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Risk Factors Associated with Postoperative CSF Leak in Extrasellar Tumors

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Abstract

Objective While postoperative cerebrospinal fluid (CSF) leak rates of pituitary tumors have been frequently studied, there are fewer studies examining postoperative CSF leak rates for extrasellar tumors. The purpose of this study was to identify risk factors for the development of postoperative CSF leak in patients undergoing endoscopic surgery for extrasellar tumors.

Methods A retrospective chart review was done for patients who underwent endoscopic resection for extrasellar tumors between 2008 and 2020. Age, gender, tumor type, tumor location, tumor size, reconstruction technique, medical comorbidities, and other potential risk factors were identified. Data was analyzed to identify significant risk factors for development of postoperative CSF leak.

Results There were 100 patients with extrasellar tumors who developed intraoperative CSF leaks. Seventeen patients (17%) developed postoperative CSF leaks. Leaks occurred at a median of 2 days following surgery (range 0–34 days). Clival tumors had a significantly higher incidence of postoperative leak than those in other sites ($p < 0.05$). There were no significant differences in other locations, body mass index, tumor size, reconstruction technique, medical comorbidities, or other factors. There were nearly twice as many intraoperative grade III leaks in those who developed postoperative CSF leak, but this was not statistically significant ($p = 0.12$).

Conclusion Extrasellar tumors, particularly clival tumors, have a higher rate of postoperative CSF leak than pituitary tumors. Prophylactic lumbar drains can be considered for patients at high risk for developing postoperative CSF leak.

Keywords
- ► skull base
- ► extrasellar
- ► cerebrospinal fluid leak
- ► repair

Introduction

With the advent of endoscopic and expanded endoscopic techniques, much of skull base surgery can now be tackled with minimal morbidity without a visible incision. A key determinant of postoperative morbidity is the occurrence of a cerebrospinal fluid (CSF) leak.[1–5] Recent studies have aimed to identify factors associated with both intraoperative and postoperative CSF leaks.[1,6–9] Extrasellar tumors, from both the anterior and posterior skull base, were identified as

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being more likely to have high-flow intraoperative CSF leaks, and therefore a higher incidence of postoperative leak than pituitary tumors. In this study, we analyzed data from a 15-year period of endoscopic skull base surgery in our institution to identify characteristics associated with increased risk of postoperative CSF leaks in extrasellar tumors. We chose to exclude pituitary adenomas because these tumors have been shown to have lower CSF leak rates than other pathologies (2.3–9%).[1,6] There has been some literature examining postoperative CSF leak rates in pituitary adenomas or in combined cohorts of anterior skull base tumors. However, there has not been much literature focusing specifically on the CSF leak rate of tumors outside the sella and that is the aim of this study.

Methods

Institutional Review Board approval was obtained for this study. A retrospective review was performed on patients who underwent endoscopic skull base surgery at a tertiary health care system performed by our group of two neurosurgeons and three otolaryngologists between 2008 and 2020. Chart review was performed to obtain past medical history, including past neurological history, cardiovascular history, gender, age, body mass index (BMI), smoking status, type and location of tumor, tumor size, grade of intraoperative CSF leak, as well as the type and timing of CSF leak repair. We included extrasellar tumors from the following locations: anterior cranial fossa, clivus, cribriform, and suprasellar, including sphenoid planum and tuberculum. Pituitary adenomas with extrasellar extension were excluded. There were no transpterygoid approaches in this cohort.

The repair of CSF leak was performed after resection of the tumor. The defect was inspected, and the decision was made to use either DuraGen Plus or abdominal fat for underlay reconstruction of the dura. The frequency in which we used DuraGen Plus increased over the study period, as we wanted to avoid the morbidity of the abdominal incision. After the underlay reconstruction, a check for persistent leak with a Valsalva maneuver to 30 mm Hg was performed. When there was confirmation of no leak, we completed the reconstruction with a nasoseptal flap, tissue glue or Surgicel, and a balloon catheter. We used a 14-French coude tip Foley catheter filled to 5 mL of saline as it offered additional support in maintaining the flap in optimal position and angle. We generally deflate and remove the catheter on postoperative day 3.

Next, we used statistical testing, including *t*-test, chi-square testing, and Fisher's exact test to compare the prevalence of each of the factors listed above between those who developed a postoperative leak and those that did not. For example, we compared the average BMI of those who developed postoperative CSF leak to those who did not develop a postoperative CSF leak. Two-sample *t*-tests were used with continuous variables such as age, BMI, and tumor size. Chi-square and Fisher's exact tests were used with the categorical variables. An α level of $p < 0.05$ was used for all analyses.

