Stereotactic Radiosurgery for Pituitary Adenomas: A Contemporary Review

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Pituitary Adenomas and SRS

- Pituitary adenomas represent 10-20% of all primary brain tumors.
- After microsurgery, incomplete resection or recurrence rates range from 20-50%
- Radiosurgery has become an important treatment of recurrent or residual pituitary adenomas.

Why Study Pituitary Adenomas through the Big Data Approaches?

- They are relatively rare tumors.
  - Prevalence 75.7 per 100,000
- Long-term follow-up required for “benign” tumors
- Most of the literature is comprised of single center retrospective studies.
  - Low statistical power
  - Few patients reaching long-term follow-up periods
  - Selection bias
  - Limited generalizability to other centers

Radium Bomb by Hirsch

Hirsch’s original schema for transnasal delivery of radium therapy to the sella

Lateral skull x-ray as used by Oskar Hirsh for image guided delivery of a radium bomb to the sella.
Kjellberg fitting a patient with a stereotactic frame for proton beam therapy at the Harvard Cyclotron circa 1960

Timeline of historical milestones along the Stereotactic Radiosurgery evolution

Q1: What factor predicts better adenoma control with SRS

- A) Tumor volume ≤5cc
- B) Margin dose <12Gy
- C) Age ≤50yo
- D) Prior fractionated radiotherapy
- E) Male gender

Nonfunctioning Pituitary Adenomas
Materials

- Total number of patients: 512
  - Male: 286 (55.9%)
  - Female: 226 (44.1%)
- Mean Age (years): 53.1 ± 13.8 (median 53, range 16-88)
- Prior Resection (%): 479 (93.7%)
- Number Patients >1 Surgery: 212 of 511 (41.5%)
- Prior Radiation Therapy (%): 34 (6.7%)
- Any Prior Hypopituitarism (%): 296 of 510 (58.2%)
- Cortisol (%): 158 of 508 (31.1%)
- Thyroid (%): 207 of 509 (40.7%)
- Gonadotropin (%): 166 of 507 (32.7%)
- Growth Hormone (%): 77 of 485 (15.9%)
- Diabetes Insipidus (%): 32 of 509 (6.3%)

Results: Progression Free Survival

- PFS
  - 5 years = 95%
  - 8 years = 91%
  - 10 years = 85%

Results: Progression Free Survival

- PFS and Tumor Volume
  - <5cc with improved PFS (p<0.05)
Clinical Response

- 9.3% has new or worsening of existing CN deficit
- CN deficit associated with
  - Larger tumor volume
  - Tumor progression
  - Prior radiation
  - Increasing age

Endocrine Response

- Hypopituitarism in 21.1%
- Associated with
  - Increasing margin dose
  - Prior radiotherapy
  - Worsening CN function

Clinical Response

- CN II dysfunction
- CN III dysfunction
- CN IV dysfunction
- CN V dysfunction
- CN VI dysfunction
- CN VII dysfunction

Endocrine Response

- Cortisol
- Thyroid
- Gonadotrope
- Growth Hormone
- Diabetes Insipidus
Radiosurgical Pituitary Score

- **RPS (0 to 4 score)**
  - Tumor volume
    - \(<5 \text{ cc} \rightarrow 1 \text{ point}\)
    - \(>5 \text{ cc} \rightarrow 0 \text{ points}\)
  - Age
    - \(>50 \text{ years old} \rightarrow 1 \text{ point}\)
    - \(<50 \text{ years old} \rightarrow 0 \text{ points}\)
  - Prior radiation
    - None \(\rightarrow 2 \text{ points}\)
    - Prior XRT \(\rightarrow 6 \text{ points}\)

RPS for NFA Patients

Early vs. Late GKRS

- Matched cohort
- Assessed for
  - Tumor control
  - Hypopituitarism
  - Need for additional tx

Early SRS in IGKRF Study
Endocrinopathy rates after GKRS in NFA patients in the early and late cohorts

P=0.036

Early SRS of residual NFA may avoid endocrinopathy (as well as tumor growth)

Q2: After SRS for CD, what is the typical time to remission?

