Perioperative Outcomes in Patients Undergoing the Translabellar/Subcranial Approach to the Anterior Skull Base

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ABSTRACT

We analyzed the effect of predefined patient demographic, disease, and perioperative variables on the rate of complications in the perioperative period following subcranial surgery for anterior skull base lesion. A secondary goal of this study was to provide a benchmark rate of perioperative mortality and morbidity through comprehensive analysis of complications. Retrospective review of a consecutive series of patients ($n = 164$) who underwent the translabellar/subcranial approach to lesions of the anterior skull base between December 1995 and November 2009 in a tertiary referral center. Main outcome measures were perioperative morbidity and mortality. No perioperative mortalities were observed over the period of consecutive review. The overall complication rate was 28.7%, with 30 (18%) patients experiencing major complication. Multivariate analysis revealed that the following variables were independent predictors of perioperative complication of any type: positive margins on final pathology, perioperative lumbar drain placement, and dural invasion. The subcranial approach provides excellent access to the anterior skull base with zero mortality and acceptable morbidity in comparison with other contemporary open surgical approaches. It should be considered a procedure with distinct advantages in terms of perioperative morbidity and mortality when selecting a therapeutic approach for patients with anterior skull base lesions.

KEYWORDS: Subcranial, anterior skull base, skull base neoplasms/surgery, postoperative complications

Open surgical approaches to the anterior cranial base have undergone progressive refinement over the past 50 years. The original description of the craniofacial resection by Smith et al in 1954¹ was followed by the popularization and broader application of the technique by Ketcham et al.² Although effective for tumor expo-

sure, the craniofacial approach is associated with fairly high morbidity; mortality rates are commonly in the range of 3 to 5% in large series.^{3–10} The need for frontal lobe retraction to access the anterior cranial base from a superiorly placed frontal craniotomy contributes to the morbidity of these procedures.^{10,11} Despite the technical

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Received: August 31, 2010. Accepted after revision: February 7, 2011. Published online: May 6, 2011.

DOI: <http://dx.doi.org/10.1055/s-0031-1277261>.

ISSN 1531-5010.

challenges and inherent difficulties of tumor extirpation in this region, many studies have reported excellent results using this technique.^{3–10} Furthermore, improved preoperative imaging, surgical technique, neuroanesthesia, targeted antibiotic regimens, and multidisciplinary cooperation have all contributed to a steady improvement in clinical outcomes over the past 50 years.^{6,8}

In an effort to evolve the surgical approach to the region, numerous authors have advocated various transorbital craniotomies to facilitate the exposure achieved with the traditional bifrontal craniotomy.¹² Raveh et al described a significant technical advancement via the transglabellar/subcranial approach, which involves the disarticulation of the nasal root in continuity with the frontal bar, resulting in improved access to the anterior cranial base.^{13–15} The original application of the procedure provided access for posttraumatic reconstruction; this was followed shortly thereafter by applications in craniofacial anomalies and skull base tumors. The advantage of the subcranial approach is the provision of broad, in-line access to the floor of the anterior cranial fossa, affording a dissection plane that is parallel to the dura and subdural vasculature, thereby reducing or eliminating frontal lobe retraction for tumor extirpation.¹⁴ A facial incision is not routinely necessary unless dictated by tumor extent into superficial soft tissue. For all of the reasons listed, the subcranial approach has been the surgical technique of choice at our institution for 17 years. An initial review of patient outcomes suggested a low rate of perioperative morbidity and zero mortality with this technique.^{11,12}

The rarity of skull base tumors poses a challenge in terms of formulating meaningful outcome data from small samples. A significant step forward in this respect was made through a multi-institution survey that pooled skull base surgical outcomes from 17 institutions that employed anterior craniofacial resection as the approach of choice.¹⁶ The international study has not only established benchmarks for complication rates but also afforded the opportunity to standardize the reporting of perioperative complications, thus improving the ability to contrast data from various institutions where surgical techniques may differ.⁵ The purpose of the current study, therefore, is to provide a detailed review of the frequency and types of perioperative complications associated with the transglabellar/subcranial approach and perform an analysis of the preoperative and perioperative data to identify factors that are independent predictors of complication. To our knowledge, this is one of the largest series in the literature to date of anterior skull base neoplasms addressed via the subcranial approach.

