Preoperative, technical, and postoperative considerations for skull base reconstruction: a practical review of critical concepts*

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Abstract

Despite widespread adoption and advances in endoscopic skull base surgery, with expanding indications and the ability to effectively treat larger and more complex pathologies, skull base reconstruction following tumor resection and prevention of cerebrospinal fluid leak remains a challenge for even the most seasoned of surgical teams. Mounting evidence in all areas have pushed our understanding of skull base reconstruction principles forward. In this narrative review, we summarize critical concepts and provide practical but comprehensive guiding principles on preoperative, intraoperative/technical, and postoperative management principles related to optimizing skull base reconstructive success. The goal is to provide an informative resource for skull base surgeons (both otolaryngologists and neurosurgeons) to reference regarding state-of-the-art evidence surrounding this ever-evolving topic.

Key words: cerebrospinal fluid leak, endoscopic endonasal approach, nasoseptal flap, outcomes, skull base reconstruction

Introduction

Skull base reconstruction is a unique and highly challenging component of endoscopic skull base surgery which intends to reconstitute the separation between the sterile intracranial cavity and the "contaminated" sinonasal tract and to prevent persistent cerebrospinal fluid (CSF) leak. It requires multidisciplinary collaboration, advanced planning, and complex decision-making preoperatively, intraoperatively, and postoperatively. It can be highly technical, especially as surgeons are working around critical neurovascular structures, and may involve both open and/or endoscopic corridors. As skull base surgery has evolved as a field, there has been a growing interest in optimizing and improving outcomes of skull base reconstruction. This review article aims to provide an updated overview of the current state of the art in skull base reconstruction, with a specific focus on preoperative, intraoperative/technical, and postoperative management principles. Prior reviews in this area remain highly relevant and informative, and the current review aims to expand on emerging evidence and newer concepts [1,2].

We will discuss preoperative risk assessment and stratification; definition of the defect; repair materials, techniques, and principles; the role of adjunctive materials; special considerations in pediatric patients; and both surgeon- and patient-directed postoperative protocols. Conversely, this review will not focus specifically on traumatic/iatrogenic, spontaneous, congenital, or other non-tumor-related causes of CSF leak or skull base defects. Naturally, the principles and concepts presented in this review may be applied to these other defect types in some capacity, but we have chosen to focus on this category of defects given their uniques challenges and complexity.

Preoperative risk factors and considerations

When seeing a patient in consultation for a skull base lesion with planned endoscopic endonasal approach and resection, there are many variables to take into consideration. This often requires multidisciplinary evaluation complexity of skull base pathologies. We can think of these considerations in two categories including anatomic location of the tumor and understan-

Table 1. Risk of Postoperative CSF Leak by Anatomical Location of Lesion.

Anatomic location	Overall postoperative CSF leak rate	Postoperative CSF leak rate if intraoperative leak is present
Sellar/Suprasellar	2.9 - 9.9% (3-7)*	10.3 - 20.8% (5)
Anterior Cranial Fossa	8 - 21% (4,6,9)	Not enough data to report
Posterior Fossa	1.8 - 32.6% (4,10)	6.7% (10)
Craniocervical Junction	Minimal (11,12)**	Minimal (12)

*Data from work published after 2006 when nasoseptal flap was an option for reconstruction. **Data limited to transnasal odontoidectomy cases.

ding how the patient's comorbidities may impact tolerance of surgery and surgical healing. Evaluating these different factors can give the surgeon a global understanding of risk for a patient and tailor presurgical discussion and counseling of a patient's risk of complications. Furthermore, if time allows, these risks can be at least partially mitigated with various interventions to optimize success of surgery.

Anatomic location of the tumor

One of the first things to recognize is that the site of the tumor not only gives information about the possible pathology of the lesion, but also dictates the risk of reconstructive failure (Table 1). Often sellar and parasellar lesions are studied together in large case series and include pathologies such as pituitary adenomas, Rathke cleft cysts, craniopharyngiomas, and tuberculum sella or planum sphenoidale meningiomas (Figure 1). The reported incidence of CSF leak after surgery ranges from 2.9-9.9% (3-7), which includes only modern series (published after 2006) where the surgeon had the option of nasoseptal flap (NSF) for reconstruction (8). When the data is separated into patients who experience intraoperative CSF leak versus those who do not, the reported postoperative CSF leak rates in those who experienced intraoperative CSF leak is higher at 10.3% and even higher at 20.8%, if the pathology was craniopharyngioma (5).

The anterior cranial fossa (ACF), which includes lesions such as primary benign and malignant sinonasal tumors (i.e., olfactory neuroblastoma) and olfactory groove meningioma, has a published postoperative CSF leak rate between 8-21% (Figure 2) (4,6,9). Posterior cranial fossa (PCF) lesions including chordomas, chondrosarcomas, and meningiomas are associated with higher flow CSF leaks secondary to continuity with the prepontine cistern, and have a postoperative CSF leak rate reported between 1.8-32.6% (Figure 3) (4,10). Finally, the last region to consider is the craniocervical junction where lesions such as rheumatoid pannus or basilar invagination occur. These lesions are often extradural and intraoperative CSF leak is not common and therefore postoperative CSF leak is also not common (11,12).

Comorbidities

Other considerations for success of skull base reconstruction are to address the systemic health of the patient and optimize any treatable conditions prior to surgery if time permits. Obesity is common among the global population with an incidence of approximately 13% (13) and increased incidence in higher income countries with the obesity rate at 41.7% in the United States (10). Several large cases series have found increased rates of postoperative CSF leak in individuals with higher body mass index (BMI) (5,14). A study which focused specifically on elevated BMI and postoperative CSF leak following transsphenoidal surgery, found that for every 5 kg/m^2 increase in BMI, patients had a 1.61 odds higher risk of having a postoperative CSF leak (14). In one retrospective review, the authors found that postoperative CSF leak was reduced from 29.5% to 15.0% when a pedicled flap was used for reconstruction in patients with BMI > 25 kg/m^2 (4), although more evidence supporting these interventions is needed for a definitive recommendation.

The etiology of increased BMI being associated with increased postoperative leak is unclear, but is theoretically linked to increased rates of idiopathic intracranial hypertension (IIH) and spontaneous CSF leaks where elevated BMI is a clear risk factor (15). Obesity is known to increase intrathoracic pressure which is hypothesized to transmit to the venous system up to the intracranial system, not allowing adequate venous drainage and as a result increased intracranial pressure (ICP) (16). Obesity is also known to be a risk factor for clotting, which could also potentially cause venous outflow obstruction in the intracranial cavity (15). While IIH is a different disease, the underlying mechanism of increased ICP in obese patients may be a causative factor in the elevated rates of CSF leaks seen postoperatively. Identifying obesity as a risk, allows one to counsel patients appropriately about risk of surgery. Furthermore, one may potentially be more conservative in postoperative restrictions and use more aggressive skull base reconstructive techniques in obese patients. Beyond obesity, evaluating specifically for preoperative hydrocephalus as an independent risk factor for postoperative CSF leak may also be useful as the same review found this was associated with postoperative CSF leak (4).

Factors associated with poor postoperative wound healing should also be considered during preoperative planning and counseling for endoscopic skull base surgery (17,18). Large pros-

