The development of endoscopic skull base surgery has revolutionized the treatment of skull base tumors over the past 2 decades. Evolution of this approach has resulted in the ability to resect large skull base tumors with a minimal access approach. The most clinically significant complication of endoscopic skull base surgery, which remains its primary criticism, is the development of a postoperative CSF leak. Despite the importance of this complication, there are limited data identifying risk factors associated with postoperative CSF leak. Both patient-specific factors as well as perioperative interventions likely contribute to risk of postoperative leak.

Spontaneous CSF leaks generally occur in middle-aged, obese women who frequently have radiographic findings consistent with idiopathic intracranial hypertension (IIH), such as Meckel’s cave diverticula and empty sella syndrome with small ventricles. The significant demographic overlap between patients with a spontaneous CSF leak and IIH as well as literature showing high rates of increased intracranial pressure (ICP) in many patients with spontaneous leaks strongly suggests that these elevated ICPs likely contribute to the development of the CSF leak. Theories on the correlation between body mass index (BMI) and ICP include impaired venous drainage due to increased intraabdominal and thoracic pressures and impact of estrogen on CSF production/absorption. Based on these known risk factors for the development of spontaneous CSF leakage, obesity is generally considered to increase a patient’s risk for postoperative leak as well.

**Objective**

The aim in this paper was to determine risk factors for the development of a postoperative CSF leak after an endoscopic endonasal approach (EEA) for resection of skull base tumors.

**Methods**

A retrospective review of patients who underwent EEA for the resection of intradural pathology between January 1997 and June 2012 was performed. Basic demographic data were collected, along with patient body mass index (BMI), tumor pathology, reconstruction technique, lumbar drainage, and outcomes.

**Results**

Of the 615 patients studied, 103 developed a postoperative CSF leak (16.7%). Sex and perioperative lumbar drainage did not affect CSF leakage rates. Posterior fossa tumors had the highest rate of CSF leakage (32.6%), followed by anterior skull base lesions (21.0%) and sellar/suprasellar lesions (9.9%) (p < 0.0001). There was a higher leakage rate for overweight and obese patients (BMI > 25 kg/m²) than for those with a healthy-weight BMI (18.7% vs 11.5%; p = 0.04). Patients in whom a pedicled vascularized flap was used for reconstruction had a lower leakage rate than those in whom a free graft was used (13.5% vs 27.8%; p = 0.0015). In patients with a BMI > 25 kg/m², the use of a pedicled flap reduced the rate of CSF leakage from 29.5% to 15.0% (p = 0.01); in patients of normal weight, this reduction did not reach statistical significance (21.9% [pedicled flap] vs 9.2% [free graft]; p = 0.09).

**Conclusions**

Preoperative BMI > 25 kg/m² and tumor location in the posterior fossa were associated with higher rates of postoperative CSF leak. Use of a pedicled vascularized flap may be associated with reduced risk of a CSF leak, particularly in overweight patients.


**Key Words**

cerebrospinal fluid leak; endoscopic endonasal; skull base surgery; risk factors; pituitary surgery

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Elevated BMI has been associated with increased risk for CSF leakage after resection of intrasellar pathology but has not been studied in the setting of intradural defects.

Few reports have compared postoperative CSF leakage rates for various tumor types. Different tumor types have multiple factors that can influence postoperative repair, including location, size, and the need for subarachnoid dissection. Endoscopic surgery for tumors located in the central skull base has been shown to have higher rates of CSF leakage when compared with anterior skull base tumors after reconstruction of dural defects with a nasoseptal flap. In contrast to this finding, a recent systematic review found no effect of dural defect/tumor site on the rate of postoperative CSF leakage after endoscopic skull base resections.

Development of vascularized flaps for defects of the skull base has led to a dramatic reduction in rates of CSF leakage and has allowed for reconstruction of larger and more complicated defects. The nasoseptal flap has become the work-horse flap for endonasal reconstruction of the skull base and has been repeatedly shown to significantly reduce rates of postoperative CSF leakage. Some authors have reported reduced rates of CSF leakage in the setting of perioperative lumbar drain placement, others have reported no benefit to lumbar drain placement or have demonstrated increased complication rates associated with drain placement.

