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The outcome of intraoperative cerebrospinal fluid leak after transsphenoidal resection of sellar neoplasms: technique of closure

Dissertation zur Erlangung des Grades eines Doktors der Medizin der Medizinischen Fakultät der Universität des Saarlandes 2024

vorgelegt von

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Abstract

Background: The endonasal transsphenoidal endoscopic surgery has become the standard technique for the resection of pathologies of the sellar region due to its effectiveness and low complication rates. However, there are still some complications associated with this approach such as cerebrospinal fluid (CSF) leak, meningitis, bleeding and more. Closure of the sellar floor after transsphenoidal endoscopic surgery is an extremely important step in order to avoid postoperative CSF leaks. Many closure techniques have been proposed to reduce the rate of postoperative CSF leaks. The vascular nasoseptal pedicled flap has shown the best postoperative outcome. However, this technique requires time and experience. Another aspect in avoiding postoperative CSF leaks is the use of lumbar drains, but its efficacy remains controversial.

Objectives: In this study I evaluated the outcome and efficacy of a multilayer closure technique of the sellar floor after transsphenoidal endoscopic approaches for sellar pathologies in correlation to the intraoperative grading of CSF leak and in correlation to the usage and possible benefit of a lumbar drain postoperatively.

Methods: I reviewed retrospectively 280 patients who underwent endonasal transsphenoidal endoscopic surgery for pathologies in the sellar region from January 2011 to April 2020 in our hospital. Among them, 87 patients had an intraoperative CSF leak and were included in this study. The outcome was evaluated based on postoperative complications and development of postoperative CSF leak in correlation to the used closure material of dural and skull base reconstruction and use of lumbar drainage. Their association with the intraoperative CSF leak grade, underlying pathology and the demographics of the patients were analyzed as well.

Results: From the 87 patients, there was a total of 54 women (62%) and 33 men (38%). The mean age was 56.3 $\pm$ 14.8. The most frequent histological diagnosis was non-secreting adenoma in 40 cases (45%), followed by the secreting adenomas with 16 cases (18%). Eight cases of meningioma (9%), six cases of Rathke’s cleft cyst (7%), six cases of craniopharyngioma (7%), four cases of colloid cysts (4%), four chordomas (4%) were observed. The intraoperative CSF grading was based on the classification by Esposito. Of the 87 patients with postoperative CSF leak, 20 cases were classified as grade 1, 37 cases as grade 2 and 30 cases as grade 3. The materials commonly used for the closure of grade 1 CSF leaks were primarily sealant sponge Tachosil ® (70%), followed by dura sealant patch (55%) and bone (55%). For the grade 2 CSF leaks, Tachosil ® (78%), bone (57%) and autologous fat (54%). In the grade 3 CSF leaks, the combination of lumbar drains (90%), autologous fat (87%) and fascia lata (60%) were mainly used. Only nine patients developed a new postoperative CSF leak, and were treated conservatively with lumbar drains, but only three of them were discontinued by this method. The remaining six patients with persistent postoperative CSF leak underwent revision surgery.

Conclusions: The analysed multilayer closure technique for the transsphenoidal surgery has been shown to be safe. My study shows a lower intraoperative CSF leak rate compared to other studies , a similar rate of postoperative CSF leak (3.1% vs 3.9%) compared to the pedicled vascular flap and other

techniques in literature. The presented study shows the effectiveness of our closure techniques including the intraoperative lumbar drain in different CSF grades. If a postoperative CSF leak appears, the use of lumbar drains to treat it has a poor benefit. In this scenario, once a postoperative CSF leak occurs, it is better to take a decision with direct revision surgery to perform a definitive closure.

Zusammenfassung

Hintergrund: Die endonasale transsphenoidale endoskopische Chirurgie hat sich als Standard für die Resektion der sellären Pathologien etabliert. Komplikationen wie z.B. Liquorfistel, Meningitis, Nachblutungen sind zwar gering aber dennoch mit dieser Technik verbunden. Der suffiziente Verschluss der Dura und des Sellabodens ist der entscheidende Schritt um, postoperative Liquorfisteln zu vermeiden. Die nasoseptale Flap-Technik zeigte bislang die besten Ergebnisse in der Literatur, erfordert jedoch Zeit und Erfahrung. Die Verwendung von Lumbaldrainagen zur Vermeidung bzw. Therapie postoperativer Liquorleck ist in der Literatur kontrovers diskutiert.

Ziel: Ich analysierte die Effektivität der genutzten mehrschichtigen Verschlusstechnik des Sellabodens und der Dura. Die postoperativen Ergebnisse wurden in Abhängigkeit von der intraoperativen Einstufung von Liquorleck und in Korrelation zu den verwandten Verschlussmaterialien sowie der Anwendung einer Lumbaldrainage untersucht.

Methoden: In einer retrospektiven Analyse wurden 280 Patienten untersucht, die sich zwischen Januar 2011 und April 2020 bei sellären Pathologien einer transnasalen transsphenoidalen endoskopischen Operation in unserer Klinik unterzogen. 87 davon wiesen ein intraoperatives Liquorleck auf und wurden in diese Studie eingeschlossen. Die Analysekriterien für das Outcome waren postoperative Komplikationen, Gradierung des intraoperativen Liquorlecks und neue postoperative neue Liquorfisteln. Dies wurde in Bezug zu der operativen Verschlusstechnik, Anlage einer lumbalen Drainage sowie Demografie der Patienten und Histopathologie analysiert.

Ergebnisse: Vierundfünfzig Patienten (62%) waren weiblich und 33 (38%) männlich. Das Durchschnittsalter betrug 56,3 ・ 14.8 Jahre. Die häufigste histopathologische Diagnose war das hormoninaktive Adenom in 40 Fällen (45%), gefolgt von sezernierenden Adenomen in 16 Fällen (18%). Des Weiteren wurden 8 Fälle von Meningeomen (9%), 6 Fälle von Rathke-Tasche Zysten (7 %), 6 Fälle von Kraniopharyngeomen (7%), 4 Fälle von Kolloidzysten (4%), 4 Chordome (4%) diagnostiziert. Von den 87 Patienten mit intraoperativem Liquorleck wurden 20 Fälle als Grad 1, 37 Fälle als Grad 2 und 30 Fälle als Grad 3 eingestuft. Die üblicherweise, zum Verschluss eines Liquorleck Grad 1 verwendeten Materialien, waren in erster Linie Tachosil (70%), Dura-Ersatz (55%) und autologer Knochen (55%). Im Fall von einem Liquorleck Grad 2 wurden Tachosil (78%), autologer Knochen (57%) und autologes Fett (54%) genutzt. Bei einem Liquorleck Grad 3 wurde eine Kombination von Lumbaldrainage (90%), autologem Fettgewebe (87%) und Faszie (60%) am häufigsten verwendet. Nur 9 (7.8%) Patienten entwickelten eine neue postoperative Liquorfistel und wurden primär konservativ mit Lumbaldrainage behandelt. Aber nur in drei (2.6%) Fällen war die Behandlung erfolgreich. Die verbleibenden sechs (5.2%) Patienten mit persistierender postoperativer Liquorfistel wurden mit einer Revisionsoperation und erneutem Verschluss therapiert.

Schlussfolgerung: Die untersuchte mehrschichtige Verschlusstechnik der Sellaregion erwies sich als sicher. Die Studie zeigt eine deutlich geringere intraoperative Liquorfistelrate im Vergleich zu anderen Studien (31 % vs. 56,6 %). Die Rate von neuen postoperativen Liquorfisteln nach der beschriebenen

mehrschichtigen Verschlusstechnik war geringfügig geringer als bei nasoseptalen Flaps (3,1 % vs. 3,9 %). Die Effektivität einer lumbalen Dauerdrainage bei postoperativ neu aufgetretener Liquorfistel ist begrenzt. Deshalb sollte im Falle einer neu auftretenden postoperative Liquorfistel direkt eine chirurgische Revision als Therapie erfolgen.

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1. Introduction

1.1.1 Anatomy of the sellar region and the pituitary gland

The pituitary gland, or also called hypophysis, is a small organ, has the size and shape of a bean, measures around 13 mm transversely, 10mm antero-posterior, 6mm vertically, and weights 600 mg on average [29]. It is located on the hypophyseal fossa, a structure of the sphenoid bone, that belongs to the middle cranial fossa and is surrounded by the sella turcica. The anterior and posterior clinoid processes of the sphenoid bone delimit the boundaries of the sella turcica. The hypophyseal fossa is bordered laterally by the cavernous sinus and within the cranial nerves: III (oculomotor), IV (trochlear), V_1 (ophthalmic division of trigeminal nerve) and VI (abducens).

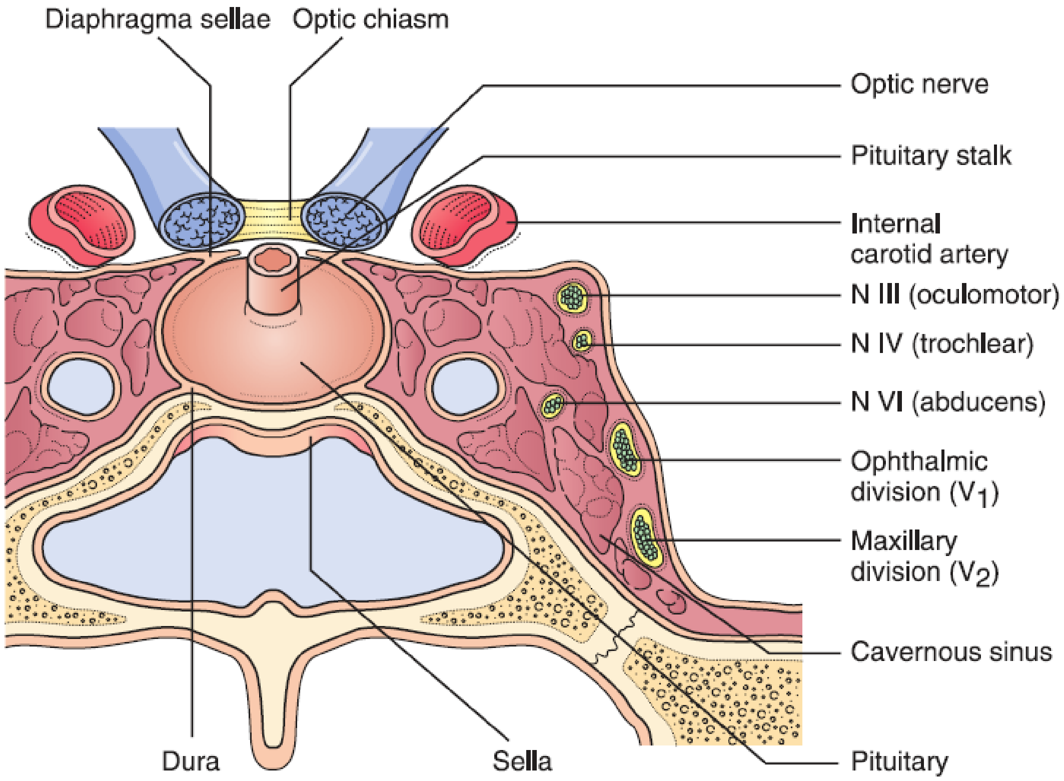

Figure 1. Coronal section through the sella turcica and pituitary gland. (from Ellenbogen, R., Principles of neurological surgery, 4th Edition, Chapter 44).

The pituitary gland is separated by two layers of dura mater [40, 88]. The sella turcica is covered by a dural fold called diaphragma sellae, which constitutes the roof and divides the intradural and extradural spaces of the pituitary fossa [63]. Superior to the sellae is the optic chiasm. Dorsal to the sella turcica is the brainstem, specifically the midbrain and the basilar artery.

The sella turcica is related to other important structures, including the internal carotid arteries (segment C3, C4 and C5), the III, IV, V_1, V_2 und VI cranial nerves, the cavernous sinus and the optic chiasm [92] (Figure 1).

The pituitary gland is composed of two morphological and functional distinct structures: the anterior lobe, also called adenohypophysis, and the posterior lobe, called the neurohypophysis. The adenohypophysis occupies around 80% of the gland and comprises three structures: the pars distalis, pars intermedia and pars tuberalis, whereas the neurohypophysis consists of the infundibulum, the pituitary stalk and the posterior lobe [4] (Figure 2).

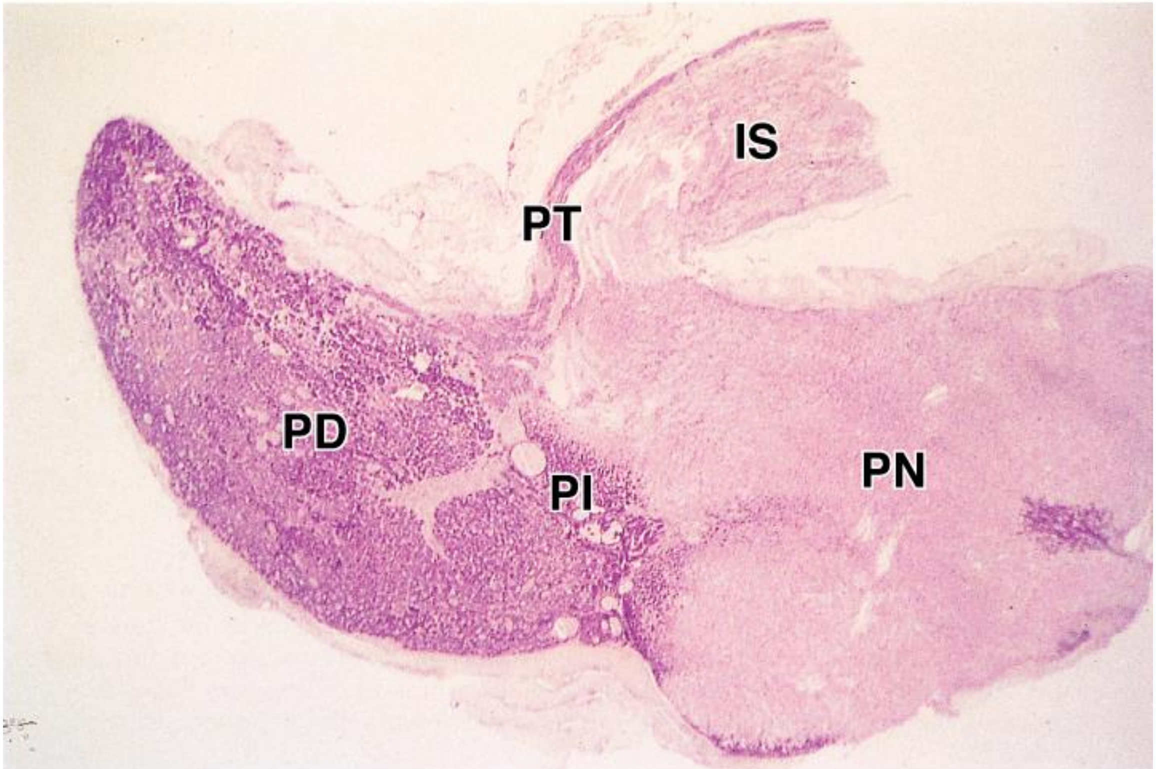

Figure 2. Histological sagittal section of the pituitary gland (Hematoxylin and eosin, x 30) showing the different structures (PD: Pars distalis, PT: Pars tuberalis, PI: Pars intermedia, IS: Pituitary stalk, PN: Pars nervosa; from https://basicmedicalkey.com/endocrine-glands-2/).