PATIENTS AND METHODS

This retrospective study was based on a review of the hospital and outpatient clinical records of a consecutive

series of patients who underwent surgery of the anterior cranial base between December 1995 and November 2009. All patients underwent surgery of the anterior cranial base via the transglabellar/subcranial approach; adjunctive surgical approaches are listed in Fig. 1. Cases were excluded from this analysis if the subcranial approach was used as an ancillary approach for a lateral lesion or for postmaxillofacial trauma reconstruction. For all lesions, the presence of orbit, dural, or brain invasion was determined based on first author (J.-P.P.) review of imaging, operative notes, and pathology reports. Patient data recorded for analysis included age, comorbidity, gender, prior ablative surgery of the paranasal sinuses or skull base, prior radiation, and prior chemotherapy. Comorbidity was defined by the Diagnosis Related Group codes for fiscal year 2010. Perioperative data included estimated blood loss, procedure duration, total hospital stay, perioperative blood transfusion volume, perioperative tracheostomy, free flap reconstruction, and perioperative lumbar drain.

The surgical technique has been described in detail previously and is founded upon seamless cooperation between the neurosurgical and otolaryngology teams.¹¹ Perioperative protocols often vary across institutions, and therefore we include some points regarding ours. We routinely insert nasopharyngeal airway stents upon completion of soft tissue closure, as they may decrease rates of tension pneumocephalus.¹⁷ Our perioperative antibiotic

Figure 1 Pathology for all lesions ($n = 164$): 104 malignancies, 60 benign lesions. "Other carcinoma" includes mucoepidermoid carcinoma, basal cell carcinoma of the nasolacrimal duct, Papillary Schneiderian carcinoma, myoepithelial carcinoma, poorly differentiated carcinoma of lacrimal sac, and one metastatic Hurthle cell tumor. "Other benign" lesions include encephalocele, meningocele, arteriovenous malformation, ameloblastoma, cholesterol granuloma, schwannoma, null cell pituitary adenoma, chondromyxoid fibroma, and ossifying fibroma. SCC, squamous cell carcinoma; SNUC, sinonasal undifferentiated carcinoma.

prophylaxis regimen consists of cefuroxime, which is discontinued at discharge date or 1 week after surgery. Routine perioperative lumbar drain placement (i.e., prophylactic lumbar drain) was largely based on neurosurgeon preference; cases with perioperative lumbar drain were recorded and analyzed for effect on complication rate. Antiseizure prophylaxis with levetiracetam and low-dose dexamethasone is administered if the dura is involved or manipulated. Reconstruction is performed via pericranial flaps pedicled on the supraorbital arteries. In cases where water- and airtight dural closure is anticipated to be difficult due to prior radiation treatment and/

or size of defect, free tissue transfer is employed. Criteria for free tissue transfer are individualized but are based on a joint preoperative assessment by the multidisciplinary team. Orbital rim reconstruction, if necessary, is performed via split calvarial bone graft or free tissue transfer, again depending on defect size.

Postoperative complications were classified as perioperative if they occurred within 30 days of the surgical procedure. Complications were divided into the following categories, consistent with recent studies in our literature^{5,8}: wound, intracranial, systemic, ocular, and mortality. Additionally, complications were divided

Table 1 Preoperative and Perioperative Patient Data

Patient and Tumor Variables	n (%)	Perioperative Variables	n (%)
Age		Days in hospital	
Mean $\pm$ SD	48 $\pm$ 18	Mean $\pm$ SD	7.0 $\pm$ 5.4
Median	52	Median	5.0
Range	7–84	Range	2–40
Gender		Duration of procedure (min)	
Female	64 (39)	Mean $\pm$ SD	590 $\pm$ 196
Male	100 (61)	Median	590
		Range	118–1563
Comorbidity		Estimated blood loss (mL)	
None	79 (48)	Mean $\pm$ SD	1118 $\pm$ 1045
Yes	85 (52)	Median	825
		Range	50–8000
Previous surgery		PRBC units transfused	
No	107 (65)	Mean $\pm$ SD	1.4 $\pm$ 2.3
Yes	57 (35)	Median	0
		Range	0–11
Previous radiotherapy		Surgical approach	
No	142 (87)	SC alone	106 (65)
Yes	22 (13)	SC + ancillary approach	58 (35)
Previous chemotherapy		Tracheostomy	
No	155 (95)	No	152 (93)
Yes	9 (5)	Yes	12 (7)
Intraorbital extension		Free flap reconstruction	
None	95 (58)	No	130 (79)
Yes	69 (42)	Yes	34 (21)
		N/A	
Dural involvement		Perioperative lumbar drain	
None	114 (70)	No	116 (71)
Yes	50 (30)	Yes	48 (29)
Brain involvement			
None	149 (91)		
Yes	15 (9)		
Malignancy			
Benign	51 (31)		
Malignant	103 (63)		
N/A	10 (6)		

