Reclassification of "Null Cell Adenomas" Based on Pituitary Transcription Factor Staining

Alexander S. Himstead, MD[1]; Sarah M. Smith, MD, PhD[1]; Joshua Kurtz, MD[1], Kristine Nguyen[1], William H. Yong, MD[2], Mari Perez-Rosendahl, MD[2]; Edward C. Kuan, MD[3]; Aaron B. Simon, MD, PhD[4]; Frank P. K. Hsu, MD, PhD[1]; Ahmed Mohyeldin, MD, PhD[1]

[1]University of California, Irvine, Department of Neurological Surgery, Orange, CA
[2]University of California, Irvine, Department of Pathology, Orange, CA
[3]University of California, Irvine, Department of Otolaryngology-Head and Neck Surgery, Orange, CA
[4]University of California, Irvine, Department of Radiation Oncology, Orange, CA

Introduction

- Null cell adenomas (NCAs) are nonfunctional pituitary neuroendocrine tumors (PitNETs) that lack hormone immunohistochemical staining[1,2].
- Historically, NCAs accounted for up to 30–40% of nonfunctional pituitary adenomas[3,4].
- With routine pituitary transcription factor (PTF) staining (SF-1, PIT-1, T-PIT), many tumors previously labeled as null cell may be reclassified[3].

Objective

To reclassify hormone-negative pituitary adenomas using PTF staining and compare clinical and radiographic features of **true null cell adenomas** versus reclassified nonfunctional PitNET subtypes.

Methods

- Retrospective single-institution cohort of transsphenoidal resections (2012–2024).
- Of 223 nonfunctional PitNETs, 54 were hormone-negative by immunohistochemistry.
- Formalin-fixed paraffin-embedded tissue was available in 36 cases.
- Slides were sent to Mayo Clinic for SF-1, PIT-1, and T-PIT staining.
- Two neuropathologists independently reviewed all specimens.
- Tumor volume (A×B×C / 2), Knosp grade, 3-month postoperative residual disease, and reoperation were recorded.
- After re-classification, comparisons were made between different null cell adenoma groups
- SF-1(+) hormone-negative tumors were compared with FSH/LH(+) cohort
- Statistical analysis performed using GraphPad Prism.

Results

- **Reclassification:**
  - 11 tumors SF-1(+), 5 PIT-1(+), 5 plurihormonal (SF-1 + PIT-1).
  - 13 tumors remained PTF-negative (true null cell adenomas).
  - 2 equivocal cases excluded.
- **Across reclassified groups**, no significant differences were observed in age, sex, tumor volume, Knosp ≥3, residual tumor, or reoperation (all p>0.05).
- **Tumor volume trended larger** in SF-1(+) tumors compared to other subtypes (20.3 cm³ vs. 15.1 [NCA], 6.0 [PIT-1], 7.3 [PHT]; p=0.66).
- **True null cell adenomas** showed higher—but nonsignificant—rates of Knosp ≥3 (46.2%), residual disease (66.7%), and reoperation (30.8%).
- When compared with a **separate cohort** of **121 FSH/LH(+)** silent gonadotroph adenomas:
  - SF-1(+) reclassified tumors were significantly larger (20.3 vs. 8.6 cm³, p<0.0001).
  - Knosp ≥3 trended higher in SF-1(+) tumors (36.4% vs. 13.6%).
  - Residual disease and reoperation rates were similar between groups.

Conclusions

Among 36 previously designated non-functional null cell adenomas, 21 (58.3%) were reclassified as either SF-1(+), PIT-1(+) or pleurihormonal

- The majority of pituitary adenomas previously labeled as null cell can be reclassified using PTF staining.
- Reclassified SF-1(+) tumors are significantly larger than hormonally silent gonadotroph adenomas and may exhibit more invasive features.
- True null cell adenomas represent a smaller subset and may demonstrate more aggressive behavior, though larger cohorts are needed.
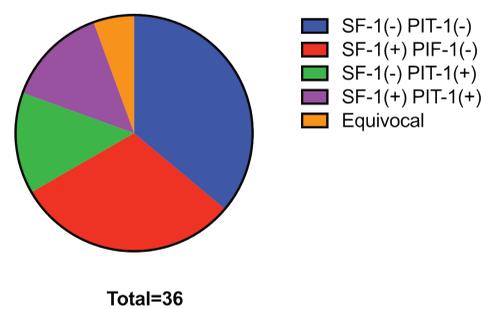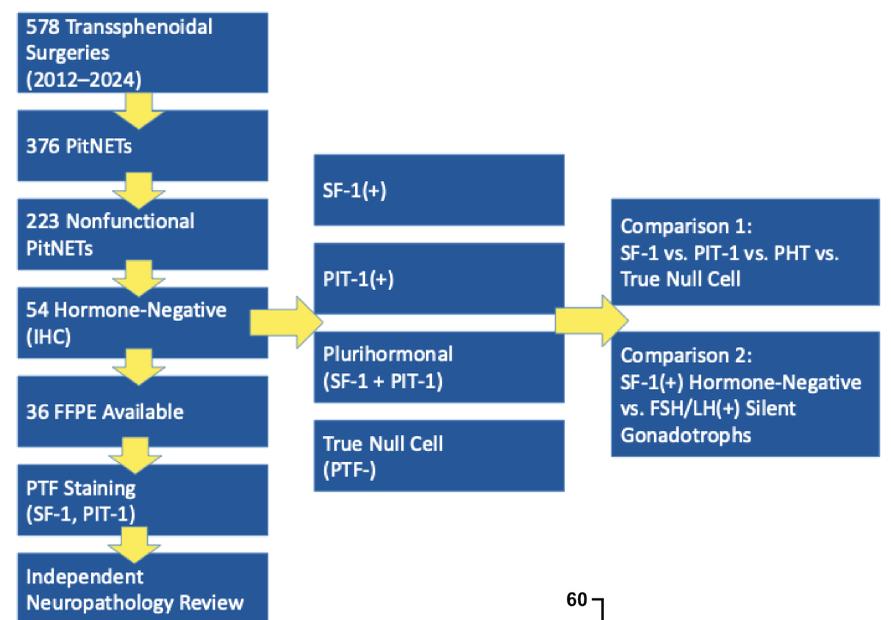- Routine PTF staining refines PitNET classification and may improve prognostication.