The pituitary gland receives blood supply from the superior and inferior hypophyseal arteries, which are both branches from the internal carotid artery, specifically from the ophthalmic segment (C6) and cavernous segment (C4) respectively [35]. The superior hypophyseal artery supplies the pars tuberalis, the infundibulum and the median eminence [64]. The inferior hypophyseal artery irrigates the neurohypophysis.

The venous drainage of the pituitary gland is made to the cavernous sinus.

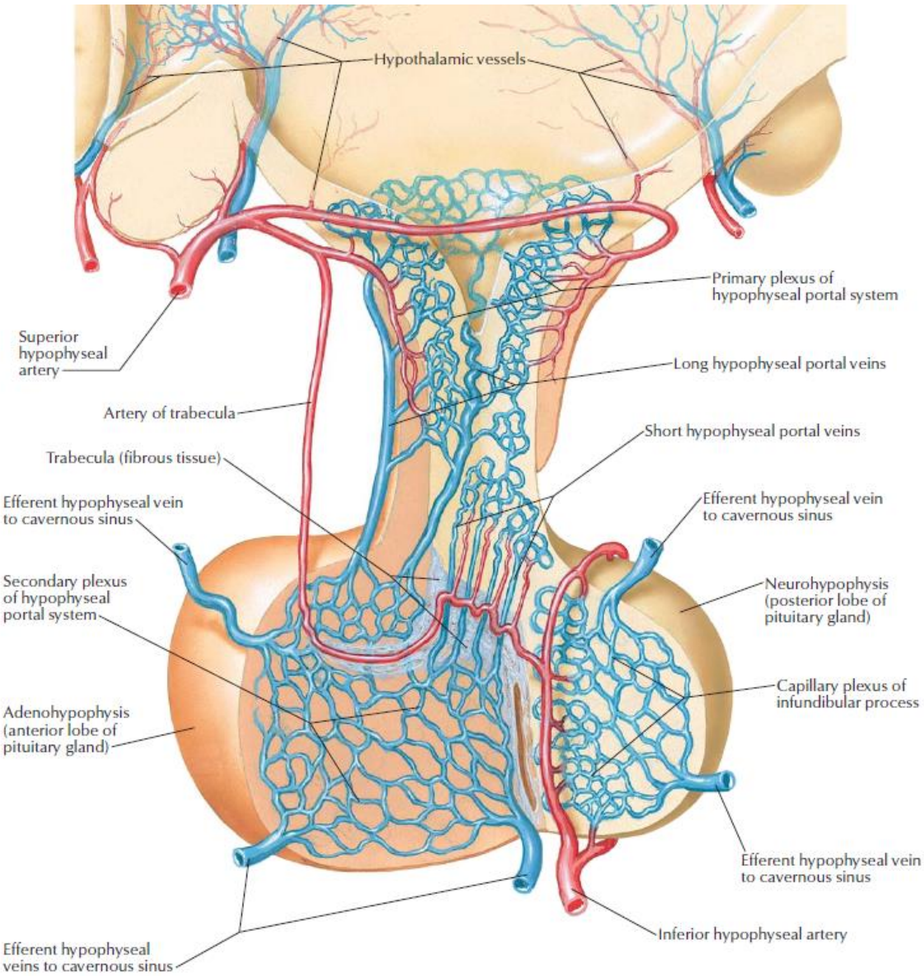

Figure 3: Arteries and veins of the hypothalamus and hypophysis (from Netter: Atlas of Human Anatomy, 6th edition).

The central nervous system (CNS) involves three germinal layers: ectoderm, mesoderm and endoderm. The ectoderm is the initiator in the development of the CNS. It develops into the neural ectoderm and the surface ectoderm. The neural ectoderm further differentiates into the neural tube and neural crest, developing later into the brain, spinal cord and peripheral nerves. The surface ectoderm forms eventually the epidermis, nails and hair.

The adenohypophysis and neurohypophysis are derived embryologically from distinct tissues [53]. The adenohypophysis is derived from the Rathke´s pouch, an endodermal invagination from the fetal primitive oral cavity (stomodeum), formed around the fourth and fifth weeks of gestation [90].

By the sixth week of gestation, the connection between oropharynx and Rathke´s pouch is completely obliterated, the Rathke´s pouch becomes a separate structure and migrates dorsally, establishing contact with the downward extension of the hypothalamus, which gives origin to the infundibulum and pars nervosa [5]. This explains the epithelial origin of the cells of the adenohypophysis while the neurohypophysis has a glial cell origin (Figure 4).

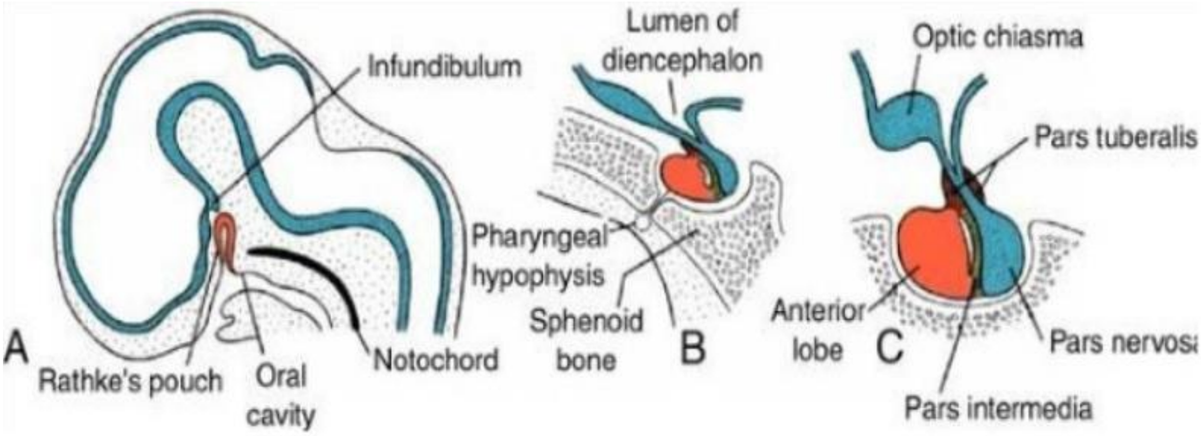

Figure 4. Development of the pituitary gland. A) Sagittal cut at the 6th week of development, B) 11th week of development, C)16th week of development. (From Langman medical embryology, 11th Edition).

By the seventh week, the sella turcica is formed [5]. The pituitary portal system begins to develop around the seventh week of gestation, and by the twelfth week the adenohypophysis is well vascularized [87].

1.1.2 Anatomy of the related structures in endonasal transsphenoidal approach to the pituitary pathology

Subcranial relationships

A surgical approach to the pituitary gland demands a good knowledge of the anatomical relationships of the sellar region. The most common access to this region is the transnasal transsphenoidal route.

The nasal cavity is located below the anterior cranial fossa and above the buccal cavity. Its roof is formed by the frontal, ethmoid and sphenoid bones. The floor is formed by the maxillary and palatine bones. The anterior opening is formed by the nostrils and posteriorly continues with the nasopharynx. The nasal cavity is divided in the middle by the nasal septum, which is a structure formed by the perpendicular plate of the ethmoid and the vomer bone. The walls of the nasal cavity are formed by the sphenoid, ethmoid, maxillary, lacrimal and palatine bones. In the lateral surface, the nasal cavity has the superior and middle concha, part of the ethmoid bone, and the inferior concha, an independent bone [89]. The sphenoid ostium is located posterosuperior to the superior concha and anterior to the body of sphenoid bone, providing communication between the nasal cavity and sphenoid bone [89] and making it an important landmark in the transsphenoidal approach [36] (Figure 5).

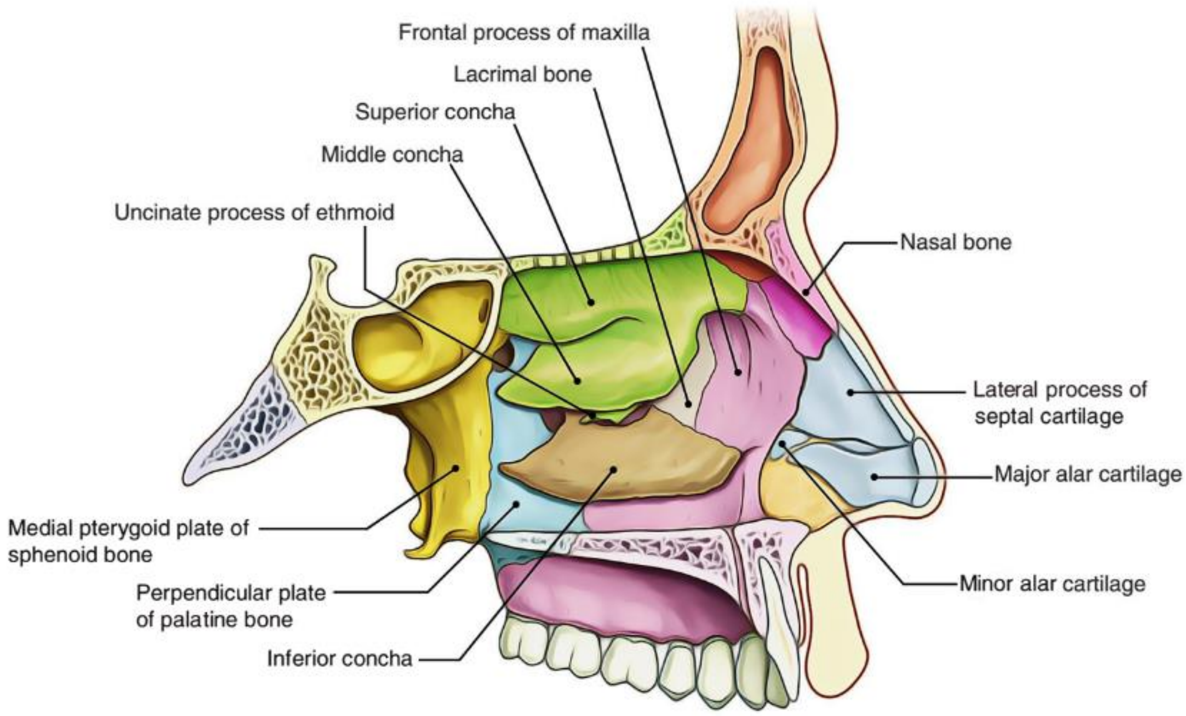

Figure 5. Anatomy of the nasal cavity (from https://www.earthslab.com/anatomy/nasal-cavity/).

The sphenoid bone is located in the center of the skull base and forms part of the middle cranial fossa. It is formed of the body, great wings and lesser wings. The sphenoid sinus is in the body of the sphenoid bone. The sphenoid sinus is divided in the middle by a sphenoid septum and its posterior wall constitutes the floor of the sella turcica [34].

The sphenoid ostium, located in the sphenoethmoid recess, in the anterosuperior part of the sphenoid body and posterosuperior to the superior concha, provides communication between the nasal cavity and sphenoid sinus [89] and makes an important landmark in the transsphenoidal approach [36] (Figure 6).

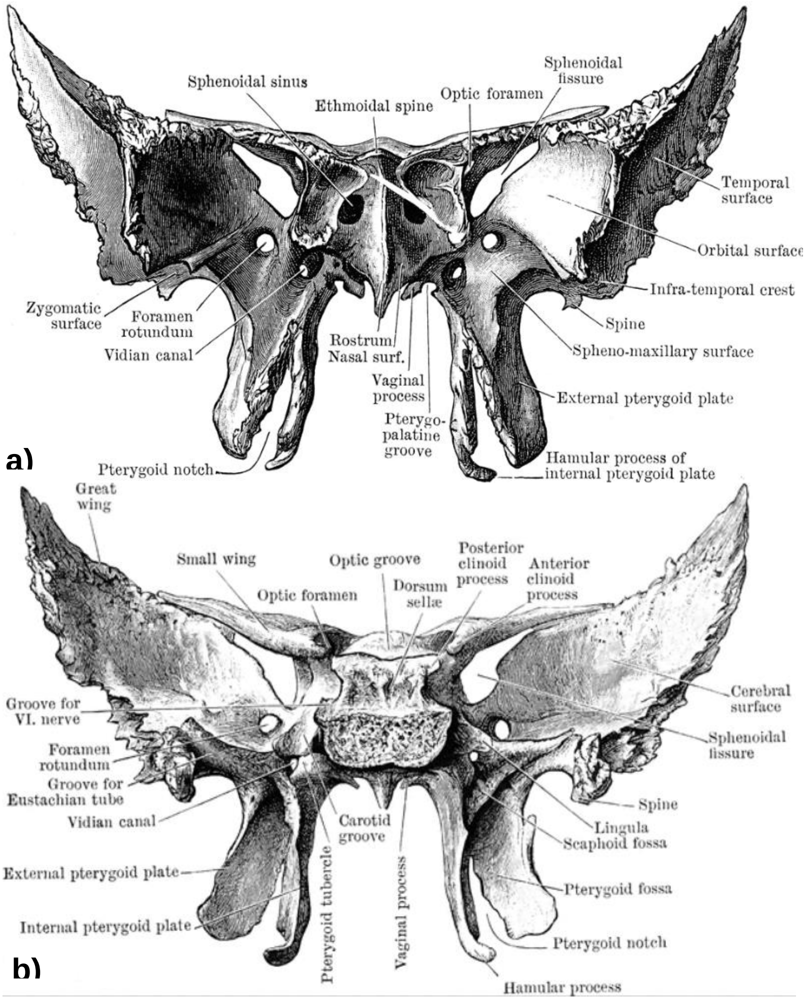

Figure 6. Anatomy of the sphenoid bone. a) Anterior view. b) Posterior view. (From https://etc.usf.edu/clipart/54600/54635/54635_sphenoid.htm).

The sphenoid bone has important arterial and venous relationships. The carotid groove located in the lateral wall of the sphenoid sinus lodges in the cavernous segment of the internal carotid artery and the cavernous sinus. The basilar artery is located on the posterior surface of the sphenoid bone [89].

1.1.3 Physiology of the hypothalamic-pituitary system

The hypothalamic-pituitary axis represents an important part of the endocrine system. The hypothalamus produces and secretes releasing factors: corticotrophin release hormone (CRH), thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone (GHRH) and dopamine. These hormones act in the pituitary gland, specifically the adenohypophysis and lead to the secretion of pituitary hormones. The adenohypophysis produces six different important peptidic hormones: growth hormone (GH), adrenocorticotropin hormone (ACTH), thyroid stimulating hormone (TSH), prolactin, luteinizing hormone (LH) and follicle-stimulating hormone (FSH); while the neurohypophysis synthesizes vasopressin and oxytocin. The hormones produced in the adenohypophysis participate in the control of the metabolic functions in the whole organism [62].

The function of the hormones is included in three main groups: growth, maintenance of homeostasis and reproduction. These hormones have specific targets in peripheric organs: adrenal gland, thyroid gland, liver, and sexual organs [62]. The peripheric organ hormones have a feedback mechanism to regulate the pituitary gland and the hypothalamus (Figure 7).