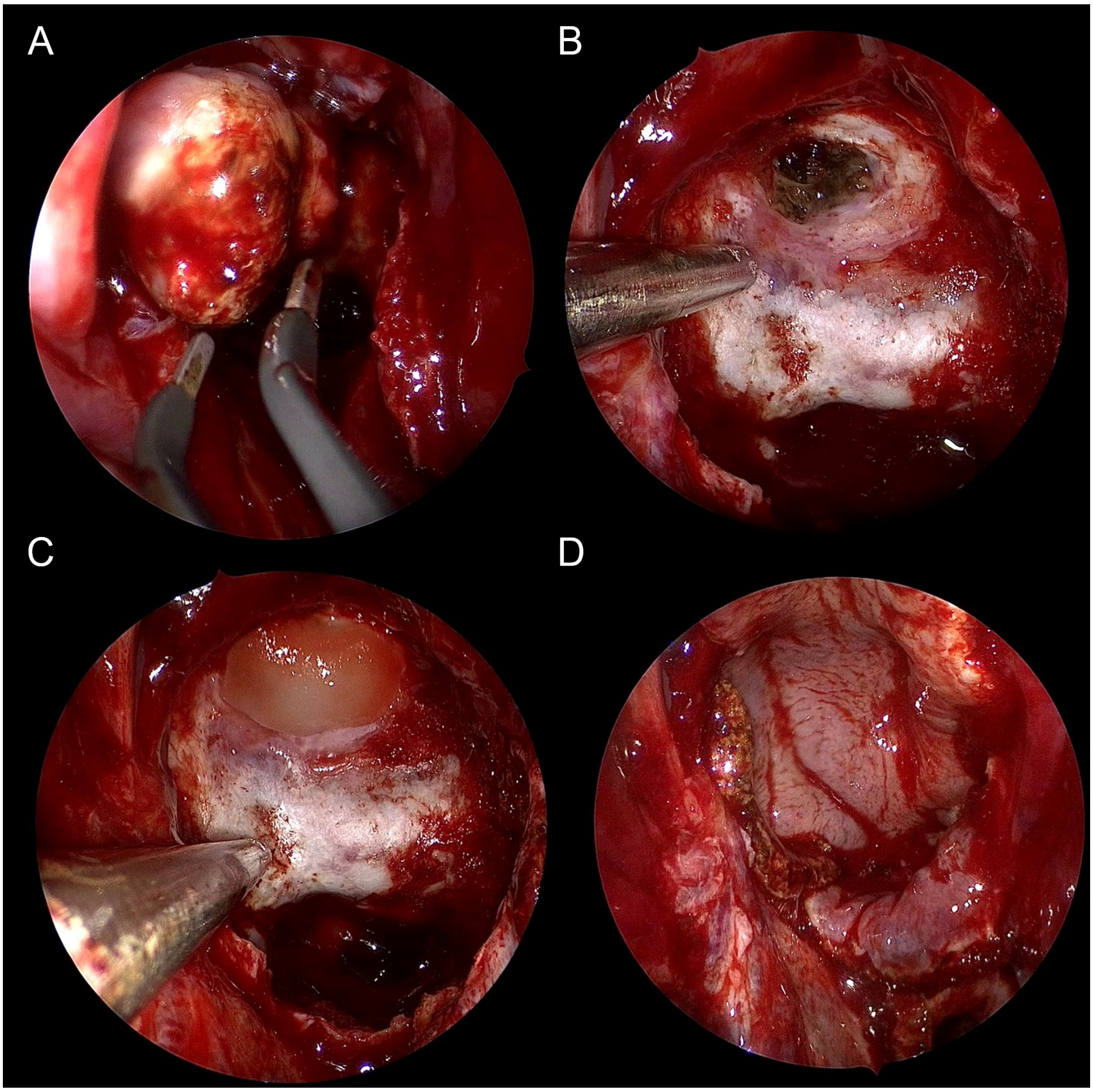

Figure 1. Suprasellar encephalocele. (A) The encephalocele is fulgurated and reduced using the endoscopic bipolar electrocautery. (B) Post-treatment, pre-repair suprasellar defect. (C) Placement of collagen matrix for intradural repair. (D) Full coverage of the suprasellar defect and exposed bone with vascularized pedicled nasoseptal flap.

pective studies have not evaluated these issues in skull base surgeries, but there have been retrospective studies which have identified factors such as tobacco use, malnutrition (i.e., low prealbumin), malignancy, previous radiation, intracranial infection, and Cushing disease as potentially impacting failure of endoscopic repair and delayed healing [19-23]. Furthermore, when evaluating readmission rates after skull base surgery, another group found that those readmitted were more likely to be obese and smokers [24], highlighting the importance of trying to optimize these factors preoperatively whenever possible. Interestingly, previous history of endoscopic skull base surgery has not been shown to be associated with perioperative adverse events [25] although further evidence is needed to make a definitive conclusion.

Intraoperative and technical considerations

For patients undergoing primary surgery, there are usually multiple options in place and one must consider the reconstructive ladder (Table 2) when choosing the method of reconstruction. This is possible with absorbable hemostatic materials (e.g., gelatin, oxidized regenerated cellulose) and dural sealants which may allow for pinpoint low-flow leaks to seal. An example is the small leak that can arise from a torn olfactory filum, which can be fulgurated with bipolar electrocautery and covered with absorbable hemostatic agents all the way up to complex defects requiring free flap reconstruction (e.g., recurrent clival leak after radiation).

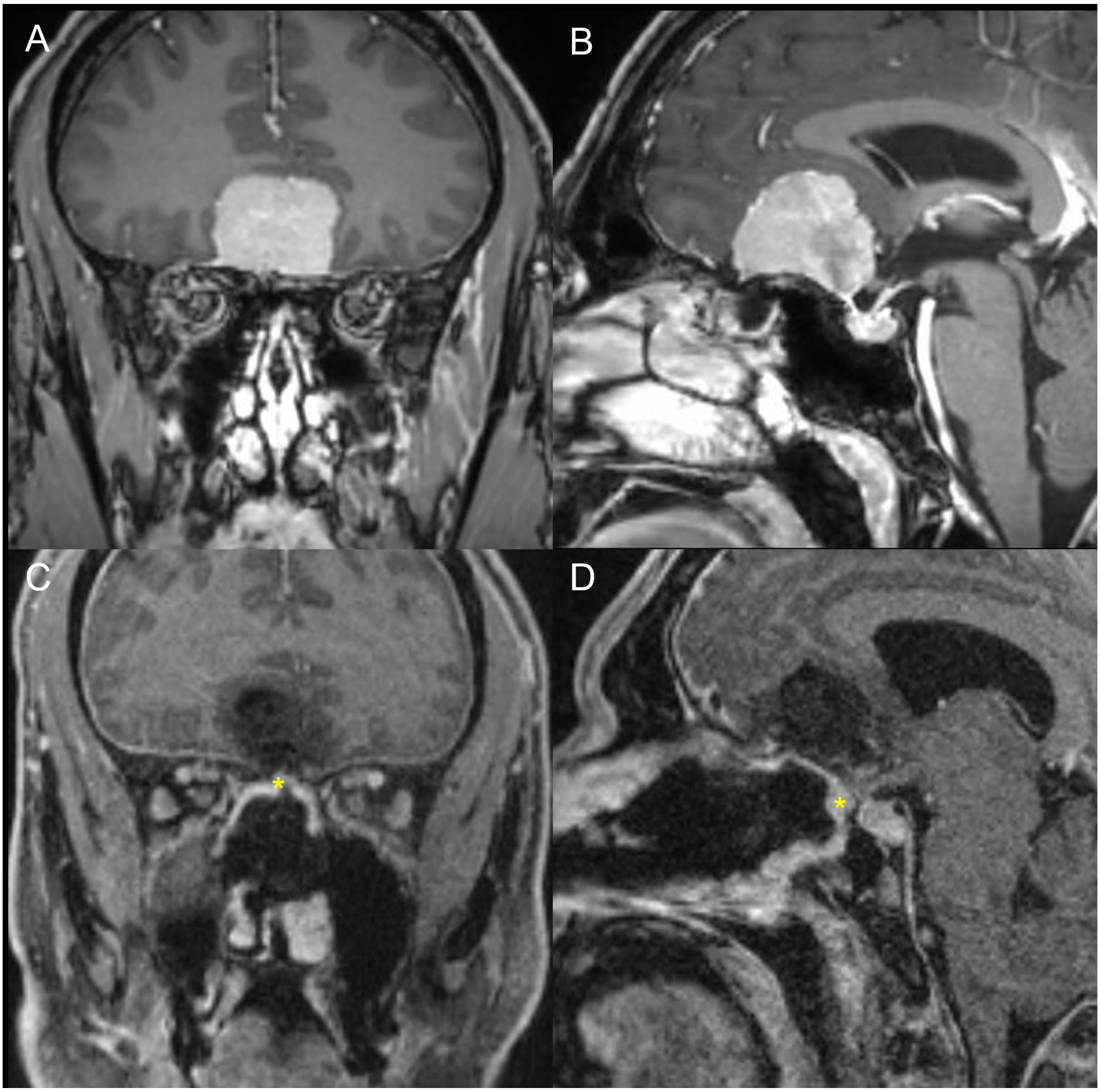

Figure 2. Olfactory groove meningioma. Preoperative post-contrast magnetic resonance imaging demonstrates (A) coronal and (B) sagittal views of a 3.8 cm tumor of the anterior cranial fossa. Postoperative imaging (C) coronal; and (D), sagittal confirms a gross total resection with reconstruction using a pedicled nasoseptal flap (asterisk).