Results

In our study, we included 100 consecutive patients with extrasellar tumors who developed an intraoperative leak. In this series of extrasellar tumors all patients had an intraoperative leak, as expected because of the tumor pathology and/or location. Seventeen patients (17%) developed a postoperative CSF leak (►**Table 1**). There were no patients who did not experience an intraoperative leak and developed a postoperative leak. The leak occurred at a median of 2 days (range 0–34 days) after the surgical date.

Of the 17 cases with postop leak, meningiomas and craniopharyngiomas made up the majority (23.5% each), followed by chordomas (17.6%) and esthesioneuroblastomas (11.8%) (►**Table 2**).

Intraoperative CSF leak grade analysis using a chi-square test revealed a higher proportion of grade III intraoperative leaks resulting in postoperative leaks, although this was not

Table 1 Patient demographics

	No postop leak	Postop leak	*p*
Total (*n*/%)	83/100	17/100	n/a
Male (*n*/%)	42/51	9/53	0.86
Female (*n*/%)	41/49	8/47	n/a
Age (median) [range]	51 [6–66]	51 [10–69]	n/a
Tumor size (mean, mm) [range]	29.8 mm [4.5–96.0]	31.5 mm [3.0–65.0]	0.36
BMI (mean) [range]	28.4 [16.8–45.0]	26.0 [21.5–31.9]	0.08
Diabetes history (*n*/%)	15/18.1	0/0	n/a
Smoking history (*n*/%)	10/12.0	0/0	n/a
Cardiovascular history (*n*/%)	29/34.9	6/35.3	0.98
Neurological history (*n*/%)	13/15.7	5/29.4	0.18
Prior neurological surgery (*n*/%)	22/26.5	4/23.5	1.0
Prior neurological radiation (*n*/%)	7/8.4	2/11.7	0.68

Abbreviations: BMI, body mass index; n/a, not available.

Table 2 Pathological diagnosis of tumor

Pathology	No postop leak (total = 83 = 100%)	Postop leak (total = 17 = 100%)
Adenocarcinoma, mucinous type (*n*/%)	1/1.2	0/0
Arachnoid cyst (*n*/%)	2/2.4	0/0
Chondrosarcoma (*n*/%)	1/1.2	0/0
Chordoma (*n*/%)	3/3.6	3/17.6
Craniopharyngioma (*n*/%)	20/24.2	4/23.5
Dermoid (*n*/%)	1/1.2	0/0
Esthesioneuroblastoma (*n*/%)	13/15.7	2/11.8
Meningioma (*n*/%)	25/30.1	4/23.5
Metastatic renal cell carcinoma (*n*/%)	1/1.2	0/0
Rathke's cleft cyst (*n*/%)	8/9.6	0/0
Schwannoma (*n*/%)	1/1.2	0/0
Sinonasal tumor (*n*/%)	4/4.8	0/0
Solitary fibrous tumor (*n*/%)	1/1.2	0/0
Squamous cell carcinoma (*n*/%)	2/2.4	0/0
Epidermoid (*n*/%)	0/0	1/5.9
Melanoma (*n*/%)	0/0	1/5.9
CPA tumor (*n*/%)	0/0	1/5.9
Lobular capillary hemangioma (*n*/%)	0/0	1/5.9

Abbreviation: CPA, cerebellopontine angle.

statistically significant ($p = 0.12$) (►**Table 3**).[10] Grade I and II intraoperative leaks did not result in significant increase in postoperative leaks.

Repair of the surgical defects included combinations of DuraGen Plus (Integra LifeSciences, Princeton, New Jersey, United States), abdominal fat grafts, nasoseptal flap, tissue glue, and balloon catheter for bolster. The type of repair evolved over the period of the study and also was at the discretion of the surgical team. Abdominal fat was used in the early years of the study, while DuraGen Plus has been used more recently. More lumbar drains were placed in the early years, with a decreasing frequency in recent years. Fifteen patients of the 100 had intraoperative placement of a lumbar drain. Nine of these 15 patients developed postoperative leaks.

As shown in ►**Table 4**, a chi-square test of proportions demonstrated that the location of the tumor in the clivus appears to be a potential risk factor for the development of postoperative leaks. Of the 9 clival tumors, 4 developed postoperative leaks (44%, $p = 0.04$). Of the 27 anterior skull base/cribriform lesions, 4 developed postoperative leaks (14.8%). Of the 59 patients with suprasellar lesions, 8 developed postoperative leaks (13.6%).