This axis has a special vascular system called the hypophyseal portal system. This portal system transports the hormones from the hypothalamus to the adenohypophysis and consists of two capillary networks. The hypophyseal portal system is formed by two capillary beds: the primary capillary plexus, which originates from the superior hypophyseal arteries (branch of the supraclinoid internal carotid artery), and the secondary capillary plexus, formed from the inferior hypophyseal arteries (branch of the cavernous internal carotid artery meningeohypophyseal trunk) [89]. The primary capillary plexus is located in the median eminence of the hypothalamus, and the secondary capillary plexus is located in the adenohypophysis [89, 40].

The hormones formed in the hypothalamus are released and reach the primary capillary plexus. Then, they travel to the secondary capillary plexus through the hypophyseal portal veins (Figure 3). The capillary plexus from the portal system consists of fenestrated sinusoid capillaries, facilitating the quick hormone transport. [66].

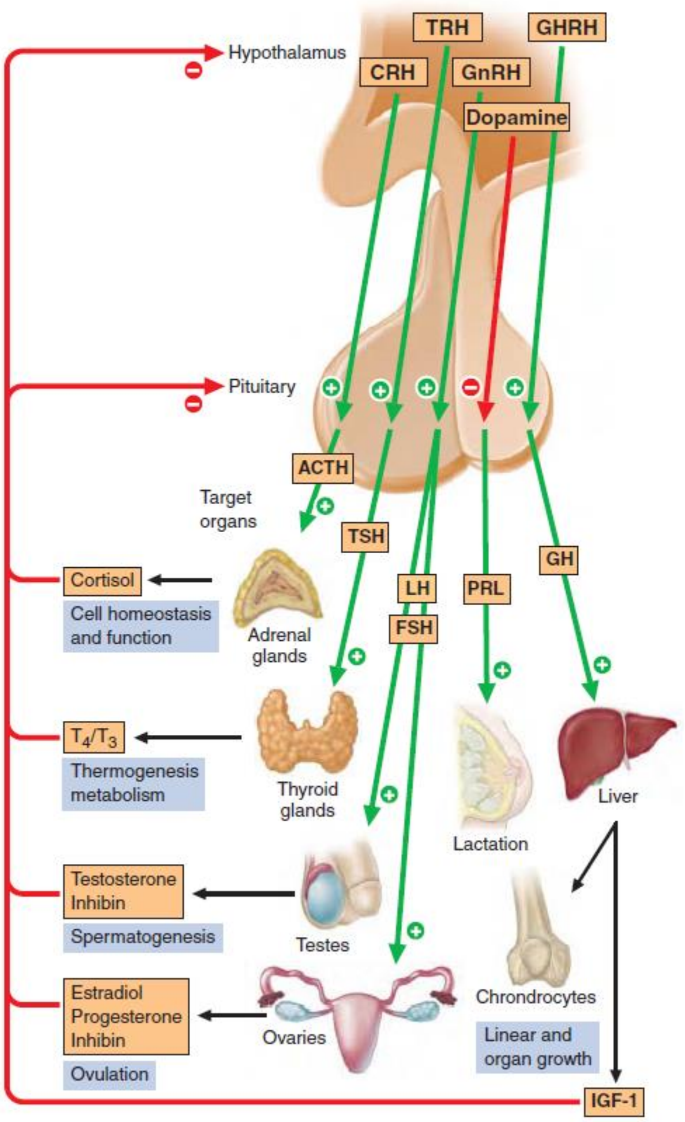

Figure 7. Pituitary axis: View of the hypothalamic-hypophyseal-end organ axis and its feedback mechanism (from Harrison´s principles of internal medicine, 17th edition).

1.2. Pituitary pathologies

Sellar pathologies involve tumors of the pituitary gland, such as pituitary adenomas or craniopharyngiomas, nontumor pathologies, such as pituitary apoplexy or hypophysitis, and pathologies of the surrounding structures, such as meningioma, Rathke cleft-cyst, and glioma.

1.2.1. Pituitary adenoma

Pituitary tumors represent from 10% to 18% of the intracranial tumors [20, 82]. The most common pituitary pathology is the pituitary adenoma. According, to the Central Brain Tumor Registry of the United States (CBTRUS) from 2018, the pituitary adenomas have an incidence of 4,36 per 100 000 people and are more common in women [82]. The median of age at diagnosis is 51 years [82].

Pituitary adenomas can be classified in many ways. Based on their dimensions, the pituitary adenomas are classified into: microadenomas (≤1cm), and macroadenomas (>1cm). They are also classified according to their functional status and hormonal activity in endocrine-inactive pituitary adenomas (nonfunctioning or silent) and endocrine-active pituitary adenomas. Endocrine-active adenomas are further subclassified according to the hormones they produce.

The most common pituitary adenoma is the prolactinoma with a prevalence of 76 to 116 cases per 100,000 population [22, 107]. This is followed by the hormone inactive pituitary adenomas, GH-secreting adenomas, ACTH-secreting adenomas, and TSH-secreting adenomas respectively [22, 13].

Pituitary incidentalomas are lesions found fortuitously for reasons unrelated to pituitary disease [19]. Autopsy studies have shown that incidentalomas have been observed in 10% of the autopsies [67]. Image studies using computed tomography and magnetic resonance imaging revealed that 20% of normal pituitary glands show an incidental lesion larger than 3 mm [29]. Nonetheless, a cohort study utilizing MRI identified pituitary macroincidentalomas in 0.16% of the participants [110].

Pituitary adenomas are usually benign neoplasms of monoclonal origin that arise from the cells of the adenohypophysis [7]. The cause of the development of sporadic pituitary adenomas is not well known. Many etiologic factors are involved, including hormonal stimulation, genetic and growth factors, and it seems that all these factors interact to initiate the transformation and promote the cell proliferation [6]. Epigenetic silence of tumor suppressors, such as cyclin-dependent kinase inhibitor (CDKI) p27 and retinoblastoma gene have been described [6].

A minority of pituitary adenomas are associated with some specific syndromes, implicating specific germline mutations. The mutation in the tumor suppressor MEN1 is associated with the multiple endocrine neoplasia type 1 (MEN1) syndrome, which is characterized by parathyroid gland adenoma, enteropancreatic tumor and pituitary adenoma [10]. Some other mutations in the AIP, GNAS and NF1 genes, are associated with the familial isolated pituitary adenoma, McCune-Albright syndrome and neurofibromatosis type 1 respectively [98].

Symptoms, signs, evaluation and treatment options will be discussed below.

1.2.2. Craniopharyngioma

Craniopharyngiomas are uncommon benign embryonic malformations originating from the remnants of the craniopharyngeal duct in the sellar region [71]. Two different types of craniopharyngiomas (CP) are known: the adamantinomatous (ACP) and the papillary (PCP). They have distinct demographics, radiological features and genetic alterations. Craniopharyngiomas constitute 1,2 to 4,6% of all intracranial tumors, with an incidence of 0,13 per 100,000 people. ACP has a bimodal distribution by age, with two peaks, between 5 and 14 years and 65 and 74 years, whereas PCP is restricted mainly to adults in the fifth and sixth decades [12, 15, 71]. ACP is driven by somatic mutations in ß-catenin whereas the PCP is associated with BRAF V600E mutations [71].

ACP usually presents cystic and calcified lesions, whereas PCP usually presents solid and infrequently calcified lesions [81]. The treatment of choice is the complete resection of the tumor, avoiding optimal and hypothalamic damage. In lesions with an unfavorable site of localization, the treatment should include a surgical resection followed by radiotherapy.

1.2.3. Rathke´s cleft cyst

Rathke´s cleft cysts (RCC) are benign, ectodermal, sellar, or suprasellar cysts originating from remnants of the Rathke´s pouch [54]. Most of the RCCs are asymptomatic, and they induce symptoms when they reach a size big enough to exert mass effect on nearby structures, resulting in headache, visual deficits and pituitary dysfunction.

The treatment of choice is the surgical draining of the cyst and the complete removal of the cyst capsule [54].

1.2.4. Tuberculum sellae meningioma

Tuberculum sellae meningiomas represent 5 to 10% of all intracranial meningiomas [24]. These tumors arise from the dura of the tuberculum sellae and tend to grow to the prechiasmatic space [93]. Symptoms include headaches and visual impairment due to chiasm and optic nerve compression.

The treatment of choice is total resection of the tumor.

1.2.5. Pituitary apoplexy

Pituitary apoplexy is an acute condition characterized by the abrupt start of symptoms such as strong headaches, visual loss, endocrinological insufficiency, and even coma [72], and is associated with the infarction of pituitary or hemorrhage of a pituitary tumor [8].

There is still a controversy about the treatment of choice, whether conservative or surgical. However, there is some evidence that surgical intervention, when necessary, should be performed early, because it has been associated with better visual outcomes [74].

1.2.6. Pituitary lymphoma

Pituitary lymphomas are a rare condition, mostly associated with B-cell lymphomas (<80%). Headaches, visual alterations, cranial nerve involvement, hypopituitarism, retroorbital pain and vomiting are symptoms associated [106]. The management of pituitary lymphoma should be evaluated individually. Surgical treatment is recommended to obtain a biopsy for pathological confirmation and posteriorly guide the adjuvant treatment [106].

1.3. The evaluation of the pituitary lesions

The initial assessment for the pituitary pathology starts with a detailed anamnesis and physical examination.

1.3.1. Signs and symptoms

The clinical symptoms and signs that the patients present depends on many factors: type of pathology, location, size and time of evolution of the lesion, endocrinological dysfunction or mass effect on adjacent structures, involvement of the cranial nerves and/or on the circulation of cerebrospinal fluid [108].

Silent pituitary tumors normally do not produce symptoms until they are large enough to compress or infiltrate the surrounding structures.

Visual symptoms are attributed to the expansion of the pituitary tumors, mostly suprasellar growth, due to compression of the optic chiasm or optic nerves [108]. Visual symptoms are characterized by visual field deficits, such as: bitemporal hemianopsia, quadrantanopia, or nasal perimetric defects [86].

Headaches are unspecific symptoms also related to pituitary tumors. They are not related to the size of the tumor, but to the compression of the dura [55]. Cranial nerve palsy is infrequent.

Specific endocrinological alterations are observed in the endocrine active adenomas. They can cause hormone overproduction of one or more of the six hormones produced in the adenohypophysis, causing specific syndromes: amenorhea-galactorrea syndrome, Cushing´s disease, gigantism or acromegaly, and hyperthyroidism [81]. Prolactinomas are the most common endocrine active adenomas. In women, prolactinoma causes galactorrhea, oligomenorrhea or amenorrhea, infertility or alteration of libido. In men, causing also alteration of libido, erectile dysfunction, hypogonadism and gynecomastia [41].

The overproduction of somatotropic hormone (GH) in the childhood results in gigantism. Whereas the overproduction of growth hormone in adults causes acromegaly, characterized by enlargement of the hands, feet, forehead and jaw [65]. It is associated with the development of diabetes mellitus, hypertension, sleep apnea, coronary artery disease and cardiac failure [30].

Hypercortisolism specifically due to the overproduction of adrenocorticotropic hormone (ACTH) from adenohypophysis is called Cushing´s disease. Central obesity, facial plethora, "moon face", hypertension, hirsutism, glucose intolerance and osteopenia are some of the symptoms related to the chronic exposure to hypercortisolism [49].

On the other hand, adenomas can also cause hormone underproduction syndromes, such as Addisonian crisis or secondary amenorrhea. These underproduction syndromes are associated with larger tumors that compress the nontumorous pituitary gland or the pituitary stalk [108].

Pituitary apoplexy is a rare complication associated with pituitary adenomas [106].

1.3.2. Ophthalmological evaluation

Ophthalmological evaluation is a crucial part of the clinical assessment in patients with sellar pathologies. This evaluation should be performed before and after any surgery of the pituitary gland.

The important steps of the ophthalmologic evaluation are assessment of visual acuity, visual fields, pupil and fundus examination, ocular motor assessment and examination for ptosis [1, 73].

It is recommended that the postoperative ophthalmological surveillance should be done directly after the operation, after 3-months and every year [1].

1.3.3. Endocrinological evaluation

Accurate and careful evaluation of pituitary function is essential for the diagnosis and treatment. Some of the pituitary hormones can be evaluated using single blood samples, whereas others with more complicated circadian or pulsatile secretion patterns require dynamic stimulation tests [85].

The evaluation routine for hormone hypersecretion or pituitary dysfunction includes: prolactin in serum, insulin-like growth factor (IGF-1), free cortisol in urine, basal cortisol and adrenocorticotropin (ACTH) in serum, free triiodothyronine (T3) and thyroxine (T4) in serum with thyrotropin (TSH), luteinizing hormone (LH) and follicle-stimulating hormone (FSH) [91].

A basal prolactin value higher than 200 ng/ml is suggestive of a prolactinoma. However, hyperprolactinemia can be observed in pregnancy, breastfeeding and use of certain medications [91]. The compression of the pituitary stalk can cause secondary hyperprolactinemia, due to the obstruction of the normal inhibitory hypothalamic influence on the prolactin producing cells [51]. Hyperprolactinemia levels above 400 ng/ml are only observed in macroprolactinomas. The prolactin level in serum normally correlates with the size of the prolactinoma [91]. It is important to rule out the "hook effect" in cases of giant and invasive macroprolactinomas in which the serum prolactin level is falsely low (25 to 150 ng/ml), this is due to excessive serum prolactin saturating the antibodies in immunoradiometric assays resulting in falsely normal levels of prolactin, therefore, subsequent dilutional testing of prolactin samples can counteract this assay phenomenon and prevent false negatives [86].

Measuring serum IGF-1 can provide the diagnosis of GH excess due to acromegaly/gigantism [91]. This test can be performed at any time of the day [2] and its normal levels depend on age and gender. Higher values of IGF-1 make the diagnosis of GH-secreting adenoma. If the IGF-1 levels are normal and the clinical suspicion of acromegaly is high, it is recommended to perform an oral glucose tolerance test to confirm the diagnosis [48]. Diabetes mellitus, sepsis, hypothyroidism and renal failure can affect the levels of IGF-1 [91].

The cortisol levels in serum have a circadian rhythm and are higher in the morning and lower at night. Basal cortisol levels in the morning can be useful in the evaluation of the hypothalamus-pituitary-adrenal axis. Ideally, basal cortisol should be measured around 8-9 am, since cortisol concentration is at its maximum at this time. Low cortisol levels suggest a deficiency [85]. For the evaluation of ACTH-secreting adenomas, the use of exogenous steroids should be excluded [76]. The test with the best sensitivity and specificity (92-100%) is the late-night salivary cortisol level, which is high in the Cushing syndrome [68]. The 24-hour free cortisol in urine can be influenced by alcohol intake, depression and contraceptive use and has a lower sensitivity and specificity than salivary cortisol test [68]. Low-dose dexamethasone suppression and high-dose dexamethasone suppression tests are dynamic tests, that are performed by giving 1 mg or 8 mg dexamethasone at 11 pm, followed by measuring serum cortisol at 9 am the next day; if the cortisol level is below the normal, Cushing syndrome is excluded, if they are elevated the diagnosis of Cushing syndrome is made [49]. ACTH levels in serum can help to distinguish between Cushing syndrome due to adrenal tumor where the ACTH levels are low, and Cushing disease where ACTH levels are elevated.

Free-T3, free-T4 and TSH in serum can lead to the right diagnosis of TSH-secreting adenoma. The levels of T3. T4 and TSH are elevated.

Low estradiol or testosterone levels in serum are suggestive of a hypogonadotropic hypogonadism [91].

