Novel tools in radiation oncology: is there any impact?

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Era of high-precision conformal radiation therapy

Larger number of beams & intensity modulation (IMRT) result in better high-dose conformality and improved organ-at-risk sparing; precisely delivered
RT+TMZ still the standard of care
Landmark EORTC/NCI study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RT n=286</th>
<th>RT+TMZ n=287</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year OS (%)</td>
<td>10.9</td>
<td>27.2</td>
</tr>
<tr>
<td>3-year OS (%)</td>
<td>4.4</td>
<td>16.4</td>
</tr>
<tr>
<td>4-year OS (%)</td>
<td>3.0</td>
<td>12.1</td>
</tr>
<tr>
<td>5-year OS (%)</td>
<td>1.9</td>
<td>9.8</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.63 [0.53-0.75]</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>

Focal conformal radiotherapy (Gross tumour+ 2-3 cm margin covering all T2 weighted abnormality) with 2-4 fields; Dose: 59.4-60 Gy/30-33#/6+ weeks

Stupp et al NEJM 2005
Stupp et al Lancet Oncol 2009
Phase III trials of dose escalation in high grade gliomas
Stereotactic radiosurgery (Gama Knife) or Brachytherapy

Souhami L et al IJROBP 2004

Brachytherapy ± RT

Laperriere NJ et al IJROBP 1998

SRS ± RT

Level 1 evidence: higher doses nor better
Targeting glioma stem cells

- By inducing differentiation (BMP, Wnt/Akt pathways)
- Glioma stem cell (GSC) signalling pathways
- GSC microenvironment (Perivascular and hypoxic niche)

Understanding the Origins of Gliomas and Developing Novel Therapies: Cerebrospinal Fluid and Subventricular Zone Interplay

Michael Glantz, Santosh Kesari, Lawrence Recht, Guðrun Fleischhack, Alexis Van Horn
A prospective study ongoing to evaluate the pattern of relapses wrt SVZ locations (n=100); accrual so far: 71
Low-grade gliomas (LGGs) : Changing landscape

Diffuse grade II astrocytomas, oligodendrogliomas, and mixed oligo-astrocytomas are **infiltrative**, less likely to be completely resected and frequently need adjuvant Rx.

**Mature results of RTOG 9802 - Overall Survival**

Focal conformal RT (all T2 tumour) and spare as much normal brain as possible
High-precision radiotherapy for craniospinal irradiation: evaluation of three-dimensional conformal radiotherapy, intensity-modulated radiation therapy and helical TomoTherapy

D S SHARMA, MSk, DipRP, T GUPTA, MD, R JALALI, MD, Z MASTER, MS, D PHURAILATPAM, MSk, DipRP and R SARIN, MD, FRCR

Craniospinal axis RT: critical in medulloblastoma: needs meticulous planning & execution

Potential suggested trials in WNT / SHH (favourable) pathway tumours

- De-escalate therapy; RT dose and chemotherapy, explore targeted therapies etc
- Delay RT as much as possible (? 5 years)
- Localised RT only/ No CSI
Highly conformal whole ventricular irradiation in germ cell tumours
Scalp-sparing WBRT in brain metastases: SIB

- Whole Brain Dose = 30 Gy
- Scalp Dose = ~15 Gy

- Whole Brain Dose = 30 Gy
- Metastatic boosts = 45 Gy
- Scalp Dose = ~18 Gy
Hippocampal sparing trial in brain metastasis
RTOG 0933 (n=100)

- Mean relative decline in HVLT-Delayed Recall from baseline to 4 months: **7.0%** (95% CI: 4.7 to 18.7%)
- Significant less than historical control: **30%** ($p=0.0003$)
- 42 patients had assessment at 4 months

Gondi JCO 2014
Benign brain tumours - Pituitary adenomas
residuals/progressive/functioning

Comparative study of 2 surgical institutions; same RT set up

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>No RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>n=63</td>
<td>n=63</td>
</tr>
<tr>
<td>5 yr</td>
<td>93%</td>
<td>68%</td>
</tr>
<tr>
<td>10 yr</td>
<td>93%</td>
<td>47%</td>
</tr>
<tr>
<td>15 yr</td>
<td>93%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Administration of RT was the only significant factor

Gittoes Clin Endocrinol 1998
Radiotherapy

Vs.