CSF leak flow rate

The choice of reconstruction depends highly on the size and location of the defect, as well as the flow rate of the intraoperative CSF leak. Conventionally, flow rate is categorized as low-flow (small dural tear with weeping CSF) and high-flow (in direct continuity with ventricular system such as the suprasellar and/or prepontine cisterns, and/or dural defects measuring 1 x 1 cm or larger). Low-flow defects are commonly encountered during sellar surgery, while high-flow defects are usually associated with ACF, suprasellar, and PCF pathologies. Another commonly used grading system for sellar/suprasellar surgery was described by Esposito et al., wherein grade 0 is no intraoperative CSF leak, grade 1 is small leak without obvious diaphragmatic defect ("weeping"), grade 2 is moderate leak, and grade 3 is large diaphragmatic or dural defect [26]. Understanding the type of flow rate is important for planning strategies for repair for any given defect, with many reports of utilizing a "graded repair" algorithm with consistently achieved outcomes [26-28].

The success of endoscopic repair of high-flow CSF leaks without CSF diversion has been studied. Zanation et al. demonstrated a 5.7% (4/70) postoperative CSF leak rate when the NSF flap was employed to repair high-flow leaks. Risk factors for failure

Table 2. Reconstructive ladder for skull base surgery.

Technique	Examples
No reconstruction or secondary intention	Absorbable hemostatic agents [32] Dural sealant [119]
Direct suturing	"Shoelace" technique [120-122]
Implants or allografts	Commercial collagen matrix [123,124] Porcine small intestine submucosa [50,125] Acellular dermal matrix [49,126-128] Bovine dura [125] Rigid reconstruction options - "Gasket seal" technique [54-56] - Bone grafts [27] - Bioabsorbable plates [53]
Free autologous grafts	Nasal mucosal graft (septum, floor, turbinate) [31,32,129-132] Orbital or abdominal fat graft [133,134] Fascia lata graft [135,136]
Local rotational flaps	Nasoseptal flap [8] Extended nasoseptal flap [137-139] - Pedicle release [140] Middle turbinate flap [141-143] Lateral nasal wall flap [35-37] Anterior ethmoid artery system - Septal flip flap [144] Rhinopharyngeal flap [38,145] Sphenoid mucosal flaps (nonpedicled) [146]
Regional tunneled rotational flap	Pericranial flap [147-149] Temporoparietal fascia flap [34,40]
Tunneled free flap via maxillary or frontal sinus	Radial forearm [41-44] Anterolateral thigh [45]

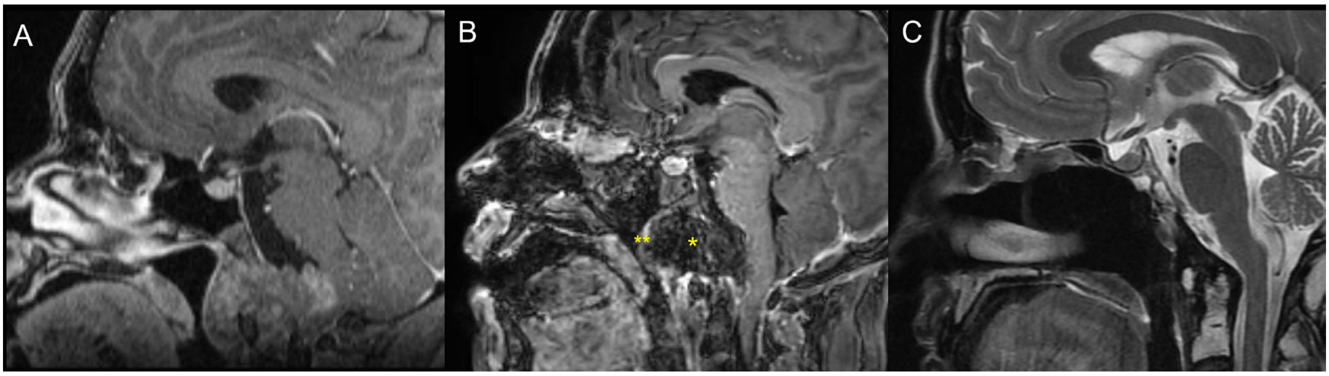

Figure 3. Lower clival/craniocervical junction chordoma. (A) Preoperative post-contrast magnetic resonance imaging demonstrates severe mass effect on the brainstem. (B) Postoperative day 1 imaging demonstrates decompression of the brainstem and reconstruction using fat and fascia lata as inlay materials (asterisk) and nasoseptal flap (double asterisks). (C) Surveillance T2-weighted imaging at 36 months reveals no recurrent disease and resorption of reconstructive materials leading to smooth contour of nasopharynx and skull base.

included large dural defects (> 2 cm), prior radiation, and pediatric patients [29]. Harvey et al. conducted a systematic review of postoperative CSF leak rates for large skull base defects, defined as those pathologies where a large defect following endoscopic craniotomy was anticipated (e.g., meningiomas, craniopharyngiomas) [30]. They found that free grafting was associated with higher postoperative CSF leak rates compared to vascularized reconstruction (15.6% vs 6.7%; p=0.001).

Flaps and grafts

Flaps (vascularized) and grafts (non-vascularized) are the cornerstone of skull base reconstruction, providing coverage over the defect and sufficient weight to counter ICP shifts in order to permit healing. Common principles for proper placement of flaps and grafts include ensuring the right orientation (mucosa side up), full coverage of the defect whenever possible, placement directly on non-mucosal tissues (i.e., bone), placement

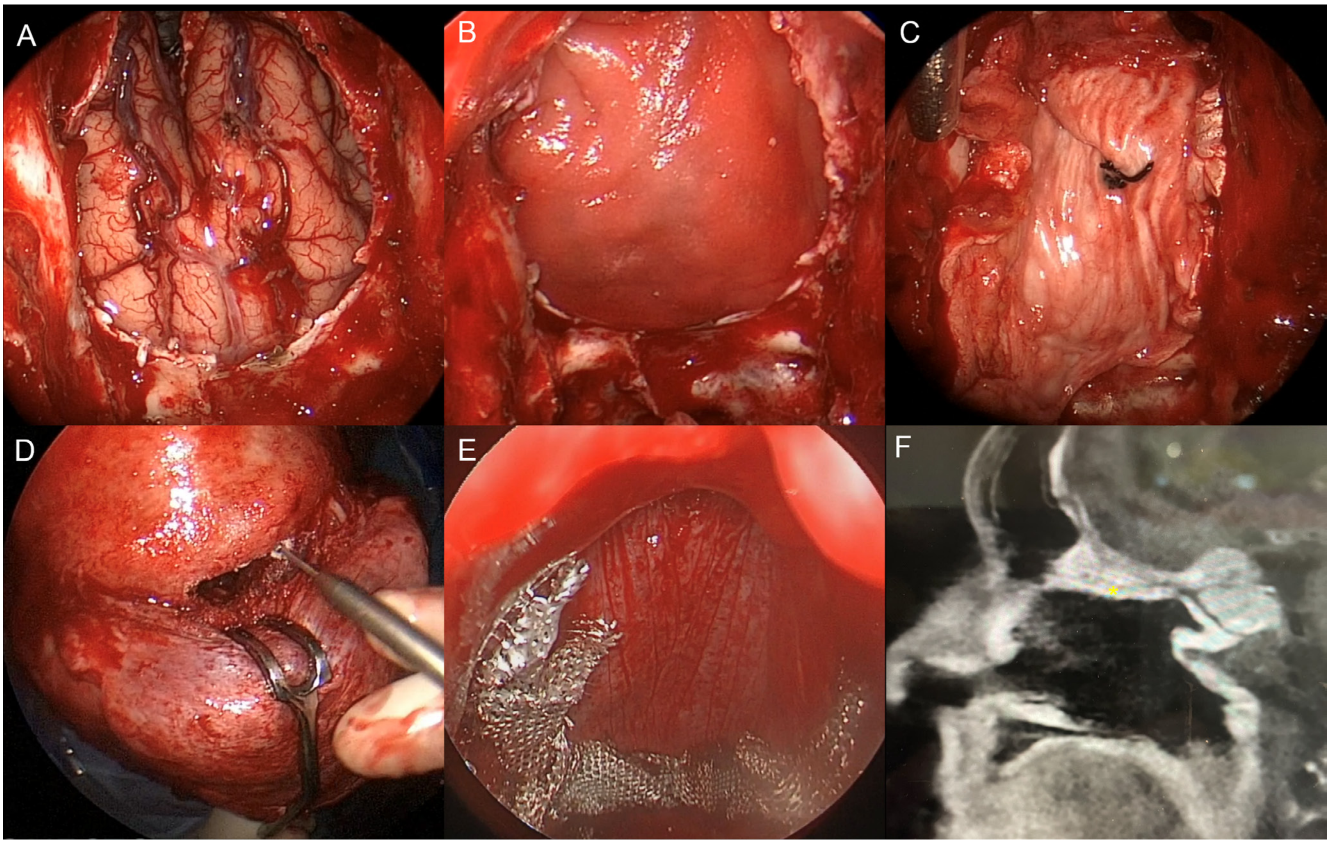

Figure 4. Pericranial flap. (A) Large bilateral anterior cranial fossa defect with frontal lobe exposure. (B) Collagen matrix subdural inlay. (C) Double-layer "button" fascia lata graft with one layer as inlay and another as onlay. (D) Creation of anterior table osteotomy to introduce pericranial flap into the nasal cavity. (E) Pericranial flap as final onlay secured in place with Surgicel® (oxidized regenerated cellulose, Johnson & Johnson, New Brunswick, NJ, USA). (F) Postoperative post-contrast imaging demonstrates enhancing flap providing full coverage of the defect without frontal obstruction.

