Ki67 in Pituitary Tumors: What Information Could We Obtain?
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Dr. Robert Y. Osamura, MD has nothing to disclose.

Pituitary adenomas

Approximately 15% of all intracranial neoplasms. Most pituitary tumors are adenomas and are benign and non-invasive. But invasive adenomas are also frequent. Pituitary carcinomas are rare, accounting for only 0.1-0.2% of all pituitary endocrine tumors.

Definition
Pituitary adenoma is a neoplastic proliferation of anterior pituitary producing cells. The tumors are frequently benign, but can be aggressive and invasive into adjacent structures.

How much does Ki67 contribute to predict “aggressive and invasive” pituitary adenomas?
PRESENTATION TITLE

How to measure Ki67 index?
Three-four high power fields(x400) were captured by Olympus Digital Camera
On the printed images, Ki67-positive nuclei were counted on 1500-2000 nuclei of the tumor cells

Antibody against Ki67
MIB1(DAKO Agilent)

PRESENTATION TITLE

Ki67 in Pituitary Tumors: What Information Could We Obtain?

1. Typical and atypical pituitary adenomas (WHO 2004)
2. How much do Ki67 indices contribute to predict aggressive pituitary adenomas
3. Adenoma subtypes and aggressive nature
4. Pituitary carcinoma and Ki67

PRESENTATION TITLE

Rule of Ki-67 proliferation index and p53 expression in predicting progression of pituitary adenomas

Human Pathology (2008) 39, 758–766

2.3.1. Analysis of Ki-67 LI
The 2 high-power fields (400×) with the highest density of positive nuclei were captured with a digital camera (Olympus Q-color 3; Olympus Inc., Center Valley, PA). Photographs were printed on plain paper and a grid was drawn over them. We counted a mean of 1000 tumor cells per case (range, 800–1500), and the results were expressed as percentage of tumor cells with positive nuclei. Only 1 photograph was used if it included 1000 cells. Only nuclei with a strongly positive label were counted.

PRESENTATION TITLE

Ki67 in Pituitary Tumors: What Information Could We Obtain?

1. Measurement of Ki67 in pituitary adenomas
2. WHO classification 2004
   Typical and atypical adenomas
3. Ki67 index and behavior of pituitary adenomas
   Ki67 and Knosp Grading
4. New WHO Classification 2017
5. Pituitary carcinoma and Ki67
6. Summary

PRESENTATION TITLE

Typical and Atypical Pituitary Adenoma

NOS Classification 2004

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Ki67 Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical adenoma</td>
<td></td>
</tr>
<tr>
<td>Atypical adenoma</td>
<td>&gt;3%</td>
</tr>
<tr>
<td>Pituitary carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

Ki67 >3%
P53 positive
Atypical adenoma


Conclusions: Atypical tumors were identified in 15% of resected pituitary adenomas, and they tended to be aggressive, invasive macroadenomas. More longitudinal follow-up is required to determine whether surgical outcomes, potential for recurrence, or metastasis of atypical adenomas vary significantly from their typical counterparts.
P53 gene mutation in pituitary adenomas and carcinomas
Tanizaki Y, Jin L, Scheithauer BW, Kovacs K, Roncaroli F, Lloyd RV
P53 gene mutation in pituitary carcinomas
Exon 5, 6, 7, 8
A case of 60% overexpression: Codon 248 Common hot spot
Another case with 90% overexpression: Codon 135
All adenomas negative for mutations
Levy A, Hall L, Yeudall WA, Lightman SL
P53 gene mutations in pituitary adenomas: rare event
Clin Endocrinol (1994) 41(6):809-14
No mutations were identified in 29 cases Exon 4, 5, 6, 7, 8

Histological criteria for atypical pituitary adenomas - data from the German pituitary adenoma registry suggests modifications
PA vs APA
Ki67(MIB-1) LI>4%

Atypical pituitary adenomas (WHO 2004)
1. Rare in incidence 5%-15%
2. Not necessarily correlated with prognosis
"Atypical adenoma" is not recommended (WHO 2017)
1. Ki67 index should be analyzed.
2. p53 is good indicator of malignancy

Atypical pituitary adenomas: 10 years of experience in a reference centre in Portugal
F. Tortosa, S.A. Medeiros

Cases of Knosp Grade 4

Ki67 indices vary from <1% to 23%
Ki67 >3% 5/20 25%
How much does Ki67 contribute to predict “aggressive and invasive” pituitary adenomas?

Contribution of Ki67 indices alone is limited, but together with images (MRI), we may predict aggressive nature of the adenomas, such as residual tumor, recurrence.


Subtypes of pituitary adenomas tend to show more aggressive behavior (WHO 2017)

Sparcely granulated somatotroph adenoma
Lactotroph macroadenoma in men
Crooke cell corticotroph adenoma
Silent corticotroph adenoma
Plurihormonal PIT-1 positive adenoma
(previous Silent subtype III adenoma)


Pituitary adenomas often associated with aggressive behavior

Morphology as biomarkers
★ Sparcely granulated somatotroph adenoma
Densely granulated lactotroph adenoma
Acidophil stem cell adenoma
Thyrotroph adenoma
Sparcely granulated corticotroph adenoma
★ Crooke’s cell adenoma
Silent subtype III adenoma (plurihormonal Pit-1 positive adeoma)


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(previous Silent subtype III adenoma)
PRESENTATION TITLE

**Table 1 – Morphofunctional Classification of Pituitary Adenomas WHO 2017**

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Clinical Presentation</th>
<th>Hormonal Profile</th>
<th>Immunohistochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>Clinical functioning</td>
<td>GH, PRL</td>
<td>Pit-1, SF-1, ERα</td>
</tr>
<tr>
<td>Corticotroph Adenoma</td>
<td>Silent</td>
<td>ACTH</td>
<td>Tpit, GATA2</td>
</tr>
<tr>
<td>Lactotroph Adenoma</td>
<td>Clinically functioning</td>
<td>PRL</td>
<td>Pit-1, SF-1, ERα</td>
</tr>
<tr>
<td>Somatotroph Adenoma</td>
<td>Clinically functioning</td>
<td>GH, PRL</td>
<td>Pit-1, SF-1, ERα, Pit</td>
</tr>
</tbody>
</table>
Ki67 in Pituitary Tumors: What Information Could We Obtain?

20M Aggressive pituitary adenoma  Knosp Grade 4  Ki67 23%  p53 80%

Post-operative Residual tumor

Ki67

P53

Point mutation
**Ki67 in Pituitary Tumors: What Information Could We Obtain?**

- **20M Aggressive pituitary adenoma** Knosp Grade 4  Ki67 23%  p53 80%
- P53 mutation and residual tumor
- Pituitary carcinoma in situ (premetastatic)?

**Summary**

1. Majority (more than 80%) of pituitary adenomas show Ki67 index lower than 3%.
2. Ki67 index does not always correlate with invasion or aggressive behavior.
3. Higher Ki67 index may be associated with aggressive behavior.
5. Morphologic changes, sparsely granulated somatotroph adenoma, Crooke’s adenoma, correlate aggressive behavior.
6. Some biomarkers may be helpful to predict prognosis.
7. Pituitary carcinomas in general demonstrate higher Ki67 index, but some cases revealed low Ki67 index.

**High-risk pituitary adenomas**

- Rapid growth
- Radiological invasion
- High Ki67 proliferative index
- Clinically aggressive pituitary adenoma

**WHO 2017**

**Thank you very much for your kind attention**