

## Free Mucosal Graft for Reconstruction after Nonfunctional Pituitary Adenoma Surgery

### Abstract

**Background:** In the search for an effective closure without nasosinusal morbidity, we have studied the efficacy of free mucosal graft as a reconstructive technique of the sellar floor after the resection of nonfunctioning pituitary adenomas (NFPA). **Methods:** In 100 endonasal endoscopic surgeries, we analyzed the personal history, radiological and intraoperative aspects that could have an impact on the risk of postoperative cerebrospinal fluid (CSF) leak. They were divided into three groups: no mucosa flap/graft, mucosal free graft, and nasoseptal pedicled flap. **Results:** The characteristics of the patients and adenomas were the same in all three groups. Intraoperative CSF leak was observed in 1/13 cases of the group without graft/flap (7%), in 16/50 of the free mucosal graft (32%) and 12/37 (32%) of pedicle flap. The proportion of cases in which other means of reconstruction were used in addition (fat, collagen matrix, and sealant) was similar in the different groups. No CSF leaks were observed, except for a doubtful one in the free mucosal graft group, which resolved spontaneously within 24 h, without receiving any type of treatment. **Conclusions:** The middle turbinate free mucosal graft can be of great value in endonasal surgery: It achieves a hermetic closure in cases of low-flow CSF leaks, it can be useful as a rescue for cases where nasoseptal mucosa is not available to perform a pedicled nasoseptal flap, minimizes the nasosinusal complications of the pedicled flap by leaving a smaller surface area of the nasal cavity devoid of the mucosa, and achieves greater nasosinusal functionality because proper reepithelialization occurs in the area.

**Keywords:** Adenoma, cerebrospinal fluid leak, free mucosal graft, nonfunctioning

### Introduction

Endoscopic endonasal transsphenoidal surgery (EEA) is the most commonly used approach for the treatment of nonfunctioning pituitary adenomas (NFPA), having overcome in recent years to the same approach, but performed under a microscope.<sup>[1]</sup> One of the biggest concerns that this surgery has generated is cerebrospinal fluid (CSF) leaks, which in different publications we have found to be as high as 10%.<sup>[2-4]</sup> The great revolution in endoscopic skull base endoscopic reconstruction would occur in 2006, with the description of the nasoseptal pedicled flap described by Hadad and Bassagasteguy,<sup>[5]</sup> dramatically decreasing CSF fistulas in subsequent series to 0%–2.9%.<sup>[6,7]</sup>

After a phase of the development and use of pedicled flaps, the important morbidity that they produce at the nasal level in the area of obtaining the flap has been

observed: as we leave a large surface of the bare mucosa septum, reepithelialization is very difficult, causing scabs, synechia, nasal discomfort, and even perforations of the nasal septum.<sup>[8,9]</sup>

Although there are congress communications<sup>[10]</sup> and publications regarding the reconstruction of the cranial base with mucosa-free flaps,<sup>[8,11,12]</sup> our work has the peculiarity that it is a homogeneous series, since all cases have the same diagnosis and have been operated by the same surgical team, under the endoscopic route, and hence, it can be useful for neurosurgeons who start in endonasal endoscopy of the skull base.

### Methods

We analyzed a series of 100 NFPA surgeries, operated with an EEA. The study was approved by the Bioethics Committee of the Hospital where the patients were

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treated, and all the patients had given their informed consent for participation in this research study fourteen cases were analyzed prospectively and 86 retrospectively; all of them were operated by the same surgical team, following the same indications, and using the same procedure and protocol in all of them.

Adult patients ( $\geq 18$  years) were included with the diagnosis of suspected NFPA who met at least one of the following criteria: neurological symptomatology, hormonal deficit, adenomas that contacted the optic pathway, or adenomas in which after deciding an expectant treatment, tumor growth was observed during follow-up.

In addition to the epidemiological and follow-up data, the history of previous sinus or sellar surgery or pituitary radiotherapy was studied. All patients underwent magnetic resonance imaging, including 2 mm axial, coronal, and sagittal cuts, in 1.5 or 3T machines. Data obtained preoperatively and postsurgical control between 3 and 6 months were compared. The volume of the lesion was studied at both times (measured in ml with the Brainlab Smartbrush software, except for some initial cases that were done with Slicer 3D,<sup>[13]</sup>) which allowed to accurately measure the degree of resection, which for analysis purposes was divided into gross total resection (100% resection), near-total resection ( $>95\%$ ), subtotal (70%–95%), and partial ( $<70\%$ ). We also measured the maximum size of the lesion in mm, the existence of suprasellar expansion or invasion of the clivus, the degree of invasion of the cavernous sinus through the classification of Knosp,<sup>[14]</sup> and the presence of some nodule in its growth pattern, which could be directed towards frontal or temporal lobes, posterior fossa or third ventricle.