on a flat surface (e.g., all septations removed to the level of the skull base), no dead space, and, for flaps, no impingement of the pedicle.

The vast majority of endoscopic skull base approaches are for sellar and parasellar pathologies. Most resultant defects for pituitary adenomas are low-flow. Hebert et al., in a retrospective multicenter cohort, found that for sellar and parasellar defects, free grafts are often sufficient and used as much as 67% of the time, with very favorable outcomes [31]. Rarely, sellar/parasellar pathologies (e.g., craniopharyngiomas) will connect to suprasellar cistern or the foramen of Monro and this typically benefits from vascularized reconstruction, most commonly in the form of a NSF. Using this general classification, leak rates are reported to be between 1.5% to 5.2% [27,31,32].

Location is another consideration when deciding repair techniques. Certain defects demand specific repairs because vascularized flaps have limitations based on average lengths and arc of rotation around the pedicle. For example, the middle turbinate or reverse septal (flip) flap is only useful for small anterior cribriform leaks in rare instances (e.g., small olfactory neuroblastoma without transseptal involvement). The traditional NSF, pedicled off of the posterior septal branch of the sphenopalatine artery, is highly versatile and remains the workhouse for skull base reconstruction, with reach covering the entire ventral skull base to the middle clivus [8]. Extended NSFs which incorporate the nasal floor and inferolateral nasal wall are needed to reach the lower clivus, posterior table of frontal sinus, or defects incurred following transpterygoid approaches [33].

Secondary flaps can be used with similar success (3.6% failure rate in one series) [34], especially when the NSF (e.g., trauma, septal perforation, revision surgery) is not available. The vascularized lateral nasal wall flap, pedicled off of the inferior turbinate branch of the sphenopalatine artery and traditionally described as the inferior turbinate flap [35], can be used to cover sellar and clival defects, though may not reach the planum sphenoidale or ACF [36,37]. The inferiorly-based rhinopharyngeal flap, supplied by branches of the ascending pharyngeal artery, can be elevated and replaced over defects of the lower clivus or craniocervical junction (e.g., odontoidectomy) [38]. Defects of the superior part of the posterior table of the frontal sinus or those resultant

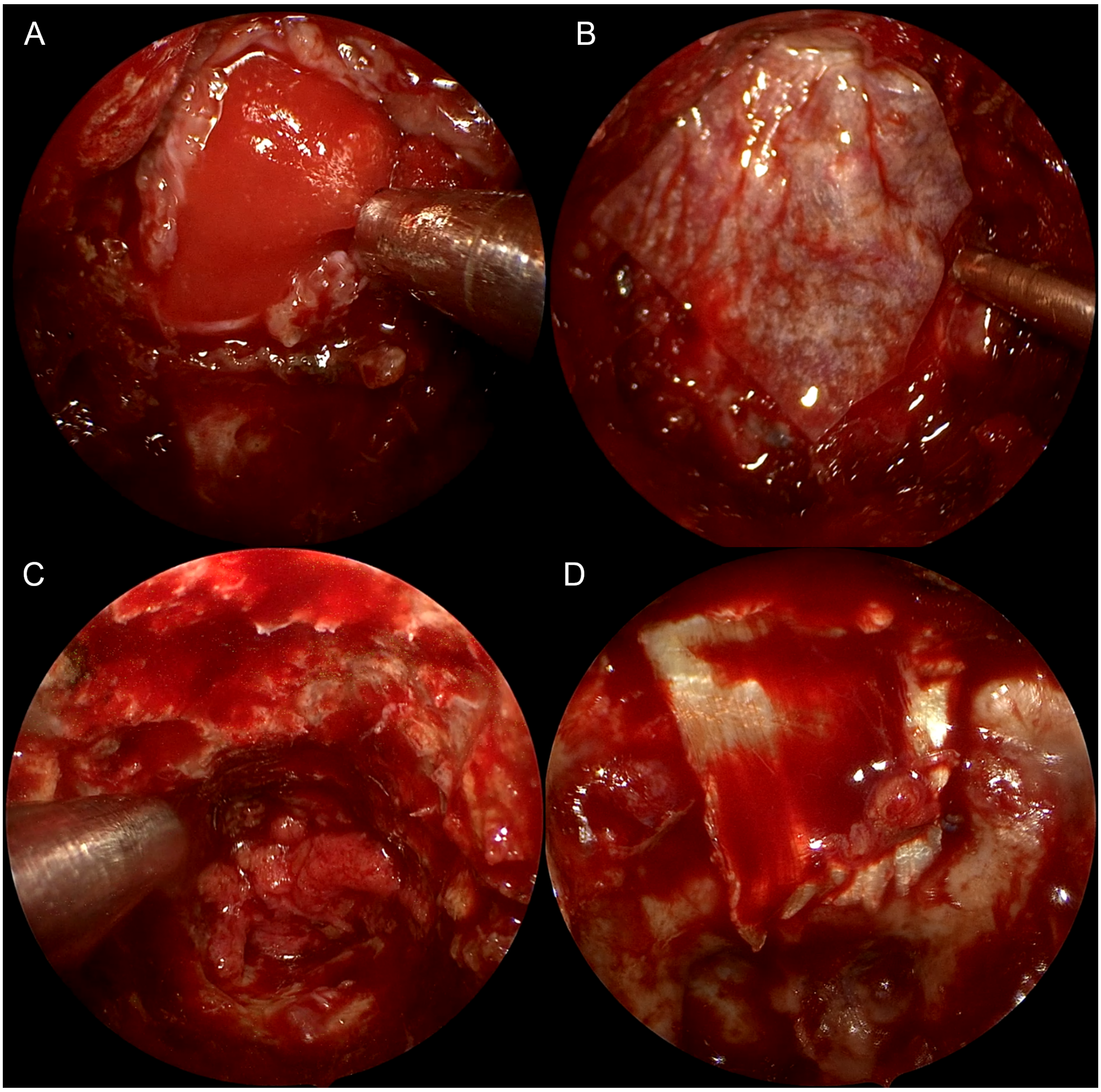

Figure 5. Examples of inlay and onlay materials. (A) Collagen matrix (DuraGen®, Integra Lifesciences, Princeton, NJ, USA) used as a subdural inlay for a middle clival defect. (B) Porcine small intestine submucosa (Biodesign®, Cook Group, Bloomington, IN, USA) used as an onlay for the same clival defect. (C) Abdominal fat used to obliterate a deep craniocervical junction defect. (D) Fascia lata placed over a sellar and suprasellar defect.

from ACF/PCF resection with septal resection may benefit from tunneled pericranial flaps, supplied by the supraorbital and supratrochlear arteries, especially if adjuvant radiation is planned (Figure 4) [39]. Tunneled transpterygoid temporoparietal fascia flaps, supplied by the superficial temporal artery, are another option to provide robust coverage of a wide range of defects in which no intranasal options are available [34,40]. Finally, free flap reconstruction tunneled via Caldwell-Luc antrostomy or modified Lothrop defect remains a reliable option for definitive closure of highly refractory defects, particularly those resulting from radiation necrosis and has only been described in small series [41-45]. If there is concern regarding vascularity of the flap itself, intraoperative indocyanine green angiography can be used to assess flap viability [46,47].

