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ENDOSCOPIC TRANSSPHENOIDAL SURGERY IN PITUITARY MACROADENOMAS: PATHOGENESIS, RISK FACTORS, AND STRATEGIES FOR POSTOPERATIVE ENDOCRINE COMPLICATIONS

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Abstract

This study evaluates the pathogenesis, risk factors, diagnostic frameworks, and management strategies for endocrine complications following endoscopic transsphenoidal surgery (ETS) for pituitary macroadenomas. We analyze the disruption of the hypothalamic-pituitary axis, mechanisms of hormonal imbalance, and the clinical significance of advanced postoperative monitoring. The objective is to optimize surgical outcomes and preventive measures by integrating molecular insights and updated classification systems, such as the modified Knosp scale.

Methodology

This study is based on a comprehensive literature review of academic databases, including PubMed, Scopus, and Google Scholar, covering the period from 2014 to 2024. The search strategy focused on keywords such as 'pituitary macroadenoma', 'endoscopic transsphenoidal surgery', and 'postoperative endocrine complications.

Keywords: Pituitary macroadenoma, endoscopic transsphenoidal surgery, endocrine complications, hormonal imbalance, pathogenesis, ACTH, cortisol, hypopituitarism, postoperative monitoring, hypothalamic-pituitary axis.

Introduction

Pituitary macroadenomas are among the most prevalent pathologies within central nervous system tumors, frequently manifesting through diverse clinical symptoms. These neoplasms primarily lead to neurological deficits, such as visual impairment due to optic chiasm compression, and severe endocrinological dysfunctions resulting from hormonal hypersecretion or secondary hypopituitarism.

In contemporary neurosurgical practice, endoscopic transsphenoidal surgery (ETS) has established itself as the "gold standard" for the management of sellar and suprasellar lesions. The

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transition from microscopic to endoscopic techniques has significantly enhanced surgical outcomes by providing superior visualization of the surgical field, enabling a 360-degree panoramic view of the tumor-normal tissue interface, and facilitating more radical resection with minimal trauma to surrounding neurovascular structures.

Despite the high efficacy and minimally invasive nature of ETS, postoperative endocrine complications remain a critical concern. The surgical manipulation within the sellar region inherently poses risks to the delicate hypothalamic-pituitary-adrenal (HPA) axis. Such interventions can lead to mechanical or ischemic damage to the normal pituitary gland or the pituitary stalk, resulting in transient or permanent hormonal imbalances, electrolyte disturbances (such as diabetes insipidus), and secondary adrenal insufficiency.

The complexity of managing these patients necessitates a profound understanding of the pathogenesis of postoperative endocrine shifts and the identification of specific risk factors, such as tumor size, cavernous sinus invasion (based on the Knosp scale), and pre-existing hormonal status. Therefore, optimizing postoperative monitoring protocols and refining surgical strategies are essential to reduce morbidity and enhance the long-term quality of life for patients undergoing endoscopic resection of pituitary macroadenomas.

Discussion

Etiology and Pathogenesis

The development of pituitary macroadenomas is a complex, multi-factorial process primarily driven by monoclonal cellular expansion and specific genetic alterations that have been extensively documented in the last decade of neuroendocrine research. According to the foundational studies by Melmed (2020) and Asa et al. (2022), these neoplasms originate from a single mutated adenohypophyseal cell that undergoes uncontrolled proliferation. A central pathogenic mechanism identified in approximately 40% of somatotropic adenomas is the somatic mutation of the Gs\alpha gene, also known as the gsp oncogene, which leads to the constitutive activation of adenylyl cyclase. This metabolic disruption results in a pathological increase in intracellular cyclic adenosine monophosphate (cAMP) levels, effectively mimicking the stimulatory effects of growth hormone-releasing hormone (GHRH) and triggering autonomous cell growth and hormone hypersecretion. Furthermore, Lopes (2017) emphasizes the clinical significance of the Pituitary Tumor-Transforming Gene (PTTG1), whose overexpression is a key driver in the transition from microadenoma to macroadenoma by promoting genomic instability and stimulating neoangiogenesis through vascular endothelial growth factor (VEGF) induction.