Radiosurgery (SRS)

- Large OR
- Touching optic nerves / chiasm

- Small AND
- ≥2-3 mm from optic n / chiasm
- AND well-defined
Modern Conformal RT process and workflow

Accurate Immobilisation

Tight Conformation

Computerized 3D planning

Stringent Quality Assurance

Precise Treatment Delivery

Jalali et al, Clin Endocrinol 2000
Long term tumour control after RT

Conventional RT (532)
Stereotactic RT (117)
<table>
<thead>
<tr>
<th>Author (year)</th>
<th>n</th>
<th>GTR</th>
<th>STR</th>
<th>STR+ RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mirimanoff (1985)</td>
<td>225</td>
<td>93% (n=145)</td>
<td>63% (n=80)</td>
<td></td>
</tr>
<tr>
<td>Taylor (1988)</td>
<td>132</td>
<td>96% (n=90)</td>
<td>43% (n=42)</td>
<td>85% (n=13)</td>
</tr>
<tr>
<td>Glaholm (1990)</td>
<td>117</td>
<td></td>
<td></td>
<td>84%</td>
</tr>
<tr>
<td>Miralbell (1992)</td>
<td>115</td>
<td>48% (n=79)</td>
<td></td>
<td>88% (n=17, 8yPFS)</td>
</tr>
<tr>
<td>Mahmood (1994)</td>
<td>254</td>
<td>98% (n=183)</td>
<td>54% (n=65)</td>
<td>4/6 stable disease</td>
</tr>
<tr>
<td>Goldsmith (1994)</td>
<td>117</td>
<td></td>
<td></td>
<td>89% (98% p1980, n=77)</td>
</tr>
<tr>
<td>Condra (1997)</td>
<td>246a</td>
<td>95% (n=174)</td>
<td>83% (n=55)</td>
<td>86% (n=17, 5 atypical)</td>
</tr>
<tr>
<td>Stafford (1998)</td>
<td>581</td>
<td>88% (n=465)b</td>
<td>61% (n=116)c</td>
<td></td>
</tr>
<tr>
<td>Nutting (1999)</td>
<td>82</td>
<td></td>
<td></td>
<td>92%</td>
</tr>
<tr>
<td>Vendrely (1999)</td>
<td>156</td>
<td></td>
<td></td>
<td>89% (12 &gt;WHO grade 1)</td>
</tr>
<tr>
<td>Debus J (2005)</td>
<td>153</td>
<td></td>
<td></td>
<td>90.5%</td>
</tr>
</tbody>
</table>

2389  88-98%  43-83%  84-98%
Impact of modern RT planning

Progression-Free Survival
STR + postop RT; p=0.002

98%: Conformal RT (n=77)

77%: Conv RT (n=40)
Craniopharyngioma

- 2-5% of all primary intracranial tumours
- Radical surgery: high incidence of hypothalamic damage
- Increasingly treated with conservative surgery + RT
- Good results with RT; 70-85% long term control

Review of 144 published data; Adamson & Yasargil 2008
Prospective data with conformal RT

Total no. of patients with craniopharyngioma accrued (2001-2011) 73
Patients completed Rx as per trial protocol 70
Patients with detailed outcome analysis (at least 1 post RT 6 month evaluation) 66

Follow up period

- Median (months) 41
- Mean (months) 44
- Range (months) 3-120

Survival at last follow up

- Deaths 3

Cause of death (electrolyte imbalance, repeated infections/septicemia/vascular events)

7 year Overall Survival: 95.0%
Prospective trial of conformal RT in children less than 3 years of age (ependymoma)

Merchant JCO 2004;22:3156-62
Protons

- Steep dose fall-off at distal edge
- Less dose to normal tissues
- Becoming more available

- Unequivocal clinical superiority yet to be demonstrated
- May be beneficial in benign tumours, ? recurrent tumours
- Potentially counter productive in infiltrating tumours as gliomas
- QA, cost
- Just not *Proton* facility; should be spot scanning, with image guidance
- Collaborative data needed