1.3.4. Radiological evaluation

Neuroradiological evaluation is mandatory, especially in the evaluation of the endocrine-inactive adenomas. CT scans reveal an enlarged sellar mass. CTs are useful to evaluate calcification, which is commonly seen in craniopharyngiomas and tuberculum sellae meningiomas. Pituitary apoplexy can also be diagnosed with CT scan [49].

Magnetic resonance with contrast is the gold standard study for evaluating the tumor size, enhancement characteristics and neurovascular relationships of pituitary pathologies [49].

It is recommended that the MRI includes: T1-, T2- and T1-with contrast sequences [43]. Most adenomas can be well detected in conventional MRI; however, small adenomas can be not evident [49].Dynamic MRI is optimal in these cases. It involves the use of contrast followed by sequential rapid acquisition of T1-weighted images for approximately 2-3 minutes [43].

Pituitary adenomas are usually isointense to cerebral cortex on the T1-sequence and enhance strongly but heterogeneously on the T1-sequence with contrast. They can show isointensity on T2 and T2Wi-sequences [81] (Figure 8). The sagittal cuts of the MRI are important to recognize the borders of the adenoma and the pneumatization of the sphenoid sinus, whereas coronal cuts can provide information about the contact of the adenoma to the optic structures, involvement of the carotid arteries and invasion of the cavernous sinus [11].

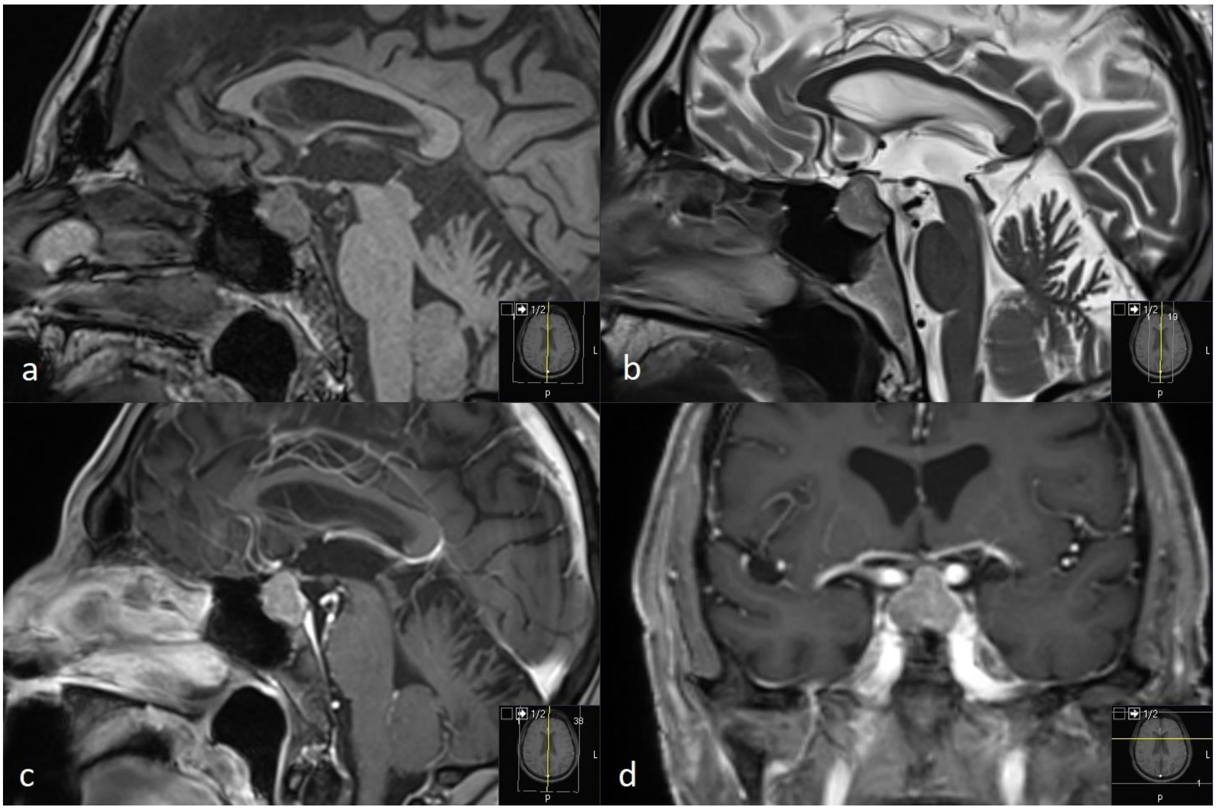

Figure 8. Magnetic resonance imaging (MRI) of a pituitary macroadenoma. a) Sagittal T1 sequence without contrast shows the isointense adenoma. b) Sagittal T2 sequence shows the hypo-isodense adenoma. c) and d) Sagittal and coronal T1 sequences with contrast sequences show the strong enhancement of the adenoma. (Courtesy of the Department of Neuroradiology Prof. Reith, UKS, Homburg).

Some classifications have been described to evaluate pituitary tumors, plan a better operative strategy and probability of total resection [49]. Hardy proposed a classification to describe pituitary adenomas [39]. The classification includes two subgroups: The first one describes the integrity of the sellar floor, tumors that do not extend over the sellar floor are called noninvasive, whereas those extending over the sellar floor are called invasive. The second one describes the degree of suprasellar extension of the tumor [39, 69].

The Knosp Classification primarily assesses the extension of tumor into the cavernous sinus with focus on relations of the cavernous segment of the internal carotid artery [49, 50] (Figure 9).

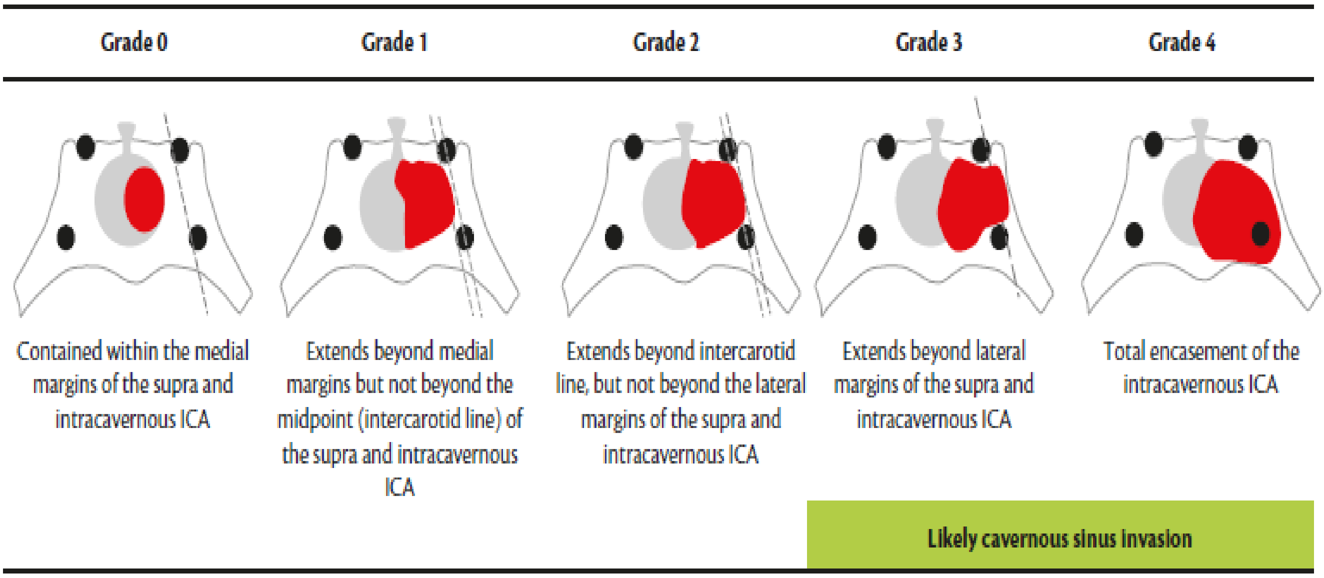

Figure 9. Knosp Classification for pituitary adenomas. (From Kirollos, Ramez and others (eds), Oxford Textbook of Neurological Surgery, 2019. Pag.304).

1.3.5. Treatment options

The management of pituitary pathologies involves a multidisciplinary team.

Surgical resection is the initial treatment for almost all pituitary tumors with the exception of prolactinomas [68]. When the indication for an operative treatment is made, the surgical approach should be discussed depending on the location, type and configuration of the tumor. The transsphenoidal approach is preferred over the transcranial approach due to low rates of morbidity and mortality [58].

The primary goal in the treatment of prolactinomas is to restore normal pituitary function, normalize the serum prolactin levels and prevent disease recurrence or progression and its sequelae [109]. Conservative therapy with dopamine receptor agonists is considered the first line of treatment. Dopamine agonists such as bromocriptine and cabergoline decrease prolactin levels within days, reducing the size of the adenoma and restoring the function of the adenohypophysis. [59]. Surgical resection is limited to patients with intolerance to side effects of therapy with dopamine agonists, or with persistent hyperprolactinemia and tumor growth in under dopamine agonists, and with impaired visual function and/or cranial nerve palsy, and iv) in patients with pituitary apoplexy [78, 86].

The goal of treatment of acromegaly is to achieve biochemical control, defined as reduction of GH levels to less than 1µg/l and IGF-1 levels to the normality [68]. Medical management for acromegaly consists of somatostatin analogues, which reduce GH levels and tumor size in almost 30% of the cases. GH receptor agonists reduce IGF-1 levels but can lead to small growth of the tumor size due to the lack of feedback [49]. However, surgery is the most effective treatment, with the goal of normalizing GH levels and decompressing surrounding structures. Surgery achieves remission by 50-90%. Radiotherapy might be recommended for residual tumors after surgery.

Surgery remains the most effective option of treatment for Cushing´s disease caused by pituitary adenoma, with a cure rate of 80-90% [76]. Medical treatment is indicated is indicated for preoperative optimization and in patients where surgery was not successful [49]. Medical treatment is targeted to inhibit steroid synthesis at different levels: direct synthesis block in the adrenal glands, inhibition of ACTH secretion in the adenoma and blocking cortisol in the peripheral tissues [68]. Some of the medicaments used are ketoconazole, metyrapone, pasireotide and mifepristone.

Radiotherapy is generally reserved for patients with inadequate tumor size reduction, serum hormone levels and no responsiveness to surgery or medical therapy [61].

The outcome is dependent on many factors: tumor size, invasion of surrounding structures and experience of surgeon [49].

1.3.6. Follow-up

Postoperative magnetic resonance images (MRI) are recommended for 3 or 6 months postoperatively and then once a year for assessment of tumor residue or tumor progression [16].

Endocrinological assessment for 3 months postoperatively focuses on the recovery of preoperative pituitary deficiencies and on the definitive nature of the postoperative deficiencies [16]. It is also recommended to remain under regular endocrinological controls once a year.

In case of preoperative ophthalmologic abnormality, follow-up is also recommended 3 months after surgery, and annual follow-ups [16].

1.4. Transsphenoidal endoscopic approach

1.4.1. Operative technique

The transsphenoidal approach was first described in 1907 by Hermann Schloffer, an Austrian ENT surgeon [95]. The technique was adapted and modified by Harvey Cushing, Oskar Hirsch, Norman Dott and other surgeons [26, 57]. The transsphenoidal approach changed through the years due to the development of specific instruments, the use of microscopes and the evolution of intraoperative radiological guidance [26].

The use of the endoscope in the transsphenoidal approach was first introduced in the late 1970s and was mostly used as technical help to the use of a microscope [25]. Cappabianca was a pioneer in the use of the pure endoscopic transsphenoidal approach [14]. In the last years, the transsphenoidal approach has been used not only to treat sellar pathologies but also in the extrasellar pathologies, due to the use of neuronavigation and Doppler ultrasonography [44].

The equipment needed to perform the endoscopic surgery consists of endoscopic rigid-rod lenses with digital camara, a high-resolution video monitor screen and a recording system. Some of the endoscopes include 0°, 30° and 45° angled lenses. Equipment for neuronavigation and fluoroscopy is essential [26].

Transnasal, sublabial, transseptal and transethmoidal approaches are the most common pathways to reach the sphenoid sinus and sellar region [26, 97]. The optimal approach is selected depending on the pathology, goals of the surgery and the experience of the surgeon. No matter which approach is selected, all follow the same principles after reaching the sphenoid sinus [97]. We will focus on the transnasal variant, because it is the most common approach used in our hospital. Our technique has been already published by Linsler in 2013 and will be described below [56].

The patient is in supine position under general anesthesia and oral intubation on the operation room´s table. The head is fixed with a skull clamp (for example Mayfield®). The head is elevated around 10-15° and slightly tilted around 10° towards left shoulder, because a right-handed surgeon normally operates from the right side of the patient, while the assistant can stand at the head of patient, the instrumentist at the left side of patient, and the anesthesiologist at patient´s feet [94]. Videoendoscopic surgical equipment (monitor, camera, light source and documentation equipment), neuronavigation system and/or lateral fluoroscopy are placed at patient´s head [94] (Figure 10).

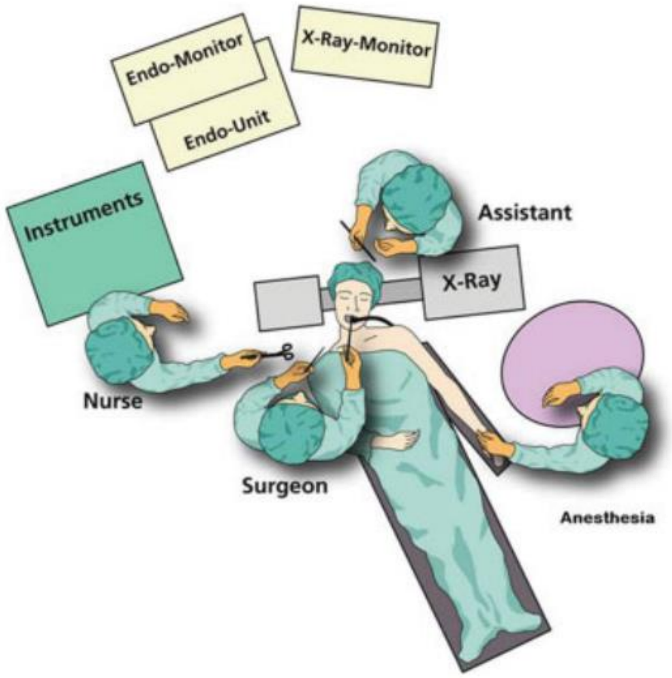

Figure 10. The normal position of the patient for a transsphenoidal endoscopic approach. The surgeon is on the right side of the patient, looking directly at the nose of the patient. The assistant at the top of the patient´s head, and the endoscopy tower with the monitor in front of the surgeon. (From Linsler S, Gaab MR, Oertel J. Endoscopic endonasal transsphenoidal approach to sellar lesions: a detailed account of our mononostril technique. *J Neurol Surg B Skull Base*. 2013;74(3):146-154. doi:10.1055/s-0033-1338258).

The administration of antibiotics, preferably a first or third generation cephalosporin before incision is recommended. Ceftriaxone (third generation cephalosporin) is preferred due to its good permeability in the central nervous system [45]. Preoperative steroid administration is recommended for tumors compressing the optic nerve or chiasm [52]. The standard placement of a lumbar drain remains controversial and will be discussed later.