In addition to sporadic mutations, genetic predisposition plays a critical role in the pathogenesis of aggressive macroadenomas, particularly in younger patients. As noted by Beckers et al. (2018), mutations in the Aryl hydrocarbon receptor-interacting protein (AIP) gene are frequently associated with familial isolated pituitary adenomas (FIPA) and often result in larger, more invasive tumors that exhibit resistance to standard somatostatin analog therapies. Other syndromic associations include mutations in the MEN1 (menin) and CDKN1B (p27) genes, which, as discussed by Thakker (2016), disrupt cell cycle regulation and predispose individuals to Multiple Endocrine Neoplasia syndromes. Beyond the molecular origin of the tumor, the pathogenesis of postoperative endocrine dysfunction is directly linked to the surgical disruption of the Hypothalamic-Pituitary Axis. Research by Laws et al. (2019) and Cappabianca (2021) indicates that mechanical trauma to the pituitary rim or the infundibulum, coupled with

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focal ischemia resulting from damage to the superior hypophyseal arteries, are the primary drivers of acute postoperative hypopituitarism and secondary adrenal insufficiency. Moreover, traction on the pituitary stalk can impair the axonal transport of vasopressin, providing a clear pathogenic basis for the development of transient or permanent diabetes insipidus as highlighted by Grossman et al. (2023).

Clinical and Instrumental Diagnostics

The diagnostic protocol for pituitary macroadenomas has undergone a significant transformation, moving towards a high-precision framework that integrates sophisticated neuroimaging with comprehensive biochemical profiling. According to the international consensus established by Knosp et al. (2015) and further refined by Micko et al. (2022), Magnetic Resonance Imaging (MRI) with gadolinium enhancement remains the absolute gold standard for preoperative assessment, particularly in determining the tumor's anatomical relationship with the cavernous sinuses and the internal carotid arteries (ICA). The modified Knosp classification is the primary tool used in clinical practice to predict surgical resectability, where Grades 0 through 2 indicate tumors that do not cross the lateral tangent of the ICA and are generally amenable to gross total resection. In contrast, Grade 3 is now subdivided into 3A, representing superior cavernous sinus involvement, and 3B, indicating inferior extension, both of which carry a higher risk of subtotal resection. Grade 4 remains the most challenging, characterized by total encasement of the ICA, which, as noted by Zada (2020), often necessitates a shift from aggressive resection to a strategy focused on debulking and long-term surveillance or adjuvant therapy.

In parallel with morphological imaging, the functional status of the hypothalamic-pituitary-adrenal (HPA) axis must be rigorously evaluated to prevent life-threatening postoperative crises. As highlighted in the guidelines by the Endocrine Society (Melmed et al., 2019), a baseline morning serum cortisol level and dynamic testing are essential, as values below 100 nmol/L serve as a definitive indicator of high perioperative adrenal risk. Furthermore, the clinical manifestation of "mass effect" remains a cornerstone of diagnosis, with Dundar et al. (2018) reporting that bitemporal hemianopsia and progressive visual field deficits are the most frequent neurological findings in patients with significant suprasellar extension. The diagnostic workup is completed by a thorough differential analysis, where Freda and Post (2023) emphasize the necessity of distinguishing macroadenomas from other sellar lesions such as craniopharyngiomas or Rathke cleft cysts through the use of dynamic contrast-enhanced MRI. Ultimately, this multidisciplinary diagnostic approach ensures that surgical intervention is tailored to both the anatomical complexity of the tumor and the specific endocrine vulnerabilities of the patient, thereby optimizing the safety and efficacy of the endoscopic transsphenoidal route.