N/A, not applicable; PRBC, packed red blood cells; SC, subcranial; SD, standard deviation.

into major and minor subgroups. Major complications were defined as those associated with mortality, reoperation, procedural intervention (i.e., lumbar drain), and/or permanent morbidity. Minor complications were those that were not associated with permanent treatment or morbidity. Additional postoperative data included surgical margins based on final pathology and delayed lumbar drain placement.

Patient, perioperative, and postoperative variables were analyzed using univariate logistic regression, with a Fisher exact test for binary variables. All preoperative variables identified as possible predictors of perioperative complication by univariate analysis were then submitted to multiple logistic regression to identify independent predictors. All statistics were analyzed on SPSS for Windows version 11.01 (SPSS Inc., Chicago, IL). Statistical analysis was performed by study team members (J.P.P. and S.A.H.), with additional consultation through the University of Michigan Center for Statistical Consultation and Research. The study protocol was approved by our university's institutional review board.

RESULTS

Table 1 lists the pre- and perioperative data collected. Of note, there were relatively few patients, 22 (13%), who had received prior radiotherapy. The proportion of tumors that invaded into adjacent anatomic subsites was high, with 69 (42%) and 50 (30%) exhibiting orbit and dural invasion, respectively. The average hospital stay following surgery of the anterior cranial base was 7.0 days. Perioperative lumbar drain placement was performed in 48 (29%) of the patients; decision to place a prophylactic drain was made by the attending neurosurgeon. Figure 1 summarizes the final pathology of all lesions. Of the total study population ($n = 164$ patients), there were 104 malignancies and 60 benign lesions. Negative margins on final pathology were achieved in 81 (78%) of the patients treated for malignancy

Table 2 Ancillary Approaches or Techniques Used in Combination with the Translabellar/Subcranial Approach Listed in Order of Frequency

Additional Surgical Approach	n (% of Total Cases)
Free tissue transfer	34 (20.7%)
Maxillectomy	31 (18.9%)
Orbital exenteration	19 (11.6%)
Weber-Ferguson, lateral rhinotomy	4 (2.4%)
Midface degloving	4 (2.4%)
Lateral approach: frontotemporal orbitozygomatic craniotomy or transzygomatic	4 (2.4%)

Note that all patients had reconstruction via pericranial flap. Selected patients were also reconstructed with free tissue transfer based on size of defect or prior radiotherapy.

($n = 104$). Table 2 illustrates the frequency and type of ancillary procedures used in conjunction with the subcranial approach.

There were no perioperative mortalities. The overall complication rate was 28.7%, with 47 patients suffering a complication of any type, and 11 patients having more than one perioperative complication. The complications are listed by category and subcategory (Table 3). Cerebrospinal fluid (CSF) leak occurred in 19 patients (11.6%) and was the most frequently encountered major complication. CSF leak was treated with delayed lumbar drain placement in a majority of cases; one patient required ventriculoperitoneal

Table 3 Total Complication Rate for Study Population, as Well as Complication Broken Down by Subtype by Major Versus Minor Criteria

Complications*,†	n (% of patients)
Mortality	0
Major complications	30 (18)
Minor complications	23 (14)
Any complication	46 (28)
Complication subtype‡§	
Intracranial	34
CSF leak	19 (11.6)
Meningitis	4 (2.4)
Encephalitis	0
Tension pneumocephalus	5 (3.0)
Cerebral edema	4 (2.4)
Cerebrovascular accident	0
Intracranial hematoma	2 (2.4)
Wound	13
Infection	6 (3.7)
Dehiscence	4 (2.4)
Hematoma	3 (1.8)
Fistula	0
Systemic	17
Myocardial infarction	0
Arrhythmia	5 (3.0)
Systemic infection	1 (0.6)
Pulmonary	6 (3.7)
Urinary tract	1 (0.6)
Metabolic	2 (2.4)
DVT	2 (2.4)
Ocular	6
Permanent diplopia	5 (3.0)
Decreased visual acuity	1 (0.6)
Orbital cellulitis	0
Total complications	70

