Assessment of Abdominal Fat Graft to Repair Anterior Skull Base after Malignant Sinonasal Tumor Extirpation

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Abstract

Objective. Adult abdominal fat, which is known to contain pluripotent stem cells, is frequently used to treat cerebrospinal fluid leak. The aim of this study was to assess the efficacy and reliability of abdominal fat graft to close large skull base defects after extirpation of malignant sinonasal tumors.

Study Design. Case series with chart review performed between 2009 and 2014.

Subjects and Methods. Twenty-nine cases were included of consecutive patients who were suffering from malignant sinonasal tumors, operated by an endoscopic endonasal approach with anterior skull base extirpation and surgically induced cerebrospinal fluid leak. Skull base was repaired by 1 layer of “en bloc” autologous fat graft used as a plug in the onlay position. Epidemiologic data, medical history, defect size, length of hospitalization, and morbidity were analyzed.

Results. Radiotherapy was given pre- and postoperatively in 4 (13.8%) and 23 (79.3%) patients, respectively. Mean defect size was 4.47 ± 2.9 cm² (range, 0.24-9.1 cm²). Mean operative time was 210 ± 86 minutes. Mean length of hospitalization was 8.6 ± 3.7 days and 4.9 ± 2 days in the intensive care unit. No lumbar drain was used in this study. There was 1 case of cerebrospinal fluid leak (3.5%) and 2 cases of meningitis (6.9%), which resolved after medical treatment. Mean follow-up was 17 ± 13 months (range, 3-53 months).

Conclusion. Abdominal fat graft is a safe and reliable material to close the anterior skull base after extirpation of malignant sinonasal tumors.

Keywords

skull base surgery, endoscopic surgery, sinonasal cancer, fat, stem cell

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The endoscopic endonasal approach for the resection of anterior skull base (ASB) tumors is considered the gold standard technique with a lower morbidity than that of transcranial approaches.¹ ² During the last 2 decades, numerous endoscopic procedures to close the ASB defect have been described, but it is difficult to compare them. In a recent literature review of the last 50 years, Harvey et al ³ found 4770 publications, of which 4738 were excluded. The latter were duplicate or irrelevant; did not describe reconstruction; used open reconstruction; lacked original data or were tantamount to a case report; concerned cerebrospinal fluid (CSF) leaks and the repair of small defects; reported cadaver or animal studies; did not clearly demonstrate their outcomes; or included mixed groups of vascular and free flap repairs with outcomes that could not be differentiated. In fact, their meta-analysis included only 32 publications comparing 326 free graft versus 283 vascularized reconstructions and showing statistically better efficacy and reliability with the vascularized flap technique. However, they did not analyze the learning curve, so there may have been an interpretation bias. Seventeen studies concerning free graft reconstruction were published between 2003 and 2010, and 12 studies concerning vascularized reconstruction were published between 2007 and 2010. Over time, surgical teams have increased their experience and quality of closure. Nevertheless, certain unresolved issues remain. How many layers should be used? What is the best position—inlay or onlay? What is the best material? And what is the best association of number of layers and materials?

Unlike in neurosurgery, local flaps cannot be used in many cases by ear/nose/throat surgeons to repair ASB defects after extirpation of malignant sinonasal tumors owing to the risk of nasal mucosal involvement. However, tissue engineering and regenerative medicine approaches provide help for skull base closure. The ideal material should be bioactive, porous, and...
biocompatible and allow a “restituo ad integrum” reconstruction with good mechanical properties to resist the hostile environment of the nasal cavity.

Adult fat is composed of 20% of adipose stem cells (ASCs). Adipose tissue has unique endocrine, paracrine, and autocrine properties and expresses several transcription factors, which underpin their multipotent differentiation potential and proliferation. In vitro, ASCs are able to differentiate fibroblasts, endothelial cells, osteoblasts, and respiratory epithelial cells. In several in vivo animal wound models, it is now widely admitted that ASCs are able to promote epithelialization and vascularization and reduce inflammation. Furthermore, Hedlund showed in vivo that ASB ossification during the early months of life is preceded by a brown adipose tissue invasion, demonstrating that ossification does not occur through an enchondral process. Moreover, surgical experience has shown that adult block fat graft is efficient for closing large defects after acoustic neuroma extirpation and for closing CSF rhinorhea by the endoscopic endonasal approach.