Onlay and inlay and graft material choice

Specific intraoperative techniques examined in the literature include the decision to perform single- (onlay) versus multi-layer repair (inlay and onlay). Conventionally, inlay or underlay techniques aim to fill the dead space of the defect by placing graft materials within the subdural and/or epidural space, while onlay or overlay techniques aim to provide full coverage of the defect from the intranasal side. Commonly used autologous graft materials include abdominal fat or fascia lata grafts, while

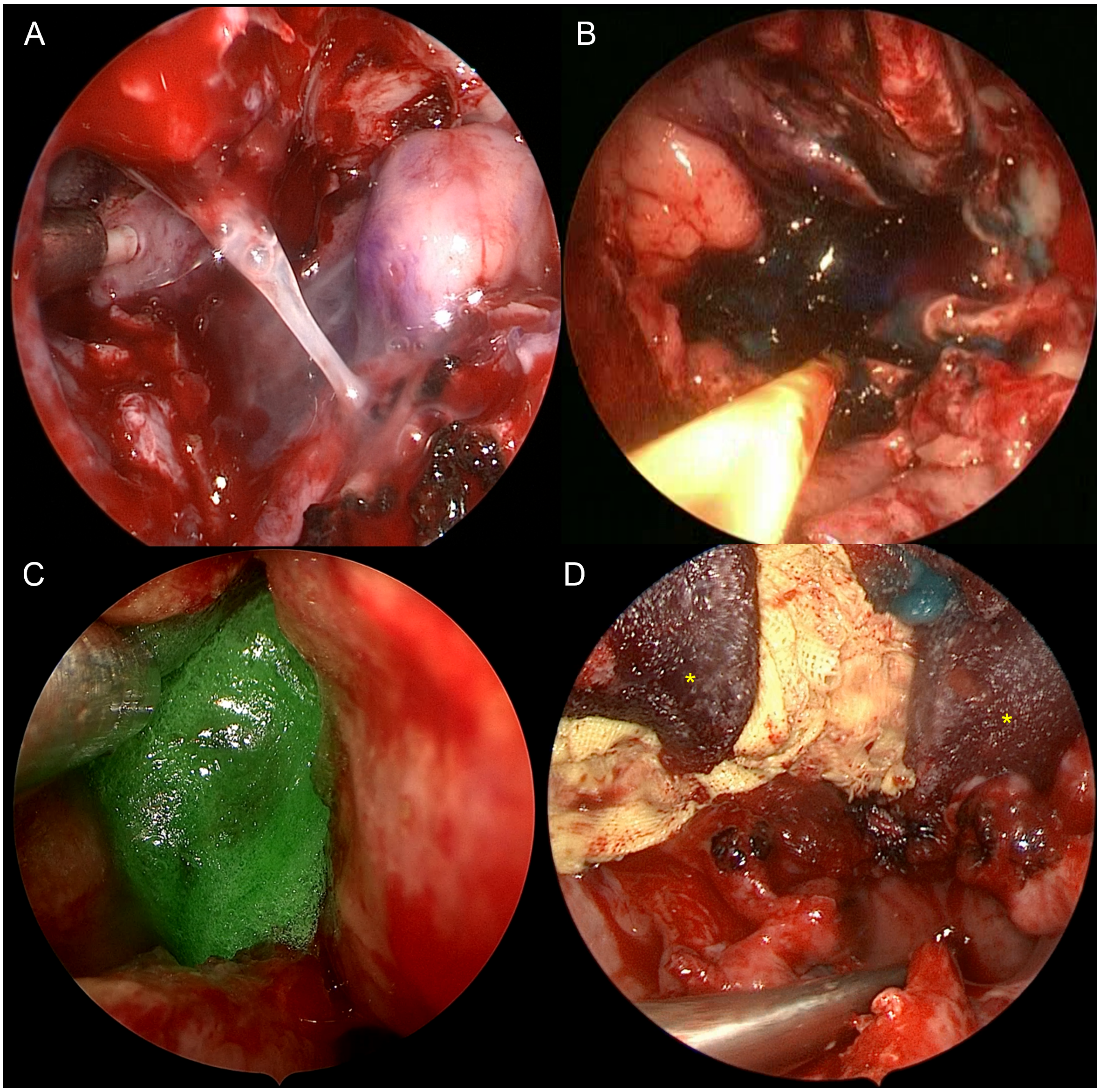

Figure 6. Common adjuncts in skull base reconstruction. Different examples of tissue sealants, including fibrin glue (A), DuraSeal® (B), Integra Lifesciences, Princeton, NJ, USA), and Adherus® (C), Stryker, Kalamazoo, MI, USA), applied over a nasoseptal flap for a sphenoid defect. (D) A combination of absorbable (asterisks, Nasopore®, Stryker) and non-absorbable (strip gauze) packing is used to bolster an anterior cranial fossa defect.

synthetic materials include collagen matrix, acellular dermal matrix, or porcine small intestine submucosa (SIS) (Figure 5). There are pros and cons to either graft type – namely, autologous materials require harvesting leading to an additional donor site, while synthetic materials may be costly and not readily available depending on the institution.

Casiano et al. studied the use of acellular dermal matrix for both sellar and larger ACF defects (> 2 cm) and reported postoperative CSF leak rates of 8.4% and 3%, respectively [48,49]. Illing et al. reported a 94.7% primary success rate for use of SIS grafts as inlay and/or onlay for a variety of different skull base defects, including tumor-related defects [50]. In terms of inlay materials, the choice of synthetic versus autologous grafts does not seem to impact postoperative CSF leak rate (4.8% vs 4.9%, respectively) but does impact meningitis rates (0.4% vs 2.3%, respectively) [51]. Ultimately, the choice of graft materials and closure techniques seems to be based on surgical training, preference, and experience, as there is no discernable difference in postoperative CSF leak rates [51,52].

Rigid reconstruction

Use of rigid skull base reconstruction with bioabsorbable plates or bone grafts to buttress fat graft repairs ("gasket seal") has been studied in several single-institutional retrospective cohorts, with generally excellent outcomes [53-57]. Piscopo et al. reported their experience with 560 cases and found that the postoperative CSF leak rate decreased from 8.5% to 1.7% after adopting rigid reconstruction [57]. Considering the need for rigid reconstruction of large ACF defects in which frontal lobe sagging may be an issue, Eloy et al. found minimal change in frontal lobe position (0.2 mm) with standard multilayer vascularized reconstruction (average 9.3 cm^2) [58]. Hypothetically, it is important to consider that, with rigid bolsters typically comprised of materials that do not develop vascular supply readily, there is a risk of infection or foreign body reaction, and particular care should be exercised when employing such techniques for patients who may receive adjuvant radiation.

Dural sealants and nasal packing

Dural sealants and fibrin glue, as well as nasal packing, are frequently used as adjuncts in skull base reconstruction, with the goal to anchor the materials in place short-term (Figure 6). Nasal packing may be classified as absorbable/dissolvable (e.g., polyurethane foam) versus non-absorbable/dissolvable (e.g., gauze, hydroxylated polyvinyl acetate), with the latter requiring removal in order to prevent infection (e.g., toxic shock) or foreign body reactions. Most studies demonstrating the safety and efficacy of sealants and glues have been in vitro, focusing on the concept of burst pressure (pressure needed to disrupt the fully formed sealant over the repair) [59-62]. The role of dural sealants has been studied in a single-institutional, retrospective study on 300 patients, which found no differences in postoperative CSF leak rates with or without sealant use [63]. Asmaro et al. examined a group of 73 patients undergoing skull base reconstructions with dural sealant alone and without nasal packing, and reported an overall 97.4% primary success rate [64]. A systematic review by Park et al. examined CSF leak rates when repairs were stabilized with packing and found lower rates of postoperative CSF leak with nasal tampons (1.0%) versus Foley balloons (10.5%) [65]. Given the limited evidence, one might conclude that one can use either packing or sealant effectively, but using both is likely unnecessary in most cases. A recent survey of skull base surgeons in Italy, anterior nasal packing was considered useful by 84% with half using it for every case [66]. Overall, evidence to support routine use of sealant or packing is scant, with future clinical studies needed to determine the impact of use versus non-use and type of materials on postoperative CSF leak outcomes.

