Aggressive pituitary adenomas: Clinical predictors for rapidly recurrent pituitary adenomas – Looking beyond proliferative markers

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BACKGROUND

Pituitary adenomas (PAs) are benign, slow-growing tumors that can be managed through surgical resection, radiation therapy, or medical treatment. While most PAs have a benign course, a subset exhibits more aggressive behavior, characterized by rapid growth, recurrence, and resistance to standard therapies. However, a clear and universally accepted definition of aggressive PAs remains elusive.

Historically, the term "atypical pituitary adenoma" was introduced in the 2004 WHO classification to describe PAs with a potential for aggressive behavior. The criteria included a Ki-67 proliferation index of >3% and extensive p53 expression. However, these histopathological markers were later found to have limited predictive value, as many clinically aggressive PAs exhibited low mitotic activity and a lack of significant p53 expression. Consequently, the classification of atypical adenomas was abandoned in subsequent WHO classifications.

Recent studies have highlighted the need for alternative markers and clinical predictors to identify PAs with aggressive potential reliably. Factors such as tumor invasiveness, early recurrence, resistance to standard treatment, and molecular characteristics are being explored. This study aims to evaluate clinical, radiological, and molecular features that may serve as predictive markers for aggressive behavior in PAs, thereby improving early identification and guiding treatment strategies.

METHODS

A retrospective review was conducted on a database of patients treated for PAs between 2013 and 2023 at the authors' institution. Cases were screened for aggressive behavior, which was defined as radiologically confirmed tumor growth on MRI within 18 months following initial surgical or radiosurgical treatment.

A comprehensive set of potential predictors was analyzed, including patient demographics (gender, age), tumor characteristics (initial adenoma size at diagnosis, KS grade, adenoma subtype, and endocrine activity), and treatment response. To account for potential confounding factors, a generalized linear model was applied to assess the independent associations between these variables and tumor aggressiveness. Statistical significance was determined using appropriate regression analysis, and findings were compared with existing literature to identify reliable clinical predictors for aggressive PAs.

RESULTS

Of 700 patients treated for PAs, 153 required additional interventions due to recurrence or progression. Among them, 25 patients met the criteria for aggressive behavior, as defined by radiological evidence of tumor growth within 18 months of initial treatment.

Aggressive PAs demonstrated a significantly shorter intervention free survival (IFS), with an average of 11.3 (±4.9) months compared to 48.3 (±61.4) months in the non-aggressive cohort. Tumors exhibiting aggressive behavior were larger at initial diagnosis (25.6mm ±11.2 vs. 19.58mm ±12.22, p=0.01) and had a significantly higher prevalence of KS grade 3–4 invasion (60% vs. 32%, p=0.004).

Additionally, specific tumor subtypes showed a higher association with aggressive behavior. Prolactinomas in male patients were more frequently observed in the aggressive group compared to the non-aggressive cohort (12% vs. 2.5%, p=0.031). Silent corticotroph adenomas were also significantly more prevalent in aggressive cases (20% vs. 2.5%, p=0.01).

FIGURE 1 – Predictors for aggressive behavior

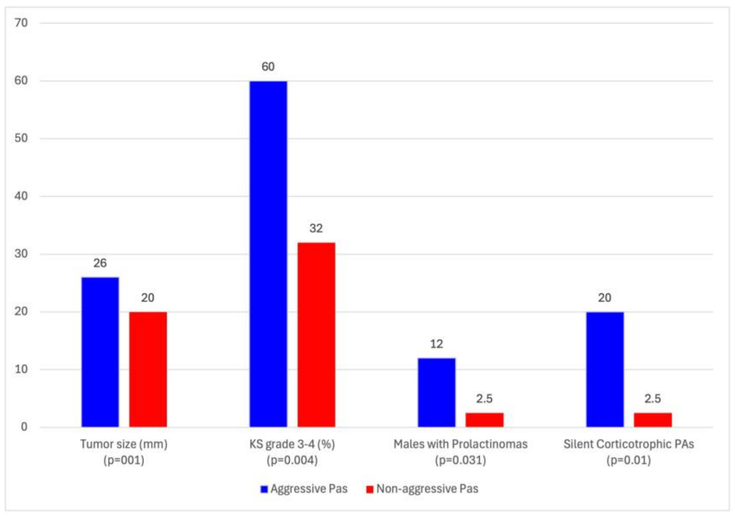
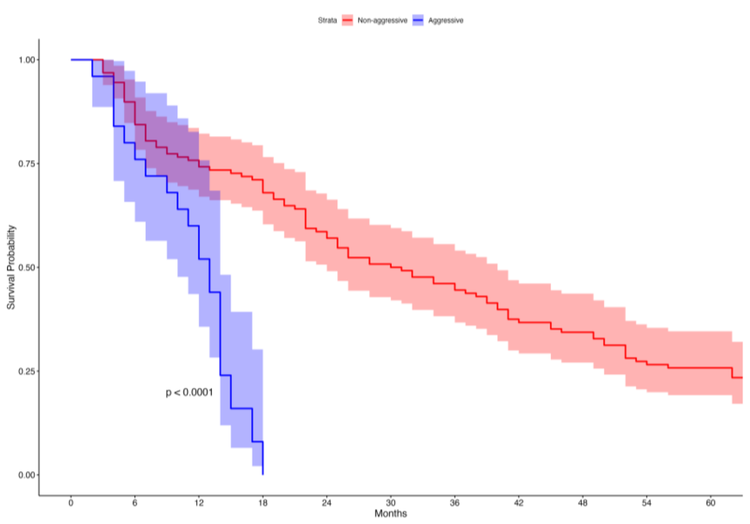


FIGURE 2 – Kaplan-Meier Plot for intervention free survival of aggressive PAs compared to the overall cohort



CONCLUSION

The predictors identified in this study correlated significantly with aggressive pituitary adenomas. Our findings suggest that patients presenting with larger tumor size, higher KS grades, silent corticotroph adenomas, or male patients with prolactinomas should undergo closer monitoring following initial treatment, as they may be at increased risk for early recurrence or progression.

Although further studies are necessary to validate these findings and refine predictive models, our results provide valuable insights that may help guide future treatment strategies. Early identification of high-risk patients could enable more timely interventions, potentially improving long-term outcomes in patients with aggressive PAs.

FIGURE 3 - 69F with an ACTH producing macroadenoma, Ki67 index <3%, negative for p53 staining.

(A) shows the preoperative imaging, (B) shows gross total resection 3 months after endoscopic endonasal resection and (C) shows significant regrowth 12 months post OP.