### Surgical intervention

Surgical interventions were performed following these principles in all cases:

- Three/four hands technique by two surgeons, always with the collaboration of ear, nose, and throat
- Use of neuronavigation in reinterventions
- Right middle turbinectomy (occasionally dislocation of the middle turbinate), wide bilateral sphenoidotomy, and removal of 0.5–1 cm from the posterior nasal septum
- Removal of the sellar bone in all cases, including the bone on cavernous sinuses for expanded coronal approaches, and sellar tuberculum/sphenoid planum in the sagittal expanded, depending on the area of tumor extension
- Use of intraoperative Doppler to identify carotid arteries and important vessels when necessary
- Performance of nasoseptal pedicled flap if we anticipated a high risk of intraoperative CSF leak. If it had not been done, it was reconstructed with middle turbinate mucosal free mucosal graft  $\pm$  fat and/or collagen matrix [Figure 1]. A spray sealant was almost always included as the last closure layer

- Placement of two silicone sheets in nostrils that were removed 2 weeks after the surgery
- The patient is recommended to perform nasal washes with physiological saline serum and maintain a relative rest for 4 weeks, avoiding sports, efforts, and blowing his nose. Patients with nocturnal continuous positive airway pressure (CPAP) will also be interrupted for 2–4 weeks
- We analyzed the existence or not of intraoperative CSF leak, extension of the performed approach, and cranial base reconstruction technique (fat, pedicle flap, free flap, collagen matrix, sealant).

The results were analyzed using the statistical package Stata version 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX, USA: StataCorp LP). Statistical significance was determined as  $P < 0.05$ .

### Results

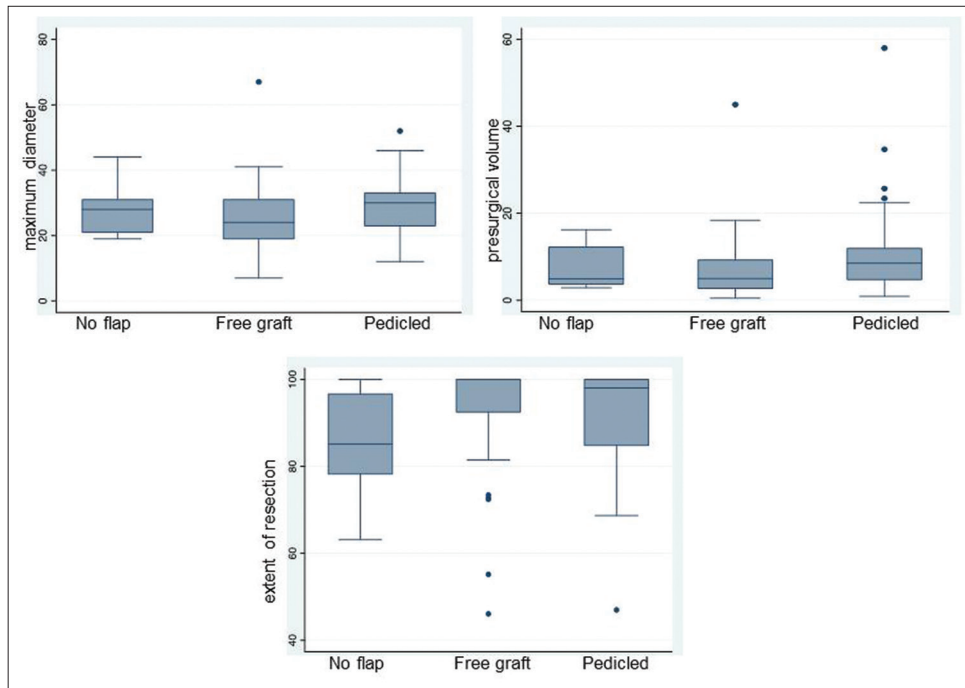
Of the 100 patients included, this was the distribution of the closure technique:

- No mucous reconstruction: Thirteen percent. Most of them correspond to the first cases of the series, before the implantation of the nasosptal pedicled flap, and to some operated cases in which there was no intraoperative CSF leak, which, in order not to injure the nose more, we opted for closure only with synthetic material
- Free mucosal graft: Fifty percent. They include patients of which any phase of the study that it was not possible to obtain a pedicled flap because of previous surgeries and to patients of the final phase in an attempt to be less aggressive, avoiding the nasoseptal pedicled flap
- Nasoseptal pedicled flap: Thirty seven. Although at one middle stage it was done routinely, its use has finally been individualized, and it has been reduced only for those very bulky adenomas with great suprasellar expansion and, therefore, high risk of CSF fistula.