For our study cohort, tumor size, BMI, prior neurological and neurosurgical history, including prior neurological disease, prior craniotomy, and prior cranial radiation, were not significant factors in determining whether the patient developed a postoperative CSF leak. Similarly, age, gender, smoking history, cardiovascular history, or diabetes history, did not play a significant role in determining the development of postoperative CSF leak (►**Table 1**).

We did not statistically analyze patients based on the timing of their postoperative leak. Based on all the patient characteristics that we gathered, there were no major differences in pathology or location from a descriptive analysis.

All 17 patients who developed postoperative CSF leaks were taken back to the operating room for surgical repair. Nine of these patients had had lumbar drain placement

Table 3 Severity of intraoperative CSF leaks

Intraoperative leak grade	No postop leak (total = 83 = 100%)	Postop leak (total = 17 = 100%)	*p*
Grade I (*n*/%)	7/8.4	1/5.9	0.59
Grade II (*n*/%)	57/68.7	9/52.9	0.21
Grade III (*n*/%)	19/22.9	7/41.2	0.12

Abbreviation: CSF, cerebrospinal fluid.

Table 4 CSF leak based on tumor location

Tumor location	No postop leak	Postop leak	*p*
Clivus	5/9 (56%)	4/9 (44%)	0.04
Anterior skull base, including cribriform	23/27 (85.2%)	4/27 (14.8%)	0.49
Suprasellar, including planum and tuberculum	51/59 (86.4%)	8/59 (13.6%	0.27

Abbreviation: CSF, cerebrospinal fluid.

during initial tumor resection, with the drain left in place and then removed postoperatively after takeback to the operating room for CSF leak repair. Two patients required placement of a lumbar drain postoperatively after the initial surgery, which was removed after takeback to the operating room for repair.

Discussion

Endoscopic sinus surgery in the past several decades has advanced tremendously to now include resection of many skull base lesions. These approaches have limited the morbidity of open craniotomy and length of hospital stay. One of the major postoperative complications that prolongs hospital stay is postoperative CSF leak. We sought to elucidate the factors contributing to this complication, specifically in extrasellar tumors, as they have higher postoperative CSF leak rates than pituitary adenomas.

There is little definitive knowledge of the incidence of postoperative CSF leaks and the factors that contribute to its development, particularly for extrasellar tumors. Several studies, including that by Patel et al, reported that the incidence of postoperative CSF leak was approximately 4.7% for pituitary cases, while others have found the rate to be 9%.[1,11] Another study analyzed the percentage of leak in all skull base tumors and noted chordomas to have postoperative CSF leak rates of approximately 3.6%, while the rate for meningiomas was 8.0%.[12] Factors associated with an increased risk included tumor pathologies such as craniopharyngiomas, presence of Cushing's disease, and intraoperative CSF leaks.[11] Tumor location played a role as well, with posterior fossa tumors having the highest rate of CSF leak at 32.6%.[13] Other factors such as elevated patient BMI have been associated with an increased incidence of postoperative leaks.[5,14,15] Conversely, other studies have found no predictive factors associated with postoperative complications in endoscopic skull base surgery.[15–17]

Most tumors with involvement of extrasellar structures are in the intracranial space and are expected to have an intraoperative leak. We hypothesize that the requirement for more dissection, a larger bony exposure, and an increased size of the dural defect result in increased risk for a higher-grade intraoperative leak and consequently postoperative leak. Anterior cranial tumors often require large openings for safe dissection around the anterior cerebral, communicating, and ophthalmic arteries. It is also difficult to reconstruct the defect with a watertight closure while avoiding trauma to the chiasm and optic nerves. An issue that increases the potential for postoperative CSF leak in clival tumors is that intracranial pressure increases with descent down toward the spine. We limited our study to those with extrasellar tumor locations and excluded pituitary adenomas to analyze the significance of these issues.

We included 100 patients with extrasellar tumors, all of whom developed intraoperative leaks. Of these patients, 17% developed postoperative leaks, more than double the published incidence in pituitary cases. The operations for our extrasellar cohort did include insertion of lumbar drain in 15 patients based on the preoperative decision that there would be a high-flow CSF leak during the surgery. Nine of these 15 patients still developed a postoperative leak. The lumbar drains were therefore left in place until postoperatively after the second repair surgery. Our technique for reconstruction of the surgical defect included DuraGen Plus, abdominal fat, nasoseptal flap, tissue glue, and a bolster with balloon catheter. These techniques varied at the discretion of the surgeons and also evolved over the years of the study; in the early years more abdominal fat grafts were used, while more recently DuraGen Plus was used instead of abdominal fat, to avoid the resulting incision and potential morbidity. During the takeback repair surgery, we found the nasoseptal flap to be viable but often with an area where the flap had pulled away from the skull base. The flap was taken down and the dural defect was repaired with an abdominal fat graft or a dural substitute. If a dural substitute had been used previously and failed, an abdominal fat graft was then placed. The flap was then repositioned to completely cover the dural defect. There were no necrotic flaps in this series.

