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## Introduction

While dopamine agonists have long been considered the standard of care for prolactinomas, the clinical role of surgical resection is being increasingly re-evaluated for its potential benefits in specific patient populations. Our previous research on non-functioning pituitary adenomas (NFPAs) established that the "high-risk" classification under the WHO 2022 criteria serves as a significant independent prognostic factor for tumor progression and recurrence. Building upon this academic foundation, the present study aims to investigate the clinicopathological heterogeneity within a cohort of surgically treated prolactinomas by applying transcription factor-based reclassification. By identifying rare and potentially drug-resistant entities such as acidophilic stem cell adenomas or high-risk immature PIT1 lineage tumors, we seek to emphasize the critical value of surgical intervention in providing precise diagnosis and informing optimized management strategies for selected patients.

## Methods and Materials

We retrospectively reviewed a consecutive series of patients with prolactin-secreting pituitary tumors who underwent surgical resection at our institution between October 2019 and March 2025. Following the methodology established in our previous study on non-functioning pituitary adenomas, all identified cases were reclassified according to the 2022 WHO Classification of Endocrine and Neuroendocrine Tumors using transcription factor-based immunohistochemistry. A comprehensive review of clinical and radiological records was performed to collect data on prior medical therapy history, preoperative prolactin levels, and the extent of surgical resection. Postoperative clinical outcomes were evaluated by assessing the achievement of endocrinologic remission (ER), defined by normalized prolactin levels without the need for adjunctive dopamine agonist therapy. This standardized approach allowed for a robust comparison of clinicopathological characteristics across various PIT1-lineage subtypes.

## Results

The clinical and pathological profiles of the nine patients included in this study are detailed in Table 1. This cohort demonstrated that while all cases were clinically diagnosed as prolactinomas based on secretory activity, reclassification under the WHO 2022 criteria revealed significant histological diversity within the PIT1 lineage, as illustrated in Chart 1. Only a minority of cases (33.3%) were identified as typical lactotroph adenomas. The majority (66.7%) comprised various subtypes including mammosomatotroph adenomas, acidophilic stem cell adenomas (ASCA), and high-risk immature PIT1-lineage adenomas. A history of prior medical therapy was present in 67% of patients, and preoperative prolactin levels were significantly higher in treatment-naïve cases, reaching as high as 1,808.40 ng/mL. Surgical outcomes were robust, with gross total resection (GTR) achieved in 88.9% of the patients. Endocrinologic remission (ER) was achieved in 66.7% of the cases through surgery alone, whereas the remaining 33.3% (primarily those with more aggressive or high-risk subtypes) failed to reach remission initially and required additional management.

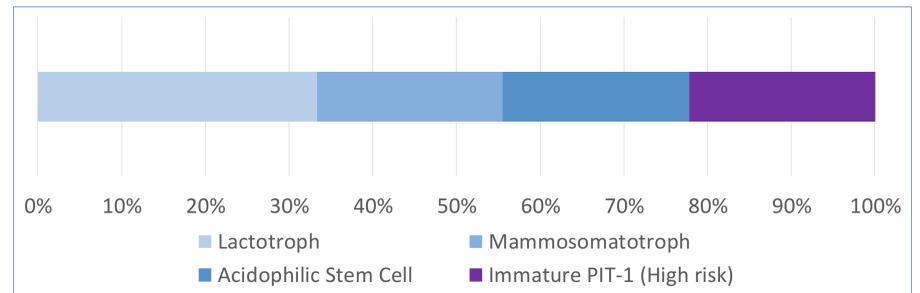


Chart 1. Distribution of PIT1-Lineage Subtypes in Surgically Treated Prolactinomas (n=9)

## Discussion

### Hidden Heterogeneity within PIT1-Lineage

Surgically treated prolactinomas exhibit significant histological diversity; in our series, pure lactotroph adenomas represented only 33% of cases. Reclassification according to the WHO 2022 criteria revealed various subtypes, including mammosomatotroph, acidophilic stem cell (ASCA), and immature PIT1-lineage adenomas. This "hidden heterogeneity" indicates that clinical presentation and serum prolactin levels may not fully reflect the underlying tumor biology, necessitating transcription factor-based diagnosis for precise management.

### Prognostic Significance and Male Aggressiveness

Our previous research on non-functioning pituitary adenomas (NFPAs) established the "high-risk" classification as a significant independent predictor of tumor progression ( $p=0.0148$ ). In this prolactinoma cohort, both male patients (Cases 3 and 7), who are traditionally considered high-risk, were reclassified as non-lactotroph PIT1 subtypes. This supports the hypothesis that the clinical aggressiveness often observed in male patients may be driven by a higher prevalence of complex or primitive PIT1-lineage biology rather than gender alone.

### Surgical Value and Selection Bias

Surgical intervention provided definitive tissue diagnosis for drug-resistant entities like ASCA, which typically exhibit lower remission rates compared to typical prolactinomas. While achieving 89% GTR and 67% ER, selection bias must be acknowledged: early cases primarily involved medical therapy failures, potentially overrepresenting high-risk subtypes, while recent female cases were often selected for a high probability of surgical cure. Despite these limitations, early surgical resection remains a critical tool for identifying aggressive subtypes and tailoring long-term surveillance protocols.

## Conclusions

The application of the WHO 2022 classification to surgically treated prolactinomas reveals significant histological heterogeneity, identifying high-risk PIT1-lineage subtypes that may mimic typical tumors but remain resistant to standard therapy. These results emphasize the critical value of surgical resection for precise diagnosis and management, consistent with the prognostic significance of high-risk groups established in our previous studies on non-functioning pituitary adenomas. To build a more comprehensive understanding of these rare entities, we propose an international multi-center collaboration to develop standardized, lineage-specific management protocols.

Table 1. Clinicopathological Profiles of Surgically Treated Prolactinomas (n=9)

Case	Sex	Age	Med Hx	Preop PRL (ng/mL)	Revised Dx (WHO 2022)	Resection	ER
1	F	54	Yes	224.25	Mammosomatotroph Adenoma	GTR	Yes
2	F	45	Yes	81.32	Densely Granulated Lactotroph Adenoma	GTR	Yes
3	M	53	Yes	178.06	Mammosomatotroph Adenoma	PR	No
4	F	37	Yes	91.51	Sparsely Granulated Lactotroph Adenoma	GTR	Yes
5	F	35	Yes	52.08	Acidophilic Stem Cell Adenoma	GTR	Yes
6	F	31	No	1,459.50	Densely Granulated Lactotroph Adenoma	GTR	No
7	M	55	No	1,808.40	Immature PIT1-lineage Adenoma	GTR	No
8	F	24	No	104.19	Acidophilic Stem Cell Adenoma	GTR	Yes
9	F	45	Yes	89.13	Immature PIT1-lineage Adenoma	GTR	Yes

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