Radiotherapy of meningiomas with special reference to proton irradiation

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Diagnosis

• Meningioma, benign  WHO grade I
  The dominant part with many subtypes:
  Meningothelial, fibroblastic, transitional, angiomatous etc.

• Atypical meningioma WHO grade II
  4.7 - 7.2%

• Anaplastic meningioma WHO grade III
  1.0 - 2.8%
Operative specimen
Bone invasion
Interventricular growth
Benign meningioma
Atypical meningioma
Anaplastic meningioma, WHO grade III
Anaplastic meningioma, WHO grade III
Anaplastic meningioma, WHO grade III

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Men</th>
<th>Women</th>
<th>All</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low malignant astrocytoma</td>
<td>79</td>
<td>57</td>
<td>136</td>
<td>10,6%</td>
</tr>
<tr>
<td>Highly malignant astrocytoma</td>
<td>203</td>
<td>156</td>
<td>359</td>
<td>28,1%</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>16</td>
<td>12</td>
<td>28</td>
<td>2,2%</td>
</tr>
<tr>
<td>Meningioma</td>
<td>114</td>
<td>275</td>
<td>389</td>
<td>30,5%</td>
</tr>
<tr>
<td>Malignant meningioma</td>
<td>4</td>
<td>6</td>
<td>10</td>
<td>0,8%</td>
</tr>
<tr>
<td>Neurinoma</td>
<td>61</td>
<td>62</td>
<td>123</td>
<td>9,6%</td>
</tr>
<tr>
<td>Plexuspapilloma</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>0,2%</td>
</tr>
<tr>
<td>Hemangioblastom, and related</td>
<td>16</td>
<td>14</td>
<td>30</td>
<td>2,3%</td>
</tr>
<tr>
<td>Kraniofaryngioma</td>
<td>6</td>
<td>6</td>
<td>12</td>
<td>0,9%</td>
</tr>
<tr>
<td>Pinealoma</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td>0,5%</td>
</tr>
<tr>
<td>Without histopathology</td>
<td>52</td>
<td>56</td>
<td>108</td>
<td>8,5%</td>
</tr>
<tr>
<td>Other</td>
<td>45</td>
<td>28</td>
<td>73</td>
<td>5,7%</td>
</tr>
<tr>
<td>Total/year</td>
<td>601</td>
<td>676</td>
<td>1277</td>
<td>100 %</td>
</tr>
</tbody>
</table>
Symptoms and signs 1

- Dependent by anatomic site
- Located supratentorially: 85 – 95%
- Presenting symptoms: headache (36%), change in mental status (21%) and paresis (22%)
Symptoms and signs 2

- Most common anatomical sites:
  
  Convexity (35%): **Medial**: Headaches, seizures, motor and sensory deficits.
  
  Parasagittal (22%): **Anterior**: Headaches, memory and behaviour changes. **Middle**: Motor and sensory deficits. **Posterior**: Homonymous hemianopsia. **All**: Venous occlusions.
  
  Sphenoidal ridge (17%): **Medial**: Visual loss, cranial nerves III, IV and IV palsies. **Lateral**: Headaches, seizures, motor and sensory deficits.

Etiology and more

- Irradiation followed by about two decades before appearance (800 – 2000 rad (sic!))
- Role of sex hormones?
- Female: male ratio 3:2 – 2:1
- Peak occurrence at 50 – 70 years
- In children more aggressive forms
- Multiple forms
Meningioma development "starter cell"

• Suggestions:
  - Arachnoidal cap cell
  - Earlier progenitor meningotheelial cell
Molecular biology 1

- Neurofibromatosis type 2 (NF 2)
  Chromosome 22.12.2q LOH
- Progesteron- and estrogen-receptors
- Somatostatin receptors
- Radiation induced meningiomas may have losses on chromosome 1p11, 6q and 7p
Molecular biology 2

- Cell cycle dysregulation
- Telomerase activation
- Genetic instability
Imaging

- Isodense dural masses, may be calcified
- Contrast enhancement
- Compression of surrounding structures
- ”Dural tail”
- ”En plaque meningioma” – growing as a flat mass
Meningioma MRI T1
Meningioma MRI T2
Treatment options