As first step, the nasal cavities up to the nasopharynx are disinfected through insertion of cotton pledges with octenidine. Thereafter, cotton pledges with pseudoephedrine or adrenaline diluted in 1% lidocaine and saline solution are introduced into the nasopharynx between the middle turbinate and nasal septum to achieve vasoconstriction of the mucosa overlying the sphenoid sinus [52, 94, 97]. If an autologous fascia lata graft for the reconstruction of the sellar floor is planned, the leg should be disinfected and prepared for possible harvesting.

Normally, a mononostril approach is adequate for intrasellar tumors. Here, the more capacious nostril is chosen. It is important to identify septal deviations and enlarged middle turbinate to choose the proper nostril. However, sellar pathologies localized lateral from the middle line, are best approached from the contralateral nostril [111].

The endoscope is introduced through the nostril parallel to the floor of the nasal cavity, and inspection of the nasal cavity is performed by identifying the inferior and middle turbinates laterally and the nasal septum medially. At the beginning, an endoscope with 0° optic lens is usually used [56]. The endoscope should be introduced until the sphenoidal recess and the anterior wall of the sphenoidal sinus are localized. The sphenoidal recess houses the ostium of the sphenoid sinus and is located medially to the superior turbinate (Figure 11). A speculum is introduced into the nasal cavity under endoscope visualization. The endoscope should be put in an endoscope holder to provide stability and allow the use of both hands [56].

After localizing the ostium, the next step is to coagulate and cut into the septal mucosa that is overlying the ostium and mobilize it laterally. A meticulous coagulation at this point is crucial to avoid early postoperative epistaxis [111]. The nasal septum should be fractured at the sphenoid floor, with the speculum pushing against the septum [56] or with a high-speed drill [111], allowing a wide exposure of the zone.

The next step is to remove the sphenoid floor with rongeurs between the ostium. After removing the sphenoid floor, the sphenoid mucosa is gently dissected laterally in the sphenoid cavity [56, 111]. The sellar floor is localized. Several anatomical landmarks can be observed at this point: the bony impressions of the pituitary fossa medially, the bony impressions of carotid arteries and optic nerves laterally, the clivus and the planum sphenoidale (Figure 11).

The sellar floor can have different thicknesses, depending on the size of the pituitary tumor. In macroadenomas, the sellar floor could be very thin, or even the tumor could break through the sellar floor, making it easy sometimes to open with the dissector and rongeur. In microadenomas or GH secretory adenomas, the sellar floor could be very thick, in this case a high-speed drill is used to expose the pituitary lesion. The lesion should be exposed well enough accordingly to the extension of the tumor [56, 79, 111].

At this point, with the dura already exposed, the durotomy should be performed in a cruciate fashion, starting in the middle and extended carefully with angled micro scissors [56, 111].The tumor can be removed in small pieces with the help of ring curettes, grasping forceps and suction [56]. Tough consistency tumors can be removed with the help of an ultrasonic aspirator [111]. The Valsalva maneuver is helpful to reduce the residual component of tumors with suprasellar extension [56, 111]. The descent of the diaphragm sellae into the pituitary fossa occurs after tumor resection or debulking. The use of angled 30-degree and 45-degree optic endoscopes is extremely helpful to visualize the lateral borders of the sella in order to confirm the radicality of the surgery [80].

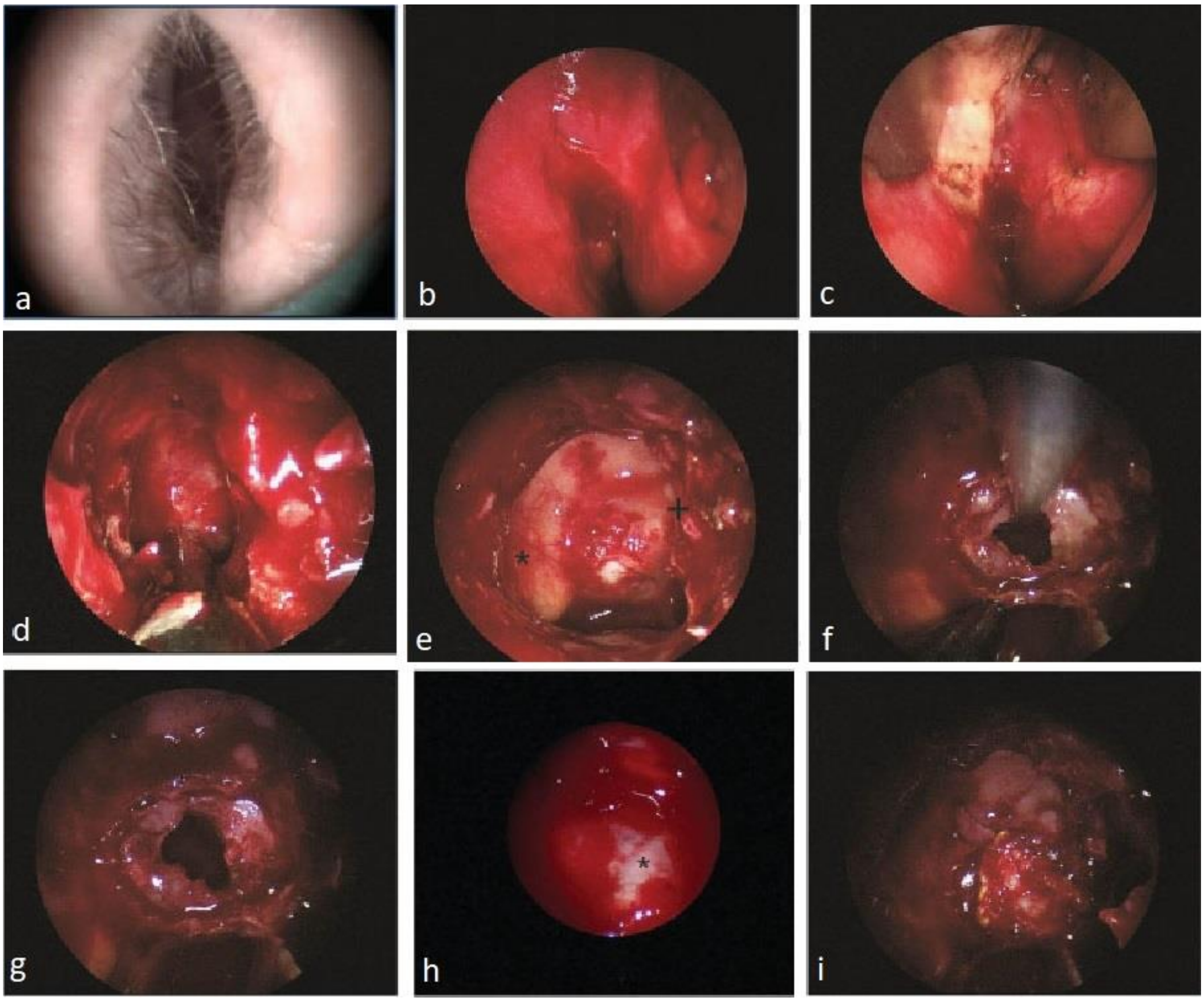

Figure 11. Endoscopic images of a transsphenoidal endoscopic approach. a) Nasal inspection before surgery. b) Localization of septum and ostium. c) View of sphenoid cavity after breaking the septum. d) Removal of the sphenoid floor with rongeur. e) View of sphenoid cavity and dura of sella floor, (*) shows bone impression of carotid artery, (+) shows the septum. f) Tumor removal. g) Inspection with 0-degree endoscopic lens. h) Inspection with angled 30-degree endoscope, (*) bone impression of carotid artery. i) Closure of the sella. (Modified from Linsler S, Gaab MR, Oertel J. Endoscopic endonasal transsphenoidal approach to sellar lesions: a detailed account of our mononostril technique. J Neurol Surg B Skull Base.)

1.4.2. Closure techniques

After the tumor has been removed and hemostasis achieved, the sella must be evaluated with accuracy and eventually a reconstruction/closure should be performed. If there is a cerebrospinal fluid (CSF) leak, closure of the dura in the sella is mandatory [108]. A series of cases of transsphenoidal surgery cases has reported intraoperative CSF leaks up to 57% [31].

Many reconstruction techniques have been proposed to repair the sellar floor, and numerous materials can be used, such as fat, muscle, fascia lata, vascularized mucosal flaps, vicryl patches, bone, absorbable and non-absorbable plates, titanium mesh plates, tissue sealants, and the use of lumbar drains [31, 37, 56, 104, 111].

A classification of the intraoperative CSF leaks has been described by Esposito, and according to its grade, the adequate repair of the sellar floor, consisting in grade 0 to grade 3 [31] (Figure12).

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

Figure 12. Grade of intraoperative CSF leak with description of each grade. (From Esposito F, Dusick JR, Fatemi N, Kelly DF. (2007). Graded repair of cranial base defects and cerebrospinal fluid leaks in transsphenoidal surgery. Oper Neurosurg (Hagerstown). 60(4 Suppl 2):295-304.

The use of the Valsalva maneuver is very helpful in testing the absence of intraoperative CSF leak that could otherwise be overlooked. Esposito proposed a protocol for sellar repair as follows: In grade 0, only collagen sponge is used. In grade 1 leaks, a single layer of collagen sponge is placed over the exposed pituitary gland, followed by a titanium mesh buttress wedged into the intrasellar, extradural space, followed by a second layer of collagen sponge placed over the mesh. In grade 2 leaks, intrasellar abdominal fat graft and collagen sponge, followed by titanium mesh buttress and additional fat. For grade 3 leaks, the same technique as for grade 2 leaks and use of a lumbar drain for 48 hours are used [31]. With this technique, leak repair failures have been described in 2,5%, where grade 3 leak failure rates being the most common [31].

Zador has described another protocol for repairing the sellar floor, according to the classification made by Esposito [111]. In grade 0, only a hemostatic gelatin sponge is placed in the tumor bed. In the grade 1 leaks, a hemostatic gelatin sponge and a dural sealant (for example DuraSeal, BioGlue) can be used. In grade 2 leaks, an additional autologous fat graft is used. For grade 3 leaks, the defect is closed with fascia lata graft, autologous fat and/or gelatin sponge and a vascularized nasoseptal flap [111].

A technique called nasospetal flap has been described by Hadad in 2006. This technique is one of the most famous and used in the repair of the sellar floor after sellar transsphenoidal surgery. It uses a neurovascular pedicled flap of the nasal septum mucoperiosteum and mucoperichondrium based on the nasoseptal artery (branch of the posterior septal artery and the terminal branch of the internal maxillary artery) and harvested carefully according to the size of the sellar floor defect [37]. Additionally, a collagen matrix is used as inlay graft, abdominal fat or onlay fascial graft, and the use of fibrin glue can be helpful to secure the flap [37].

The nasoseptal flap has significantly reduced the incidence of postoperative CSF leaks [46] and has become one of the most effective techniques in the sellar floor reconstruction with CSF leakage. However, its use requires a meticulous preparation in order to preserve the integrity of the flap, resulting in longer surgery times.

After the closure of the skull base, the nasal septum should be pushed back in its midline position and the speculum is removed. Usually, nasal packing is required to prevent postoperative nasal complications [56].

1.4.3. Use of lumbar drain

The best time for the placement of a lumbar drain is a matter of debate. Some surgeons place a lumbar drain prior to surgery, and some do it only if an intraoperative CSF leak occurs [42]. The use of a preoperative lumbar drain to prevent postoperative CSF leaks is still controversial. Some studies have shown that preoperative/intraoperative use of a lumbar drain played no benefit in preventing postoperative CSF leakage after endoscopic transsphenoidal surgery [23, 104].

Nevertheless, a meta-analysis showed that the intraoperative use of a lumbar drain can reduce the risk of CSF leaks in transsphenoidal surgery [105].

If a postoperative CSF leak occurs, it is recommended to manage it with a lumbar drain for 3 to 5 days, or directly with a surgical repair [42]. Its use for conservative treatment of postoperative CSF leaks has shown success rates from 60% to 94% [33, 38, 99].

1.4.4. Postoperative complications

The risk of hypopituitarism following surgery varies depending on several factors, including the nature of tumor, type and size, and degree of compromise of pituitary function preoperatively. The risk of pituitary hormone deficiency has been estimated by 10-20% after transsphenoidal surgery [49].

Diabetes insipidus is the most common cause of postoperative hypernatremia. Many studies have shown that the risk of developing transient diabetes insipidus varies between 1.6 and 45% in the transnasal microsurgical approach, compared to 2.5-15% in the transsnasal endoscopic approach [96]. The risk of developing permanent diabetes insipidus has been described to be between 1.3 and 3.4% [100]. However, in patients with craniopharyngiomas and pituitary metastases, the risk of developing diabetes insipidus is higher [49].

Postoperative hyponatremia is an infrequent complication after pituitary surgery, related to the syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting syndrome (CSW).

The intraoperative CSF leak is the result of the disruption of the sellar diaphragm [21, 108]. Postoperative CSF leaks occur due to failure to recognize an intraoperative CSF leak or to the failure of the repair technique [105]. The CSF leak prevalence postoperatively after transsphenoidal surgery has been observed to be up to 3.9%, especially in macroadenomas and tumors with suprasellar extension [42, 102].

In the postoperative period, the fast recognition of a CSF leak is essential to avoid meningitis. Meningitis is also a frequent complication associated mostly with postoperative CSF leak, it has been described in 2.1% [103] and with the use of lumbar drain up to 3% [42].

Visual impairment is an uncommon complication that can occur from direct surgical trauma, hemorrhage or ischemia [108].

Postsurgical hematoma at the site of surgery has been described up to 8.5%, with mostly asymptomatic patients and treated conservatively and successfully [103].

Nasal complications include hyposmia, nasal obstruction, epistaxis, septal perforation, rhinosinusitis and mucocele. A series of cases have reported postoperative epistaxis incidences of 0.6 to 3.3% [3]. Hyposmia has been described up to 2.1% postoperatively [75].

2. Aim of the study

The endonasal transsphenoidal endoscopic approach is nowadays the standard procedure for the resection of pathologies in the sellar region and other skull base tumors, due to its high resection rate with low complication rate.

One of the most common complications after transsphenoidal surgery is the intraoperative cerebrospinal fluid (CSF) leak and the postoperative CSF fistula. Multiple closure techniques have been developed in order to avoid postoperative CSF fistulas. The pedicled flaps are widely used and have a great efficacy in avoiding CSF fistulas, and it has been used as standard technique in many hospitals.

This study analyzes the outcomes of the closure technique applied in our neurosurgical department. It is a multilayered closure technique consisting of bone, autologous fat, fascia, sealant sponge (TachoSil®), dura sealant patch, and if a CSF leakage is detected, the use of lumbar drainage directly intraoperatively.

The main goal of this study is to analyze the effectiveness of the used closure technique and rate of postoperative CSF leakages and the use of a lumbar drainage and compare it to the literature describing the results of the pedicles neurovascular flap.

Thus, we propose to answer related questions:

- Does pituitary pathology, tumor volume and other factors predict the risk of developing a postoperative CSF fistula?
- Does the use of intraoperative lumbar drain reduce the rate of postoperative CSF fistula?
- Is the use of lumbar drain effective to treat a new persisting postoperative CSF leakage?

3. Materials and Methodology

3.1.Patient data

I retrospectively reviewed the data of all patients who presented with intrasellar pathologies and underwent transnasal transsphenoidal endoscopic surgery in our university hospital. Data collection involved reviewing all medical records, such as surgical and histopathological reports, video recordings, clinical history and visit data, imaging studies, follow-up controls and discharge letters. This retrospective study received approval from the ethical committee of the medical association of the Saarland (Nr. 186/15).

