Update in Pituitary Radiotherapy and Radiosurgery

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• Radiotherapy – long history in management of pituitary tumours.

Hirsch – 1911 – Radium implant

Harvard Cyclotron 1960’s
Evolution of Techniques – 2D -3D CRT

- Use of CT for planning treatment
- 3D conformal radiotherapy (3D CRT)
- Improve therapeutic ratio
Development of **Stereotactic** approaches
Application from Neurosurgery

Precision in delivery of radiotherapy
Radiosurgery Vs Radiotherapy

- Single high dose of radiation (12-150Gy)
- Tissue ablation/destruction
- Requires defined ‘target’
- Typically for targets less than 3-4cm

- Multiple small doses of radiation (1.8-3.0Gy)
- Mitotic cell death (DNA damage) in dividing cells
- Often used with margins to treat regions
- Can be used for large volumes
Stereotactic Radiosurgery

- Stereotactic = precision
  - Minimally invasive frame

- Radiosurgery
  - Ablative/destructive doses of radiation
Pituitary stereotactic radiotherapy - SRS

• Stereotactic Radiosurgery
  – Ablative doses
  – Non-functioning 12-18 Gy
  – Functioning 18-28 Gy
Fractionated Stereotactic Radiotherapy - FSRT

- Fractionated Stereotactic (daily treatments)
  - Non-functioning (45-54 Gy in 25-30 #)
  - Functioning (50.4-54 Gy in 28-30 #)
  - Very tight margins – decreased dose to normal structures
Radiosurgery Units
Radiotherapy - Non-functioning Pituitary Adenomas

- Very effective to control tumour mass
  - **Largely residual disease post-op**
  - Medically inoperable/surgical high risk with growing tumour
  - Invasive recurrent tumours

- Safe to follow patients with small residual – location dependent
# SRS Non-functioning Pituitary Adenomas

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<th>Study</th>
<th>Year</th>
<th>GK/LINAC</th>
<th>No of patients (n)</th>
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Non-functioning Pituitary Adenomas – SRS OR FSRT

- Volume dependent (< 5cc for SRS)
  - Planned debulk and SRS

- Proximity to Optic structures

- Recurrent/residual disease that is multifocal or *invasive*

- Histology dependent
  - Atypical (Ki-67)

**May be difference in risk profile**

- During treatment - fatigue
- Intermediate – fatigue and neurocognitive
- Late – optics/pituitary/CVA
Early Vs Delayed SRS – Non-functioning

- Early postoperative SRS treatment (STR)
  - decrease the rate of tumour progression (from time of SRS)
  - Reduced risk of subsequent endocrinopathy
  - Consider if growth may increase risk of SRS (2-3mm optics)

- Safe to follow patients with small residual
  - Older pt with small residual
  - panhypopit
• Larger number of patients (> 500 patients in literature)

• Dominated by GK with a few LINAC

• Range of dose 16Gy – 28 Gy single fraction

• Tumour control 90-100%

• Endocrine remission 60 – 80 %

2 Groups – target OR fossa
Latency of normalisation of UFC
Particularly important in Cushings

• GK
  – Median 1.5 yrs (ongoing to 5 yr)

• FSRT
  – Usually 2-3 yrs (ongoing to 10 yr)

SRS for Functioning Pituitary Adenomas - Acromegaly

- GK – residual disease (cavernous sinus) post surgery
  - Intolerant/resistant to somatostatin analogue
  - Surgically high risk

- Aims of radiotherapy
  - Attain biochemical control (IGF-1 level) and cessation of medical therapy
  - Control tumour mass
  - Preserve pituitary function with minimal side-effects

- Role to prevent long term use of GH antagonists
  - Cost and patient preference
  - Balanced against risk of new pituitary dysfunction
GK in Acromegaly

• Radiosurgery
  – Min covering dose of 20 Gy (aim 24-26Gy)
  – Treat to 24-26Gy if safe to do so
    – 120-150 Gy (fractionated)

Biochemical Remission: ~ 60-70%
Mean time to achieve remission: ~ 2-3 years
Dependent on PreXRT IGF-1 levels
Tumour Control: 90-100%
SRS outcome similar for both densely granulated and sparsely granulated