Learning curve

Given the highly technical nature of surgery, learning curves have been studied in all surgical subspecialties and the most common inflection point for significant improvement in complications is around 30 procedures. Large series have shows that the curve is long as the surgical team ascends different levels of complexity, takes on different pathologies, and depending on the endpoints considered [67]. Postoperative CSF leak rates decrease with the ascension of the learning curve and is significantly different with increasing experience, as evidenced by Park et al.'s focused on 125 high-flow defects (23.3% after 30 cases, 10% after 60 cases, 6.7% after 90 cases, and 2.9% after 120 cases) [68]. Similarly, Younus et al. specifically examined CSF leak rates following pituitary surgery and found that postoperative CSF leaks decreased from 3.3% to 0.7% at the same time as the use of lumbar drainage (LD) decreased from 28% to 6% [69].

Postoperative management and protocols

Equally important, if not more important in certain circumstances, is the role of postoperative management following skull base reconstruction. Such precautions are directed towards not provoking or disrupting the fresh repair in order to ensure natural healing of the reconstruction. As is the case for most concepts in skull base surgery, there are heterogeneous practices and no consensus has been achieved in this area. In this section, we review the most commonly considered postoperative practices, including lumbar drainage, management of obstructive sleep apnea (OSA) patients and use of positive pressure, postoperative imaging, activity restrictions, and sinonasal care.

Lumbar drainage

An important question in postoperative management following endoscopic skull base surgery is use of LD for CSF diversion. The CSF space is a closed system, whereby fluid diversion and egress through the lumbar cistern to an external reservoir takes pressure off of a cranial/skull base reconstruction, therefore improving reconstructive outcomes. Though commonly used in cranial and spinal surgery, the routine use of LD for endoscopic skull base surgery is debated. At the time of the International Consensus Statement for Endoscopic Skull Base Surgery 2019 document [1], LD usage was listed as an option and an aggregate grade of evidence of C (based on observational studies) was designated; the updated review by Abiri et al. [70] found that the evidence grade had increased to B (randomized controlled trial [RCT] and consistent evidence from observational studies). Early higher-level evidence for the role of LD for skull base reconstruction came from a systematic review and meta-analysis which identified 12 studies (one RCT and 11 case series through 2015) and 508 eligible cases of perioperative LD use in the setting of endoscopic repair of CSF rhinorrhea (spontaneous, traumatic, iatrogenic during sinus surgery, and following ACF resection) [71]. In aggregate, the authors found no significant difference in postoperative CSF leak rates with and without perioperative LD use (OR 0.89 [95% CI: 0.40-1.95]). A subgroup analysis of ACF tumor-related repair outcomes (n=157) was similarly nonsignificant (OR 2.67 [95% CI: 0.64-11.10]). However, this study did not consider patient and clinicopathologic factors such as defect size and subsite.

The highest level of evidence to date pertaining to perioperative LD usage and its impact on reconstructive outcomes comes from a single-institutional, prospective randomized controlled trial involving large dural defects of the suprasellar area, ACF, and PCF (72). 170 patients undergoing endoscopic skull base surgery with subsequent intraoperative high-flow CSF leaks were randomized to receive LD placement with drainage at 10 cc/hr for 72 hours versus no intervention (85 in each group). The average defect size for the ACF, suprasellar area, and PCF were 7.2, 1.6, and 3.2 cm^2, respectively. In total, seven (8.2%) patients in the LD group and 18 (21.2%) patients in the control group developed postoperative CSF leaks (OR 3.0 [95% CI: 1.2-7.6]). By defect location, only the ACF demonstrated a significant difference between the LD and control groups, though the PCF subgroup approached significance and was likely underpowered. Finally, multivariate logistic regression found that defect size was the only predictor of postoperative CSF leak (OR 1.86 [95% CI 1.05-3.3]). The authors thus concluded that routine LD usage for large ACF and PCF defects may improve reconstructive success.

Despite promising evidence surrounding postoperative LD use for large defects, one must also consider the morbidity related to LD placement when routinely used. An early study of 65 patients undergoing endoscopic skull base surgery found that nine LD-related complications occurred in eight (12.3%) patients, including six blood patches, six instances of repeat imaging, one open removal of retained catheter fragments, and an infectious disease workup (73). More recently, Birkenbeuel et al. reviewed medical and technical complications related to LD placement in 64 patients who underwent endoscopic skull base surgery (74). No patients experienced pneumocephalus, intracranial bleeding, venous thromboembolic events, or meningitis, and two (1.9%) patients required blood patch for spinal headache following drain removal. Regardless, LD usage remains an important adjunct in skull base reconstruction, and indications for use will be based on both the growing evidence and clinical judgment. Consider LD usage in cases of anticipated high-flow leaks and large dural defects, elevated ICP or known intracranial hypertension, cases in which there are few reconstructive options, history of radiation or skull base surgery, or patients with known risk factors for poor wound healing (e.g., obesity, poorly controlled diabetics, immunocompromised state, chronic steroid use).

Restarting positive pressure ventilation/support

OSA is an increasingly recognized diagnosis, with a corresponding increasing prevalence due to the obesity epidemic. In the setting of skull base surgery, Huyett et al. found in a cohort of 414 patients that, of the 54 (13.0%) with known OSA, there was no increased risk of serious respiratory complications (defined as reintubation, prolonged intubation, significant desaturations) or postoperative CSF leak. However, the authors recognize that OSA was likely underdiagnosed in this group, and further analysis of a surrogate "at-risk" group consisting of patients with BMI > 30 kg/m^2 and hypertension identified a higher risk of serious respiratory events (OR 4.41 [95% CI 1.24-15.7]) and postoperative CSF leak (OR 2.17 [95% CI 1.16-8.66]) (75).

With respect to the resumption of continuous positive airway pressure (CPAP), the timing of resumption following skull base reconstruction poses a unique challenge. The potential need for positive pressure ventilation represents another source of direct trauma to a freshly repaired skull base. The natural concern is that high-pressure air may disrupt the reconstructive materials and introduce air intracranially (pneumocephalus), which has been rarely reported (76). A survey of the North American Skull Base Society (NASBS) membership found that 50% of respondents believed that knowledge of OSA status influenced intraoperative decision making during skull base reconstruction, indicating generally good knowledge of OSA, positive pressure, and possible implications (77).

Empiric evidence surrounding the safety of CPAP resumption for skull base surgery patients is lacking and has been extrapolated from ex vivo models and retrospective reviews of rhinologic (non-skull base) surgery. A cadaveric study of CPAP pressure transmission into the nasal cavity found that approximately 85% of the delivered pressure is passed into the nasal cavity (range, 77% for 5 cm H_2O to 89% for 20 cm H_2O) (78). A follow up study found that 80% of pressure was delivered to the sella (79), and modeling different sellar repair techniques found that use of a NSF appeared to consistently withstand even the highest of CPAP settings (20 cm H_2O) (79). White-Dzuro et al. reviewed 349 transsphenoidal procedures in 324 patients, of which 69 (21.3%) had known OSA, and found that only two (0.6%) patients developed postoperative pneumocephalus. Of note, none of the patients who resumed CPAP use several weeks postoperatively developed pneumocephalus, suggesting that this risk may be lower than previously thought (80). Finally, Gravbrot et al. identified 42 OSA patients undergoing transsphenoidal surgery, of which 20 (47.6%) had an intraoperative CSF leak and 38 (90.5%) eventually restarted CPAP. None of the patients developed pneumocephalus or postoperative CSF leak (81).

Recently, there has been interest in the development of "standardized" protocols to restart CPAP or apply positive pressure ventilation after skull base surgery. A separate survey of the NASBS membership found that, at the surgeon's discretion, the mean number of days from surgery to restarting CPAP are 10.1 ± 10.2, 14.3 ± 9.8, and 20.7 ± 11.8 days for no intraoperative leak, "small" leak, and "large" leak, respectively (82). Rabinowitz et al. outlined a protocol for guiding timing of restarting CPAP following sellar surgery (83). For patients without intraoperative CSF leak, CPAP may be resumed one week postoperatively. For patients with intraoperative leak and no urgent need to restart

Table 3. Common postoperative precautions and interventions following endoscopic skull base surgery (adapted from Abiri et al. [70]).