Table 1 and Figure 1 show the personal history that could be related to the adenoma and the radiological findings. We observe that there is no significant difference between the characteristics of the cases of the free graft and pedicle groups, except for a slightly higher incidence of previous surgery in the pedicled flap group, so we assume that the samples are similar.

In relation to CSF leaks, intraoperative CSF output was observed in 29% of cases, and a combination of the following elements was used for reconstruction: fat (35%), dural substitute (43%) and sealant (94), combining them as we see in Table 2. Again, we observe that there were no significant differences between the free graft group and the pedicled group in terms of the means used in the closure or in the range of approaches.

Regarding the intraoperative CSF output, its rate was similar in both groups. Postoperatively, no case of CSF



**Figure 1: Grouping of cases by treatment groups applied in relation to the maximum tumor dimension, tumor volume and degree of resection. We see that the three groups collect cases of similar characteristics**

**Table 1: Preoperative and surgical resection data**

	No flap	Free graft	Pedicled flap	P
Age	54.4±2.7 (40-68)	53.7±2.1 (18-82)	56.3±2.1 (26-84)	0.201
Gender (%)				
Male	10/13 (76.92)	23/50 (46)	22/37 (59.46)	0.108
Female	3/13 (23.08)	27/50 (54)	15/37 (40.54)	
Prior radiotherapy (%)	1/13 (7.69)	1/50 (2)	1/37 (2.7)	0.514
Prior sinus surgery (%)	0/13 (0)	4/50 (8)	2/37 (5.4)	0.858
Prior pituitary surgery (%)	6/13 (46.15)	6/50 (12)	8/37 (21.62)	0.024
Knosp grade (%)				
0-2	4/13 (30.77)	30/50 (60)	21/37 (56.76)	0.174
3-4	9/13 (69.23)	20/50 (40)	16/37 (43.24)	
Suprasellar extension (%)	12/13 (92.31)	40/50 (80)	33/37 (89.19)	0.451
Clival invasion (%)	5/13 (38.46)	14/50 (28)	13/37 (35.13)	0.632
Nodular expansion (%)	2/13 (15.38)	8/50 (16)	9/37 (24.32)	0.677
Ventricle invasion (%)	1/13 (7.69)	1/50 (2)	2/37 (5.4)	0.875
Diameter (mm)	28.1±7.8 (19-44)	25±9.5 (7-67)	30.1±8.9 (12-52)	
<30 (%)	9/13 (69.23)	36/50 (72)	18/37 (48.65)	0.081
≥30 (%)	4/13 (30.77)	14/50 (28)	19/37 (51.35)	
Volume (ml)	7.4±5 (2.8-16.2)	7±7.2 (0.5-45)	11.1±10.7 (1-58)	
<10 (%)	8/13 (61.54)	40/50 (80)	21/37 (56.76)	0.058
≥10 (%)	5/13 (38.46)	10/50 (20)	16/37 (43.24)	
Extent of resection	86±12.6 (63-100)	93.6±11.8 (46-100)	91.1±12.3 (46-100)	
GTR (%)	3/13 (23.08)	28/50 (56)	18/37 (48.65)	0.107
No-GTR (%)	10/13 (76.92)	22/50 (44)	19/37 (41.35)	
Near-total (%)	3/13 (23.08)	7/50 (14)	4/37 (10.8)	
Subtotal (%)	6/13 (46.15)	13/50 (26)	13/37 (35.5)	
Partial (%)	1/13 (7.69)	2/50 (4)	2/37 (5.4)	

The statistical analysis was performed between the free graft group and the pedicled flap group. GTR – Gross total resection

fistula was diagnosed; only in one patient of the free graft group, 10 days after surgery, there was a doubtful CSF

leak that would not be confirmed. Given this suspicion, the patient was kept under hospital observation for 24 h,