Although various studies have addressed the role of perioperative lumbar drain placement, debate persists over whether this intervention affects rates of intraoperative or postoperative CSF leakage. While some authors have reported reduced rates of CSF leakage in the setting of perioperative lumbar drain placement, others have reported no benefit to lumbar drain placement or have demonstrated increased complication rates associated with drain placement.

Here, to our knowledge, we present the largest series to date of endonasal intradural skull base tumor resections. We sought to identify whether patient-specific factors (BMI, sex, tumor pathology, and tumor location) and perioperative interventions (lumbar drain and type of reconstructive technique, preoperative hydrocephalus, perioperative lumbar drain, and presence of a postoperative CSF leak) were associated with significantly lower rates of CSF leakage when compared with free tissue grafts.

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Here, to our knowledge, we present the largest series to date of endonasal intradural skull base tumor resections. We sought to identify whether patient-specific factors (BMI, sex, tumor pathology, and tumor location) and perioperative interventions (lumbar drain and type of reconstruction) are independent risk factors for the development of postoperative CSF leak after an endoscopic endonasal approach (EEA) for the resection of intradural skull base tumors.

Methods

The University of Pittsburgh Center for Cranial Base Surgery database was queried to identify cases of endoscopic endonasal skull base surgery for resection of intradural pathology between January 1997 and June 2012. Records of all adult and pediatric patients with a potential for intradural involvement were screened for inclusion. The presence of intradural involvement was confirmed by review of operative notes and was required for inclusion of a case in the study. Sellar pathology was included only if a CSF leak requiring dural repair was noted in the operative report. Primary and planned staged surgeries were included. Lumbar drains were used throughout the majority of this study period for any large defect with a high-flow leak, and the nasoseptal flap was used similarly following its introduction in 2006. Prior to this period, multilayer allograft was used for reconstruction.

Exclusion criteria included the inability to confirm intradural tumor involvement and BMI data not recorded at the preoperative clinic visit or at the time of surgical admission. In addition, patients with a history of a previous CSF leak, skull base trauma, or active infection at the time of surgery were excluded. Patients were excluded from the study if a complete data set could not be collected.

The initial search resulted in 1333 patients with potential intradural pathology. A retrospective review was then performed to confirm intradural involvement based on operative notes. A total of 103 postoperative CSF leaks were identified in the study group, thereby allowing us to include 7 variables in a multivariate analysis based on the generally accepted 10–12 variables per complication. Patient charts were then reviewed for collection of the following data: age, sex, BMI, tumor pathology, tumor location, reconstructive technique, preoperative hydrocephalus, perioperative lumbar drain, and presence of a postoperative CSF leak. The presence of hydrocephalus was determined based on official radiology reports of preoperative imaging. Patients were not evaluated for IIH unless they had repeated leaks, and opening pressure was not measured at the time of lumbar drain placement, as these values were not felt to be accurate due to intraoperative CSF drainage.

The following 7 study variables were selected for inclusion in the multivariate analysis: patient sex, BMI (< 25 kg/m² vs > 25 kg/m²), reconstruction technique (vascularized vs free graft), tumor location (sellar/suprasellar vs anterior skull base vs posterior fossa), tumor pathology, perioperative lumbar drain status, and year of surgery. Rates of CSF leakage were calculated with respect to each of these variables. A BMI of 25 kg/m² was chosen as the cutoff for our analysis in accordance with the World Health Organization definition of overweight and obese.

Rates of postoperative CSF leakage with respect to each variable were analyzed using the chi-square test. Comparisons were made between patients with and without CSF leaks. Group differences were examined by Student t-tests as well as chi-square tests. A second analysis of leakage rates with respect to reconstructive technique was performed with stratification by patient BMI. Rates of postoperative leakage for each reconstructive technique (vascularized flap vs free graft) were calculated based on patient BMI (> 25 kg/m² vs < 25 kg/m²). These rates were similarly analyzed using a chi-square analysis.

A logistic regression model was conducted to assess the multivariate association between CSF leak and clinical characteristics while adjusting for patient age, sex, and BMI. The analyses were performed using SAS (version 9.3, SAS Institute), and a p value < 0.05 was considered statistically significant.

Results

A total of 1333 patients were screened for inclusion in the study. Four hundred fifty-four patients were excluded due to lack of intradural involvement, and 263 patients were excluded for missing data. One patient was excluded because of active sinusitis at the time of surgery. No pa-
tient had a documented history of prior CSF leak or skull base trauma. A total of 615 patients with confirmed intradural pathology were included in the final analysis. Patient demographics are detailed in Table 1.