*Major complications were predefined as associated with death, return to operating room, or permanent morbidity (for example, permanent diplopia). Minor criteria were defined as conditions resolving without permanent treatment or return to operating room (for example, wound infection).

†Note that 11 patients experienced more than one complication during the perioperative period.

‡Complication broken down by subcategory.

§The most common complication subtype was intracranial, with the most common specific complication being postoperative CSF leak. CSF, cerebrospinal fluid; DVT, deep venous thrombosis.

shunt due to concomitant cerebral edema and a desire to closely monitor intracerebral pressure.

The patient and perioperative data that were used for univariate analysis are listed in Table 4. As shown, univariate analysis reveals the following variables to be associated with perioperative complication: age, comorbidity, dural involvement, placement of a perioperative lumbar drain, and final surgical margins. The variables demonstrated by univariate analysis to have a significant association with perioperative complication were then submitted for multivariate analysis to control for the effect of the covariates. In addition, variables with near-significant effect on total complication were also included for multivariate analysis. The results of the multivariate analyses are highlighted in Table 5, which shows that dural involvement, perioperative lumbar drain, and surgical margins were found to be independent predictors of perioperative complication on final analysis.

DISCUSSION

A detailed analysis of the largest series to date of patients treated with the transglabellar/subcranial approach for anterior skull base lesions yields an encouraging 0% mortality rate and an overall complication rate of 28.7% in the perioperative period. The variables shown to be independent predictors of perioperative complication were dural invasion, surgical margins, and routine use of perioperative lumbar drain. Despite inclusion of a significant number of tumors demonstrating aggressive histology, high rates of invasion of nearby anatomic subsites, and a significant number of patient comorbidities, we were able to achieve negative margins in 78% patients and no mortalities. This data compare favorably with recent landmark articles on perioperative complications following anterior skull base surgery with the standard anterior craniofacial resection as the surgical approach of choice.³⁻¹⁰

An international collaborative study with 17 participating institutions performed an analysis of complications of craniofacial resection employed for malignancies of the skull base.⁵ With a database containing over 1300 patients, this study serves as a benchmark for anterior skull base surgery outcomes. Multivariate analysis of the data revealed that the presence of medical comorbidity was the only independent predictor of perioperative mortality. Independent predictors of postoperative complications were medical comorbidity, prior radiotherapy, and extent of intracranial involvement. In comparison, similar analysis of our data series also showed extent of intracranial involvement to be an important predictor of complication. By contrast, prior radiotherapy did not predispose to higher risk of complication, which may argue for the utility of the subcranial approach in the setting of prior radio- or chemotherapy.

One notable distinction is that the present study, as opposed to the aforementioned multi-institutional study, classified complications into major versus minor subcategories, in addition to listing individual complications by category. Our classification of major versus minor complication draws upon analogous outcomes research in reconstructive surgery in our discipline.¹⁸ The rate of major perioperative complication in this analysis was 18.0%. The benchmark study did not break down complications in major versus minor subtype. We believe that this distinction is important, however, in terms of interpreting complication results and in addition how we counsel patients prior to surgery.

The multi-institutional study calculated the mortality rate among patients undergoing anterior craniofacial resection for malignant tumors of the anterior skull base as 4.7%.⁵ The perioperative complication rate was 36.3%. For comparison purposes, the calculated complication rate among our malignant tumor group ($n = 104$) was 31.7%. Gil et al recently published a large series of patients treated with traditional craniofacial resection for malignant disease over a period of ~30 years. The overall complication rate was 42.7%, and the perioperative mortality rate was 3.9%.⁸ They separated their results into historical versus recent cohorts; over the last decade, the complication rate has significantly decreased from 52 to 33%.⁸ The authors have attributed this improvement to a more broad-spectrum antibiotic regimen that was developed from wound culture data from the historic cohort.¹⁹ Specifically, the authors employed a standardized, broad-spectrum regimen that consisted of cefazidime, metronidazole, and vancomycin.

