of the demographic variables analyzed, only visual deficits on presentation and lack of tumor functionality were associated with intraoperative CSF visualization. On multivariate analysis, neither variable retained significance. The univariate relationship can be explained by the confounder of tumor size. Larger pituitary tumors are more likely to cause optic chiasm compression and subsequent visual field dysfunction.[23] In addition, patients with functional masses typically present earlier secondary to symptoms associated with hormone excess and as such have smaller tumors.[19]

The previous studies have inconsistently reported an association between elevated BMI and intraoperative CSF visualization.[4,12,22] Our study does not show a significant difference between BMI in those with an intraoperative CSF versus those without intraoperative CSF.

Other studies have shown repeat surgery to be a risk factor for the visualization of intraoperative CSF.[8,26] It can be

**Table 4:** Multivariate models: predictors of intraoperative CSF visualization

| | Odds CSF seen (95% CI) | *P* value |
|---|---|---|
| **Model 1** | | |
| Greatest tumor height | | |
| <1 cm | Ref | Ref |
| 1–2 cm | 7.61 (1.44–40.18) | 0.017 |
| 2–3 cm | 10.33 (1.68–63.48) | 0.012 |
| >3 cm | 19.02 (2.78–130.33) | 0.003 |
| Greatest tumor width | | |
| <1 cm | Ref | Ref |
| 1–2 cm | 0.70 (0.097–5.04) | 0.724 |
| 2–3 cm | 0.19 (0.02–1.99) | 0.165 |
| >3 cm | 0.232 (0.02–2.93) | 0.260 |
| Tumor extension into the third ventricle | | |
| Yes | 4.60 (1.57–13.46) | 0.005 |
| No | Ref | Ref |
| >2 cm predicted sellar defect | | |
| Yes | 1.63 (0.41–6.52) | 0.488 |
| No | Ref | Ref |
| Presenting with visual deficits | | |
| Yes | 0.76 (0.39–1.50) | 0.435 |
| No | Ref | Ref |
| Functioning pituitary mass | | |
| Yes | 0.76 (0.36–1.59) | 0.460 |
| No | Ref | Ref |
| **Model 2** | | |
| Tumor extension above clinoid | | |
| None | Ref | Ref |
| <1 cm | 6.40 (2.10–19.52) | 0.001 |
| 1–2 cm | 4.18 (1.21–14.46) | 0.024 |
| >2 cm | 9.26 (1.49–57.56) | 0.017 |
| Greatest tumor width | | |
| <1 cm | Ref | Ref |
| 1–2 cm | 1.44 (0.30–6.88) | 0.647 |
| 2–3 cm | 0.46 (0.06–3.47) | 0.452 |
| >3 cm | 0.77 (0.09–6.65) | 0.809 |
| Tumor extension into the third ventricle | | |
| Yes | 4.38 (1.43–13.37) | 0.010 |
| No | Ref | Ref |
| >2 cm predicted sellar defect | | |
| Yes | 1.83 (0.49–6.88) | 0.371 |
| No | Ref | Ref |
| Presenting with visual deficits | | |
| Yes | 0.94 (0.48–1.85) | 0.852 |
| No | Ref | Ref |
| Functioning pituitary mass | | |
| Yes | 0.91 (0.43–1.95) | 0.810 |
| No | Ref | Ref |

CSF: Cerebrospinal fluid

postulated that repeat surgery is associated with increased risk of intraoperative and postoperative CSF egress as surgeons must navigate distorted anatomy and scarring leading.[8,18] Our study did not demonstrate a significant difference in intraoperative CSF visualization rates in patients undergoing repeat transsphenoidal surgery. The small number of repeat surgeries ($n$ = 25) and operator experience may explain why no association was found between repeat surgery and intraoperative CSF visualization in our population.