The aim of this study was to assess the efficacy and reliability of 1 layer of abdominal fat graft for closing large ASB defects after extirpation of malignant sinonasal tumors. Our hypothesis was that adult fat, which contains ASCs, is an efficient reliable material for obtaining an immediate and durable water- and air-tight joint.

**Materials and Methods**

**Patients**

A case series with chart review was performed in a tertiary referral center between July 2009 and January 2014. Inclusion criteria were as follows: all consecutive patients suffering from malignant sinonasal tumor, previously operated or not without ASB extirpation, previously treated or not by adjuvant radiotherapy, operated only by an endoscopic endonasal approach with ASB extirpation for the first treatment or recurrence, and where the ASB was repaired with 1 layer of “en bloc” autologous abdominal fat graft to close the ASB defect. All included patients presented an endoscopic resection of the bone, dura mater, and arachnoid membrane in the same area corresponding to the tumor pedicle and safety margins. All tumors were staged by preoperative imaging, including computed tomography (CT) scan and magnetic resonance imaging (MRI; Figure 1A, 1B). TNM classification was based on the seventh edition of the Union of International Cancer Control of head and neck cancers depending on the histological type. Treatment strategy was based on discussion at a multidisciplinary head and neck tumor board meeting. Postoperative CT scan was performed to diagnose postoperative complications according to clinical status and/or before radiotherapy. We systematically measured the size of the defect during the surgical procedure and/or on a postoperative CT scan (Osirix; Pixmeo, Geneva, Switzerland), the total time of surgery (extirpation and reconstruction), intensive care unit and total hospitalization times, positive margins on pathologic outcomes, and adjuvant radiotherapy indication or not. Next, we collected the incidence of peri- and postoperative complications, such as CSF leak, meningitis, confusion, infection, parietal abdominal hematoma, and Draf III stenosis.

The study was approved by the institutional review board of the University Hospital of Bordeaux.

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**Figure 1.** Olfactory neuroblastoma pT4b. Preoperative computed tomography scan (A) and magnetic resonance imaging (C). Postoperative MRI 12 months after surgery + radiotherapy (B, D); fat-lobule inclusions in newly formed skull base are observable (arrow).
Skull Base Defect Measurements

ASB defect measurements were performed on the sagittal plane to the anteroposterior measurement on the midline of the defect and on the coronal and axial planes at 3 different points according to the widest points (Figure 2).

Surgical Technique

All the patients were operated by the same senior surgeon with a strictly endoscopic endonasal approach. Complete resection was performed by a transcribriform approach of the tumor with partial or total ASB full removal. In all cases, ASB extirpation was performed in full thickness by removing the bone and dura mater in the same area. Next, the bone edges of the defect were completely free of the mucosa and made regular by drilling. In the meantime, abdominal fat graft was harvested around the umbilicus. The abdominal incision was closed and a drain set up.

The size of the graft is adapted to fit the defect by overlapping the bone edges by a 1-cm margin. The thickness of the graft should be at least 2 cm to obtain complete immediate air- and water-tightness (Figure 2). Fat is very malleable, so a bulky en bloc graft can be introduced into the nostril. Next, a 3-hand technique is used to position the graft in an onlay position on the ASB (Figure 3A). No material is interposed between the fat and skull base, notably between the edges of the defect and the graft. The surgeon must ensure the correct position of the fat by maintaining the graft with one hand while using the other to fix it with fibrin glue (TISSUCOL; Baxter International Inc, Deerfield, Illinois). Fibrin glue is applied only on the nasal side of the graft. In this way, the effect of gravity is counteracted, and the correct position of the graft can be checked all around the defect before setting up the bolster system to maintain the graft with mild pressure on the roof of the nasal cavity (Figure 3B). Closure is a relatively short step (around 10 to 15 minutes), during which the production of CSF is not sufficient to cause an abundant CSF leak. So the quality of closure is determined by the thickness of the monolayer fat, the excess fat according to the defect size, the control of the correct position of the graft, and the absence of visible CSF leak, notably through the posterior area of closure into a wide cavity without pools of blood and irrigation. Next, the bolster system can be set up. It comprises a SILASTIC sheet placed in arch under the graft and the fibrin glue. Next, 2 to 4 MEROCEL Standard