It is therefore notable that the present study demonstrated at least comparable perioperative outcomes and employed a perioperative antibiotic regimen of cefuroxime only. In any approach to the anterior cranial base, the presumed nidus of infection was the contaminated sinonasal cavity that was exposed to the neuraxis during exposure and tumor resection.²⁰ It is possible that the subcranial approach offered more direct access to the tumor, thus minimizing the time of exposure intraoperatively and facilitating closure.

It is also worth noting that the most common individual major complication in this series was CSF leak, occurring in 19 patients (11.6%). This is a relatively consistent finding across other large series that employ anterior craniofacial resection as the surgical approach.^{3,4,7,9,10} However, studies focusing on the subcranial approach have not noted similar rates of postoperative CSF leak.^{13,21} Some authors argue that CSF leak is a key predisposing factor to the development of postoperative meningitis.⁹ Despite an appreciable rate of postoperative CSF leak in our study (11.6%), the incidence of meningitis was very low (1.3%). This may provide indirect validation of the standard perioperative antibiotic regimen utilized (cefuroxime) or perhaps provide evidence against

Table 4 Univariate Analysis of to Identify Variables Associated with Perioperative Complications after Anterior Skull Base Surgery

Patient and Tumor Characteristics	Associated Complication Rate (%)	Univariate Analysis <i>p</i> Value	Odds Ratio (95% CI)*
Patient and tumor characteristics			
Age			
< 60	27/115 (24)	0.046*	2.1 (1.0–4.2)
> 60	19/49 (39)		
Gender			
Female	18/64 (28)	NS*	
Male	28/100 (28)		
Comorbidity			
No	16/79 (20)	0.025*	2.3 (1.1–4.6)
Yes	30/85 (35)		
Previous surgery			
No	28/107 (26)	NS*	
Yes	18/57 (32)		
Previous radiotherapy [†]		NS*	
No	27/87 (31)		
Yes	6/17 (35)		
Previous chemotherapy [‡]		NS*	
No	32/95 (34)		
Yes	1/9 (11)		
Intraorbital extension			
No	26/95 (27)	NS*	
Yes	20/69 (29)		
Dural involvement			
No	24/114 (21)	0.005*	2.8 (1.4–5.7)
Yes	22/50 (44)		
Brain involvement			
No	40/149 (27)	NS*	
Yes	6/15 (40)		
Malignancy [‡]			
Benign	13/51 (25)	NS*	
Malignant	32/103 (31)		
Perioperative variables			
Duration of procedure	–	NS [§]	
Estimated blood loss	–	NS [§]	
PRBC units transferred	–	NS [§]	
Surgical approach		NS*	
SC	28/106 (26)		
SC + ancillary approach	18/58 (31)		
Tracheostomy			
No	41/152 (27)	NS*	
Yes	5/12 (42)		
Free flap reconstruction		NS*	
No	32/130 (25)		
Yes	14/24 (41)		
Perioperative lumbar drain		0.008*	2.7 (1.3–5.5)
No	26/116 (22)		
Yes	20/48 (42)		
Surgical margins			
Negative	30/132 (23)	0.008*	3.1 (1.4–6.9)
Positive	15/31 (48)		

*Fisher exact test.

[†]Malignant tumors only.[‡]Cancer patients only.[§]Not significant.

CI, confidence interval; PRBC, packed red blood cells; SC, subcranial; NS, not significant.

Table 5 Multivariate Analysis of Factors Associated with Perioperative Complications*

Patient and Tumor Characteristics	Perioperative Complications (p Value)
Age	NS
Comorbidity	NS
Dural involvement	0.018
Perioperative lumbar drain	0.002
Surgical margins	0.036

*Analysis performed on malignant tumors only.

a direct causal relationship between CSF leak and meningitis in these patients.