### Radiographic characteristics and intraoperative CSF visualization

Differences in tumor measurement methodologies in previously published studies have caused the relationship between tumor size and the risk of visualizing CSF intraoperatively to remain poorly understood. Zhou *et al.* demonstrated significantly greater suprasellar extension and tumor "size" in cases with intraoperative CSF visualization; however, it is unclear whether "size" is referring to tumor width or height, and suprasellar extension does not appear to have been included in multivariate analyses.[26] Patel *et al.* found the presence of suprasellar tumor extension to be associated with increased odds of visualizing CSF intraoperatively; however, suprasellar tumor extension was presented as a dichotomous "yes" or "no" variable rather than a measurement.[22] Finally, Jakimovski *et al.* found higher CSF visualization rates for tumors with diameters >2 cm and volumes >1.5 $cm^3$.[11] However, this study fails to conduct a multivariate analysis, fails to look at tumor height independently, and includes intraoperative variables. In our study, tumor height was found to be more predictive of intraoperative CSF visualization than tumor width, emphasizing the importance of considering tumor dimensions independently. In addition, inclusion of intraoperative variables alters the relationship between preoperative variables and CSF visualization, thereby reducing the value of Jakimovski *et al.*'s study's results in aiding surgical teams in operative planning and patient counseling.

In our study, tumor size was described both quantitatively and qualitatively. It is not surprising that measures of the anteroposterior and left-right dimensions of the tumors, including >2 cm predicted sellar defect, tumor width, sellar erosion, and extrasellar extension into the sphenoid sinus, were not significantly associated with intraoperative CSF visualization on multivariate analysis. These variables are felt to predict the size of sellar defect and impact repair selection, but larger defects in the anteroposterior and left-right dimensions should not increase the risk of intraoperative CSF egress. Comparatively, variables that quantify the craniocaudal dimension of the tumors, including tumor height, intraventricular extension, and suprasellar extension above the anterior clinoid, were significantly associated with the visualization of intraoperative CSF. While the exact mechanism is not well understood, it has been hypothesized that tumors with greater craniocaudal extension develop incompetence of the diaphragma sellae secondary to sellar

expansion, leading to exposed arachnoid that is at risk for thinning or developing defects, thereby increasing the risk of CSF egress.[16]

Management in the setting of visualized intraoperative CSF varies by institution. Conger *et al.* recently suggested a graded approach based on volume of intraoperative CSF egress with an overall postoperative CSF leak rate of 1.6% and a postoperative leak rate of 3.2% for patients with CSF visualized intraoperatively.[3,5] Volume of intraoperative CSF egress was defined by a previously published grading scale, which has yet to be assessed for reliability.[5] While no formal graded approach is used at our institution for repair selection, with repair method chosen by the surgical team based on defect size and presence of CSF egress, our overall postoperative CSF leak rate was 3.5% and our postoperative leak rate in those with visualized intraoperative CSF was 5.8%. These rates are reflective of what has previously been documented in the literature but are higher than what was seen using the graded approach presented by Conger *et al.* It is possible that the varying results are secondary to differences in repair selection in low grade versus high grade of intraoperative CSF egress, which cannot be determined from our data. Further studies assessing the reliability of the intraoperative CSF grading scale and assessing the validity of the graded repair approach would be useful to better understand the reproducibility of these results.

### Limitations

Due to the retrospective nature of this study, there is a potential for inaccuracy in data collection and reporting, as well as unintentional data entry errors. In our study, the visualization of intraoperative CSF was determined from operative reports, in which intraoperative findings are described, but no formal grading system or standardized method of reporting is used. It follows that formal grading of the amount of intraoperative CSF visualization, as previously described by Esposito *et al.*, could not reliably be determined for our data.[5,26] In addition, our study's population includes only patients with pituitary adenoma. Studies have suggested that different tumor pathologies are associated with higher risk of intraoperative CSF visualization.[6,8,12,22,26] Our findings may not be generalizable to sellar pathologies other than pituitary adenoma and future research should address more varied sellar pathologies.

Despite these limitations, our findings yield key insights that build on our understanding of preoperative risk factors associated with intraoperative CSF visualization during endoscopic transsphenoidal resection of pituitary adenomas.

## CONCLUSION

In this study, we found that tumor height, extension into the third ventricle, and extension above the clinoids are predictive of intraoperative CSF egress. Understanding risk factors for intraoperative CSF visualization helps predict which patients are more likely to require complex skull base repair, which can assist in counseling patients of the higher morbidity associated with complex repairs and can aid surgical teams in planning, as complex repairs are typically performed in a multidisciplinary fashion.

### Declaration of patient consent

Patients consent not required as patients identity is not disclosed or compromised.

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### Conflicts of interest

There are no conflicts of interest.

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