Figure 2. (A) Sagittal and (B) Coronal postoperative computed tomography scan of adenocarcinoma of olfactory cleft pT4b 5 days after surgery: fat graft size (arrows; L × W × T: 3.9 × 1.8 × 2 cm) and defect size (dotted line; L × W: 2.7 × 1.3 cm).

Figure 3. Surgical views: (A) fat graft placed directly in defect without any other layer and (B) graft fixed by fibrin glue.
Dressings (4.5 cm long; Medtronic Inc, Minneapolis, Minnesota) are placed between the orbits and pillars of the SILASTIC arch to fill the upper part of the nasal fossa. Finally, one 8-cm-long MEROCEL Standard Dressing is placed in each nostril under the upper part of the nasal packing to reinforce the bolster system and prevent fat from moving.

**Peri- and Postoperative Management**

Antibiotic prophylaxis is given during surgery according to the guidelines of the French Anaesthesia Society: cefazolin (2 g, intravenous) administered 30 minutes before skull base opening and repeated every 4 hours during the surgery. Antibiotic prophylaxis is not given after the surgery to avoid masking meningitis. No lumbar drain is used during or after surgery.

All patients stay in the intensive care unit at least 48 hours. During this period, the patient is in the dorsal decubitus position with the head raised 30 degrees. The patient can sit down on the third day and walk on the fourth. The nurse tells the patient to avoid sneezing by adopting Valsalva maneuvers and not to place the head in a sloping position. Intracranial hypertension is prevented by administering acetazolamide (250 mg) twice daily for 5 days and 1 spoonful of glycerol (glycerotone 50%) 3 times a day for 1 month. Sneezing is prevented by administering desloratadine for 5 days, and constipation is avoided with lactulose. Thromboembolic complications are prevented by heparin and contention. Vaccination against pneumococcal infection is given systematically.

During the postoperative period, close neurologic monitoring is performed. Cranial CT scan, followed by lumbar puncture, was systematically performed when meningitis symptoms appeared: fever \(>38.5^\circ\text{C}\), confusion, severe headache, and/or neurologic deficit. Bacterial and aseptic meningitis (meningismus) were defined according to Zarrouk and Fantin\(^{12}\). Meningitis was considered to be of bacterial origin if CSF was positive on direct examination and/or by culture and contained leukocytes \(>100/\text{mm}^3\). It was considered to be inflammatory and aseptic if a CSF sample contained leukocytes \(>100/\text{mm}^3\) and direct examination and culture results were negative after 72 hours.

Nasal packing is removed on day 4 after surgery under local anesthesia. The nasal lavage technique is learned and performed 3 times per day with 240 mL of sea water per lavage for at least 6 weeks. Nasal fibroscopy is performed on the day that the packing is removed, then 7 days and 4 weeks after surgery to detect any CSF leak and perform debridement of the surgical site.

During the healing process, the fat in contact with the tissues is included in the newly formed skull base (around one fifth) as shown in **Figure 1C and 1D**. Simultaneously, the intranasal portion (excess of fat) steadily dehydrates, shrinks, becomes necrotic, falls away, and is removed with nasal lavage 3 to 4 weeks later. The extent of resorption is well visible by comparing the graft volume between **Figures 2** and **Figure 1C and 1D**.