**Table 2: Intraoperative aspects related to the extension of the approach, and reconstruction techniques used**

	No flap	Free graft	Pedicled flap	P
Sagittal expanded	2/13 (15.38)	13/50 (26)	9/37 (24.32)	0.850
Coronal expanded	3/13 (23.08)	12/50 (24)	7/37 (18.92)	0.795
Fat graft	2/13 (15.38)	18/50 (36)	15/37 (40.54)	0.266
Collagen dural graft	3/13 (23.08)	21/50 (42)	19/37 (51.35)	0.204
Sealant	8/13 (61.64)	50/50 (100)	36/37 (97.29)	0.425
Intraoperative CSF leak	1/13 (7.69)	16/50 (32)	12/37 (32.43)	0.192
Postoperative CSF leak	0/13 (0)	1/50 (2)	0/37 (0)	0.610

The statistical analysis was performed between the free graft group and the pedicled flap group. CSF – Cerebrospinal fluid

without any treatment, and at no time CSF was observed, and hence, we suspect it was not a true CSF leak.

As for other types of complications that could be related to the type of mucous reconstruction, there were four cases of sinusitis throughout the series, two in the pedicled flap group and two in the free mucosa group. There were five cases of epistaxis (one in the group without flap and two in each of the groups with it), and as a common factor, all of them had been under treatment with antiplatelet agents or anticoagulants, so special attention should be paid to nasal hemostasis in these patients, regardless of the type of reconstruction used.

## Discussion

The main objective of the reconstruction of the cranial base after the removal of an NFPA is to prevent CSF leak while maintaining good sinus health. The most reliable reconstructive technique to achieve this objective is the nasoseptal pedicled flap, but since it greatly alters the nasal anatomy leaving it devoid of mucosa in much of the septum, different solutions have been sought, from trying to rebuild the donor area to the use of mucosa-free grafts,<sup>[15]</sup> passing through other less physiological without mucosa<sup>[2,6,7,16]</sup> such as fat, oxidized cellulose, collagen matrix or even not rebuild, and the use of free flaps for the reconstruction of the cranial base.<sup>[8,11,12]</sup>

The key to minimizing the risk of CSF leak is to adapt our reconstruction to each case. In general, if we believe that there will be an important outflow of CSF, a nasoseptal pedicled flap is planned to be input, and in the surgical bed, we place fat (sometimes with collagen matrix) that we cover with the obtained flap. If we do not anticipate significant CSF output, a pedicled flap is not designed, and a middle turbinate free mucosal graft will be placed. If there has been an outflow of CSF, we will also place fat and/or collagen matrix below the free mucosa. Thus, before placing the mucous flap, we will have reduced a part of the CSF flow, with which the flap will heal more easily. Currently, in all cases, after one type or another of flap, we apply a pulverized sealant. It should be taken into account that this series includes patients operated for years, and today we design a rescue flap for doubtful cases, and we are avoiding the right middle turbinectomy whenever possible.

Therefore, since the main objective of the reconstruction is to eliminate the risk of postoperative CSF fistula, we need to plan preoperatively according to the risk of intraoperative CSF leakage:

- Minimum risk: Conventional approach without pedicle flap
- Moderate risk: Rescue flap design (that could be turned into a pedicled flap)
- High risk: Obtaining a nasoseptal pedicle flap.

To measure the severity of intraoperative CSF fistula, we used the classification described by Esposito *et al.* [Table 3].<sup>[17]</sup> This classification will help us stratify the risk level of postoperative fistula, and thus, we will adapt the reconstruction to that risk.

Therefore, our closure strategy will depend on the prediction of CSF output performed preoperatively and on the degree of CSF output in the surgical field, for which the following protocol is usually used<sup>[18]</sup> [Figure 2].

Even though in 32% of cases of intraoperative CSF leak in the free mucosal graft group, there were no postoperative leakage, which supports the data from recent studies of Scagnelli<sup>[11]</sup> and Kuan,<sup>[19]</sup> where it is concluded that in cases with intraoperative high flow CSF leaks, as happens after resection intradural lesions (meningiomas, craniopharyngiomas.), the cranial base must be reconstructed with pedicled flaps, while in cases of low flow CSF leaks, such as those that occur after resection of pituitary adenomas, a free mucosal graft is sufficient after reducing the dead space existing in the tumor cavity with fat or collagen matrix.