• Surgery
  Total removal, partial resection, biopsy

• Radiotherapy
  Protons, photons (3-D conformal, IMRT, stereotactic techniques)

• Medical therapies?
  Interferons? Hydroxurea?
  Inhibition or targeting with signal transduction molecules?
Surgical risk in skull base meningioma operations
Results of surgery alone

• Recurrence rate after "total removal":

  Benign meningiomas:  7 – 20%
  Atypical meningiomas:  29 – 38%
  Anaplastic meningiomas:  50 – 78%

Aim of radiotherapy

• A. In benign meningiomas – in case of a residual meningioma to prevent regrowth and the need for reoperation.

B. To diminish symptoms

• In atypical meningioma – to ”cure”

• In anaplastic meningioma – advanced palliation
How does radiotherapy work in patients with benign meningiomas?

Suggestions:
1. Inhibition of division of cycling cells
2. Parenchymal ”exhaustion”
3. Obliteration of small vessels
Radiotherapy

Photons
Conventional 3-D, IMRT, stereotactic techniques, (gammaknife)

Protons
Conventional fractionation
Hypofractionation

Light ions?
Important message

- Restriction of dose around the target
- Lesser dose to surrounding normal tissue
- Hypofractionation possible
Radiotherapy with protons

• Conventional fractionation: 1.8 - 2.0 Gy x 25 – 30. Total doses: 50 - 56 (60) Gy

• Hypofractionation: 3 - 6 Gy x 4 – 8 mostly 5 – 6 Gy x 4. Total doses: 24 Gy to 32 Gy
Dose plans

Meningeoma
2-field proton plan

Meningeoma
2-field proton plan
IMRT - solution
(Milker-Zabel, IJROBP 2007)

Fig. 1. Exemplary treatment plan of a patient with a World Health Organization Grade 1 meningioma of the left sphenoidal wing. Figure appears in color online.
Dose distribution photon-proton combination
Lopes et al, IJROBP, 2003

Fig. 1. Composite dose distribution to 55.8 CEM for the combined photon-proton technique. This plan incorporates 3 photon beams and 4 proton beams.
Target definition. Noel et al. IJROBP 2005

Fig. 5. (a) Delineation of sinus cavernous meningioma. Dose distribution with (b) photons and (c) protons.
Dose modulation

- Monoenergetic beam
- Range modulated beam
- Range compensator / bolus
The Optical Bench
Positioning

* Fiducial markers in the bone of the skull
* Isocentric position
* Two orthogonal x-ray images
Dose planning with protons

* Helax -TMS dose planning system
* Ray tracing and a semi-analytic pencil beam algorithm
* Same patient data as for planning with photons and elektrons
Dose planning with protons

- A comparison with "conventional photons"

* All fields must have:
  - an individually made collimator
  - a range modulator
  - a range compensation filter
Collimators
Range compensation filters
Patients positioned for treatment
Positioning and fixation
Evaluation of results

• Change in volume over time
• Progression or shrinkage measured in mm?
• Relief of symptoms or upcoming of new symptoms
• Avoidance of reoperation
Results

• No phase III study exists (?)
• Most authors claim shrinkage of meningioma after certain time intervals
• Long term follow-up is necessary – 10 years or more!
• Prolongation of survival after successful treatment?
Proton therapy of meningeoma patients 2003

81 patients
M/F 19/62
Mean age: 54.1 y  Range: 22 - 85 y
Dose: Fractional dose: 5 – 6 Gy  Total dose: 20 – 24 Gy

Results: 76 patients without progressive disease

Complications:
1 progressive disease
3 reoperations: development of a cyst, patients own wish, growth outside primary target
1 partial temporal lobe necrosis: mainly not in the treatment field

EB/2003
A short History of Proton Beam Therapy

1946 Wilson suggests high energy protons for radiotherapy
1954 First patient treated with protons at Berkley
1957 First cancer in a patient treated with protons in Uppsala
1961 First patient treated at the Harvard cyclotron
1989 Treatment restarted in Uppsala
1990 First hospital-based proton beam facility at Loma Linda, CA, USA
Thanks for Your attention!