

# Pituitary Tumor Surgery

## *Factors Influencing Outcome*

Akademisk avhandling

Som för avläggande av medicine doktorexamen vid Sahlgrenska akademien, Göteborgs universitet kommer att offentligens försvaras i lokal 2119, Hälsovetarbacken/Medicinareberget, fredagen den 28 maj 2021 klockan 9.00.

av **Tobias Hallén**

Fakultetsopponent:

Professor Peter Siesjö, Universitetssjukhuset i Lund, Sverige

### Avhandlingen baseras på följande delarbeten:

- I. Hallén T, Olsson D.S, Hammarstrand C, Farahmand D, Olofsson A-C, Jakobsson Ung E, Jakobsson S, Bergquist H, Blennow K, Zetterberg H, Johannsson G, Skoglund T.  
**Circulating brain injury biomarkers increase after endoscopic surgery for pituitary tumors**  
*Submitted*
- II. Hallén T, Olsson D.S, Farahmand D, Esposito D, Olofsson A-C, Jakobsson S, Jakobsson Ung E, Sahlstrand-Johnson P, Johannsson G, Skoglund T, Bergquist H.  
**Sinonasal symptoms and self-reported health before and after endoscopic pituitary surgery – a prospective study**  
*J Neurol Surg B. 2021 Feb 18; doi:10.1055/s-0041-1722929*
- III. Hallén T, Olsson D.S, Hammarstrand C, Örndal C, Engvall A, Ragnarsson O, Skoglund T, Johannsson G.  
**MCM7 as a marker of postsurgical progression in non-functioning pituitary adenomas**  
*Eur J Endocrinol. 2021;184(4):521-535; doi:10.1530/EJE-20-1086*
- IV. Hallén T, Johannsson G, Dahlén R, Glad, C, Örndal C, Engvall A, Carén H, Skoglund T, Olsson D.S.  
**Genome-wide DNA methylation differences in non-functioning pituitary adenomas with or without postsurgical tumor progression**  
*Manuscript*

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### Abstract

**Background:** Pituitary tumors represent 15–20% of intracranial tumors. The majority are benign adenomas, of which 30 % are hormonally inactive, the non-functioning pituitary adenomas (NFPAs). A possible neuronal damage during treatment of pituitary tumors with endoscopic transsphenoidal surgery (ETSS) has not been previously investigated, and postoperative sinonasal morbidity is frequently overlooked. Current markers predicting postoperative tumor progression of NFPAs are insufficient.

**Aims:** To quantify a possible neuronal and astroglial damage during ETSS and to assess sinonasal morbidity before and six months after surgery. To investigate novel immunohistochemical and epigenetic markers as predictive factors for postoperative tumor progression in NFPAs.

**Methods:** In *paper I*, sequential blood sampling of brain injury biomarkers GFAP, tau and NFL was performed before and after ETSS. Correlations between their increase and perioperative factors and fatigue outcome were investigated. In *paper II*, sinonasal and self-reported general health was assessed preoperatively and 6 months postoperatively with the Sinonasal Outcome Test 22 (SNOT-22) and EQ-5D. In *paper III and IV*, tumoral expression of minichromosome maintenance protein 7 (MCM7) and DNA-methylation patterns were studied regarding their association with postoperative tumor progression in NFPAs.

**Results:** GFAP, tau and NFL increased postoperatively, with peaks at different time points. The increase of GFAP and tau correlated to preoperative suprasellar tumor extension. At 6 months after surgery, self-reported general health was improved, but rhinologic symptoms had worsened. Increased MCM7 expression and specific DNA methylation patterns were associated with postoperative tumor progression.

**Conclusions:** GFAP and tau might be markers of neuronal and/or astroglial damage during ETSS, but the clinical significance needs to be further investigated. ETSS is generally well-tolerated, but rhinologic symptoms should not be overlooked during follow-up. MCM7 might be a valuable adjunct as a predictive marker for postoperative tumor progression in NFPAs. Specific methylation patterns might be used as epigenetic signatures predictive of tumor progression in NFPAs.

**Keywords:** *Endoscopic transsphenoidal surgery, biomarkers, glial fibrillary acidic protein, neurofilaments, tau protein, pituitary tumors, sinonasal health, tumor progression, predictive markers, MCM7, methylation patterns, NFPA*