**Results**

Twenty-nine patients were included: 26 men and 3 women, with a mean age of 66 ± 11 years (range, 30-79 years). All patients suffered from a malignant sinonasal tumor: 18 adenocarcinoma of the olfactory cleft (62%), 7 olfactory neuroblastoma (24.1%), 2 adenoid cystic carcinoma (6.9%), 1 rhabdomyosarcoma (3.5%), and 1 squamous cell carcinoma (3.5%). There were 5 T3 (17.2%), 16 T4a (55.2%), and 8 T4b (27.6%).

Twenty-four patients were untreated cases. Four patients were referred to the department to undergo revision surgery for an early tumoral recurrence without prior ASB resection. A second sinonasal tumor 17 years after the first localization was diagnosed in 1 case. Four patients had prior skull base radiotherapy (13.7%).

The defect was measured in 25 of 29 patients. Postoperative imaging was not available in 4 patients. The mean defect size was 4.47 ± 2.9 cm\(^2\) (range, 0.24-9.1 cm\(^2\)).

Mean operative time was 210 ± 86 minutes (range, 70-530 minutes). Mean hospitalization time was 8.5 ± 3.7 days (range, 5-21 days), and intensive care unit stay was 4.9 ± 2 days (range, 3-12 days).

Twenty-three patients (79.3%) had postoperative radiotherapy on the tumor site 5 to 7 weeks after surgery. The mean radiation dose was 59 ± 7.6 Gy. Eight patients (35% of postoperative irradiated patients) received 50 Gy at the tumor site; 10 patients (43%) received 60 Gy; and 5 patients (22%) were given 70 Gy.

The mean follow-up was 17.6 ± 13.1 months, with a median of 11 months (range, 4-53 months).

There was 1 case (3.5%) of postoperative CSF leak in a patient presenting spontaneous rhinorrhea 4 days after surgery that was not confirmed by nasal fibroscopy. Results of the CT scan performed on the day of this episode were normal and did not reveal any pneumocephalus. Beta-2-transferrin marker in the rhinorrhea was positive. Intracranial hypertension was prevented for 48 supplementary hours by maintaining the patient in dorsal decubitus and administering acetazolamide and glycerol. No lumbar drain was used, and revision surgery was not necessary. Rhinorrhea did not recur after initiating the treatment.

Two (6.9%) cases of bacterial meningitis were confirmed by lumbar puncture and were treated successfully by 14 days of antibiotics. Meningitis symptoms appeared on the third day after surgery in 1 patient and on the fourth day in the second—with fever, headache, and confusion in both. Results of the postoperative CT scan were normal for both of them, and neither CSF leak nor rhinorrhea occurred. Three (10.3%) other patients were presented meningismus. Symptoms appeared between 3 and 5 days after surgery: isolated confusion in 1 and fever in the other 2. Results of CT scan, lumbar puncture, and direct bacteriologic examination and culture were all normal. Antibiotics were administered for 48 hours until the result of the CSF analysis was known. All the symptoms abated in all 3 in <48 hours. **Tables 1** and **2** show the specific complications of reconstruction.
One case (3.5%) of nasal bleeding was observed in the perioperative period and was treated under general anesthesia without any recurrence. There was 1 case (3.5%) of periumbilical hematoma that was drained under local anesthesia. Finally, 1 case (3.5%) of Draf III stenosis was diagnosed 10 months after surgery and was successfully treated by endoscopic revision surgery without any recurrence. During the follow-up, postoperative imaging was systematically performed at 3, 6, and 12 months and thereafter once a year. Reconstruction was controlled on postoperative MRI (Figure 1C, 1D) in each patient.