Which is better for Functioning Disease – SRS Vs FSRT

- BOTH
  - Similar biochemical control
  - Similar tumour control

- Side-effects
  - Risk of new pituitary dysfunction
  - Proximity to optic structures
Cost effectiveness of Radiosurgery (GK) Acromegaly

• Factors to consider
  – Effectiveness
  – Impacts on patient QOL
  – Latency of effect
  – Risk of complications (hypopit)

• Cost GK in Aus - $10-15k (lifetime)
  – Once off treatment

• Cost octreotide/lanreotide

SRS and interaction with medical therapy

- Consistent across series

- Cushings – temporary cessation of ketoconazole halves the time to achieve endocrine remission

- Acromegaly – reduced rate of endocrine remission in patients on somatostatin analogues during SRS

- Confounder – disease status

- Practical guide
  - cease 6-8 weeks prior
  - recommence 1-4 weeks after.
SRS for Functioning Pituitary Adenomas – Prolactinomas

- Uncommon limited data

- Limited to non-responders Dopamine agonists (rare) or intolerant of side effects

- Unable to have surgery or dural/cavernous sinus invasion

- Endocrine remission (normal prolactin off DA)
  - 50%

- Tumour control > 90%

- DA at time of SRS – tended to decrease endocrine remission

Imaging - Use of DCE Pituitary Scans
Acromegaly case – Experienced Neuroradiol.
Imaging – 3T MRI

• Superior for cavernous sinus invasion
  – Surgical planning
  – Implications for SRS

• May explain why early series of SRS showed LC 85-90%.

• Visualisation of optic structures

• May pick up microadenoma in Cushings

SRS retreat previous FSRT

- Safe and effective for both functioning and NFPA
- Very effective to control tumour mass (> 75%)
- 72% patients were panhypopituitary
- 42% of the remainder have developed new anterior pituitary hormone deficiencies
- No other late sequelae


- Repeat SRS
  - CN in cavernous sinus
  - Trigeminal neuralgia
New Pituitary dysfunction after Radiotherapy

• Most significant effect post SRS
• Can often be delayed – 2-3 years post treatment
• NO known safe dose to pituitary or stalk
• After SRS NFPA – 20-30%
• After SRS functioning >50%
• NO patients were panhypopituitary
• DI – 2% risk

NAGKS – 512 patients
Other sequelae after Radiotherapy (SRS)

- **OPTIC NEUROPATHY**
  - Dose of optic nerve and chiasm
  - Occurs within 2 years
  - Appropriate patient selection
    - NFPA – 1-2mm gap
    - Functioning – 2-3mm gap
  - Dose selection
    - < 10Gy (1% or less)
    - < 12Gy (< 5%)
    - 12-15Gy (>10%)
  - Risk higher if retreat

- **OTHER CRANIAL NERVE DYSFUNCTION**
  - CN III, IV, V and VI in cav sinus
  - Diplopia
    - 1-2% NFPA
    - 5% in functioning
    - 10% in retreat
  - Facial numbness or pain
    - 1-2%
    - > 50% respond if have facial pain
Other sequelae after Radiotherapy

• **RISK CVA**
  - Early fractionated (FSRT) data
    - 2-3 times increased risk
    - Multiple factors account
    - Length and volume of carotid treated
    - SRS – cases of acute infarction

• **IMPACT ON OVERALL MORTALITY**
  - Risk of second malignancy or malignant tranformation
    - Estimated 1:2000-2500
  - NO convincing evidence that FSRT or SRS increase mortality

Other sequelae after Radiotherapy

• **NEUROCOGNITIVE**

  - Dose to medial temporal lobes
  - RT was independently associated with an impairment on verbal memory and executive function


Future considerations – pituitary radiotherapy

• Individualised treatment based on tumour histology/genetics

• Atypical/aggressive pituitary adenomas (upfront)
  • FSRT with radiosensitisers – TMZ

• ? Charged particles – Protons

• Medical imaging and targeting residual disease
  • DOTATATE-PET - MRI