• A) 1 month
• B) 6 months
• C) 1 year
• D) 3 years
• E) 5 years

Cushing's Disease
IGKRF Cushing’s Series
N=278 patients

Prognostic factors

Lower dose portended greater risk of Endocrine recurrence after remission

Cushing’s SRS: Case Illustration

Mean Remission 65%

Other SRS Cushing’s Series
Acromegaly

- Result of excess growth hormone secretion
- Effects secondary to IGF-1
- Classic physical stigmata.
- Associated with hypertension, soft tissue hypertrophy, glucose intolerance

IGKRF Acromegaly Study
N=371 pts; mean f/u 79 months

Factors Related to Remission and Recurrence

<table>
<thead>
<tr>
<th>Factor</th>
<th>Initial remission</th>
<th>Durable remission</th>
<th>Recurrence after remission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.59</td>
<td>0.89</td>
<td>0.59</td>
</tr>
<tr>
<td>Gender</td>
<td>0.12</td>
<td>0.26</td>
<td>0.93</td>
</tr>
<tr>
<td>Prior surgery</td>
<td>0.03</td>
<td>0.02</td>
<td>0.10</td>
</tr>
<tr>
<td>Random</td>
<td>0.0004</td>
<td>0.0004</td>
<td>0.07</td>
</tr>
<tr>
<td>Cessation of medications prior to SRS</td>
<td>0.04</td>
<td>0.47</td>
<td>0.64</td>
</tr>
<tr>
<td>Tumor volume</td>
<td>0.04</td>
<td>0.64</td>
<td>0.54</td>
</tr>
<tr>
<td>Whole sella targeted by SRS</td>
<td>0.04</td>
<td>0.64</td>
<td>0.54</td>
</tr>
<tr>
<td>SRS margin dose</td>
<td>0.04</td>
<td>0.64</td>
<td>0.54</td>
</tr>
<tr>
<td>SRS maintenance dose</td>
<td>0.04</td>
<td>0.64</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Acromegaly Case Illustration
Remission at 24 months Post GKRS
### Other SRS Acromegaly Series

| Authors, Year | n  | F/U (mo) | Margin dose (Gy) | Tumor Control | Remission criteria | Remission rate (%) | Hypopit (%)
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ikeda, 2001</td>
<td>90</td>
<td>58.8</td>
<td>25.0 N/A</td>
<td>N/A</td>
<td>OGTT GH&lt;2, Normal IGF-1</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>Castinetti, 2005</td>
<td>82</td>
<td>48.5</td>
<td>25.7 N/A</td>
<td>N/A</td>
<td>GH&lt;2, Normal IGF-1</td>
<td>17</td>
<td>11</td>
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<tr>
<td>Kobayashi, 2005</td>
<td>67</td>
<td>58.9</td>
<td>N/A</td>
<td>N/A</td>
<td>GH&lt;2, Normal IGF-1</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Jezkova, 2006</td>
<td>54</td>
<td>35.0</td>
<td>100% N/A</td>
<td>N/A</td>
<td>GH&lt;1, Normal IGF-1</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Vic-Mo, 2007</td>
<td>53</td>
<td>66.1</td>
<td>100% N/A</td>
<td>N/A</td>
<td>GH&lt;1 and Normal IGF-1</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>Lin, 2008</td>
<td>83</td>
<td>60.4</td>
<td>21.5 97.6%</td>
<td>N/A</td>
<td>GH&lt;1, Normal IGF-1</td>
<td>10</td>
<td>8.5</td>
</tr>
<tr>
<td>Kobayashi, 2009</td>
<td>64</td>
<td>68.9</td>
<td>N/A</td>
<td>GH&lt;1</td>
<td>GH&lt;1, Normal IGF-1</td>
<td>9.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Men, 2009</td>
<td>102</td>
<td>21.4</td>
<td>N/A</td>
<td>N/A</td>
<td>GH&lt;1, Normal IGF-1</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>UVA, 2013</td>
<td>116</td>
<td>58.2</td>
<td>25.0 98.3%</td>
<td>Normal IGF-1</td>
<td>GH&lt;1, Normal IGF-1</td>
<td>95.4</td>
<td>33.3</td>
</tr>
</tbody>
</table>