I analyzed our database in SAP between January 2011 and April 2020.

The inclusion criteria were as follows:

- Patients operated via a transsphenoidal endoscopic approach for sellar pathology
- Patients who had an intraoperative CSF leak
- Patients with pre- and postoperative ophthalmological, endocrinological and radiological evaluation.

The exclusion criteria were:

- Patients younger than 18 years.
- Patients with head trauma.
- Patients without follow-up data.

The examined data encompassed tumor and patient attributes, surgical procedures, preoperative symptoms, postoperative results, such as complications and tumor recurrence. Endocrinological symptoms, outcomes and complications were assessed through serological testing of hormone levels, specifically measuring morning cortisol, FSH, LH, prolactin, TSH, GH, ACTH and IGF-1. Visual function was assessed through visual field and visual acuity tests performed by an ophthalmologist. Neurological outcomes were assessed through neurological physical examination.

The data collected on each patient who fulfilled the criteria was entered into an excel sheet, and included:

- Age.
- Gender.
- Duration of the surgery.
- Size and Volume of the tumor.
- Histopathological diagnosis.
- Intraoperative CSF leak grade according to the Esposito Classification.
- Use of closure materials
- Use of intraoperative lumbar drain.
- Postoperative complications: CSF leak, neurological complications, endocrinological complications, bleeding, nasal complications.
- Treatment of the postoperative complications.
- Days of hospitalization after surgery.
- Follow-up after surgery: 6 weeks, 3 months and last follow-up (up to December 2022).

3.2 Imaging studies and tumor volume

All patients underwent preoperative magnetic resonance imaging with Gadolinium as contrast media. Routine follow-up included magnetic resonance imaging studies every 12 months. Tumor volume was determined by measuring the longest diameter of its lateral extent and its extent from anterior to posterior in the axial plane, in addition to the longest axial diameter shown in coronal T1-weighted images enhanced with Gadolinium contrast media. Preoperative CT imaging was performed to plan surgical approaches, and postoperative CT imaging evaluated the extent of resection and postoperative complications, such as bleeding.

3.3 Surgical technique and perioperative management

All surgeries were conducted by two experienced neurosurgeons in our department. Procedures were performed under general anesthesia with orotracheal intubation, following a standardized protocol: patients were positioned supine with the upper body slightly elevated and the head tilted to the left, with head fixation using a three-pin system. Intraoperative imaging was routinely performed using lateral fluoroscopy (C-arm) and MRI- or CT-based Neuronavigation. Endoscopic procedures were performed in the sellar region and endonasal approaches, utilizing rigid endoscopes with varying angled lenses. Closure techniques for intraoperative CSF leaks depended on their severity, with materials such as autologous fat, fascia lata, Tachosil®, dura sealant patch, bone, or lumbar drains utilized accordingly. Dural closure involved sandwiching with an autologous periumbilical fat graft. Patients with pituitary adenomas or lesions extending into the sellar region received a stress dose of hydrocortisone perioperatively. Postoperatively, patients were monitored in the intermediate or intensive care unit [56].

Patients with pituitary adenomas and lesions extending into the sellar region received a standard perioperative stress dose of hydrocortisone (100 mg/24 hours).

The details surgical setting and technique is described above in chapter 1.4.1.

The authors conducted endoscopic procedures in the sellar region and endonasal approaches following protocols outlined in previous larger studies [56]. Intraoperative imaging utilized lateral fluoroscopy (C-arm) and MRI-based neuronavigation. Surgical procedures employed 4 mm or 2.7 mm rigid endoscopes (Karl Storz, Tuttlingen, Germany) with Hopkins optics and 0°-angled lenses for approach and tumor removal, while scopes with 30°- and 70°-angled lenses were utilized for final inspection and tumor resection. Closure techniques for intraoperative CSF leaks varied based on the Esposito classification, utilizing materials such as autologous fat, fascia lata, Tachosil®, dura sealant patch, bone, or lumbar drains. Dural closure involved a sandwich technique with an autologous periumbilical fat graft in an underlay technique. A lumbar drainage was occasionally inserted postoperatively. Skull base defects were reconstructed with bone pieces, and the sphenoid cavity was filled with fibrin glue. Vascularized nasoseptal flap was not utilized. All procedures were recorded.

3.4. Use of lumbar drainage

The necessity of a lumbar drain during surgery was determined by an individual decision based on the surgeon's judgment during the operation depending on the intraoperative dural defect and CSF leakage.

The lumbar drain was placed direct after the end of the surgical prodecure in the OR at the lumbar level of L4/5 or L5/S1.

3.5. Statistical Analysis

The statistical analyses were performed using the Program SPSS Statistics Software (v.28, IBM Corporation, USA). Categorical variables were presented as frequency distributions, while continuous variables were expressed as mean ± standard error. Significance was tested at the 0.05% level. The χ^2 test assessed the association between categorical variables, while student’s *t*-test and ANOVA were employed to evaluate significance for continuous normally distributed variables. Upon finding a significant relationship ($p<0.05$), posthoc residual analysis for categorical variables and Fisher’s least significant difference test for continuous variables were utilized to determine precise significance between groups.

4. Results

4.1. Sample characteristics

A total of 280 patients between January 2011 and April 2020 underwent transsphenoidal surgery due to intrasellar pathology. 87 patients presented an intraoperative CSF leakage. The study cohort is exclusively composed of these 87 patients.

Fifty-four (62%) were female and 33 (38%) males. The mean age was 56.3 ± 14.8, range 22 – 84 years, as summarized in Table 1 and Figure 13.

Table 1. Patient characteristics: demographics and clinical variables

Sex	Number of patients	Percentage (%)
Female	54	62%
Male	33	38%
Total	87	100%

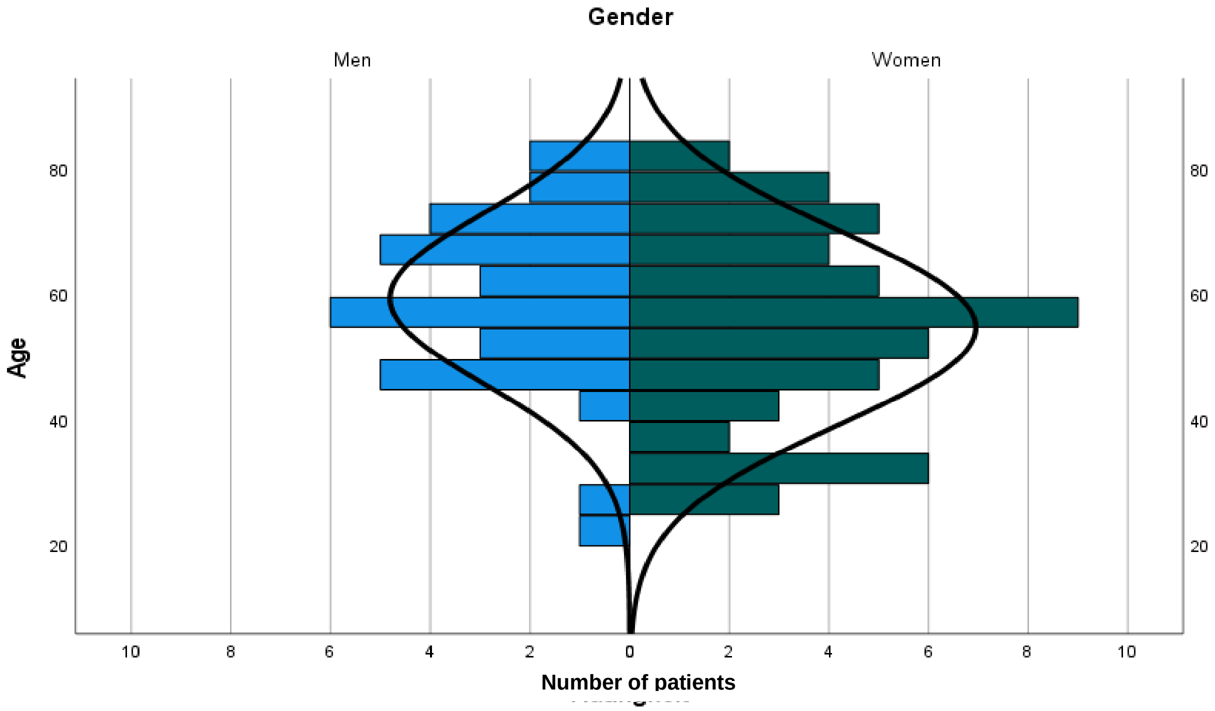

Figure 13. The distribution of the age and the different genders of the patients included for this study.

All transsphenoidal endoscopic approaches to the sellar region were performed via a mononostril approach.

The mean surgical time scored was 106 minutes + 11.4.

The average of hospitalization after surgery was 8.2 + 2.2 days.

There was no mortality in our patients related to surgery.

4.2. Histopathological characteristics

The most frequent histological diagnosis was the non-secreting adenoma in 40 cases (45%). Secreting adenomas were the second most common diagnosis with 16 cases (18%), in which seven cases of adrenocorticotropic hormone secreting adenoma, five cases of prolactinoma and four cases of growth hormone releasing adenoma were observed. Eight cases of meningioma were diagnosed (9%), six cases of Rathke's cleft cyst (7%), six cases of craniopharyngioma (7%), four cases of colloid cysts (4%), four chordomas (4%) and in each category there was only one single case of hemangioma, arachnoid cysts and metastatic lesion respectively were observed. These data are summarized in Table 2 and in Figure 14.

Table 2. Underlying pathologies.

Pathology	Total cases (%)	
Non-secreting adenoma	40 (45%)	Pituitary adenoma (including hormone-secreting and non-secreting): 56 (64%)
ACTH-secreting adenoma	7 (8%)	
GH-secreting adenoma	4 (5%)	
Prolactinoma	5 (6%)	
Meningioma	8 (9%)	
Rathke´s cleft cyst	6 (7%)	
Craniopharyngioma	6 (7%)	
Chordoma	4 (5%)	
Colloid cyst	4 (5%)	Other pathologies: 7 (8%)
Hemangioma	1 (1%)	
Arachnoid cyst	1 (1%)	
Metastasis	1 (1%)	

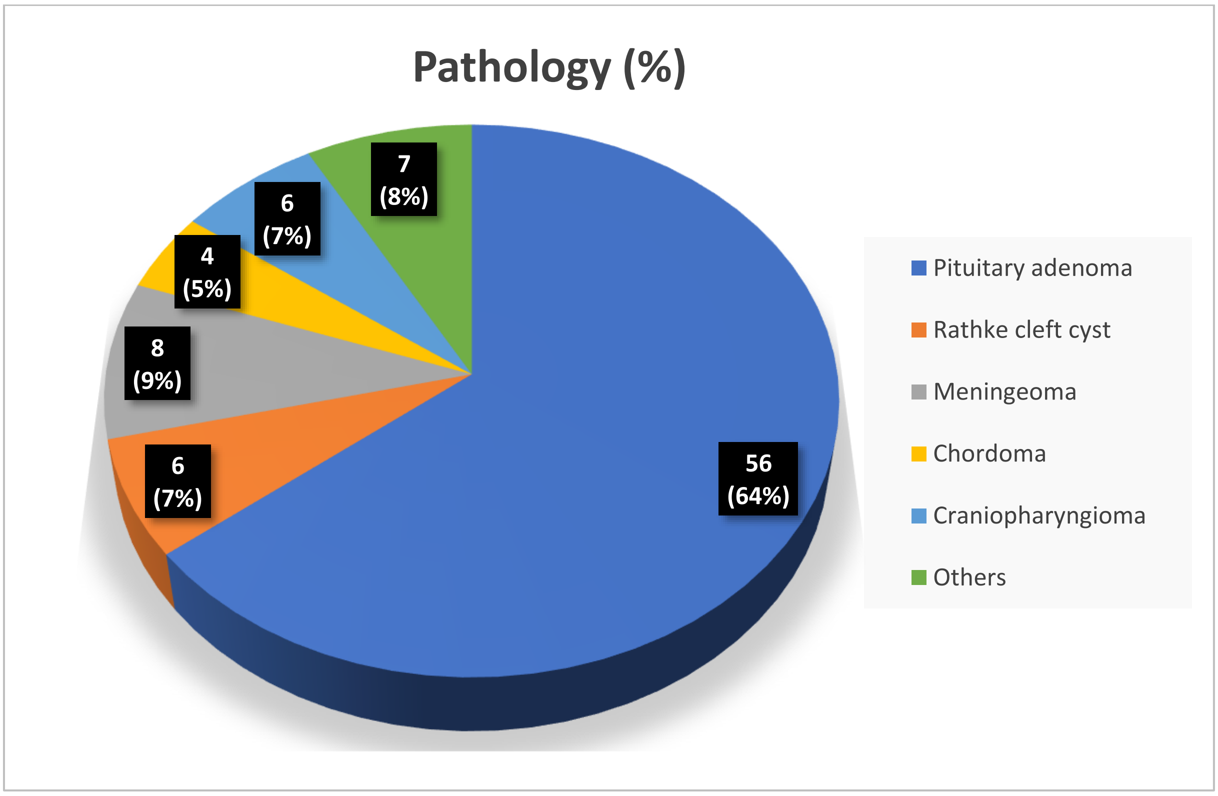

Figure 14. Distribution of the observed pathologies.

The pathologies were classified as microadenoma (<1cm) and macroadenoma (≥1cm). Eighty cases were macroadenomas (92%) and only seven of the pathologies were microadenomas (8%) (Figure 15).

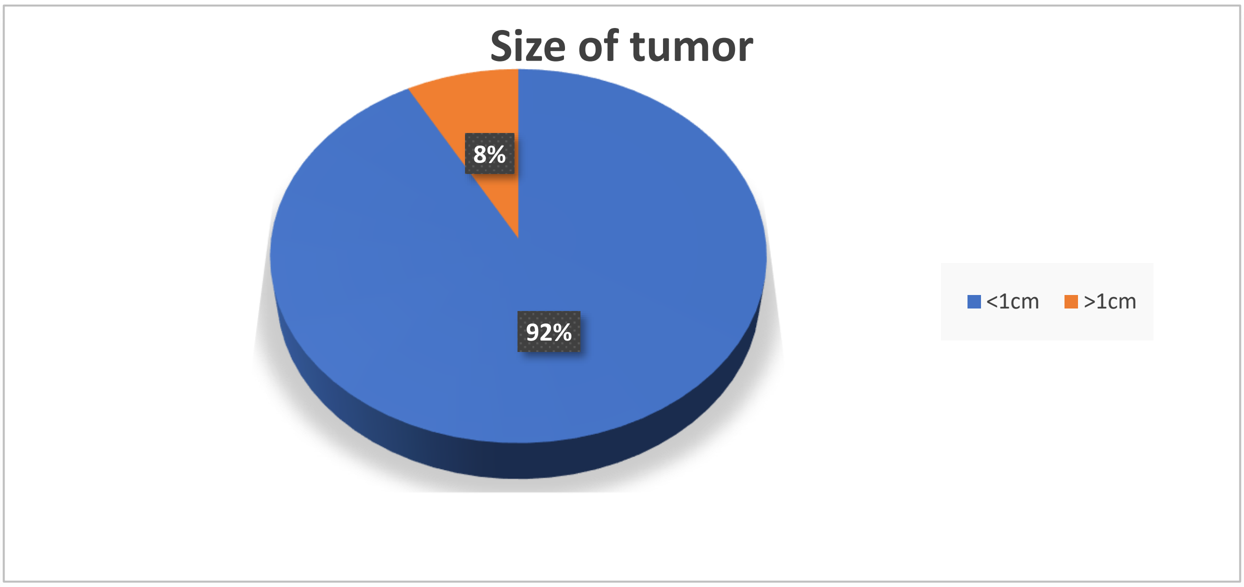

Figure 15. Classification of tumors in (<1cm) and (≥1cm).