Yock & Tarbell, NCPO 2009
High-precision radiotherapy for progressive/residual low grade/benign brain tumours

- Excellent long term control
- Advances in technology and increasing use of high precision techniques (Stereotactic RT, IMRT, Proton beam therapy, Tomotherapy, Cyber knife, etc)

Evaluation of efficacy of modern high-precision RT

- **Physics / dosimetric**
  Dose distributions, dose volume histograms, indices
- **Clinical**
  Reduction of RT induced toxicity
  Survival

Clinical evidence is based on retrospective or relatively few prospective studies
Primary endpoint
Incidence and magnitude of neuropsychological, cognitive, neuroendocrine and neurological dysfunction in the two arms

Secondary endpoint
Survival

- **Sample size**: N=200; 80% power to detect a 15-20% reduction in primary endpoints in Conformal RT arm compared to conventional RT arm at a significant level of p<0.05
- **Informed consent** (English, Hindi, Marathi)
Trial schema

- Age 3-25 years
- Residual/progressive low grade and benign tumours needing RT
- Informed consent
- Detailed neurological, endocrine, and neuropsychological evaluation

Stratification
- Pre vs. post pubertal
- NPS 0-1 vs. 2-3
- Hydrocephalus nil/mild vs. moderate/severe

IRB Clearance: May 2001
Accrual: 2001 - 2011
## RT techniques in the two arms

<table>
<thead>
<tr>
<th></th>
<th>High precision Conformal RT</th>
<th>Conventional RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immobilisation</td>
<td>BrainLAB stereotactic mask</td>
<td>Thermoplastic mask</td>
</tr>
<tr>
<td>Imaging datasets</td>
<td>CT + MRI (3D-FSPGR/T2 FLAIR)</td>
<td>CT simulation</td>
</tr>
<tr>
<td>Volume delineation</td>
<td>CTV= Residual tumour/ tumour bed GTV+3-5mm</td>
<td>CTV=Residual tumour/ tumour bed GTV+3-5mm</td>
</tr>
<tr>
<td>Safety margin or Planning target volume (PTV)</td>
<td><strong>2mm</strong>: RT delivery under stereotactic guidance</td>
<td><strong>5 mm</strong></td>
</tr>
<tr>
<td>Beam planning</td>
<td>microMLC based Conformal, non coplanar 6-9 beams</td>
<td>2-3 coplanar beams, appropriate wedges and shielding</td>
</tr>
<tr>
<td>Dose/fractionation</td>
<td><strong>54 Gy/ 30 #/ 6 weeks</strong></td>
<td><strong>54 Gy/ 30 #/ 6 weeks</strong></td>
</tr>
</tbody>
</table>

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Jalali *et al*, Radiotherapy and Oncology 2005
## Patient demographic profile (n=200)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CRT</th>
<th>Conv RT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age median (IQR)</strong></td>
<td>13yr (8-17.5)</td>
<td>12yr (9-17)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Male 69</td>
<td>Female 64</td>
</tr>
<tr>
<td></td>
<td>Female 36</td>
<td></td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td>Cranio 39</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Astrocytoma 34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>OPG 22</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ependymoma 6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others 4</td>
<td></td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td>Supratentorial 82</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infratentorial 23</td>
<td></td>
</tr>
<tr>
<td><strong>Vision</strong></td>
<td>Normal 98</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impaired 7</td>
<td></td>
</tr>
<tr>
<td><strong>Hydrocephalus</strong></td>
<td>Mild 34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mod/Severe 71</td>
<td></td>
</tr>
<tr>
<td><strong>NPS</strong></td>
<td>0/1 79</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/3 26</td>
<td></td>
</tr>
<tr>
<td><strong>Pubertal status</strong></td>
<td>Prepubertal 65</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Postpubertal 40</td>
<td></td>
</tr>
</tbody>
</table>
### IQ before starting adj Rx in benign/low grade tumours

45% of pediatric patients with low grade and benign tumours in a prospective study (n=103) at had low IQ (performance IQ) baseline before starting SRT