Few studies have delineated the postoperative CSF leak incidence in patients with extrasellar tumors, excluding pituitary adenomas. In our analysis of factors contributing to postoperative leaks, we analyzed age, sex, BMI, as well as cardiovascular and neurological history, including any neurosurgical history. Also included were tumor size, type, location, and grade of intraoperative leak. We found that tumor location, particularly the clivus, led to a statistically significant increase in postoperative leak development. In our series 44% of clival tumors developed postoperative CSF leak, consistent with the findings of Fraser et al. Clival tumors required drilling through the clivus and disrupting the arachnoid that could lead to a high-flow CSF leak. Indeed, all of our clival tumor patients had grade II and III leaks. Although the grade of intraoperative leak did not yield a statistically significant correlation to postoperative leaks, it was interesting to note that there were twice as many grade III intraoperative leaks in those who developed postoperative leaks as those who did not (41.2% vs. 22.9%, $p = 0.12$).

Whether a prophylactic lumbar drain should be inserted requires analysis of the risk:benefit ratio for each case. Insertion of a lumbar drain does carry the risk of headache, nausea, vomiting, meningitis (reported to be 4–10% but can increase with the duration of placement),[18] excessive drainage with tonsillar herniation, pneumocephalus, lumbar nerve root irritation, and increased immobilization that can potentially lead to deep vein thrombosis and pulmonary embolus.[19–21] Furthermore, a patient with a lumbar drain will also be subject to an increased length of hospital stay. Because of the paucity of information on the factors contributing to postoperative CSF leaks, some studies and meta-analyses conclude that one should err on the side of caution and not insert prophylactic lumbar drains, particularly when a robust nasoseptal flap is available.[22–24] A prospective randomized trial by Zwagerman et al showed that in patients with high-flow leaks, insertion of a lumbar drain halved the number of patients with postoperative CSF leak from 21.2 to 8.2%. The authors therefore advocated for prophylactic lumbar drain insertion for patients at risk of high-flow leaks.[25] Based on the literature and our own study, we considered insertion of a prophylactic lumbar drain in those with clival tumors and those at risk for high-grade intraoperative leaks.

Even though prophylactic lumbar drains were placed during the initial operation in 15 patients, 9 of these patients still developed postoperative CSF leaks. In our population of 9 clival tumor patients, 5 received prophylactic lumbar drains but 4 of these still developed postoperative leaks. For patients with clival tumors, a combination of a prophylactic lumbar drain, a robust nasoseptal flap, and a watertight intradural and extradural repair is crucial. We will consider using fat grafts to augment the intradural repair, given our own success and that reported in the literature.[26,27]

Other factors that did not yield a significant correlation with the development of postoperative leak include age, gender, tumor size, and past neurological history, including prior surgery or radiation. A positive cardiovascular history and smoking history did not correlate significantly either. BMI neared significance, with a p-value of 0.08. We resorted to a descriptive study for types of tumors as some tumor types are very rare, and multiple statistical testing may yield false positives.

The limitations of this study include the retrospective analysis and the sample size. We had 100 total patients in our data set and only 17 patients developed a postoperative CSF leak. Increasing the sample size and thus the power of our study is a reasonable next step. Perhaps we will then be able to detect the influences of BMI and grade of intraoperative CSF leak on development of postoperative leak. Another limitation of the study is that the patients came from a single health care system and the operative experiences of five surgeons.

It is therefore reasonable to consider placement of prophylactic lumbar drains in selected patients undergoing endoscopic skull base surgery, considering factors such as tumor location, anticipated dural defect, and anticipated grade of intraoperative CSF leak. Our goal remains to decrease the incidence of postoperative CSF leaks, with their associated morbidity, and elevated health care costs.

Conclusion

Extrasellar tumors have a higher rate of postoperative CSF leak than pituitary adenomas following endoscopic skull base surgery. Risk for postoperative CSF leak is particularly high in clival tumors. Other factors may include the severity of intraoperative CSF leaks, although more power to the statistical study is needed to gain significance.

Conflict of Interest
None declared.

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