We want to insist on some technical details for reconstruction with mucosa, especially in free flaps, and since they are not vascularized, they are more sensitive to any error in their implantation: the size must exceed the area of the defect to be closed (several millimeters must be supported on the hard mother whenever it exists; if this is not the case, they must do it on the mucous-free bone), and of course, do not make the mistake of placing the flap upside down; that is, the face of the mucus-producing cells must be the one that does not rest on the bone or dura mater. To avoid this mistake, it is useful to place a sheet of oxidized cellulose (Surgicel) on one of the sides of the flap

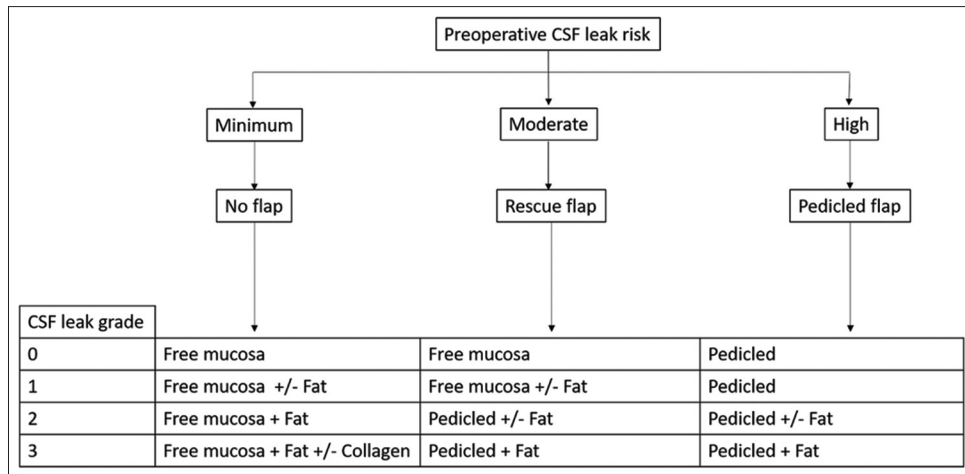


Figure 2: Algorithm for the management of the cerebrospinal fluid leak including the free mucosal graft

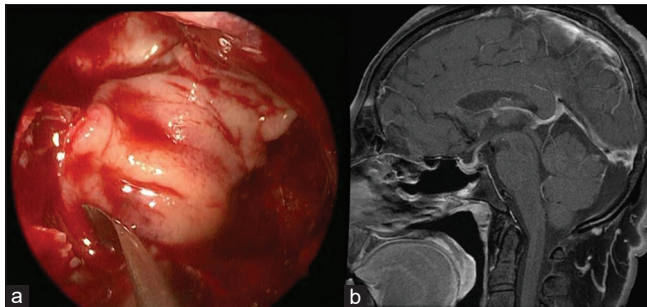


Figure 3: (a) Placing the free mucosal graft. It is easy to get a wide piece that covers a lot of surface and has a thickness that makes it resistant (b) Sagittal magnetic resonance image showing the closure of the cranial base with free mucosa, 6 months after resection of a nonfunctioning pituitary adenoma

to avoid doubts at the final moment of the placement of the flap [Figure 3].

Regarding other measures to take into account, we believe that the use of silicone sheets in the nostrils is important, with the aim of reducing the risk of synechiae, and doing nasal washes with physiological saline. In those cases that intraoperative CSF output has been observed, we recommend that patients maintain relative rest for 4 weeks, avoiding sports, efforts, and blowing their nose. Patients who use nocturnal CPAP will interrupt it for 2–4 weeks.

### Conclusions

It is very important to be flexible in terms of the reconstruction technique used and individualize each case to create only the necessary nasal morbidity that allows us to safely remove the adenoma, and perform a reconstruction of the sellar floor with the lowest risk of CSF fistula. Within this individualized management, the free mucosa graft has an excellent result avoiding CSF fistulas and maintaining nasosinus health, so it must be included among the tools that can be used in the reconstruction of the cranial base.

Table 3: Cerebrospinal fluid leak grading system

Grade	Description of leak
0	Absence of cerebrospinal fluid leak
1	Small leak without obvious or with only small diaphragmatic defect
2	Moderate cerebrospinal fluid leak, with obvious diaphragmatic defect
3	Large cerebrospinal fluid leak, typically created as part of extended transsphenoidal approach through the supradiaphragmatic or clival dura for tumor access

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### Conflicts of interest

There are no conflicts of interest.

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