Our algorithm for management of postoperative CSF rhinorrhea begins with a head computed tomography (CT) to assess for significant pneumocephalus. In addition to conservative measures that include stool softeners, head of bed elevation, and avoidance of Valsalva, a lumbar drain is inserted under sterile conditions at bedside. We employ a closed continuous lumbar drainage system that is connected to a mechanical pump that maintains drainage at a constant rate. We begin drainage at a conservative rate, usually 6 mL per hour, and titrate this based on clinical response. Intermittent head CT scans are obtained to assess for increasing pneumocephalus. If the patient fails to respond over the next 48 to 72 hours, we consider surgical repair. We have increasingly moved toward endoscopic repair of these persistent CSF leaks as our primary means of surgical management.

A post hoc review of the 19 patients who had delayed CSF leak was performed to better characterize our management strategy of this complication. Of the 19 patients with evidence of delayed CSF fistula following subcranial surgery, six had postoperative CSF leak despite having a lumbar drain inserted prior to tumor resection. Twelve patients did not have lumbar drains inserted at the time of surgery, and therefore underwent delayed lumbar drain placement. As noted above, one patient in this series with postoperative CSF leak underwent ventriculostomy placement instead of lumbar drain. This patient had evidence of cerebral edema on postoperative CT scan, and therefore the neurosurgery team decided to insert a ventriculostomy to closely monitor the intracerebral pressure. In total, five patients in this series eventually required revision surgery to definitively close the CSF fistula. Surgical techniques included free tissue transfer, temporoparietal fascia flap, and abdominal fat graft placement with bovine xenograph reinforcement.

An interesting finding of the multivariate analysis was that prophylactic placement of a lumbar drain at the time of surgery was an independent predictor of complication. The decision to place a lumbar drain was based on neurosurgeon preference, and therefore this analysis

is prone to selection bias. Lumbar drain placement has been associated with a 12.5% rate of major complication following skull base surgery.²² Kryzanski et al maintain that judicious use of perioperative CSF drains in skull base surgery is warranted in light of these data.²³ In contrast, routine CSF drain has been shown to decrease rates of postoperative CSF leak after posterior fossa surgery.²⁴ The neurosurgical members of our multidisciplinary team currently feel that the benefits of routine CSF drainage are outweighed by possible risks, and these data seem to confirm their suspicion. It is possible that the more inferiorly placed craniotomy associated with the subcranial approach requires less retraction of parenchyma and thereby reduces the need for routine CSF drainage at the time of surgery.¹⁰

We routinely place nasopharyngeal airways to divert the flow of air from the site of surgical repair. In accordance with current principles of airway management in skull base surgery, the routine placement of a tracheostomy for airway diversion is felt to be unnecessary.^{25,26} Overall, we observed five episodes of tension pneumocephalus in this review. Nasopharyngeal stents are associated with lower rates of tension pneumocephalus¹⁷ and may underlie the relatively low rate of this complication over the period reviewed (3.0%).

Limitations of this study include its retrospective nature and the inherent difficulty in making even indirect comparisons to other studies that employed standard anterior craniofacial resection. Given the rare and heterogeneous nature of anterior skull base lesions, head-to-head comparisons are exceedingly rare. As with any single institution study of this type, key determinants of outcome and variability include tumor histology, extent of disease, as well as operative techniques and perioperative protocols. Despite these limitations, it is worthwhile to analyze large series of patients that feature a unique surgical approach to achieve a full grasp of the efficacy of these treatments.

As a whole, data presented in this study affirm the transglabellar/subcranial approach as having a favorable risk profile in the treatment of a wide variety of anterior skull base lesions. This issue is of utmost relevance given the recent surge in interest in endoscopic approaches to the anterior cranial base.²⁷ Indeed, the advent of advanced endoscopic approaches has brought the issue of perioperative morbidity and mortality into sharp focus. There are an increasing number of studies that compare endoscopic resection against open resection through anterior craniofacial resection.^{28,29} As such, it is critical to obtain an accurate gauge of the perioperative complication rates associated with all varieties of open procedures, with the understanding that not all "open" procedures necessarily pose the same perioperative risk to the patient.¹⁴ In particular, procedures that spare facial incisions and brain retraction yet offer excellent surgical access, such as the subcranial approach, will

continue to have a high level of utility and can be used as an appropriate reference for open procedures when scrutinizing operative morbidity.

ACKNOWLEDGMENTS

The authors would like to thank Janet Urban, P.A., for her efforts in initial database design and maintenance. The authors have no financial interests to disclose.

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