Precaution / intervention	Focus area	Recommendation	AGE
Level of care	Inpatient care	Pituitary patients may be SDU/floor status, expanded approaches ICU	C
Pain management		Utilize non-opioid multimodal pain regimen whenever possible	B
Prophylactic antiemetics		Standing antiemetics may reduce risk of postoperative CSF leak	C
Prophylactic antibiotics		Infection rate low overall, uncertain value for antibiotics	B
Postoperative anticoagulation		Mechanical VTE prophylaxis for all patients, consider chemical VTE prophylaxis for all high-risk patients	D
Head of bed elevation		Keep head of above > 30 degrees to temper ICP shifts	D
Urinary catheter use		Consider Foley while patient on bedrest to prevent straining; must be balanced with risk of UTI	D
Postoperative lumbar drainage	CSF leak prevention and detection	Consider lumbar drain for 48-72 hours for high-flow leaks and large dural defects, independent of elevated ICP	B
Medical ICP control		Consider ICP-lowering agents after surgery; no dedicated studies	D
Stool softeners		Consider standing stool softeners postoperatively to prevent straining	D
Nasal packing		Nasal packing may help bolster reconstruction in place; highly heterogeneous studies and packing materials available	D
Provocative tilt test		Provocative tilt test: false negatives or positives possible	C
Saline nasal sprays	Sinonasal morbidity and QOL	Saline sprays can help prevent crusting and improve QOL	D
Nasal irrigation		Nasal irrigations can help restore nasal health; caution with use immediately postop to prevent disruption of repair	D
Nasal debridement		Postop nasal debridement after reconstruction healed restores nasal health; no evidence on timing of debridement	C
Activity restrictions	Postoperative restrictions	Postoperative activity restrictions to prevent ICP shifts and Valsalva; no consensus on timing	D
OSA and PPV		OSA/CPAP: Restart CPAP after skull base reconstruction has healed Intubation: rapid sequence intubation, no PPV	C
Straw use		Probably safe to use straws	D

AGE, aggregate grade of evidence; CSF, cerebrospinal fluid; ICP, intracranial pressure; OSA, obstructive sleep apnea; PPV, positive pressure ventilation; QOL, quality-of-life; UTI, urinary tract infection.

CPAP, the skull base is reconstructed with dural substitute inlay and sealant and CPAP is restarted three weeks postoperatively. Finally, for those with intraoperative leak and urgent need to restart CPAP, a NSF is utilized for reconstruction and CPAP is restarted immediately postoperatively. Nonetheless, there remains lack of consensus on this issue with particular attention to how one should incorporate restarting CPAP in patients with higher risk of postoperative CSF leak (i.e., high risk anatomic location, high-flow leak, obesity, etc.).

Postoperative imaging

There have been various studies focused on the appearance of reconstructive materials in the early and later postoperative period following skull base reconstruction. Understanding the layers and their positions and orientations may provide some insight into the likelihood of success for completed reconstructions. For reconstructions performed using a vascularized pedicled NSF, commonly used metrics include enhancement of the flap surface and pedicle on magnetic resonance imaging (MRI) [84], whether it provides complete coverage of the defect, and whether it adheres fully to the skull base. Adappa et al. first reported the lack of correlation between flap enhancement and reconstructive success in cases with high-flow CSF leaks following tumor resection [85]. Of 19 eligible cases with NSF seen on postoperative MRI, three developed postoperative CSF leaks, all with enhancing flaps; however, there were three cases of no leak with non-enhancing flaps. They followed this work with additional analyses of flap position, where incomplete flap coverage of the defect and displacement of the NSF appeared to be predictors of postoperative CSF leak [86] concluding flap position is probably a better predictor of reconstructive success than flap enhancement. The need for postoperative imaging to assess skull base reconstruction has not met consensus for standard of care, but may be helpful in situations high risk for postoperative CSF leak development.

Long-term imaging findings which suggest maturation of the repair have been reported. The typical time frame for this occur is within 3-6 months; autologous tissue such as fat and fascia grafts tend to undergo resorption and thinning [87]. Flaps which were initially non-enhancing tend to enhance over time, with many "self-adjusting" and contouring to the skull base over time as healing ensues [88]. Similar findings have been reported even with free mucosal grafts, which tend to develop enhancement over time as well [89].

Activity restrictions and precautions

Following reconstruction, general efforts are directed towards several goals in order to optimize reconstructive outcomes:

1. Minimizing shifts in ICP as to not place undue stress on the repair
2. Preventing trauma to and movement of the reconstructive materials
3. Educating patients and caregivers regarding protective behaviors and those which place risk upon the repair

Despite increasingly rigorous work being performed in our understanding of skull base reconstruction principles, there currently remains no standardized protocols or pathways for guiding postoperative management. Many of the principles have been derived from traditional open cranial and facial surgeries and may, in fact, represent the most conservative of precautions. An evidence-based review with recommendations by Abiri et al. provides an overview of many of these topics, and identification of deficiencies in the literature (Table 3) [70]. In fact, 10 of the 18 areas reviewed have an aggregate grade of evidence of D (expert opinion). There is a dire need for more evidence in this area, which would aim to not only balance reconstructive success with risks of overly onerous interventions and precautions, but also determine preventative factors that would contribute to improved quality of life (QOL). Though there is no dedicated research on duration of restrictions, most authors have recommended keeping patients off activities such as heavy lifting or strenuous activities for at least 4-6 weeks postoperatively [90]. Creating protocols to guide consultants, trainees, and hospital staff may be helpful in the complex management of patients who have undergone skull base reconstruction. These protocols may be modified based on changing experiences and expansion of the literature base, and may be developed through multidisciplinary discussions.

Sinonasal care

As skull base surgeons achieve consistently favorable resection and reconstructive outcomes, there has been a push towards preserving QOL and minimizing sinonasal morbidity [91]. Saline sprays and irrigations are commonly used in the postoperative setting to cleanse the sinonasal cavity of blood, crusts, hemostatic materials, and other debris in order to restore mucociliary function. Generally, there is likely little risk to the skull base repair with saline sprays given lack of shear stress by the spray fluid. However, saline irrigations, specifically as delivered by forceful squeeze and/or powered devices, pose more of a theoretical risk to the repair, though this is likely mitigated by nasal dressings providing coverage directly over the repair site. Additionally, having saline within the nose can potentially mask a subtle presentation of CSF leak. Most surgeon practices have been based on survey opinion as opposed to rigorous study. There are variations in timing, but most accounts report that saline sprays and rinses are typically initiated within 1-2 days postoperatively, with higher-risk defects (high-flow leak and/or large defects) having a later start date [82,90,92,93].

The role of sinonasal debridements has been well-established for inflammatory disease, and there has also been variation in practices for debridements following skull base surgery. Most debridements entail removal of nasal dressings/packings (i.e., particularly non-dissolvable types), lysis of synechiae, and decrusting of healing, denuded areas. Most procedures generally take place between 1-2 weeks after surgery, with debridement over the repair site taking place later than within the nasal cavity itself [92,93]. The literature on debridements disrupting repair sites is scarce, with a singular case reported from "aggressive debridement" around a suprasellar defect leading to a postoperative CSF leak [94]. There has also been limited evidence on debridements impacting QOL. Specific to endoscopic transsphenoidal surgery, Little et al. found that debridements did not affect QOL, though only 55% of cases treated in this study involved an otolaryngologist [95]. In all likelihood, careful serial debridement is likely beneficial to promote healing of the sinonasal tract and prevent synchaie over time, and may decrease the need for future revision surgery to treat dysfunctional sinuses (estimated at 4-18% based on length of follow up [96,97]).

Special considerations for pediatric patients

Anatomic considerations

The pediatric skull base differs from the adult skull base in several ways (Figure 7) [98]. For the first four years of life the skull base is undergoing rapid growth which then slows down after year four and then spikes again in puberty. The spheno-occipital synchondrosis fuses at age 12 and then ossifies at age 15 [99]. Furthermore, there are differences in the density, slope, and fragility of the skull base and neurovascular structures. Specifically related to anterior skull base, the piriform aperture can be narrow especially in children under seven years old, the distance between the internal carotid arteries can be narrow, and the sphenoid and frontal sinuses have a lack of pneumatization early in life [100]. The sphenoid sinus has typically pneumatized by the age of 10 and the frontal sinuses pneumatizes in puberty [99,101]. Furthermore, in children who have not yet erupted permanent teeth, it is important not to disrupt the undescended roots which have not yet descended from the maxillary complex. Previous concerns regarding extensive sinonasal and septal dissection in young children impacting midface development