### IGKRF Pediatric CD and Acromegaly Patients
- Pediatric pituitary adenoma cohort
  - 24 CD patients
  - 12 Acromegaly patients
- Endocrine remission associated with
  - Higher margin dose (p=0.042)
  - Younger age (<15yo) (p=0.006)

### Pediatric Pituitary Patients
Endocrine remission more likely with CD

### Nelson’s Syndrome
- Patients with ACTH secreting pituitary adenomas may require adrenalectomy to treat their Cushing’s disease.
- 1/3 of these patients develop Nelson’s syndrome
  - Enlarging pituitary adenoma
  - Hyperpigmentation
  - Elevated serum ACTH
- Patients were assessed for
  - ACTH normalization
  - Adenoma volume control
IGKRF Nelson’s Study

- 51 patients treated with GKRS
- Median margin dose of 25 Gy
- Tumor control = 92%
- Endocrine improvement in ACTH = 63%
- Complete remission in 29.4%
- Hypopituitarism in 22%

Prolactinomas

- Medical management is the first line of treatment for prolactinomas.
- However, 20% of patients with prolactinomas fail medical management.
- Gamma surgery has become an increasing important neurosurgical technique for treatment of refractory prolactinomas.

IGKRF Prolactinoma Study

- 289 patients
- Endocrine remission = 43%
- Endocrine control = 63%
- Hypopit = 25%
- Time to Endocrine remission
  - PreSRS PRL < 270 ng/ml (p = 0.001)
  - Cessation of pit suppressive meds (p = 0.049)
  - Cav Sinus Extension (p = 0.018)
  - Smaller adenoma volume (p = 0.014)

Whole Sellar SRS

- Clear hypersecretory state
- Prior failed TSR
- No discrete adenoma on MRI
- Surgical equivalent of total hypophysectomy
Factors for remission in whole-sellar SRS

- Endocrine remission in 63.2% of patients
  - Better remission with a dose >23 Gy (p=0.033)
- 22.7% with post-SRS endocrinopathies
- No differences in remission or endocrinopathy between those with whole sella vs. discrete adenoma SRS

Initial cumulative control for endocrinopathy after SRS:

- Whole Sella
- Discrete Adenoma Target

Time to endocrinopathy after SRS:

- Whole Sella
- Discrete Adenoma Target
Patients and Methods

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
<th>Percentage or range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>FU at least once</td>
<td>46</td>
<td>85.2%</td>
</tr>
<tr>
<td>Median age (y/o)</td>
<td>61</td>
<td>37.0-87.0</td>
</tr>
<tr>
<td>Sex (Male: Female)</td>
<td>20:26</td>
<td></td>
</tr>
<tr>
<td>Median tumor volume (ml)</td>
<td>2.6</td>
<td>0.3-9.2</td>
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### Treatment parameters

#### For non-functional adenomas

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<tr>
<th>Parameters</th>
<th>Median</th>
<th>Range</th>
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<td>P-Adrenochrome</td>
<td>45</td>
<td>158/119</td>
</tr>
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<td>P-Norepinephrine</td>
<td>55.3</td>
<td>9.5-170.19</td>
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<tr>
<td>P-Serotonin</td>
<td>91.0</td>
<td>6.0-994</td>
</tr>
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<td>P-Hepatocyte growth factor</td>
<td>60.3</td>
<td>11.0-981.6</td>
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<td>P-Hypophysectomy (in/on)</td>
<td>110</td>
<td>1.0-100</td>
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#### For functional adenomas

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### Tumor response and hormone outcomes

- **Tumor response**
  - Decrease: 19 cases
  - Stable: 23 cases
  - Increase: 16 cases