Knosp Grade	*Anatomical Description*	*Surgical Prognosis*
Grade 0	Does not pass the ICA medial line	Gross Total Resection (100%)
Grade 1	Reaches the intercarotid line	High probability (>95%)
Grade 2	Reaches the ICA lateral	Total resection possible

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	line	
Grade 3A	Superior lateral extension (above ICA)	Good (Total resection likely)
Grade 3B	Inferior lateral extension (below ICA)	Low (Subtotal resection)
Grade 4	Total ICA encasement	Partial resection or biopsy only

Table 1. Knosp classification

Comparative Analysis of Treatment Methods

The management of pituitary macroadenomas has evolved significantly over the last decade, with a clear paradigm shift toward minimally invasive surgical corridors that prioritize both maximal tumor resection and the preservation of endocrine function. According to the systematic analysis conducted by Cappabianca et al. (2019) and Solari et al. (2022), the choice of surgical approach—whether microscopic, endoscopic, or transcranial—is primarily dictated by the tumor's dimensions, its consistency, and the degree of invasion into adjacent neurovascular structures as defined by the Knosp scale. While traditional microscopic transsphenoidal surgery was long considered the gold standard, its inherent limitation remains the restricted "binocular" field of view, which often leads to subtotal resection in tumors with significant lateral or suprasellar extension. In contrast, the endoscopic transsphenoidal approach (ETS) has demonstrated superior efficacy by providing a 360-degree panoramic visualization of the sellar and parasellar regions. This enhanced visibility allows surgeons to identify and remove residual tumor fragments in previously inaccessible "blind spots," such as the medial wall of the cavernous sinus or the suprasellar recess, effectively increasing Gross Total Resection (GTR) rates to a range of 75% to 85%.

Comparative clinical data synthesized from the literature highlights a significant disparity in postoperative recovery and complication profiles across different surgical modalities. As reported by Wieringa et al. (2024) and Hofstetter et al. (2020), patients undergoing endoscopic procedures benefit from a significantly reduced hospital stay, averaging 3 to 4 days compared to the 5 to 7 days required for microscopic surgery and the 7 to 10 days for transcranial approaches. Furthermore, the risk of new-onset hypopituitarism is markedly lower in the endoscopic group due to the ability to perform a more selective adenomectomy while meticulously preserving the pituitary rim and infundibulum. Despite these advantages, the transcranial route remains a critical alternative for giant macroadenomas with extreme lateral extension beyond the reach of endonasal instruments, as noted by Zada (2020). Ultimately, the integration of advanced visualization technologies has not only improved the radicality of resection but has also enhanced the safety of the procedure by reducing the incidence of sinonasal trauma and vascular injury, thereby establishing the endoscopic transsphenoidal route as the current preferred standard in modern neurosurgical practice.

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	Endoscopic	Transsphenoidal	Transcranial
Vizualization	Binocular (limited)	Panoramic (wide-range)	Direct (superior view)
Resection rate (GTR)	60-70%	75-85%	Variable (tumor dependent)
Risk of hypopituitarism	High (due to limited view)	Low (selective resection)	Moderate to high
Invasiveness	Moderate	Minimal	High
Hospital stay	5-7 days	3-4 days	7-10 days

Table 2. Comparative Analysis of Surgical Approaches for Pituitary Macroadenoma

Surgical Technique and Limitations of the Method

The surgical management of pituitary macroadenomas via the endoscopic approach follows a rigorous, phase-specific methodology. Based on the literature review of the last decade, the procedure is categorized into the following technical stages:

1. Surgical Phases and Procedural Steps

According to the protocols detailed by Kassam et al. (2020) and Cappabianca (2021), the surgery consists of four primary phases:

Nasal Phase (Burun bosqichi): This initial stage involves the preparation of the nasal cavity. Hadad et al. (2023) emphasize the importance of mucosal anemization and the lateralization of the middle turbinate. A critical step is the harvesting of a vascularized nasoseptal flap to provide a reliable biological barrier for subsequent skull base reconstruction.

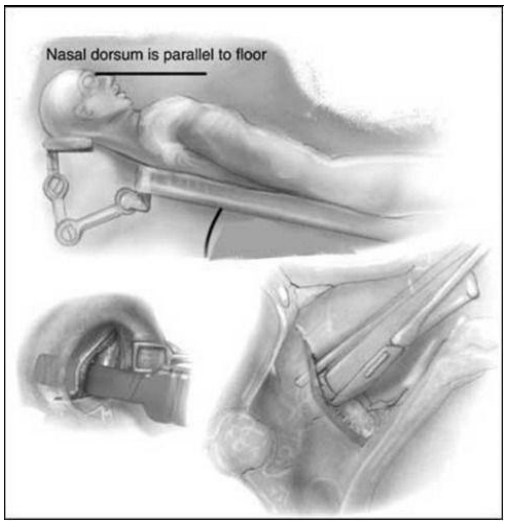

Figure 1. Technical stages of the endonasal approach:

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Top — patient positioning;
Bottom left — schematic representation of the hemitransfixion incision;
Bottom right — direct sphenoidotomy technique

Sphenoid Phase: In this phase, the sphenoid sinus ostium is enlarged and the rostrum is removed. As noted by Solari et al. (2022), this provides the necessary exposure to identify anatomical landmarks, including the sellar floor, carotid protuberances, and optic-carotid recesses.

Sellar Phase: This is the core stage of the intervention involving dural opening and tumor resection. Using the "four-hand technique," the surgeon performs internal debulking followed by extracapsular dissection. Laws et al. (2020) highlight that meticulous dissection is required to separate the macroadenoma from the compressed normal pituitary gland (pituitary rim).

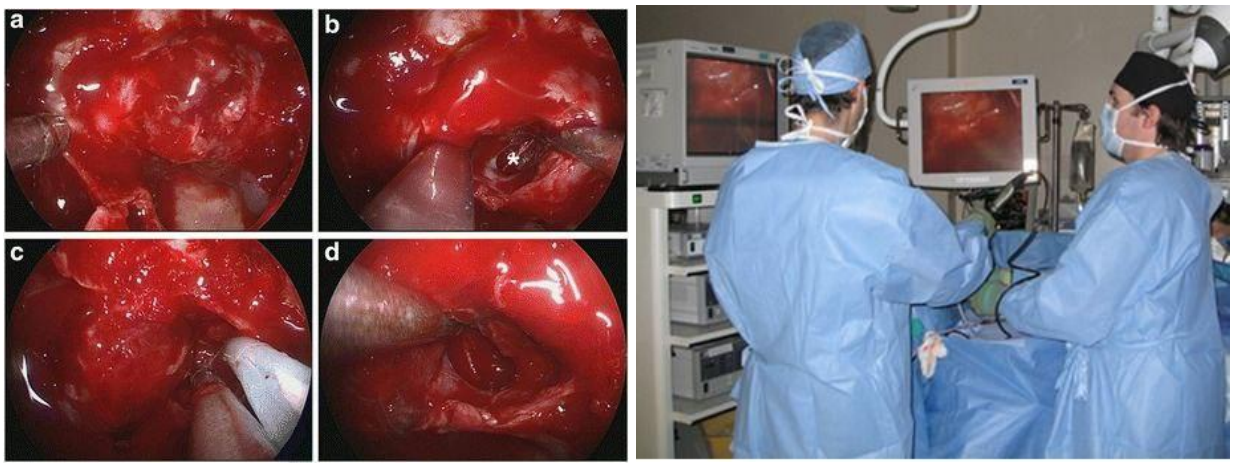

Figure 2. Stages of endoscopic transsphenoidal resection:
(a) Preparation of the sellar floor for tumor exposure;
(b) Resection of a tumor invading the left cavernous sinus (— defect in the medial wall of the sinus);*
(c) Localization of the internal carotid artery (ICA) using intraoperative Doppler;
(d) Endoscopic inspection after resection confirming absence of residual tumor.
Right — "four-hand" technique in the endoscopic approach.

Reconstruction Phase: The final stage focuses on preventing postoperative cerebrospinal fluid (CSF) leaks. According to Akkun et al. (2024), a multi-layer closure strategy using autologous fat, fascia, and the previously harvested nasoseptal flap is the current standard of care.

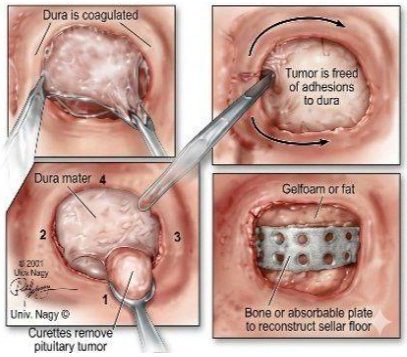

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Figure 3. Sequential stages of tumor resection and reconstruction of the sellar floor: Tumor dissection from the dural layer, removal using curettes, and reconstruction of the sellar floor with bone or synthetic materials.