Carpentieri et al Neurosurg 2003

60.4% patients at pre RT baseline had below normal values (n=78)

<table>
<thead>
<tr>
<th>IQ Category</th>
<th>IQ Range</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Defective</td>
<td>&lt;69</td>
<td>12 (15.4%)</td>
</tr>
<tr>
<td>Borderline</td>
<td>70-79</td>
<td>23 (29.5%)</td>
</tr>
<tr>
<td>Dull Normal</td>
<td>80-89</td>
<td>17 (21.8%)</td>
</tr>
<tr>
<td>Average</td>
<td>90-109</td>
<td>22 (28.2%)</td>
</tr>
<tr>
<td>Bright Normal</td>
<td>110-119</td>
<td>4 (5.1%)</td>
</tr>
<tr>
<td>Superior</td>
<td>120-129</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Very Superior</td>
<td>&gt;130</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Jalali et al IJROBP 2006, 2010
Time trends in Full scale IQ (FSIQ)
Linear mixed model

difference in slope = 1.48; P=0.042
Reference value for clinically significant change was taken as 5 point decline/improvement (3%)
Time trends in MQ
Linear mixed model

difference in slope = 0.7684; P=0.451
Time trends in VQ
Linear mixed model (LMM)

- Pre-RT
- 6m
- 2y
- 3y
- 4y
- 5y

CRT vs Conv RT
Possible dose constraint model

No IQ decline

Left temporal lobe

• < 13% volume receiving > 43 Gy
# Left Hippocampus RT dose & IQ preservation at 5 years

Logistic regression analysis, model fit

<table>
<thead>
<tr>
<th></th>
<th>5 year evaluation</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean dose (Gy)</td>
<td>p-value*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FSIQ</strong></td>
<td>&gt;10% drop</td>
<td>31.0</td>
<td><strong>0.040</strong></td>
</tr>
<tr>
<td></td>
<td>&lt;10% drop</td>
<td>26.5</td>
<td></td>
</tr>
<tr>
<td><strong>VQ</strong></td>
<td>&gt;10% drop</td>
<td>32.0</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td>&lt;10% drop</td>
<td>25.6</td>
<td></td>
</tr>
<tr>
<td><strong>PQ</strong></td>
<td>&gt;10% drop</td>
<td>32.0</td>
<td><strong>0.037</strong></td>
</tr>
<tr>
<td></td>
<td>&lt;10% drop</td>
<td>26.0</td>
<td></td>
</tr>
</tbody>
</table>

Mean doses ≤30 Gy as a possible dose constraint cut off for IQ decline
Cumulative incidence of new endocrine dysfunction

Difference in slope = 0.047; $P = 0.0112$

31% CRT Vs. 51% Conv RT

<table>
<thead>
<tr>
<th>Patients at risk</th>
<th>6 months</th>
<th>2 yr</th>
<th>3 yr</th>
<th>4 yr</th>
<th>5 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT</td>
<td>91</td>
<td>66</td>
<td>56</td>
<td>49</td>
<td>33</td>
</tr>
<tr>
<td>Conv RT</td>
<td>82</td>
<td>68</td>
<td>56</td>
<td>46</td>
<td>39</td>
</tr>
</tbody>
</table>
Overall Survival

- Conv RT
- C RT

Proportion surviving

Follow-up time (in years)

- 5 y: 94% (95% CI: 86-97) vs. 88% (95% CI: 78-93)
- 10 y: 78% (95% CI: 56-90) vs. 82% (95% CI: 68-90)

P = 0.4697
Conclusions

• RT indicated and vital in optimal management of many CNS tumours

• Modern conformal RT spares critical areas safely

• Efficacy of conformal RT proven in a randomised controlled trial in terms of preservation of neurocognition and significantly less endocrine dysfunctions at 5 years follow up following radiotherapy; all meaningful and clinically relevant late endpoints

• Could be used as a template/corroboration for other modern evolving high precision RT techniques (including possibly particle therapy)
“Therapy should be permanently backed up by scientific research without which no progress is possible. Moreover the search for pure knowledge is one of the most important needs for mankind…”

Maria Skłodowska Curie