The mean volume of tumors was 4.99 $cm^3 \pm 0.69$. Figure 16 shows the distribution of patients in relation to their tumor volume.

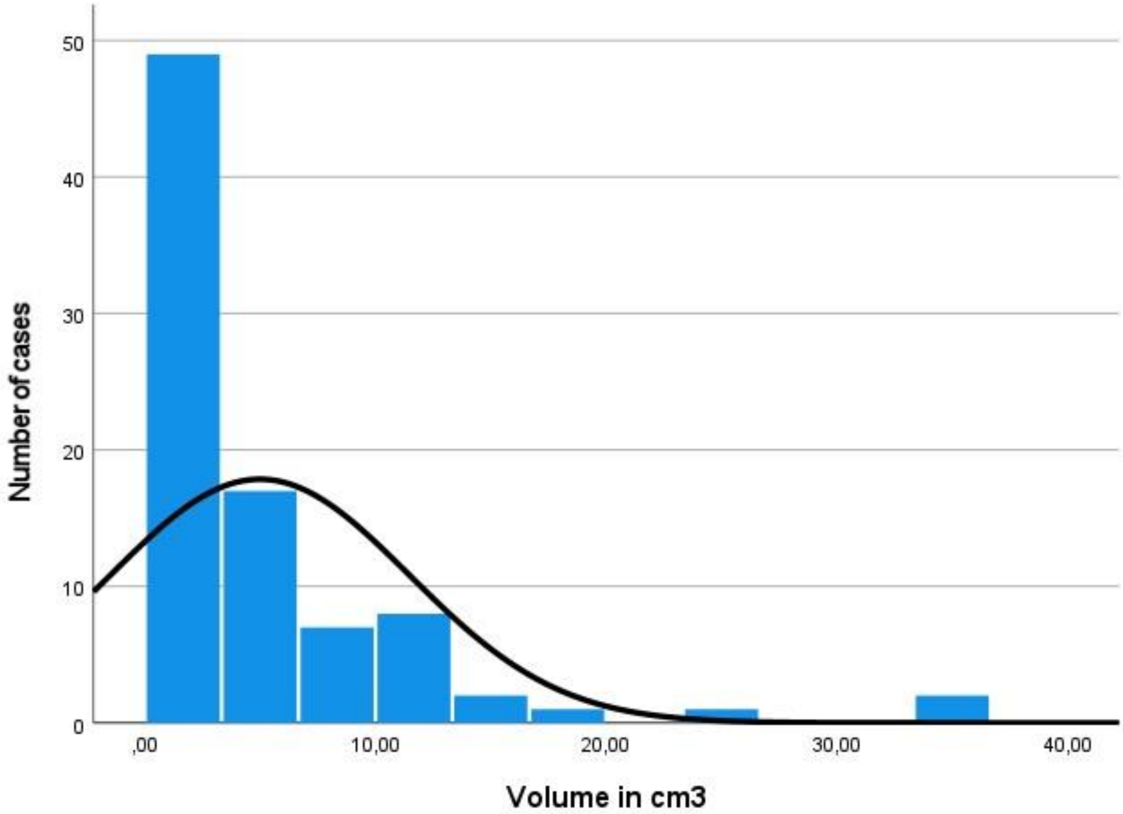

Figure 16. The volume of the tumor in cm^3 and its distribution of all cases.

4.3. General outcomes

The postoperative complications observed in the analysis were postoperative CSF fistula in nine cases (10%), meningitis in five cases (5,7%), bleeding in the operated area in five cases (5,7%), transient diabetes insipidus in eight cases (9%), permanent diabetes insipidus in four cases (4,5%), nasal complications in five cases (5,7%) and other complications in six cases (6,8%) such as cranial nerve palsy. There was no mortality in our patients related to surgery. The complications are described in detail in Table 3.

Table 3. Postoperative complications

Complications	Number of cases	Percentage of patients
Postoperative CSF fistula	9	10%
Meningitis	5	5,7%
Transient diabetes insipidus	8	9%
Permanent diabetes insipidus	4	4,5%
Bleeding	5	5,7%
Nasal symptoms	5	5,7%
Others	6	6,8%
Total	42	

4.4. Intraoperative CSF leak

The intraoperative CSF leaks were graded using the classification by Esposito (see table 4). There were no grade 0 patients in our cohort. The most encountered CSF leak was grade 2 (n=37, 42.5%), followed by grade 3 leak (n=30, 34.5%) and grade 1 (n=20, 23%) and are listed in table 4.

Table 4. Intraoperative CSF leak.

Grade by Esposito	Number of patients	Percentage
Grade 1	20	23%
Grade 2	37	42.5%
Grade 3	30	34.5%
Total	87	100%

The materials commonly used for the closure of grade 1 CSF leaks were primarily sealant sponge Tachosil ® (70%), dura sealant patch (55%) and bone (55%). For grade 2 CSF leaks, Tachosil ® (78%), bone (57%) and autologous fat (54%), here the dura sealant patch is less routinely used. In the grade 3 CSF leaks, the combination of lumbar drains (90%), autologous fat graft (87%) and fascia lata (60%) constitutes the primary strategy for the closure. Table 5 summarizes how frequent each closure material was used in each CSF leak grade.

Table 5. Closure materials.

Number of cases (percentage per grade)	Autologous fat	Fascia lata	Sealant sponge (Tachosil ®)	Dura sealant patch	Bone
Grade 1	2 (10%)	1 (5%)	14 (70%)	11 (55%)	11(55%)
Grade 2	20 (54%)	4 (11%)	29 (78%)	17 (46%)	21 (57%)
Grade 3	26 (87%)	18 (60%)	20 (67%)	7 (23%)	14 (47%)
Total	48	23	63	35	46

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A total of 63 patients received an intraoperative lumbar drain (72%). The distribution of the use of lumbar drains in correlation to the CSF leakage grading are summarized in Table 6 and figure 17.

Table 6. Use of intraoperative lumbar drain and CSF grade.

CSF Grade by Esposito	Patients with lumbar drain	Patients without lumbar drain	Total
CSF Grade 1	4 (20%)	16 (80%)	20
CSF Grade 2	32 (86%)	5 (14%)	37
CSF Grade 3	27 (90%)	3 (10%)	30
Total	63 (72%)	24 (28%)	87

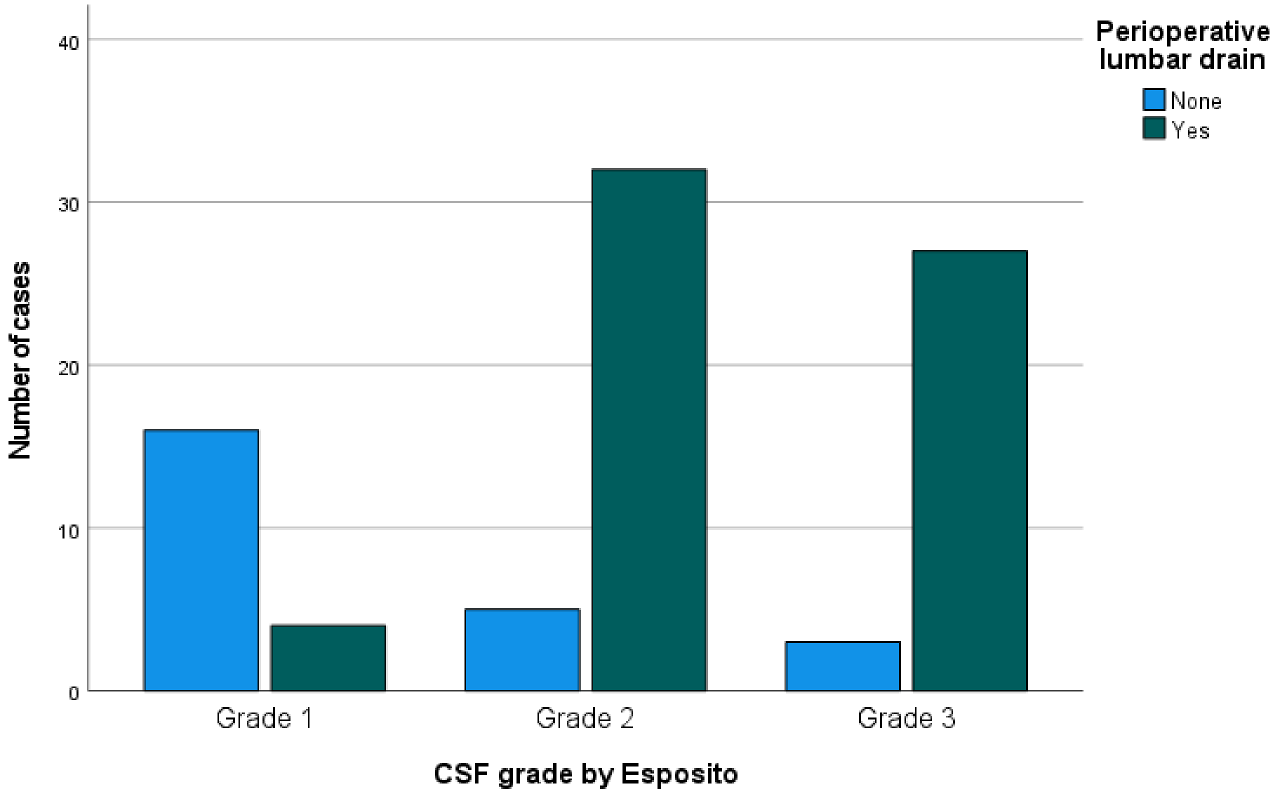

Figure 17. Number of cases of lumbar drains in the different intraoperative CSF grades.

4.5. Postoperative CSF fistula

None of the patients without intraoperative detected CSF leak developed postoperative a new CSF fistula. Of a total of 280 patients collected in our database, only 9 cases of new postoperative CSF fistulas, making a total of 3.2% of new postoperative CSF fistulas were detected generally.

A new postoperative CSF fistula was observed in 9 of 87 patients with intraoperative CSF leakage, which corresponds to 10% of the patients with intraoperative CSF flow. There was no significant difference in the probability of a postoperative CSF fistula according to the intraoperative grading of CSF flow: 10% (n=2) of all Grade 1 leaks, 10.8% (n=4) of all Grade 2 leaks and 10% (n=3) of all Grade 3 leaks developed a postoperative CSF leak. This implies that within each CSF leak grade approximately 10% will experience failure of the intraoperative closure technique.

Of the nine patients with new postoperative CSF fistulas, two (22.2%) had a Grade 1 intraoperative CSF leak, four (44.4%) a Grade 2 intraoperative CSF leak and three (33.3%) had a Grade 3 intraoperative CSF leak. This data suggests that Grade 2, followed by Grade 3 are more prone to develop a new postoperative CSF fistula.

The materials used and the underlying pathologies of the patients with postoperative new CSF fistulas are listed in detail in table 7. There was no statistical relevant correlation between the used material and the probability of a persistent postoperative CSF fistula.

The analysis revealed no association between postoperative CSF leaks and intraoperative CSF grade (p=0.362), age of patients (p=0.402), gender (p= 0.675), pathology (p= 0.472), tumor volume (p= 0.212), use of lumbar drain (p=0.751), or closure materials (autologous fat, fascia, sealant sponge, dura sealant patch, bone).

Table 7. Characteristics of the patients with postoperative CSF leak.

Cases	Pathology	Intraoperative CSF Grade	Closure material	Lumbar drain	Meningitis
Case 1	Adenoma	Grade 1	Bone, Tachosil, dura sealant patch.	No	No
Case 2	Adenoma	Grade 1	Autologous fat, bone.	No	No
Case 3	Adenoma	Grade 2	Autologous fat, bone, Tachosil.	Yes	No
Case 4	Adenoma	Grade 2	Autologous fat, bone, Tachosil, dura sealant patch.	Yes	Yes
Case 5	Adenoma	Grade 2	Autologous fat, Tachosil, dura sealant patch.	Yes	Yes

Case 6	Meningioma	Grade 3	Autologous fat, dura sealant patch, fascia lata.	No	Yes
Case 7	Chordoma	Grade 3	Autologous fat, fascia lata.	Yes	No
Case 8	Arachnoid cyst	Grade 3	Autologous fat, Tachosil, dura sealant patch, fascia lata.	Yes	Yes
Case 9	Rathke cleft cyst	Grade 2	Bone, Tachosil, dura sealant patch.	Yes	No

From those patients who developed postoperative CSF leaks, only two patients did not receive a lumbar drain (one patient with grade 1, and one patient with grade 3 leaks). Details see Figure 18.

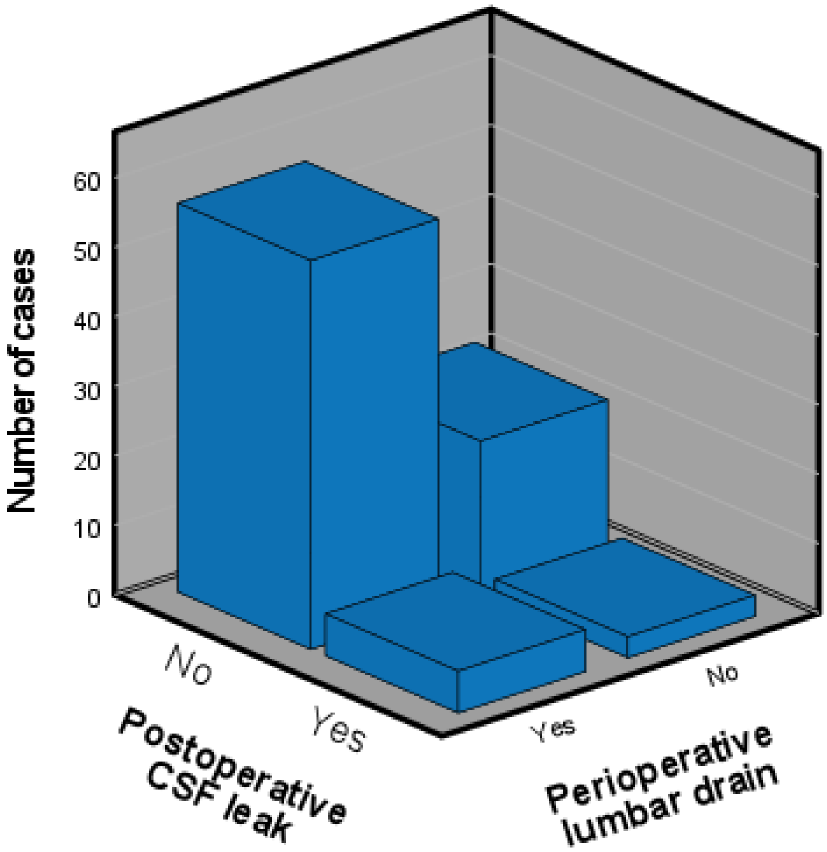

Figure 18. Relationship between patients who developed postoperative CSF fistula and became intraoperative lumbar drains.