Discussion

ASB reconstruction with autologous en bloc abdominal fat graft after extirpation of a malignant sinonasal tumor is safe and has a low rate of complications. Studies to date have reported a variety of reconstruction procedures covering a wide range of patients, pathologies, and skull base defect localizations.\(^\text{3,13}\) Our study comprised a homogeneous population of patients with malignant sinonasal tumors operated by a transcribriform approach with the same reconstruction technique. Vascular pedicled nasoseptal flap\(^\text{14}\) is at present the most widely used technique.\(^\text{15}\) In our study, olfactory cleft cancer compromised its use because the tumoral pedicle is often located on the nasal septum. In other cases, the nasal septum is often included in the safety margins, so it is partially or totally removed to obtain sufficient oncological margins, thus making it unusable. Finally, the size of the defect cannot always be anticipated before surgery, and the resection of the ASB may make the defect about 10 cm\(^2\) in size, which is too large to be covered by a nasoseptal flap. In 2009, Zanation et al\(^\text{16}\) described the minimally invasive pericranial flap for patients with an unavailable nasal septum. The technique is safe with a low rate of CSF leak,\(^\text{17}\) but it creates a facial scar, needs a specific surgical step for harvesting, and is therefore rarely used.

Abdominal fat graft is a versatile technique that may be used for all sizes and forms of defects. The heterogeneity of the size skull base defects may be explained by the learning curve of this technique, which was used at the start for smaller defects (range, 0.24-4 cm\(^2\) for the first 10 patients) and progressively extended to all sizes of defect (range, 1.6-9.1 cm\(^2\) for the rest of the patients). The largest osteodural defect closed by this technique in our study measured 35 mm in length and 26 mm in width, which corresponds to ASB resection between the 2 orbit roofs in width and between the posterior wall of the frontal sinus and the roof of the sphenoid sinus in length.

CSF leak is the most relevant primary outcome measure to date and reflects the degree of success of the reconstruction. We had 1 case of CSF leak (3.5%) that resolved with medical treatment, a rate comparable to nasoseptal flap reconstructions reported in other studies (ie, 3.1%-5.7%).\(^\text{14,18-20}\) However, previous studies are difficult to compare because they included different indications and skull base areas.\(^\text{13}\) Furthermore, we never used any peri- or postoperative lumbar drain in our study. Its indication during and after endoscopic skull base surgery still requires clarification. Soudry et al suggest its use as a first-line treatment for a persistent postoperative CSF leak,\(^\text{13}\) but its morbidity may be considerable, and the risk/benefit ratio tends to plead against using it.\(^\text{21}\) Our results suggest that peri- or postoperative lumbar drains are not necessary. We believe that medical treatment is efficient for treating mild or moderate postoperative CSF leak if it is well tolerated by the patient without any signs of severity. In our opinion, revision surgery is indicated (1)

### Table 1. Incidence of Complications Related to Defect Size.

<table>
<thead>
<tr>
<th>ASB Resection</th>
<th>Patients (n = 25), n</th>
<th>Mean Defect Size, cm(^2)</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral(^b)</td>
<td>10</td>
<td>1.7 ± 1.3</td>
<td>1 meningitis</td>
</tr>
<tr>
<td>Bilateral(^c)</td>
<td>15</td>
<td>6.3 ± 1.9</td>
<td>1 CSF leak, 1 meningitis</td>
</tr>
</tbody>
</table>

Abbreviations: ASB, anterior skull base; CSF, cerebrospinal fluid.

\(^a\) Defect size was unavailable for 4 patients.

\(^b\) Resection of 1 ethmoid roof and olfactory groove.

\(^c\) With resection of the 2 ethmoid roofs and olfactory groove.

### Table 2. T-Stage, Histologic, and Radiotherapy Status of 3 Patients with Complications.

<table>
<thead>
<tr>
<th>TNM</th>
<th>Patients (n = 29), n</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>T3</td>
<td>5</td>
<td>1 CSF leak</td>
</tr>
<tr>
<td>T4a</td>
<td>16</td>
<td>1 meningitis</td>
</tr>
<tr>
<td>T4b</td>
<td>8</td>
<td>1 meningitis</td>
</tr>
<tr>
<td>Histologic outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative margins</td>
<td>22</td>
<td>1 CSF leak, 1 meningitis</td>
</tr>
<tr>
<td>Positive margins</td>
<td>7</td>
<td>1 meningitis</td>
</tr>
<tr>
<td>Postoperative radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>1 CSF leak, 2 meningitis</td>
</tr>
<tr>
<td>No</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>History of radiotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>No</td>
<td>25</td>
<td>1 CSF leak, 2 meningitis</td>
</tr>
</tbody>
</table>

Abbreviation: CSF, cerebrospinal fluid.