- **Endocrine outcome**
  - Profuse: 19 cases
  - Acromegaly: 2 cases
  - Connors' disease: 1 case
  - Diabetic: 1 case
  - Pheochromocytoma: 1 case
  - Hypothyroid: 1 case

Total adenoma cases: 46
Median imaging f/u: 64 months

Total FA cases: 19
Median endocrine f/u: 65 months
**Subtypes of adenoma Remission (%) Median time to remission (mo)**

<table>
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<th>Remission (%)</th>
<th>Median time to remission (mo)</th>
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<td>Steroidogenic (SI)</td>
<td>66.7 ± 3.8 %</td>
<td>5 ± 0.98 ± 9.5 %</td>
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<td>98 ± 9 %</td>
<td>5 ± 4 ± 0.95 %</td>
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<td>48 ± 3%</td>
<td>4 ± 0.3 %</td>
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<tr>
<td>Q band radiotherapy</td>
<td>38 ± 4%</td>
<td>0 ± 0 %</td>
</tr>
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*Remission criteria: normal serum prolactin level (<20ug/mL both in UVa and VGH) for prolactinoma, normal IGF-1 according to patient’s age for acromegaly, normal urine free cortisol (<90ug/d) for Cushing disease, normal serum ACTH level (<52 pg/mL) for Nelson’s disease.*

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**Complications**

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<th>Complications</th>
<th>Case no.</th>
<th>Median time to occur (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation necrosis</td>
<td>0 (0%)</td>
<td>18</td>
</tr>
<tr>
<td>Visual deterioration</td>
<td>1 (2.2%)</td>
<td>-</td>
</tr>
<tr>
<td>New cranial nerve palsy</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Secondary tumor</td>
<td>0 (0%)</td>
<td>-</td>
</tr>
<tr>
<td>Hypopituitarism</td>
<td>10 (21.7%)</td>
<td>37 (24-73)</td>
</tr>
<tr>
<td>Panhypopituitarism</td>
<td>1 (2.2%)</td>
<td>96</td>
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</table>

**Definition for new onset panhypopituitarism:**
1. Corticotroph deficiency: low serum morning cortisol low 24 hr UFC
2. Thyroid deficiency: low free T4 with normal or decreased TSH
3. GH deficiency: a subnormal GH response during GCTT ITT test
4. Gonadotroph deficiency: low gonadotropin levels, low plasma testosterone in men, low plasma estradiol in women

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**Median time to remission**

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Upfront SRS for Pituitary Adenomas

This may be reasonable for selected cases

Resection, however, still remains the mainstay of initial treatment

Q3: What is the typical rate of post-SRS hypopituitarism?

- A) 5-10%
- B) 20-30%
- C) 40-50%
- D) 50-60%
- E) >60%

IRRF Hypopituitary Study

- 1023 pituitary adenoma patients
- Hypopituitarism
  - 1 year: 7.8%
  - 3 year: 16.2%
  - 5 year: 22.4%
  - 7 year: 27.5%
  - 10 years: 31.3%
Fractionated RT

- Fractionated RT provides consistently high tumor control for most pituitary adenomas
- Typically remission occurs more slowly with XRT compared to SRS
- Refinement of techniques with:
  - IMRT
  - SRT
  - Proton
- Coming soon:
  - Flash
  - MRI LINAC
  - Carbon ion

NPA National SRS Registry

23 diverse sites from across the U.S.

SRS Registry Contributors
Since 2016
Conclusions

- SRS is a valuable treatment option for
  - Recurrent/residual pituitary adenomas
    - Excellent rate of adenoma control
    - Reasonable rate of remission
    - Early SRS may be preferable
    - Higher dose and temporarily holding antisecretory medications
  - An initial treatment for carefully selected pituitary adenomas
  - Hypopituitarism remains the largest post SRS risk but occurs in a minority of patients and is correctable.
- Fractionated RT still reasonable for larger tumors
- Multicenter trial studies and registry data are likely to move the field forward.