Flowchart:
578 Transsphenoidal Surgeries (2012–2024) → 376 PitNETs → 223 Nonfunctional PitNETs → 54 Hormone-Negative (IHC) → 36 FFPE Available → PTF Staining (SF-1, PIT-1) → Independent Neuropathology Review

SF-1(+), PIT-1(+), Plurihormonal (SF-1 + PIT-1), True Null Cell (PTF-)

Comparison 1: SF-1 vs. PIT-1 vs. PHT vs. True Null Cell
Comparison 2: SF-1(+) Hormone-Negative vs. FSH/LH(+) Silent Gonadotrophs

Legend: SF-1(-) PIT-1(-); SF-1(+) PIF-1(-); SF-1(-) PIT-1(+); SF-1(+) PIT-1(+); Equivocal

Total=36

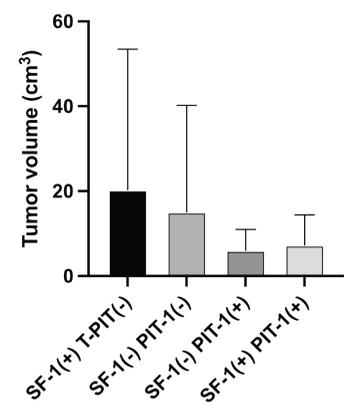**Figure 1.** Pie chart showing proportions of reclassified NCAs

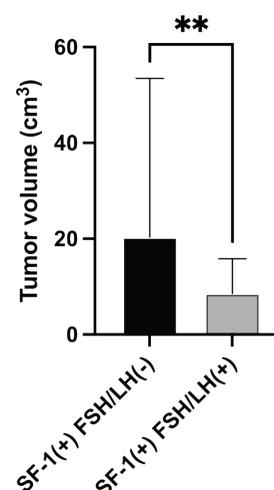**Figure 2.** Mean tumor volume across reclassified NCA subtypes; no significant differences detected.

Figure 3. Mean tumor volume between reclassified NCA (left) vs. FSH/LH(+) gonadotrophs (right)
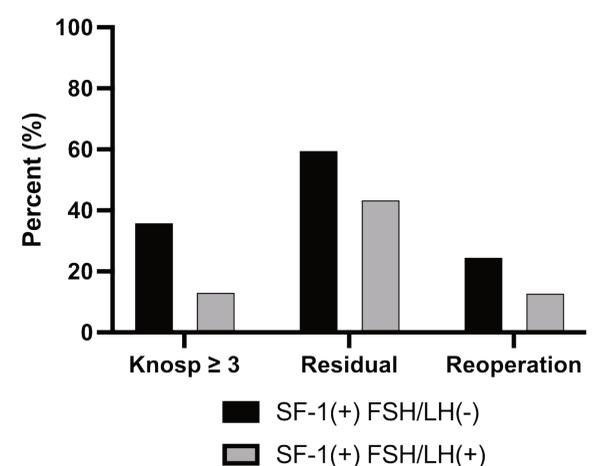
Figure 4. Trend towards more invasiveness, likelihood of residual, and need for reoperation in reclassified NCA

Contact

Ahmed Mohyeldin, M.D., Ph.D.
University of California, Irvine
Department of Neurological Surgery
200 S Manchester Ave, Suite 210
amohyeld@hs.uci.edu
714-456-6966

References

1. Kobalka PJ, Huntoon K, Becker AP. Neuropathology of Pituitary Adenomas and Sellar Lesions. *Neurosurgery*. 2021;88(5):900-918. doi:10.1093/neuros/nyaa548
2. Saeger W, Koch A. Clinical Implications of the New WHO Classification 2017 for Pituitary Tumors. *Exp Clin Endocrinol Diabetes*. 2021;129(3):146-156. doi:10.1055/a-1310-7900
3. Nasi-Kordhishti I, Hladik M, Kandilaris K, Behling F, Honegger J, Schittenhelm J. Transcription factor-based classification of pituitary adenomas / PitNETs: a comparative analysis and clinical implications across WHO 2004, 2017 and 2022 in 921 cases. *Acta Neuropathol Commun*. 2025;13(1):135. Published 2025 Jun 28. doi:10.1186/s40478-025-02050-8
4. Chatrath A, Kosyakovsky J, Patel P, et al. Impact of histopathological classification of non-functioning adenomas on long term outcomes: comparison of the 2004 and 2017 WHO classifications. *Pituitary*. 2022;25(6):988-996. doi:10.1007/s11102-022-01281-5