Vascular pedicled nasoseptal flap\(^\text{14}\) is at present the most widely used technique.\(^\text{15}\) In our study, olfactory cleft cancer compromised its use because the tumoral pedicle is often located on the nasal septum. In other cases, the nasal septum is often included in the safety margins, so it is partially or totally removed to obtain sufficient oncological margins, thus making it unusable. Finally, the size of the defect cannot always be anticipated before surgery, and the resection of the ASB may make the defect about 10 cm\(^2\) in size, which is too large to be covered by a nasoseptal flap. In 2009, Zanation et al\(^\text{16}\) described the minimally invasive pericranial flap for patients with an unavailable nasal septum. The technique is safe with a low rate of CSF leak,\(^\text{17}\) but it creates a facial scar, needs a specific surgical step for harvesting, and is therefore rarely used.

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if signs of severity appear and/or (2) if, after 48 hours of medical therapy, failure occurs with persistent CSF leak and/or (3) if significant pneumocephalus on CT scan.

Bacterial meningitis was the main complication in our study, with 2 cases (6.9%) treated successfully by antibiotic therapy. We never used systemic postoperative antibiotic prophylaxis, to avoid masking any sign of meningitis. However, we performed close clinical and neurologic monitoring and CT scan, followed by a lumbar puncture, whenever meningitis symptoms were suspected so that probabilistic antibiotic therapy could be initiated as soon as possible. Harvey et al found no case of meningitis with the pedicled flap technique, but in fact this complication was not systematically reported in all studies analyzed. Yet, 0% to 14% of meningitis cases were reported in a series of free graft reconstructions. Our results are therefore in agreement with the literature despite the lack of data concerning vascularized flap reconstructions.

The ASB is composed of the meninx, bone, and nasal mucosa, which are mesenchymal and ectodermal tissue. ASCs have a high proliferation and differentiation capacity for mesenchymal and ectodermal tissues. In vitro, they are able to perform osteogenic, angiogenic, and epithelial differentiation. This was demonstrated in vivo in animals, and the first case report was published in 2004. Since then, several authors had shown the capacity of ASCs to promote the healing process in human skin ulcers after radiotherapy and in perianal fistulas. However, only a few clinical studies have been undertaken with ASCs, and current knowledge on this subject is restricted to case reports and early phase I or II trials. Therefore, while the ASCs contained in abdominal adult fat graft are probably able to provide all the types of tissue that compose the ASB, their role and their mode of action are still not clearly understood. Of course, other studies are needed to confirm our hypothesis.

Finally, 27 (93.1%) of our patients received radiotherapy either before or after surgery. All irradiated patients could start radiotherapy between 5 and 7 weeks after surgery, according to French Expert Rare Head and Neck Cancer Network guidelines, with a cleaned and healed nasal cavity. Our results suggest that the healing capacity of abdominal fat is not altered by radiotherapy and that it retains its efficiency and reliability in irradiated patients.

Conclusion

Autologous abdominal fat block can be used safely as a monolayer onlay for ASB reconstruction after tumor resection. The technique is efficient and reliable, is easy to perform, and does not increase the operating time.

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Author Contributions

David Fonmarty, acquisition, analysis and interpretation of data, wrote article, revision; Pierre-Louis Bastier, analysis and interpretation of data, revision; Amandine Lechot, acquisition of data, revision; Edouard Gimbert, acquisition of data, revision, approval; Ludovic de Gabory, concept and design, acquisition of data, interpretation of data, revision and approval.

Disclosures

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