There were 271 male patients and 344 female patients. The average patient age was 50.3 years (1.6–89.7 years); average BMI was 29.4 kg/m² (range 15–61.6 kg/m²). Based on radiographic criteria, 35 patients had preoperative hydrocephalus. Of this subgroup, 71.4% (25/35 patients) underwent perioperative CSF diversion with placement of a ventriculoperitoneal shunt.

Of the 615 patients included in the study, 103 developed a postoperative CSF leak (16.75%). Based on Student t-test analysis, there was no difference in sex breakdown or patient age between those without and with postoperative leaks. The average length of stay was longer for patients who developed a CSF leak (19.8 days vs 5.7 days; p < 0.0001). Patients who underwent staged procedures had a higher rate of CSF leakage compared with single-stage surgeries (37.5% [24/64] vs 14.3% [78/551]; p < 0.0001). Seventy-one percent of all patients had a BMI > 25 when compared with those of healthy-weight BMI (24.7% [53/215] vs 11.2% [10/89]; p = 0.02). Seventy-one percent of all postoperative leaks occurred in overweight or obese patients.

Female patients with a postoperative CSF leak had a higher average BMI than those who did not develop a CSF leak (31.54 kg/m² vs 29.38 kg/m²; p = 0.02); in males there was no difference in BMI between these 2 groups (29.3 kg/m² vs 29.2 kg/m²; p = 0.9). Overall, there was no difference in the leakage rate between male and female patients (18.5% [50/271] vs 15.4% [53/344]; p = 0.31).

Pedicled vascularized flaps were used in 76% (468/615) of cases. Vascularized tissue reconstruction was performed at a higher rate for posterior fossa tumors (92%, 48/52) than for anterior skull base tumors (80%, 243/304) and sellar tumors (62%, 161/259).

Patients in whom a pedicled vascularized flap was used for skull base reconstruction had a significantly lower leakage rate than those in whom a free graft was used (13.2% [62/468] vs 27.89% [41/147]; p = 0.0015). In patients with a BMI > 25, use of a pedicled flap significantly reduced the rate of CSF leakage from 29.57% (34/115) to 15.0% (49/327) (p = 0.001); in patients of normal weight, this reduction did not reach statistical significance (21.9% [7/32; pedicled flap] vs 9.2% [13/141; free graft]; p = 0.09) (Fig. 1).

Rates of CSF leakage varied based on tumor pathology, with the highest leakage rates occurring in patients with chondroid tumors (30.77%, 16/52) and meningiomas (24.12%, 48/199) and the lowest rate in those with esthesioneuroblastoma (ENB) (5.88%, 2/34) (Fig. 2). These relationships were not statistically significant, however, and tumor pathology was not an independent risk factor for a CSF leak. In patients treated for ENB, the nasoseptal flap was the predominant reconstructive flap used (27/34); a pericranial flap was used in 7 patients.

Tumor location in the posterior fossa was associated with the highest rate of CSF leakage (17/52, 32.7%), followed by those located in the anterior skull base (63/304, 20.7%), while sellar and suprasellar lesions were associated with the lowest postoperative CSF leak rate 26/259 (10.0%) (p < 0.001) (Fig. 3). The CSF leakage rate for each anatomical site was then compared based on BMI. In the anterior fossa, there was a higher leakage rate in patients with a BMI > 25 when compared with those of healthy-weight BMI (24.7% [53/215] vs 11.2% [10/89]; p = 0.02). This was similarly identified in sellar/suprasellar lesions (11% [21/190] vs 5.8% [4/69]; p < 0.05), while it was not a significant risk factor for lesions isolated to the posterior fossa (31.6% [12/38] vs 35.7% [5/14]; p = 0.57).

A total of 147 patients had a lumbar drain placed at the time of surgery (23.9%). Of these patients, 21.7% developed a postoperative CSF leak compared with 15.2% of patients without perioperative lumbar drain placement. This difference approached statistical significance (p = 0.0812).

Prior to 2006, the rate of postoperative CSF leakage was 36.5%, which decreased to 15.7% after 2006 (p < 0.0001). Multivariate analysis found this to be significant independent of vascularized reconstruction (p < 0.0001). In 2011–2012, the postoperative CSF leakage rate was 9.6%.

