Pituitary Neuroendocrine Tumor Outcome

A study suggests that elderly patients carefully selected for endoscopic endonasal approach removal can have excellent short-term outcomes including high resection rates, low complication rates and short length of stay. The experience supports a multidisciplinary approach and the concept of pituitary centers of excellence. Based on observations, approximately 25% of elderly patients with pituitary neuroendocrine tumors referred for possible surgery can be monitored closely without surgery [1].

Although they are considered benign tumors, some of them are difficult to treat due to their tendency to recur despite standardized treatment. Functional tumors present other challenges for normalizing their biochemical activity. Novel approaches for early diagnosis, as well as different perspectives on classification, may help to identify subgroups of patients with similar characteristics, creating opportunities to match each patient with the best personalized treatment option [2].

Pituitary Neuroendocrine Tumor Progression

Tumor progression involves a combination of genetic, epigenetic, molecular, and microenvironmental factors that contribute to increased proliferation, invasiveness, and resistance to treatment.

1. Molecular Mechanisms of Progression a. Genetic and Epigenetic Changes Mutations and Chromosomal Aberrations: Unlike other neuroendocrine tumors, PitNETs rarely harbor recurrent driver mutations. However, some aggressive variants exhibit alterations in genes such as MEN1, AIP, TP53, and USP8. Epigenetic Modifications: Hypermethylation of tumor suppressor genes and histone modifications can contribute to PitNET progression. For example, altered expression of p16INK4A and RASSF1A is associated with aggressive tumor behavior. b. Hormonal and Growth Factor Signaling Excessive Hormone Secretion: Some PitNETs (e.g., growth hormone-secreting or ACTH-secreting tumors) induce secondary metabolic changes that promote tumor expansion. Growth Factors and Cytokines: Increased expression of EGFR, VEGF, and FGF enhances angiogenesis and invasiveness, especially in aggressive and recurrent tumors. c. Cell Cycle Dysregulation Loss of p27/Kip1 and overexpression of cyclin D1 lead to unchecked cell proliferation. Dysregulated MAPK/ERK and PI3K/Akt/mTOR pathways contribute to cell survival and resistance to apoptosis. 2. Tumor Microenvironment and Invasion Immune Evasion: PitNETs create an immunosuppressive environment by reducing T-cell infiltration and increasing TGF-β expression. Extracellular Matrix Remodeling: Increased MMP-9 and MMP-2 activity enables basement membrane degradation, facilitating tumor invasion into the cavernous sinus and dura mater. Hypoxia and Angiogenesis: Hypoxic conditions upregulate HIF-1α, promoting neovascularization and treatment resistance. 3. Clinical Implications of Tumor Progression a. Classification of Aggressive PitNETs Non-invasive, slow-growing tumors: Most PitNETs fall into this category. Invasive tumors: Exhibit cavernous sinus invasion and have a higher recurrence risk. Refractory and malignant PitNETs: Resistant to conventional treatments, sometimes progressing to pituitary carcinoma with distant metastases. b. Predictors of Aggressiveness Ki-67 index >3% and p53 positivity suggest a higher risk of progression. Tumor invasion on MRI (e.g., Knosp grade ≥3) correlates with surgical challenges and recurrence. c. Treatment Challenges and Emerging Therapies Surgical Resection: The primary treatment, but incomplete removal increases recurrence risk. Radiotherapy: Used for residual or recurrent tumors, particularly when invading critical

structures. Targeted Therapies: Dopamine agonists (e.g., cabergoline) for prolactinomas. Somatostatin analogs for GH-secreting tumors. mTOR and CDK4/6 inhibitors are under investigation for resistant cases. Immunotherapy approaches targeting the tumor microenvironment may provide future treatment avenues. Conclusion Pituitary neuroendocrine tumor progression is a multifactorial process involving genetic mutations, hormonal dysregulation, and microenvironmental changes. While most tumors remain indolent, aggressive subtypes require multimodal treatment and ongoing research to develop effective therapeutic strategies. Understanding the underlying mechanisms will help improve prognostic markers and targeted interventions for high-risk patients.

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Thakur JD, Corlin A, Mallari RJ, et al. pituitary neuroendocrine tumors in older adults (≥ 65 years): 90-day outcomes and readmissions: a 10-year endoscopic endonasal surgical experience [published online ahead of print, 2020 Sep 16]. Pituitary. 2020;10.1007/s11102-020-01081-9. doi:10.1007/s11102-020-01081-9

2)

Syro LV, Rotondo F, Ramirez A, Di Ieva A, Sav MA, Restrepo LM, Serna CA, Kovacs K. Progress in the Diagnosis and Classification of pituitary neuroendocrine tumors. Front Endocrinol (Lausanne). 2015 Jun 12;6:97. doi: 10.3389/fendo.2015.00097. eCollection 2015. Review. PubMed PMID: 26124750; PubMed Central PMCID: PMC4464221.