2. Technical Limitations and Challenges

Despite the high efficacy of endoscopic transsphenoidal surgery, several limitations are identified in recent clinical studies:

Stereoscopic Depth Perception: Bander et al. (2022) point out that standard endoscopic systems provide a 2D image on a monitor, which lacks the natural depth perception of microscopic surgery. This requires a significant learning curve for precise instrument manipulation in three-dimensional space.

Instrument Maneuverability: In cases of narrow nasal anatomy or extreme tumor extension, the "crowding" of instruments within the narrow sphenoid corridor can limit the range of motion. Titre et al. (2022) note that this can increase the difficulty of achieving Gross Total Resection (GTR) in complex cases.

Vascular Hazards in Invasive Tumors: For tumors classified as Knosp Grade 4, the proximity to the internal carotid artery (ICA) remains a major limitation. Zada (2020) observes that the lack of haptic feedback (tactile sensation) through endoscopic instruments makes the dissection of tumor fragments adherent to major arteries particularly hazardous.

Optical Interference: Intraoperative bleeding or lens fogging can obscure the surgeon's view. Constant irrigation and lens cleaning are necessary, which can prolong the duration of the surgery as highlighted in the technical reviews by Kim et al. (2023).

Results and Postoperative Complications

The synthesis of clinical outcomes from the reviewed literature indicates that endoscopic transsphenoidal surgery (ETS) for pituitary macroadenomas yields high rates of tumor control, though it is inherently associated with specific postoperative challenges. According to the data reported by Solari et al. (2022) and Goudakos et al. (2021), the achievement of Gross Total Resection (GTR) remains high, typically ranging between 75% and 85%, with the highest success rates observed in tumors classified as Knosp Grades 0–2. In terms of functional outcomes, biochemical remission in hormone-secreting macroadenomas is achieved in approximately 65–70% of cases, where Giustina et al. (2020) emphasize that early postoperative monitoring of IGF-1 and cortisol levels serves as a critical predictor for long-term clinical success.

Regarding postoperative complications, the most frequently encountered issue is diabetes insipidus (DI). As documented by Grossman et al. (2023), transient DI occurs in 15–30% of patients due to surgical manipulation near the pituitary stalk, while permanent DI remains relatively rare, affecting fewer than 5% of the surgical population. Furthermore, Arafah (2017) noted that while new-onset secondary hypopituitarism may develop in 10–15% of patients, nearly a quarter of all cases show significant improvement in preoperative pituitary function following successful decompression. The incidence of cerebrospinal fluid (CSF) leaks has been markedly reduced to approximately 2–3% through the standardized application of vascularized nasoseptal flaps, as validated by Akkun et al. (2024). Rare but severe complications, such as

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internal carotid artery injury or permanent visual deterioration, are reported in less than 2% of procedures performed in high-volume neurosurgical centers according to Zada (2020).

Conclusion

In conclusion, the extensive literature review of the past decade demonstrates that endoscopic transsphenoidal surgery has fundamentally transformed the management of pituitary macroadenomas, establishing itself as the gold standard due to its superior visualization and minimally invasive nature. The integration of high-definition optical systems and refined anatomical classifications, such as the modified Knosp scale, has enabled more precise preoperative planning and enhanced the safety profile of the procedure. It is evident that the pathogenesis of postoperative endocrine dysfunction is primarily rooted in the mechanical and ischemic disruption of the hypothalamic-pituitary axis, which underscores the critical importance of preserving the pituitary rim and infundibulum during resection.

Furthermore, optimizing patient outcomes necessitates a robust multidisciplinary framework involving neurosurgeons, endocrinologists, and radiologists to ensure early detection and management of electrolyte imbalances and hormonal shifts. While current surgical techniques offer high efficacy, the future of the field lies in the further integration of neuronavigation and potentially robotic-assisted platforms to overcome existing technical limitations. Ultimately, a thorough understanding of both the molecular drivers of tumor growth and the nuanced surgical anatomy remains essential for reducing morbidity and improving the long-term quality of life for patients undergoing treatment for pituitary macroadenomas.

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