TABLE 1. Patient demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>No CSF Leak (n = 512)</th>
<th>CSF Leak (n = 103)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, no.</td>
<td></td>
<td></td>
<td>0.371</td>
</tr>
<tr>
<td>Male</td>
<td>221</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>291</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Mean age in yrs</td>
<td>50.4</td>
<td>50.0</td>
<td>0.899</td>
</tr>
<tr>
<td>Mean BMI in kg/m²</td>
<td>29.2</td>
<td>30.4</td>
<td>0.0803</td>
</tr>
<tr>
<td>Mean LOS in days</td>
<td>5.7</td>
<td>19.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Staged procedure, no. (%)</td>
<td>40 (7.8)</td>
<td>24 (23.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumbar drain, no. (%)</td>
<td>115 (22.5)</td>
<td>32 (30.8)</td>
<td>0.081</td>
</tr>
<tr>
<td>Preop hydrocephalus, no. (%)</td>
<td>23 (4.5)</td>
<td>12 (11.5)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

LOS = length of stay.
A logistic regression analysis confirmed that BMI, year of surgery, and presence of preoperative hydrocephalus were significantly related to the development of a postoperative CSF leak (p < 0.05). Patients with a BMI > 25 were 1.75 times more likely to have a CSF leak when compared with those with a BMI < 25. Patients who underwent surgery prior to 2006 were 2.64 times more likely to have a CSF leak than patients treated after 2006. Patients with preoperative hydrocephalus were 2.8 times more likely to have a CSF leak (Table 2).

Discussion

Based on our data, we conclude that the incidence of postoperative CSF leak after an EEA is significantly increased in overweight and obese patients. This finding is consistent with previously published literature and the current understanding of CSF physiology. From a well-documented association of increased BMI and IIH, it logically follows that increased ICP in overweight and obese patients (even in the absence of documented IIH) would place additional strain on surgical reconstructions of the skull base, leading to the potential for an increased risk of postoperative CSF leaks. While BMI has previously been documented to be a risk factor for postoperative CSF leakage in endoscopic pituitary surgery, this study is the first to verify its importance in high-flow intraoperative CSF leaks.

Consistent with the current literature, in our study group, use of a vascularized flap for reconstruction of the skull base was associated with a significant reduction in the rate of postoperative CSF leakage. While BMI has previously been documented to be a risk factor for postoperative CSF leakage in endoscopic pituitary surgery, this study is the first to verify its importance in high-flow intraoperative CSF leaks.

Comparing tumor location in this population, tumors located in the posterior fossa were associated with the highest rate of CSF leakage. Factors contributing to this difference may include technically more difficult resection and reconstruction combined with higher posterior fossa CSF pressure and direct communication with arachnoid cisterns. This is in contrast to resection of tumors of the anterior fossa because of lower CSF pressure and descent of the frontal lobe into the surgical defect. In addition, there is evidence of increased compartmental CSF pressure, as endoscopic transcribriform resections have resulted in pontine encephaloceles. This is in contrast to a lack of descent after endoscopic transcribriform resections where minimal descent of the nasoseptal flap is frequently noted.

While BMI was an independent risk factor for postoperative CSF leakage across all tumor locations by a multivariate logistic regression model, it was found to be statistically significant in the subgroup analysis for anterior fossa and sellar/suprasellar lesions only. This finding should be tempered by the smaller sample size and relatively high CSF leakage rate for posterior fossa tumors, as the current study is likely underpowered to detect this difference.

Placement of a postoperative lumbar drain is often used for the purpose of combating transient increases in ICP or creating lower-than-normal pressure during initial healing. In this series, all drains were used to prevent postoperative leaks, rather than intraoperative leaks, and were placed at the end of surgery in patients with high-flow leaks. Lumbar drains can be used to prevent intraoperative leak, but this generally does not apply to high-flow leaks, which are a result of a significant dural defect from the tumor resection or for surgical access to the tumor. In our study population, placement of a drain was associated with a trend toward higher rates of postoperative CSF leakage; however, this did not reach statistical significance (p = 0.08). This association is likely a reflection of selection bias related to placement of a lumbar drain in patients who intraoperatively are deemed to be at high risk for the development of a postoperative CSF leak. Our practice for the majority of this study was to use lumbar drains in high-risk patients (large defects and high-flow leaks). This
current practice is largely confirmed by results of a randomized, controlled trial that was just completed at our institution showing that lumbar drains significantly decrease leak rates (unpublished data).