A meningitis was detected postoperatively in six patients, of which five also had a postoperative CSF fistula and were treated with lumbar drains. Only one patient with meningitis never had a lumbar drain. Figure 19 shows the number of patients who developed meningitis and the association with postoperative CSF leak.

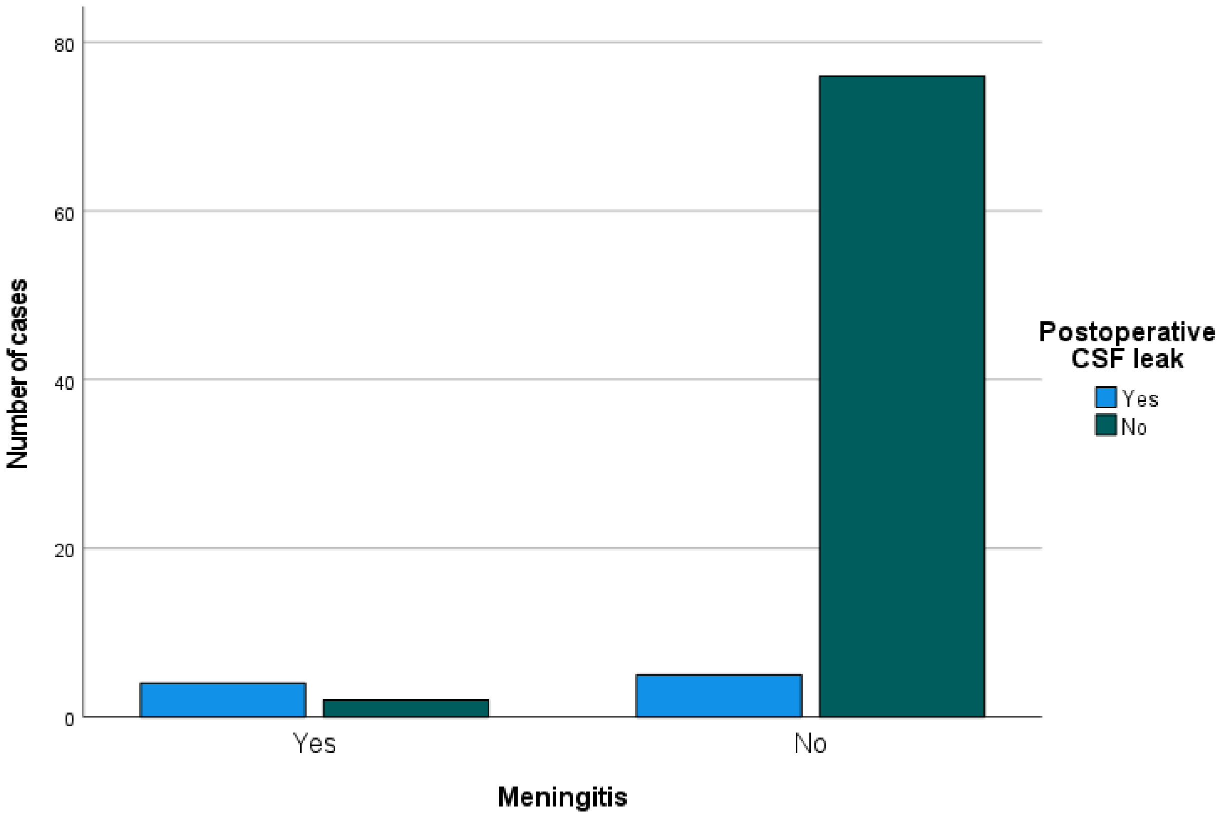

Figure 19. Relationship between patients who developed postoperative CSF fistula and meningitis.

Overall, the incidence of postoperative meningitis was correlated to the postoperative CSF leakage. (Pearson test $p<0.001$)

The use of lumbar drains was significantly higher in the patients with intraoperative grade 2 (86%) and 3 CSF leak (90%) compared to the patients with grade 1 CSF leak (only 20%) ($p\leq0.005$).

All of the nine patients with a new postoperative CSF fistula, were treated with a lumbar drain and bed rest for at least 5 days. In only three cases (33.3%), the use of a lumbar drain was successful. The other six patients (66.6%) with persistent postoperative CSF fistulas had to undergo revision surgery with revision of the dural reconstruction. All of them were treated successfully finally and presented no complications.

In the statistical analysis, longer hospitalization stays were related to the use of lumbar drains ($p=0.015$) and postoperative CSF leakage ($p<0.001$).

4.6 Correlation of the results to previous reports and other reported techniques

In order to establish the efficacy of our technique, I compared our cohort with other results in the literature with different surgical techniques. The outcomes evaluated were the development of intraoperative und postoperative CSF leakages. These results are shown in the following table 8.

Table 8. Comparison of our study results and other studies in literature.

Studies	Number of patients	Intraoperative identified CSF flow	Postoperative CSF leakage	Closure technique used
Our study	280	31%	3.2%	Dura sealant patch, Tachosil, bone, fascia lata, lumbar drain.
Esposito, et al.	668	57%	2.5%	Collagen sponge, abdominal fat, titanium mesh, tissue glue.
Patel, et al.	330	-	3.6%	Vascularized nasoseptal flap.
Chen, et al.	131	58%	8.4%	Multilayer closure.

5. Discussion

Different strategies und surgical steps have been developed and reported in the literature to minimize the complication rate of postoperative CSF fistula. While some neurosurgeons use a nasal flap [31, 37, 47] others perform the closure of the skull base only with fibrin glue or similar materials [27], or the use of autologous fat grafts or dura graft. Potentially, the most important factor to avoid a postoperative CSF leakage is the surgical closure technique [21].

Esposito reported a rate of 56.6% for intraoperative CSF leakage and a postoperative CSF leakage of 2.5%, intraoperative CSF leakage grade 3 subject to substantial postoperative CSF leakage (total of 12% in all grades 3 CSF leaks) [31]. Another important study reported a postoperative CSF leakage of 3.2% [60]. A meta-analysis showed that postoperative CSF leakages occurred in 3.4% of the patients undergoing transsphenoidal surgery [102].

In our department, 280 patients underwent an endonasal transsphenoidal procedure. From all of them, in 87 cases an intraoperative CSF fistula was detected by the surgeon: this is a rate of intraoperative detected CSF fistula of 31%. An intraoperative CSF fistula grade 1 occurred in 23%, grade 2 in 42% and grade 3 in 32% of the cases. At this point, I suggest that the Valsalva maneuver plays an important role in the detection of the small leaks, leading to an optimal closure and treatment of the intraoperative CSF grade 1 leaks. Based in this surgical technique, I presume that the neurosurgeons of our department detected every CSF flow intraoperatively, even if it was only a minimal flow.

Finally, out of the 280 patients, only 9 patients (3.2%) developed a postoperative persisting CSF fistula. None of the patients who did not have an intraoperative CSF leak developed a new postoperative CSF leakage. Thus underlines the effectiveness of detecting an intraoperative CSF fistula by an experienced neurosurgeon with the endoscope. This rate indicates that patients with intraoperative CSF flow have a significantly higher risk of developing postoperative persisting CSF fistulas compared to patients without intraoperative CSF leakage ($p<0.001$). In our cohort, grade 2 and grade 3 classified intraoperative CSF leakages (44.4% and 33.3%) were more prone to develop a postoperative persisting CSF fistula compared to the grade 1 cohort (22.2%). This implies that we will see more closure technique failures in grade 2 and 3 patients and that in these grades a meticulous attention should be paid to the reconstruction of the dural defect.

Of the 87 patients with intraoperative CSF leak nine patients (10.3%) had also a postoperative CSF fistula. Within the intraoperative CSF grades 1 – 3, the rate of developing a postoperative CSF leak was evenly distributed (10% to 10.8%). This suggests that independent of the intraoperative dural opening 1/10 patients will develop a postoperative persistent CSF fistula. The use of different types of material for the closure was analyzed and we found no association for a better outcome in correlation to a specific material. However, the use of autologous fat graft and fascia was significantly higher in the cohort of grade 2 and 3 leakages intraoperatively. Additionally, the use of lumbar drains was significantly higher in the patients with intraoperative grade 2 (86%) and 3 CSF leak (90%) compared to the patients with grade 1 CSF leak (only 20%) ($p \leq 0.005$).

There was no significant association between the used material and the postoperative CSF fistula rate for bone (p=0.598), autologous fat graft (p=0.153), fascia lata (p=0.625), sealant sponge (TachoSil®) (p=0.688), dura sealant patch (p=0.09), and intraoperative use of lumbar drains (p=0.751). That shows that none of the materials was associated with an increase or decrease in the risk of developing a postoperative CSF fistula. I underline that the experience of the surgeon is of great importance to the surgical outcome and the risk of a new postoperative CSF fistula. Although, this fact cannot be analyzed objectively in this data setting. Nevertheless, I did not see a decrease in the probability of a persisting postoperative CSF fistula during the analyzed time period.

The grading of CSF leak intraoperatively showed no association in the development of postoperative persisting CSF fistulas. That demonstrates that bigger intraoperative CSF leaks are not necessarily related to higher postoperative CSF fistulas. That could be explained by the different measures taken for the closure techniques in the different grades of CSF leak. The higher the grade of intraoperative CSF leakage, the more intensive and complex was the reconstruction technique. In the grade 1 group, most patients were treated mostly with TachoSil and Dura sealant patches, whereas in grade 2 the closure was performed with Tachosil and beginning the use of fat graft and lumbar drains, and in the grade 3, almost all patients had an autologous fat graft and lumbar drains.

The use of lumbar drains remains controversial. In a study with patients presenting intraoperative high flow CSF leakages, who were treated with a pedicled nasoseptal flap, there was no benefit observed with the use of lumbar drains, but there were more complications related to it [27]. Our results show that the use of intraoperative lumbar drains in avoiding the development of postoperative CSF fistula are effective in preventing the postoperative CSF fistula and that the use of a lumbar drain is not related to an increased risk of developing any postoperative complications, such as meningitis, visual deficits, neurological deficits, or diabetes insipidus.

Longer hospitalization stays were related to the use of lumbar drains and with postoperative new developed CSF fistulas. This is because of the therapeutical strategy of bed rest and lying positioning for at least 5 days with a lumbar drain. All the postoperative CSF fistulas were diagnosed during the postoperative stay in the hospital between day 1 and day 5 after surgery. None of the patients presented a new postoperative CSF fistula after being discharged and during the follow-up.

Of the nine patients that developed a postoperative CSF fistula, all of them received a conservative treatment with lumbar drainage for 5 days initially. If after 5 days, they still presented with a persisting CSF fistula, they were treated with endoscopic endonasal surgery for revision and reclosure of the dural defect. Only in three cases the treatment with lumbar drain was successful finally, establishing a success rate of only 33%.

These results mean that the use of lumbar drains in patients who present a new postoperative CSF fistula is not effective at all. Only the initial application of a lumbar drainage in the OR demonstrates an effect and can prevent a persisting postoperative CSF fistula. In the presented cohort the revision surgery was successful in all cases, establishing that it provides a definitive treatment.

Therefore, the use of a lumbar drainage should be avoided in the postoperative follow-up due to its poor success rate and relation to longer hospital stay. In case of a new postoperative CSF fistula after endonasal skull base surgery, a revision surgery should be recommended directly and is the primary treatment of choice in patients with a persistent postoperative CSF fistula.

In order to establish the efficacy of our technique, I compared our cohort with other results in the literature. Thereby, the results revealed comparable results with similar rates of persistent postoperative CSF fistulas with nasoseptal pedicled flap and other techniques. Chen et al. presented a risks of postoperative CSF fistulas of 8.4% with a multilayer technique. The better result of my analysis might be induced by the consequent use of a lumbar drainage. Furthermore, many authors did not analyze and correlate their final numbers of postoperative CSF fistulas to the intraoperative identified probability of CSF flow and the grade of the CSF leakage intraoperatively. This intraoperative identification and analysis by the neurosurgeon are essential for the use of the best closure technique and the postoperative result.

In conclusion, our presented sandwich technique of dural closure with autologous fat graft and the use of a lumbar drainage were equal to the surgical outcome using a nasoseptal flap.

In some studies, the postoperative CSF fistula was statistically higher in patients with meningiomas [31]. In the presented patient cohort, the pathology of the tumor as well as tumor size was not associated with a significant risk for the development of a postoperative CSF fistula. In my analysis, meningiomas, craniopharyngeomas and chordomas were associated with higher grades of intraoperative CSF leak but not to an increased risk of developing new postoperative CSF leakages. This could be explained by the fact that the surgeon would expect a CSF leak in these intradural or invading tumors, since they involve the dura and are more extensive in the sella region. Due to that, the surgeon is more careful and performs a more meticulous and precise closure in those types of pathologies.

On the contrary, according to other studies that confirm that the rate of postoperative CSF leakage is lower in pathologies without dural involvement, such as pituitary adenomas [102], we did not observe lower postoperative CSF leaks in the pituitary adenomas. This could be explained by the same argument as above. The surgeon, not anticipating a leakage in these pathologies, might have underestimated the adenomas and the extension of the pathology, meaning that the closure was not as meticulous and careful as in the other pathologies such as meningiomas or chordomas.

The only patient with an arachnoid cyst in the cohort developed also a new postoperative CSF leakage. Like described before, this type of pathology involves an intra arachnoid lesion that is related to a directly intraoperative high flow CSF fistula. Especially the high flow CSF fistula in this case may induce an increased risk of developing a postoperative CSF leakage. However, I can only assume this aspect because in my study, only one patient presented this type of pathology.

According to my study, tumor volume is not related to an increased risk of developing a new postoperative CSF leakage. This result is based on the fact that the size of the tumor is not necessarily associated to the size of the diaphragmatic defect intraoperatively. Additionally, these tumors were not removed on block normally by the neurosurgeons. The typical surgical technique is a debulking and piecemeal technique.

I suggest that our closure technique should be standardized in the future. It means that we must establish a standard closure procedure with a standardized use of the same materials in the transsphenoidal endoscopic surgery according to the identified grade of intraoperative CSF fistula. I propose that all cases with intraoperative CSF fistula should be reconstructed with dura sealant patch, autologous bone and Tachosil. All intraoperative CSF fistulas grade 2 should be reconstructed with the same materials as in grade 1 cases with additional autologous fat graft, and a lumbar drain. And all intraoperative CSF fistulas grade 3 should be reconstructed as before with the additional use of facia lata as a underlay technique intradural. With a standardized surgical technique, we could possibly reduce even more the rate of postoperative CSF leakage.

6. Conclusion

I can conclude that the presented multilayer technique in combination with lumbar drainage offers a safe, effective alternative technique for the closure and reconstruction of the dura and sellar floor after transsphenoidal surgery. The described and analyzed closure technique shows an excellent outcome with similar results compared to previous described closure techniques in the literature, especially with a vascularized nasoseptal flap. As an important resource, the Valsalva maneuver should be applied in all cases to detect even very small defects of the diaphragm and minimal CSF flow intraoperatively. Lumbar drains are a helpful and effective tool to prevent a persisting postoperative CSF fistula with application directly in the OR after surgery.

In case of new postoperative CSF fistulas, there is no beneficial need of the application of a lumbar drain. In these cases, a revision surgery should be recommended as treatment option.

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8. Curriculum vitae

For data protection reasons, the curriculum vitae will not be published in the electronic version of the doctoral thesis.

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