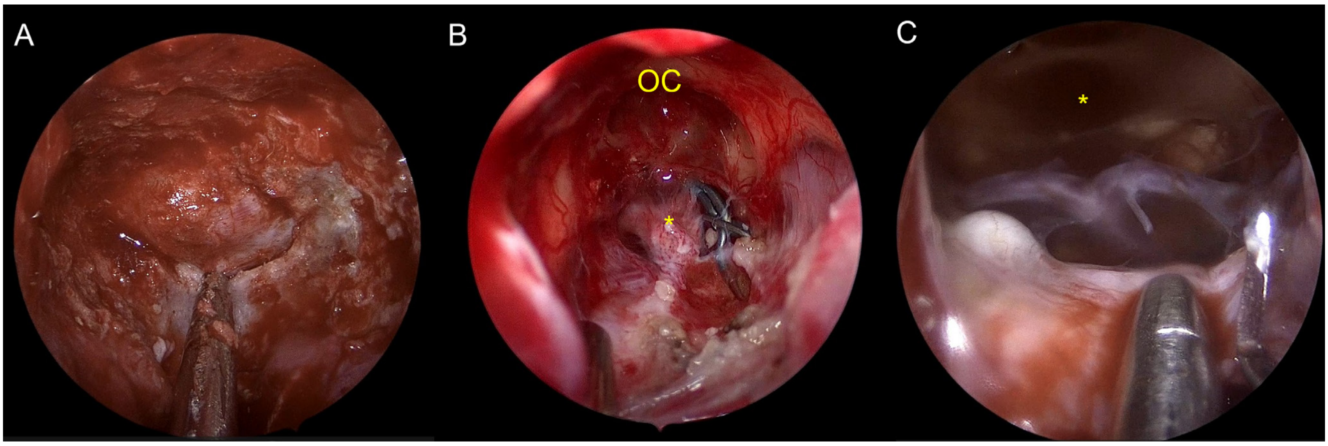

Figure 7. Pediatric craniopharyngioma. (A) Exposure of the suprasellar dura via a transplanum/transtuberculum approach. (B) Dissection within the tumor capsule located in the suprasellar cistern, with preservation of the pituitary stalk (asterisk) and mass-related distortion of the optic chiasm (OC) superiorly. A vascular clip has been placed over a small artery branch off of the left posterior cerebral artery. (C) Final defect in continuity with the third ventricle (asterisk) with clear visualization of the basilar tip, bilateral posterior cerebral arteries, and hypothalamus.

have largely been disproven through longitudinal comparative studies with open approaches. In a retrospective review of 12 patients who underwent skull base resection of tumor and reconstruction with a NSF, no impact on craniofacial growth was noted [(102)]. Another retrospective review compared pediatric patients undergoing endoscopic surgery to open procedures for craniopharyngioma and found no difference in midface growth based on several anatomic measurements over three years of follow up [(103)]. Moreover, a different group compared young pediatric patients (age<7, n=11) to older pediatric patients (age>7, n=33) who underwent endoscopic surgery and found there were no differences in craniofacial development between the two cohorts over an average follow up period of five years [(104)]. The nuances of pediatric sinonasal anatomy can create subtle differences in surgical approaches, resection, and reconstruction techniques. For example, with a narrow piriform aperture, a telescope with a smaller diameter (2.7 mm versus 4 mm) may be used. Additional slimmer instruments such as endoscopic otology instruments may also be used to optimize the space in the working corridor [(105)]. Moreover for transellar, transplanum and transclival approaches, when the sphenoid sinus is not yet pneumatized, this bone must be drilled carefully with the assistance of image guidance to avoid critical neurovascular structures, such as the optic nerve and ICA, and obtain access to the lesion. A recent case series evaluated how lack of sphenoid pneumatization impacts outcomes and found there was no significant impact on surgical outcomes [(106)]. Despite feasibility, one should be prepared for a longer operative time for the approach given the necessity of drilling next to these critical neurovascular structures.

Reconstruction in pediatric patients

Much like in adults, planning the reconstruction incorporates information from preoperative imaging, the size and location of the lesion, surgical approach, and previous history of treatment such as surgery or radiation. Similar to adults, the reconstructive ladder from non-vascularized options (either autologous or non-autologous tissue) to pedicled flaps to multilayer reconstruction all the way to free flaps are possible in the pediatric population. With the smaller size of the pediatric septum, concerns were initially raised regarding the utility of the NSF in pediatric patients when faced with skull base reconstruction. This issue has been further studied in both radiographic studies evaluating anatomical measurements and in small clinical cohorts [(107-109)]. An initial study from 2009 evaluated radiographic anatomical measurements and concluded that for younger patients (> 6 years old), the NSF may not be adequate in length to provide adequate coverage for transsellar defects. Furthermore, they found that in all pediatric patients, the NSF may not be adequate for transclival defects [(107)]. Two separate studies published in 2015 specifically evaluated sellar and planum defects only and concluded that, from a radiographic anatomic perspective [(108)] and in a cohort of 16 patients [(109)], the NSF provided adequate coverage for transsellar and planum defects.

Outcomes in pediatric patients

Pathologies encountered in pediatric skull base surgery are different from and rarer than those encountered in adults. Craniopharyngioma is the most common pathology encountered in pediatric patients, followed by pituitary adenoma [(110,111)]. Aside from these two pathologies, there are several other possibilities which is beyond of the scope of this review [(112)]. With decreased incidence, there is a decreased level of evidence for skull base reconstruction in pediatric patients relative to adults. Nonetheless, several retrospective case studies have been published evaluating outcomes. As with adults, operative technique has shifted from open to endoscopic with a recent study evaluating data from the National Cancer Database from 2004 to 2015 seeing a shift in endoscopic cases from 48% to 65% over the study period [113].

Specifically evaluating postoperative CSF leaks, published incidence in case series range from 0-16% [102,110,111,114,115]. When comparing high-flow leak closure rates between adult and pediatric patients, Papagiannopoulos et al. has reported comparable success rates between pediatric versus adult (3.8% vs 7.5%, p=0.462) cases. When evaluating CSF leaks based on pathology, clival chordoma had the highest rate of postoperative CSF leak at 36%; interestingly, LD use or incidence of postoperative hydrocephalus were not significantly associated with incidence of postoperative CSF leak, although the study population was small (n=15) [114].

Finally, postoperative management in pediatric patients also has special considerations. Postoperative restrictions such as avoiding strenuous activity or Valsalva maneuvers can be difficult in younger or developmentally delayed patients which may necessitate longer bedrest or chemical sedation periods in patients at high risk for postoperative CSF leak. Nasal hygiene practices may also be difficult to adhere to in young children, although previous studies have shown it is possible to get children to use nasal saline consistently [116]. Finally, the pediatric patients may not tolerate postoperative debridement while awake, necessitating the need for debridement in the operating room to prevent synechiae and clean out crusting [117,118].

Future research areas

There remains multiple unanswered questions regarding how to best ensure positive reconstructive outcomes in order to prevent postoperative CSF leak or intracranial infection. The following list covers several of the key questions, though is by no means exhaustive:

- Wound healing of the skull base, including timing of maturation, tissue-tissue and tissue-material interactions, and the role of the inflammatory response
- Precision-based, defect-tailored approaches to selection of reconstructive materials
- The role of support materials and adjuncts such as tissue sealants, nasal packing, and lumbar drainage or combinations thereof
- Optimal timing of relaxing and lifting activity restrictions
- Opportunities to engage both patients, systemic, and physician perspectives to determine the appropriate balance in technical and postoperative factors as so to optimize reconstructive success, QOL, and cost.

Conclusions

Endoscopic skull base surgery follows a paradigm commonly seen with many novel surgical techniques – by pushing the limits of traditional surgical access corridors, though there is overwhelming positive benefit for patients, there is the increased potential for CSF leak and growing recognition of a need to develop systematic and evidence-based algorithms for skull base repair. Though there has been significant progress into understanding and delineating factors and techniques that improve outcomes, much of skull base reconstruction today remains "dealer's choice" given overall low evidence quality. Further research in this area will hopefully guide clinicians towards to incorporate evidence-based practices that management best management of each skull base defect, minimize reconstruction failure, decrease learning curves, and reduce risks to patients.

Abbreviations

ACF: Anterior cranial fossa; BMI: Body-mass index; CPAP: Continuous positive airway pressure; CSF: Cerebrospinal fluid; ICP: Intracranial pressure; IIH: Idiopathic intracranial hypertension; LD: Lumbar drain; MRI: Magnetic resonance imaging; NASBS: North American Skull Base Society; NSF: Nasoseptal flap; OR: Odds ratio; OSA: Obstructive sleep apnea; PCF: Posterior cranial fossa; QOL: Quality of life; RCT: Randomized controlled trial; SIS: Small intestine submucosa.

Authorship contribution

All authors (KMP, MTT, ECK) contributed to conception and design: acquisition of data and images; analysis and interpretation of literature; drafting of the manuscript; critical revision of the manuscript; and final approval.

Conflict of interest

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