Analysis of the postoperative CSF leakage rate over time shows reduced rates in more recent years. Factors contributing to a change in the incidence of CSF leakage include the development of the nasoseptal flap and an increase in surgeon experience. The latter is a reflection of the learning curve associated with the development and application of these relatively new approaches and is independent of vascularized reconstruction in multivariate analysis. This highlights the importance of clinical volume and the concentration of these cases at tertiary centers to reduce complication rates.

In comparison with findings in a literature review by Soudry et al., the rates of postoperative CSF leakage in our study were higher than expected.17 We believe that several factors contributed to the increased rate of CSF leakage. First, sellar lesions without an intraoperative leak were excluded from the analysis, resulting in the inclusion of only high-risk sellar lesions; much of the literature reporting postoperative leakage rates does so inclusive of lesions without intraoperative intradural exposure. Moreover, overweight and obese patients were overrepresented within the study group (71% with a BMI > 25) and our patient population in general. Based on our analysis, these patients are at a higher risk of postoperative leak, which likely drove up our overall leakage rate. Lastly, many of the cases included in the study were of a high level of complexity with a significant number of staged procedures and recurrent tumors requiring repeat surgery. The large proportion of these complex cases likely affected the overall rate of CSF leakage.

In this study, BMI, tumor location, preoperative hydrocephalus, and vascularized reconstruction all influenced postoperative CSF leakage. These variables remained significant in our analysis despite likely escalated care for these patients, and this further emphasizes their importance in the pathogenesis of postoperative CSF leaks. While many of these risk factors are well published in other series, our experience most importantly documents improvement in patient outcomes with increasing surgeon volume. We saw a significant reduction of postoperative CSF leaks in intradural cases (36.5% to 15.7%) from before to after 2006. This was independent of increasing use of the nasoseptal flap in our multivariate analysis.

Limitations of our study include its retrospective nature and the inherent biases that accompany such studies. Additionally, a large number of our initial 1333 patients were excluded due to lack of a complete data set; most commonly, BMI data were not recorded at the time of surgery. This significantly reduced our total study population, potentially affecting the final data set and outcome measures. In addition, factors such as flow rate of the CSF leak, surgical defect size, and history of previous radiation treatment were not accounted for in our analysis. Finally, reconstruction techniques and complexity of cases as well as defects changed over the course of this study, introducing a variable that cannot be accurately measured and could impact the overall results.

Conclusions

Based on our findings, we believe that a nasoseptal flap should be used in all patients with BMI > 25 kg/m² in whom an intraoperative CSF leak is encountered. The benefit of the nasoseptal flap for reducing postoperative CSF leak is clear, and our data support that this benefit is even greater in the overweight and obese population. Moreover, it is reasonable to consider perioperative management of elevated ICP in the obese population, although further investigation is required to determine the role of lumbar drainage in this scenario. Consideration should also be given to the use of alternative approaches in patients who have multiple risk factors for developing a postoperative CSF leak after endoscopic tumor resection.

References


TABLE 2. Multivariate logistic regression for predictors of postoperative CSF leak

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00 (0.99–1.01)</td>
<td>0.839</td>
</tr>
<tr>
<td>Sex: female</td>
<td>0.93 (0.59–1.45)</td>
<td>0.739</td>
</tr>
<tr>
<td>BMI: &gt;25 kg/m²</td>
<td>1.75 (1.01–3.03)</td>
<td>0.047</td>
</tr>
<tr>
<td>Lumbar drain</td>
<td>1.61 (0.99–2.62)</td>
<td>0.056</td>
</tr>
<tr>
<td>Vascularized reconstruction</td>
<td>0.70 (0.36–1.37)</td>
<td>0.296</td>
</tr>
<tr>
<td>Surgery prior to 2006</td>
<td>2.64 (1.25–5.60)</td>
<td>0.011</td>
</tr>
<tr>
<td>Preop hydrocephalus</td>
<td>2.8 (1.29–6.07)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Wang, Fraser, Gardner. Acquisition of data: Fraser, Koutourousiou, Kubik. Analysis and interpretation of data: Wang, Fraser, Koutourousiou. Critically revising the article: Wang, Gardner, Koutourousiou, Kubik, Fernandez-Miranda, Snyderman.

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